

The Effect of a Lower Target Blood Pressure on the Progression of Kidney Disease: Long-Term Follow-up of the Modification of Diet in Renal Disease Study

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Background: Hypertension is a risk factor for progression of chronic kidney disease. The optimal blood pressure to slow progression is unknown.

Objective: To evaluate the effects of a low target blood pressure on kidney failure and all-cause mortality.

Design: Long-term follow-up of the Modification of Diet in Renal Disease Study, a randomized, controlled trial conducted from 1989 to 1993.

Setting: 15 outpatient nephrology practices.

Participants: 840 persons with predominantly nondiabetic kidney disease and a glomerular filtration rate of 13 to 55 mL/min per 1.73 m².

Intervention: A low target blood pressure (mean arterial pressure < 92 mm Hg) or a usual target blood pressure (mean arterial pressure < 107 mm Hg).

Measurements: After the randomized trial was completed, kidney failure (defined as initiation of dialysis or kidney transplanta-

tion) and a composite outcome of kidney failure or all-cause mortality were ascertained through 31 December 2000.

Results: Kidney failure occurred in 554 participants (66%), and the composite outcome occurred in 624 participants (74%). After Cox proportional hazards modeling and intention-to-treat analysis, the adjusted hazard ratios were 0.68 (95% CI, 0.57 to 0.82; *P* < 0.001) for kidney failure and 0.77 (CI, 0.65 to 0.91; *P* = 0.0024) for the composite outcome in the low target blood pressure group compared with the usual target blood pressure group. Evidence was insufficient to conclude that the benefit of a low target blood pressure differed according to the cause of kidney disease, baseline glomerular filtration rate, or degree of proteinuria.

Limitations: The exact mechanism underlying the benefit of a low target blood pressure is unknown.

Conclusions: Assignment to a low target blood pressure slowed the progression of nondiabetic kidney disease in patients with a moderately to severely decreased glomerular filtration rate.

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The Seventh Report of the Joint National Commission on Prevention, Detection, Assessment and Treatment of Hypertension and the National Kidney Foundation Kidney Disease Outcome Quality Initiative Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease recommend a target blood pressure of less than 130/80 mm Hg in patients with chronic kidney disease (1, 2). These guidelines are based on data from observational studies demonstrating that persons with chronic kidney disease are at high risk for cardiovascular disease and from subgroup analyses of the Modification of Diet in Renal Disease (MDRD) Study suggesting that a low target blood pressure may slow the decline in kidney function in persons with moderate to high levels of proteinuria (3). However, no published trials in diabetic or nondiabetic kidney disease have demonstrated that a lower target blood pressure reduces the incidence of kidney failure.

Many types of chronic kidney disease progress slowly, requiring years for the onset of kidney failure. In clinical trials, progression of kidney disease is usually assessed by change in kidney function, which is measured as the glomerular filtration rate (GFR) or serum creatinine concentration. Two randomized, controlled trials in nondiabetic kidney disease have compared the effects of a low target blood pressure with those of a usual target blood pressure on the decline in GFR (3, 4). The MDRD Study enrolled

participants with predominantly nondiabetic kidney diseases, a baseline GFR of 13 to 55 mL/min per 1.73 m², and median proteinuria of 0.35 g/d (3). In that study, a low target blood pressure did not produce a slower projected mean decline in GFR at 3 years compared with the usual target blood pressure. However, participants with greater proteinuria significantly benefited from the low target blood pressure (3). On the basis of these findings, it was recommended that participants with proteinuria greater than 1 g/d have a lower target blood pressure.

The African American Study of Kidney Disease and Hypertension (AASK) enrolled participants with hypertensive nephrosclerosis, a baseline GFR of 20 to 70 mL/min per 1.73 m², and median baseline proteinuria of 0.081 g/d (4). In that study, a lower target blood pressure did not reduce the mean decline in GFR or the risk for the composite outcome of

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reduction in GFR of at least 50%, kidney failure, or all-cause mortality during a median follow-up of 4 years.

The average rates of decline in GFR in the MDRD Study and AASK were 4 mL/min per 1.73 m² per year and 2 mL/min per 1.73 m² per year, respectively, and relatively few participants developed kidney failure during the observation period. The long-term effect of a low target blood pressure on the onset of kidney failure may differ from the effect on decline in GFR observed during the trial. Therefore, we evaluated the effects of a low target blood pressure on the onset of kidney failure and all-cause mortality through extended follow-up after completion of the MDRD Study.

METHODS

The MDRD Randomized, Controlled Trial

The MDRD Study was a randomized, controlled trial of the effect of dietary protein restriction and strict control of blood pressure on the progression of kidney disease. Details of the design and randomization criteria are provided elsewhere (5, 6). The trial was conducted from 1989 to 1993. Eligibility criteria for enrollment were age 18 to 70 years and presence of chronic kidney disease, with a serum creatinine concentration of 123.8 μmol/L (1.4 mg/dL) to 618.8 μmol/L (7.0 mg/dL) in men and 106.1 μmol/L (1.2 mg/dL) to 618.8 μmol/L (7.0 mg/dL) in women. Persons with diabetes requiring therapy with insulin, class III or IV congestive heart failure, renal artery stenosis, history of kidney transplantation, or frequent hospitalizations were excluded. Eight hundred forty participants were enrolled: Study A included 585 participants with a baseline GFR of 25 to 55 mL/min per 1.73 m², and study B included 255 participants with a baseline GFR of 13 to 24 mL/min per 1.73 m².

Participants in both studies were randomly assigned to a low or a usual target blood pressure. The low target blood pressure was a mean arterial pressure less than 92 mm Hg (equivalent to a blood pressure less than 125/75 mm Hg) for participants 60 years of age or younger and less than 98 mm Hg for participants 61 years of age or older. The usual target blood pressure was a mean arterial pressure less than 107 mm Hg (equivalent to a blood pressure of 140/90 mm Hg) for participants 60 years of age or younger and less than 113 mm Hg for participants 61 years of age or older.

