

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

Vasilios Papademetriou<sup>1</sup>, Laura Lovato<sup>2</sup>, Michael Doumas<sup>3</sup>, Eric Nylen<sup>3</sup>, Amy Mottl<sup>4</sup>, Robert M. Cohen<sup>5,6</sup>, William B. Applegate<sup>7</sup>, Zubin Puntakee<sup>8</sup>, Jean Francois Yale<sup>9</sup> and William C. Cushman<sup>10</sup> for the ACCORD Study Group

<sup>1</sup>Veteran Affairs Medical Center and Georgetown University, Washington, DC, USA; <sup>2</sup>Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; <sup>3</sup>Veteran Affairs Medical Center and George Washington University, Washington, DC, USA; <sup>4</sup>University of North Carolina, Chapel Hill, North Carolina, USA; <sup>5</sup>University of Cincinnati, Cincinnati, Ohio, USA; <sup>6</sup>VA Medical Center, Cincinnati, Ohio, USA; <sup>7</sup>WFUHS Geriatric/Gerontology, Winston-Salem, Ohio, USA; <sup>8</sup>McMaster Medical Center, Hamilton, Ontario, Canada; <sup>9</sup>Royal Victoria Hospital, Barrie, Ontario, Canada and <sup>10</sup>Veterans Affairs Medical Center, VA Clinical Center Network, Memphis, Tennessee, USA

**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.**

*Kidney International* (2015) **87**, 649–659; doi:10.1038/ki.2014.296; published online 17 September 2014

**KEYWORDS:** cardiovascular morbidity; chronic kidney disease; intensive glycemic therapy; mortality; type 2 diabetes mellitus

**Correspondence:** Vasilios Papademetriou, Veteran Affairs Medical Center and Georgetown University, 50 Irving Street, Northwest, Washington, DC 20422, USA. E-mail: Vasilios.papademetriou@va.gov

Received 14 February 2014; revised 24 June 2014; accepted 10 July 2014; published online 17 September 2014

Chronic kidney disease (CKD) is a highly prevalent microvascular complication of diabetes mellitus, and approximately 40% of patients with diabetes develop CKD.<sup>1</sup> 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.<sup>2</sup> 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).<sup>2</sup>

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.<sup>3</sup> However, the risk was less clear for mild and moderate CKD<sup>3</sup> and was even questioned for older subjects.<sup>4</sup> Albuminuria is also a strong predictor of mortality and cardiovascular events independently of the glomerular filtration rate.<sup>5–7</sup> Data in diabetic patients with CKD are limited and do not permit for definite conclusions.<sup>8–12</sup>

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.<sup>13</sup> Other large trials<sup>14,15</sup> 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.<sup>16</sup>

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

**Table 1 | Baseline characteristics of the entire cohort and by baseline CKD status**

|                                    | Overall (N = 10,142) | Baseline CKD status |                     | P-value  |
|------------------------------------|----------------------|---------------------|---------------------|----------|
|                                    |                      | No CKD (N = 6506)   | With CKD (N = 3636) |          |
| Age (years)                        | 62.2 ± 6.8           | 61.7 ± 6.5          | 63.3 ± 7.2          | < 0.0001 |
| Sex (female)                       | 3904 (38.5%)         | 2577 (39.6%)        | 1327 (36.5%)        | 0.0020   |
| Race/ethnicity                     |                      |                     |                     | 0.3775   |
| African American                   | 1925 (19.0%)         | 1209 (18.6%)        | 716 (19.7%)         |          |
| White                              | 6341 (62.5%)         | 4100 (63.0%)        | 2241 (61.6%)        |          |
| Hispanic                           | 716 (7.1%)           | 448 (6.9%)          | 268 (7.4%)          |          |
| Other                              | 1160 (11.4%)         | 749 (11.5%)         | 411 (11.3%)         |          |
| Weight (kg)                        | 93.6 ± 18.7          | 93.2 ± 18.4         | 94.2 ± 19.1         | 0.0161   |
| Waist (cm)                         | 106.8 ± 13.9         | 106.1 ± 13.6        | 107.9 ± 14.2        | < 0.0001 |
| BMI (kg/m <sup>2</sup> )           | 32.2 ± 5.5           | 32.1 ± 5.4          | 32.5 ± 5.6          | 0.0025   |
| Smoking status                     |                      |                     |                     | 0.0003   |
| Never                              | 4231 (41.8%)         | 2795 (43.0%)        | 1436 (39.6%)        |          |
| Former                             | 4486 (44.3%)         | 2854 (43.9%)        | 1632 (45.0%)        |          |
| Current                            | 1412 (13.9%)         | 851 (13.1%)         | 561 (15.5%)         |          |
| Serum creatinine (mg/dl)           | 0.9 ± 0.2            | 0.9 ± 0.2           | 1.0 ± 0.3           | < 0.0001 |
| eGFR (ml/min/1.73 m <sup>2</sup> ) |                      |                     |                     | < 0.0001 |
| 0–59                               | 821 (8.1%)           | 0 (0.0%)            | 821 (22.6%)         |          |
| 60–89                              | 4375 (43.1%)         | 3009 (46.2%)        | 1366 (37.6%)        |          |
| 90 +                               | 4946 (48.8%)         | 3497 (53.8%)        | 1449 (39.9%)        |          |
| UACR (mg/g)                        |                      |                     |                     | < 0.0001 |
| < 30                               | 6970 (68.8%)         | 6506 (100%)         | 464 (12.8%)         |          |
| 30–300                             | 2492 (24.6%)         | 0 (0.0%)            | 2492 (68.8%)        |          |
| > 300                              | 668 (6.6%)           | 0 (0.0%)            | 668 (18.4%)         |          |
| CKD                                |                      |                     |                     | < 0.0001 |
| No CKD                             | 6506 (64.1%)         | 6506 (100%)         | 0 (0.0%)            |          |
| CKD Stage 1                        | 1449 (14.3%)         | 0 (0.0%)            | 1449 (39.9%)        |          |
| CKD Stage 2                        | 1366 (13.5%)         | 0 (0.0%)            | 1366 (37.6%)        |          |
| CKD Stage 3                        | 821 (8.1%)           | 0 (0.0%)            | 821 (22.6%)         |          |
| Serum glucose (mg/dl)              | 175.3 ± 56.2         | 172.3 ± 52.4        | 180.5 ± 62.1        | < 0.0001 |
| HbA1c (%)                          | 8.3 ± 1.1            | 8.2 ± 1.0           | 8.4 ± 1.1           | < 0.0001 |
| Duration of DM-years               | 10.9 ± 7.8           | 10.0 ± 7.4          | 12.4 ± 8.2          | < 0.0001 |
| Systolic BP                        | 136.4 ± 17.1         | 133.8 ± 16.0        | 141.0 ± 18.1        | < 0.0001 |
| Diastolic BP                       | 74.9 ± 10.7          | 74.8 ± 10.4         | 75.0 ± 11.2         | 0.2592   |
| Heart rate                         | 72.6 ± 11.7          | 72.5 ± 11.4         | 72.8 ± 12.3         | 0.2245   |
| History of CVD                     | 3570 (35.2%)         | 2067 (31.8%)        | 1503 (41.3%)        | < 0.0001 |
| History of CHF                     | 488 (4.9%)           | 244 (3.8%)          | 244 (6.8%)          | < 0.0001 |
| Insulin                            | 3545 (35.0%)         | 2005 (30.8%)        | 1540 (42.4%)        | < 0.0001 |
| Merformin                          | 6070 (59.9%)         | 3982 (61.2%)        | 2088 (57.4%)        | 0.0002   |
| Any sulfonylurea                   | 5087 (50.2%)         | 3330 (51.2%)        | 1757 (48.3%)        | 0.0057   |
| Any anti-hypertensive agent        | 8674 (85.5%)         | 5373 (82.6%)        | 3301 (90.8%)        | < 0.0001 |
| ACE-inhibitors                     | 5377 (53.0%)         | 3298 (50.7%)        | 2079 (57.2%)        | < 0.0001 |
| ARBs                               | 1624 (16.0%)         | 985 (15.1%)         | 639 (17.6%)         | 0.0013   |
| Any thiazide diuretic              | 1961 (19.3%)         | 1261 (19.4%)        | 700 (19.3%)         | 0.8735   |
| Beta blockers                      | 2978 (29.4%)         | 1718 (26.4%)        | 1260 (34.7%)        | < 0.0001 |
| Dihydropyridine CCBs               | 1179 (11.6%)         | 629 (9.7%)          | 550 (15.1%)         | < 0.0001 |
| Non-dihydropyridine CCBs           | 730 (7.2%)           | 381 (5.9%)          | 349 (9.6%)          | < 0.0001 |
| Aspirin                            | 5530 (54.5%)         | 3516 (54.0%)        | 2014 (55.4%)        | 0.1910   |
| Statin                             | 6300 (62.1%)         | 4031 (62.0%)        | 2269 (62.4%)        | 0.6573   |
| Fibrate                            | 600 (5.9%)           | 366 (5.6%)          | 234 (6.4%)          | 0.0973   |
| Potassium                          | 4.5 ± 0.6            | 4.4 ± 0.4           | 4.5 ± 0.7           | < 0.0001 |
| LDL                                | 104.9 ± 33.9         | 105.1 ± 33.1        | 104.5 ± 35.3        | 0.4269   |
| HDL—female                         | 47.1 ± 12.6          | 47.5 ± 12.5         | 46.2 ± 12.7         | 0.0034   |
| HDL—male                           | 38.6 ± 9.6           | 38.9 ± 9.3          | 38.1 ± 10.1         | 0.0019   |
| Triglycerides                      | 155.0 [106.0,228.0]  | 150.0 [103.0,219.0] | 165.0 [112.0,243.0] | < 0.0001 |
| Education                          |                      |                     |                     | < 0.0001 |
| < HS Graduate                      | 1489 (14.7%)         | 868 (13.3%)         | 621 (17.1%)         |          |
| HS graduate/GED                    | 2684 (26.5%)         | 1699 (26.1%)        | 985 (27.1%)         |          |
| Some college/tech                  | 3330 (32.9%)         | 2161 (33.2%)        | 1169 (32.2%)        |          |
| College graduate or more           | 2632 (26.0%)         | 1776 (27.3%)        | 856 (23.6%)         |          |
| Network                            |                      |                     |                     | 0.0018   |
| A                                  | 1492 (14.7%)         | 1001 (15.4%)        | 491 (13.5%)         |          |
| B                                  | 1722 (17.0%)         | 1141 (17.5%)        | 581 (16.0%)         |          |
| C                                  | 1240 (12.2%)         | 818 (12.6%)         | 422 (11.6%)         |          |
| D                                  | 1562 (15.4%)         | 975 (15.0%)         | 587 (16.1%)         |          |
| E                                  | 1193 (11.8%)         | 724 (11.1%)         | 469 (12.9%)         |          |
| F                                  | 1530 (15.1%)         | 956 (14.7%)         | 574 (15.8%)         |          |
| G                                  | 1403 (13.8%)         | 891 (13.7%)         | 512 (14.1%)         |          |

