

Diabetes and Cardiovascular Disease

Seminal clinical trials have revealed the power of good control of blood glucose (sugar) early during the course of type 1 and type 2 diabetes to reduce later risk for eye, kidney, and nerve complications. Now, clinical trials are examining the more complex relationship between blood glucose control and cardiovascular disease (CVD) in type 2 diabetes. One recent study showed that more intensive control than currently recommended, targeting near normal blood glucose levels, can be dangerous in those with long-duration type 2 diabetes with established CVD or at high risk of developing CVD. Two other recent trials found neither cardiovascular harm nor benefit of moving from “good” to near-normal glucose levels. However, another study found that targeting good glucose control early in the course of disease can reduce cardiovascular risks decades later for many patients with type 2 diabetes. Similar cardiovascular benefits emerging long after a finite period of intensive glucose control were reported previously for individuals with type 1

diabetes. Because CVD is the leading cause of death in people with type 2 diabetes, identification of ways to reduce this risk is particularly important. There is very strong evidence that blood pressure and cholesterol control can markedly reduce CVD, but the effects of glucose control on CVD in type 2 diabetes remained an open question. Taken together, the new results refine the approach to treating diabetes and demonstrate the importance of tailoring therapy to individual patient characteristics.

Diabetes Increases the Risk of Death from Cardiovascular Disease

An estimated 23.6 million Americans have diabetes, about 5.7 million of whom have not been diagnosed.¹ Type 1 diabetes, which accounts for 5-10 percent of diagnosed diabetes cases, is an autoimmune disease that often begins in childhood or early adulthood, although it can strike at any age. The majority of people with diabetes have type 2 diabetes—a form

Drug Therapies for Type 2 Diabetes

There are many medications available to help people with type 2 diabetes lower their blood glucose. These medications fall into several classes:

- Insulin: moves glucose from blood into cells
- Metformin: reduces output of glucose from the liver and reduces insulin resistance
- Thiazolidinediones: reduce insulin resistance, by a different mechanism than metformin
- Sulfonylureas: promote release of insulin by the pancreas
- Meglitinides: promote release of insulin by the pancreas (shorter and faster acting than sulfonylureas)
- D-phenylalanine derivative: promotes release of insulin
- GLP1-analogs: stimulate production of insulin and slow gastric (stomach) emptying
- DPP-4 inhibitors: slow destruction of GLP1 and stimulate production of insulin
- Amylin analogs: slow glucose absorption from intestine, reduce glucose production by liver, and decrease appetite
- Alpha-glucosidase inhibitors: interfere with digestion and utilization of carbohydrates like starch and table sugar

Other promising therapeutic approaches are currently in development.

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of the disease that is typically associated with excess body weight and older age. In part due to the increase in childhood obesity, however, children increasingly are being diagnosed with type 2 diabetes. Both type 1 and type 2 diabetes are also influenced by genetic susceptibility. While both forms of diabetes are characterized by excessively high levels of glucose in the blood, type 1 diabetes and type 2 diabetes have different causes and are treated differently, particularly at disease onset. From the moment of diagnosis, because their insulin-producing cells have been destroyed, people with type 1 diabetes must depend on exogenous insulin, provided by injections or an insulin pump, for survival. Type 2 diabetes, in contrast, is often managed with changes in diet and exercise in its early stages. Insulin-producing cells may still be functioning in type 2 diabetes, but not sufficiently to overcome the insulin resistance that characterizes this form of the disease. A wide variety of prescription medications have been developed to help lower blood glucose in people with type 2 diabetes. (See inset box). Because these drugs act in various ways to lower blood glucose levels, some may be used in combination with others. Many people with type 2 diabetes also need to take insulin to optimally control their blood glucose levels, especially after having the disease for many years.

Despite markedly different causes and treatment options, type 1 diabetes and type 2 diabetes share a common outcome: excess glucose in the blood gradually leads to damaged blood vessels in organs throughout the body. Injury to small blood vessels, known as microvascular disease, increases the risk of blindness, kidney failure, nerve damage, and lower limb amputation. Injury to larger blood vessels, known as macrovascular disease, leads to elevated rates of heart attack, stroke, and other cardiovascular complications in people with diabetes. In general, two out of three adults with diabetes will die of cardiovascular disease or stroke—a risk that is two to four times higher than that for people without diabetes.¹ For people with type 1 diabetes, the risk of death

from CVD may be as much as 10-fold greater than the general population of the same age.^{2,3} This elevated risk of cardiovascular death shortens the expected life span of people with diabetes by several years.

Long-Term Benefits of Intensive Glucose Control Established for Microvascular Complications

Diabetic complications result from many years of gradual glucose-mediated damage to blood vessels. Thus, clinical trials of new therapies for preventing complications are designed to follow participants' health outcomes over long periods of time following initial treatment.