Participants in study A were randomly assigned to receive a usual-protein diet (1.0 g/kg of body weight daily) or a low-protein diet (0.6 g/kg daily), whereas participants in study B were randomly assigned to receive a low-protein diet (0.6 g/kg daily) or a very-low-protein diet (0.28 g/kg daily, with keto acid and amino acid supplementation). No interactions were noted between the dietary intervention and the blood pressure intervention (3).

Participants were followed up to 4 years. The rate of decline in GFR, measured as kidney clearance of ¹²⁵I-iothalamate, was the primary outcome.

Context

We do not know the optimal blood pressure needed to slow progression of chronic kidney disease.

Contribution

In this multicenter trial, 840 adults with mostly nondiabetic kidney disease and moderately to severely decreased glomerular filtration rate were randomly assigned to usual blood pressure control (target: mean arterial pressure < 107 mm Hg) or a low blood pressure goal (target: mean arterial pressure < 92 mm Hg). Approximately 10 years later, the hazard ratio for kidney failure in the low compared with the usual blood pressure group was 0.68 (95% CI, 0.57 to 0.82).

Implications

A low blood pressure target slows progression of nondiabetic kidney disease.

—The Editors

Long-Term Follow-up (1993–2000) of the MDRD Study

The investigational review boards of the Cleveland Clinic (Data Coordinating Center for the MDRD Study) and Tufts-New England Medical Center approved the long-term follow-up study. Kidney failure, defined by the requirement for dialysis or kidney transplantation, and a composite of kidney failure or all-cause mortality were the outcomes of interest for our analysis. All-cause mortality before kidney failure was included in the composite outcome because it is a competing risk factor for kidney failure. Participants were censored on 31 December 2000 if neither of these outcomes had occurred.

Blood Pressure Measurement

During the Trial (1989–1993)

Trained personnel measured blood pressure monthly by using a random-zero mercury sphygmomanometer. Therapeutic regimens were modified monthly or more often as needed to achieve target blood pressure. For our analysis, mean follow-up blood pressure during the study was defined as the average of all blood pressure measurements obtained after the 4th month of follow-up. This definition differs from that of previous studies, in which the average of all blood pressure measurements during follow-up was calculated (3, 7). The change in definition was introduced to allow comparison with the AASK Study.

During Long-Term Follow-up (1993–2000)

No specific target blood pressure was recommended after completion of the trial. Blood pressure was measured by using the same methods in a large subgroup of participants 9 months after the end of the study (“phase V”). Thereafter, blood pressure measurements are not available.

Antihypertensive Regimens

During the Trial (1989–1993)

After random allocation, therapeutic regimens were modified to achieve the target blood pressure. Nonpharmacologic therapy consisted of recommendations for exercise and weight loss and reductions in intake of dietary sodium and alcohol. For pharmacologic therapy, use of all agents was allowed, in the interest of achieving blood pressure goals. However, angiotensin-converting enzyme (ACE) inhibitors, with or without a diuretic, were encouraged as agents of first choice. Calcium-channel blockers, with or without a diuretic, were encouraged as agents of second choice.

During Long-Term Follow-up (1993–2000)

Because the MDRD Study did not evaluate the effects of individual antihypertensive agents on decline in kidney function, no specific pharmacologic therapy was recommended after completion of the trial.

Outcomes

The onset of kidney failure was ascertained from the U.S. Renal Data System by using participants' Social Security number, name, sex, and date of birth. Data on all-cause mortality were obtained from the National Death Index by using the same identifying information.

One hundred eighty-five participants were recorded as starting dialysis or receiving a kidney transplant during or shortly after the randomized trial in both the MDRD Study database and the U.S. Renal Data System database. The recorded date of kidney failure agreed between the 2 databases to within 1 day for 50% of these participants, to within 30 days for 90%, and to within 120 days for 97%. Nine participants recorded as reaching kidney failure in the MDRD Study database were not found in the U.S. Renal Data System database. Except in the case of these 9 participants (4 of whom were in the usual target blood pressure group and 5 of whom were in the low target blood pressure group), data obtained from U.S. Renal Data System database were used in all analyses to define the date of kidney failure.

All deaths that were coded in the U.S. Renal Data System database were confirmed in the National Death Index. For all analyses, the date in the National Death Index was used as the date of death so as to maintain consistency with participants who died but had not reached kidney failure and therefore were not included in the U.S. Renal Data System database.

Statistical Analyses

We combined participants from studies A and B to improve statistical power. This approach was justified because analysis of the short-term outcomes of the MDRD Study showed no differences between the studies in terms of the effect of target blood pressure.

We evaluated the effect of blood pressure group on the risk for kidney failure and the composite outcome by using

Cox regression with stratification for clinical center and study (study A vs. study B). The follow-up period included both the randomized trial (mean duration of follow-up, 2.2 years) and subsequent long-term follow-up until administrative censoring on 31 December 2000. Death was censored as a competing risk in the analysis of kidney failure alone. All analyses were performed on an intention-to-treat basis, in which participants were analyzed according to blood pressure group throughout the randomized trial and long-term follow-up.

To increase statistical power, hazard ratios with adjustment for baseline factors were obtained. In addition to diet group, 6 baseline factors were specified a priori on the basis of previous analyses showing that they were independently associated with rates of decline in GFR (8): urinary protein excretion (logarithmic transformation), presence of polycystic kidney disease, black ethnicity, serum transferrin concentration, serum high-density lipoprotein cholesterol concentration, and mean arterial pressure. We performed additional adjustment for baseline GFR and age because of their known effects on time to kidney failure and death, respectively. Finally, the proportional hazards assumption of the Cox regression models was checked by testing the interaction of each baseline factor with duration of follow-up. As a result, the interaction terms of follow-up time with baseline urine protein excretion and diagnosis of polycystic kidney disease were included.

