VIEWPOINT

Measuring What Matters in Diabetes

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Optimal diabetes care is predicated on balancing the immediate and long-term sequelae of the disease and its therapies, improving patient health and well-being, and mindfully stewarding health care resources for both the patient and society. Professional societies, public health organizations, regulatory agencies, patients, and clinicians have focused on hemoglobin A_{1c} (HbA_{1c}) levels to gauge the quality of diabetes care.[1] Over time, HbA_{1c} level has supplanted other indicators of the quality of diabetes care, such as blood glucose levels and symptoms of hyperglycemia, despite being a surrogate rather than a direct marker of glycemic control, and reflecting average levels of glycemia during the preceding 3 months. Although potentially more challenging to measure or difficult to change, other measures of the quality of diabetes care may better represent the outcomes that are truly meaningful to people living with diabetes, including immediate symptoms of hypoglycemia or hyperglycemia, burden of treatment,[2] quality of life, and long-term sequelae of inadequately controlled diabetes.

Concerns about reliance on HbA_{1c} levels have been raised previously, particularly because clinical outcomes of glycemic control are not agnostic to the medications used to achieve it.[3] For instance, Lipska and Krumholz[3] have pointed out that patients achieved better cardiovascular and kidney-related outcomes with use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists vs placebo controls independent of any reduction in HbA_{1c} level. The preferential use of HbA_{1c} levels in research, policy, and practice stems from the demonstrated association between lower HbA_{1c} levels and improved microvascular disease end points in early pivotal clinical trials that evaluated the benefits of intensive glycemic control.[4,5] However, these studies did not demonstrate improvements in outcomes that are most meaningful to patients such as blindness, end-stage kidney disease (ESKD), painful neuropathy, amputation, stroke, and mortality. Instead, these trials relied on surrogate end points (eg, albuminuria, photocoagulation, nerve conduction abnormalities) or composite outcomes with a clear gradient of importance (eg, mortality and cataract extraction as 1 outcome).[4] A positive result on a composite end point that results from benefits in surrogate end points is misleading if misperceived to suggest that all components of the composite shared in the benefit of lower HbA_{1c} levels. Thus, HbA_{1c} level is a surrogate marker for a proxy of uncontrolled disease.

A Time and Place for Surrogate Markers

Surrogate end points remain the gold standard in many clinical trials, including those used by the US Food and Drug Administration (FDA) for the evaluation and approval of diabetes therapies and there is good reason for this. It takes time for diabetes complications to develop, symptomatic complications are less frequent than preclinical precursors, and ideal diabetes management would preempt symptomatic complications altogether. From the regulatory and research perspectives, clinical trials examining outcomes that are important to patients require extended follow-up and large numbers of participants, making these studies more expensive and logistically complicated. Surrogate markers like HbA_{1c} levels, nerve conduction abnormalities, and albuminuria are more immediate, prevalent, and therefore attractive to researchers and industry, allowing for quicker evaluation of drug efficacy. Similarly, for clinicians, HbA_{1c} level is an effective monitoring tool that is responsive to real-time changes in care. It is also a number that patients can understand and monitor. Levels of HbA_{1c} are actionable and modifiable in ways that newly developed complications and death are not. Nevertheless, even though HbA_{1c} level is a valuable forewarning of future events in patients with diabetes and has an important role in reflecting the patient's average level of glycemia, it should not be the outcome that matters more than or is prioritized at the expense of meaningful outcomes that are important to patients.

Fallacy of the Surrogate

The rationale for using HbA_{1c} level as a surrogate for diabetes outcomes is predicated on the assumption of its direct correlation with outcomes that patients ultimately value, including clinical microvascular disease (eg, ESKD and need for dialysis, blindness, neuropathic pain, amputation), macrovascular disease (eg, myocardial infarction, stroke, painful neuropathy), quality of life, and death. Yet, the strength of this relationship has been called into question. Meta-analyses revealed a null association between intensive glycemic control and these patient-important outcomes, with the sole exception of a 10% to 15% relative risk reduction of nonfatal myocardial infarction.[4]

In major clinical trials including patients with type 2 diabetes, favorable surrogate and composite-driven outcomes as well as improvements in several hard clinical outcomes (such as death or myocardial infarction that were detected among participants in the UK Prospective Diabetes Study[6] after an extended observation period) corroborated the positive results for patients with type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications trials[7] to establish the centrality of the HbA_{1c} level in diabetes management. However, the importance of glycemic control for patients with type 2 diabetes cannot be extrapolated from data developed among patients with type 1 diabetes. These conditions diverge on key pathophysiological, metabolic, and treatment-related factors, with the glucose-centric model of type 1 diabetes not immediately transferrable to the management of type 2 diabetes.

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VIEWPOINT

Resurgence in Diabetes-Related Complications

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The improved long-term outlook for adults after receiving a diagnosis of diabetes is one of the most important clinical and public health successes in recent decades. During the early 1990s, patients with diabetes had reductions in lifespan of 7 to 10 years and an increased risk of lower-extremity amputation (LEA) vs those without diabetes (58 vs 3 cases/10 000 persons/year, respectively) and kidney failure (28 vs 2 cases/10 000 persons/year).[1] Risk of cardiovascular events, which caused the most deaths, also was higher among persons with diabetes vs those without diabetes (141 vs 38 hospitalizations for acute myocardial infarction [AMI] per 10 000 persons/year).[1] But through multifaceted improvements in diabetes care, risk factor management, self-management education and support, and better integration of care, these risk differences were reduced by 28% to 68% across a range of complications between 1990 and 2010, with gains most notable for reductions in AMI, stroke, and death due to hyperglycemia.[1,2] Although the excess morbidity risk remained too high and the reduction in cardiovascular disease mortality led to new types of complications and causes of death,[3] a continued reduction in the overall public health burden caused by diabetes seemed promising.

However, in an unanticipated new challenge to these improvements, a resurgence of diabetes complications has appeared in national statistics and in the epidemiology literature. Between 2010 and 2015, an increase in diabetes-related LEAs occurred nationally, reversing more than one-third of the 20-year decline in only 5 years.[4,5] For hyperglycemic crisis, annual emergency department visits almost doubled between 2009 and 2015 (from 16.2 to 29.4 per 1000), hospitalizations increased by 73% (from 15.3 to 26.6 per 1000), and deaths increased by 55% (from 15.7 to 24.2 per 1000).[4] For end-stage kidney disease, AMI, and stroke, the long-term improvements stalled after 2010. Updated national statistics indicate that the recent increase in complication rates is occurring in young and middle-aged adults (Figure), among whom the risk of hyperglycemic crisis, AMI, stroke, and LEAs each increased by more than 25% during only 5 years. Although the rebound in rates has been most apparent in young adults (aged 18-44 years), middle-aged adults (aged 45-64 years) have higher absolute rates and account for most of the increase. Among older adults, the long-term reductions in rates have reached a plateau (Figure). These changes may not be limited just to the population diagnosed with diabetes because improvements in AMI and stroke in the general population also have plateaued, and most counties in the United States have seen an increase in cardiovascular disease mortality among younger adults.[6]

Explaining these trends is difficult because of myriad potential factors in preventive care, patient characteristics, and society. Tracking incidence of major chronic conditions relies on diagnoses and procedures that appear in administrative files, making systematic changes in coding a key consideration. For example, reimbursement incentives that affect upcoding of diabetes or changing diagnostic schemes could conceivably affect rates. However, there are no data to suggest that this has occurred, and the diversity of outcomes, consistency across data sources, and the use of 1 diagnostic classification system (*International Classification of Diseases, Ninth Revision, Clinical Modification*) points to broader causes. Four key plausible sources of these changes warrant examination because understanding the modifiable etiology of this resurgence could be helpful in developing an effective response.

First, there may be increasing heterogeneity or a changing profile for the population of new diabetes cases. The age divide in trends points toward the millennial generation (born roughly between 1980 and 2000) and their high obesity prevalence (approximately 35% with body mass index [calculated as weight in kilograms divided by height in meters squared] >30), compounded by higher levels of smoking and poorer blood pressure and lipid level management seen among younger than older adults.[2] These factors may be combining with chronic kidney disease to influence an earlier onset of macrovascular complications. Whether trends in complication rates vary between type 1 and type 2 diabetes is not clear due to data limitations in national surveys, but it is possible that a greater increase in type 2 diabetes than type 1 diabetes among nonwhites is gradually increasing the ratio of type 2 to type 1 diabetes and affecting the character of diabetes-related morbidity. For the middle-aged and older population in particular, the combination of decreasing mortality among those with diabetes and recent decreases in diabetes incidence is increasing the average duration of diabetes in the population.[4] This shift in the distribution for the duration of diabetes may now be affecting the risk of complications. The effect of Medicaid expansion on detection of diabetes and the characteristics of the underlying population with diagnosed diabetes is also an open question.

Second, there may be stagnation in preventive care, again most prominent among young adults. After encouraging reductions in hemoglobin A_{1c} (HbA_{1c}) levels among patients with diabetes through most of the 2000s, the proportion meeting individualized HbA_{1c} targets declined from the 1990s to 2011-2014 by 6 percentage points overall and by 10 percentage points among young adults.[7] The increase in suboptimal HbA_{1c} levels occurred at a time when clinical organizations have encouraged better age and comorbidity personalization of treatment targets and prevention of hypoglycemia for older adults. Such efforts have been accompanied by a reduction in major hypoglycemic events,[4] but also could be accompanied by an unintended relaxation of glycemic control targets for younger adults.