In 1983, the NIDDK's Diabetes Control and Complications Trial (DCCT) was launched with 1,441 volunteers with type 1 diabetes randomly divided into two groups. One group received what was standard insulin therapy at the time—one or two insulin injections per day. The other group was taught to manage their blood glucose intensively with frequent monitoring of glucose levels and multiple insulin injections daily or use of an insulin pump. The study was designed to test the ability of intensive glucose control to reduce eye damage and other microvascular complications. The study relied on a blood test (HbA1c) which gauges the average blood glucose over the previous 2 to 3 months. A normal HbA1c is below 6 percent. Throughout the study the average HbA1c value in the standard therapy group was 9.1 percent, whereas in the intensive therapy group the value was 7.3 percent—a significant difference in glucose control.

This difference, when maintained over an average of 6.5 years, yielded multiple health benefits: participants in the intensive therapy group exhibited lower rates of eye disease (76 percent reduction in risk), kidney disease (50 percent reduction), and nerve damage (60 percent reduction). Thus, the intervention to improve glucose control was clearly an effective means to lower the risk of microvascular complications in type 1 diabetes. However, because the DCCT participants were relatively young and healthy at

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the start of the trial, and because CVD typically takes a longer time to develop than other diabetes complications in patients with type 1 diabetes, it was not possible for researchers to assess the effect of intensive glucose control on cardiovascular risks during the 10 years of the trial.

Longer follow-up demonstrated additional benefits. At the conclusion of the DCCT, participants returned to the care of their regular health care providers. However, researchers continued to observe the health of more than 90 percent of the DCCT participants in an ongoing follow-up NIDDK effort called the Epidemiology of Diabetes Interventions and Complications Study (EDIC). By continuing to observe these well-characterized patient groups, the investigators hoped to determine whether the interventions that had worked so well to reduce microvascular disease risk might also yield a long-term benefit of reducing CVD.

In the EDIC study, the HbA1c levels of the study groups gradually equalized over time as glucose control in the original conventional therapy group improved, while that of the intensive therapy group worsened. Intriguingly, the EDIC initially found that differences in risk for microvascular complications between the original study groups persisted for at least 8 to 10 years, *even though the difference in HbA1c levels disappeared*. Then, in 2005, EDIC investigators reported for the first time that intensive glucose control during the DCCT trial period could also reduce long-term CVD risks in type 1 diabetes. Twelve years after the DCCT had ended, members of the original intensive therapy control group had a *42 percent lower risk for heart disease and a 57 percent lower risk for non-fatal heart attacks, strokes, or death from a cardiovascular event* compared with those who had been in the standard treatment group.

A similar trial for type 2 diabetes was conducted in the United Kingdom (U.K.) from 1977 to 1997. In the U.K. Prospective Diabetes Study (UKPDS), which was supported in part by NIDDK, more than 4,000 newly-

diagnosed type 2 diabetes patients were stratified by body weight and randomly assigned to one of four treatment groups: conventional therapy, primarily through dietary changes, or intensive therapy to lower blood glucose levels to close to normal using one of the following three diabetes medications: (1) insulin; (2) a sulfonylurea drug; or (3) metformin. (Only participants who met the trial definition of overweight could be randomly assigned to primary metformin treatment in the UKPDS.) Like the DCCT, the UKPDS demonstrated that intensive therapy to control blood glucose and lower HbA1c levels could reduce the risk of microvascular disease in people with diabetes. UKPDS results suggested that intensive therapy might also confer a benefit with respect to CVD, but, at the conclusion of the intervention—patients were followed for an average of 10 years—the differences were not statistically significant. Therefore, an important question remained unanswered as to whether intensive control could protect people with type 2 diabetes from CVD.

Long-Sought Information Emerges on Glucose Control and Cardiovascular Disease

Because of its substantial impact on the health and lives of people with diabetes, researchers have long sought effective strategies to prevent or manage diabetic CVD. Several clinical trials had proven that carefully controlling blood pressure and cholesterol levels—both of which contribute to CVD risk—substantially reduces cardiovascular events in people with type 2 diabetes. At the conclusion of the intervention, the UKPDS, the first major clinical trial to examine the effects of intensive glucose control in type 2 diabetes, fell short of proving that improved control of blood glucose levels reduced CVD.

Because the DCCT and the UKPDS trials had proven that good glucose control reduced microvascular complications in both type 1 and type 2 diabetes, subsequent expert guidelines for blood glucose management recommended an HbA1c target of 7 percent, the level of control targeted in UKPDS and

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proven to reduce eye, kidney, and nerve complications. Widespread acceptance of those recommendations meant that any subsequent attempt to prove glucose control could lessen CVD must study even more stringent control so that participants would not be put at increased risk of microvascular disease.

During the past decade, several studies were begun to answer this key question, most notably the Action to Control Cardiovascular Risk in Diabetes Study (ACCORD), which is led by the National Heart, Lung, and Blood Institute with NIDDK support. ACCORD was designed to test three treatment approaches to decrease the high rate of CVD among adults with established type 2 diabetes who are at especially high risk for heart attack and stroke. More than 10,000 patients with type 2 diabetes were assigned to one of two regimens for blood glucose control: now-standard therapy designed to attain an HbA1c value of 7.0-7.9 percent, or intensive therapy with the intent of lowering HbA1c levels to below 6.0 percent. After patients had been treated for an average of 3.5 years, the intensive therapy arm was halted 18 months ahead of schedule due to a higher rate of deaths and no significant reduction in cardiovascular events in this treatment group.