Time-dependent Cox regression was also used to estimate the hazard ratios associated with the blood pressure intervention separately for the trial period and the post-trial follow-up period, and within successive 2-year intervals throughout the entire follow-up period.

We performed prespecified tests for interactions to determine whether the effects of the blood pressure intervention differed between subgroups, defined by the following baseline variables: study (A or B), diet assignment (usual, low protein, or very low protein), baseline level of proteinuria (<0.3 g/d, 0.3 to 1 g/d, 1 to 3 g/d, or >3 g/d), and cause of kidney disease (polycystic kidney disease, glomerular disease, or other).

Finally, we performed a sensitivity analysis in which the Cox regressions evaluating the effect of the blood pressure goal were repeated after adjustment for use of ACE inhibitors during the trial. "Use" was defined as receipt of an ACE inhibitor for at least 50% of follow-up visits during the trial. We chose to perform this sensitivity analysis exclusively for ACE inhibitors because these agents are known to slow progression of kidney disease independent of their blood pressure-lowering effects (9, 10).

Role of the Funding Source

The National Institutes of Diabetes and Digestive and Kidney Diseases funded this study and had no role in its design, conduct, or reporting or in the decision to submit the manuscript for publication.

Table 1. Characteristics of Participants in the Modification of Diet in Renal Disease Study (1989 to 1993), at Baseline and during Follow-up*

Characteristic	Low Target Blood Pressure Group (n = 432)	Usual Target Blood Pressure Group (n = 408)
Baseline		
Age, y	51.5 ± 12.6	52.0 ± 12.2
Men, %	61.8	59.1
African-American ethnicity, %	7.9	7.8
Median proteinuria, g/d	0.39	0.31
Kidney disease diagnosis, %		
Polycystic kidney disease	24.5	23.0
Glomerular disease	23.8	25.7
Other	51.7	51.3
Glomerular filtration rate, mL/min per 1.73 m ²	32.7 ± 12.1	32.3 ± 11.9
Blood pressure, mm Hg		
Mean arterial	96 ± 10	97 ± 11
Systolic	130 ± 16	131 ± 18
Diastolic	80 ± 10	80 ± 10
Diabetes, %	5.3	4.9
Serum cholesterol level, mmol/L (mg/dL)		
Total	5.62 ± 1.19 (217 ± 46)	5.70 ± 1.14 (220 ± 44)
High-density lipoprotein	1.04 ± 0.36 (40.0 ± 13.9)	1.04 ± 0.37 (40.1 ± 14.3)
Serum albumin level, g/L	40.0 ± 3.0	40.0 ± 3.0
Serum transferrin level, g/L	2.73 ± 0.43	2.73 ± 0.44
During follow-up		
Blood pressure, mm Hg†		
Mean arterial	93.3 ± 6.9	98.4 ± 7.4
Systolic	126.2 ± 13.6	133.8 ± 14.9
Diastolic	76.9 ± 6.4	80.7 ± 7.2
Use of an antihypertensive agent, %‡		
Angiotensin-converting enzyme inhibitors	51	32
β-Blockers	30	30
Calcium-channel blockers	40	30
Diuretics	50	42
Other	21	17

* Unless otherwise specified, data are presented as the mean ± SD.

† Mean blood pressure from month 4 through the end of follow-up of the study (median, 2.2 years). Blood pressures after month 4 were available for 422 participants in the low target blood pressure group and 402 participants in the usual target blood pressure group.

‡ "Use" was defined as receipt of the antihypertensive agent for more than 50% of follow-up visits. Data were available for 430 participants in the low target blood pressure group and 407 participants in the usual target blood pressure group.

RESULTS

Baseline Clinical and Demographic Characteristics of the MDRD Study Participants

The mean age of participants was 52 years, and 61% of participants were male (Table 1). Eight percent were African American, and 5% had type 2 diabetes. Polycystic kidney disease and glomerular disease were the causes of chronic kidney disease in 24% and 25% of participants, respectively. The mean proteinuria was 1.09 g/d (median, 0.35 g/d). Baseline characteristics were well balanced between the usual and low target blood pressure groups.

Blood Pressure and Use of Medication during Follow-up

The mean differences in mean arterial blood pressure, systolic blood pressure, and diastolic blood pressure between the low target blood pressure group (422 participants) and the usual target blood pressure group (402 participants) after 4 months until the end of the trial were 5.1 mm Hg, 7.6 mm Hg, and 3.8 mm Hg, respectively (Figure 1). At phase V, the differences in mean arterial pressure, systolic blood pressure, and diastolic blood pressure between the low target blood pressure group (266 participants) and

