Renal Function in Type 2 Diabetes with Rosiglitazone, Metformin, and Glyburide Monotherapy

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Summary

Background and objectives In ADOPT (A Diabetes Outcomes Prevention Trial), initial monotherapy with rosiglitazone provided more durable glycemic control than metformin or glyburide in patients with recently diagnosed type 2 diabetes. Herein, we examine differences in albumin excretion, renal function (estimated GFR), and BP over 5 years between treatment groups.

Design, setting, participants, & measurements A total of 4351 recently diagnosed, drug-naïve patients with type 2 diabetes were treated and followed for up to 5 years with rosiglitazone, metformin, or glyburide and were examined with periodic assessments of albumin/creatinine ratio (ACR), modification of diet in renal disease (MDRD)-estimated GFR, and BP.

Results The ACR rose slowly with metformin. It fell with rosiglitazone and less so with glyburide over the first 2 years, and then rose slowly over time. Estimated GFR (eGFR) with all therapies rose into the high normal range over the first 3 to 4 years, more so with rosiglitazone, and then declined, more so with glyburide. Systolic BP was stable over time, values with rosiglitazone being lower, and diastolic BP declined over time, more so with rosiglitazone than with metformin or glyburide. There was no difference among groups in the incidence of emergent albuminuria (ACR $\geq$30 mg/g), hypertension, or impaired eGFR ($<$60 ml/min per 1.73 m^2).

Conclusions Over a 5-year period, initial monotherapy with rosiglitazone retards the rise of ACR compared with metformin, preserves eGFR compared with glyburide, and lowers BP relative to both comparators.

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Introduction

Albuminuria increases the risk of renal and cardiovascular disease in diabetes and in essential hypertension, and of mortality in the general population (1). Owing to a log-linear relationship, albumin excretion rate (AER) levels in the upper normal range confer an increased risk of cardio-renal disease that further worsens exponentially as the AER rises into the categories of microalbuminuria and macroalbuminuria.

In both type 1 and type 2 diabetes, strict glycemic control significantly reduces the risk of developing albuminuria and retards its progression in patients with elevated AER (2–4). It is unclear, however, whether different antihyperglycemic agents have specific antialbuminuria effects independent of their blood glucose–lowering effects. Animal data and short-term studies in humans suggest that thiazolidinediones that have anti-inflammatory properties and affect levels of adipokines and cytokines may be more potent at lowering albuminuria and preventing its rise than other oral glucose-lowering agents (5–7).

ADOPT was a randomized, double-blind, clinical trial comparing the effect of initial monotherapy with the thiazolidinedione rosiglitazone, the biguanide metformin, and the sulfonylurea glyburide on glucose control in recently diagnosed type 2 drug-naïve diabetes patients over a median follow-up of 4 years (8,9). Rosiglitazone provided more durable glycemic control than did metformin or glyburide as assessed by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c). Herein, we examine the long-term effects of these three agents on albuminuria as measured by the albumin/creatinine ratio (ACR), estimated GFR (eGFR), and BP.

Materials and Methods

Study Design

ADOPT (ClinicalTrials.gov number, NCT00279045) randomly assigned 4351 patients in Europe and North America, 30 to 75 years of age, with $\leq$3 years of type 2 diabetes, FPG concentrations 7 to 10 mmol/L on diet and prior lifestyle modification therapy only to double-masked twice daily monotherapy with rosiglitazone (n = 1456), metformin (n = 1454), or glyburide (n = 1441) who received study medication (9). Patients with clinically significant liver disease, renal impairment (serum creatinine >1.3 mg/dl [114

μmol/L] for males or >1.2 mg/dl [106 μmol/L] for females), history of lactic acidosis, unstable or severe angina, known congestive heart failure, or uncontrolled hypertension (systolic BP [SBP]/diastolic BP [DBP] > 180/110 mmHg) were excluded (8). There were no exclusion criteria for urinary albumin or eGFR.

For FPG levels ≥7.8 mmol/L, the assigned therapy was titrated (double-masked) to a maximum of 8 mg/d of rosiglitazone, 2 g/d of metformin, and 15 mg/d of glyburide, with dose reductions for adverse events. The primary outcome was time to monotherapy failure on maximum-tolerated dose, defined as FPG >10 mmol/L on two successive occasions, or by independent adjudication (8).

Methods

Clinical, metabolic, and other outcome assessments were performed using standardized procedures at baseline and every 6 months until the patient reached monotherapy failure or withdrew from the study. Albumin and creatinine were collected at baseline, 6 months, 12 months, and annually thereafter. All assays were conducted by a central laboratory (8,9).

