Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes

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Results of the main Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial indicate that intensive glucose lowering increases cardiovascular and all-cause mortality. As the contribution of mild-to-moderate chronic kidney disease (CKD) to these risks is not known, we assessed the impact on cardiovascular outcomes in this population. Renal function data were available on 10,136 patients of the original ACCORD cohort. Of those, 6,506 were free of CKD at baseline and 3,636 met the criteria for CKD. Participants were randomly assigned to a treatment strategy of either intensive or standard glycemic goal. The primary outcome, all-cause and cardiovascular mortality, and prespecified secondary outcomes were evaluated. Risk for the primary outcome was 87% higher in patients with than in those without CKD (hazard ratio of 1.866; 95% CI: 1.651–2.110). All prespecified secondary outcomes were 1.5 to 3 times more frequent in patients with than in those without CKD. In patients with CKD, compared with standard therapy, intensive glucose lowering was significantly associated with both 31% higher all-cause mortality (1.306: 1.065–1.600) and 41% higher cardiovascular mortality (1.412: 1.052–1.892). No significant effects were found in patients without CKD. Thus, in high-risk patients with type II diabetes, mild and moderate CKD is associated with increased cardiovascular risk. Intensive glycemic control significantly increases the risk of cardiovascular and all-cause mortality in this population.

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Chronic kidney disease (CKD) is a highly prevalent microvascular complication of diabetes mellitus, and approximately 40% of patients with diabetes develop CKD.[1] Type 2 diabetes is the leading cause of end-stage renal disease in developed countries. The incidence of CKD is estimated at 13.1% in the general adult population, and more than 26 million adults in the US are affected by CKD.[2] Of note, the vast majority of CKD patients have mild-to-moderate CKD (Stage I–III), whereas Stage IV and V CKD is rare (0.35% and 0.11%, respectively).[2]

A large community-based study of more than one million individuals showed a graded increase in cardiovascular events with decreasing glomerular filtration rate levels, establishing CKD as a strong cardiovascular risk factor.[3] However, the risk was less clear for mild and moderate CKD[3] and was even questioned for older subjects.[4] Albuminuria is also a strong predictor of mortality and cardiovascular events independently of the glomerular filtration rate.[5–7] Data in diabetic patients with CKD are limited and do not permit for definite conclusions.[8–12]

Data from the main Action to Control Cardiovascular Risk in Diabetes (ACCORD) study have previously shown that intensive glycemic control is associated with higher cardiovascular and all-cause mortality rates compared with standard therapy.[13] Other large trials[14,15] found no reduction in cardiovascular events with intensive therapy, raising concerns about the wisdom of intensive glucose lowering. As of today, however, no specific explanation has been proposed.[16]

Given the close association of CKD with cardiovascular and all-cause mortality and the possibility that CKD may predispose to less efficient clearance of hypoglycemic and other agents, we hypothesized that the presence of mild-to-moderate CKD at baseline might increase cardiovascular events, particularly in the intensively treated group.

In this study therefore we evaluated the effects of mild and moderate CKD (Stage I–III) on cardiovascular morbidity and

mortality and the impact of intensive glycemic control on cardiovascular outcomes in a population of high-risk diabetic patients with or without CKD.

RESULTS

Renal function data were available for 10,142 of the 10,251 participants in the ACCORD study. CKD was present in about one-third of them (3,636 patients, 35.9%), whereas 6,506 patients (64.1%) were free from CKD. Of patients with CKD, 1,449 (14.3%) were classified as Stage 1 CKD, 1,366 (13.5%) as Stage 2 CKD, and 821 (8%) as Stage 3 CKD. Key baseline characteristics of the whole study population and according to the presence or not of CKD are depicted in Table 1.

When compared with patients free of CKD, patients with CKD were older, had higher body mass index, fasting glucose, HbA1c, and systolic blood pressure, as well as higher rates for history of cardiovascular disease, chronic heart failure, and duration of diabetes. In addition, CKD patients used insulin and most anti-hypertensive agents more frequently and oral hypoglycemic agents less frequently compared with patients without CKD. Moreover, patients with CKD had higher triglyceride and lower high-density lipoprotein levels compared with non-CKD patients.

