Diabetes mellitus remains a formidable public health issue, affecting 171 million people worldwide as of 2000, a number estimated to more than double, up to 366 million, by 2030. The majority (>90%) have type 2 diabetes (T2DM), which is linked to westernized diets, obesity, and inactivity. This condition is associated with decreased survival, predominately due to cardiovascular disease (CVD), which appears earlier and more extensively than in nondiabetic persons. A recent large epidemiological study from Denmark found diabetes to be associated with greater mortality from virtually all specific causes. Impressively, at the age of 30 years, a diagnosis of diabetes was associated with a 9-year reduction in life span. Although the typical patient with T2DM possesses other CVD risk factors, such as obesity, hypertension, and dyslipidemia, increased mortality and morbidity persist, even after adjustment for these factors. Diabetes is, therefore, widely recognized as an independent CVD risk factor. Indeed, many authorities consider diabetes to be a coronary heart disease (CHD) “risk equivalent,” although this concept has recently been challenged by others.

Perhaps one of the most perplexing aspects of diabetes care, however, is our inability to affect this excess CVD risk through glucose control alone. Addressing the cardinal manifestation of the disease (namely, hyperglycemia) has had either no or minimal impact on the future risk of cardiovascular events. Major clinical trials have conclusively determined that more intensive glycemic control significantly reduces the risk of microvascular complications (ie, retinopathy and nephropathy). In contrast, however, and despite a strong positive epidemiological association between CVD and measures of chronic hyperglycemia, there is little evidence that reducing circulating glucose concentrations translates to a significant improvement in macrovascular outcomes. Specifically, the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes (VADT) trials each found that a treatment strategy designed to lower hemoglobin A1c to a near-normal range did not decrease overall CVD events. Indeed, cardiovascular mortality was increased in ACCORD in those patients assigned to more intensive therapy; an explanation for this observation remains elusive. Whether the effects of hyperglycemia on macrovascular complications have been exaggerated, whether the clinical strategies in use to reduce glucose levels have been suboptimal, or whether the benefits of glucose control on the development and progression of atherosclerosis require a longer time to become manifest remain arguable. In support of the latter explanation, posttrial monitoring of participants in the UK Prospective Diabetes Study (UKPDS) revealed that a sustained period of glycemic control in patients with newly diagnosed T2DM may reduce cardiovascular morbidity and mortality, although the effects may not be statistically apparent for 2 decades or more.

In contrast, attention geared toward other CVD risk factors, such as control of blood pressure, has proved to be much more effective in the prevention of the macrovascular sequelae of diabetes. Approximately 50% of patients with T2DM have hypertension at diagnosis; the remainder are highly likely to develop it during their care. The relationship between diabetes and hypertension is complex; they may not be merely 2 conditions that develop with aging and obesity. For example, hyperinsulinemia constitutes the pancreatic response to insulin resistance (or decreased insulin sensitivity), a major underlying metabolic abnormality leading to T2DM. In turn, elevated insulin levels are associated with increased sympathetic tone, augmented renal tubular sodium retention, and reduced endothelial production of nitric oxide, a potent vasodilator. Moreover, hypertension itself is recognized as an insulin-resistant state, even in those with normal glucose metabolism. Perhaps as a result, hypertension is widely regarded as a diabetes risk factor. There is also extensive experimental evidence to suggest that the adverse vascular sequelae of diabetes are exacerbated in the presence of hypertension. Indeed, hypertension confers an age-adjusted 82% increase in the risk of diabetes-related death. On the basis of a robust clinical trial database showing that more aggressive blood pressure control improves both microvascular and macrovascular outcomes, guidelines have long endorsed more aggressive blood pressure targets in diabetic patients. Thus, although diabetes and hypertension are both independent risk factors for CVD, their origins may be pathophysiologically linked, their deleterious vascular effects may be synergistic, and both require cautious therapeutic approaches.