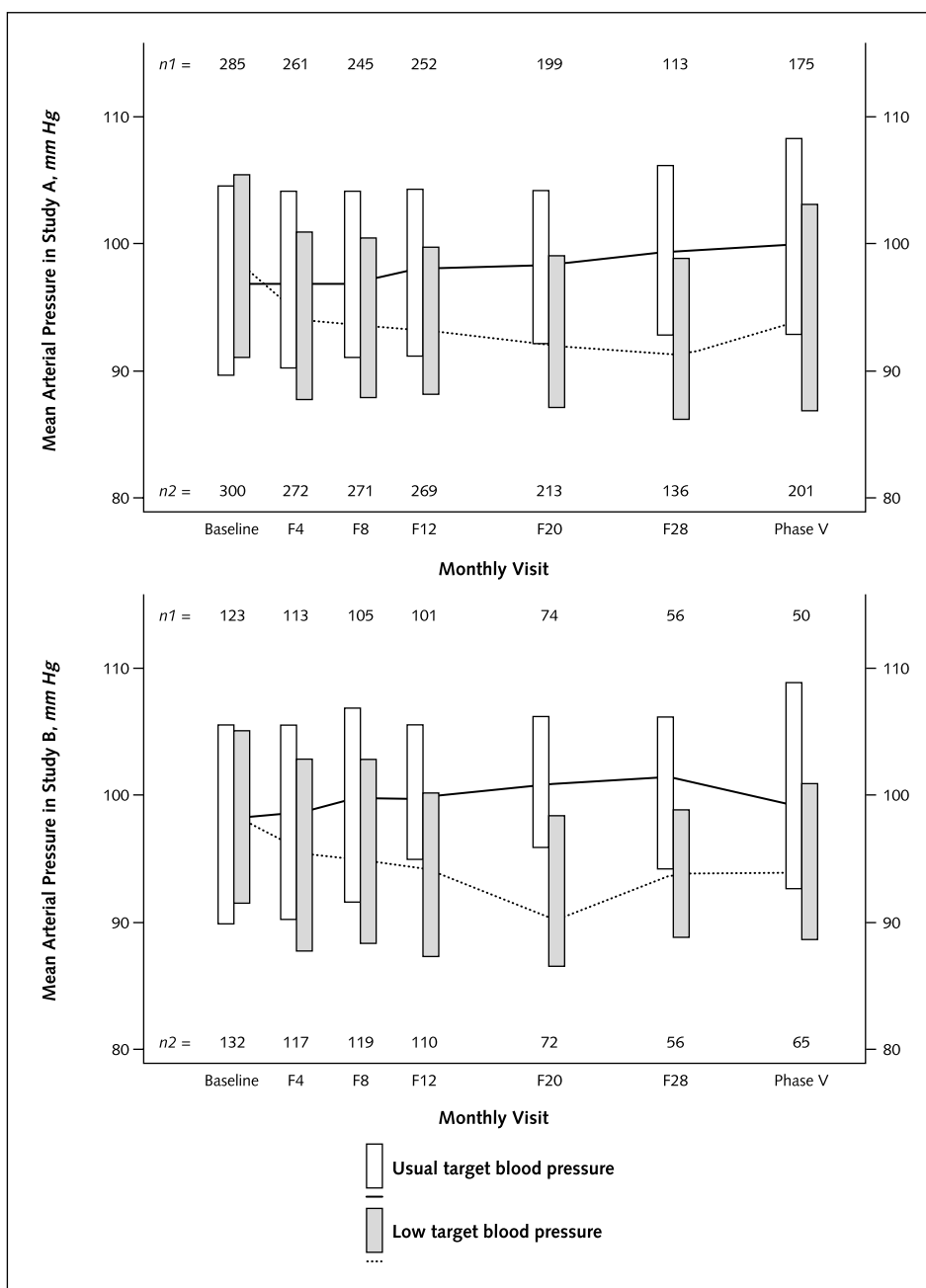
usual target blood pressure group (225 participants) were 5.1 mm Hg, 8.0 mm Hg, and 3.2 mm Hg, respectively.

During the trial, 51% of participants in the low target blood pressure group and 32% of participants in the high target blood pressure group received ACE inhibitors for more than 50% of follow-up visits (Table 1). A similar percentage of participants in both blood pressure groups received β-blockers, whereas a slightly higher percentage of participants in the low target blood pressure group received diuretics and calcium-channel blockers.

Effect of the Blood Pressure Intervention on Kidney Failure and the Composite Outcome

The mean duration of follow-up until kidney failure, death, or censoring on 31 December 2000 was 6.2 years (median, 5.9 years). The mean potential duration of follow-up from randomization to 31 December 2000 was 10.6 years (median, 10.7 years). After randomization, 554 participants (66%) developed kidney failure, and 70 died before kidney failure occurred (Figure 2). Kidney failure developed in 268 participants (62%) in the low target blood pressure group and 286 participants (70%) in the usual

Figure 1. Mean arterial blood pressure during the Modification of Diet in Renal Disease Study (1989 to 1993).



The bars extend from the 25th to the 75th percentiles, and the dotted and solid lines connect the medians. F = month of follow-up; *n1* = participants in the usual target blood pressure group for whom a blood pressure measurement was available at the indicated follow-up time point; *n2* = participants in the low target blood pressure group for whom a blood pressure measurement was available at the indicated follow-up time point; phase V = 9 months after completion of the trial.

target blood pressure group. Three hundred twelve participants (72%) in the low target blood pressure group and 312 participants (76%) in the usual target blood pressure group reached the composite outcome. The mean duration of follow-up was 6.4 years (median, 6.2 years) in the low target blood pressure group and 6.1 years (median, 5.6 years) in the usual target blood pressure group.

The low target blood pressure was associated with a reduced risk for kidney failure or the composite outcome

compared with the usual target blood pressure throughout the extended follow-up period (Figure 3, Table 2). The unadjusted hazard ratios in the low target blood pressure group were 0.78 (95% CI, 0.66 to 0.93) for kidney failure ($P = 0.0056$) and 0.85 (CI, 0.72 to 1.00) for the composite outcome ($P = 0.05$). After we controlled for covariates, the hazard ratios in the low target blood pressure group were 0.68 (CI, 0.57 to 0.82) for kidney failure ($P < 0.001$) and 0.77 (CI, 0.65 to 0.91) for the composite outcome ($P = 0.0024$).

Because the hazard ratios in the Cox regression analyses compare the blood pressure groups at specific times throughout follow-up, values less than 1.0 reflect delays in progression to kidney failure or the composite outcome, rather than prevention. The risk reductions associated with the low target blood pressure were similar between the 2 diet groups in studies A and B ($P > 0.15$ for interaction of diet group by blood pressure for both the kidney failure and composite outcomes in studies A and B).

