Improving Outcomes in Patients With Diabetes Mellitus

David Aguilar, MD, MSc

The prevalence of diabetes mellitus continues to increase in the United States and across the globe. There are ≈30 million individuals in the United States (9.4% of the population) currently living with diabetes mellitus, including ≈7.2 million who, despite efforts to increase awareness of the disease and its risk factors, remain undiagnosed.[1] Importantly, the prevalence of diabetes mellitus is not equally shared among ethnic/racial groups, with blacks, Hispanics, and Native Americans having a higher prevalence. In addition to the tremendous health toll attributed to diabetes mellitus, the US economic impact of diabetes mellitus is staggering, as the cost of caring for diabetes mellitus is greater than $327 billion annually.[2]

Despite improvements in the treatment of diabetes mellitus and its risk factors, the majority of premature deaths associated with diabetes mellitus are attributable to cardiovascular disease.[3,4] Fortunately, recent decades have seen substantial decreases in cardiovascular mortality among people with and without diabetes mellitus.[3,4] In this issue of the *Journal of the American Heart Association* (*JAHA*), Raghavan et al reassess the diabetes mellitus–associated risk for total mortality and cardiovascular mortality in a large contemporary US cohort.[5] The authors perform an observational study utilizing a US Veterans Affairs (VA) cohort of nearly 1 million patients, including ≈34% with diabetes mellitus. Individuals were included in the cohort if they had at least 4 VA primary care provider visits from 2002 to 2003, at least 3 random glucose measurements during that period, and data for other key comorbid conditions. Similar to other VA cohorts, the group consisted of 97% men, and the mean age was 65 years. Comorbid conditions were common, with 44% having baseline cardiovascular disease and 28.7% having cancer. Mortality in this cohort was high, with an ≈44% incidence of all-cause mortality over a mean follow-up of 8 years. After adjustments for body mass index, non–high-density lipoprotein cholesterol, systolic blood pressure, smoking status, and baseline cardiovascular disease, individuals with diabetes mellitus were at a 16% and 18% greater risk for all-cause mortality and cardiovascular mortality, respectively. Those with prior cardiovascular disease and diabetes mellitus represented the highest-risk group. Subsequent inclusion of random blood glucose further attenuated the diabetes mellitus–associated risk. In those with diabetes mellitus, a hemoglobin A1c (HbA1c) between 6% and 6.9% was associated with lowest incidence of all-cause and CVD mortality, with a stepwise increase in all-cause and cardiovascular mortality in those with an HbA1c >7%. The authors note that the diabetes mellitus–associated hazard for all-cause and cardiovascular mortality is lower than historical studies, a finding that is consistent with other large observational studies of the general population, which have demonstrated much-welcome improvements in cardiovascular risk in those with diabetes mellitus over recent years.

Inherent to all observational studies, several limitations of the current study need to be considered when placing this study in the context of prior work and generalizing findings to other populations. First, individuals in this VA cohort were included if they had 4 primary care visits from 2002 to 2003, and they had a high burden of comorbid baseline conditions, including cancer and prior cardiovascular disease. This cohort represents a higher risk group with significantly greater rates of all-cause and cardiovascular mortality than other studies,[3,4] and it is possible that the higher rates of death, including in those without diabetes mellitus, could have attenuated the relative hazard that was seen in this cohort compared with previous studies. Similarly, deaths that occurred within the first 2 years were censored. While censoring of early events may minimize potential bias caused by baseline pre-existing conditions that may contribute to early death, censoring of these early deaths may also lead to a selection bias by excluding early diabetes mellitus–associated deaths that occurred during this time period. Finally, as the authors state, causation cannot be established when interpreting the relationship between dysglycemia and all-cause and total

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From the Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, TX; Division of Cardiology, UT McGovern Medical School, Houston, TX .

Correspondence to: David Aguilar, MD, MSc, University of Texas Health Science Center at Houston, 1200 Pressler St, Suite E431, Houston, TX 77030. E-mail: david.aguilar@uth.tmc.edu

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mortality in this cohort. While the finding that an HbA1c between 6.0% and 6.9% is associated with the lowest mortality mirrors other observational data, randomized controlled trials have not supported more aggressive intensive glycemic control strategies in high cardiovascular risk individuals to lower all-cause mortality or cardiovascular mortality.[6] Therefore, one should continue to use current targets of glycemic control (predominantly based on the benefits of glycemic control to reduce microvascular complications) as set forth by guidelines, which suggest a HbA1c goal of <7% for most individuals with less or more stringent HbA1c goals based on duration of diabetes mellitus, safety and ease in reaching glycemic targets, hypoglycemic risk, and competing comorbid conditions.[7]