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CCBs, calcium-channel blockers; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GED, graduate equivalency diploma; HDL, high-density lipoprotein; HS, high school; LDL, low-density lipoprotein; UACR, urine albumin-to-creatinine ratio.

**Table 2 | Baseline characteristics by glycemia arm and baseline CKD status**

|                                    | With CKD intensive<br>(N = 1836) | With CKD standard<br>(N = 1800) | No-CKD intensive<br>(N = 3244) | No-CKD standard<br>(N = 3262) | P-value |
|------------------------------------|----------------------------------|---------------------------------|--------------------------------|-------------------------------|---------|
| Age (years)                        | 63.4 ± 7.3                       | 63.1 ± 7.2                      | 61.6 ± 6.4                     | 61.8 ± 6.6                    | <0.0001 |
| Sex (Female)                       | 680 (37.0%)                      | 647 (35.9%)                     | 1279 (39.4%)                   | 1298 (39.8%)                  | 0.0177  |
| Race/ethnicity                     |                                  |                                 |                                |                               | 0.7253  |
| African American                   | 358 (19.5%)                      | 358 (19.9%)                     | 625 (19.3%)                    | 584 (17.9%)                   |         |
| White                              | 1142 (62.2%)                     | 1099 (61.1%)                    | 2033 (62.7%)                   | 2067 (63.4%)                  |         |
| Hispanic                           | 132 (7.2%)                       | 136 (7.6%)                      | 214 (6.6%)                     | 234 (7.2%)                    |         |
| Other                              | 204 (11.1%)                      | 207 (11.5%)                     | 372 (11.5%)                    | 377 (11.6%)                   |         |
| Weight (kg)                        | 94.1 ± 19.0                      | 94.3 ± 19.2                     | 93.2 ± 18.5                    | 93.2 ± 18.3                   | 0.4048  |
| Waist (cm)                         | 107.8 ± 13.9                     | 108.0 ± 14.5                    | 106.1 ± 13.9                   | 106.2 ± 13.3                  | 0.0151  |
| BMI (kg/m <sup>2</sup> )           | 32.4 ± 5.6                       | 32.5 ± 5.7                      | 32.1 ± 5.4                     | 32.1 ± 5.3                    | 0.3167  |
| Smoking status                     |                                  |                                 |                                |                               | 0.0027  |
| Never                              | 699 (38.1%)                      | 737 (41.0%)                     | 1394 (43.0%)                   | 1401 (43.0%)                  |         |
| Former                             | 839 (45.8%)                      | 793 (44.2%)                     | 1418 (43.8%)                   | 1436 (44.1%)                  |         |
| Current                            | 295 (16.1%)                      | 266 (14.8%)                     | 429 (13.2%)                    | 422 (12.9%)                   |         |
| Serum creatinine (mg/dl)           | 1.0 ± 0.3                        | 1.0 ± 0.3                       | 0.9 ± 0.2                      | 0.9 ± 0.2                     | <0.0001 |
| eGFR (ml/min/1.73 m <sup>2</sup> ) |                                  |                                 |                                |                               | <0.0001 |
| 0-59                               | 431 (23.5%)                      | 390 (21.7%)                     | 0 (0.0%)                       | 0 (0.0%)                      |         |
| 60-89                              | 685 (37.3%)                      | 681 (37.8%)                     | 1501 (46.3%)                   | 1508 (46.2%)                  |         |
| 90+                                | 720 (39.2%)                      | 729 (40.5%)                     | 1743 (53.7%)                   | 1754 (53.8%)                  |         |
| UACR (mg/g)                        |                                  |                                 |                                |                               | <0.0001 |
| < 30                               | 246 (13.4%)                      | 218 (12.2%)                     | 3244 (100%)                    | 3262 (100%)                   |         |
| 30-300                             | 1254 (68.5%)                     | 1238 (69.0%)                    | 0 (0.0%)                       | 0 (0.0%)                      |         |
| > 300                              | 330 (18.0%)                      | 338 (18.8%)                     | 0 (0.0%)                       | 0 (0.0%)                      |         |
| CKD                                |                                  |                                 |                                |                               | <0.0001 |
| No CKD                             | 0 (0.0%)                         | 0 (0.0%)                        | 3244 (100%)                    | 3262 (100%)                   |         |
| CKD Stage 1                        | 720 (39.2%)                      | 729 (40.5%)                     | 0 (0.0%)                       | 0 (0.0%)                      |         |
| CKD Stage 2                        | 685 (37.3%)                      | 681 (37.8%)                     | 0 (0.0%)                       | 0 (0.0%)                      |         |
| CKD Stage 3                        | 431 (23.5%)                      | 390 (21.7%)                     | 0 (0.0%)                       | 0 (0.0%)                      |         |
| Serum glucose(mg/dl)               | 179.2 ± 61.4                     | 181.8 ± 62.9                    | 172.5 ± 52.5                   | 172.2 ± 52.2                  | 0.0137  |
| HbA1c(%)                           | 8.4 ± 1.1                        | 8.5 ± 1.1                       | 8.2 ± 1.0                      | 8.2 ± 1.0                     | 0.0002  |
| Duration of DM-years               | 12.5 ± 8.2                       | 12.4 ± 8.1                      | 9.8 ± 7.3                      | 10.1 ± 7.4                    | <0.0001 |
| Systolic BP                        | 140.7 ± 18.1                     | 141.2 ± 18.1                    | 133.7 ± 15.9                   | 133.9 ± 16.1                  | <0.0001 |
