

ORIGINAL INVESTIGATIONS

Pathogenesis and Treatment of Kidney Disease

Progression of Kidney Disease in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin Versus Usual Care: A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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Background: Dyslipidemia is common in patients with chronic kidney disease. The role of statin therapy in the progression of kidney disease is unclear.

Study Design: Prospective randomized clinical trial, post hoc analyses.

Setting & Participants: 10,060 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (lipid-lowering component) stratified by baseline estimated glomerular filtration rate (eGFR): less than 60, 60 to 89, and 90 or greater mL/min/1.73 m². Mean follow-up was 4.8 years.

Intervention: Randomized; pravastatin, 40 mg/d, or usual care.

Outcomes & Measurements: Total, high-density lipoprotein, and low-density lipoprotein cholesterol; end-stage renal disease (ESRD), eGFR.

Results: Through year 6, total cholesterol levels decreased in the pravastatin (−20.7%) and usual-care groups (−11.2%). No significant differences were seen between groups for rates of ESRD (1.36 v 1.45/100 patient-years; *P* = 0.9), composite end points of ESRD and 50% or 25% decrease in eGFR, or rate of change in eGFR. Findings were consistent across eGFR strata. In patients with eGFR of 90 mL/min/1.73 m² or greater, the pravastatin arm tended to have a higher eGFR.

Limitations: Proteinuria data unavailable, post hoc analyses, unconfirmed validity of the Modification of Diet in Renal Disease Study equation in normal eGFR range, statin drop-in rate in usual-care group with small cholesterol differential between groups.

Conclusions: In hypertensive patients with moderate dyslipidemia and decreased eGFR, pravastatin was not superior to usual care in preventing clinical renal outcomes. This was consistent across the strata of baseline eGFR. However, benefit from statin therapy may depend on the degree of the cholesterol level decrease achieved.

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INDEX WORDS: Hyperlipidemia; glomerular filtration rate; pravastatin.

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It is estimated that more than 10 million Americans have chronic kidney disease (CKD) and are at high risk of progression to end-stage renal

disease (ESRD).¹ Hyperlipidemia is common in patients with CKD,² and there are good reasons to postulate a beneficial effect of statin therapy on progression of kidney disease. Epidemiological studies show that greater cholesterol levels are associated with a more rapid decrease in

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kidney function.^{3,4} Statins have physiological actions beyond lipid lowering, such as improvement in vascular compliance⁵ and decrease in chronic inflammation,⁶ that may have a beneficial effect in patients with kidney disease.⁷ However, some,⁸ but not all, studies^{9,10} have documented a beneficial effect of statin therapy on kidney disease outcomes. Therefore, whether statin therapy in patients with CKD with modest dyslipidemia slows the decrease in kidney function is unresolved.

The lipid-lowering component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) was conducted to determine whether pravastatin compared with usual care decreased mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional risk factor for coronary heart disease (CHD).¹¹ The main results showed no significant difference in all-cause mortality or CHD events (nonfatal myocardial infarction or fatal CHD combined) between the 2 groups. The purpose of this article is to report a post hoc analysis of the effect of pravastatin therapy compared with usual care on kidney disease outcomes stratified by baseline estimated glomerular filtration rate (eGFR).

