Mortality Risk in Long-Standing Type 1 Diabetes: Hope and Concern

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In this issue of *Diabetes*, Secrest et al. (1) explore the long-term cause-specific mortality experience of youth diagnosed with type 1 diabetes (<18 years of age over the 15-year period from 1965 to 1979) to determine if improvements in mortality have occurred over time. The findings are at the same time both hopeful and concerning. The results among these youth (now middle-aged adults) come from the Alleghany County Type 1 Diabetes Registry established in the mid-1970s. One of the first U.S. registries of type 1 diabetic subjects, it was one of the archetypical registries that forged the international collaboration linking registries in the U.S., Europe, and Asia (2). The report by Secrest et al. focuses on over 30 years of follow-up among 1,043 subjects with diabetes from the original 1,075 identified in the county. This represents 97% known vital status of the original cohort, which ascertained over 95% of the diagnosed cases. This is an amazing result in this era of rapid residential mobility and increasing nonresponse to research since vital status was determined by individual contact of cohort members and next-of-kin. Cause of death was classified using internationally standardized definitions (3) and all available clinical, hospital, and autopsy information for 80% of the deaths. Death certificates were obtained for all deaths but were only relied upon for 20% of classifications, and these underwent adjudication. This is important since variability of death certificate coding and ordering of cause of death can make temporal or geographic comparisons problematic (4).

What then did the investigators report that I find hopeful? First, among this largely Caucasian cohort (93%; 7% African American), total mortality over 30 years of diabetes duration has declined from 800/100,000 person-years in the earliest cohort (1965–1969) to 530/100,000 person-years (1975–1979), a 34% reduction in 15 years. Second, mortality rates for acute complications (largely diabetic ketoacidosis and hypoglycemia) declined by 57%, along with reductions in renal disease mortality (38%). Somewhat smaller reductions in cardiovascular disease (CVD) mortality were also observed (30%). These results are very hopeful in showing important improvements in mortality for individuals with type 1 diabetes.

However, among females, there were 30% higher rates from all diabetes-related causes (overall rate ratio = 1.3, $P \leq 0.05$) than among males. Total mortality among the smaller number of African Americans was also more than doubled compared with Caucasians (relative risk [RR] = 2.5, $P < 0.001$), especially from acute (RR = 4.8), renal (RR = 4.6), CVD (RR = 1.9), and infectious causes (RR = 2.8). I find the results for women and for African Americans concerning, especially for the excess of potentially preventable outcomes such as acute complications. As the investigators note, this could be the result of socioeconomic disadvantages and poorer access to care, though this seems less likely for women of Caucasian origin who still experience excess mortality compared with men. Increased attention to such disparities is needed and is not limited to individuals of minority race/ethnicity. Since women usually have lower rates of mortality than men at these ages, clinicians must be acutely aware of this differential and be aggressive in diabetes management.

The other concerning results come from the comparisons of cohort mortality to the referent county population. Overall, cohort members were 13 times more likely than their nondiabetic counterparts to die of CVD-related causes, 104 times more likely for renal disease, and 41 times more likely for infections. Many studies of CVD incidence and mortality in adults have suggested only a two- to threefold excess among older adults (5). What are the explanations for the very large excesses seen here? It is likely that some of it is due to the relatively young age of the cohort (mean age of 40–45 years) with the oldest members only now reaching their early sixties. These are decades where CVD mortality in subjects without diabetes was relatively low, which would exaggerate the excesses seen. It may also come from the fact that most studies of CVD mortality are conducted in subjects with type 2 (or unspecified) diabetes, and it is possible that the risk is much greater among subjects with longstanding type 1 diabetes and with a much earlier onset of CVD.

Perhaps the most troubling observation is that there have been few improvements in cause-specific mortality in the more recently diagnosed cohorts when compared with county residents. For example, CVD mortality was elevated 13.9-fold for the 1965–1969 cohort, and 14.7-fold for the 1975–1979 cohort. How does one reconcile declining absolute rates across these cohorts (noted above) with static or rising standardized mortality ratios (SMRs) compared with the general population? An SMR estimates the number of deaths expected in a study cohort based on the mortality rates of the reference population of the same age, sex, race, and time period. Since total and CVD mortality have been declining in the nondiabetic population at rates often faster than among individuals with diabetes (6,7), such declines in the county population rates could actually cause the SMR to rise over time, or, as observed here, to stay relatively the same. This suggests that improvements in CVD mortality among nondiabetic subjects have outpaced the improvements for those with type 1 diabetes in an era where increased clinical and

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research attention to CVD risk factors among subjects with diabetes has been a major goal.

This cohort developed diabetes during the 1960s and 1970s, well before aggressive treatment of hyperglycemia and hypertension became the cornerstones of treatment (8). This may partially explain the excesses in CVD and renal disease seen in the cohort, given the apparently long metabolic memory such glycemia entails (9). As Secrest et al. note, this cohort does not provide a contemporary picture of mortality early in the course of diabetes, but provides a much needed description of mortality in currently middle-aged persons with type 1 diabetes, which leaves much to be desired. A contemporary exploration of early mortality among youth newly diagnosed in 2002 and later is being conducted by the SEARCH for Diabetes in Youth study group (10).

The Secrest report also does not provide a picture of how these risk factors were managed. Many of these factors have been explored by the Pittsburgh group among a subset of this cohort participating in the Epidemiology of Diabetes Complications (EDC) study (11) and in comparison with the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trial (12). The EDC study, together with this study of the entire Alleghany County type 1 cohort, provide a unique population-anchored picture that can serve as a reference standard for the developing comparative effectiveness research that comes from non-population-based clinical sources. Such a registry and cohort studies are valuable national assets in our understanding of the continued impact of type 1 diabetes in the U.S. They should be extended and expanded.

These findings also show us that there is much yet to learn about the most effective ways to translate evidence-based strategies from clinical trials into real-world practice on a national scale so that the excess mortality observed in Alleghany County can be further reduced. Targeted strategies aimed at reducing renal and CVD mortality among individuals with type 1 diabetes—especially women and minorities—must be improved. Hope and concern often coexist.

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