| Diastolic BP                       | 74.8 ± 11.2                      | 75.2 ± 11.2                     | 74.7 ± 10.3                    | 74.8 ± 10.4                   | 0.6686  |
| Heart rate                         | 73.0 ± 12.4                      | 72.7 ± 12.3                     | 72.6 ± 11.3                    | 72.4 ± 11.5                   | 0.1810  |
| History of CVD                     | 762 (41.5%)                      | 741 (41.2%)                     | 1047 (32.3%)                   | 1020 (31.3%)                  | <0.0001 |
| History of CHF                     | 127 (7.0%)                       | 117 (6.6%)                      | 121 (3.8%)                     | 123 (3.8%)                    | <0.0001 |
| Insulin                            | 770 (41.9%)                      | 770 (42.8%)                     | 961 (29.6%)                    | 1044 (32.0%)                  | <0.0001 |
| Merformin                          | 1069 (58.2%)                     | 1019 (56.6%)                    | 1965 (60.6%)                   | 2017 (61.8%)                  | 0.0012  |
| Any sulfonylurea                   | 921 (50.2%)                      | 836 (46.4%)                     | 1666 (51.4%)                   | 1664 (51.0%)                  | 0.0052  |
| Any anti-hypertensive agent        | 1663 (90.6%)                     | 1638 (91.0%)                    | 2653 (81.8%)                   | 2720 (83.4%)                  | <0.0001 |
| ACE-inhibitors                     | 1069 (58.2%)                     | 1010 (56.1%)                    | 1624 (50.1%)                   | 1674 (51.3%)                  | <0.0001 |
| ARBs                               | 315 (17.2%)                      | 324 (18.0%)                     | 479 (14.8%)                    | 506 (15.5%)                   | 0.0096  |
| Any thiazide diuretic              | 348 (19.0%)                      | 352 (19.6%)                     | 642 (19.8%)                    | 619 (19.0%)                   | 0.8188  |
| Beta blockers                      | 616 (33.6%)                      | 644 (35.8%)                     | 844 (26.0%)                    | 874 (26.8%)                   | <0.0001 |
| Dihydropyridine CCBs               | 266 (14.5%)                      | 284 (15.8%)                     | 321 (9.9%)                     | 308 (9.4%)                    | <0.0001 |
| Non-dihydropyridine CCBs           | 167 (9.1%)                       | 182 (10.1%)                     | 176 (5.4%)                     | 205 (6.3%)                    | <0.0001 |
| Aspirin                            | 1027 (55.9%)                     | 987 (54.8%)                     | 1756 (54.1%)                   | 1760 (54.0%)                  | 0.5366  |
| Statin                             | 1155 (62.9%)                     | 1114 (61.9%)                    | 1982 (61.1%)                   | 2049 (62.8%)                  | 0.4513  |
| Fibrate                            | 120 (6.5%)                       | 114 (6.3%)                      | 194 (6.0%)                     | 172 (5.3%)                    | 0.2328  |
| Potassium                          | 4.5 ± 0.5                        | 4.5 ± 0.9                       | 4.4 ± 0.4                      | 4.4 ± 0.4                     | 0.0007  |
| LDL                                | 103.6 ± 35.4                     | 105.5 ± 35.2                    | 105.6 ± 33.2                   | 104.6 ± 33.0                  | 0.6493  |
| HDL—female                         | 46.4 ± 13.2                      | 46.0 ± 12.1                     | 47.6 ± 12.8                    | 47.3 ± 12.3                   | 0.5713  |
| HDL—male                           | 37.8 ± 9.9                       | 38.4 ± 10.2                     | 38.8 ± 9.3                     | 39.0 ± 9.3                    | 0.0063  |
| Triglycerides                      | 166.0 [112.0,243.0]              | 165.0 [112.0,243.0]             | 151.0 [102.0,223.0]            | 150.0 [105.0,216.0]           | <0.0001 |
| Education                          |                                  |                                 |                                |                               | <0.0001 |
| <HS graduate                       | 338 (18.4%)                      | 283 (15.7%)                     | 453 (14.0%)                    | 415 (12.7%)                   |         |
| HS Graduate/GED                    | 502 (27.4%)                      | 483 (26.9%)                     | 826 (25.5%)                    | 873 (26.8%)                   |         |
| Some college/tech                  | 571 (31.2%)                      | 598 (33.3%)                     | 1091 (33.6%)                   | 1070 (32.8%)                  |         |
| College graduate or more           | 422 (23.0%)                      | 434 (24.1%)                     | 873 (26.9%)                    | 903 (27.7%)                   |         |
| Network                            |                                  |                                 |                                |                               | 0.1129  |
| A                                  | 247 (13.5%)                      | 244 (13.6%)                     | 499 (15.4%)                    | 502 (15.4%)                   |         |
| B                                  | 287 (15.6%)                      | 294 (16.3%)                     | 567 (17.5%)                    | 574 (17.6%)                   |         |
| C                                  | 221 (12.0%)                      | 201 (11.2%)                     | 400 (12.3%)                    | 418 (12.8%)                   |         |
| D                                  | 303 (16.5%)                      | 284 (15.8%)                     | 481 (14.8%)                    | 494 (15.1%)                   |         |
| E                                  | 230 (12.5%)                      | 239 (13.3%)                     | 369 (11.4%)                    | 355 (10.9%)                   |         |
| F                                  | 297 (16.2%)                      | 277 (15.4%)                     | 469 (14.5%)                    | 487 (14.9%)                   |         |
| G                                  | 251 (13.7%)                      | 261 (14.5%)                     | 459 (14.1%)                    | 432 (13.2%)                   |         |

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CCBs, calcium-channel blockers; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GED, graduate equivalency diploma; HDL, high-density lipoprotein; HS, high school; LDL, low-density lipoprotein; UACR, urine albumin-to-creatinine ratio.