Because of the frequent coexistence of hypertension and diabetes, diabetic patients are often treated with one or more blood pressure–lowering medications. Understanding their potential impact on metabolic control is, therefore, of major importance. The effects of these drugs on glucose levels and diabetes risk have been a point of controversy for years. For
example, thiazide diuretics deplete body potassium stores, which are important for insulin release from pancreatic beta cells. Furthermore, diuresis may lead to decreased blood volume and cardiac output, which can activate the sympathetic nervous system, leading to reduced blood flow to the skeletal muscle, ultimately causing peripheral insulin resistance.\textsuperscript{13,14} Perhaps as a consequence of these changes, thiazide use, especially at higher doses, has been associated with higher glucose levels and increased diabetes risk. Angiotensin-converting enzyme inhibitors, on the other hand, may actually improve glyemia by upregulation of bradykinin and nitric oxide, both of which promote increased skeletal muscle and pancreatic blood flow, and improvement in angiotensin-II-mediated oxidative stress in the beta cell.\textsuperscript{15} Their use has been associated with reduced diabetes risk in epidemiological studies, although a large clinical trial testing ramipril found no substantive effect on the progression to diabetes in high-risk patients with impaired glucose tolerance. Certain calcium channel blockers may inhibit insulin release, but this is counterbalanced by vasodilatation, leading to increased peripheral glucose uptake and improved insulin sensitivity.\textsuperscript{15} As a group, the calcium channel blockers show no major effect on glucose metabolism, although some reports have linked overdoses of certain calcium channel blockers (verapamil and diltiazem) with severe hyperglycemia.\textsuperscript{16} Data concerning β-blockers are variable. Older agents, such as propranolol and metoprolol, have been associated with worsening glycemic control and increased diabetes risk, possibly because of inhibition of pancreatic insulin secretion through blockade of β2-adrenergic receptors, inhibition of peripheral glucose uptake, and resultant unopposed α2-adrenergic receptor–mediated stimulation of hepatic glycogenolysis. Highly selective β1-adrenergic blockers, especially those with either intrinsic sympathomimetic activity or α-blocking effects, have minimal effects on glucose.\textsuperscript{14,15} Carvedilol may actually possess mild insulin-sensitizing activity. Despite such extensive information, however, there are no clear guidelines regarding the avoidance of antihypertensive agents in those with or at risk for diabetes. In fact, thiazides remain the most popular second-line drug for treating hypertension in patients with T2DM, just after angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, as endorsed by the American Diabetes Association.\textsuperscript{17}

In this issue of Circulation: Cardiovascular Quality and Outcomes, Barzily et al\textsuperscript{18} provide encouraging data on the benefits of thiazides in patients with dysglycemia. They report a post hoc analysis from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), its Diabetes Extension Study. Herein, 22,418 ALLHAT participants with baseline, incident, or no diabetes at 2 years of in-trial follow-up were observed for a mean total of 6.9 years (including 4.9 years in the trial, with 2 years of additional follow-up) for occurrence of CVD mortality as a primary outcome. Other outcomes analyzed included all-cause mortality, non–CVD mortality, and CHD events (nonfatal myocardial infarction and fatal CHD). As demonstrated by others, the group randomized to primary therapy with the thiazide diuretic, chlorthalidone, had a significantly higher mean plasma glucose level (fasting and nonfasting) at the 2-year mark (98.7 mg/dL) compared with the amlodipine (95.9 mg/dL, \( P<0.001 \)) and lisinopril (94.1 mg/dL, \( P<0.001 \)) groups. The significantly higher degree of glycaemia in chlorthalidone-treated patients persisted through the end of the study, although trends beyond year 2 were similar among all 3 treatment groups. Moreover, the development of incident diabetes over 6.9 years with chlorthalidone (12.7%) was significantly higher than with amlodipine (9.5%, \( P<0.001 \)) or lisinopril (7.9%, \( P<0.001 \)). These trends largely reflected the increase in incident diabetes at year 2 (chlorthalidone, 7.5%, and amlodipine, 5.6% \( P=0.002 \); and lisinopril, 4.3% \( P<0.001 \)), with essentially no further subsequent relative differences.

