


Long-Term Effects of Intensive Glycemic and Blood Pressure Control and Fenofibrate Use on Kidney Outcomes

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Abstract

Background and objectives In people with type 2 diabetes, aggressive control of glycemia, BP, and lipids have resulted in conflicting short-term (<5 years) kidney outcomes. We aimed to determine the long-term kidney effects of these interventions.

Design, setting, participants, & measurements The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a multifactorial intervention study in people with type 2 diabetes at high risk for cardiovascular disease ($n=10,251$), to examine the effects of intensive glycemic control (hemoglobin A1c <6.0% versus 7%–7.9%), BP control (systolic BP <120 mm Hg versus <140 mm Hg) or fenofibrate versus placebo added to simvastatin on cardiovascular events and death. The glycemia trial lasted 3.7 years and participants were followed for another 6.5 years in ACCORDION, the ACCORD Follow-On Study. The *post hoc* primary composite kidney outcome was defined as incident macroalbuminuria, creatinine doubling, need for dialysis, or death by any cause. Cox proportional hazards regression estimated the effect of each intervention on the composite outcome and individual components. In secondary outcome analyses, competing risk regression was used to account for the risk of death in incident kidney outcomes. Analyses were adjusted for sociodemographics, randomization groups, and clinical factors.

Results There were 988 cases of incident macroalbuminuria, 954 with doubling of creatinine, 351 requiring dialysis, and 1905 deaths. Hazard ratios (HRs) for the composite outcome with intensive glycemic, BP control, and fenofibrate use compared with standard therapy were 0.92 (95% confidence interval [95% CI], 0.86 to 0.98), 1.16 (95% CI, 1.05 to 1.28), and 1.16 (95% CI, 1.06 to 1.27). Multivariable, secondary outcome analyses showed that in the glycemia trial, only macroalbuminuria was significantly decreased (HR, 0.68; 95% CI, 0.59 to 0.77). In the BP and lipid trials, only creatinine doubling was affected (HR, 1.64; 95% CI, 1.30 to 2.06 and HR, 2.00; 95% CI, 1.61 to 2.49, respectively).

Conclusions In people with type 2 diabetes at high risk for cardiovascular disease, intensive glycemic control may result in a long-term reduction in macroalbuminuria; however, intensive BP control and fenofibrates may increase the risk for adverse kidney events.

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Introduction

Diabetic kidney disease (DKD) is the leading cause of ESKD, resulting in an annual fiscal burden of billions to society and a marked decrease in quality of life for the individual (1,2). The vast majority of patients with DKD do not develop ESKD because of the very high incidence of death in this population (3,4). The risks for ESKD and cardiovascular events and death increase with rising albuminuria and declining eGFR (5,6). The reverse is also applicable, as the presence of cardiovascular disease increases the incidence of creatinine doubling and ESKD (7,8). Although patients with diabetes and cardiovascular disease are at very high risk for progressive kidney disease and death, the optimal management of these patients is still unclear.

For decades, clinical trials have sought the ideal clinical targets for glycemic and BP control and lipid therapies to provide reduction in kidney risk. Historic trials led to the commonly accepted notion that reduction in hemoglobin A1c (HbA1c) <7% and BP <140/90 mm Hg decrease the risk for progression of DKD (9,10). More recent trials have examined the kidney effects of further reductions in HbA1c to <6%–6.5% and systolic BP to <120 mm Hg. Although these trials have consistently found reductions in albuminuria, results are conflicting with regard to creatinine doubling and ESKD (11–15). The effect of lipid therapies on DKD have been more consistent: statin medications do not appear to affect DKD progression but are recommended for cardiovascular protection in

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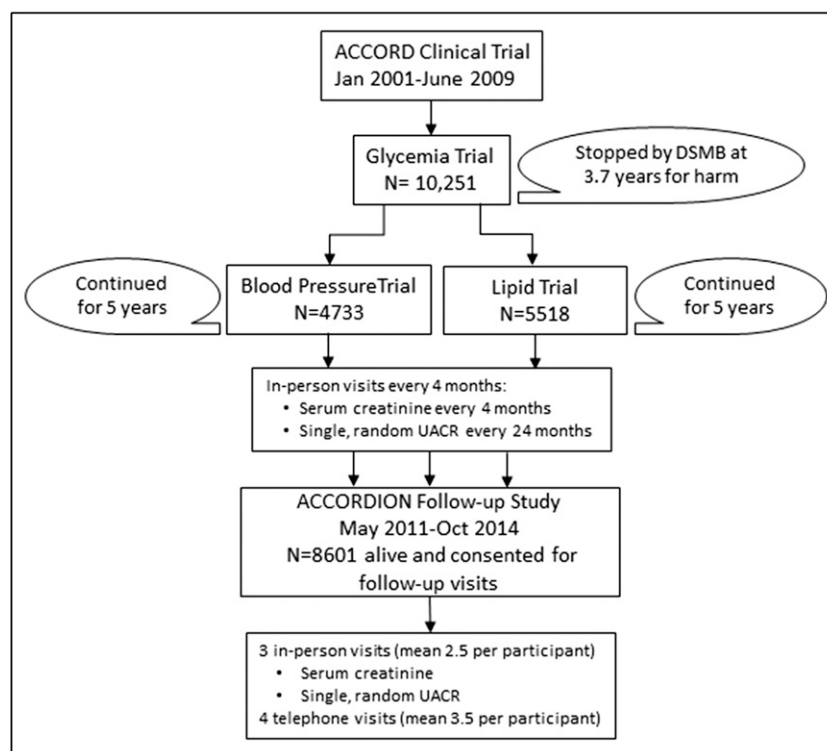


