Should Hemoglobin A1C Be Routinely Measured in Patients with CKD?

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In the study by Trivin et al. (1) in this issue of CJASN, hemoglobin A1C is explored as a novel risk factor for two important adverse outcomes—death and ESRD—among patients without diabetes and with CKD. Specifically, Trivin et al. (1) examined the association between hemoglobin A1C and progression to ESRD and mortality in a population of 1165 adults with moderate CKD and without diabetes mellitus in the hospital-based NephroTest cohort. The range of baseline hemoglobin A1C was 3.4%–6.4%, and a strength of the study was the use of measured GFR to define CKD. Over a median follow-up time of 3.48 years, patients with hemoglobin A1C = 5.7%–6.5% had 79% higher adjusted risk of overall mortality compared with those with hemoglobin A1C <5.3%. The findings were similar when time-updated covariates, including measured GFR, were used in the statistical models. However, in the adjusted analyses, Trivin et al. (1) found no association between hemoglobin A1C and risk of ESRD.

From a methodologic standpoint, the study was very well conducted, and the risk factor of interest, hemoglobin A1C, is widely available, although not routinely measured in nondiabetic CKD patients. Therefore, this study offers an excellent opportunity to review the interpretation of a candidate novel risk factor in patients with CKD and the intellectual process that we must use to answer the question posed by our title. In classic epidemiology, we evaluate associations between characteristics of interest (predictors) and disease end points (outcomes) to better understand the disease process. Characteristics that can be linked to disease outcomes in epidemiologic studies are called risk factors; any proposed risk factor is scrutinized by several follow-up questions. We will use the following four questions to evaluate the clinical effect of the paper by Trivin et al. (1) and as a road map for where the literature on hemoglobin A1C in nondiabetic CKD must go to reach the point of clinical effect.

(1) Is the risk factor independent of other known or established risk factors for the disease outcome? This question is addressed by multivariate adjustment, and our role as readers is to verify that the other critical risk factors are included in the analytic model. In this paper, Trivin et al. (1) adjusted for a number of important confounders for the association of hemoglobin A1C with risk of mortality and ESRD. The confounders were modeled in two ways—fixed from baseline and time updated—which yielded consistent results. Of course, in any observational study, there is a possibility of residual confounding, because it may be impossible to account for all differences between persons with higher and lower hemoglobin A1C levels. In our opinion, the selection of covariates was appropriate in this manuscript by Trivin et al. (1).

(2) Is the association causal? This question addresses our level of certainty that the risk factor actually contributes to mortality as opposed to just being a marker of higher risk. Among the classic Bradford–Hill criteria for causality are strength of the association, consistency across studies, specificity of the risk factor, temporality of the risk factor/outcome association, biologic gradient of the risk factor (dose dependence), and biologic plausibility (2). In this study by Trivin et al. (1) in CJASN, the strength of the association of hemoglobin A1C with mortality was strong and graded. Interestingly, the findings differ somewhat from previous studies, which have shown a J-shaped association between hemoglobin A1C and mortality (3,4). In addition, the association of hemoglobin A1C with all-cause mortality but not with ESRD suggests that the mechanism is likely not by CKD progression and may be analogous to the well-known associations of hemoglobin A1C with mortality risk in the general population (3). In this context, the findings of Trivin et al. (1) may have extended the prior literature on hemoglobin A1C and prognosis to the CKD population rather than identified a CKD-specific risk factor.

Finally, the biologic plausibility linking hemoglobin A1C and adverse outcomes in patient without diabetes and with CKD warrants discussion. The physiology of glucose homeostasis is very complicated, particularly in patients with CKD in whom a number of alterations (e.g., decreased insulin catabolism) may lead to increased risk of hypoglycemia. Monitoring glycemic levels is also not straightforward. Although hemoglobin A1C is the traditional marker used to monitor long-term blood glucose levels in the general population, in the setting of CKD, there may be changes in hemoglobin that make hemoglobin A1C less informative. One hypothesis is that there may be increased turnover of red blood cells in CKD, particularly with erythropoietin-stimulating agents (ESAs), which may lead to underestimation of blood glucose levels with the use of hemoglobin A1C (5). In this study, Trivin et al. (1) noted...
that very few participants were taking ESAs, and they adjusted for ESAs in their statistical models, which did not change the observed associations. Hemoglobin A1C may also be an insensitive measure of the variability of blood glucose that often occurs in patients with CKD and is important in overall prognosis (6). Thus, additional investigation to understand the biology reflected by hemoglobin A1C levels in this prediabetic range is needed. For these reasons, the association of hemoglobin A1c with mortality risk may actually be weaker in the CKD population than in the general population.

