Lowering Blood Pressure Reduces Renal Events in Type 2 Diabetes

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ABSTRACT

BP is an important determinant of kidney disease among patients with diabetes. The recommended thresholds to initiate treatment to lower BP are 130/80 and 125/75 mmHg for people with diabetes and nephropathy, respectively. We sought to determine the effects of lowering BP below these currently recommended thresholds on renal outcomes among 11,140 patients who had type 2 diabetes and participated in the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study. Patients were randomly assigned to fixed combination perindopril-indapamide or placebo, regardless of their BP at entry. During a mean follow-up of 4.3 yr, active treatment reduced the risk for renal events by 21% ($P <$ 0.0001), which was driven by reduced risks for developing microalbuminuria and macroalbuminuria (both $P <$ 0.003). Effects of active treatment were consistent across subgroups defined by baseline systolic or diastolic BP. Lower systolic BP levels during follow-up, even to $<$110 mmHg, was associated with progressively lower rates of renal events. In conclusion, BP-lowering treatment with perindopril-indapamide administered routinely to individuals with type 2 diabetes provides important renoprotection, even among those with initial BP $<$120/70 mmHg. We could not identify a BP threshold below which renal benefit is lost.

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Type 2 diabetes is the leading cause of end-stage kidney disease, accounting for 30 to 50% of new cases in the industrialized world.[1] Microalbumin-

uria is one of the earliest detectable manifestations of kidney disease in diabetes, with a prevalence of 25% after 10 yr of diabetes duration and with an

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Table 1. Baseline characteristics recorded before active run-in[a]

Variable	Randomized Treatment	
	Perindopril-Indapamide (n = 5569)	Placebo (n = 5571)
Age (yr; mean [SD])	66 (6)	66 (7)
Female (n [%])	2366 (42.5)	2369 (42.5)
Age when diabetes first diagnosed (yr; mean [SD])	58 (9)	58 (9)
Duration of diabetes (yr; mean [SD])	8 (6)	8 (6)
BP control (mmHg; mean [SD])		
SBP	145 (22)	145 (21)
DBP	81 (11)	81 (11)
history of currently treated hypertension (n [%])	3802 (68.3)	3853 (69.2)
Renal parameters		
UACR (μg/mg; median [IQR])	15 (7 to 40)	15 (7 to 40)
microalbuminuria (n [%])	1441 (25.9)	1421 (25.5)
macroalbuminuria (n [%])[b]	197 (3.5)	204 (3.7)
serum creatinine (μmol/L; mean [SD])[c]	87 (23)	87 (26)
eGFR (ml/min per 1.73 m^2; mean [SD])	78 (25)	78 (25)
eGFR <60 ml/min per 1.73 m^2 (n [%])	1063 (19.1)	1094 (19.6)
Previous vascular disease		
history of major macrovascular disease (n [%])	1798 (32.3)	1792 (32.2)
history of myocardial infarction (n [%])	678 (12.2)	656 (11.8)
history of stroke (n [%])	502 (9.0)	520 (9.3)
history of microvascular eye disease (n [%])[d]	389 (7.0)	404 (7.3)
Other major risk factors		
current smoker (n [%])	804 (14.4)	878 (15.8)
serum total cholesterol (mmol/L; mean [SD])[e]	5.2 (1.2)	5.2 (1.2)
serum HDL cholesterol (mmol/L; mean [SD])[e]	1.3 (0.3)	1.3 (0.4)
serum HbA$_{1c}$ concentration (%; mean [SD])	7.5 (1.6)	7.5 (1.6)
body weight (kg; mean [SD])	78.3 (16.8)	78.0 (16.8)
BMI (kg/m^2; mean [SD])	28.3 (5.2)	28.3 (5.1)
waist-to-hip ratio (mean [SD])	0.93 (0.08)	0.93 (0.08)
Region of origin (n [%])		
Europe	2539 (45.6)	2544 (45.7)
Asia	2070 (37.2)	2066 (37.1)
Treatment (n [%])		
ACEIs	2402 (43.1)	2388 (42.9)
ARBs	289 (5.2)	320 (5.7)
calcium channel blockers	1669 (30.0)	1758 (31.6)
β blockers	1344 (24.1)	1385 (24.9)
diuretics	1260 (22.6)	1247 (22.4)
antiplatelets	2597 (46.6)	2601 (46.7)
lipid-modifying drugs	1938 (34.8)	1996 (35.8)

[a]Reprinted in part from Patel et al.,[18] with permission from Elsevier. ARB, angiotensin receptor blocker; BMI, body mass index; HbA$_{1c}$, glycosylated hemoglobin; IQR, interquartile range.
[b]UACR >300 μg/mg.
[c]To convert values to mg/dl, divide by 88.4.
[d]Proliferative diabetic retinopathy, retinal photocoagulation therapy, macular edema, or blindness in one eye thought to be caused by diabetes.
[e]To convert values to mg/dl, divide by 0.259.

annual rate of progression to overt nephropathy of approximately 3%.[2] The risk for the development and progression of microalbuminuria is highly dependent on BP.[3] Accumulating evidence suggests that BP lowering reduces the risk for new-onset or progressive nephropathy, particularly when angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are used.[4–9]

Current guidelines recommend commencement of BP-lowering treatment for patients with diabetes and a BP of ≥130/80 mmHg to a therapeutic target of <130/80 mmHg.[10–13] The threshold for those with diabetes and nephropathy has been set at 125/75 mmHg.[13] These cut points are based largely on the strong, positive, and graded association between higher levels of BP and the risk for clinical events, including end-stage renal disease.[14] Evidence from major intervention trials to support these thresholds is, limited however, because average BP levels at study entry were often much higher.[5–9,15] Conversely, observational analyses reporting con-

tinuous associations of renal disease with BP[16,17] suggested that individuals with initial BP levels below the currently recommended thresholds may benefit from BP-lowering treatment. Again, evidence from randomized comparisons supporting such a hypothesis is lacking.