Figure 1. | Schematic of the ACCORD and ACCORDION study designs and surveillance for kidney outcomes. DSMB, Data Safety Monitoring Board; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACCORDION, ACCORD Follow-On Study.

this high-risk population (16); fibrates have been found to cause a rise in creatinine that is reversible with drug withdrawal and so are felt to not increase the risk for long-term kidney events (17–19).

The majority of these studies were conducted over a relatively short time period. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial continued to monitor consenting participants in the ACCORD follow-on trial (ACCORDION) for several years after trial completion, for a total mean follow-up of 7.7 years. In this *post hoc* follow-up study, we aimed to determine effects of intensive glycemic and BP control and fenofibrate use on long-term kidney outcomes.

Materials and Methods

Study Population

The full protocol for the main ACCORD trial has been previously published (20,21). Inclusion criteria included (1) type 2 diabetes and HbA1c \geq 7.5%; (2) age 40–79 years and known cardiovascular disease; or (3) age 55–79 years with anatomic evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for cardiovascular disease (dyslipidemia, hypertension, obesity, or current smoker status). Exclusion criteria included body mass index >45 kg/m² and serum creatinine >132.6 μ mol/L (1.5 mg/dl). Potential participants also had to be eligible for the BP and/or lipid trials, each of which had additional criteria as previously published (22,23). There were 77 clinical centers in the United States and Canada; ethics committees at each center approved the

protocol, which adhered to the Declaration of Helsinki. All participants provided written, informed consent. The parent ACCORD study is registered with Clinicaltrials.gov under identifier NCT00000620. Individual deidentified participant data including the protocols for ACCORD and ACCORDION, the data dictionary, manual of procedures, and forms are currently available at <https://biolincc.nhlbi.nih.gov/studies/accord/>.

Study Design, Measurements, and Outcomes

The ACCORD trial was a double two-by-two factorial, parallel treatment trial (see Figure 1) in which patients were randomized to one of two glycemic treatment arms, with the intensive arm targeting HbA1c $<$ 6.0% and the standard arm targeting HbA1c 7.0%–7.9%. On the basis of eligibility criteria, half of the participants were allotted to a lipid intervention consisting of randomization to fenofibrate versus placebo, both in addition to statin therapy. The other half were allotted to one of two randomly assigned BP treatment arms, with the intensive arm targeting systolic BP $<$ 120 mm Hg and the standard arm targeting systolic BP $<$ 140 mm Hg. The ACCORD glycemia trial lasted for a mean of 3.7 years; it was stopped early because of the Data Safety Monitoring Board finding of excess mortality in the intensive glucose-lowering group (24). Participants were subsequently managed according to the standard glucose protocol and monitored for an additional 17 months while the BP and lipid trials were completed.

All surviving participants who could be contacted were invited to participate in the follow-up study (ACCORDION) for a mean period of 7.7 years (median 5.6 years) from the time of initial randomization (see Figure 1) (25). During the

ACCORDION trial follow-up period, participants were seen or contacted for surveillance of cardiovascular outcomes, death, and dialysis. The chronicity and indications for dialysis were not obtained. Surveillance for deaths in the United States was supplemented for participants withdrawn or lost to follow-up using the National Death Index. Serum creatinine and urine albumin-to-creatinine (UACR) were measured centrally on two occasions, separated by approximately 30 months. eGFR was calculated using the CKD Epidemiology Collaboration Creatinine Equation (26).

All participants from the ACCORD trial with any surveillance postrandomization for kidney outcomes were included in analyses. Participants without surveillance for kidney outcomes ($n=112$) either died, withdrew, or were lost to follow-up. We defined the primary composite kidney outcome as incident macroalbuminuria (UACR >300 $\mu\text{g}/\text{mg}$), creatinine doubling, self-reported need for dialysis, or death from any cause. Secondary outcomes included individual end points comprising the primary outcome. Participants with overt albuminuria were excluded from analyses of incident macroalbuminuria but were maintained in analyses of the composite outcome if they sustained one of the other outcomes (incident doubling of creatinine or ESKD).