Urinary albumin was measured by rate nephelometry and urinary creatinine by the Jaffe reaction. The ACR was calculated as mg/g. Categories were defined as albuminuria (ACR ≥30 mg/g), microalbuminuria (30 < ACR < 300 mg/g), and macroalbuminuria (ACR ≥300 mg/g).

eGFR was estimated from serum creatinine (SCr) by the Modification of Diet in Renal Disease (MDRD) equation (10) and classified into categories of <60, 60 to 130, or >130 ml/min per 1.73 m^2. The MDRD equation was derived from North American patients and has not been validated for use in other ethnicities. No correction (*e.g.,* 1.21 for African Americans) was applied to 338 patients who were neither Caucasian nor African American. There was no difference among groups in the various ethnicities enrolled (8,9).

BP was measured on the patient's nondominant arm supported at heart level. In these and prior analyses, hypertension was defined as SBP ≥130 mmHg and/or DBP ≥85 mmHg, or a history of hypertension (9).

Statistical Methods

The intention-to-treat cohort comprised the 4127 patients who completed the first scheduled efficacy evaluation, of whom 1393 received rosiglitazone, 1397 metformin, and 1337 glyburide. Wilcoxon rank sum tests compared baseline quantitative variables between groups and contingency χ^2 tests compared qualitative variables (11).

Normal errors longitudinal linear models (12) estimated mean levels of variables over time within groups using all observations in all patients up to 5 years of follow-up. Analyses employed the natural log ACR and eGFR to better approximate a homoscedastic normal errors distribution and are presented as the geometric mean and the 95% asymmetric confidence limits obtained as exp(confidence limits on the log values).

The prespecified long-term treatment effects on outcomes were assessed at 4 years of follow-up (9), and the short-term effects by the mean change from baseline to 6 months. A random-effects model assessed the treatment effects on the mean rate of change over 6 to 60 months (13). The cumulative incidence of events over time was estimated using a modified Kaplan–Meier estimate and the Cox proportional hazards model assessed the relative hazard (relative risk) (14). Analyses adjusted for country, gender, and the baseline value of each measure.

The Hochberg procedure adjusted *P* values for two comparisons among groups (15). $P \leq 0.05$ (two-sided) was considered statistically significant.

Results

Baseline Characteristics

At baseline (Table 1), there were no significant differences between treatment groups. The overall geometric mean ACR was 9.5 mg/g; 84% of the patients had normal levels (ACR <30 mg/g), 16% had already developed albuminuria (ACR ≥30 mg/g), and 1.6% had macroalbuminuria (ACR ≥300 mg/g). The mean levels of SBP and DBP were 133 and 80 mmHg, respectively, and 78% of patients were hypertensive. The geometric mean eGFR was 97 ml/min per 1.73 m^2; 451 (10.4%) patients had an eGFR >130 ml/min per 1.73 m^2 and 110 (2.5%) showed signs of renal impairment (<60 ml/min per 1.73 m^2).

Albumin-to-Creatinine Ratio

The longitudinal geometric mean ACR with metformin (Figure 1A) was stable for the first year and then began to rise, whereas it declined with rosiglitazone and glyburide over the first 2 years before rising more slowly with rosiglitazone than glyburide. There were no significant differences among groups in the baseline-adjusted geometric mean changes from baseline to 6 months (Table 2). At 48 months the levels with rosiglitazone were significantly less than those with metformin, but not compared with glyburide. Over the period from 6 months to 5 years, the ACR with rosiglitazone rose on average 1.77% per year (95% CI −0.29, 3.88%) compared with 5.2% per year (95% CI 3.0, 7.4%) with metformin and 4.6% per year (95% CI 2.2, 7.0%) with glyburide. The difference between rosiglitazone and metformin approached significance ($P = 0.052$; adjusted for two comparisons). The pattern of group differences in ACR over time was not influenced by the baseline ACR value, gender, age, ethnicity, weight, SBP, presence of hypertension, or level of HbA1c, each assessed by a group by covariate interaction. These group differences also persisted after adjusting for differences in hypertension, use of ACE inhibitor (ACEi) or angiotensin II receptor blocker (ARB) medications, calcium channel blockers, body weight, HbA1c, FPG, and SBP over time as time-dependent covariates (each separately).