P-values compared CKD with No-CKD subgroups. There were no significant differences between intensive and standard subgroups in either the CKD or the No-CKD categories.

evident even when the original (pre-transition) phase of the trial was analyzed. The interaction between CKD status and glycemia arm on hypoglycemic episodes was not statistically significant.

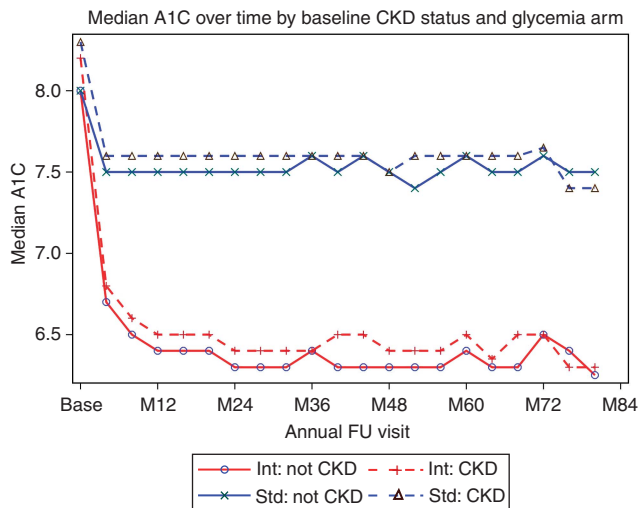
**DISCUSSION**

Results of the current analysis of the ACCORD data indicate two major findings: one, that patients with mild-to-moderate CKD (Stage I-III) carry a much higher cardiovascular risk as

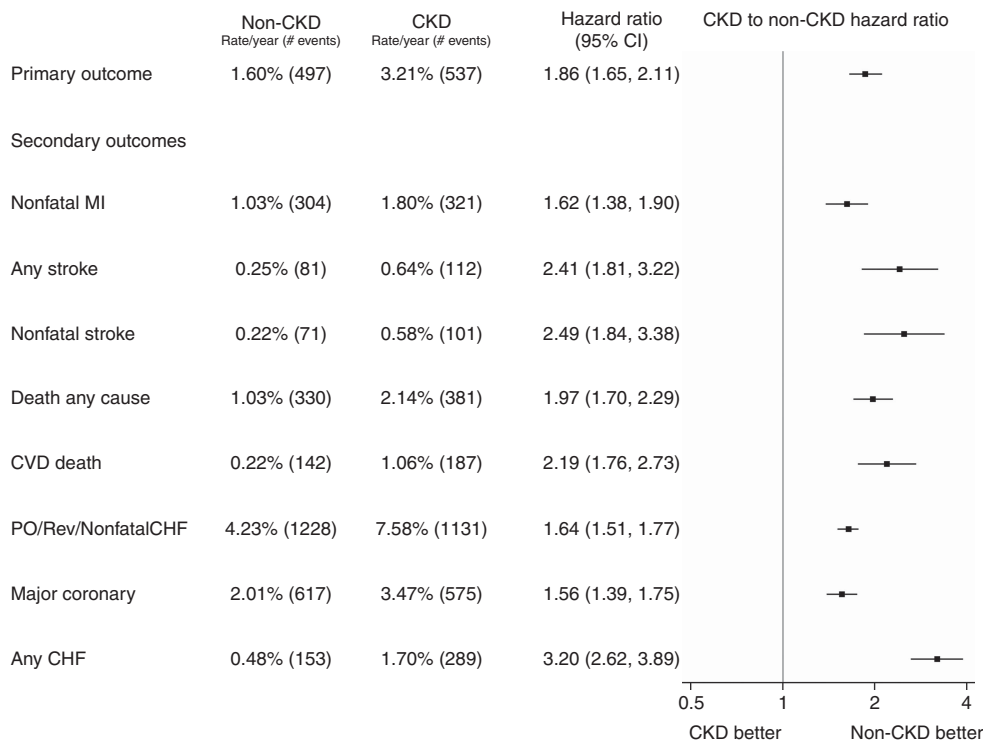
compared with non-CKD patients and, two, that tight glycemic control in patients with CKD results in a significant increase in both cardiovascular and all-cause mortality. Diabetic patients with no evidence of CKD do not seem to carry the same risk. These findings are of major clinical importance and have the potential to influence clinical practice. We recognize that these are *post-hoc* subgroup comparisons and as such are underpowered.

Several cohort or observational studies have shown that CKD is a predictor of cardiovascular morbidity and mortality. In mixed populations, studies have shown that even a mild decrease in estimated glomerular filtration rate (eGFR) or albuminuria can predict cardiovascular and all-cause mortality.<sup>3,17-19</sup> Evidence, however, in patients with type 2 diabetes and mild CKD is scarce and limited to four rather small observational studies in Italy and Japan.<sup>8-11</sup> The ACCORD study has several strengths, compared with the existing literature: (a) it is a prospective randomized study with high-quality data; (b) it was conducted in a purely diabetic population; (c) it included a large patient sample of more than 10,000 patients, larger than the summation of available observational studies evaluating similar parameters;<sup>8-11</sup> and (d) it is a study of patients with mild-to-moderate CKD (mostly mild), and thus applicable to the majority of patients with diabetic CKD.

The findings of our study indicate an almost doubling of all cardiovascular events in patients with CKD as compared with those without. Substantial increase was noted in the composite primary end point, all-cause and cardiovascular