Two other studies, an industry sponsored trial (ADVANCE) and the Veterans Administration Diabetes Trial (VADT), also compared the effects of standard and intensive blood glucose control on CVD in participants with longstanding type 2 diabetes similar to the ACCORD participants. Although neither of these studies found increased mortality with intensive therapy, they both failed to find any significant reduction in cardiovascular events.

The results of the three recent trials generated huge interest in the medical community and their full implications are still being explored. Further analyses over the next year may help to clarify some factors, such as patient characteristics and treatment regimens, contributing to the differences, but may

not identify the cause of the excess deaths in the ACCORD trial.

While the ACCORD trial demonstrated the danger of intensive glucose management to near normal glucose levels in patients with longstanding type 2 diabetes who were at especially high risk of CVD, it did not address the question of cardiovascular benefit of good glucose control instituted shortly after diagnosis when good control can be achieved with simpler diabetes control regimens. The best evidence of the benefits of early treatment comes from the recently reported long-term follow-up of the UKPDS participants. There were no early adverse effects of intensive glucose control in the newly-diagnosed type 2 diabetes patients studied in the UKPDS. Three-quarters of UKPDS participants were observed for 10 years after the end of the original intervention trial. In 2008, the UKPDS follow-up study reported similar benefits for type 2 diabetes patients as had been seen in EDIC for type 1 diabetes. The intensive therapy groups had persistent reductions in microvascular complications and substantial reductions in risk for heart attack compared to those assigned to standard therapy. Intensive therapy participants also had a lower overall risk of death during the course of the study. In the UKPDS follow-up study, as in EDIC, the HbA1c levels between groups became equal for most of the follow-up period. Thus, a period of intensive diabetes management to control glucose levels appears to confer enduring benefits in terms of reducing diabetic complications—including CVD—even if an individual's glucose control subsequently becomes less stringent. This phenomenon, which has been termed “metabolic memory” or the “legacy effect,” provides a powerful motivation for most diabetes patients to maintain their glucose levels as close to normal as possible early in the disease.

One Treatment Approach Is Not Suitable for All People with Diabetes

The results of the DCCT/EDIC and UKPDS represent landmark advances in validating intensive glucose

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management as a strategy to prevent microvascular and cardiovascular complications in both type 1 and type 2 diabetes. But ACCORD and other large clinical trials of blood glucose control and cardiovascular risk in type 2 diabetes arrived at a seemingly conflicting conclusion. On the surface, the ACCORD outcome seems at odds with the UKPDS finding that intensive glucose control is protective in terms of reducing cardiovascular risks, including death, in people with type 2 diabetes. However, there are important differences between the studies. UKPDS participants had a median age of 53 years and were newly diagnosed with diabetes at the time of enrollment. In contrast, the ACCORD cohort was older, with an average age of 62 years, and had been living with diabetes for a median duration of 10 years. ACCORD participants were also at especially high risk of CVD, and more than a third had already experienced at least one cardiovascular event before the trial began. Moreover, the ACCORD “intensive” therapy protocol attempted to reduce HbA1c values to “near normal” (i.e., non-diabetic) levels, a considerably more aggressive approach to glucose control than the “intensive” therapy regimens of the UKPDS and DCCT. Viewed together, the results of ACCORD and UKPDS suggest that a *personalized* approach to glucose control in type 2 diabetes might be needed—one that takes into account a person’s duration of diabetes, the presence or absence of diabetes complications, risk of low blood glucose, other complicating illnesses and life expectancy, as well as other health, behavioral, and social factors.

Conclusions

The recent results of long-term clinical trials to reduce diabetes complications are expanding our knowledge of the best ways to manage diabetes. Despite some challenges, progress is being made in improving

glucose control and reducing both micro- and macrovascular complications related to both type 1 and type 2 diabetes. Further investigation is needed, since no current treatment regimens fully replicate the tightly regulated control of glucose levels found in people without diabetes.

Type 1 and type 2 diabetes are complex chronic diseases that have multiple clinical presentations, variability in their rates of progression, and variability in susceptibility to development of chronic micro- and macrovascular complications. Strategies for controlling blood glucose to prevent complications may need to be modified for different groups of patients or even for a single patient as their disease progresses. Such strategies must also take into account other therapies to manage CVD risks, such as drugs that normalize blood pressure, reduce blood lipid levels, or alter blood coagulation.

As the number of people with diabetes in the U.S. continues to climb, the NIDDK investment in long-term clinical trials to optimize diabetes management will help reduce the burden of CVD and premature death in this large segment of the population. In addition, basic research to understand the phenomenon of metabolic memory will shed light on the way intensive glucose control early in the course of diabetes can pay off in terms of fewer complications years later. In time, it may be possible to reproduce the effects of metabolic memory even in patients with poorly controlled diabetes and, thereby, help all people with diabetes achieve better health and longer lives.

¹ <http://www.cdc.gov/diabetes/pubs/factsheet07.htm>

² Krolewski AS, et al: *Am J Cardiol* 59:750-755, 1987.

³ Dorman JS, et al: *Diabetes* 33:271-276, 1984.