The magnitude of the risk reduction associated with the low target blood pressure was similar throughout follow-up, and no significant differences were observed in the effect of the blood pressure intervention between different intervals during or after the randomized trial (Table 2).

Figure 4 shows hazard ratios in the low and usual target blood pressure groups for kidney failure and the composite outcome, by diagnosis of kidney disease, study (A or B), and degree of baseline proteinuria. The risk reduction associated with the low target blood pressure was similar in all 3 subgroups of kidney disease diagnosis (interaction $P > 0.2$ for risk for kidney failure and for the composite outcome). Although the hazard ratios tended to be lower in study A than study B, the interaction of study and target blood pressure did not reach statistical significance ($P = 0.08$ for kidney failure and 0.07 for the composite outcome). Furthermore, a similar trend was not ob-

served when baseline GFR was treated as a continuous variable ($P > 0.2$ for kidney failure and for the composite outcome). The risk reductions in the low target blood pressure group tended to be larger for participants with high proteinuria, but the interaction of blood pressure group with baseline proteinuria did not reach statistical significance ($P = 0.09$ for kidney failure and 0.08 for the composite outcome). When the 2 subgroups with lower baseline proteinuria (< 1 g/d) were combined, the hazard ratios associated with the low target blood pressure group were 0.79 (CI, 0.63 to 0.99) for kidney failure ($P = 0.04$) and 0.87 (CI, 0.71 to 1.08) for the composite outcome ($P = 0.2$).

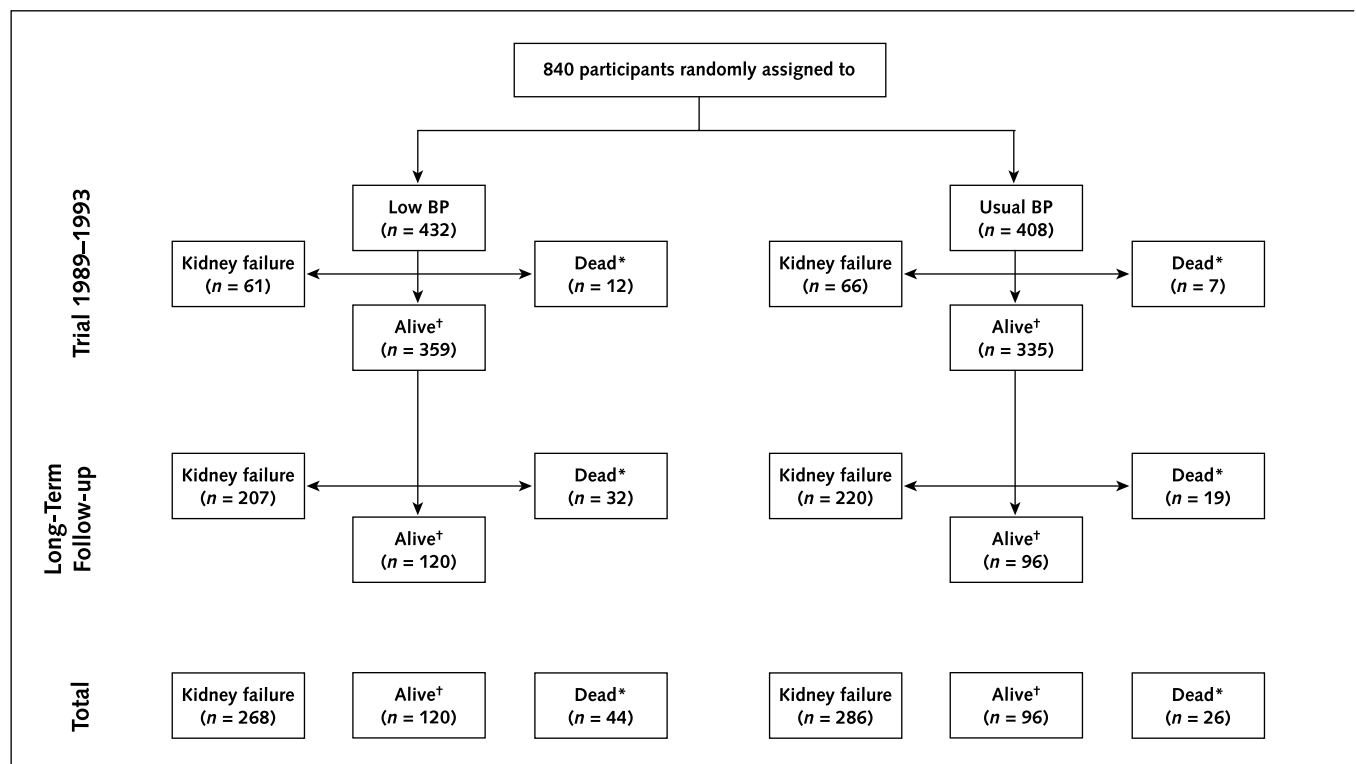
Sensitivity Analysis for Use of ACE Inhibitors

Additional adjustment for use of ACE inhibitors in follow-up during the trial did not substantially change the results. The adjusted hazard ratios in the low target blood pressure group were 0.69 (CI, 0.57 to 0.83) for kidney failure ($P < 0.001$) and 0.79 (CI, 0.66 to 0.93) for the composite outcome ($P = 0.0058$).