The BP arm of the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study recently reported that the routine administration of a fixed combination of the ACEI perindopril and the diuretic indapamide to a broad cross-section of patients with type 2 diabetes reduced the risks for major vascular events and death from all causes.[18] The risk for renal events was reduced by 21% overall. In this report, we examine the effects of study treatment on a range of renal outcomes in more detail and assess whether there are benefits of such treatment in patients with BP levels below those currently recommended as thresholds for commencing BP-lowering treatment.

RESULTS

A total of 12,877 potentially eligible participants were registered; 1737 (13.5%) were subsequently withdrawn during the 6-wk active run-in period, and 11,140 (86.5%) were randomly assigned. The characteristics of the ADVANCE study participants are summarized in Table 1. Entry BP levels averaged 145/81 mmHg overall, and 20% of patients had a BP <130/80 mmHg.

Vital status was known at the end of follow-up for all but 15 patients.[18] The mean systolic BP (SBP) during follow-up was 134.7 mmHg in patients assigned active treatment and 140.3 mmHg in patients assigned placebo ($P < 0.0001$); mean diastolic BP (DBP) levels were 74.8 and 77.0 mmHg in the two groups, respectively ($P < 0.0001$). Mean body weight decreased by 0.3 kg in patients assigned active and increased by 0.2 kg in patients assigned placebo treatment ($P < 0.0001$), but there were no differences with respect to glycosylated hemoglobin (6.9%) or total cholesterol levels (5.0 mmol/L) at study completion. At the end of follow-up, 4081 (73%) patients assigned active treatment and 4143 (74%) patients assigned placebo were adherent to study medication, whereas concomitant BP-lowering drugs were used more by patients on placebo than by those on active treatment (Table 2).

Values for serum creatinine and urinary albumin-creatinine ratio (UACR) were available at baseline for 10,996 (99%) and 10,640 (95.5%) patients, respectively. Nineteen percent of participants had an estimated GFR (eGFR) <60 ml/min per 1.73 m². Microalbuminuria was present in 26% and macroalbuminuria in 4% of the participants. The presence of microalbuminuria or macroalbuminuria was independently associated with higher risks for developing end-stage kidney disease, cardiovascular events, cardiovascular death, and death from any cause (all $P < 0.03$; Table 3).

Table 2. Concomitant BP-lowering treatment at the end of follow-up[a]

Variable	End of Follow-up (n [%])	
	Perindopril-Indapamide	Placebo
Open-label perindopril	2128 (44.5)	2591 (54.9)
Other ACEIs	232 (4.9)	213 (4.5)
ARBs	453 (9.5)	618 (13.1)
β blockers	1492 (31.2)	1671 (35.4)
Calcium antagonists	1531 (32.0)	2040 (43.2)
Thiazide diuretics	158 (3.3)	217 (4.6)
Other diuretics	673 (14.1)	749 (15.9)
Other BP-lowering drugs	463 (9.7)	638 (13.5)
Any BP-lowering drugs	3634 (74.0)	4024 (82.7)

[a]Reprinted from Patel et al.,[18] with permission from Elsevier.

Effect of Randomized Treatment on Renal Outcomes

A total of 1243 (22.3%) patients assigned active treatment and 1500 (26.9%) patients assigned placebo developed the composite renal outcome of new-onset microalbuminuria, new-onset nephropathy, doubling of serum creatinine above 200 μmol/L, or end-stage kidney disease (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.73 to 0.85; $P < 0.0001$; Table 4). On this basis, one such event would be prevented among every 20 (95% CI 15 to 30) patients assigned active treatment for a 5-yr period.

Active treatment also reduced the risk for progression of albuminuria among patients who had either normo- or microalbuminuria at baseline (HR 0.78; 95% CI 0.72 to 0.84; $P < 0.0001$) and the risk for new-onset microalbuminuria in patients with normoalbuminuria at baseline (HR 0.79; 95% CI 0.73 to 0.86; $P < 0.0001$; Table 4).

A total of 286 patients developed overt nephropathy, as defined by macroalbuminuria, during follow-up: 114 (2.1%) patients assigned active treatment and 163 (3.0%) patients assigned placebo (HR 0.69; 95% CI 0.54 to 0.88; $P = 0.003$). The relative risk reductions were of comparable magnitude in patients with normoalbuminuria or microalbuminuria at baseline ($P = 0.3$ for heterogeneity).