(3) Does the measurement change our estimate of prognosis in the target population? This is a prediction question, and it is quantified not by relative risks but by estimates of risk discrimination, like the c statistic and the net reclassification index. When there is an existing prognostic model, the question asks whether the addition of the new risk factor would make a major improvement to risk prediction. Trivin et al. (1) suggest that hemoglobin A1C may be an important predictive measure in patients with CKD. Diabetes mellitus itself is known to be a strong predictor of adverse outcomes. Recently, Bansal et al. (7) published a prediction model for mortality among elderly participants with CKD and found that the presence of diabetes mellitus was one of nine final variables (of 16 candidate variables) that predicted all-cause mortality. In a community-based study of adults without diabetes, hemoglobin A1C improved risk discrimination only for coronary heart disease in a model that included fasting glucose and other covariates (3). Tangri et al. (8) evaluated diabetes mellitus as a candidate variable for an ESRD prediction model. Supporting the findings of Trivin et al. (1), diabetes was not retained in the final prediction model. It is possible that the pathologic threshold of hemoglobin A1C may differ on the basis of the outcome of interest, which may explain the discordant findings for ESRD and mortality that were observed in this study. Evaluation of hemoglobin A1C as a prediction tool was not a primary purpose of this paper by Trivin et al. (1) but should be important in the next steps. For the goal of informing prognosis, researchers would need to show that hemoglobin A1c significantly improves the performance of a prediction model relative to its performance without hemoglobin A1C. These are the criteria for novel risk factors to be considered clinically relevant for outcome prediction.

(4) Should we treat this risk factor to improve the outcomes for the target population? The term modifiable risk factor is reserved for measurements or conditions that can be altered by a target intervention and when the degree of benefit on a clinical outcome is proportional to the extent of risk factor change. Hemoglobin A1C is a well recognized treatment target for patients with diabetes mellitus. However, both the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials have suggested that more intensive control (as indicated by lower hemoglobin A1C) is not advantageous to decrease the risk of mortality in adults with type 2 diabetes (9–11). Whereas previous trials have largely excluded patients with CKD, a post hoc analysis of 3636 participants with CKD and known diabetes from the ACCORD trial was recently published (12); those randomly assigned to the intensive A1C control arm had significantly higher all-cause and cardiovascular mortality (12). Given these findings in patients with clinical diabetes mellitus and CKD, it seems unlikely that hemoglobin A1C lowering in the setting of nondiabetic CKD would decrease risk for mortality. Moreover, it is unlikely that a clinical trial would be conducted because of concerns that lowering hemoglobin A1C would be harmful. Interestingly, in the work by Trivin et al. (1), time-updated measures of hemoglobin A1C did not substantially change the observed association between hemoglobin A1C and risk of death. This may suggest that measures of hemoglobin A1C are not dynamic risk factors but rather, reflect underlying patient characteristics.

In conclusion, this interesting epidemiologic study by Trivin et al. (1) has augmented the ongoing discussion on the important role of hemoglobin A1C as a risk factor in the CKD population. Furthermore, Trivin et al. (1) have identified a possible new high-risk subset of patients: those with CKD and prediabetes. Exploration of novel risk factors in patients with CKD remains a difficult but important endeavor, but it leads to new insights on pathophysiology, improved identification of high-risk patients, and development of treatment strategies. Although the findings of this study may not be translatable to clinical practice yet, the results present opportunities for future scientific studies to dissect the complex biology of glycemia in CKD (1).

Disclosures
None.

References


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