DISCUSSION

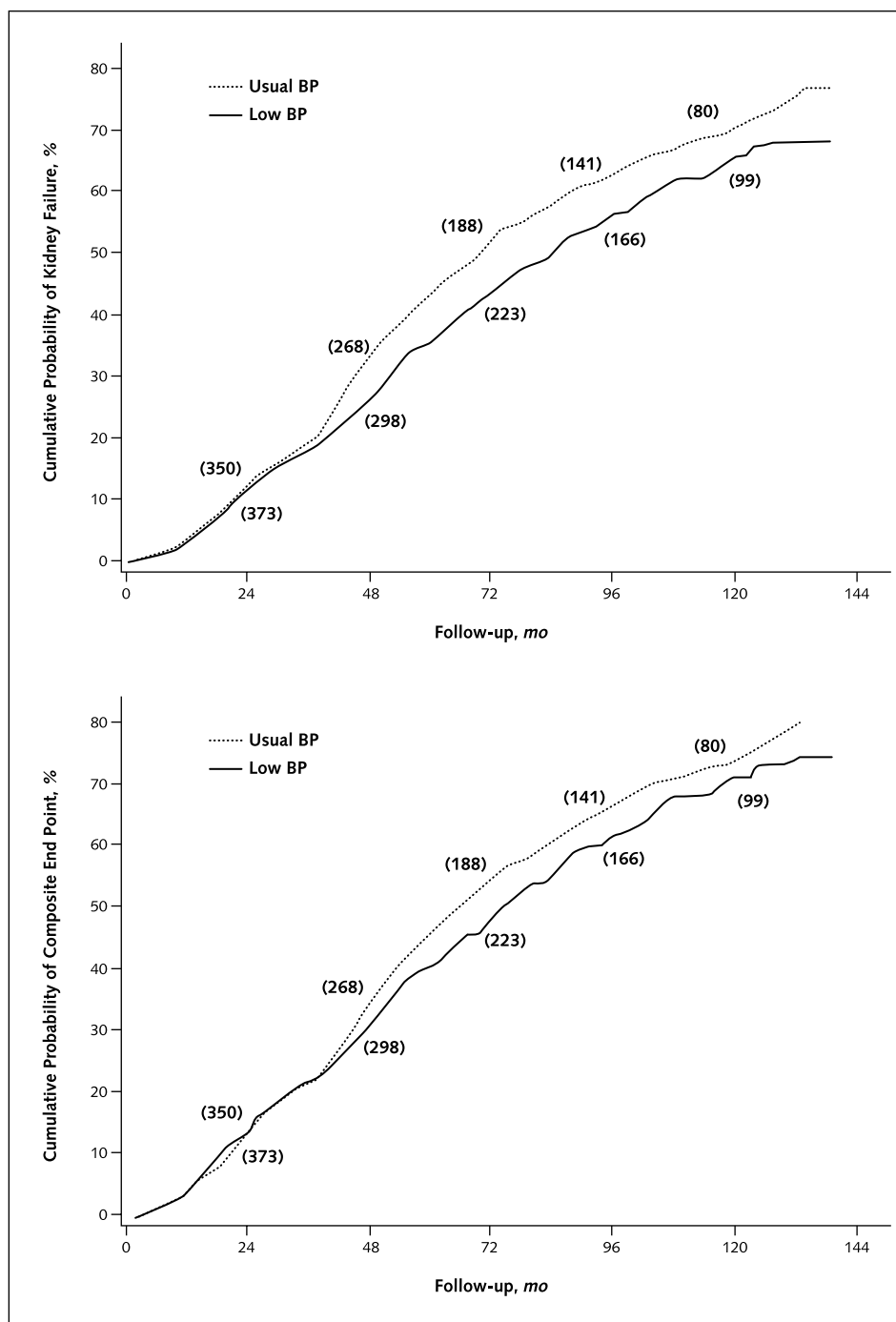
The outcomes observed after long-term follow-up of the MDRD Study show that participants in the low target blood pressure group took longer to develop kidney failure and the composite outcome of kidney failure or all-cause

Figure 2. Outcomes during the Modification of Diet in Renal Disease Study (1989 to 1993) and during long-term follow-up (1993 to 2000).



*The number of deaths include only those that occurred before kidney failure. †“Alive” refers to participants who did not develop kidney failure or who died during the period of interest. BP = blood pressure.

Figure 3. Cumulative probability of kidney failure (top) and cumulative probability of the composite of kidney failure or all-cause mortality before kidney failure (bottom).



“Low blood pressure” and “usual blood pressure” refer to a target mean arterial pressure of less than 92 mm Hg and less than 107 mm Hg, respectively. Numbers in parentheses are numbers of participants. For the top panel, there were 554 events (unadjusted $P = 0.0056$; adjusted $P = 0.00003$). For the bottom panel, there were 624 events (unadjusted $P = 0.0502$; adjusted $P = 0.0024$). BP = blood pressure.

mortality. The benefit of the low target blood pressure was observed in participants with various types of kidney disease, including polycystic kidney disease, and may extend to participants with proteinuria less than 1 g/d.

The strengths of our study are the random assignment of target blood pressure group, complete ascertainment of

data by using “hard” outcomes, and use of the intention-to-treat principle in analyses. The primary limitation is the lack of blood pressure measurements during long-term follow-up; as a result, the mechanism underlying the benefit of assignment to the low target blood pressure group remains unclear.

The long-term results differ from those observed during the trial, in which the effect of the low target blood pressure was inconclusive (3). The low target blood pressure group had a significantly faster initial decrease in GFR (baseline to 4 months), then a slower decrease thereafter (4 months to end of follow-up), but the groups did not differ in the mean GFR projected to 3 years of follow-up. The findings from long-term follow-up resolve the uncertainties in results from the trial by establishing that the low blood pressure intervention slowed the progression of kidney disease, as judged by the delayed onset of kidney failure and the composite outcome of kidney failure or all-cause mortality.