The increases in LEAs could be driven more by clinical decision making about the management of

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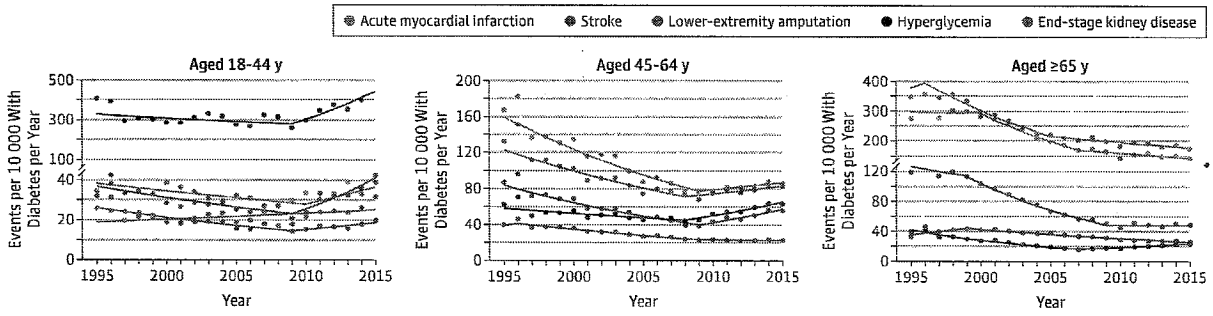
Figure. Incidence of Hospitalization for Major Diabetes-Related Complications Among the US Population With Diagnosed Diabetes by Age Group



Dots indicate observed yearly rates. The lines are modeled rates and are based on joinpoint regression analysis. Incidence rates were calculated according to methods described previously,[1,4] with extension to year 2015, and addition of hyperglycemic crises, defined as hospitalization with *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 250.1-250.2 as the first-listed clinical diagnosis. Data are from the US Centers for Disease Control and Prevention.[4]

patients at high risk for foot-related complications. Most of the recent increase in amputations has occurred in toes and feet, suggesting that surgeons may be performing minor amputations sooner rather than prolonging attempts to heal infected ulcers, possibly driven by incentives to prevent rehospitalizations.[5] However, smaller preemptive amputations do not account for all of the increase in LEA rates because long-term reductions in more severe amputations also have plateaued.

Third, some broader policy-level factors may be driving the access to preventive care and influencing the risk for complications. Although the proportion of the population that is uninsured has decreased in the United States since passage of the Affordable Care Act, the use of high-deductible health plans (HDHPs) has proliferated and may have contributed to reductions in early preventive care. Employer-based switches to HDHPs, which now cover 43% of the young adult and middle-aged population, have a particularly deleterious effect on those of low income, and have led to both delayed and more frequent treatment for high-acuity complications.[8] Variation in coverage of foot care services could be further affecting the risk and timing of amputations. In addition, the continually increasing cost of insulin and other antihyperglycemic medications could be leading patients to cut back on treatment to cut costs,[9] although the effects of these cost increases on health outcomes has not been quantified.

Fourth, and perhaps most concerning, broader social and economic factors may be affecting vulnerable populations that drive trends in outcomes. Increasing mortality rates during middle age following the economic recession that started in 2008-2009 have received considerable attention and were initially thought to be driven by suicides, opioid overdoses, and social disadvantage.[10] However, other analyses suggest that the increase in middle-age mortality may also include metabolic causes. The economic downturn, employment loss, and financial hardship disproportionately occurred in communities that also have high diabetes prevalence, which means that upstream socioeconomic factors could contribute to a range of adverse complications of diabetes.[4]

Even though concurrent observations of declining rates of diagnosed diabetes are encouraging, the population prevalence of diabetes is 12% and is unlikely to decrease soon because of the long-term increases in prevalence of obesity and lifespan.[4] This means that the future direction of diabetes complications has enormous collective implications for health and costs. The fact that it is only possible to speculate about the causes of such trends in the diabetes-related burden exposes gaps in epidemiology and surveillance, and in the interconnectedness of valuable clinical data. National averages can obscure important variation in morbidity, and conversely, minorities of high-risk individuals can influence overall trends. However, current monitoring systems do not have the granularity to detect or characterize the subgroups that are driving the trends. Rather than assessing the static etiology of disease (whether behavioral, genetic, physiological, or environmental), the current questions call for a more textured comparison of health care practices, policies, and environmental changes underway and how such factors affect the etiology of trends in population health.

ARTICLE INFORMATION

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Moreover, HbA_{1c} level may be misleading and its singular prioritization could lead to patient harm. Pursuit of low glycemic targets may necessitate polypharmacy and use of insulin, and could contribute to hypoglycemia, treatment burden,[2] and higher costs of care. Moreover, because HbA_{1c} level is a measure of average level of glycemia during approximately 3 months, it does not capture daily glycemic variation. For example, a normal HbA_{1c} level may create a false sense of security for patients and clinicians who may be unaware about underlying glycemic lability and hypoglycemia.

In addition, HbA_{1c} level is not without methodological limitations and has inherent variability within and among testing laboratories. Levels of HbA_{1c} are affected by a variety of health conditions (including chronic kidney disease and liver disease), anemia, and hemoglobinopathy. Black patients have higher HbA_{1c} levels than white patients for the same average glucose level, potentially contributing to observed disparities in diabetes management, outcomes, and hypoglycemia.

Inadequacy of the HbA_{1c} Level

Cardiovascular outcomes trials were mandated by the FDA since 2008 to examine the cardiovascular safety of glucose-lowering drugs. With minimal differences in HbA_{1c} levels achieved in the intervention vs active comparator treatment groups, variation in study end points could be attributed to the study drugs rather than the presumed benefit of reduction in HbA_{1c} level. As a result, 2 GLP-1 receptor agonists (liraglutide and semaglutide) and 3 SGLT-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) were demonstrated to reduce major microvascular and macrovascular events and death independent of glycemic control.[8] Clinical practice guidelines now acknowledge the nonglycemic benefits of these medication classes and suggest their use independent of the need to lower the HbA_{1c} level.[9] However, if HbA_{1c} level does not fully capture the macrovascular and microvascular benefits of glucose-lowering therapy,[1] why continue to rely on this measure as the primary marker of diabetes care quality?

Outcomes to Measure Instead

Consideration should be given to reverse the routine use of surrogate markers and refocus on the following outcomes that are important to people living with diabetes and their caregivers: symptomatic hypoglycemia and hyperglycemia, vision deterioration, symptomatic peripheral and autonomic neuropathy, lower-extremity ulceration or amputation, kidney function impairment, cardiovascular disease, and others. Measures of immediate glycemic control obtained through self-monitoring of blood glucose level or continuous glucose monitoring can reveal glycemic lability, symptomatic hyperglycemia, and hypoglycemia. Patient-reported outcomes, including those assessing self-reported hypoglycemia, treatment adverse effects, diabetes distress, disordered eating behaviors, burden of treatment,[2] and financial hardship may reveal vital aspects of the life of a patient with diabetes that warrant treatment modification or other targeted interventions.

Integration of these meaningful, patient-centered, tangible outcomes might improve patient care, drug development, and regulatory functions. Trials that focus on patient-reported outcomes may need to be larger and more expensive, and will inevitably require a collaborative effort between academic and clinical sites, regulatory bodies, professional societies, pharmaceutical companies, and funding agencies. However, the success of cardiovascular outcomes trials has demonstrated that such collaboration is not only possible, but potentially transformative. Funding agencies and the FDA can put greater emphasis on outcomes that are important to patients. Performance measurement can similarly shift toward hard outcomes, patient-reported outcomes, and goal-concordant care. Encouraging clinicians to embrace patient-centered care unencumbered by the constraints of the HbA_{1c} level could allow them to instead focus on the outcomes identified by patients and their caregivers.

More than 30 million people in the United States live with diabetes, as do more than 450 million around the world. The US 21st Century Cure Act sought to place patients at the forefront of the health care system, engaging patients as participants in patient-focused drug development guided by their input and experience. To improve the quality and value of diabetes care, it will be necessary for patients and all those involved in their care to focus on what truly matters to the people living with diabetes—improving their lives, not their laboratory numbers.

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Lack of Glycemic Legacy Effects in the Veterans Affairs Diabetes Trial

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In randomized trials, intensive glycemic control has not resulted in lower risks of major cardiovascular events or death than standard glycemic control among patients with type 1 or type 2 diabetes during intervention periods. However, extended follow-up in some of these trials indicates that cardiovascular benefits may emerge over time. For example, follow-up in the Diabetes Control and Complications Trial (DCCT) involving patients with type 1 diabetes showed that intensive glycemic control was associated with beneficial effects with regard to cardiovascular events.[1] Similar postintervention follow-up in the United Kingdom Prospective Diabetes Study (UKPDS) showed reductions in the risks of cardiovascular events and death among patients with newly diagnosed type 2 diabetes who had been randomly assigned to intensive glycemic control,[2] a finding replicated in observational cohort studies.[3,4] Such beneficial effects — termed "metabolic memory" or "legacy effects" — emerged after glycemic levels no longer differed between treatment groups.