Regression of albuminuria was observed in more than half of all patients with micro- or macroalbuminuria at baseline, most of whom regressed to normoalbuminuria (Table 4). Proportionally more patients assigned active than assigned placebo treatment achieved restoration of normoalbuminuria ($P = 0.006$), with approximately similar absolute UACR declines according to treatment assignment (patients with microalbuminuria: from 55.0 to 10.6 μg/mg [active treatment] versus from 54.2 to 11.0 μg/mg [placebo]; patients with macroalbuminuria: from 490.6 to 9.0 μg/mg [active treatment] versus from 465.9 to 13.4 μg/mg [placebo]).

Active treatment reduced eGFR to a greater extent than placebo ($P < 0.0001$) in the first 4 mo (Figure 1), but annual declines in eGFR were similar in the active and placebo treatment groups thereafter (0.5 versus 0.6 ml/min per 1.73 m²). This was true for patients with normoalbuminuria (0.1 versus

Table 3. Adjusted risks of end-stage kidney disease, macrovascular events, cardiovascular death, and all-cause death by baseline albuminuria level[a]

End Point	Normoalbuminuria (n = 7877)	Micro- or Macroalbuminuria (n = 3263)	HR (95% CI)
End-stage kidney disease[b]	19 (0.2%)	27 (0.8%)	1.99 (1.08 to 3.70)
Macrovascular events[c]	585 (7.4%)	415 (12.7%)	1.61 (1.42 to 1.84)
Cardiovascular death	239 (3.0%)	229 (7.0%)	2.07 (1.72 to 2.50)
All-cause death	496 (6.3%)	383 (11.7%)	1.70 (1.48 to 1.96)

[a]Adjusted for age, gender, HbA$_{1c}$, SBP, DBP, LDL cholesterol, HDL cholesterol, triglycerides, BMI, eGFR, current smoking, and current alcohol use.
[b]Defined as requirement of renal replacement therapy or renal death.
[c]Composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

Table 4. Incidence of renal end points[a]

End Point	Perindopril- Indapamide (No. of Events/Patient [%])	Placebo	HR (95% CI)	P	NNT
Progression of nephropathy					
all renal events	1243/5569 (22.3)	1500/5571 (26.9)	0.79 (0.73 to 0.85)	<0.0001	20
progression of ≥1 albuminuria stage	1179/5436 (21.7)	1442/5412 (26.6)	0.78 (0.72 to 0.84)	<0.0001	18
new-onset microalbuminuria	1094/3995 (27.4)	1317/3991 (33.0)	0.79 (0.73 to 0.86)	<0.0001	16
new-onset macroalbuminuria	114/5436 (2.1)	163/5412 (3.0)	0.69 (0.54 to 0.88)	0.0027	97
patients with normoalbuminuria	25/3995 (0.6)	35/3991 (0.9)	0.71 (0.42 to 1.18)	0.1841	NA
patients with microalbuminuria	89/1441 (6.2)	128/1421 (9.0)	0.69 (0.52 to 0.91)	0.0074	32
doubling of serum creatinine >200 μmol/L	55/5569 (1.0)	45/5571 (0.8)	1.21 (0.81 to 1.79)	0.3483	NA
end-stage kidney disease[b]	25/5569 (0.4)	21/5571 (0.4)	1.18 (0.66 to 2.11)	0.5736	NA
Regression of nephropathy					
regression of ≥1 albuminuria stage	908/1638 (55.4)	816/1625 (50.2)	1.16 (1.06 to 1.28)	0.0017	19
regression to normoalbuminuria	848/1638 (51.8)	745/1625 (45.8)	1.15 (1.04 to 1.27)	0.0059	16
patients with microalbuminuria	797/1441 (55.3)	698/1421 (49.1)	1.15 (1.04 to 1.27)	0.0067	16
patients with macroalbuminuria	51/197 (25.9)	47/204 (23.0)	1.08 (0.72 to 1.60)	0.7146	NA

[a]NA, not applicable; NNT, number needed to treat to prevent one event of nephropathy progression or to promote one event of nephropathy regression over 5 yr.
[b]Defined as requirement of renal replacement therapy or renal death.

0.0 ml/min per 1.73 m^2; $P = 0.69$), patients with microalbuminuria (1.1 *versus* 1.4 ml/min per 1.73 m^2; $P = 0.45$), and patients with macroalbuminuria (1.5 *versus* 2.7 ml/min per 1.73 m^2; $P = 0.34$). Both end-stage kidney disease and doubling of serum creatinine to a level >200 μmol/L were infrequently observed in ADVANCE, and the occurrence of these two outcomes was not significantly different between randomly assigned groups (Table 4).

Effects of Randomized Treatment in Patient Subgroups

Median initial values of SBP for the four groups defined by baseline SBP ranged from 113 to 172 mmHg, and those of DBP for DBP subgroups ranged from 66 to 95 mmHg. Separately significant reductions in the occurrence of renal events and the composite of macrovascular events, renal events, and all-cause mortality were observed for almost every BP subgroup with no evidence of differences in the size of effect at different levels of baseline SBP or DBP (Figure 2). Even in the subgroup with lowest baseline SBP (<120 mmHg; median 113 mmHg), active treatment reduced the risk for the composite renal outcome in patients with normoalbuminuria (HR 0.78; 95% CI 0.61 to

0.99; $P = 0.04$) and in patients with higher levels of albuminuria (HR 0.37; 95% CI 0.16 to 0.83; $P = 0.02$) at baseline.