During the trial, the effect of blood pressure intervention on decrease in GFR varied by degree of baseline proteinuria (that is, a statistically significant interaction was observed between baseline proteinuria and treatment effect) (3, 7), and subgroup analyses suggested that the low target blood pressure reduced the rate of decrease in GFR in participants with baseline proteinuria greater than 1 g/d. A meta-analysis of randomized trials of ACE inhibitors in patients with nondiabetic kidney disease also suggested a greater benefit of lower blood pressure in participants with greater proteinuria (10). The long-term follow-up study confirms the benefit of a low target blood pressure in the subgroup with baseline proteinuria greater than 1 g/d: Patients had delayed progression to kidney failure and the composite outcome. However, unlike during the trial, the interaction of baseline proteinuria with blood pressure group was not statistically significant. A significant interaction may not have been detected in long-term follow-up because of limited power. The dependence of the effect of blood pressure on baseline proteinuria also may have been weakened by the long interval between the baseline measurement and the occurrence of most outcomes.

Results observed during the trial have been interpreted as suggesting that the effect of a low target blood pressure

may differ depending on the cause of kidney disease (11). However, the benefit of the low target blood pressure on the long-term outcomes was consistent in participants with polycystic kidney disease, glomerular diseases, and other causes of kidney disease (Figure 4).

The long-term results of the MDRD Study appear to differ from those of AASK, which reported no significant benefit of a low target blood pressure despite a longer intervention period (median, 4 years) and a wider difference in blood pressure between the blood pressure groups (average difference in mean arterial pressure after 4 months, 8 mm Hg in AASK compared with 5 mm Hg in the MDRD Study) (4). These discrepancies may have resulted from differences in ethnicity and type of kidney disease between the study samples, a lower degree of proteinuria in AASK than the MDRD Study, and longer follow-up and more patients who reached kidney failure in long-term follow-up of the MDRD Study. Continued follow-up of the AASK participants in the ongoing AASK cohort study (12) will permit ascertainment of outcomes with a duration of follow-up similar to that of the long-term follow-up of the MDRD Study and may clarify comparison of the 2 studies.

Ascertainment of clinical outcomes through registries long after completion of a randomized trial highlights matters of statistical and clinical interpretation. The intention-to-treat interpretation of the results from long-term follow-up of the MDRD Study is that the observed long-term reduction in risk reflects the effect of random assignment to a low target blood pressure versus a usual target blood pressure over a mean intervention period of 2.2 years. If the beneficial effect of the low target blood pressure was due to lower achieved blood pressure during these 2.2 years, the effect might have been even larger if the differences in blood pressure had been sustained throughout follow-up. The major limitation to the clinical interpretation of the study is

Table 2. Adjusted Hazard Ratios for Low Target Blood Pressure Compared with Usual Target Blood Pressure throughout Follow-up

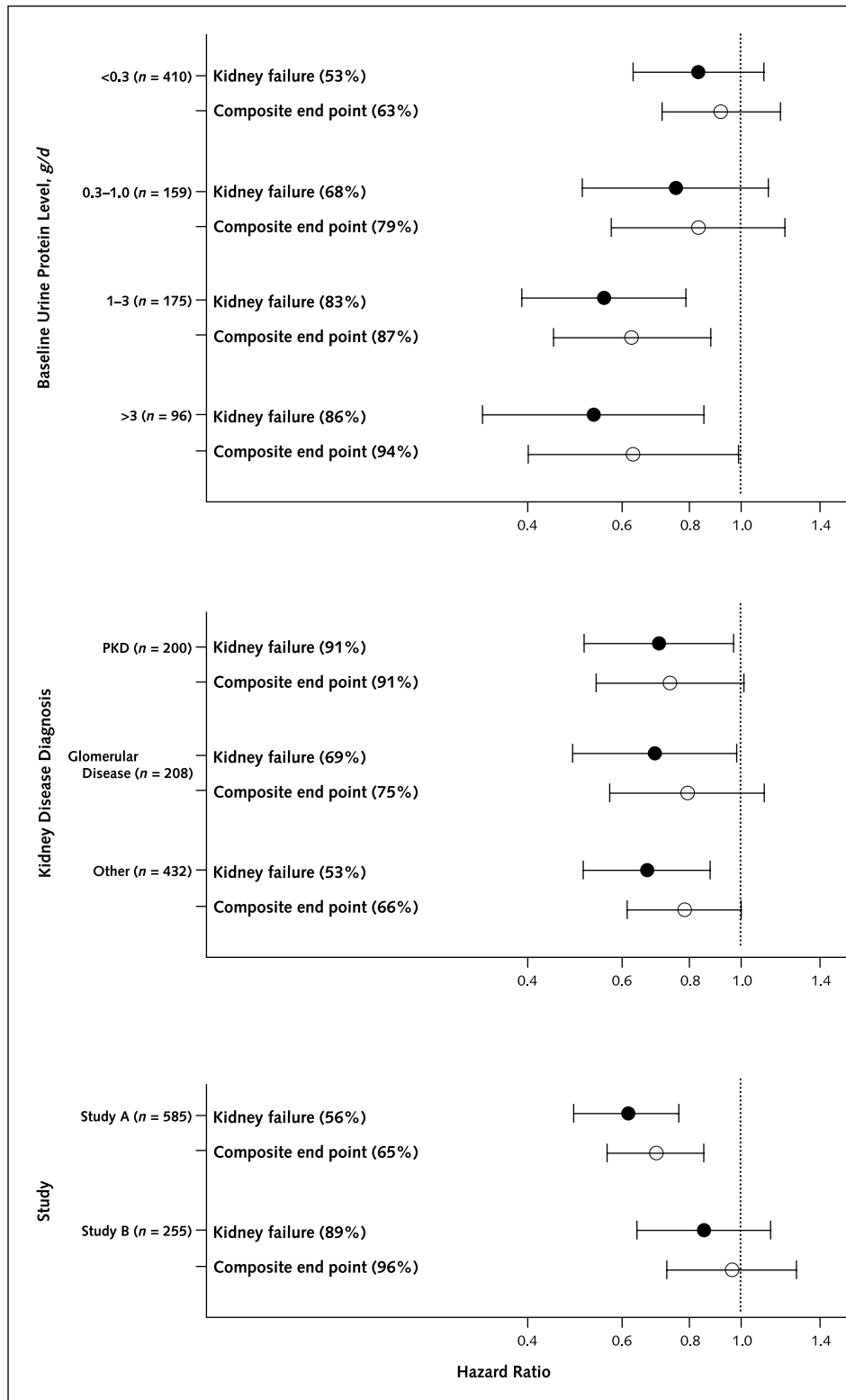
Analysis*	Kidney Failure			Kidney Failure or All-Cause Mortality		
	Hazard Ratio (95% CI)	P Value	Events, n	Hazard Ratio (95% CI)	P Value	Events, n
No adjustment for covariates	0.78 (0.66–0.93)	0.0056	554	0.85 (0.72–1.00)	0.0502	624
Adjusted for baseline covariate†	0.68 (0.57–0.82)	<0.001	554	0.77 (0.65–0.91)	0.0024	624
Interval						
0–2 y†	0.80 (0.53–1.21)	>0.2	100	0.89 (0.61–1.29)	>0.2	117
2–4 y†	0.63 (0.44–0.90)	0.01	142	0.77 (0.55–1.06)	0.12	156
4–6 y†	0.63 (0.45–0.90)	0.01	146	0.69 (0.49–0.97)	0.03	156
6–8 y†	0.80 (0.51–1.25)	0.2	87	0.85 (0.57–1.28)	0.2	104
8 y†	0.59 (0.36–0.98)	0.04	79	0.67 (0.42–1.07)	0.09	91
During the trial‡	0.76 (0.52–1.10)	0.15	127	0.77 (0.54–1.11)	0.2	146
After the trial‡	0.66 (0.53–0.81)	<0.001	427	0.76 (0.63–0.91)	0.0038	478