Long-term follow-up in the Veterans Affairs Diabetes Trial (VADT) has provided the opportunity to ask whether a glycemic legacy effect exists in patients with advanced type 2 diabetes. The VADT included 1791 military veterans who had received a diagnosis of type 2 diabetes a mean of 11.5 years earlier and who had been randomly assigned to intensive or standard glucose control for a median of 5.6 years.[5] The trial showed a between-group difference of 1.5 percentage points in the median glycated hemoglobin levels (6.9% in the intensive-therapy group vs. 8.4% in the standard-therapy group).[5] At trial completion, there was no significant between-group difference in the incidence of cardiovascular events, cardiovascular mortality, or all-cause mortality.[5] However, an interim analysis after 10 years of follow-up showed that the intensive-therapy group had a significantly lower incidence of cardiovascular events than the standard-therapy group.[6] Because a modest difference in glycated hemoglobin levels (0.2 to 0.3 percentage points) between the trial groups persisted during follow-up, the existence of a legacy effect could not be fully assessed.

In this issue of the *Journal*, Reaven et al.[7] report the results from a 15-year follow-up study in the VADT. The difference in the glycated hemoglobin levels between the two groups was no longer apparent after 9 years (glycated hemoglobin level, approximately 8% in each group). After the present extended follow-up, the risk of the primary composite cardiovascular outcome (nonfatal heart attack, nonfatal stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes) was nonsignificantly lower, by 9%, in the intensive-therapy group than in the standard-therapy group (47.3 vs. 51.8 events per 1000 person-years; hazard ratio, 0.91; 95% confidence interval, 0.78 to 1.06). Likewise, no significant between-group difference in cardiovascular mortality or all-cause mortality was seen. Moreover, the association between treatment group and cardiovascular events was almost entirely explained by the glycated hemoglobin levels over the preceding 3 years rather than by earlier glycemic levels, which suggests that glycemic control does not have a prolonged effect on cardiovascular events. Consistent with these findings, follow-up in two major trials of intensive as compared with standard glycemic control in patients with advanced diabetes (ACCORD [Action to Control Cardiovascular Risk in Diabetes] and ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation]) also showed no evidence of emergent cardiovascular benefits.[8,9]

Thus, a glycemic legacy effect was observed in the post-trial follow-up in the DCCT and UKPDS but not the VADT, ACCORD, or ADVANCE trials. Several possible explanations for this difference exist. First, an attractive hypothesis for the glycemic legacy effect is that early intensive control reduces oxidative stress and advanced glycation end products, which otherwise lead to vascular damage over many years. On the basis of that

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hypothesis, patients with a longer duration of type 2 diabetes may have preexisting vascular injury; thus, at 15 years, benefits from intensive glycemic control no longer exist. Second, the DCCT and UKPDS were conducted three decades ago, when the use of cardioprotective strategies, such as antiplatelet agents, angiotensin-converting–enzyme inhibitors, and statins, was not standard practice. In contrast, the VADT tested the effect of intensive glycemic control during a new era in which cardiovascular risk factors are aggressively controlled.

The VADT was not designed to evaluate the effect of specific glucose-lowering agents on outcomes, and similar drug classes were used in both treatment groups. Recent cardiovascular-outcomes trials of glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors have shown benefits, as compared with placebo, regarding major cardiovascular events in patients with established cardiovascular disease. These benefits were independent of glycemic control.[10] Thus, for patients with advanced diabetes, clinical focus on how glucose levels are lowered rather than on achieving intensive targets may lead to better cardiovascular outcomes.

A major implication of the VADT follow-up study is that older patients with advanced diabetes should not expect long-term cardiovascular benefits from intensive glycemic control. Instead, interventions that clearly reduce cardiovascular risk — such as smoking cessation, blood-pressure control, statin therapy, use of antiplatelet agents, and the use of glucose-lowering agents with proven cardiovascular benefits in patients with established cardiovascular disease — should be prioritized. Although a glycemic legacy effect may exist for younger patients, the current era of comprehensive cardiovascular risk-factor control may reduce, if not eliminate, legacy effects. Glycemic goals that are likely to produce both cardiovascular and microvascular benefits and minimize harms, consistent with patient preferences and values, may be the most effective, evidence-based, and safest strategy for patients with type 2 diabetes.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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ORIGINAL ARTICLE

Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up

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ABSTRACT

BACKGROUND

We previously reported that a median of 5.6 years of intensive as compared with standard glucose lowering in 1791 military veterans with type 2 diabetes resulted in a risk of major cardiovascular events that was significantly lower (by 17%) after a total of 10 years of combined intervention and observational follow-up. We now report the full 15-year follow-up.

METHODS

We observationally followed enrolled participants (complete cohort) after the conclusion of the original clinical trial by using central databases to identify cardiovascular events, hospitalizations, and deaths. Participants were asked whether they would be willing to provide additional data by means of surveys and chart reviews (survey cohort). The prespecified primary outcome was a composite of major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, and death from cardiovascular causes. Death from any cause was a prespecified secondary outcome.

RESULTS

There were 1655 participants in the complete cohort and 1391 in the survey cohort. During the trial (which originally enrolled 1791 participants), the separation of the glycated hemoglobin curves between the intensive-therapy group (892 participants) and the standard-therapy group (899 participants) averaged 1.5 percentage points, and this difference declined to 0.2 to 0.3 percentage points by 3 years after the trial ended. Over a period of 15 years of follow-up (active treatment plus post-trial observation), the risks of major cardiovascular events or death were not lower in the intensive-therapy group than in the standard-therapy group (hazard ratio for primary outcome, 0.91; 95% confidence interval [CI], 0.78 to 1.06; P=0.23; hazard ratio for death, 1.02; 95% CI, 0.88 to 1.18). The risk of major cardiovascular disease outcomes was reduced, however, during an extended interval of separation of the glycated hemoglobin curves (hazard ratio, 0.83; 95% CI, 0.70 to 0.99), but this benefit did not continue after equalization of the glycated hemoglobin levels (hazard ratio, 1.26; 95% CI, 0.90 to 1.75).

CONCLUSIONS

Participants with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had a lower risk of cardiovascular events than those who received standard therapy only during the prolonged period in which the glycated hemoglobin curves were separated. There was no evidence of a legacy effect or a mortality benefit with intensive glucose control. (Funded by the VA Cooperative Studies Program; VADT ClinicalTrials.gov number, NCT00032487.)

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*A complete list of the investigators in the Veterans Affairs Diabetes Trial (VADT) is provided in the Supplementary Appendix, available at NEJM.org.

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Observational cohort studies have shown increasing risks of both macrovascular and microvascular events with increasing average blood glucose levels.[1-7] Trials involving patients with type 1 diabetes and patients with new-onset type 2 diabetes showed that improving glucose control reduced the incidence of microvascular complications of diabetes.[8,9] Although these trials did not show significant reductions in the incidence of cardiovascular disease, their observational follow-up reports indicated a reduced risk of cardiovascular outcomes and reduced mortality.[10,11] In contrast, trials involving patients with advanced type 2 diabetes (such as ACCORD [Action to Control Cardiovascular Risk in Diabetes], ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation], and our own VADT [Veterans Affairs Diabetes Trial]) showed that improved glucose control over a median of 3 to 6 years provided modest and nonsignificant reductions in the incidence of cardiovascular events and did not reduce cardiovascular disease–related mortality or total mortality.[12-15] However, a 10-year follow-up of the VADT showed an emerging benefit from the original intensive glucose lowering with regard to cardiovascular events.[16]

Longer-term follow-up of glucose lowering in patients with type 2 diabetes may help to clarify the duration of the potential benefit with regard to cardiovascular disease. Unlike in the United Kingdom Prospective Diabetes Study (UKPDS),[17] observational follow-up of these three aforementioned trials involving patients with type 2 diabetes has yet to yield evidence of a "legacy effect." However, with greater separation of the glycated hemoglobin curves between the treatment groups and with longer observational follow-up, the VADT was well suited to examine whether a reduction in the risk of new cardiovascular events with improved glucose control in the past was preserved or expanded after the glucose levels equalized between the treatment groups. Extended follow-up may also be necessary to reveal the effects of intensive glucose lowering on the outcome of total mortality.

The VADT follow-up study (VADT-F) was designed to examine long-term consequences of intensive glycemic control on cardiovascular disease outcomes, quality of life, and mortality and, as previously reported,[16] provides an opportunity for assessing legacy effects.[18] We now present the prespecified 15-year results of our trial, which included nearly 10 years of observational follow-up after almost 6 years of intensive glucose lowering as compared with standard glucose lowering.

METHODS

STUDY DESIGN

The original and follow-up designs of our trial have been published previously.[13,16,19] In brief, the original trial included 1791 military veterans with type 2 diabetes who were randomly assigned to receive either intensive or standard glucose control. The goal for the intensive-therapy group was normal glycated hemoglobin levels, with a median level that was more than 1.5 percentage points lower than that in the standard-therapy group. The goal in the standard-therapy group was a glycated hemoglobin level between 8% and 9%. Participants who were alive and had not withdrawn at the conclusion of the trial (median follow-up, 5.6 years) were followed through national data registries (the complete cohort). Some participants (the survey cohort) consented to additional data collection, including yearly survey and chart reviews to detect outcomes and quality-of-life assessments[20] that were not obtained from central data registries. Health-related quality of life was assessed on a scale from 0 to 100, with higher scores indicating better quality of life; a difference of 5 points was considered to be clinically meaningful. Detailed descriptions of these cohorts and assessments, as previously reported,[13,16] are provided in Methods Sections A through I in the Supplementary Appendix (available with the full text of this article at NEJM.org).

Two authors who are statisticians vouch for the completeness and accuracy of the data and analyses. The authors vouch for the fidelity of the study to the protocol (available at NEJM.org). The first author wrote the manuscript, with all the coauthors approving the final version for submission. The statistical analysis plan was prespecified by the lead investigators before data access or knowledge of results. The protocol was approved by the Hines and Ann Arbor Veterans Affairs (VA) health system institutional review boards and was reviewed annually by a data and safety monitoring committee.