The same pattern was observed with regard to renal benefits for subgroups defined by commonly used BP thresholds. As such, comparable proportional benefits were achieved in patients with starting BP levels above (HR 0.79; 95% CI 0.73 to 0.85; $P < 0.0001$) and below 125/75 mmHg (HR 0.78; 95% CI 0.63 to 0.96; $P = 0.02$; $P = 0.88$ for heterogeneity) and similarly for patients with BP levels above and below 130/80 or 140/90 mmHg (both $P > 0.1$ for heterogeneity).

The benefits of active treatment with respect to renal events were also consistent across a broad range of participant subgroups defined by background use of a variety of concomitant therapies, age, gender, kidney function, diabetes duration, and glycemic control (all $P > 0.1$ for trend; Figure 3). Specifically, there was no evidence that background ACEI treatment modified the effects of study treatment.

Very few serious adverse events were observed in ADVANCE. Overall, there were slightly higher rates of hypotension (0.5 *versus* 0.3%) and electrolyte disorders (0.7 *versus* 0.3%) in patients assigned active than in those assigned pla-
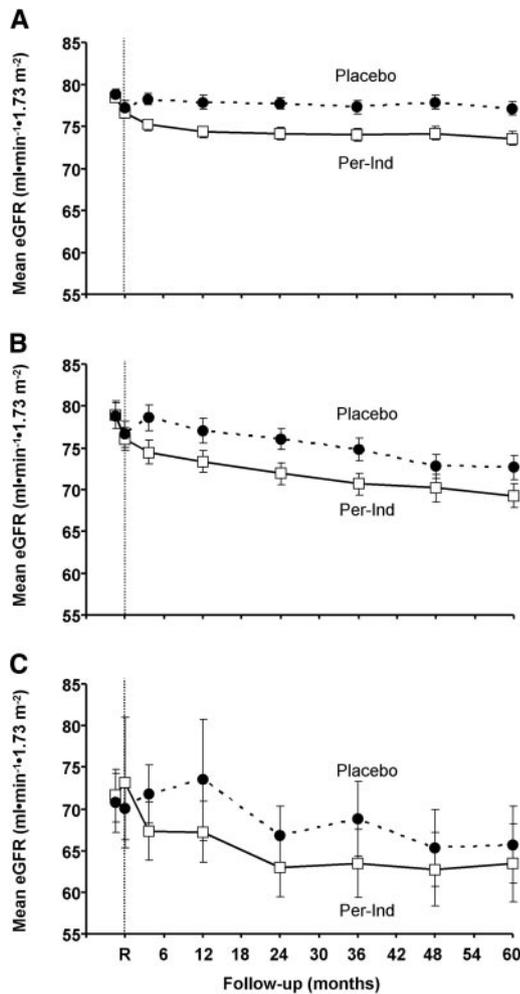
Figure 1. (A through C) Mean eGFR during follow-up according to treatment assignment in patients with normoalbuminuria (A), microalbuminuria (B), and macroalbuminuria (C) at baseline. R, randomization; Per-Ind, perindopril-indapamide treatment group.

cebo treatment. These findings were similar for all baseline BP subgroups (data not shown).