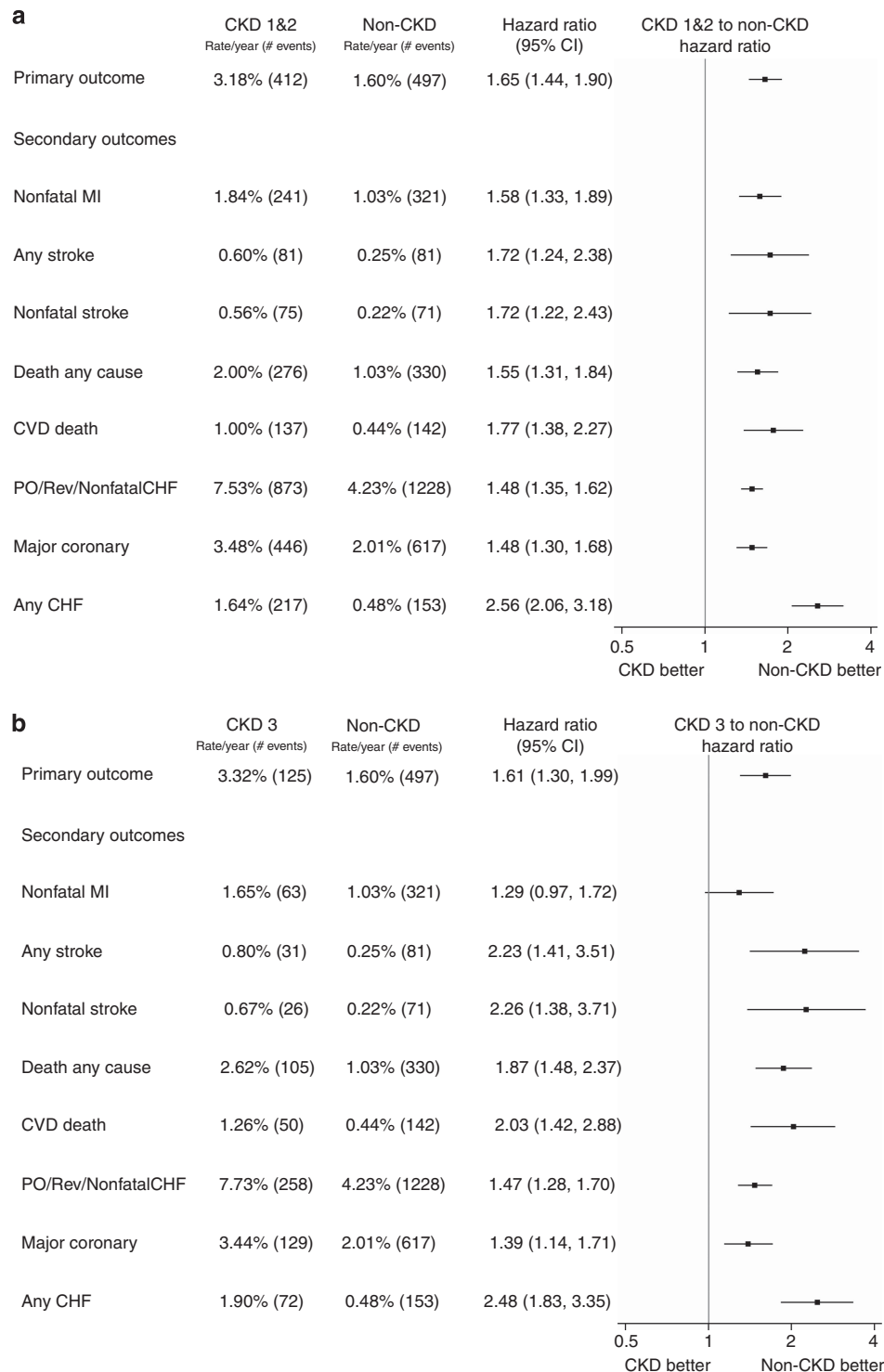
**Figure 1 | Glycated hemoglobin levels with intensive and standard therapy in patients with or without chronic kidney disease (CKD).** FU, follow-up; Int, intensive; Std, standard.



**Figure 2 | Rates for the primary and secondary outcomes in patients with and without chronic kidney disease (CKD).**

mortality, fatal and nonfatal stroke and myocardial infarction, and fatal and non-fatal congestive heart failure. In these patients with mild-to-moderate CKD, the excess risk of death from any cause was 97% and from cardiovascular causes was 119%. A *post-hoc* analysis of the Action in Diabetes and

Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study also found that albuminuria and low eGFR are independent predictors of cardiovascular and renal events in patients with type 2 diabetes mellitus.<sup>12</sup> Findings from both studies clearly establish mild-to-moderate



**Figure 3 | Rates of primary and secondary outcomes by chronic kidney disease status.** Rates for the primary and secondary outcomes in patients without CKD compared to patients with mild CKD I and II (a), CKD III (b) and albuminuria (c).

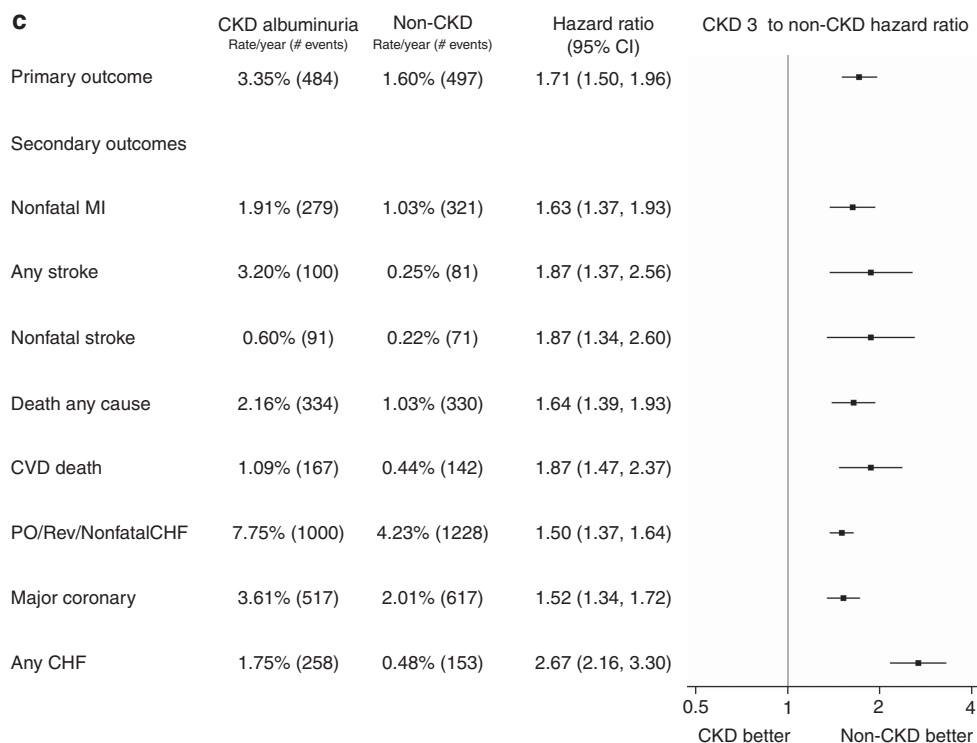


Figure 3 | Continued.

CKD (Stages I–III) as a strong correlate of morbidity and mortality in patients with type 2 diabetes mellitus.