DATA SOURCES

As previously described,[16] four national data registries — the central VA medical files, the Centers

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for Medicare and Medicaid Services (CMS) claims files, the VA death files, and the National Death Index (NDI) — were used to collect data and information about outcomes. Participants in the survey cohort also received annual self-administered surveys that queried for major events (e.g., myocardial infarctions and strokes) during the previous year. Medical records were reviewed and adjudicated as previously described[16] (see the Methods Sections and Table S1 in the Supplementary Appendix) for participants younger than 65 years of age (CMS ineligible) reporting an event outside the VA system. Because of delays in the availability of registry data for some outcomes, we decided a priori that our primary analysis of the first major cardiovascular event (in a time-to-event analysis) would be limited to the period with complete capture of data about primary-outcome events (median follow-up, 13.6 years). Analyses of total mortality (in the complete cohort) used available outcome data at a median follow-up of nearly 15 years.

PRIMARY AND SECONDARY OUTCOMES

The prespecified primary outcome was the first major cardiovascular event (composite of nonfatal myocardial infarction, nonfatal stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes) in a time-to-event analysis. Prespecified secondary outcomes included death from cardiovascular causes, death from any cause, any major diabetes outcome (primary composite outcome plus end-stage renal disease [defined as a glomerular filtration rate of <15 ml per minute per 1.73 m^2 of body-surface area, dialysis, or kidney transplantation] or nontraumatic amputation), and health-related quality of life. Hospitalizations were captured as part of protocol-specified goals to monitor health costs and were considered to be a prespecified tertiary outcome. During observational follow-up, outcomes were identified by means of the primary discharge diagnosis in VA or CMS registry files (as previously validated)[21,22] or by review of outside records, as previously described (see Methods Section B in the Supplementary Appendix).[16]

STATISTICAL ANALYSIS

Data were censored when participants had a primary-outcome event, died, or withdrew from the study. The main intention-to-treat analyses used Kaplan–Meier survival curves generated by the product-limit method. Cox proportional-hazards modeling was used to estimate hazard ratios. In prespecified mediation analyses, Cox proportional-hazards models were used to examine the effects of the glycated hemoglobin level on the primary cardiovascular disease outcome and on the observed treatment effects. Specifically, the log-linear association of the cumulative glycated hemoglobin level (modeled as a time-varying covariate) with the primary cardiovascular disease outcome was assessed during the period of separation of the glycated hemoglobin curves and after convergence (see Methods Section G in the Supplementary Appendix). Models examined the effect of treatment group (intensive therapy or standard therapy) on the primary outcome in an unadjusted analysis (model 1) or while accounting for baseline, most recent, or cumulative mean glycated hemoglobin level (models 2, 3, and 4, respectively).

We also conducted post hoc sensitivity analyses (not included in the protocol; with time intervals prespecified by the lead investigators) to compare the role of glucose control in different intervals of the cumulative follow-up period. The last observation of the glycated hemoglobin level was carried forward in these analyses owing to slow changes in glycated hemoglobin values over time and the low frequency of missing data. Proportionality assumptions held for 10 years but not thereafter, but relaxing the assumptions did not substantially affect any results.

We prespecified three variables (duration of diabetes, baseline cardiovascular risk [according to the baseline UKPDS score[23]], and history of cardiovascular disease) to examine heterogeneity within the treatment effects with regard to the primary outcome and any major diabetes outcome.[24] Negative binomial regression was used to examine the number of hospitalizations, with adjustment for follow-up time. Sample-selection bias in persons who consented to participate in the survey cohort in the follow-up study was assessed with the use of primary and secondary outcomes in the complete cohort. We estimated that data collection in the larger, complete cohort missed less than 6% of the outcomes owing to delays in the availability of CMS and NDI data (see Methods Section B in the Supplementary Appendix). The frequency of missing data for key covariates, such as for the glycated hemoglobin level (missing for <5% of visits), was modest and was handled by carrying the most recent value forward.

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RESULTS

CHARACTERISTICS OF THE PARTICIPANTS AT BASELINE

According to the baseline characteristics, most of the participants were men, were overweight or obese, and had a mean duration of diabetes of approximately 12 years (Table 1). No meaningful differences were observed between the baseline characteristics of the complete and survey cohorts or between the treatment groups (Table S2 in the Supplementary Appendix). The recruitment and follow-up flowchart has been published previously[16] and is provided in Figure S1 in the Supplementary Appendix.

During the VADT, the median glycated hemoglobin level in the intensive-therapy group was 6.9%, and the median separation of the glycated hemoglobin curves between treatment groups was 1.5 percentage points over a median of 5.6 years (Fig. 1), as previously reported.[13] The separation of the glycated hemoglobin curves gradually diminished to 0.2 to 0.3% in the 3 years after trial completion, and the glycated hemoglobin levels subsequently stabilized at a median of approximately 8% in both groups. The medications for treating diabetes that were used during the VADT to lower glucose levels were similar in the two groups, with only slightly higher doses of thiazolidinediones, insulin, oral sulfonylureas, and acarbose used in the intensive-therapy group than in the standard-therapy group during the active treatment period (Table S3 in the Supplementary Appendix). Use of these medications was almost identical in the two treatment groups by the end of the VADT-F.

Intensive glucose control was associated with weight gain during active treatment, which remained higher (by a mean body-mass index [the weight in kilograms divided by the square of the height in meters] of 1.3; 95% confidence interval [CI], 1.1 to 1.5) from year 3 (i.e., the time when all participants were enrolled) through year 17 (Fig. S2A in the Supplementary Appendix). Per protocol, other cardiovascular disease risk factors were aggressively treated in both treatment groups during the VADT, and the levels of blood pressure, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and triglycerides were similar in the two groups throughout the cumulative follow-up period (Fig. S2B through S2F in the Supplementary Appendix). The use of statins and medications for hypertension was similar during both the VADT and VADT-F (Tables S3 through S5 in the Supplementary Appendix).

PRIMARY AND SECONDARY OUTCOMES

At a median follow-up of 13.6 years, we found that the risk of the primary composite cardiovascular disease outcome was nonsignificantly lower, by 9%, in the intensive-therapy group than in the standard-therapy group (hazard ratio, 0.91; 95% CI, 0.78 to 1.06; P=0.23) (Table 2). Nonsignificantly lower risks of any major diabetes event (hazard ratio, 0.90; 95% CI, 0.78 to 1.04) and death from cardiovascular causes (hazard ratio, 0.94; 95% CI, 0.73 to 1.20) were also seen in the intensive-therapy group than in the standard therapy group. At a median follow-up of 15 years, there was no evidence of shorter time to death with intensive treatment than with standard therapy (hazard ratio, 1.02; 95% CI, 0.88 to 1.18), nor was there evidence of improved quality-of-life scores (mean scores, 63.8 and 62.2, respectively) (Table 2). Results for the individual components of the above composite outcomes are provided in Tables S7 through S9 in the Supplementary Appendix.

Kaplan–Meier survival curves for the primary and secondary outcomes are shown in Figure 2 and provide a more detailed overview of our time-to-event results. To examine the robustness of these findings, we repeated analyses for the primary outcome using the larger, complete cohort and found similar results (hazard ratio, 0.95; 95% CI, 0.83 to 1.09). We found no evidence that treatment effects varied across our three prespecified risk factors of duration of diabetes, history of cardiovascular disease, or cardiovascular disease risk (Table S10 in the Supplementary Appendix). Rates of hospitalization were similar in the two treatment groups (160 events per 1000 person-years in the intensive-therapy group and 165 events per 1000 person-years in the standard-therapy group; hazard ratio, 0.98; 95% CI, 0.88 to 1.09), as was the median number of hospitalizations (3 hospitalizations in each group; incidence rate ratio, 1.02; 95% CI, 0.89 to 1.17) (Table S11 in the Supplementary Appendix).

GLUCOSE CONTROL AS A MEDIATOR OF RISK AND A LEGACY EFFECT

We first compared the event rates of major outcomes during and after the VADT (Table S12 in the Supplementary Appendix). There was no benefit with regard to any major outcome during the

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Table 1. Baseline Characteristics of the Participants in the Follow-up Study, According to Cohort.*

Characteristic	Complete Cohort (N=1655)	Survey Cohort (N=1391)
Age — yr	60.5±8.7	61.1±8.7
Sex — no. (%)		
Male	1608 (97.2)	1353 (97.3)
Female	47 (2.8)	38 (2.7)
Time since diabetes diagnosis — yr	11.6±7.5	11.8±7.7
Previous cardiovascular event — no. (%)	673 (40.7)	595 (42.8)
Hypertension — no./total no. (%)†	1197/1652 (72.5)	1014/1389 (73.0)
Race or ethnic group — no. (%)‡		
Non-Hispanic white	1024 (61.9)	886 (63.7)
Hispanic white	265 (16.0)	222 (16.0)
Black	282 (17.0)	220 (15.8)
Other	84 (5.1)	63 (4.5)
Tobacco smoking status — no./total no. (%)		
Current	270/1653 (16.3)	210/1389 (15.1)
Past	933/1653 (56.4)	791/1389 (56.9)
Never	450/1653 (27.2)	388/1389 (27.9)
Body-mass index§	31.2±4.4	31.2±4.4
Blood pressure — mm Hg		
Systolic	131.6±16.6	131.9±16.6
Diastolic	76.1±10.2	76.0±10.2
Glycated hemoglobin level — %	9.4±1.5	9.4±1.5
Cholesterol — mg/dl		
Total	183.1±47.4	181.8±43.6
Low-density lipoprotein	107.7±32.5	106.4±31.5
High-density lipoprotein	36.0±10.2	35.7±9.8
Triglycerides — mg/dl		
Mean	211.3±281.1	210.5±215.7
Median (interquartile range)	159 (112–238)	162 (113–241)
Estimated GFR¶	82.0±22.2	81.1±22.1
Creatinine — mg/dl	1.0±0.2	1.0±0.2
Ratio of albumin (in milligrams) to creatinine (in grams)	113.0±338.1	118.9±352.7
Estimated 10-yr cardiovascular risk — %‖	40±20	40±20

* Plus–minus values are means ±SD. Baseline values were measured on entry into the original trial. The complete cohort included all the participants who were alive and enrolled at the conclusion of the trial and who had not specifically requested to withdraw from all additional follow-up. The survey cohort included a subgroup of participants who agreed to additional yearly survey follow-up. Percentages may not total 100 because of rounding. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.50. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for creatinine to millimoles per liter, multiply by 88.4. The baseline characteristics according to trial group within each cohort are presented in Table S2 in the Supplementary Appendix.