Risk for Renal Events According to Achieved BP during Follow-up

In age- and gender-adjusted analyses, there was an approximately log-linear relationship between the rate of any renal event and achieved SBP during follow-up. This association was unchanged after adjustment for a wide range of other risk factors ($P < 0.0001$ trend; Figure 4). The lowest risk for renal events was observed among those with a median achieved SBP of 106 mmHg. The same association was observed for achieved follow-up DBP levels within the range 62 to 93 mmHg ($P = 0.008$).
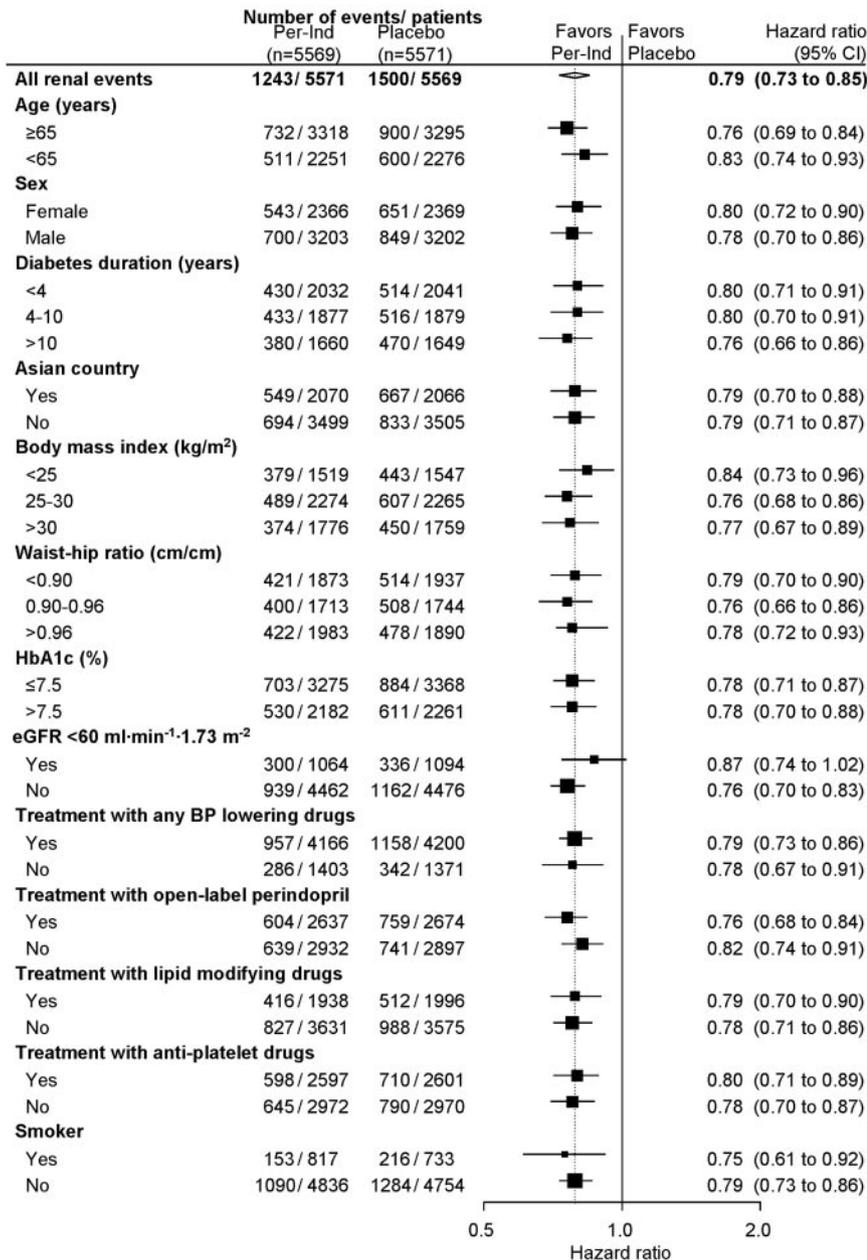
DISCUSSION

The main report from the BP-lowering part of ADVANCE showed that routine BP-lowering treatment with perindopril-

indapamide produced a one-fifth reduction in the risk for developing a renal outcome among patients with type 2 diabetes.[18] These analyses expand on that first report demonstrating both reductions in the risks for albuminuria progression and an increased likelihood of regression of albuminuria. We also found that widely used BP thresholds for treatment initiation do not differentiate between patient groups that will and will not derive benefit from BP lowering. The effects of active treatment on renal events in ADVANCE seem independent of the initial BP level with subgroup analyses showing clear benefits among individuals with baseline BP levels <120/70 mmHg. Separate observational analyses support these findings with the lowest risk for renal events observed among participants with achieved BP levels <110 mmHg systolic or 65 mmHg diastolic.

Most guidelines have progressively lowered the threshold BP level at which treatment is recommended for patients with diabetes, although evidence from randomized, controlled trials to support these recommendations is limited.[10–13] The data presented here provide new evidence that goes toward justifying the lower BP thresholds used in this patient group with respect to renal disease. The consistency of benefits across the broad range of initial BP levels for both all renal events and the composite end point that included macrovascular events and all-cause mortality studied here suggests that the decision to use BP-lowering treatment in patients with diabetes should not be based on the BP level. Indeed, applying current recommendations to the ADVANCE trial population would have denied renoprotective treatment to one fifth of the ADVANCE study population, one quarter of whom developed a renal event during follow-up. This conclusion is directly compatible with that of the main study result: Treatment was shown to be safe and to reduce the risks for major vascular events and death to the same extent in patients with BP levels below or above 140/90 mmHg.[18] Other data showing that BP lowering reduced the risks for macrovascular outcomes in patients with normotension and type 2 diabetes[19] and in patients with normotension and coronary artery disease[20] also support the more liberal use of BP-lowering treatment in high-risk individuals.

The benefits of active treatment were observed against a background of standard care that caused regression to normoalbuminuria in almost half of the patients who had micro- or macroalbuminuria and were assigned placebo. Treatments based on blockade of the renin-angiotensin system have generally been associated with remission rates of approximately 30% among patients with microalbuminuria,[6,21] although rates up to 64% have been reported with combination drug therapy.[22] Both optimal levels of glycemic control and lipid modification and a protocol that permitted open-label perindopril treatment to all patients may have contributed to the high rate of albuminuria regression in ADVANCE.

In ADVANCE, levels of GFR declined acutely after the institution of BP-lowering therapy before stabilizing. This pattern is the typical response to treatment with agents that block the renin-angiotensin system.[23] For the remainder of the study, GFR declined at lower than anticipated rates[24] in patients with nor-