Statistical Analyses

All analyses used an intention-to-treat approach. The probability of reaching the composite kidney outcome was calculated using the cumulative incidence function. Cox proportional hazards regression estimated the effect of each intervention on the primary composite kidney outcome. In secondary outcome analyses of the individual (nonfatal) composite outcome components, a competing risk regression was used to estimate the subdistribution hazard ratio (SHR), which accounts for the competing risk of death (27). Multivariable regression analyses included baseline values for age, sex, ethnicity, study site, randomization to tight BP group, randomization to fenofibrate group, previous cardiovascular event, eGFR, UACR, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, HbA1c, and systolic BP as covariates. Estimates of treatment assignment in each subtrial (intensive versus standard control in BP or fibrate versus placebo in lipid) were performed using contrast statements in proportional hazards regression models.

Differential effects of treatment arm assignment during active treatment versus posttrial follow-up were examined for the primary kidney outcome using two-way interactions between a time-varying indicator event occurrence before or after the end of the active intervention period and treatment arm assignment. Interaction terms were also explored for sex, ethnicity, and baseline CKD status (defined as macroalbuminuria or eGFR <60 ml/min per 1.73 m^2). If the interaction term was significant to $P<0.1$, we performed stratified analyses. For all other analyses, we utilized a nominal P value of <0.05 , without correction for multiple testing. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Baseline characteristics of participants, stratified by randomization in the glycemia trial, are displayed in Table 1.

The presence of any CKD was common, with 37% of participants having eGFR <60 ml/min per 1.73 m^2 and/or UACR ≥ 30 $\mu\text{g}/\text{mg}$. In those with CKD, the severity was mild in the vast majority, with 10% having an eGFR <60 ml/min per 1.73 m^2 and 5% with macroalbuminuria.

Mean follow-up for kidney-related outcomes was 7.7 (median 5.7 years) for the glycemic intervention. Among 10,139 participants with at least some follow-up surveillance for kidney-related outcomes, 7076 (69%) either experienced the primary kidney outcome during the ACCORD trial or had assessment for kidney outcomes during the ACCORDION post-trial follow-up. One third ($n=3410$) of participants reached the primary composite kidney outcome. There were 988 cases of incident macroalbuminuria, 954 with doubling of creatinine, 351 participants requiring dialysis, and 1905 deaths. Of the 3410 participants with the primary composite kidney outcome, two thirds ($n=2249$) had two or more components of the composite outcome. Because the need for dialysis was not adjudicated, some may have been due to AKI requiring transient dialysis. The final serum creatinine was <2.0 mg/dl in 257 (73%) out of 351 participants self-reporting an occurrence of dialysis.

Figure 2, A–C illustrates the cumulative incidence for the composite outcome, stratified by treatment groups. Table 2 displays the univariable and multivariable results for the effects of the three treatment trials on the composite and secondary kidney outcomes. Randomization to the intensive glycemic control arm reduced the incidence of the composite kidney outcome (hazard ratio [HR], 0.92; 95% confidence interval [95% CI], 0.86 to 0.98) but this effect was primarily driven by a reduction in incident macroalbuminuria (SHR, 0.68; 95% CI, 0.59 to 0.77). *Post hoc* analysis for “probable maintenance dialysis” in the glycemia trial censored participants with a final serum creatinine <2.0 , yielding a univariable SHR of 0.85 (95% CI, 0.57 to 1.28).

Randomization to intensive BP control resulted in an increased risk for the composite kidney outcome (HR, 1.16; 95% CI, 1.05 to 1.28); however, doubling of serum creatinine was the only secondary outcome to be affected (SHR, 1.64; 95% CI, 1.30 to 2.06). Similar results were obtained *via* randomization to fenofibrate versus placebo (HR, 1.16; 95% CI, 1.06 to 1.27) with a strong effect from increased risk for doubling of serum creatinine (HR, 2.00; 95% CI, 1.61 to 2.49). *Post hoc* analyses for the composite kidney outcome excluding death in the definition did not significantly change the results.

Post hoc analyses for a differential glycemic intervention effect was marginally significant ($P=0.05$), whereas the test for a differential effect in the BP or lipid trials was significant ($P=0.01$). During active treatment, there was almost no difference in incidence of the primary kidney outcome between intensive and standard glycemic arms (HR, 0.99; 95% CI, 0.91 to 1.06), whereas in the post-trial follow-up, the observed incidence was reduced in intensive arm participants (HR, 0.83; 95% CI, 0.71 to 0.97). In the BP trial, an increased incidence of the primary kidney outcome in the intensive versus standard arm observed during the active trial period (HR, 1.12; 95% CI, 1.00 to 1.26) became larger during the post-trial follow-up (HR, 1.41; 95% CI, 1.11 to 1.79). Similarly, in the lipid trial, the increased incidence in the fibrate versus placebo arm during the