The key baseline characteristics by CKD status at baseline and by glycemia arm are presented in Table 2. Many of the differences between CKD and non-CKD patients mentioned above were also maintained in each of the glycemia arms. However, there were no significant differences between intensive and standard therapy either for CKD or for non-CKD patients.

Glycated hemoglobin levels fell significantly in the first 4 months into the study, to 6.7% in the intensive glycemic therapy and to 7.5% in the standard arm; however, no significant differences in glycated hemoglobin levels were observed between CKD and non-CKD patients (Figure 1).

The rates of primary and secondary outcomes in patients with and without CKD are shown in Figure 2. When compared with non-CKD, patients with CKD were about twice as likely to have a cardiovascular event or die. Compared with non-CKD, the presence of CKD was associated with a 97% (hazard ratio: 1.973; 95% confidence interval (CI): 1.701–2.288; $P<0.0001$) higher risk for all-cause mortality and 119% (hazard ratio: 2.189; 95% CI: 1.758–2.726; $P<0.0001$) higher risk for cardiovascular mortality (Figure 2). The risk of having the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) was 87% (hazard ratio: 1.866; 95% CI: 1.651–2.110; $P<0.0001$) higher in CKD compared with non-CKD patients. Furthermore, patients with CKD had significantly higher risks for nonfatal myocardial infarction (62%), nonfatal stroke (149%), any stroke (141%), major coronary artery disease events (56%), and fatal or nonfatal congestive heart failure (219%).

Increased rates of primary and secondary outcomes were evident even when CKD Stages I and II were compared separately with non-CKD (Figure 3a). Likewise, CKD Stage III, even with small numbers, was associated with worse outcomes compared with non-CKD (Figure 3b). Furthermore, when albuminuria alone (Figure 3c) was considered, the association with the primary and secondary outcomes remained highly significant.

The rates of primary and secondary outcomes in patients with CKD according to intensive or standard therapy in the glycemia arm of the study are shown in Figure 4a, whereas the corresponding rates for patients without CKD are shown in Figure 4b.

Compared with standard glycemia therapy, intensive glucose lowering in CKD patients was associated with a 31% higher risk for all-cause mortality (hazard ratio: 1.306; 95% CI: 1.065–1.600; $P=0.01$) and a 41% higher risk for cardiovascular mortality (hazard ratio: 1.412; 95% CI: 1.052–1.892; $P=0.02$) (Figure 4a). This association remained statistically significant and practically unchanged even after adjustments for all key baseline characteristics (age, sex, body mass index, glycated hemoglobin, systolic blood pressure, smoking status, history of cardiovascular disease and heart failure, and use of insulin and anti-hypertensive medications). The use of metformin or thiazolidinediones at baseline was not associated with increased all-cause mortality ($P=0.42$ and $P=0.98$, respectively). In contrast, there were no significant differences in all-cause and cardiovascular mortality risks between intensive and standard glycemia therapy in patients without CKD (Figure 4b). The test for interaction between CKD status and glycemia arm was not statistically significant. In CKD patients, the risk for nonfatal myocardial infarction was significantly lower (26%) with intensive therapy compared with standard glucose lowering (hazard ratio: 0.740; 95% CI: 0.590–0.930; $P=0.0093$). A similar trend was observed for the primary and remaining secondary outcomes, with lower risk in the intensive glycemic arm; however, this was not statistically significant (Figure 4a).

The cumulative incidence curves for cardiovascular and all-cause mortality are depicted in Figure 5. There were no significant differences between the two treatment groups in patients without CKD, whereas intensive therapy was associated with worse outcomes compared with standard therapy in patients with CKD. Of major clinical importance, the curves for both outcomes (cardiovascular and all-cause mortality) in patients with CKD separated very early, within 6 months after randomization to intensive or standard therapy and continued to widen with time, whereas the same curves in the non-CKD group remained virtually superimposed.

The rates of hypoglycemic events requiring assistance are shown in Table 3. Patients with CKD had significantly higher rates of hypoglycemia compared with patients without CKD. Likewise, the annualized rates of hypoglycemic episodes requiring assistance were significantly more common with intensive therapy compared with standard therapy, both in patients with CKD (5.3% vs. 2.0%) and in patients without CKD (3.5% vs. 1.1%). The same association was