	No. of events/patients		Median	Favors	Favors	Hazard ratio	P for
	Per-Ind	Placebo	blood pressure	Per-Ind	Placebo	(95% CI)	trend
All renal events							
All participants	1243/ 5569	1500/ 5571				0.79 (0.73 to 0.85)	
Baseline systolic blood pressure (mmHg)							
<120	134/ 615	167/ 560	113 mmHg			0.70 (0.56 to 0.88)	0.75
120-139	367/ 1736	431/ 1793	131 mmHg			0.85 (0.74 to 0.97)	
140-159	439/ 1945	563/ 2003	149 mmHg			0.75 (0.66 to 0.85)	
≥160	303/ 1273	339/ 1215	172 mmHg			0.81 (0.70 to 0.95)	
Baseline diastolic blood pressure (mmHg)							
<70	208/ 846	240 / 881	66 mmHg			0.84 (0.70 to 1.02)	0.85
70-79	387/ 1748	481/ 1758	75 mmHg			0.77 (0.67 to 0.88)	
80-89	386/ 1862	479/ 1834	84 mmHg			0.76 (0.66 to 0.87)	
≥90	262/ 1113	300/ 1098	95 mmHg			0.81 (0.69 to 0.96)	
All renal events, macrovascular events, all-cause death							
All participants	1781/ 5569	2064/ 5571				0.82 (0.77 to 0.88)	
Baseline systolic blood pressure (mmHg)							
<120	190/ 615	205/ 560	113 mmHg			0.82 (0.68 to 1.00)	0.35
120-139	527/ 1736	590/ 1793	131 mmHg			0.89 (0.79 to 1.00)	
140-159	615/ 1945	771/ 2003	149 mmHg			0.77 (0.69 to 0.86)	
≥160	449/ 1273	498/ 1215	172 mmHg			0.81 (0.72 to 0.93)	
Baseline diastolic blood pressure (mmHg)							
<70	304/ 846	352/ 881	66 mmHg			0.85 (0.73 to 1.00)	0.60
70-79	551/ 1748	637/ 1758	75 mmHg			0.83 (0.74 to 0.93)	
80-89	554/ 1852	651/ 1834	84 mmHg			0.81 (0.72 to 0.90)	
≥90	372/ 1113	424/ 1098	95 mmHg			0.81 (0.71 to 0.94)	

0.5   1.0   2.0
Hazard ratio (95% CI)

Figure 2. Effect of randomized treatment on all renal events (top) and the composite of all renal events, macrovascular events, or all-cause mortality (bottom) according to baseline SBP and DBP. The center of the diamond represents the estimate and its width the 95% CI for overall treatment effect. Solid boxes represent estimates of treatment effect in subgroups; the centers of the boxes are placed at the estimates of effect, the areas of boxes are proportional to the number of events, and horizontal lines represent the corresponding 95% CIs. The vertical dotted line represents the point estimate for overall effect. The "P trend" tested the consistency of treatment effect in subgroups.

moalbuminuria and at slightly higher rates in those with micro- or microalbuminuria with no effect of treatment assignment detectable. Similar acute reductions in GFR, without seeming benefit during 3 to 4 yr of follow-up, have been reported with the use of ACE inhibition in other populations with more severe forms of kidney disease.[25,26] In those studies, however, the group assigned to the lower BP target did have a reduction in the risk for kidney failure after prolonged follow-up.[27] Given that the risk for end-stage kidney disease is directly and strongly related to the level of albuminuria,[28,29] that reductions in albuminuria are associated with reductions in the risk for end-stage kidney disease,[30] and that remissions to normoalbuminuria predict an attenuated decline in kidney function,[21] beneficial effects of the ADVANCE regimen on such outcomes would be anticipated in the longer term. Moreover, levels of albuminuria are strongly associated with risks for

cardiovascular events and death (Table 3), which would be positively affected by treatment that reduces albuminuria.[31]

At the end of follow-up, patients who were randomly assigned to active treatment had lost 0.5 kg of body weight relative to patients who were randomly assigned to placebo. This difference is suggestive of modest volume depletion possibly as a result of the diuretic component of the fixed combination drug used in ADVANCE and the more limited use of diuretics by patients who were randomly assigned to placebo treatment. However, because instructions to reduce body weight could be provided in relation to the intensive glucose control arm of the study[32] and no data were collected on intake or excretion of sodium, this remains speculative. Although the diuretic component is likely to have contributed to the BP-lowering and antiproteinuric effect of the fixed combination perindopril-indapamide,[33] ADVANCE was not designed and is therefore not able to determine the separate effects of its components, the results of which can reliably be attributed only to the combination as a whole. Moreover, BP lowering *per se* is probably more important than the means by which such lowering is achieved.[10–13,34] The strong and continuous association we and others[16,17] observed between achieved BP and renal events supports this assertion. The absence of a lower limit of BP below which the risks for renal events did not continue to decline reemphasizes the broad range of individuals with diabetes who could derive benefit from BP-lowering therapy.

These analyses show that routine treatment with a fixed combination of perindopril and indapamide significantly reduced the risk for renal disease progression in a large representative population of patients with type 2 diabetes. In absolute terms, this simple, well-tolerated treatment strategy prevented one renal event among every 20 patients who were treated for 5 yr, with no selection of patients on the basis of BP or BP-lowering treatment. These data therefore suggest that BP lowering may be considered routinely for the prevention of renal complications in all patients with diabetes, regardless of the baseline BP level.