Table 1. Characteristics of 10,139 participants of the ACCORD study at baseline according to randomization to intensive versus standard glycemic control

Baseline Characteristics ^a	Intensive Therapy		Standard Therapy	
	N	Mean±SD or N (%)	N	Mean±SD or N (%)
Age, yr	5074	62±7	5065	62±7
Women, %	5074	1959 (39%)	5065	1940 (38%)
Non-Hispanic white, %	5074	3266 (64%)	5065	3305 (65%)
Glycated hemoglobin, %	5066	8.3±1.1	5053	8.3±1.1
BP, mm Hg	5050		5046	
Systolic		136±17		137±17
Diastolic		75±11		75±11
Cholesterol, g/dl	5048		5035	
Total		183±42		183±41.6
LDL		105±34		105±34
HDL		42±12		42±12
Triglycerides		191±148		190±149
Body mass index, kg/m ²	5071	32±6	5062	32±6
Waist circumference, cm	5019	107±14	5021	107±14
Previous cardiovascular event, %	5074	1804 (36%)	5065	1755 (35%)
Baseline CKD status, %^b	5042		5022	
No CKD		3173 (63%)		3163 (63%)
Stage 1		626 (12%)		641 (13%)
Stage 2		714 (14%)		713 (14%)
Stage 3a		425 (8%)		419 (8%)
Stage 3b		98 (2%)		92 (2%)
Stage 4		6 (0.1%)		0
Baseline UACR, %	5042		5022	
≥30 μg/mg		1247 (25%)		1225 (24%)
≥300 μg/mg		226 (5%)		241 (5%)
≥1000 μg/mg		97 (2%)		99 (2%)
eGFR, ml/min per 1.73 m ² ^b	5074	83±17	5065	84±17
UACR, μg/mg ^c	5042	13.5 [6.8, 43.8]	5022	13.6 [6.8, 44.4]
ACEI/ARB use, %	5074	3428 (68%)	5065	3445 (68.0%)
Thiazolidinedione use, %	5074	986 (19%)	5065	976 (19%)

ACCORD, Action to Control Cardiovascular Risk in Diabetes; UACR, urine albumin-to-creatinine ratio; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

^aIncludes all ACCORD trial participants with at least some surveillance for primary outcome. Description of ACCORDION study population is available (43).

^beGFR was calculated using the CKD Epidemiology Collaboration Creatinine Equation. Stage 1 CKD: eGFR≥90 ml/min per 1.73 m² and UACR≥30 μg/mg; stage 2 CKD: eGFR 60–89 ml/min per 1.73 m² and UACR≥30 μg/mg; stage 3a CKD: eGFR 45–59 ml/min per 1.73 m²; stage 3b CKD: eGFR 30–44 ml/min per 1.73 m²; stage 4 CKD: eGFR 15–29 ml/min per 1.73 m².

^cData are presented as median [IQR].

active phase (HR, 1.16; 95% CI, 1.05 to 1.29) became larger during post-trial follow-up as well (HR, 1.36; 95% CI, 1.10 to 1.69).

There was evidence for effect modification by sex in the glycemia trial for the primary composite kidney outcome ($P=0.06$), incident macroalbuminuria ($P=0.02$), and dialysis outcomes ($P=0.04$), and in the BP and lipid trials for the primary composite kidney outcome, macroalbuminuria and dialysis ($P<0.1$). There was also evidence for effect modification by race in the BP and lipid trials for the primary composite kidney outcome ($P=0.01$), doubling of serum creatinine ($P<0.01$), and all-cause mortality ($P=0.01$). Results of the stratified analyses are shown in Tables 3–5.

Discussion

This long-term follow-up study of >10,000 individuals with type 2 diabetes at high risk for cardiovascular events provides further data against targeting intensive glycemic

and BP control or the use of fibrates in this population. Specifically, although intensive glycemic control ameliorated the risk for incident macroalbuminuria, there was a dearth of evidence to support an effect on creatinine doubling or incident dialysis. Moreover, we found probable harm from intensive BP control or fibrate use on these kidney outcomes.