† Hypertension was defined as current treatment for hypertension or a blood pressure of 140/90 mm Hg or more.

‡ Race and ethnic group were reported by the participant.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ The estimated glomerular filtration rate (GFR) was calculated with the use of the Modification of Diet in Renal Disease Study equation.

‖ The estimated 10-year cardiovascular risk was calculated with the use of the United Kingdom Prospective Diabetes Study Risk Engine, which takes into account weight and the levels of glycated hemoglobin, cholesterol, creatinine, and triglycerides (www.dtu.ox.ac.uk/riskengine).

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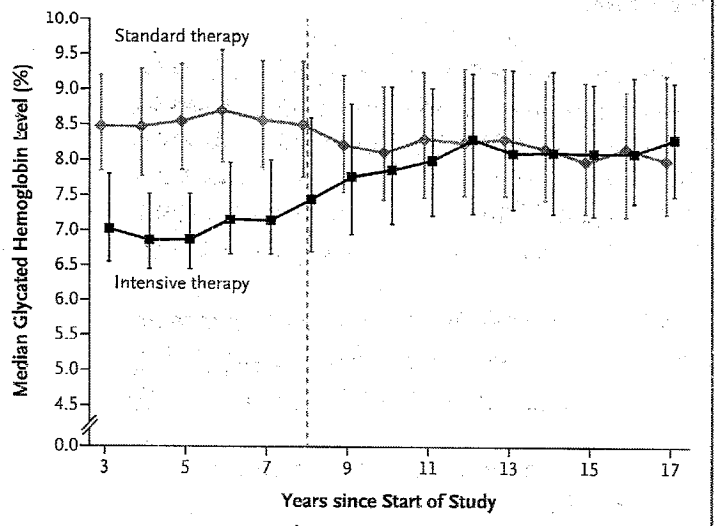

Figure 1. Median Glycated Hemoglobin Levels According to Year since Start of the Trial, Starting at Year 3.

Year 3 was a point at which all the participants had been enrolled and had been receiving treatment per protocol for at least 3 months. The I bars (slightly offset for better visibility) represent interquartile ranges. The dotted line represents the end of the interventional component of the trial and the beginning of the follow-up period. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.50.

observational follow-up period for the trial. We then evaluated the treatment effect in the period before and after glycemic control nearly equalized in the two groups. We found that the risk of primary cardiovascular events was 17% lower in the intensive-therapy group than in the standard-therapy group during the approximate 10-year period when there was a separation of the glycated hemoglobin curves between the two groups (model 1: hazard ratio, 0.83; 95% CI, 0.70 to 0.99) (Table 3). In contrast, in the 5-year period after the glycated hemoglobin levels equalized in the treatment groups, the intensive-therapy group had a modestly higher risk of major cardiovascular events than the standard-therapy group (hazard ratio, 1.26; 95% CI, 0.90 to 1.75). In a sensitivity analysis that used the larger, complete cohort, similar results were seen. However, adjustment for the cumulative mean glycated hemoglobin level during the entire study (Table S13 in the Supplementary Appendix) or during the first 10-year period in which glucose control differed between groups abolished treatment-related differences in the risk of cardiovascular disease (model 4) (Table 3). This finding highlighted the importance of overall differences in glucose control between groups in mediating this outcome. The lack of a glucose-control legacy effect was also supported in a sensitivity analysis that showed that glycated hemoglobin levels over the most recent 3 years, but not more distant levels, were associated with cardiovascular events (Table S14 in the Supplementary Appendix).

DISCUSSION

In this 15-year follow-up study, we found that 5.6 years of intensive glucose lowering that led to a median separation of 1.5 percentage points in the glycated hemoglobin curves did not result in a significantly lower risk of major cardiovascular events than standard therapy. These results did not vary according to baseline cardiovascular disease risk. Furthermore, we found no evidence of a mortality benefit, no decrease in the incidence of hospitalizations over the full follow-up period, and no long-term difference in quality of life.

The results show that during the approximate 10-year period of separation of the glycated hemoglobin curves (median duration, approximately 7.1 years), there was a significant reduction of nearly 17% (or roughly 10% per 1-point decline in the glycated hemoglobin level) in the risk of the primary cardiovascular disease outcome. These latter results suggest that there are modest long-term cardiovascular benefits of intensive glucose-lowering therapy in patients with more advanced diabetes. Results also show that long-term maintenance of a lower glycated hemoglobin level may be necessary to maintain these improvements. In contrast, there was no continued benefit with regard to the risk of cardiovascular disease after glycated hemoglobin levels equalized in the treatment groups. In fact, there was a decline in benefit with regard to the risk of cardiovascular disease that coincided with equalization of glucose control within treatment groups and this continued during the 5 (or more) years of equal glycemic control that followed.

In addition, almost all the association between glucose control and major cardiovascular events was explained by the mean glycated hemoglobin level in the 3 most recent years, with no evidence that earlier years of glucose control had a carryover effect. Several sensitivity analyses showed no evidence that 5.6 years of tight glucose control resulted in a legacy effect in our study population. Because the duration of separation of the glycated hemoglobin curves during our original trial and the post-trial observational follow-up

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Table 2. Effect of Intensive Glucose Treatment on Major Cardiovascular Events, Mortality, and Health-Related Quality of Life.*

Outcome	Intensive Therapy	Standard Therapy	Hazard Ratio or Difference (95% CI)	P Value
Primary outcome: major cardiovascular event — no./total no. (rate per 1000 person-yr)	325/703 (47.3)	336/688 (51.8)	0.91 (0.78 to 1.06)	0.23
Secondary outcomes				
Any major diabetes outcome — no./total no. (rate per 1000 person-yr)	342/703 (50.4)	355/688 (55.7)	0.90 (0.78 to 1.04)	
Death from cardiovascular causes — no./total no. (rate per 1000 person-yr)	118/837 (12.3)	125/818 (13.1)	0.94 (0.73 to 1.20)	
Death from any cause — no./total no. (rate per 1000 person-yr)	376/837 (36.6)	366/818 (35.9)	1.02 (0.88 to 1.18)	
Health-related quality-of-life score†	63.8±17.2	62.2±17.6	1.6 (−0.7 to 3.9)	

* The primary outcome was a composite of myocardial infarction, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular disease causes and was analyzed in the survey cohort. Any major diabetes outcome included the primary composite outcome plus nontraumatic amputations and end-stage renal disease (defined as an estimated GFR of <15 during the original trial period or as an estimated GFR of <15 or dialysis or kidney transplantation during the follow-up study) and, along with health-related quality of life, was analyzed in the survey cohort. Mortality outcomes were analyzed in the complete cohort. All outcomes were prespecified. The confidence intervals were not adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible.

† Health-related quality of life was assessed on a scale from 0 to 100, with higher scores indicating better quality of life. The difference between the mean values is presented. A difference in the health-related quality-of-life score of 5 points was considered to be clinically meaningful.

was long, our findings of no legacy effect and no mortality benefit expand on similar results in the ACCORD and ADVANCE trials, which also involved older patients with well-established type 2 diabetes.[12,13,25,26]

Our results of an approximate 10% lower risk of major cardiovascular disease outcomes per 1-point reduction in the glycated hemoglobin level over a period of 4 to 6 years are consistent with the pooled results (9% lower risk of cardiovascular disease) of the four major trials of tighter glucose control,[15] which suggests this is a reasonable estimate of the glucose-lowering benefit in these recent moderate-duration trials in type 2 diabetes. Further support for this finding comes from the mediation analysis showing that cumulative separation of the glycated hemoglobin curves could largely explain the degree of difference in the risk of cardiovascular disease that was observed in the intensive-therapy group as compared with the standard-therapy group. However, these benefits must be weighed against adverse effects such as hypoglycemia and weight gain. Studies showing major reductions in the risk of cardiovascular outcomes with diabetes agents, such as sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, that only achieve modest improvements in glycemic control[27-29] highlight the importance of also considering nonglycemic approaches to reducing the risks of cardiovascular events and death among high-risk patients with type 2 diabetes.