* All analyses are stratified by clinical center and study.

† Hazard ratios were adjusted for the following baseline variables: log urinary protein, log urine protein × duration of follow-up, polycystic kidney disease, polycystic kidney disease × duration of follow-up, black ethnicity, transferrin level, high-density lipoprotein cholesterol level, mean arterial pressure, glomerular filtration rate, age, and dietary protein assignment.

‡ The effect of the blood pressure intervention did not differ significantly among periods of follow-up when duration of follow-up was treated as a continuous variable (*P* for interaction > 0.2 for kidney failure and the composite outcome), categorized by 2-year intervals (*P* for interaction > 0.2 for kidney failure and the composite outcome), or between periods of follow-up during and after completion of the trial (*P* for interaction > 0.2 for kidney failure and the composite outcome, respectively).

Figure 4. Adjusted hazard ratios in the low target blood pressure group and the usual target blood pressure group, by subgroup.



The *P* value for interaction of target blood pressure with proteinuria was 0.09 for kidney failure and 0.08 for the composite outcome. The *P* value for interaction of target blood pressure with kidney disease diagnosis was 0.97 for kidney failure and 0.94 for the composite outcome. The *P* values for the interaction of target blood pressure with study (A versus B) were 0.08 for kidney failure and 0.07 for the composite outcome. All analyses are adjusted for the following baseline variables: log urinary protein, log urinary protein × duration of follow-up, polycystic kidney disease, polycystic kidney disease × duration of follow-up, black ethnicity, transferrin level, high-density lipoprotein cholesterol level, mean arterial pressure, glomerular filtration rate, age, and dietary protein group assignment. The analysis is stratified by clinical center and study. The composite outcome is kidney failure or all-cause mortality before kidney failure. The percentages in parentheses are the proportion of patients in each subgroup with kidney failure or the composite outcome.

that blood pressures after the trial are not known. We considered several potential explanations for the results.

First, the difference in blood pressure between randomized groups may have persisted because of continuation during long-term follow-up of practices observed during trial. Evidence supporting this idea is the phase V blood pressures, which continued to differ between the randomized groups (Figure 1).

Second, even if blood pressure did not differ between groups during long-term follow-up, the low blood pressure achieved during the trial may have beneficial effects on progression of kidney disease that are seen only during long-term follow-up. The kidney may be especially vulnerable to damage from hypertension when the GFR is in the range of that seen in the MDRD Study participants (13 to 55 mL/min per 1.73 m²), and interventions during this time may have a long-term effect even if they are not sustained.

Finally, ACE inhibitors slow the progression of both diabetic and nondiabetic kidney disease (9, 13) by mechanisms in addition to decreasing blood pressure, and more participants in the low target blood pressure group received ACE inhibitors. We believe that this explanation for the results is unlikely, for 2 reasons. First, the sensitivity analysis did not affect the results. We acknowledge, however, the limitations of this sensitivity analysis in that use of ACE inhibitors was not randomized. Also, only 19% more patients in the low target blood pressure group than the usual target blood pressure group used ACE inhibitors, yet the adjusted hazard ratio for kidney failure in the low target blood pressure group was 0.68. This finding is similar to the benefit observed in studies in which participants were randomly assigned to therapy with ACE inhibitors or other classes of antihypertensive agents (a 100% difference in use of ACE inhibitors) (9, 13), suggesting that the discrepancy in ACE inhibitor use would be unlikely to explain the results.

In summary, a low target blood pressure delayed the onset of kidney failure and a composite outcome of kidney failure and all-cause mortality in long-term follow-up of the MDRD Study. This beneficial effect was observed in participants with various causes of nondiabetic kidney disease and may extend across a wide range of proteinuria. These results are consistent with recent guidelines (1, 2) that recommend a target blood pressure of 130/80 mm Hg, primarily to reduce cardiovascular disease outcomes. Moreover, these results show the value of linking a randomized trial with a national database including long-term outcomes, and the need to consider long-term follow-up of interventions designed to slow progression of a chronic disease.

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