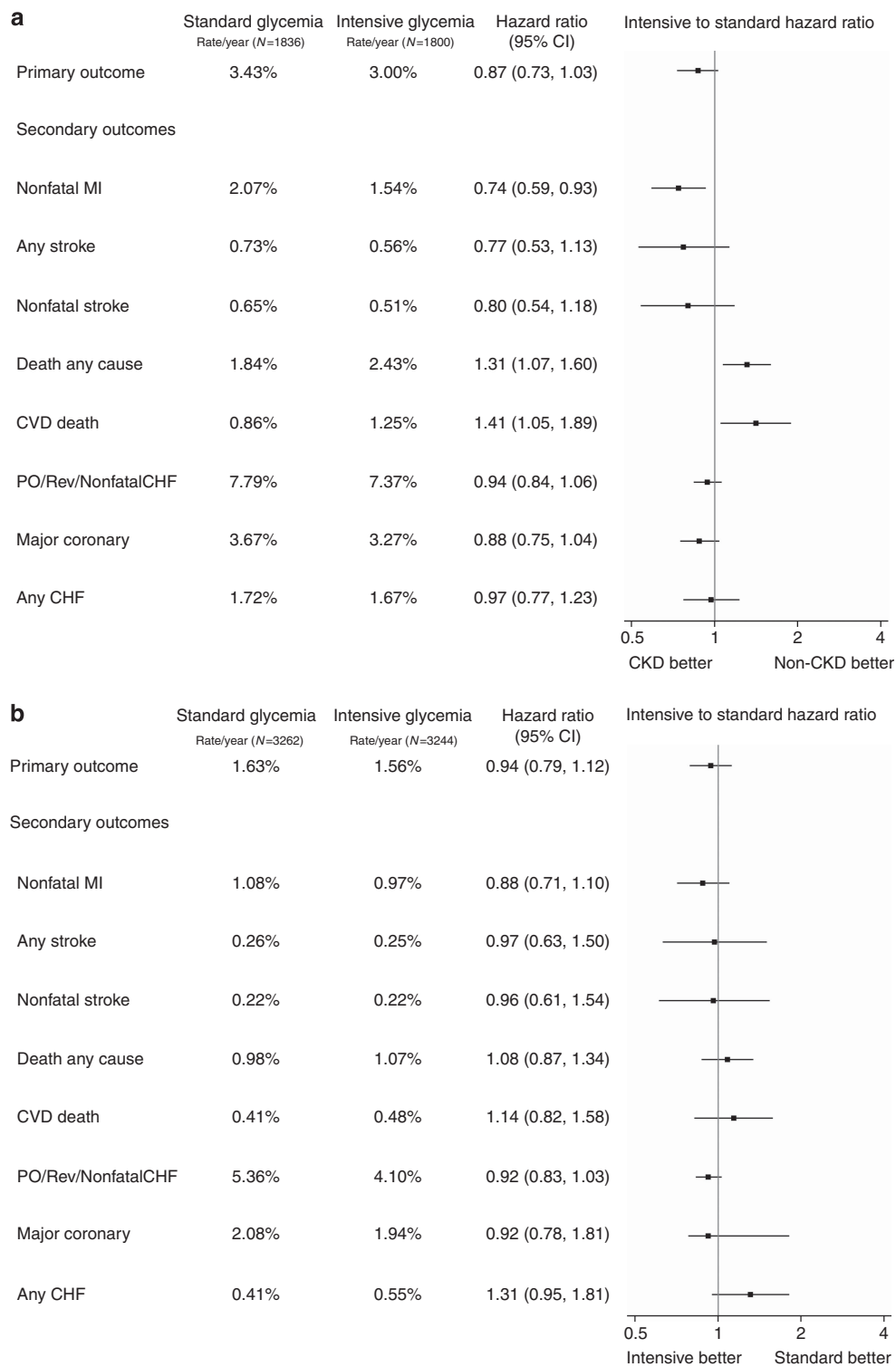
The second and likely most important finding of our study is the effect of intensive glycaemic control on cardiovascular and all-cause mortality in patients with mild-to-moderate CKD. In these patients, intensive glycaemic control was associated with a 41% increase in cardiovascular mortality and a 31% increase in all-cause mortality. This finding is concordant with a recent observational study from Canada, in more than 23,000 diabetic patients with CKD, in which aggressive glycaemic control with glycated hemoglobin levels below 6.5% was associated with excess mortality.<sup>20</sup>

In our study, the rates of hypoglycemia were almost doubled in patients with CKD compared with patients without CKD. Of equal importance, the annualized rates of hypoglycemic episodes requiring assistance were almost threefold more common with intensive therapy compared with standard therapy in patients with CKD. Hypoglycemic events are more frequent in patients with CKD compared with patients without CKD. A very large retrospective cohort of about 250,000 patients with more than two million glucose measurements revealed the higher incidence of hypoglycemia in CKD patients and the close association between hypoglycemia and mortality.<sup>21</sup> Indeed, the adjusted hypoglycemia rates were approximately double in CKD patients compared with non-CKD diabetic patients (10.72 vs. 5.33 episodes/100 patient-months;  $P < 0.0001$ ). This was also true for severe hypoglycemia (blood glucose  $< 50$  mg/dl) as well (2.99 vs. 1.45

episodes/100 patient-months;  $P < 0.0001$ ). Moreover, hypoglycemia was strongly associated with mortality within the first day following a hypoglycemic episode experienced either out of or in the hospital, exhibiting a severity-dependent gradual relationship—i.e., the more severe the hypoglycemia, the higher the mortality. These findings underscore the special attention that is needed for the proper and safe management of diabetes in patients with CKD.

Exogenous insulin is normally metabolized by the kidney, and in patients with impaired kidney function the half-life of insulin is prolonged. Similarly, clearance of many drugs is decreased in patients with CKD, resulting in prolonged exposure to higher levels of the drug or its metabolites. The higher rate of hypoglycemia therefore in patients with mild-to-moderate CKD could be related to impaired drug metabolism, whereas in patients with more advanced CKD it could be, in addition, related to decreased renal neoglycogenesis or malnutrition and cachexia and subsequent decreased glycogen stores.<sup>22</sup>

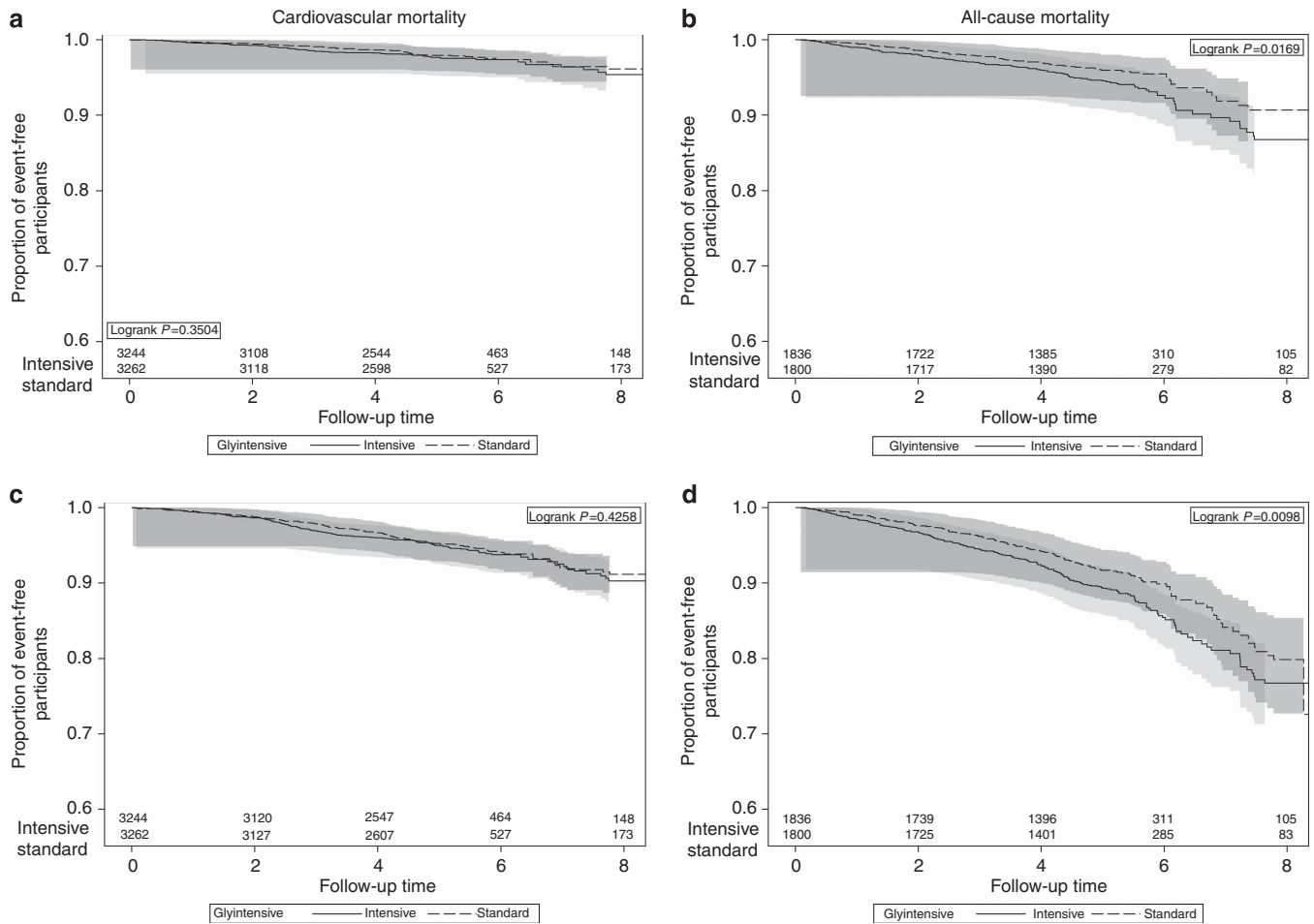
Several studies have shown that the risk for adverse events and medication errors increases significantly as the number of drugs in a therapeutic regimen increases.<sup>23</sup> The number of drugs administered in the intensive therapy group was significantly higher compared with standard therapy in the ACCORD trial. The percentage of patients using three or more oral hypoglycemic agents either alone (17%) or in combination with insulin (25%) was more than double in intensive therapy compared with standard therapy.