METHODS

ALLHAT adhered to the Declaration of Helsinki, and written informed consent was obtained. The design and conduct of ALLHAT-LLT have been reported previously.¹¹ Briefly, ALLHAT-LLT was a randomized open-label large simple trial conducted from February 1994 through March 2002 at 513 of the 623 ALLHAT clinical centers in the United States, Puerto Rico, US Virgin Islands, and Canada. The intervention was open-label pravastatin (40 mg/d) versus usual care. Participants were drawn from ALLHAT, a 4-armed antihypertensive trial in which a calcium channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), and an α -adrenergic blocking agent (doxazosin) were each compared with a thiazide-like diuretic (chlorthalidone). Eligibility criteria for the ALLHAT-LLT included prior enrollment in ALLHAT (age ≥ 55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor); fasting low-density lipoprotein (LDL) cholesterol level of 120 to 189 mg/dL (3.1 to 4.9 mmol/L) for those with no known CHD or 100 to 129 mg/dL (2.6 to 3.3 mmol/L) for those with known CHD, and fasting triglyceride level less than 350 mg/dL (< 3.9 mmol/L). Participants were excluded who were currently using prescribed lipid-lowering agents or large doses (≥ 500 mg/d) of nonprescription niacin, were known to be intolerant of statins or to have significant liver dysfunction (serum alanine aminotransferase > 100 IU/L), had other contraindications for statin therapy, or had a

known secondary cause of hyperlipidemia. Follow-up visits were scheduled to coincide with visits for the ALLHAT parent trial, ie, at 3, 6, 9, and 12 months after randomization into ALLHAT and every 4 months thereafter. A fasting lipid profile was obtained for all ALLHAT-LLT participants at LLT baseline and during follow-up in random preselected samples of usual-care (5%) and pravastatin (10%) participants. All ALLHAT-LLT participants were advised to follow the National Cholesterol Education Program Step I diet. The usual-care group was treated according to the discretion of their primary care physicians.

Serial determinations of serum creatinine were obtained in a single central laboratory using the Ortho Clinical Diagnostics Vitros Chemistry System (Rochester, NY) and were calibrated to the Modification of Diet in Renal Disease (MDRD) Study laboratory, as described previously.¹² Calibration for drift over time was not repeated. All baseline data refer to the date of randomization into the ALLHAT-LLT. Creatinine measurements were repeated at 1 month, 1 year, 2 years, and then every other year during follow-up from the antihypertensive randomization. The 4-variable MDRD Study equation was used to estimate GFR according to the following formula: $(186.3 \cdot \text{serum creatinine}^{-1.154} \cdot \text{age in years}^{-0.203} \cdot 1.212 \text{ (if black)} \cdot 0.742 \text{ (if female)})$.¹³ Patients were classified into categories of baseline eGFR: normal or increased (≥ 90 mL/min/1.73 m²), mild decrease (60 to 89 mL/min/1.73 m²), and moderate-severe decrease (< 60 mL/min/1.73 m² [≥ 1.50 , 1.00 to 1.48, and < 1.00 mL/s/1.73 m², respectively]).

The following kidney disease outcomes were assessed: (1) development of ESRD, defined as a combined end point of start of long-term dialysis therapy, death caused by kidney disease, or kidney transplantation, as reported from the clinical sites; the reliability of ESRD reporting from sites was not validated through external sources at this time; however, any limitation in ascertainment is likely to affect both randomized groups in a similar manner; (2) a composite end point of ESRD or 50% or greater decrease in eGFR from baseline; (3) composite end point of ESRD or 25% or greater decrease in eGFR from baseline; (4) mean eGFR during study follow-up; and (5) rate of change in eGFR. The primary outcome for the LLT was all-cause mortality.¹¹ Data were analyzed according to participants' randomized treatment assignments regardless of their subsequent medications (intent-to-treat analysis). Baseline characteristics were compared across treatment and baseline eGFR groups by using *t*-test for continuous covariates and contingency table analyses for categorical data. Mean eGFRs for participants assigned to the pravastatin group were compared with those from the usual-care group at each follow-up point by using mixed-effects linear regressions of eGFR against time, treatment group, and baseline eGFR variables. Cox proportional hazards model was used to obtain hazard ratios (hereafter called relative risks) and 95% confidence intervals for time to ESRD, as well as for the composite outcomes. To assess possible bias from censoring because of competing causes of death, vital status (non-kidney disease deaths, unknown vital status, and known alive) was tabulated for those without renal end points, and the composite end point was analyzed by using methods already described. eGFR rate of change estimates were obtained as linear combinations of

coefficients of the appropriate time and time-interaction variables after mixed-effects linear regressions of eGFR versus treatment and time. The appropriateness of the proportional hazards assumption was assessed by using Schoenfeld residuals,¹⁴ as well as log-log survival plots.¹⁵ The appropriateness of the linear mixed-effects models was confirmed by using log-likelihood ratio tests, as well as reductions in the Akaike information criterion, tests for normality of raw and standardized residuals, and graphical checks of homoscedasticity in plots of raw residuals versus fitted values.¹⁶