The majority (3426, 85%) of patients entered with normal levels of albuminuria (<30 mg/g), and 3212 had ≥1 subsequent ACR assessments, of whom 566 (18%) developed albuminuria (≥30 mg/g) during follow-up, with an estimated cumulative incidence of about 20% at 5 years (Figure 2A). Rosiglitazone reduced the risk of progression by about 15% compared with metformin or glyburide, neither being statistically significant (Table 3). The treatment group differences in the crude percentages are smaller but potentially misleading because rosiglitazone had a higher duration of exposure (4954 patient-years) than either metformin (4906) or glyburide (4244), which

Table 1. Baseline characteristics of patients randomized to receive rosiglitazone, metformin, or glyburide

	Rosiglitazone (n = 1456)	Metformin (n = 1454)	Glyburide (n = 1441)
Age, years	56.3 ± 10.0	57.9 ± 9.9	56.4 ± 10.2
Men, *n* (%)	811 (55.7)	864 (59.4)	836 (58.0)
Time since diagnosis of diabetes, n (%)			
<1 year	650 (44.6)	673 (46.3)	637 (44.2)
1 to 2 years	759 (52.1)	724 (49.8)	751 (52.1)
>2 years	47 (3.2)	57 (3.9)	53 (3.7)
Weight, kg	91.5 ± 19.7	91.6 ± 18.7	92.0 ± 20.0
Body mass index, kg/m^2	32.2 ± 6.7	32.1 ± 6.1	32.2 ± 6.3
Systolic BP, mmHg	133 ± 16	133 ± 15	133 ± 15
Diastolic BP, mmHg	80 ± 9	80 ± 9	79 ± 9
Hypertension, *n* (%)	1144 (78.6)	1137 (78.2)	1124 (78.0)
ACEi/ARB therapy, *n* (%)	479 (32.9)	486 (33.4)	477 (33.1)
Fasting plasma glucose, mg/dl	151.5 ± 25.8	151.3 ± 25.6	152.4 ± 27.3
HbA1c, %	7.36 ± 0.93	7.36 ± 0.93	7.35 ± 0.92
Urine ACR geometric mean (CV %),[a,b] mg/g	9.9 (179.5)	9.3 (172.3)	9.4 (174.4)
<30 mg/g, *n* (%)	1185 (82.9)	1201 (84.9)	1210 (85.5)
≥30 mg/g, *n* (%)	244 (17.1)	213 (15.1)	205 (14.5)
≥300 mg/g, *n* (%)	24 (1.7)	19 (1.3)	24 (1.7)
MDRD eGFR geometric mean (CV%),[a,b] ml/min per 1.73 m^2	98.0 (24.6)	97.1 (25.6)	95.7 (27.6)
>130 ml/min per 1.73 m^2, *n* (%)	168 (11.5)	152 (10.5)	131 (9.1)
60 to 130 ml/min per 1.73 m^2, *n* (%)	(86.5)	1265 (87.0)	1264 (87.7)
<60 ml/min per 1.73 m^2, *n* (%)	29 (2.0)	36 (2.5)	45 (3.1)

[a]Quantitative data are expressed as mean ± SD. Log-transformed data are presented as the geometric mean and the CV %, the latter obtained as 100 × (exp[SD − mean]) where SD and mean are of the log-transformed values.
[b]Denominator does not include 93 with missing ACR at baseline, or 2 with missing eGFR.

reflected the lower rate of monotherapy failure with rosiglitazone.

During follow-up, 566 patients developed albuminuria (ACR ≥30 mg/g), of whom 398 were subsequently assessed and 196 (49%) had confirmed albuminuria. Among 616 patients who entered with albuminuria (ACR ≥30 mg/g), 326 (52.9%) regressed to normal albuminuria (ACR <30 mg/g) on at least one occasion, with no difference among groups (Table 3).

Among 3985 patients who entered with ACR <300 mg/g, 93 (2.5% of the 3722 assessed) progressed to macroalbuminuria (ACR ≥300 mg/g), with no difference among groups. Of these, 60 were subsequently assessed and 17 had confirmed macroalbuminuria. Among the 57 who entered with pre-existing macroalbuminuria, only 13 later regressed to levels <30 mg/g (5/21 with rosiglitazone, 2/15 with metformin, and 6/21 with glyburide).

Estimated Glomerular Filtration Rate

With rosiglitazone and metformin, the longitudinal geometric eGFR means rose steadily over the first 3 years and then declined, as did those with glyburide after a small decline over the first year (Figure 1B). The changes in eGFR from baseline to 6 months, and from baseline to 4 years, were significantly higher with rosiglitazone than glyburide, as were those between rosiglitazone and metformin at 4 years (Table 2). These differences were not influenced by baseline factors (*i.e.*, no treatment by baseline covariate interactions) and the differences persisted after adjusting for the same set of baseline and time-dependent covariates as used in the analyses of ACR.

