# The Cardiovascular Legacy of Good Glycemic Control: Clues About Mediators From the DCCT/EDIC Study

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Diabetes is defined by hyperglycemia, but whether optimizing glycemic control can reduce its complications was long in doubt. In 1968 Siperstein et al. proposed the hypothesis that microvascular injury accompanying diabetes could be genetically determined (1), and there was concern that, even if the "glucose hypothesis" (2,3) were valid, seeking good control of hyperglycemia was overly risky. Nevertheless, epidemiologic evidence linking hyperglycemia with both microvascular and cardiovascular complications prompted assessment of the effects of intensive glycemic control in the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes (T1D) and the UK Prospective Diabetes Study (UKPDS) for type 2 diabetes (T2D). When the results of the DCCT were reported in Las Vegas on a hot (>110°F) day in June 1993, many people were surprised by the approximately 50% reduction of microvascular changes that was associated with 6.5 years of maintaining hemoglobin $A_{1c}$ ($HbA_{1c}$) close to 7% (53 mmol/mol) compared with 9% (75 mmol/mol) in the control arm (4). Because the DCCT participants were young, cardiovascular events were too few to analyze and long-term effects on cardiovascular risk remained unknown. Results in T2D from the UKPDS reinforced the message of the DCCT. More intensive glycemic control attaining about a 1% difference in $HbA_{1c}$ in T2D for 10 years led to 25% lower rates of microvascular outcomes (5) and a nonsignificant 16% lower rate of myocardial infarction (5).

For more than two decades after these reports the dominant view has been that improving glycemic control reduces eye, nerve, and kidney complications but not cardiovascular risk. Four large randomized clinical trials testing whether seeking $HbA_{1c}$ levels at or below 7% could reduce cardiovascular events showed limited benefits during their periods of active treatment (5–8). Although analysis of data pooled from these four trials showed a 15% reduction of myocardial infarction (9), the still unexplained 22% increase of mortality (6) in the intensive arm of one trial (Action to Control Cardiovascular Risk in Diabetes [ACCORD]) may have influenced clinical practice more. To the present day there is concern about seeking $HbA_{1c}$ levels below 7% in broad groups of patients, based on the perception that risks may outweigh benefits (10).

Meanwhile, the DCCT investigators continue to follow their original cohort of participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study. Meticulously collected data are now available for up to 30 years after randomization, long after cessation of efforts to optimize glycemic control in the intensive arm. Increasing numbers of cardiovascular events and deaths have occurred as the population grows older, and consistent differences between the treatment groups are apparent. After a mean of 17 years following randomization, the risk of any cardiovascular event was 42% lower in the group previously assigned to intensive therapy, and that of major adverse cardiovascular events (MACE) (nonfatal myocardial infarction, stroke, or cardiovascular death) 57% lower (11). A similar analysis at 27 years after randomization yielded a 30% lower risk of any cardiovascular event and 32% lower for MACE (12). At about the same interval after randomization, all-cause mortality in the formerly intensively treated group was 33% lower than after conventional treatment (13) and was estimated to be no different than that in the general population of the U.S. (14). Emergence of clinically important between-group differences more than two decades after cessation of randomized intervention has been attributed to a "legacy effect" or "metabolic memory" of prior glycemic control.

Evidence for long-term cardiovascular benefits of good glycemic control early in the course of diabetes has received less attention than it deserves. This may be because the mechanisms linking prior hyperglycemic exposure to medical outcomes have been poorly understood.

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**See accompanying articles, pp. 1202 and 1284.**

Persistence of glycated proteins and complex molecules termed advanced glycation end products, tissue injury related to hypoxia, and oxidative reactions represent a variety of possibilities. However, exactly how these biochemical processes increase cardiovascular risk has been unclear.

A series of reports from the DCCT/EDIC group has addressed this gap of information, providing insights into pathways that may be mediating the long-term legacy effect of a limited period of intensive glycemic control. The first important analysis demonstrated that most of the long-term cardiovascular benefit of randomization to intensive glycemic therapy could be statistically explained (that is, accounted for) by the between-group difference in $HbA_{1c}$ that was achieved during the 6.5-year active treatment period (11). Ways in which this difference in $HbA_{1c}$ could have reduced long-term cardiovascular outcomes were further explored by the DCCT/EDIC investigators in a new report in this issue of *Diabetes Care* (15), using data collected during nearly three decades of observation. A multivariable analysis by randomized treatment group showed that mean values for pulse, log albumin excretion rate (AER), and total cholesterol—each a recognized risk factor for cardiovascular disease—accounted for 41% of the overall effect of $HbA_{1c}$ on any cardiovascular event and 54% of the effect on MACE. Supportive epidemiologic analyses in the whole study population also showed that a 1% higher updated mean $HbA_{1c}$ was associated with a 68% greater risk of MACE. The portion of this $HbA_{1c}$ effect that was statistically attributable to—that is, mediated by—each of the potential cardiovascular risk factors that were observed during follow-up was estimated as the proportion by which the effect of $HbA_{1c}$ alone was reduced when the model was adjusted for each one alone. The contributions to $HbA_{1c}$-associated risk of the MACE outcome were 29% for pulse rate, 24% for AER, 13% for triglycerides, 11% for LDL cholesterol (LDLc), 11% for estimated glomerular filtration rate (eGFR), 10% for systolic blood pressure, and 10% for pulse pressure (systolic minus diastolic blood pressure). In a fully adjusted model including all these covariates, 43% of the $HbA_{1c}$-associated effect was accounted for by identified mediators whereas the remainder, more than 50%, was presumably due to others as yet unknown.