Our results run counter to the mortality benefits regarding cardiovascular disease and to the legacy effects that have been observed in patients with recently diagnosed type 1 diabetes (in the Diabetes Control and Complications Trial [DCCT]) and in patients with new-onset type 2 diabetes (in the UKPDS).[8,9] Several explanations have been proposed regarding a reduced benefit from glucose lowering in older patients with long-standing type 2 diabetes (such as the participants in the ACCORD and ADVANCE trials and in our original trial).[30-32] It is possible that underlying atherosclerosis and cardiovascular injury were too advanced in these participants to be effectively altered by glucose lowering. Support for this notion comes from a substudy of our original trial, which showed that participants with high coronary-artery calcium scores (a validated measure of atherosclerosis) at baseline had less reduction in the risk of cardiovascular events with intensive glucose lowering than those with lower coronary-artery calcium scores.[33] The DCCT and UKPDS were also conducted at a time before widespread statin use and tight blood-pressure control, whereas participants in the VADT and other recent trials have had aggressive treatment of all cardiovascular disease risk factors. It is plausible that the cardiovascular protective effects of tight glycemic control have diminishing re-

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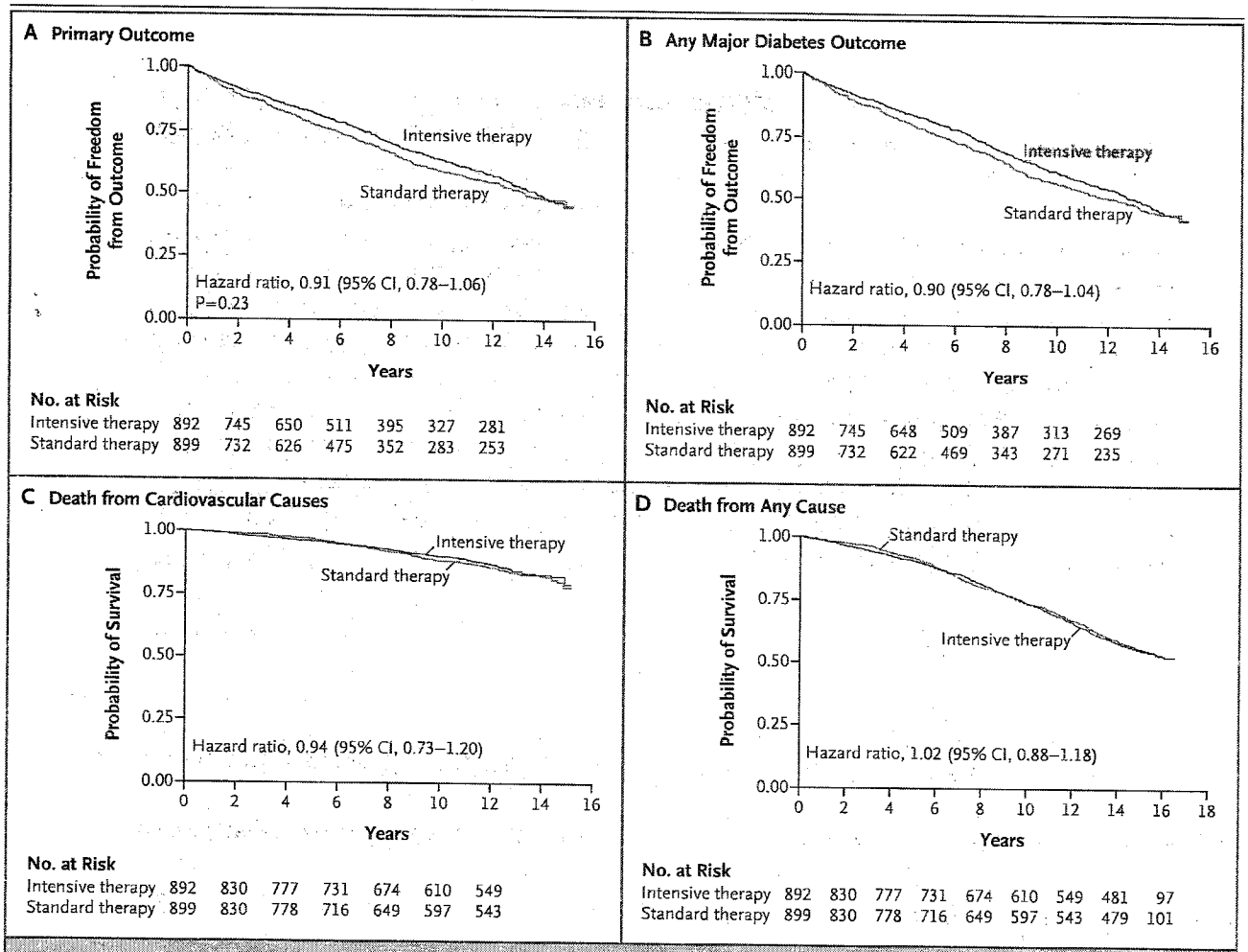

Figure 2. Kaplan–Meier Curves for the Primary and Secondary Outcomes during the Trial and Follow-up Period.

The primary outcome was a major cardiovascular event (a composite of myocardial infarction, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes). Secondary outcomes were any major diabetes event (primary composite outcome plus nontraumatic amputation or end-stage renal disease, defined as an estimated glomerular filtration rate [GFR] of <15 during the original trial period or as an estimated GFR of <15 or dialysis or kidney transplantation during the follow-up study), death from cardiovascular causes, and death from any cause.

turns once other cardiovascular disease risk factors are well controlled by medications that may also have vasoactive properties.

There are several limitations to the current study. The cohort in our original trial consisted largely of older men. However, our results are generally consistent with the findings of the ACCORD and ADVANCE follow-up studies, which had greater representation of women.[25,26] Because the post-trial follow-up of events was conducted with the use of electronic records, by necessity the definitions of outcomes varied slightly from those during the active trial. However, patterns of outcomes between treatment groups did not vary notably during the transition from the active trial phase to the observation period, which suggests that these constraints did not alter the results. We also acknowledge that variables not well captured by medical records could have differed between groups and influenced outcomes during the observational follow-up. Our findings that the risk of cardiovascular disease was reduced during the period of separation of the glycated hemoglobin curves and not after equalization and that recent, but not distant, glycated hemoglobin levels mediated the reduction in risk of cardiovascular disease are observational and do not carry the same strength of a true experi-

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Table 3. Effect of Intensive Glucose Therapy on Major Cardiovascular Events during Periods of Separation of Glycated Hemoglobin Curves (Years 0–10) and No Separation (Years 11–15).*

Variable	Years 0–10	Years 11–15
No. of participants	1791	633
No. of events	502	145
Model and predictors — hazard ratio (95% CI)		
Model 1		
Intensive therapy or standard therapy	0.83 (0.70–0.99)	1.26 (0.90–1.75)
Model 2		
Intensive therapy or standard therapy	0.83 (0.70–0.99)	1.27 (0.91–1.76)
Baseline glycated hemoglobin level	1.06 (1.00–1.12)	1.08 (0.96–1.21)
Model 3		
Intensive therapy or standard therapy	0.86 (0.71–1.04)	1.24 (0.89–1.74)
Most recent glycated hemoglobin level, as a time-varying covariate	1.03 (0.97–1.09)	0.93 (0.84–1.04)
Model 4		
Intensive therapy or standard therapy	0.94 (0.77–1.15)	1.37 (0.95–1.96)
Cumulative mean glycated hemoglobin level, as a time-varying covariate	1.11 (1.02–1.20)	1.09 (0.92–1.28)

* Shown are results from Cox proportional-hazards models for primary cardiovascular outcomes according to time intervals during the Veterans Affairs Diabetes Trial and the follow-up study. Years 0 through 10 reflect the interval of time for which there was evident separation of the glucose curves between the treatment groups. Years 11 through 15 reflect the initial interval when the glycated hemoglobin levels had merged between the two treatment groups and during which all data (from the Veterans Affairs, Centers for Medicare and Medicaid Services, and National Death Index databases) were available. Model 1 examined the effect of treatment group only on primary cardiovascular events during two time periods (years 0 through 10 and years 11 through 15). Models 2, 3, and 4 were applied to the same two time periods and included two predictors: the treatment group (intensive therapy or standard therapy) and the glycated hemoglobin level (baseline value, most recent value as a time-varying covariate, or cumulative mean as a time-varying covariate, respectively). In a sensitivity analysis, we found that only glycated hemoglobin levels from the most recent 3 years were needed to explain the treatment effect and that levels that were observed more than 3 years earlier had no evidence of either predictive value for cardiovascular events or evidence of mediation of the observed reduction in the risk of cardiovascular events in the clinical trial (see the Results Section in the Supplementary Appendix). The numbers of participants in each group reflect the number of participants enrolled in the trial who had not yet had a primary outcome at the beginning of the indicated intervals. The confidence intervals were not adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible.

ment.[34] This type of post-trial follow-up also prevented our collection of data regarding retinopathy and neuropathy, thus preventing our ability to address these microvascular complications. Finally, although the duration of glucose lowering in our original trial was substantial, it is possible that more sustained efforts may have led to greater long-term benefits.

In conclusion, in this group of participants with type 2 diabetes who were at high risk for cardiovascular disease, 5.6 years of intensive glucose lowering to a glycated hemoglobin level of 6.9% did not reduce the incidence of major cardiovascular events over a follow-up of 13.6 years or reduce total mortality or improve quality of life over a total follow-up of 15 years. Although there was a significantly lower risk of major cardiovascular events during the 7.1 years of separation of the glycated hemoglobin curves (during the trial and observation periods), there was no evidence of a beneficial legacy effect after this period of improved glucose control.

