Editorial

Hemoglobin A1c in Hemodialysis Patients: Should One Size Fit All?

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Currently recommended hemoglobin A1c (HbA1c) targets in ESRD patients are identical to those for the general population; an issue of considerable debate. In this issue, Williams and colleagues provide observational data on the association of HbA1c with mortality among nearly 25,000 hemodialysis patients in the United States. Statistically significant findings were observed only among subjects with HbA1c levels >11% in final models in individuals with type 2 diabetes. For the first time, this study separately evaluates individuals with type 1 diabetes, among whom associations of HbA1c with mortality were stronger than among those with type 2 diabetes. This editorial considers this study in the context of existing literature and suggests directions for future research. In the absence of randomized trial data, it may be preferable to individualize HbA1c targets rather than targeting less than 7% in all patients.

Diabetes mellitus remains the leading cause of ESRD in the United States (1). On average, four in ten patients encountered on dialysis rounds will have diabetes mellitus (1), among whom hemoglobin A1c (HbA1c) levels are often measured quarterly. Management of HbA1c values is therefore an extremely common clinical scenario in contemporary nephrology practice, with considerable risk of harm if treated too aggressively or not aggressively enough. Currently, the Kidney Disease: Improving Global Outcomes (KDIGO) foundation does not provide clinical practice guidelines for HbA1c management; their website is linked to the Kidney Disease Outcomes Quality Initiative (KDOQI) on this issue (2). KDOQI recommendations, last updated in 2007, state "Target HbA1c for people with diabetes should be <7%, irrespective of presence or absence of CKD." (3). This recommendation is in line with diabetes management in the general population (4,5), and KDOQI acknowledges, "Very few studies addressed the benefits and risks of intensive glycemic control in late stages of CKD, let alone patients who are undergoing dialysis . . . " (3).

Recent evidence from randomized studies of statins renders caution about extension of data from the general population to ESRD, even for therapies with well established benefits in the general population (6,7). Notwithstanding, several manuscripts published since the KDOQI recommendations have highlighted the potential risks of aggressive glycemic control in non-ESRD diabetic populations (8–10). Three recent well powered trials randomized individuals with type 2 diabetes to lower HbA1c targets. Each failed to demonstrate lower cardiovascular disease (CVD) event rates in the intensive treatment arm (8–10). In one study, overall mortality was higher in the intensive arm (8), and in all three the intensive arm experienced greater hypoglycemic events. Because kidney failure leads to decreased clearance of insulin and loss of renal gluconeogenesis, the risk of hypoglycemia may be higher in ESRD patients (11,12). Moreover, because many ESRD patients are frail, malnourished, and nonambulatory, they may be less able to respond appropriately to hypoglycemia. Last, recent studies in the general population have heightened concerns that drugs used to treat diabetes in ESRD patients may increase risk of CVD events (13,14).

In this issue of *CJASN*, Williams and colleagues present observational data evaluating the association of HbA1c levels and mortality among nearly 25,000 hemodialysis patients with diabetes treated in Fresenius Medical Care facilities since 2003 (15). This interesting and carefully conducted study extends observations from a prior manuscript by the same authors (16), providing longer follow-up time, separately evaluating individuals with type 1 diabetes, and providing a comparison to a similar manuscript published in *Diabetes Care* in 2007 by Kalantar-Zadeh and colleagues (17). The latter manuscript evaluated a similar number of patients cared for in DaVita facilities. Both manuscripts use elegant statistical modeling to update laboratory data during follow-up, and to account for comorbidities, markers of malnutrition, inflammation, and vascular access as best as possible using available data. Although there are differences between the manuscripts, their similarities are more remarkable. Both studies demonstrate that mean HbA1c levels in their respective populations were lower than KDOQI recommendations, approximately 6.5% in each. Both studies also demonstrate that the nature of the

relationship of HbA1c with mortality changes dramatically with adjustment for demographic and confounding variables. In unadjusted analyses, individuals with HbA1c levels between 7% and 9% had the lowest overall mortality, and those with HbA1c levels <5% had the greatest mortality. With statistical adjustment, the risk of death associated with low HbA1c levels was attenuated, and mortality risk was accentuated at the highest HbA1c levels. In the study by Williams in this issue, HbA1c levels >11.0% were required to observe statistically significantly higher mortality risk, but few subjects had HbA1c levels in this category (15). In the study by Kalantar-Zadeh, the nature of the relationship of HbA1c with mortality changed in a similar fashion; however, those with HbA1c levels <5% or ≥7% remained at statistically significantly higher mortality risk compared with individuals with intermediate HbA1c levels in fully adjusted models (17).