Among the 4018 patients who entered with an eGFR ≥60 ml/min per 1.73 m^2, 265 (7.0% of the 3814 assessed) developed an impaired eGFR <60 ml/min among the treatment groups. An eGFR <60 ml/min per 1.73 m^2 was confirmed in 107 of the 206 patients subsequently assessed, with no differences between groups.

Among the 3606 patients who entered with a normal eGFR (60 ≤ eGFR ≤ 130 ml/min per 1.73 m^2), 726 (21.1% of the 3434 assessed) later shifted to a high eGFR >130 ml/min per 1.73 m^2. This risk was 44% greater with rosiglitazone than with glyburide (P = 0.001) but was similar between rosiglitazone and metformin (Figure 2C, Table 3).

Among the 412 patients who entered with a high eGFR >130 ml/min per 1.73 m^2, 264 (69.5% of the 380 assessed) later reverted to normal levels (60 ≤ eGFR ≤ 130 ml/min per 1.73 m^2) with no difference among groups. Too few patients entered with an eGFR <60 ml/min per 1.73 m^2 to permit reliable analysis.

These group differences in eGFR transitions were unchanged after adjustment for changes in other factors over time as time-dependent covariates. Neither the current HbA1c nor the current FPG over time were associated with the eGFR mean levels over time or the risk of eGFR <60 or >130 ml/min per 1.73 m^2 in separate models, with or without adjustment for treatment group.

Blood Pressure

There was an early increase in SBP with glyburide but no change with rosiglitazone or metformin (Figure 1C), the values remaining level through 5 years, those with rosiglitazone being significantly lower than those with glyburide