Intensive Glycemic Control

To put these findings into context, it is important to review in-trial and long term follow-up results from the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), which provided clear evidence that improved glycemic control significantly reduced the risk for progression of both albuminuria and worsening eGFR (9,28–30). Although these landmark studies transformed treatment of diabetes and demonstrated an enduring effect of controlled glycemia on microvascular outcomes over decades, it is important to underscore the trial designs and characteristics of

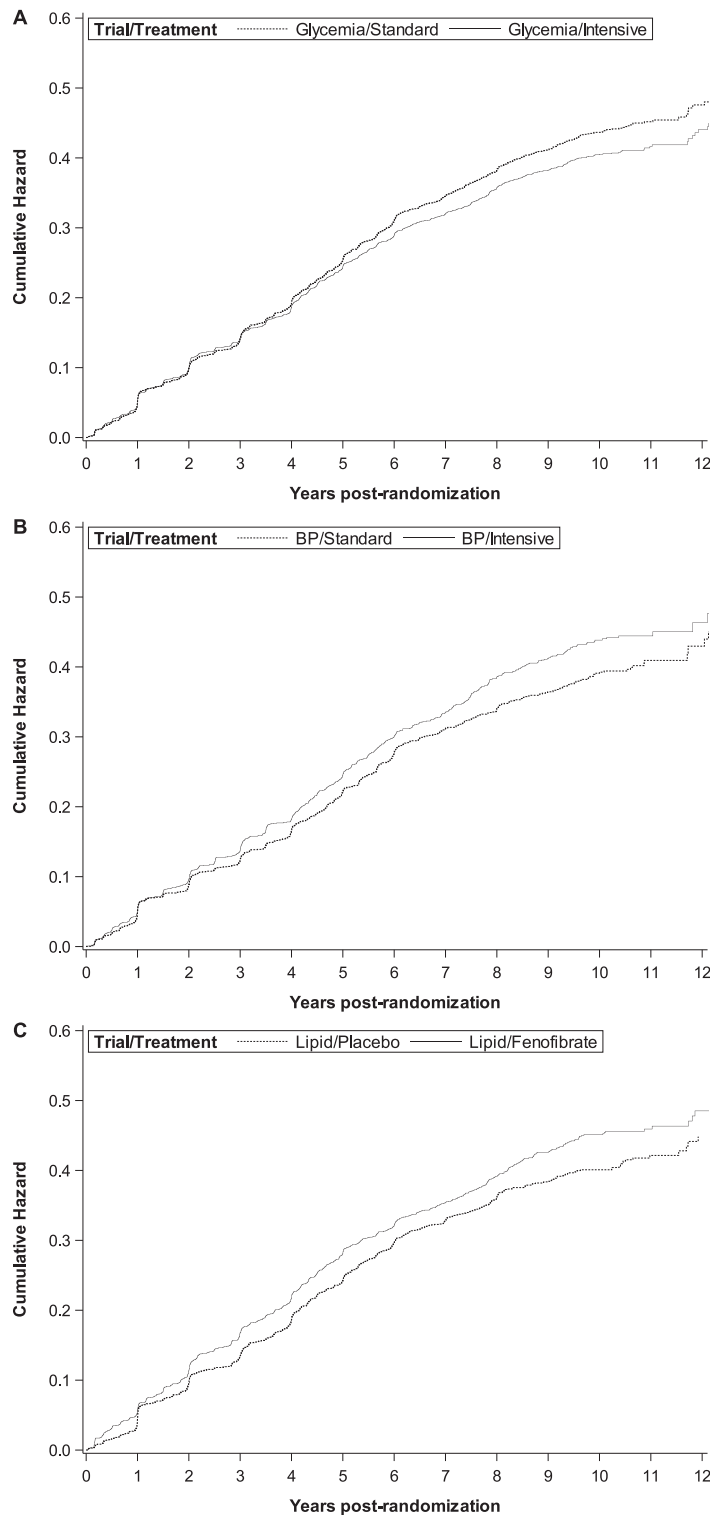


Figure 2. | Cumulative incidence of the primary composite kidney outcome (incident macroalbuminuria [UACR>300 μ g/mg], doubling of creatinine, incident dialysis or all-cause mortality) according to randomization arm. (A) Glycemia trial (HbA1c: intensive arm <6.0% versus standard arm 7.0%–7.9%) with the intensive arm showing reduced risk, (B) BP trial (systolic BP: intensive arm <120 mm Hg versus standard arm <140 mm Hg) with the intensive arm showing higher risk, and (C) lipid trial (fenofibrate versus placebo) with the fenofibrate arm showing higher risk.

Table 2. Effects of intensive glycemic control, BP control, and fenofibrate on long-term kidney outcomes in 10,139 participants of the ACCORD study