To date, there are no data available from randomized clinical trials targeting different HbA1c levels and powered for CVD events or mortality in ESRD populations. In their absence, the marked statistical power and elegant analyses provided by these two groups of investigators provide useful insights. However, administrative databases may lack the granularity required to root out important confounders, and both studies demonstrate that adjustment for the available variables dramatically influences the nature of the results. Drechsler and colleagues (18) recently published a *post hoc* analysis of the 4-D study that evaluated HbA1c at baseline with CVD events. Although smaller and not among U.S. dialysis patients, this study provided uniform measurement of traditional CVD risk factors and adjudicated CVD events. This study showed that higher HbA1c levels were associated with sudden death but not myocardial infarction or stroke. Higher HbA1c was associated with all-cause mortality, driven largely by its relation with sudden death. Randomized trials would be the optimal next step, but their feasibility depends largely on the effect size estimate. The largest effect reported to date was in the study by Drechsler (18), in which subjects with HbA1c levels >6% had a hazard ratio of 1.34 for mortality compared with those with lower HbA1c levels. As a quick approximation, assuming a 20% annual mortality rate, a randomized trial would need to enroll approximately 550 patients and follow for a mean of 5 years to detect a statistically significant difference of this magnitude or greater 80% of the time. This seems potentially feasible. Using the much weaker effect estimates in the study by Kalentar-Zadeh (hazard ratio = 1.08 for HbA1c 7% to 7.9% compared with 5% to 5.9%) (17), the number of study participants required is inflated to approximately 8800 and would be even greater using estimates provided in the manuscript in this issue by Williams (15).

In lieu of randomized trial data, there are many important questions that need to be addressed to help guide clinical management. In subgroup analysis in the study by Kalentar-Zadeh (17), individuals who were older, had lower serum albumin levels, lower protein intake, and shorter dialysis vintage appeared to benefit less from lower HbA1c levels. These findings require confirmation; however, they suggest that higher HbA1c targets might be preferable in patients with greater burdens of comorbidity and/or malnutrition. The study by Williams makes the important contribution of separately evaluating individuals with type 1 diabetes. Higher HbA1c was

more strongly associated with mortality in this subset, reaching hazard ratios of 1.5 for those with HbA1c levels >9% (15). This suggests that more stringent targets may benefit individuals with type 1 diabetes. Next, the accuracy of HbA1c as an indicator of average glycemia has been questioned in ESRD patients (19,20). Decreased erythrocyte lifespan and anemia are potential contributing factors. A small study ($n = 31$) suggests that HbA1c values <7% were similarly correlated with average blood glucose in ESRD as in the general populations, yet at higher levels average serum glucose levels were lower at any given HbA1c in ESRD (19). Other small studies have demonstrated that HbA1c remains correlated with fasting and post-challenge glucose levels in ESRD (21), but the correlations are weaker than those reported in the general population (22,23). If indeed HbA1c is less accurate, this might help explain relatively weak associations with clinical outcomes in ESRD and might ultimately lead to different monitoring and treatment strategies. Last, all-cause and CVD mortality are not the only outcomes of importance to ESRD patients with diabetes or their nephrologists. HbA1c control may influence risk of peripheral arterial disease and amputation, an extremely common and morbid event in our patients (24,25). Glycemic control may influence patency of permanent dialysis access and infection risk (26,27). Tighter control might decrease progression of retinopathy and neuropathy in ESRD as it does in the general population (28,29). Although possible, none of these are proven. Careful evaluation of the relation of HbA1c with these outcomes in ESRD patients should be a high priority for future research to inform us about the risks and benefits of different HbA1c targets. Until then, individualized HbA1c targets with consideration of the degree of comorbidity, age, life expectancy, and the ability of patients and their caregivers to respond to hypoglycemic events might be more appropriate than a "one size fits all" target derived from studies in the general population.

Disclosures
None.

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