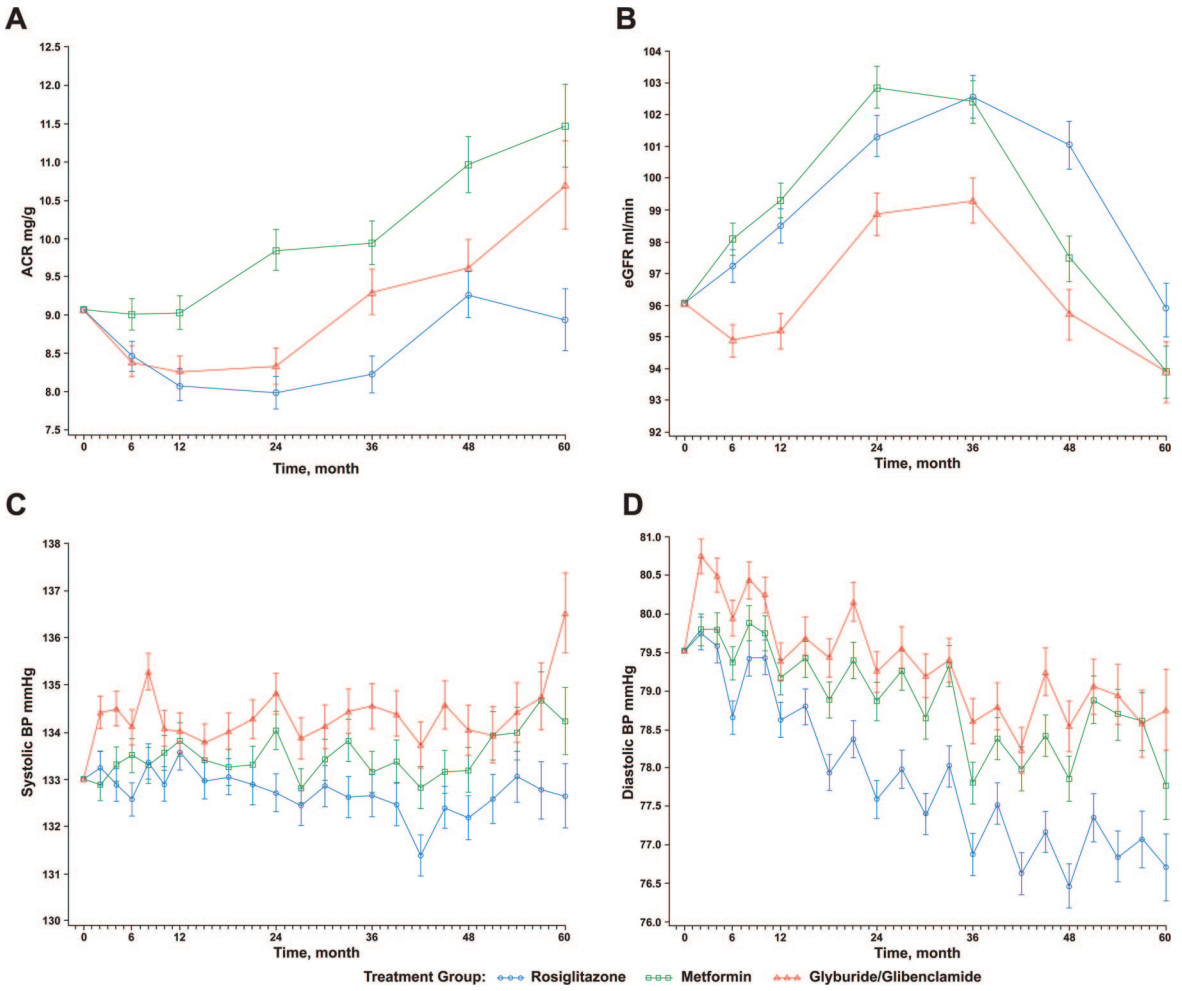

Figure 1. | Mean or geometric mean levels of measures from a baseline-adjusted longitudinal normal errors regression model with 95% confidence limits. (A) Albumin-to-creatinine ratio (ACR, mg/g); (B) MDRD-estimated GFR (GFR; ml/min per 1.73 m^2); (C) systolic BP (mmHg); (D) diastolic BP (mmHg).

by 1.5 mmHg at 6 months ($P = 0.005$) and by 1.8 mmHg at 48 months ($P = 0.018$). Values with rosiglitazone were lower than those with metformin, but not significantly. Over 6 to 60 months, the SBP with rosiglitazone declined on average by 0.15 mmHg/yr (95% CI −0.1, 0.41) compared with an increase of 0.019 mmHg/yr (95% CI −0.24, 0.27) with metformin and 0.07 mmHg/yr (95% CI −0.21, 0.35) with glyburide, the differences among groups not being statistically significant.

DBP (Figure 1D, Table 2) also showed an initial rise with glyburide but not with rosiglitazone or metformin. Thereafter, DBP declined in all groups, more so with rosiglitazone, the mean at 6 months being 1.3 mmHg lower than that with glyburide ($P < 0.001$) and 0.7 mmHg lower than that with metformin ($P = 0.0225$), and at 48 months being 2.1 mmHg lower than that with glyburide ($P < 0.001$) and 1.4 mmHg lower than that with metformin ($P = 0.0006$). Over 6 to 60 months, the DBP with rosiglitazone declined on average 0.59 mmHg/yr (95% CI 0.44, 0.74) compared with a decrease of 0.36 mmHg/yr (95% CI 0.21, 0.51) with metformin and 0.36 mmHg/yr (95% CI 0.20, 0.53) with glyburide, each with $P = 0.049$.

These differences persisted after adjusting for baseline hypertension, or use of ACEi, ARBs, or calcium channel blockers over time, or levels of FPG or HbA1c over time.

Among the 733 patients who entered without hypertension, in all groups some 90% of these patients developed hypertension, with no difference among groups (Figure 2D, Table 3). Among the 2763 patients not taking either ACEi or ARB medications on entry, 781 (27%) did so during follow-up, with no difference among groups.

Discussion

The development of albuminuria in type 2 diabetes not only signals renal microvascular disease but increases the risk of cardiovascular disease morbidity and mortality by about fourfold. The higher the level of albuminuria, the greater the risk. Maneuvers that reduce albuminuria are renoprotective and improve cardiovascular outcomes (16). Intensive control of glycemia and of BP are effective in both preventing the onset and reducing the progression of albuminuria (2,17). However, antihypertensive agents differ significantly in their albuminuria-lowering capacity despite similar BP-lowering potency, with inhibitors of the

Table 2. Absolute mean change from baseline or percentage change in the geometric mean from baseline, and 95% CI, in urinary ACR (mg/g), MDRD-eGFR, systolic BP (mmHg), and diastolic BP (mmHg) within each treatment group