Outcome	Intensive Glycemic Control			Intensive BP Control			Fenofibrate Treatment		
	n=10,139 (5074 Intensive; 5065 Standard)			n=4682 (2345 Intensive; 2337 Standard)			n=5457 (2736 Fibrate; 2721 Placebo)		
	Event Number	Univariable HR/SHR (95% CI)	Multivariable ^a HR/SHR (95% CI)	Event Number	Univariable HR/SHR (95% CI)	Multivariable ^a HR/SHR (95% CI)	Event Number	Univariable HR/SHR (95% CI)	Multivariable ^a HR/SHR (95% CI)
Composite kidney outcome	1652 Int 1759 Std	0.92 (0.86 to 0.99) ^d	0.92 (0.86 to 0.98) ^d	780 Int 721 Std	1.15 (1.04 to 1.23) ^d	1.16 (1.05 to 1.28) ^d	1007 Feno 903 Plac	1.15 (1.05 to 1.26) ^d	1.16 (1.06 to 1.27) ^d
Macroalbuminuria ^{b,c}	421 Int 567 Std	0.72 (0.64 to 0.82) ^d	0.68 (0.59 to 0.77) ^d	212 Int 219 Std	1.00 (0.83 to 1.21)	0.97 (0.79 to 1.17)	304 Feno 253 Plac	1.19 (1.00 to 1.40)	1.11 (0.93 to 1.33)
Doubling of creatinine ^c	490 Int 464 Std	1.05 (0.93 to 1.20)	1.09 (0.94 to 1.23)	245 Int 170 Std	1.52 (1.25 to 1.85) ^d	1.64 (1.30 to 2.06) ^d	344 Feno 195 Plac	1.83 (1.54 to 2.18) ^d	2.00 (1.61 to 2.49) ^d
Dialysis ^c	161 Int 190 Std	0.84 (0.68 to 1.04)	0.92 (0.72 to 1.16)	72 Int 81 Std	0.91 (0.67 to 1.25)	0.90 (0.63 to 1.28)	98 Feno 100 Plac	0.97 (0.74 to 1.29)	1.09 (0.80 to 1.50)
All-cause mortality	952 Int 953 Std	1.00 (0.92 to 1.09)	1.00 (0.91 to 1.10)	406 Int 403 Std	1.03 (0.90 to 1.18)	1.01 (0.88 to 1.17)	537 Feno 559 Plac	0.95 (0.84 to 1.06)	0.96 (0.85 to 1.08)

ACCORD, Action to Control Cardiovascular Risk in Diabetes; HR, hazard ratio; SHR, subhazard ratio; 95% CI, 95% confidence interval; Int, intensive; Std, standard; Feno, fenofibrate; Plac, placebo.

^aMultivariable analyses are adjusted for: baseline age, sex, ethnicity, study site, randomization to tight BP group, randomization to fenofibrate group, previous cardiovascular event, eGFR, urine albumin-to-creatinine ratio, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, hemoglobin A1c, and systolic BP.

^bDenominators for macroalbuminuria outcome: 4410 intensive glycemic, 4431 standard glycemic; 2065 intensive BP, 2040 standard BP; 2388 fenofibrate, 2348 placebo.

^cModels for nonfatal components of the composite outcome include death as a competing risk.

^dStatistically significant results.

these study populations. DCCT participants had type 1 diabetes and a mean age of 26 years; HbA1c was 7% for the intensive treatment group versus 9% for the conventional group. The UKPDS studied older people (mean age 54 years) with type 2 diabetes but excluded congestive heart failure or history of multiple vascular events, and HbA1c was 7.0% in the intensive group compared with 7.9% in the conventional group. In contrast, ACCORD trial participant mean age was 63 years, most had a history of macrovascular disease, and HbA1c was 6.4% for the intensive group versus 7.5% for the conventional group. Consideration of these differences dispel much of the quandary over the differences in findings between these distinct patient populations.

Discrepant findings from the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial, a cohort more similar to that of the ACCORD trial, are more difficult to explain (11,31). Although the ADVANCE trial found that intensive glycemia conveyed a decrease in incident macroalbuminuria (HR, 0.70; 95% CI, 0.57 to 0.85), an estimate very similar to our results, they also found a reduced risk for ESKD after a mean of 9.9 years (HR, 0.54; 95% CI, 0.34 to 0.85). A third trial (97% men), the Veterans Affairs Diabetes Trial (VADT), did not find an independent effect of intensive glycemic control on either progressive albuminuria or decline in eGFR or ESKD (12,32); however, the intensive control group did have a slightly greater (albeit statistically insignificant) percent with eGFR > 60 ml/min per 1.73 m² (32). An important distinction between these three cohorts is the difference in severity of diabetes. Participants in the ADVANCE study had a baseline hemoglobin A1c of 7.2% versus 8.1% and 9.4% in the ACCORD and VADT trials, respectively (33). Only 1.5% of participants in the

ADVANCE trial required insulin at baseline, versus 35% in the ACCORD trial and 52% in VADT.

Intensive BP Control

Randomized trials searching for the ideal BP goal for patients with DKD have also generated inconsistent results. Although it is broadly accepted that macro- and microvascular risk is reduced with BPs <140/90 mm Hg (34,35), conflicting findings exist with reductions below this threshold (14,36,37). During the ACCORD study period, targeting a systolic BP to <120 mm Hg yielded a reduction in incident macroalbuminuria 4.7 years after randomization, but only in participants with baseline microalbuminuria, and had no effect on the composite outcome of doubling of serum creatinine, elevated serum creatinine ≥ 3.2 mg/dl, or need for dialysis (14). Our follow-up study of these participants 7.7 years after randomization demonstrates no benefit to sustained incident macroalbuminuria, and more importantly, a harm to the composite kidney outcome, predominantly carried by doubling of creatinine. Moreover, a separate analysis of ACCORD trial data found that in participants with baseline CKD (UACR ≥ 30 μ g/mg or eGFR < 60 ml/min per 1.73 m²), randomization to intensive BP control did not yield significant benefit to cerebrovascular outcomes as it did in participants without baseline CKD (38).