**Figure 4 | Rates of primary and secondary outcomes by randomized treatment group (intensive versus standard).** Rates for the primary and secondary outcomes with intensive versus standard glycaemic therapy in patients with chronic kidney disease (CKD) (a) and non CKD (b).

Furthermore, insulin was used in higher doses by patients assigned to the intensive compared with the standard therapy group, as the study design recommended an increase in previous insulin dose by 10% if the target was not achieved. In our analysis, both insulin and oral hypoglycemic agents

were used more frequently in CKD compared with non-CKD patients. A large amount of evidence suggests that the incidence of adverse drug events is significantly higher in CKD compared with non-CKD patients.<sup>24</sup> A recent study in a community hospital shows that adverse drug events were



**Figure 5 | Cardiovascular and all-cause mortality stratified by intensive or standard treatment group and by chronic kidney disease (CKD) status.** Cardiovascular and all-cause mortality with intensive versus standard glycemetic control in patients without CKD (a, c) and with CKD (b, d).

**Table 3 | Hypoglycemic episodes requiring assistance with intensive versus standard glycemetic therapy in patients with and without CKD**

| CKD at baseline   | Glycemia arm | Events | Percent | Annual incidence |
|---|--------------|--------|---------|------------------|
| <b>Overall percent and annual incidence of hypoglycemia requiring assistance</b>        |              |        |         |                  |
| Non-CKD   | Standard     | 172    | 5.2     | 1.1              |
| Non-CKD   | Intensive    | 500    | 15.3    | 3.5              |
| CKD   | Standard     | 165    | 9.1     | 2.0              |
| CKD   | Intensive    | 398    | 21.5    | 5.3              |
| <b>Pre-transition percent and annual incidence of hypoglycemia requiring assistance</b> |              |        |         |                  |
| Non-CKD   | Standard     | 145    | 4.4     | 1.2              |
| Non-CKD   | Intensive    | 474    | 14.5    | 4.2              |
| CKD   | Standard     | 129    | 7.1     | 2.0              |
| CKD   | Intensive    | 375    | 20.2    | 6.1              |

Abbreviation: CKD, chronic kidney disease.  
 P-value for interaction between CKD status and glycemetic arm is 0.1811.  
 P-value for interaction between CKD status and glycemetic arm is 0.3305.

common in CKD patients; half of them were serious and some of them were life-threatening, and most of them were potentially preventable.<sup>25</sup> In our study, there were no

significant differences in all-cause and cardiovascular mortality between intensive and standard glycemetic control in patients without CKD. This finding is clinically relevant and should be reassuring to clinicians who desire to pursue tight glycemetic control in some patients. Previous efforts to identify clinically meaningful predictors of increased mortality with tight glycemetic control have not been adequately successful. These factors include hypoglycemia, HgA1c, drug interactions, and even play of chance.<sup>16,26-30</sup> An exploratory analysis assessing the association between baseline characteristics and increased mortality with intensive therapy in the main ACCORD study was similarly discouraging.<sup>31</sup> To our knowledge, this is the first report to show that aggressive glucose control is detrimental in patients with mild and moderate CKD. It is of paramount importance, therefore, that CKD status be established in all newly diagnosed and existing diabetic patients and be taken into account in tailoring hypoglycemic therapy. The strengths of this study are several and include the large sample size, the high quality of the data, and a representative sample of patients with CKD. The prospective nature of the study and the meticulous follow-up make the data more consistent and reliable.

Moreover, the thorough monitoring of an extensive list of baseline risk factors allows for appropriate adjustments and accurate evaluations. There are a few limitations as well. The analysis is *post-hoc* and as such hypothesis generating. Patients with advanced CKD (Stage IV and V) were not included, and study findings are not generalizable. In conclusion, this *post-hoc* analysis of the ACCORD data uncovered two important findings: (a) patients with moderate or even mild CKD have two to three times higher cardiovascular risk; and (b) intensive glycemic control in patients with mild-to-moderate CKD results in substantial increase of cardiovascular and all-cause mortality. As the management of diabetic patients with CKD is difficult and intensive glucose lowering appears to be inappropriate, new approaches are likely to be required if we are to alter the cardiovascular outcome of this patient population.

## MATERIALS AND METHODS

### Patient population and study design

ACCORD was a randomized trial of 10,251 high-risk patients with diabetes mellitus type 2. The rationale and design of the study have been published previously in detail.<sup>15</sup> In brief, ACCORD recruited participants who had type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more and who either were between the ages of 40 and 79 years and had cardiovascular disease or were between the ages of 55 and 79 years and had anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity). Key exclusion criteria included frequent or recent serious hypoglycemic events, unwillingness to do home glucose monitoring or inject insulin, a body mass index (the weight in kilograms divided by the square of the height in meters) of more than 45, a serum creatinine level of more than 1.5 mg per deciliter (133  $\mu$ mol per liter), or other serious illness. All 10,251 patients were randomly assigned to receive comprehensive intensive therapy targeting a glycated hemoglobin level of <6.0% or to receive standard therapy targeting a level of 7.0–7.9%. A double two-by-two factorial design was used to further randomize participants; 4,733 patients were randomly assigned to lower their blood pressure by receiving either intensive therapy (systolic blood-pressure target, <120 mm Hg) or standard therapy (systolic blood-pressure target, <140 mm Hg). In addition, 5,518 patients were randomly assigned to receive either fenofibrate or placebo while maintaining good control of low-density lipoprotein cholesterol with simvastatin.<sup>32,33</sup> Written informed consent was granted by all study participants, and the protocol was approved by a review panel at the NHLBI and the IRB or ethics committee of each participating center, and the study was performed in accordance with the Helsinki declaration principles.