	Geometric Mean (95% CI)			*P* value	
	Rosiglitazone	Metformin	Glyburide	Rosiglitazone *versus* Metformin	Rosiglitazone *versus* Glyburide
Urinary ACR, mg/g	$n = 1283$	$n = 1274$	$n = 1216$		
mean change, % from baseline to:					
0.5 years	−6.7 (−10.8, −2.4)	−0.7 (−5.1, 3.9)	−7.5 (−11.7, −3.1)	NS	NS
4 years	2.1 (−4.2, 8.8)	20.9 (13.3, 28.9)	6.1 (−1.2, 14.0)	<0.001	NS
MDRD-eGFR, ml/min per 1.73 m^2	$n = 1317$	$n = 1327$	$n = 1270$		
mean change, % from baseline to:					
0.5 years	1.2 (0.1, 2.2)	2.1 (1.0, 3.1)	−1.3 (−2.3, −0.2)	NS	0.0014
4 years	5.1 (3.6, 6.7)	1.4 (0.0, 2.9)	−0.4 (−2.0, 1.2)	0.0005	<0.001
Systolic BP, mmHg	$n = 1390$	$n = 1396$	$n = 1326$		
absolute mean change from baseline to:					
0.5 years	−0.4 (−1.1, 0.3)	0.5 (−0.2, 1.2)	1.1 (0.4, 1.8)	NS	0.005
4 years	−0.8 (−1.7, 0.1)	0.2 (−0.7, 1.1)	1.0 (0.0, 2.1)	NS	0.018
Diastolic BP, mmHg	$n = 1390$	$n = 1396$	$n = 1326$		
absolute mean change from baseline to:					
0.5 years	−0.9 (−1.3, −0.4)	−0.2 (−0.6, 0.3)	0.4 (0.0, 0.9)	0.0225	<0.001
4 years	−3.0 (−3.6, −2.5)	−1.7 (−2.2, −1.1)	−1.0 (−1.6, −0.3)	0.0006	<0.001

The test of differences between treatment groups at 6 months and 4 years is based on a longitudinal model adjusted for the baseline value, country, and gender; *P* values were adjusted for two comparisons. NS, not significant.