Across all treatment groups, not surprisingly, patients with diabetes at baseline experienced higher CVD outcome rates than those without diabetes, and those with incident diabetes generally had outcome rates that were intermediate. The more provocative finding of the ALLHAT Diabetes Extension Study involved the comparison between those participants who did and those who did not develop diabetes (mainly T2DM) during the trial, based on treatment assignment.\textsuperscript{18} The hazard ratios (HRs) in the chlorthalidone cohort with versus without incident diabetes for CVD mortality (HR, 1.04 [95% CI, 0.74–1.47]), all-cause mortality (HR, 1.04 [95% CI, 0.82–1.30]), and non–CVD mortality (HR, 1.05 [95% CI, 0.77–1.42]) were consistently lower than the comparable HRs in the corresponding amlodipine and lisinopril cohorts (HRs, 1.22–1.53). More specifically, those who developed diabetes while taking chlorthalidone had a statistically insignificant increase in the risk for total CHD events when compared with those who remained nondiabetic (HR, 1.18 [95% CI, 0.77–1.81]), whereas the opposite was true for participants with versus without incident diabetes assigned to lisinopril (HR, 2.57 [95% CI, 1.45–4.54]). Similarly, the HRs (CIs) for all-cause mortality and stroke were not significantly different in the chlorthalidone cohort based on incident diabetes status: 1.04 (0.82–1.30) and 0.91 (0.49–1.67), respectively. However, in the amlodipine group, those with versus without incident diabetes had significantly higher risks for these end points (HR, 1.40 [95% CI, 1.01–1.95] and 1.95 [95% CI, 1.04–3.65], respectively).

How can we explain these results? Actually, they might have been predicted. Diabetes provoked by a thiazide likely emerges from an alteration in the set point for insulin release, with resultant mild hyperglycemia. Given the previously mentioned complex relationship between glucose and CVD outcomes, it might be expected that (at least in the near term) such a mild biochemical deterioration would not necessarily impart significant injury to the macrovasculature. In contrast, in the more natural course of worsening dysglycemia observed in those trial participants assigned to 1 of the other 2 treatments, incident diabetes was the net result of many years of progressive antecedent metabolic derangements, including obesity, insulin resistance, and hyperinsulinemia, followed by beta cell decompensation. In this overall context, glucose itself may serve as little more than a surrogate of CVD risk, a relatively recent concept buttressed by the findings from ACCORD, ADVANCE, and VADT. These studies have taught us that, in management of patients with T2DM, a myopic focus on hyperglycemia alone is no longer justifiable.
A word of caution, however, is warranted. Several methodological limitations restrain any absolute conclusions regarding the implications of “diuretic-induced diabetes.” First, the follow-up beyond the randomized component of ALLHAT consisted of National Death Index surveillance and did not constitute a traditional, more rigorous, assessment of clinical outcomes. For example, whether death certificates are reliable enough to assess actual causes of an individual’s demise remains debatable. Moreover, nearly half of the original ALLHAT cohort was not included in the analysis, most because of missing glucose data. Although there is no inherent reason why this would introduce a bias as far as outcome ascertainment is concerned, it remains unknown if the conclusions of this report would withstand a more comprehensive analysis of all eligible trial participants. Finally, whether the authors’ findings would persist beyond the relatively brief 4 to 6 years of follow-up is unknown. There are some data to suggest that the effects of glucose on the vasculature evolve over decades, not years.7,19

Despite these concerns, the main finding of Barzilay et al.,18 that the development of diabetes in thiazide-treated hypertensive patients may not incur the same vascular penalty as the more “natural” development of hyperglycemia in other individuals, is an important one. It is also largely consistent with our emerging and more nuanced understanding of the murky relationship between glucose and CVD risk. Based on these data, thiazide diuretics should continue to have a major role in the treatment of the hypertensive patient with or at risk for diabetes.

Disclosures

None.

References