The views expressed in this article are those of the authors and do not represent the views of the Department of Veterans Affairs (VA) or the U.S. government.

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Background

Three different glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk with high glycated haemoglobin A $_{1c}$ (HbA $_{1c}$) concentrations. We assessed the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycaemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control.

Methods

This multicentre, randomised, double-blind, placebo-controlled trial was done at 371 sites in 24 countries. Men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo. Randomisation was done by a computer-generated random code with stratification by site. All investigators and participants were masked to treatment assignment. Participants were followed up at least every 6 months for incident cardiovascular and other serious clinical outcomes. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes), which was assessed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, numberNCT01394952.

Findings

Between Aug 18, 2011, and Aug 14, 2013, 9901 participants (mean age 66·2 years [SD 6·5], median HbA $_{1c}$ 7·2% [IQR 6·6–8·1], 4589 [46·3%] women) were enrolled and randomly assigned to receive dulaglutide (n=4949) or placebo (n=4952). During a median follow-up of 5·4 years (IQR 5·1–5·9), the primary composite outcome occurred in 594 (12·0%) participants at an incidence rate of 2·4 per 100 person-years in the dulaglutide group and in 663 (13·4%) participants at an incidence rate of 2·7 per 100 person-years in the placebo group (hazard ratio [HR] 0·88, 95% CI 0·79–0·99; p=0·026). All-cause mortality did not differ between groups (536 [10·8%] in the dulaglutide group *vs* 592 [12·0%] in the placebo group; HR 0·90, 95% CI 0·80–1·01; p=0·067). 2347 (47·4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34·1%) participants assigned to placebo (p<0·0001).

Interpretation

Dulaglutide could be considered for the management of glycaemic control in middle-aged and older people with type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors.

Funding

Eli Lilly and Company.

D - 4949 — 594 — 12%

P - 4952 — 663 — 13.4%

13.4 − 12 = 1.4% ARR

1.4 ÷ 13.4% = 10.5% RR

NNT = $\frac{1}{1.4}$ = 71 NNT

1.4 ÷ 12% = 12% RR ← THEY ARE WRONG

It's 10.5%, NOT 12%

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REWIND: Dulaglutide reduces CV, renal risk in broad type 2 diabetes population

June 10, 2019

ADD TOPIC TO EMAIL ALERTS

SAN FRANCISCO — In a large cohort of adults with type 2 diabetes with and without established cardiovascular disease, the once-weekly GLP-1 receptor agonist dulaglutide reduced the risk for nonfatal myocardial infarction, nonfatal stroke and CV death by 12% compared with placebo, according to data from the REWIND study presented at the American Diabetes Association Scientific Sessions.

Hertzel C. Gerstein

"We've shown in the REWIND trial that in middle-aged and older men and women who are similar to people with type 2 diabetes in the general population and had a broad range of glucose control ... adding dulaglutide (Trulicity, Eli Lilly) safely reduces CV outcomes for more than 5 years," **Hertzel C. Gerstein, MD, MSc, FRCPC,** professor and population health institute chair in diabetes research at McMaster University and Hamilton Health Sciences in Ontario, Canada, said during a presentation. "Similar benefits were seen in men and women, in people with higher BMI and lower BMI, in people with prior CVD and no prior CVD and in people with higher and lower HbA1c levels."

The findings from REWIND — the first major CV outcomes trial for an antidiabetes therapy to include a large primary prevention population — also demonstrated renal benefits in participants assigned the drug, with the greatest benefit observed in development of new macroalbuminuria.

"REWIND adds to and extends the growing body of evidence that intermediate- or long-acting GLP-1 receptor agonists — in this case, dulaglutide — is superior to standard care for three-point [major adverse cardiac events], including people with CV risk factors," **Sophia Zoungas, MBBS, PhD,** FRACP, head of the diabetes and vascular medicine research program at Monash University in Melbourne, Australia, said during an independent commentary after the findings were presented. "There are going to be numerous potential mechanisms of action, beyond glucose, blood

pressure and weight effects, and we look forward to those mechanistic studies where we will understand better the role of inflammation, endothelial function and other CV protective effects."

Largest primary prevention cohort

Gerstein and colleagues analyzed data from 9,901 adults aged at least 50 years with type 2 diabetes (HbA1c 9.5%) and a history of a previous CV event or CV risk factors, recruited from 374 sites in 24 countries from August 2011 to August 2013 (mean age, 66 years; 46.3% women; median diabetes duration, 9.5 years; median HbA1c, 7.2%). Participants were taking stable doses of up to two oral glucose-lowering drugs, with or without basal insulin therapy.

Within the cohort, only 31.5% of participants had prior CVD, making the trial the largest primary prevention CV outcomes study with a GLP-1 receptor agonist, Gerstein said.

"When we look at subgroups of people without prior CVD, REWIND has a lot to add ... 6,221 people in REWIND did not have prior CVD," Gerstein said during a presentation of the summary findings. "REWIND is the first, and hopefully not the last trial to look at this subgroup of people without prior CVD."

Researchers randomly assigned patients to receive once-weekly dulaglutide (n = 4,949) or placebo (n = 4,952). Primary endpoint was first occurrence of any component of the composite CV outcome of nonfatal MI, nonfatal stroke and CV death. Secondary outcomes were a composite clinical microvascular outcome including diabetic retinopathy, renal disease, hospitalization for unstable angina and heart failure requiring hospitalization. Follow-up occurred at 2 weeks, 3 and 6 months, and then every 6 months until 1,200 confirmed primary events occurred. Researchers also measured urinary albumin to creatinine ratio and estimated glomerular filtration rate (eGFR) every 12 months.

The data were simultaneously published in the *Lancet.*

CV findings

During a median 5.4 years, the primary composite outcome occurred in 12% of patients in the dulaglutide arm (incidence rate, 2.4 per 100 person-years) vs. 13.4% of patients in the placebo arm (incidence rate, 2.7 per 100 person-years), for an HR of 0.88 (95% CI, 0.79-0.99).

"As you can see, dulaglutide reduced the occurrence of this primary composite outcome," Gerstein said to applause as he presented the CV findings. "You can see the effect of the intervention begins before the first year, and continues in a progressive, proportional fashion throughout the full follow-up period, which exceeds 5 years."

In assessing the individual components of the composite outcome, Gerstein noted that there was no discernable effect on nonfatal MI with dulaglutide (HR = 0.96; 95% CI, 0.79-1.16) and a neutral effect observed for CV death (HR = 0.91; 95% CI, 0.78-1.06), however, researchers observed a 24% reduction in stroke in the dulaglutide arm (HR = 0.76; 95% CI, 0.61-0.95). There were no between-group differences in all-cause mortality.

In subgroup analyses, the CV results were similar when comparing participants with and without previous CVD (*P* for interaction = .97) and in comparing patients with an HbA1c above and below 7.2% (*P* for interaction = .75). Results persisted in analyses further stratified by age, sex, diabetes duration and BMI.

Renal findings

In an exploratory analysis assessing the prospectively defined renal effects of dulaglutide, the drug reduced the HR for the composite renal outcome compared with placebo, with the largest effect noted for the development of albuminuria.

During follow-up, the renal outcome developed in 17.1% of participants assigned to dulaglutide (incidence rate, 3.5 per 100 person-years) vs. 19.6% of the placebo arm (incidence rate, 4.1 per 100 person-years), for an HR of 0.85 (95% CI, 0.77-0.93). The greatest observed effect with dulaglutide was observed for new macroalbuminuria, with an HR of 0.77 (95% CI, 0.68-0.87), although researchers also observed reductions in the rates of sustained decline in eGFR of 30% or more (HR = 0.89; 95% CI, 0.78-1.01) and for chronic renal replacement therapy (HR = 0.75; 95% CI, 0.39-1.44).

"Our sensitivity analyses suggested a reduced incidence of a 40% and 50% decline in eGFR with dulaglutide, supporting the possibility that dulaglutide might preserve renal function; this association merits further scrutiny," the researchers wrote in the *Lancet*.

'Embrace therapy early'

In commentary accompanying the two studies, **Subodh Verma, MD, PhD, FRCSC**, from the division of cardiac surgery at St. Michael's Hospital, University of Toronto, and colleagues noted that the magnitude of benefit on the composite CV outcome was

"modest" and numerically lower compared with CV benefits observed in the LEADER (liraglutide; Victoza, Novo Nordisk) and SUSTAIN-6 (semaglutide; Ozempic, Novo Nordisk) trials; however, the findings were consistent with the overall effect size of the class observed in a meta-analysis of all previous GLP-1 receptor agonist trials.

"Although SGLT2 inhibitors and GLP-1 receptor agonists are recommended in patients with established atherosclerotic vascular disease, we now have evidence from the DECLARE-TIMI 58 and REWIND trials that SGLT2 inhibitors and GLP-1 receptor agonists afford cardiovascular superiority even in primary prevention; with SGLT2 inhibitors preventing heart failure and GLP-1 receptor agonists preventing atherosclerotic events, and both potentially affording renal protection," Verma and colleagues wrote. "If we are to reduce the burgeoning pump, pipes and filter complications of diabetes, we will need to overcome clinical inertia, and embrace these disease-modifying therapies early, and preferably in combination. The REWIND trial makes a strong case in this regard." – *by Regina Schaffer*

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Gerstein HC, et al. *Lancet.* 2019; doi:10.1016/S0140-6736(19)31150-X.

Verma S, et al. *Lancet.* 2019; doi:10.1016/S0140-6736(19)31267-X.