### CKD definition

The Modification of Diet in Renal Disease formula was used to calculate the eGFR. CKD was defined according to the 2013 National Kidney Foundation—Kidney Disease Outcomes Quality Initiative five-stage classification system.<sup>7</sup> In particular, Stage I CKD was defined as eGFR  $\geq$ 90 ml/min/1.73 m<sup>2</sup> and urine albumin/creatinine ratio  $\geq$ 30  $\mu$ g/mg; Stage II CKD was defined as eGFR between 60 and 89 ml/min/1.73 m<sup>2</sup> and urine albumin/creatinine ratio  $\geq$ 30  $\mu$ g/mg; Stage III was defined as eGFR between 30 and 59 ml/min/1.73 m<sup>2</sup>

with or without albuminuria. Mild CKD included patients with Stage I and II, and moderate CKD included patients with Stage III CKD. Patients with Stage IV and V CKD were excluded from the ACCORD trial.

### Outcomes

The primary outcome for the study was the composite of the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Several secondary outcomes were prespecified, including all-cause and cardiovascular mortality, nonfatal myocardial infarction, nonfatal and fatal stroke, fatal and nonfatal congestive heart failure, revascularization, and major coronary disease events.<sup>13</sup>

### Statistical analysis

For Tables 1 and 2, continuous variables are expressed as mean  $\pm$  s.d. When the distribution was highly skewed the median was used, and the interquartile range is reported. Categorical variables are reported as percentages. Baseline characteristics between CKD and non-CKD patients as well as intensive versus standard therapy in each group were compared using  $\chi^2$  and two-sample *t*-tests. Fisher's exact test was used to compare the incidence of key safety outcomes.

Cox proportional hazard models were used for the analyses of primary and secondary outcomes in the intensive versus standard glycemic control groups and according to the presence or not of CKD. Two-sided *P*-values were obtained from likelihood ratio tests from Cox proportional hazard regression analyses.

Event rates are expressed as the percentage of events per follow-up year, taking into account censoring of follow-up data. Kaplan–Meier estimates were used to obtain the proportion of patients who had an event during follow-up.

Cox models contained a term representing study group assignments plus terms accounting for the following prespecified stratification variables: assignment to either the blood-pressure trial or the lipid trial, assignment to the intensive blood pressure intervention in the blood-pressure trial, assignment to receive fibrate in the lipid trial, the seven clinical-center networks, the presence or absence of a previous cardiovascular event, and the following baseline covariates (cardiovascular history, clinical-center network, age (years), female (yes/no), body mass index (kg/m<sup>2</sup>), HbA1c %, systolic blood pressure, smoking status (yes/no), insulin use (yes/no), and anti-hypertensive use (yes/no)).

Subgroup analyses for the consistency of the effects among subgroups of study participants were performed using interaction tests between subgroups and therapy effects.

No adjustments were made for multiple testing. Nominal *P*-values are reported throughout as simple guides to possible associations. All analyses were performed at a central coordinating center using SAS 9.3 software (SAS Institute, Cary, NC).

### DISCLOSURE

All the authors declared no competing interests.

### ACKNOWLEDGMENTS

Funding: the National Heart, Lung and Blood Institute. TRIAL REGISTRATION clinicaltrials.gov identifier: NCT00000620. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## REFERENCES

1. De Boer IH, Rue TC, Hall YN *et al.* Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011; **305**: 2532–2539.
2. Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038–2048.
3. Go AS, Chertow GM, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305.
4. Roderick PJ, Atkins RJ, Smeeth L *et al.* CKD and mortality risk in older people: a community-based population study in the United Kingdom. *Am J Kidney Dis* 2009; **53**: 950–960.
5. Matsushita K, van der Velde M, Astor BC *et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073–2081.
6. van der Velde M, Matsushita K, Coresh J *et al.* Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; **79**: 1341–1352.
7. KDIGO. 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013; **3**: S1–S150.
8. So W, Kong A, Ma R *et al.* Glomerular filtration rate, cardiorenal endpoints, and all-cause mortality in type 2 diabetic patients. *Diabetes Care* 2006; **29**: 2046–2052.
9. Bruno G, Merletti F, Bargerò G *et al.* Estimated glomerular filtration rate, albuminuria and mortality in type 2 diabetes: the Casale Monferrato study. *Diabetologia* 2007; **50**: 941–948.
10. Targher G, Zoppini G, Chonchol M *et al.* Glomerular filtration rate, albuminuria and risk of cardiovascular and all-cause mortality in type 2 diabetic individuals. *Nutr Metab Cardiovasc Dis* 2011; **21**: 294–301.
11. Yokoyama H, Araki S, Haneda M *et al.* Chronic kidney disease categories and renal cardiovascular outcomes in Type 2 diabetes without prevalent cardiovascular disease: a prospective cohort study. *Diabetologia* 2012; **55**: 1911–1918.
12. Ninomiya T, Perkovic V, de Galan BE *et al.* Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol* 2009; **20**: 1813–1821.
13. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–2559.
14. Patel A, MacMahon S, Chalmers J *et al.* The ADVANCE Collaborative Group Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560–2572.
15. Duckworth W, Abraira C, Moritz T *et al.* Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129–139.
16. Lachin JM. Point: intensive glycemic control and mortality in ACCORD—a chance finding? *Diabetes Care* 2010; **33**: 2719–2721.
17. Weiner DE, Tighiouart H, Amin MG *et al.* Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004; **15**: 1307–1315.
18. Vanholder R, Massy Z, Argiles A *et al.* Chronic kidney disease as a cause of cardiovascular morbidity and mortality. *Nephrol Dial Transplant* 2005; **20**: 1048–1056.
19. Kannel WB, Stampfer MJ, Castelli WP *et al.* The prognostic significance of proteinuria: the Framingham study. *Am Heart J* 1985; **108**: 1347–1352.
20. Shurraw S, Hemmelgarn B, Lin M *et al.* Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease. *Arch Intern Med* 2011; **171**: 1920–1927.
21. Moen MF, Zhan M, Hsu VD *et al.* Frequency of hypoglycaemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol* 2009; **4**: 1121–1127.
22. Snyder RW, Bernds JS. Use of insulin and oral hypoglycaemic medications in patients with diabetes mellitus and advanced kidney disease. *Semin Dial* 2004; **17**: 365–370.
23. Institute of Medicine of the National AcademiesIn: Aspden PA, Wolcott JA, Bootman JL, Cronenwett LR (eds)Committee on identifying and preventing medication errors: 'medication errors: incidence and cost'. *Preventing Medication Errors: Quality Chasm Series*. National Academies Press: Washington DC, Washington, USA, 2006; 105–142.
24. Gabardi S, Abramson S. Drug dosing in chronic kidney disease. *Med Clin North Am* 2005; **89**: 649–687.
25. Hug BL, Witkowski DJ, Sox CM *et al.* Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney. *Kidney Int* 2009; **76**: 1192–1198.
26. Cryer PE. Death during intensive glycemic therapy of diabetes: mechanisms and implications. *Am J Med* 2011; **124**: 993–996.
27. Bonds DE, Miller ME, Bergenstal RM *et al.* The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010; **340**: b4909.
28. Seaquist ER, Miller ME, Bonds DE *et al.* The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. *Diabetes Care* 2012; **35**: 409–414.
29. Riddle MC, Ambrosius WT, Brillon DJ *et al.* Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010; **33**: 983–990.
30. Pop-Busui R, Evans GW, Gerstein HC *et al.* Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010; **33**: 1578–1584.
31. Calles-Escandón J, Lovato LC, Simons-Morton DG *et al.* Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010; **33**: 721–727.
32. ACCORD Study Group, Cushman WC, Evans GW *et al.* Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1575–1585.
33. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1563–1574.