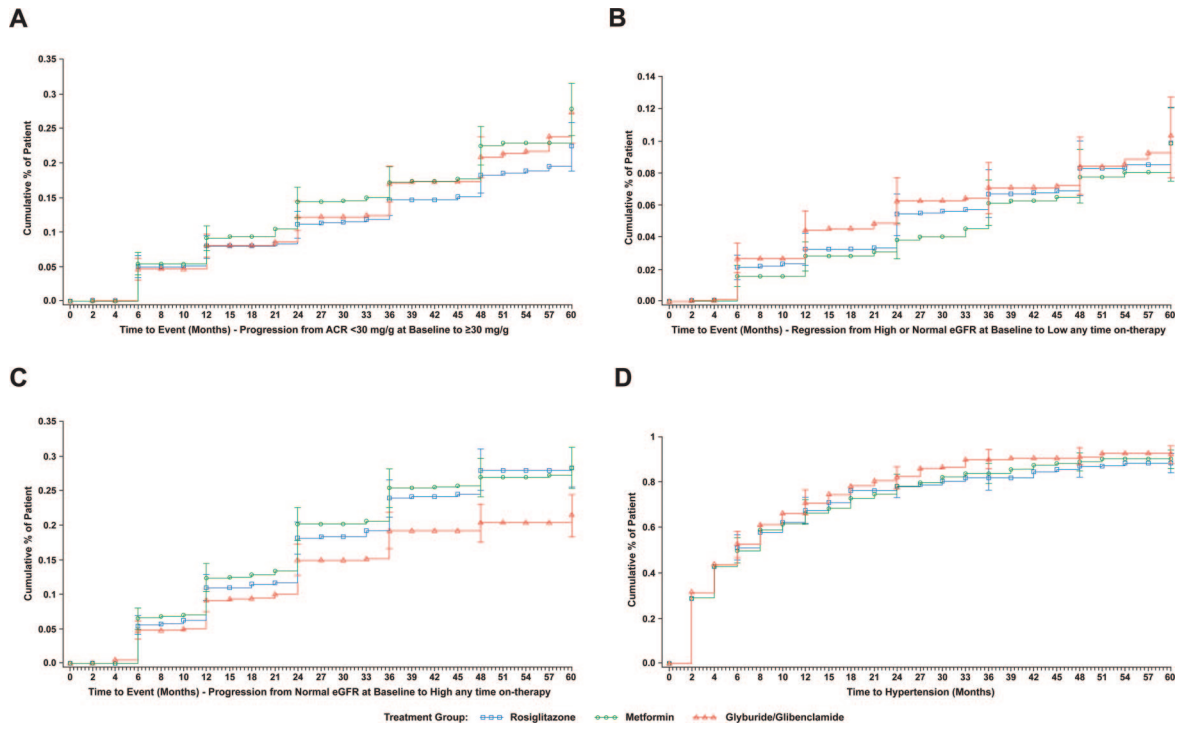

Figure 2. | **Cumulative incidence of events among groups with 95% confidence limits.** (A) Progression from normal albumin-to-creatinine ratio (ACR <30 mg/g) to albuminuria (ACR ≥30 mg/g); (B) progression from normal or high estimated GFR (eGFR ≥60 ml/min per 1.73 m^2) to impaired eGFR (<60 ml/min per 1.73 m^2); (C) change from normal eGFR (60 ≤ eGFR ≤ 130 ml/min per 1.73 m^2) to high eGFR (>130 ml/min per 1.73 m^2); (D) onset of hypertension or initiation of antihypertensive medications.

renin-angiotensin system being more effective than calcium channel blockers (18,19). In contrast, little information is available regarding the ability of anti-hyperglycemia agents to prevent or lower albuminuria.

ADOPT demonstrates that long-term treatment with metformin results in a slow but progressive rise in ACR. Metformin is ineffective in reducing albuminuria in the short-term (7) and, more importantly, shows no microvascular protection in the longer term (3). One small study that showed a reduction in microalbuminuria with metformin compared with glibenclamide was confounded by a significantly greater reduction of BP with metformin (20). By contrast, with rosiglitazone and glyburide the ACR declined over the first 2 years but rose thereafter, although more slowly with rosiglitazone. The rate of change of ACR over time was slowest with rosiglitazone (1.8% per year) *versus* metformin (5.2% per year), and glyburide (4.6% per year), although nonsignificant (barely). After 4 years, the ACR levels were significantly lower with rosiglitazone compared with metformin, but not glyburide. Of note, the different pattern of ACR change over time between rosiglitazone and metformin was independent of known risk factors for albuminuria, such as baseline ACR, weight, BP, use of ACEi or ARBs, and blood glucose control. Longer term observations would be required to establish whether the slower rise in quantitative ACR values with rosiglitazone translates into microvascular protection in recently diagnosed type 2 diabetes patients.

Among patients entering with ACR <30 mg/g, the 4-year cumulative incidence of albuminuria was lowest with rosiglitazone (18.2%) and highest with metformin (22.5%). Among patients entering with albuminuria (ACR ≥30 mg/g), a greater proportion reverted to normoalbuminuria with rosiglitazone (69.5%) *versus* about 64% in the other two groups. However, neither set of differences were statistically significant. Shorter term studies with pioglitazone in patients with normo- or microalbuminuria likewise showed a consistently greater lowering of urine albumin excretion, although of varying degrees, compared with active comparator or placebo (21).

A limitation of ADOPT is that ACR was measured infrequently, adding variability and imprecision when assessing categorical changes in either progression or regression of albuminuria. ADOPT may also have been too short to show that quantitative group differences in ACR over time translate into differences in ACR categorical changes among groups, especially progression to overt nephropathy. Moreover, there is robust evidence that vascular risk increases continuously over the whole range of ACR values and it is plausible that patients with ACR rising more rapidly across the upper reaches of the normal range are the subgroup destined to develop albuminuria.

Previous reports suggested that the effects of rosiglitazone on ACR are mediated by changes in adiponectin, TNFα, and free fatty acids—factors little affected by metformin (7,22). ADOPT did not investigate these or related mechanisms. However, the beneficial effects of rosiglitazone on progression of ACR were not explained by differences between groups in traditional promoters of progression such as BP, weight, and glycemia. This makes it likely

Table 3. Number and proportion of patients with changes in the level of albuminuria, MDRD-eGFR, and BP within each treatment group, and hazard ratio obtained from the Cox proportional hazards model adjusted for the baseline level of each factor, country, and gender