In line with our findings are secondary kidney outcomes from the Systolic Blood Pressure Intervention Trial, a study of similar design to the ACCORD BP trial, conducted in participants without diabetes (39). Although randomization to systolic BP <120 mm Hg did not significantly affect the composite or individual kidney outcomes in participants with baseline CKD, in those without baseline CKD there was an increased risk for $\geq 30\%$ decline in eGFR to

Table 3. Incidence of long-term kidney outcomes according to initial randomization to intensive glycemic control (hemoglobin A1c <6.0%), stratified by sex

Outcome ^a	Women		Men	
	n=3825 (1917 Intensive; 1908 Standard)		n=6146 (3075 Intensive; 3071 Standard)	
	Event Number	HR/SHR (95% CI)	Event Number	HR/SHR (95% CI)
Composite outcome	579 Int 589 Std	1.0 (0.89 to 1.12)	1036 Int 1131 Std	0.88 (0.81 to 0.95) ^c
Macroalbuminuria ^b	150 Int 170 Std	0.83 (0.66 to 1.05)	258 Int 394 Std	0.61 (0.51 to 0.71) ^c
Dialysis	67 Int 57 Std	1.11 (0.76 to 1.62)	94 Int 129 Std	0.83 (0.61 to 1.13)

HR, hazard ratio; SHR, subhazard ratio; 95% CI, 95% confidence interval; Int, intensive; Std, standard.

^aHRs and 95% CIs are for fully adjusted multivariable analyses.

^bDenominators for macroalbuminuria outcome among women: 1664 intensive, 1689 standard; among men: 2688 intensive, 2704 standard.

^cStatistically significant results.

<60 ml/min per 1.73 m² (HR, 3.49; 95% CI, 2.44 to 5.10). There was also a three-fold increase in AKI requiring hospitalization in the entire cohort (*P*<0.001). Also in support of our results was the lack of significant benefit of intensive BP control to the primary outcome in the subgroup with baseline CKD (39).

Fenofibrate

The ACCORD lipid trial and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Studies have both documented a reversible increase in serum creatinine with fibrates over a short-term period (17,19). In a washout substudy of FIELD participants, there was a statistically significant smaller decline in eGFR from baseline to an 8-week postwashout visit in the fibrate versus placebo groups (1.9 versus 6.9 ml/min per 1.73 m², respectively) (17).

However, this change in eGFR occurred over a mean treatment time of 5 years, calling into question the clinical significance of this change when viewed as an annual rate of change. The ACCORD lipid trial also found that withdrawal of fibrate therapy resulted in a reduction in creatinine after 51 days (19). Although there are probably reversible physiologic effects from fibrates on serum creatinine levels, there may also be long-term, irreversible consequences for DKD. Our finding that the effect of fibrates on the composite kidney outcome became larger during the post-trial follow-up period further substantiates this notion.

Strengths and Limitations

A problematic issue in our study was the self-report of “need for dialysis” without adjudication or information regarding whether this need was sustained. Because of

Table 4. Incidence of long-term kidney outcomes according to initial randomization to intensive BP control (systolic BP <120 mm Hg), stratified by sex and also by white race

Outcome ^a	Women		Men		White Race		Nonwhite Race	
	n=2191 (1089 Intensive; 1102 Standard)		n=2425 (1219 Intensive; 1206 Standard)		n=2808 (1382 Intensive, 1426 Standard)		n=3487	
	Event Number	HR/SHR (95% CI)	Event Number	HR/SHR (95% CI)	Event Number	HR/SHR (95% CI)	Event Number	HR/SHR (95% CI)
Composite kidney outcome	352 Int 300 Std	1.27 (1.09 to 1.49) ^c	417 Int 400 Std	1.07 (0.94 to 1.23)	503 Int 456 Std	1.11 (0.98 to 1.26)	266 Int 244 Std	1.26 (1.06 to 1.51) ^f
Macroalbuminuria ^b	86 Int 89 Std	0.86 (0.64 to 1.18)	126 Int 124 Std	1.04 (0.81 to 1.34)	—	—	—	—
Doubling of creatinine	—	—	—	—	169 Int 86 Std	2.13 (1.63 to 2.77) ^c	72 Int 70 Std	1.17 (0.84 to 1.63)
Dialysis	28 Int 34 Std	0.90 (0.52 to 1.56)	43 Int 44 Std	0.89 (0.55 to 1.45)	—	—	—	—
All-cause mortality	—	—	—	—	265 Int 282 Std	0.92 (0.78 to 1.09)	133 Int 114 Std	1.24 (0.97 to 1.59)

HR, hazard ratio; SHR, subhazard ratio; 95% CI, 95% confidence interval; Int, intensive; Std, standard; —, analysis not performed because interaction term was not significant.