CONCISE METHODS

ADVANCE is a randomized factorial trial of BP and glucose-lowering regimens. The ADVANCE study methods have been previously pub-

	Number of events/ patients		Favors	Favors	Hazard ratio
	Per-Ind (n=5569)	Placebo (n=5571)	Per-Ind	Placebo	(95% CI)
All renal events	**1243/ 5571**	**1500/ 5569**			0.79 (0.73 to 0.85)
Age (years)					
≥65	732/ 3318	900/ 3295			0.76 (0.69 to 0.84)
<65	511/ 2251	600/ 2276			0.83 (0.74 to 0.93)
Sex					
Female	543/ 2366	651/ 2369			0.80 (0.72 to 0.90)
Male	700/ 3203	849/ 3202			0.78 (0.70 to 0.86)
Diabetes duration (years)					
<4	430/ 2032	514/ 2041			0.80 (0.71 to 0.91)
4-10	433/ 1877	516/ 1879			0.80 (0.70 to 0.91)
>10	380/ 1660	470/ 1649			0.76 (0.66 to 0.86)
Asian country					
Yes	549/ 2070	667/ 2066			0.79 (0.70 to 0.88)
No	694/ 3499	833/ 3505			0.79 (0.71 to 0.87)
Body mass index (kg/m²)					
<25	379/ 1519	443/ 1547			0.84 (0.73 to 0.96)
25-30	489/ 2274	607/ 2265			0.76 (0.68 to 0.86)
>30	374/ 1776	450/ 1759			0.77 (0.67 to 0.89)
Waist-hip ratio (cm/cm)					
<0.90	421/ 1873	514/ 1937			0.79 (0.70 to 0.90)
0.90-0.96	400/ 1713	508/ 1744			0.76 (0.66 to 0.86)
>0.96	422/ 1983	478/ 1890			0.78 (0.72 to 0.93)
HbA1c (%)					
≤7.5	703/ 3275	884/ 3368			0.78 (0.71 to 0.87)
>7.5	530/ 2182	611/ 2261			0.78 (0.70 to 0.88)
eGFR <60 ml·min⁻¹·1.73 m⁻²					
Yes	300/ 1064	336/ 1094			0.87 (0.74 to 1.02)
No	939/ 4462	1162/ 4476			0.76 (0.70 to 0.83)
Treatment with any BP lowering drugs					
Yes	957/ 4166	1158/ 4200			0.79 (0.73 to 0.86)
No	286/ 1403	342/ 1371			0.78 (0.67 to 0.91)
Treatment with open-label perindopril					
Yes	604/ 2637	759/ 2674			0.76 (0.68 to 0.84)
No	639/ 2932	741/ 2897			0.82 (0.74 to 0.91)
Treatment with lipid modifying drugs					
Yes	416/ 1938	512/ 1996			0.79 (0.70 to 0.90)
No	827/ 3631	988/ 3575			0.78 (0.71 to 0.86)
Treatment with anti-platelet drugs					
Yes	598/ 2597	710/ 2601			0.80 (0.71 to 0.89)
No	645/ 2972	790/ 2970			0.78 (0.70 to 0.87)
Smoker					
Yes	153/ 817	216/ 733			0.75 (0.61 to 0.92)
No	1090/ 4836	1284/ 4754			0.79 (0.73 to 0.86)

0.5   1.0   2.0
Hazard ratio

Figure 3. Effect of randomized treatment on all renal events in subgroups of participants defined by characteristics at baseline. For other conventions, see Figure 1. $P >$ 0.1 for trend for all subgroup comparisons.

lished[35] and are described here in brief. The findings reported here relate to the double-blind BP-lowering component of the trial, which ended in June 2007. The results of the glucose-lowering arm have been reported separately.[32]

Participants
A total of 11,140 individuals who had type 2 diabetes and were aged ≥55 yr were enrolled from 215 centers in 20 countries. Patients with diabetes were potentially eligible when they had evidence of a substantially elevated risk for vascular disease, as described in detail elsewhere.[18] Of note, there were no inclusion or exclusion criteria with

respect to BP, albuminuria rate, renal function, or use of BP-lowering agents. Approval for the trial was obtained from each center's institutional review board, and all participants provided written informed consent.

Study Treatment
Eligible participants were randomly assigned to either fixed-combination perindopril-indapamide (2 mg/0.625 mg) or matching placebo after a 6-wk run-in period during which all patients received active treatment. Study treatment dosages were doubled after 3 mo so that participants were receiving either perindopril-indapamide 4 mg/1.25 mg or matching placebo. Other treatments were continued at the discretion of the responsible physician, except that ACEIs other than perindopril were substituted with open-label perindopril at a dosage of 2 or 4 mg/d, which could be prescribed at any time through to the end of follow-up, thereby ensuring that the maximum recommended dosage of 8 mg was not exceeded. Use of thiazide or thiazide-like diuretics was not permitted[18]; however, if at any time a definite indication arose for a thiazide or an ACEI other than perindopril 4 mg/d, study treatment could be withdrawn and open-label therapy provided. There were neither limitations nor instructions formulated with respect to the use of concomitant treatments, diets, or other lifestyle interventions during follow-up related to the BP-lowering comparison, which all remained at the discretion of the responsible physician.