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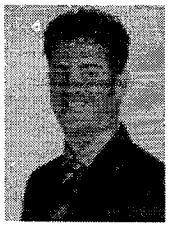

Kevin M. Pantalone

While there are important differences between the GLP-1 receptor agonist molecules and their pharmacology, and the study populations and designs of their respective CV outcomes trials, as a whole, the evidence is very clear that long-acting GLP-1 receptor agonists confer a benefit on the risk for adverse CV outcomes, particularly in those with established CVD. It was novel and reassuring to observe a reduction of major adverse CV events in REWIND, which was comprised of a large lower-risk population (lower baseline A1C and lower prevalence of established CVD) when compared with the CV outcomes trials for other long-acting GLP-1 receptor agonists. Given the CV outcomes trials for other long-acting GLP-1 receptor agonists either did not contain primary prevention subjects (HARMONY; albiglutide), or contained a much smaller number of primary prevention subjects (LEADER; liraglutide; EXSCEL; exenatide; and SUSTAIN-6; semaglutide) vs. REWIND, primary prevention, as a class-effect, remains less clear. Regardless, one must remember that the primary indication for GLP-1 receptor agonists therapy in patients with type 2 diabetes is to improve glycemic control. Additional reasons to use these therapies, in patients with or without established CVD, are the potential for weight loss and avoidance of hypoglycemia. The CV (and potential renal) benefits observed in REWIND, and observed in the CV outcomes trials with other long-acting GLP-1 receptor agonists, provide yet additional reasons to use GLP-1 receptor agonist therapy across the entire spectrum of patients with type 2 diabetes.

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Disclosures: Pantalone reports he has received research support from Merck and Novo Nordisk, speaker honoraria from AstraZeneca, Merck and Novo Nordisk, and consulting honoraria from Merck, Novo Nordisk, Sanofi and Eli Lilly.

Debra L. Simmons

To me, the VADT data are consistent with findings from other studies of older patients with advanced type 2 diabetes and established CV risk, and I think that is good? With respect to a legacy effect, the authors make the point that earlier studies, like DCCT and UKPDS, which did demonstrate a legacy effect with early, tight control, were very different vs. studies conducted later, after a longer disease duration. VADT, which did not show a legacy effect, emphasizes what many of us believe, which is the earlier you can diagnose and start treating someone with type 2 diabetes, the more benefits they will derive later.

In this study, the standard-treatment group were treated to an HbA1c between 8% and 9%, which is higher than current recommendations, but participants in VADT were complex in both disease and comorbidities. It is important for clinicians treating older adults with type 2 diabetes and comorbidities to carefully look at the whole person and remember that we do have guidelines for potentially deescalating medications when the benefits derived may be less vs. the higher risks. Additionally, newer drugs that were not FDA approved when VADT began, including SGLT2 inhibitors and GLP-1 receptor agonists, have other benefits aside from glycemic control that may be useful in this patient population. Overall, this is very good data and helpful to us as a community. How is THIS Good?

Debra L. Simmons, MD, MS, FACE, FACP

Professor of Medicine,
University of Utah Director of Clinical Affairs,
Utah Diabetes and Endocrinology Center, Salt Lake City

Disclosures: Simmons reports no relevant financial disclosures.

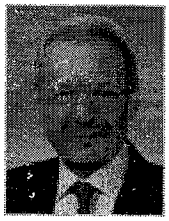
Heart in Diabetes

Weight loss mediates CV damage of fatty liver in diabetes

July 16, 2019

ADD TOPIC TO EMAIL ALERTS

PHILADELPHIA — Nonalcoholic fatty liver disease is an "unrecognized epidemic" among people with type 2 diabetes, according to a speaker at the Heart in Diabetes conference.



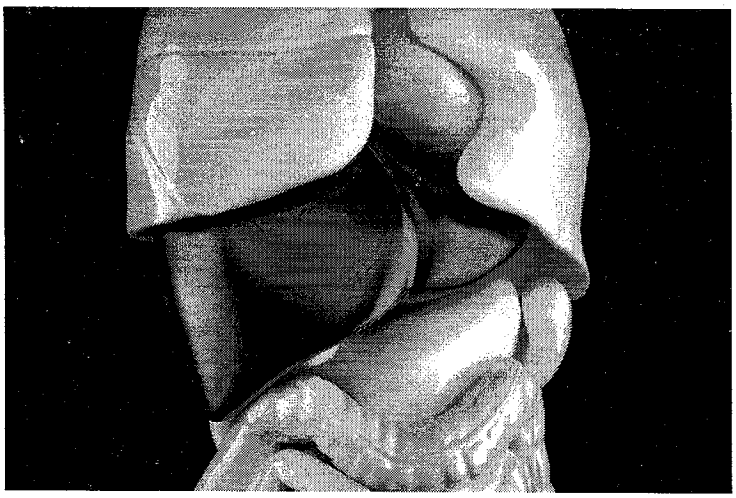
Samuel Klein

Nonalcoholic fatty liver disease (NAFLD) is directly correlated with cardiometabolic abnormalities, and sustained weight loss can reduce the risk for incident cardiovascular events in patients with the condition, **Samuel Klein, MD,** the William H. Danforth professor of medicine and nutritional science and director of the Center for Human Nutrition at Washington University School of Medicine, said during his presentation.

"Both NAFLD and coronary heart disease represent end-organ manifestations of the same systemic metabolic insult, primarily related to insulin resistance," Klein told *Endocrine Today*. "NAFLD and CVD are part of the constellation of metabolic abnormalities associated with obesity, and more people who have NAFLD die from CVD than from liver disease."

As obesity develops so do metabolic complications, including NAFLD and its more severe stage, nonalcoholic steatohepatitis (NASH), atherogenic dyslipidemia, prediabetes and type 2 diabetes — all important risk factors for CVD, Klein said.

NAFLD is defined as more than 5.6% of liver volume made up of triglycerides located inside of liver cells, and about 34% of adults in the U.S. and 70% of people with type 2 diabetes have NAFLD, he said. However, very few patients with fatty liver alone will go on to develop NASH. Of those with NASH, about 20% will develop cirrhosis, according to Klein.



Nonalcoholic fatty liver disease is an "unrecognized epidemic" among people with type 2 diabetes.

Adobe Stock

"We have no idea who with NAFLD will develop NASH and who with NASH will develop cirrhosis," Klein said. "But even though only a small percentage of people with steatosis will ultimarely develop serious liver disease, the number is still large because so many people have steatosis. About 2 million people have cirrhosis caused by NAFLD in the U.S. Some have silent compensated cirrhosis and do not even know it."

NAFLD as risk factor

The more liver fibrosis a patient has, the greater the mortality risk, Klein said. Progression across stages of fibrosis takes a long time — on average, progressing one stage every 7 years, Klein said, although a subgroup of people with NAFLD are what he called "rapid progressors."

"The main cause of death is CVD, not liver disease," Klein said. "Only when you get to cirrhosis do you see a big spike in death from liver disease. When you have cirrhosis, about 50% of the deaths are attributed to liver disease, so half die from non-liver disease causes."

Klein said NAFLD is "clearly a risk factor" for developing cardiometabolic abnormalities, noting that one-third of people with NAFLD have metabolic syndrome, and 90% have at least one component of metabolic syndrome criteria. In a Mayo Clinic study that looked at the incidence of cardiometabolic disease over 5 to 7 years in people with NAFLD, 25% died from CVD, and similar percentages of people developed type 2 diabetes, dyslipidemia and hypertension, Klein said.

"Fatty liver tracks with cardiometabolic abnormalities," Klein said. "The more severe the fatty liver, the more severe the atherosclerosis."

One major risk factor for CVD that is associated with fatty liver is an increase in blood triglyceride concentration, which Klein called an important marker for increased fat in the liver.

"We know that VLDL triglyceride, which is made by the liver and is a major source of triglyceride in the bloodstream, is an important risk factor for heart disease," Klein said. The rate of hepatic VLDL triglyceride secretion in people who are obese with NAFLD are twice as high as people who are obese with normal liver fat content, he said.

Increased fat in the liver is associated with insulin resistance in adipose tissue and muscle tissue and the liver and also with multi-organ systemic insulin resistance, Klein said.

Fatty liver is increasingly observed in adolescents who are obese, Klein said. In a study of lean adolescents and adolescents with obesity, Klein and colleagues observed that increased liver fat seen in teens with obesity was associated with increased triglycerides in the heart, he said.

"These are children who have routine blood tests in the normal range, so their physician can't tell who has fatty liver," Klein said. "Addressing this problem early in life will have the best effect vs. later in life."

Importance of weight loss

Weight loss reduces liver fat content and NASH has been shown to improve CV structure and function, including early diastolic and systolic myocardial velocity, left ventricular mass and carotid intima-media thickness, Klein said.

"Fatty liver disease, chronic kidney disease, cardiovascular disease, diabetes are all organ damages responding to a systemic metabolic insult," Klein said. "A lot of us look at these different organ systems independently and forget to consider the simultaneous biological dysfunction systems biology of all multiple organs, which are caused by obesity." – *by Regina Schaffer*

Reference:

Klein S. Impact of obesity on liver and the heart. Presented at: Heart in Diabetes CME Conference; July 12-14, 2019; Philadelphia.

Disclosure: Klein reports he holds stock in Aspire Bariatrics and has received research support from Centene, Janssen and Pershing Square Foundation, consultant fees from Dannon-Yakult, Lobesity, Merck, Novo Nordisk and Pfizer and endowments from the Atkins Philanthropic Trust and the Kilo Foundation.

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