Despite these potential limitations, the authors should be congratulated for their important contribution to this public health issue and adding to a growing body of literature demonstrating that we are improving in lowering the increased mortality associated with diabetes mellitus. This beneficial temporal trend is likely attributable to increased awareness and treatment of associated cardiovascular risk factors. Nonetheless, the residual risk associated with diabetes mellitus persists in most studies, and, given the increasing prevalence of diabetes mellitus, reducing the health burden attributed to diabetes mellitus remains a public health priority. Despite our awareness of the importance of multifactorial cardiovascular risk factor control in reducing mortality,[8,9] significant gaps in achieving risk factor control exist. In a recent study of "real world" data from the US Diabetes Collaborative Registry, only 1 in 5 individuals achieved American Diabetes Association–recommended target risk factor control for all 4 major risk factors (glucose, low-density lipoprotein cholesterol, blood pressure, and smoking status), with significant disparities in women, blacks, and individuals from lower socioeconomic status.[10] Future interventions to improve risk factor control will not be easy and will involve strategies to improve lifestyle management, adherence to medication, and further implementation of evidence-based therapies.

Recent data from cardiovascular outcome trials have ushered in a new era of cardiovascular risk management as certain antihyperglycemic medications have demonstrated benefit in reducing major adverse cardiovascular outcomes in diabetic patients who are at high risk or who have established cardiovascular disease. These medications include certain sodium-glucose cotransporter-2 inhibitors[11–13] and glucagon-like peptide-1 agonists.[14–16] Both empagliflozin and liraglutide have also been associated with reductions in cardiovascular mortality.[13,16] While cardiology-care providers are adept at the management of cardiovascular risk factors such as hypertension and dyslipidemia, what is the role of a cardiology-care provider in prescribing drugs that have been seen primarily as antihyperglycemic medications but that have been associated with improvements in major adverse cardiovascular events that appear independent of glycemic effects? The most recent American Diabetes Association guidelines have incorporated these clinical trial data into recent guidelines and recommend that sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 agonists with demonstrated cardiovascular benefit be added as the next agent after metformin in patients with type 2 diabetes mellitus who have established atherosclerotic cardiovascular disease.[17] In individuals with atherosclerotic cardiovascular disease at high risk for heart failure, sodium-glucose cotransporter-2 inhibitors are recommended as second-line agents after metformin.[17]

As we continue our efforts to lower the residual cardiovascular risk associated with diabetes mellitus, cardiology-care providers are well positioned to adopt a more active role in ensuring that all strategies that lower cardiovascular risk in patients with diabetes mellitus are appropriately implemented, including these American Diabetes Association recommendations. Implementing new diabetic- and cardiovascular disease–lowering medications will require that cardiology-care providers have increased awareness of evidence from completed and ongoing diabetic cardiovascular outcome trials and have access to specific educational resources describing the risk/benefit profile of these medications that lower cardiovascular risk. Such efforts will require a collaborative, multidisciplinary approach to determine the best strategy to manage diabetic treatment. In response to this need, cardiology professional organizations have embarked on multiple efforts to help cardiology-care providers understand these new medications and develop strategies to incorporate them into clinical practice. For example, a recent Consensus Pathway on Novel Therapies for CV Risk Reduction has been published by the American College of Cardiology.[18] This consensus pathway provides practical information regarding screening for diabetes mellitus and incorporating these diabetic medications with proven cardiovascular benefit into clinical practice. Similarly, the American Heart Association and the American Diabetes Association recently launched a collaborative intervention, Know Diabetes by Heart, with the goal of reducing cardiovascular deaths, heart attacks, and strokes in people living with type 2 diabetes mellitus.[19] This collaborative effort will engage patients, healthcare providers, and policy makers to increase awareness and understanding of the link between diabetes mellitus and cardiovascular disease, provide educational and management tools to empower patients to manage their diabetes mellitus and associated cardiovascular risk factors, and provide an educational platform for healthcare providers to further learn and increase willingness to manage cardiovascular risk in patients with type 2 diabetes mellitus.

The past several decades have seen much-welcome progress in reducing the cardiovascular-associated burden of diabetes mellitus, and recent data from clinical trials provide even greater hope that we can further reduce the residual risk attributed to diabetes mellitus.

Disclosures

None.

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