Follow-up and Assessments
Participants were seen at 3, 4, and 6 mo after randomization and subsequently every 6 mo. Mean participant follow-up was 4.3 yr. At each study visit, BP was recorded as the mean of two measurements made in the seated position using an automated sphygmomanometer (Omron HEM-705 CP; Omron, Kyoto, Japan). Measurement of UACR was performed on spot urine samples at 24, 48, and 60 mo after randomization and at the end of follow-up. Serum creatinine was measured 4 and 12 mo after randomization and subsequently at yearly intervals. Both UACR and serum creatinine levels were measured at local laboratories. The Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR.[36]

Outcomes
The main outcome for this analysis was a composite of renal events defined by new-onset microalbuminuria (UACR 30 to 300 μg/mg), new-onset nephropathy (new-onset macroalbuminuria defined as UACR >300 μg/mg, which required confirmation by a second sam-
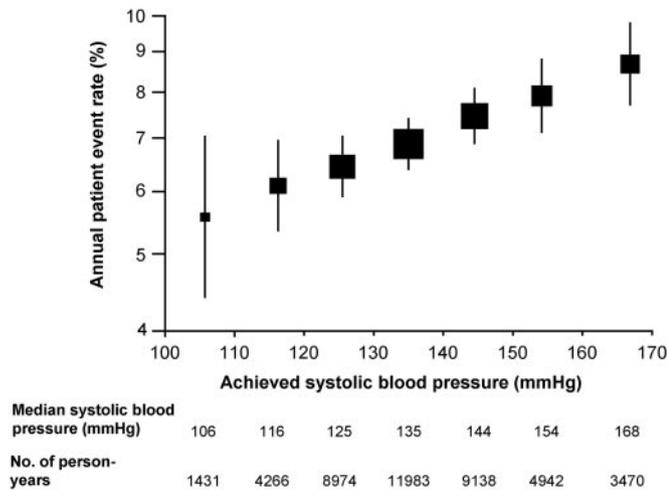
Figure 4. Incidence of all renal events according to achieved BP levels, adjusted for age, gender, duration of diabetes, glycosylated hemoglobin, currently treated hypertension, history of macrovascular disease, electrocardiogram abnormalities (ventricular hypertrophy, Q waves, or atrial fibrillation), triglycerides, LDL cholesterol, HDL cholesterol, body mass index, current smoking, current alcohol use, and study drug. Solid boxes represent estimates of event rates, centers of which are placed at the intersection of the point estimate and median SBP value. Areas of the boxes are proportional to the number of events, and vertical bars represent 95% CI. The rate of all renal events was significantly associated with achieved SBP levels ($P < 0.0001$ for trend).

ple), doubling of serum creatinine to >200 μmol/L, or end-stage kidney disease (defined as requirement for renal replacement therapy or renal death). Other outcomes included separate components of the main outcome; progression of albuminuria, defined as the worsening of at least one albuminuria stage (from normoalbuminuria to either micro- or macroalbuminuria or from micro- to macroalbuminuria); regression of albuminuria, defined as improvement of at least one albuminuria stage; and the composite of renal events, nonfatal macrovascular events (nonfatal stroke or nonfatal myocardial infarction), or all-cause mortality.

Statistical Analysis

The effects of randomized treatment on primary and secondary end points were estimated from unadjusted Cox proportional hazard models, based on the intention-to-treat principle. For participants with more than one outcome event during follow-up, survival time to the first relevant end point was used in each analysis. Participants were censored at their date of death or, for those still alive at the end of follow-up, the date of their last clinic visit before the termination of this study arm. Patients with unknown vital status were censored when they were last known to be alive. Relative risk reductions are described in the text and figures as percentage reductions ([1 − hazard ratio] × 100). Differences between randomized groups in BP during follow-up were estimated from linear mixed models.[37] Numbers needed to treat were calculated as reciprocals of the absolute risk differences with their normally approximated 95% CIs.[38]

Separate estimates for treatment effects were calculated for subgroups of participants defined by demographic factors, ancillary treatments, and standard microvascular and macrovascular risk factors at study entry. For BP, participants were grouped into two sets of the following four ordinal categories: SBP <120, 120 to 139, 140 to 159, and ≥ 160 mmHg and DBP <70, 70 to 79, 80 to 89, and ≥ 90 mmHg. Trends for treatment effects assessed as both categorical and continuous variables were tested by adding interaction terms to the relevant Cox models.

Associations between achieved BP levels and renal outcomes were assessed using the pooling of repeated observations method.[39,40] Briefly, each participant's follow-up period was divided into a series of intervals defined by the 2-yr visits. The presence or absence of the relevant outcome was documented during each interval and coupled to the time-weighted average of BP levels recorded during each interval. Missing follow-up BP values at any one visit (8.2% missing for all visits) were imputed by using the BP values recorded during the previous visit. The participants generated 28,969 intervals with follow-up SBP and DBP for the intervals ranging from 78 to 241 mmHg and from 41 to 121 mmHg, respectively. These intervals were then divided into seven ordinal achieved follow-up BP categories, separated by 10 mmHg for SBP and by 5 mmHg for DBP. Incidence rates of the relevant outcome were estimated using Poisson log-linear regression model that included risk factors for the development of chronic kidney disease.[41] Trends in relationships between achieved BP levels and the risk for outcomes were tested using each median value of BP for BP categories. The SAS 9.1 for Windows (SAS Institute, Cary, NC) was used to perform all statistical analyses. All P values were calculated from two-tailed tests of statistical significance with a type I error rate of 5%.

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