Outcome	Rosiglitazone	Metformin	Glyburide	Rosiglitazone *versus* Metformin		Rosiglitazone *versus* Glyburide	
				HR (95% CI)	*P*	HR (95% CI)	*P*
Albumin-to-creatinine ratio (ACR)							
normal ACR (<30 mg/mg) at baseline to albuminuria (ACR ≥30 mg/g)	*n* = 1142	1156	1128				
patients, *n* (%)	174 (15.2)	217 (18.8)	175 (15.5)				
4-year cumulative incidence, % (CI)	18.2 (15.7, 20.9)	22.5 (19.7, 25.3)	20.9 (17.9, 23.9)	0.84 (0.68, 1.04)	NS	0.86 (0.69, 1.08)	NS
albuminuria (ACR ≥30 mg/g) at baseline to normoalbuminuria	*n* = 227	202	187				
patients, *n* (%)	128 (56.4)	99 (49.0)	99 (52.9)				
4-year cumulative incidence, % (CI)	69.5 (62.0, 77.0)	63.8 (55.0, 72.5)	63.9 (55.1, 72.7)	1.27 (0.92, 1.74)	NS	1.10 (0.80, 1.50)	NS
MDRD-eGFR (ml/min per 1.73 m^2)							
normal or high eGFR (≥60 ml/min per 1.73 m^2) at baseline to low eGFR (<60 ml/min per 1.73 m^2)	*n* = 1364	1361	1293				
patients, *n* (%)	93 (6.82)	86 (6.32)	86 (6.65)				
4-year cumulative incidence, % (CI)	8.3 (6.6, 10.0)	7.8 (6.1, 9.5)	8.4 (6.6, 10.2)	1.04 (0.77, 1.40)	NS	0.91 (0.67, 1.23)	NS
normal eGFR (60 ≤ eGFR ≤ 130 ml/min per 1.73 m^2) at baseline to high eGFR (>130 ml/min per 1.73 m^2)	*n* = 1212	1218	1176				
patients, *n* (%)	271 (22.4)	271 (22.3)	184 (15.7)				
4-year cumulative incidence, % (CI)	28.1 (25.2, 31.0)	27.0 (24.1, 29.8)	20.4 (17.7, 23.1)	0.951 (0.79, 1.14)	NS	1.44 (1.17, 1.76)	0.001
Blood pressure							
without hypertension at baseline to hypertension	*n* = 303	307	290				
patients, *n* (%)	242 (79.9)	250 (81.4)	241 (83.1)				
4-year cumulative incidence, % (CI)	87.0 (82.6, 91.4)	89.1 (85.0, 93.2)	91.7 (87.9, 95.5)	98 (0.80, 1.19)	NS	0.84 (0.69, 1.03)	NS

P values adjusted for two comparisons. NS, not significant.

that other mediators, which display drug-specific responses, may have been involved.

BP was also reduced to a greater extent with rosiglitazone than either metformin or glyburide, particularly DBP. These modest differences in office BP were consistent with previous reports that either used casual BP measurements (23,24) or, more importantly, monitored 24-hour ambulatory BP (25,26). In our study the effect was independent of pre-existing hypertension, or treatment with ACEi, ARBs, or calcium channel blockers over time, or the level of glycemia. However, the incidence of emergent hypertension did not differ among groups. Furthermore, the changes in BP appeared unrelated to the different patterns of ACR among the treatment groups. Others have questioned whether rosiglitazone has effects on BP independent of effects on urine albumin excretion. Although a biologic effect of BP lowering could not be entirely excluded, it appears that other mediators, rather than or in addition to BP, are likely to be involved (27).

All three agents showed a rise in eGFR into the high normal range followed by a decline, the values with rosiglitazone still being significantly greater than those with metformin or glyburide at 4 years. However, these results must be interpreted cautiously as the MDRD eGFR calculation has not been validated over the range of GFR >60 ml/min per 1.73 m^2 into which most of our patients fell (28). This rise in GFR did not appear to be mediated by glycemic changes, as neither HbA1c nor FPG were significantly associated with the level of eGFR over time, or the risk of an eGFR <60 ml/min per 1.73 m^2. It is unclear whether a high eGFR early in diabetes indicates preservation of renal function, or whether it may be detrimental in the long term (29). Reassuringly, worsening of renal function to an impaired eGFR <60 ml/min per 1.73 m^2 was uncommon, with no differences among groups.

Conclusions

In ADOPT, rosiglitazone compared with metformin and glyburide provided greater durability of glycemic control, lowered DBP to a greater extent, and reduced the rate of rise of ACR while preserving a higher eGFR. Whether these effects would have translated into microvascular and, perhaps more importantly, macrovascular protection is unknown, as ADOPT was not designed to assess these long-term outcomes. Both the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes and the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes have shown that an extended period of observation is required to establish whether an apparently favorable change in biomarkers, such as those observed herein, translates into favorable clinical vascular outcomes (3,30,31). In patients with type 2 diabetes with longer duration and at higher vascular risk than in ADOPT, rosiglitazone does not appear to provide specific cardiovascular protection (32–34). Nevertheless, it must be realized that early and late phases of a disease may respond quite differently to similar therapeutic agents and treatment strategies, as highlighted recently by trials of intensive glycemic control in type 2 diabetes (3,32–34).

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Disclosures

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