^aHRs and 95% CIs are for fully adjusted multivariable analyses using contrast statements from models with participants from both subtrials.

^bDenominators for macroalbuminuria outcome among women: 965 intensive, 966 standard; among men: 1081 intensive, 1063 standard; among whites: 1249 intensive, 1274 standard; among nonwhites: 797 intensive, 755 standard.

^cStatistically significant results.

Table 5. Incidence of long-term kidney outcomes according to initial randomization to fenofibrate versus placebo (in addition to statin therapy), stratified by sex

Outcome ^a	Women		Men		White Race		Nonwhite Race	
	<i>n</i> =1634 (821 Fibrate, 813 Placebo)		<i>n</i> =3721 (1864 Fibrate, 1857 Placebo)		<i>n</i> =3676 (1858 Fibrate, 1818 Placebo)		<i>n</i> =1679 (827 Fibrate, 852 Placebo)	
	Event Number	HR/SHR (95% CI)	Event Number	HR/SHR (95% CI)	Event Number	HR/SHR (95% CI)	Event Number	HR/SHR (95% CI)
Composite kidney outcome	284 Fenofibrate 232 Placebo	1.32 (1.11 to 1.57) ^c	703 Fenofibrate 647 Placebo	1.10 (0.99 to 1.22)	680 Fenofibrate 629 Placebo	1.08 (0.97 to 1.20)	307 Fenofibrate 250 Placebo	1.36 (1.15 to 1.61) ^c
Macroalbuminuria ^b	88 Fenofibrate 57 Placebo	1.51 (1.07 to 2.14) ^c	212 Fenofibrate 190 Placebo	1.01 (0.82 to 1.24)	—	—	—	—
Doubling of creatinine	—	—	—	—	220 Fenofibrate 121 Placebo	1.82 (1.46 to 2.28) ^c	111 Fenofibrate 63 Placebo	2.08 (1.51 to 2.86) ^c
Dialysis	31 Fenofibrate 31 Placebo	1.03 (0.61 to 1.75)	67 Fenofibrate 69 Placebo	1.12 (0.76 to 1.66)	—	—	—	—
All-cause mortality	—	—	—	—	379 Fenofibrate 416 Placebo	0.88 (0.76, 1.01)	152 Fenofibrate 128 Placebo	1.26 (1.0, 1.60)

HR, hazard ratio; SHR, subhazard ratio; 95% CI, 95% confidence interval; Fenofibrate, fenofibrate; Placebo, placebo; —, analysis not performed because interaction term was not significant.

^aHRs and 95% CIs are for fully adjusted multivariable analyses using contrast statements from models with participants from both subtrials.

^bDenominators for macroalbuminuria outcome among women: 709 fenofibrate, 713 placebo; among men: 1645 fenofibrate, 1603 placebo; among whites: 1646 fenofibrate, 1587 placebo; among nonwhites: 708 fenofibrate, 729 placebo.

^cStatistically significant results.

study design constraints, we also analyzed doubling of serum creatinine using a single rather than multiple creatinine values. Although the in-trial protocol measured serum creatinine every 4 months in lipid trial participants, creatinine was only measured annually after the first year of follow-up in BP trial participants; furthermore, in the extension phase, it was only measured a maximum of three other occasions over no more than five additional years. Another limitation was the use of a single, random UACR (40), which can result in misclassification of microalbuminuria and a higher risk of a type I error (41). Strengths of the study include the large sample size, the randomized controlled design, and intention-to-treat analysis. In addition, the use of a competing risk approach allows for a less biased and more easily interpreted risk assessment for kidney outcomes, which are always associated with increased risk of death (42).

In summary, this study shows a benefit of intensive glycemic control primarily on incident macroalbuminuria, and an increased risk of harm from intensive BP control and fenofibrate therapy on sustained doubling of serum creatinine. It is important to consider the effect of intensive therapies on microvascular outcomes along with macrovascular outcomes. The original ACCORD trial and its extension phase, the ACCORDION trial, both demonstrated a lack of benefit from intensive glycemic control, intensive BP control, or fibrate use, on the risk for incident cardiovascular events and death in people with type 2 diabetes at high risk for cardiovascular disease. The lack of substantive benefit from these interventions on micro- and macrovascular outcomes, and now evidence of harm on kidney outcomes, should be considered when revising current guidelines particularly for BP control and lipid therapies.

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