These findings build on previously published epidemiologic analyses showing that: *1*) after age, mean follow-up $HbA_{1c}$ is the leading risk factor for the cardiovascular end points (16); *2*) mean follow-up $HbA_{1c}$ is the strongest predictor of renal injury (17); and *3*) the effect of $HbA_{1c}$ on cardiovascular outcomes is partially reflected in its effect on systolic blood pressure, LDLc, triglycerides, and pulse rate, with the greatest effect of these mediators evident after 20 years of observation (18).

In plain language, how do these observations help us? First, we have evidence that intensive glycemic control for 6.5 years early in T1D leads to meaningful reductions of cardiovascular events and deaths more than 20 years later. Second, in a randomized comparison of treatment strategies, the benefit of intensive treatment is statistically accounted for mainly by differences in $HbA_{1c}$ over time. Third, several specific risk factors—especially pulse rate, blood pressure, and renal injury—are likely mediators of glycemic treatment effects. Fourth, effects of these mediators emerge slowly and persist long after intensive treatment. They are, therefore, measurable manifestations of the mysterious legacy effect.

These are huge contributions from a small but carefully managed and long-term research effort. We are indebted to the DCCT/EDIC group, the 1,441 participants in the study, and the sponsorship provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Of course, there are limitations to the study and these analyses. Compared with many cardiovascular trials, the numbers of participants and events are small and statistical power is therefore limited. We do not understand in molecular terms the basis for changes of heart rate, blood pressure, and renal function that result from hyperglycemia and enhance cardiovascular risk. Also, mediation analyses can only be conducted for risk factors that were identified long ago and assessed systematically over time. Because at least 50% of the long-term effect of hyperglycemia remains unaccounted for, we are missing other physiologic mediators.

Notwithstanding these limitations, we can expand upon the DCCT/EDIC investigators' comments regarding potential mechanisms of the legacy effect. Higher pulse rate is an established risk factor and can be due to the greater impairment of parasympathetic relative to sympathetic neural tone that is known to be common among patients with diabetic autonomic neuropathy (19,20). Autonomic neuropathy can also impair other cardiac and vascular responses and is itself a risk factor for cardiac events (20,21). Wider pulse pressures and increased systolic pressure can be related to increased stiffness of larger arteries caused by glycation or other processes related to prolonged exposure to hyperglycemia (22). Glycated proteins in the skin also are associated with risk of retinopathy, nephropathy, and cardiovascular disease and likely reflect a similar process throughout the body (23,24). Likewise, albuminuria and reduced eGFR associated with prior hyperglycemia may reflect additional abnormalities, such as increased capillary permeability in other tissues (25) and reduced clearance of both drugs and endogenous molecules. Tissue hypoxia mediated by capillary damage may underlie many of these effects. For example, a recent report suggests the density of the microcirculation (vasa vasorum) is reduced in coronary arteries of individuals with diabetes (26). Similar processes involving the structure and function of capillaries and arterioles in various locations may promote myocardial ischemia and dysfunction, arterial stiffness and systolic hypertension, and albuminuria and reduced renal function. Whereas some of these mediators have direct effects on cardiovascular risk that can be reduced by specific therapies late in the natural history of diabetes, it is likely that many of them are markers for additional tissue injury that cannot be reversed. For example, elevations of blood pressure and LDLc can be treated, but sclerosis, narrowing, and occlusion of small blood vessels in the heart and elsewhere may not be easily modified.

An important further question is whether the mechanisms underlying a legacy effect in T1D can be extrapolated to T2D. Despite lack of direct evidence, there seems no reason that similar mechanisms linking prior hyperglycemia with later cardiovascular risk would not be present in T2D. The question is highly relevant because of data supporting a legacy effect of initial glycemic control in population-based studies (27) and at

least two trials of intensive glycemic control in T2D (28,29).

These observations in people with both T1D and T2D and the sophisticated statistical analyses of the DCCT/EDIC cohort are clinically important. They also provide clues regarding pathways by which changes in glycemic control today could reduce cardiovascular outcomes tomorrow. Focusing on good glycemic control early in diabetes reduces symptoms and microvascular complications within a short period of time. Furthermore, there is clear evidence that good glycemic control can deliver a legacy of lower cardiovascular risk in the longer term in T1D, and there is supportive evidence that it can do so in T2D. The challenge now, for all types of diabetes, lies in further development of simple, inexpensive glucose-lowering strategies that minimize the barriers to achieving and maintaining good glycemic control.

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