RESULTS

A description of randomization and follow-up of 10,060 ALLHAT-LLT participants is shown in Fig 1. At baseline, 2,640 participants (26%) had normal or increased eGFR, 5,863 (58%) had a mild decrease in eGFR, and 1,557 (16%) had a moderate or severe decrease in eGFR. In the moderate-severe stratum, the vast majority of participants (97.3%) were in the stage 3 CKD category (eGFR, 30 to 59 mL/min/1.73 m² [0.50 to 0.98 mL/s/1.73 m²]). There were no differences in baseline characteristics of participants randomly assigned to pravastatin compared with usual care, except for ethnicity (more black non-Hispanics in the pravastatin group, and more white Hispanics in the usual-care group) and history of CHD (greater in the usual-care group) at baseline in patients with moderate to severe decrease in eGFR (Table 1).

Mean duration of follow up was 4.8 years. Adherence to statin therapy in those randomly

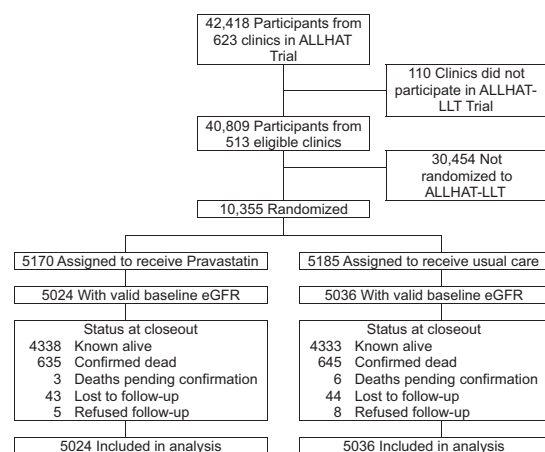


Figure 1. Randomization and follow-up of participants with a valid baseline estimated glomerular filtration rate (eGFR) in the lipid-lowering component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT).

assigned to pravastatin decreased during the course of the study from 89.8% at year 2 to 86.2% at year 4 to 86.6% at year 6 (Fig 2). Use of statin therapy in participants assigned to usual care increased over time (8.1% at year 2, 16.3% at year 4, and 23.3% at year 6).¹¹ These patterns were consistent across the baseline eGFR strata (Fig S1; provided as online supplementary material available with this article at www.ajkd.org).

Total cholesterol levels decreased by 20.7% in the pravastatin group and 11.2% in the usual-care group, with resultant 6-year total cholesterol levels of 176.3 mg/dL (4.56 mmol/L) and 196.8 mg/dL (5.09 mmol/L), respectively (Fig 2). Changes and differential in total cholesterol levels between the pravastatin and usual-care groups followed a similar pattern in the 3 eGFR subgroups (Fig S1). During the follow-up period, LDL cholesterol, high-density lipoprotein cholesterol, and triglyceride measurements were available for only a small subset of patients (5% of the usual-care group, 10% of the pravastatin group). LDL cholesterol levels decreased by 30.2% in the pravastatin group and 15.1% in the usual-care group, with resultant 6-year LDL cholesterol levels of 103.2 mg/dL (2.67 mmol/L) and 121.3 mg/dL (3.14 mmol/L), respectively ($P < 0.05$). There were no statistically significant differences between the pravastatin and usual-care groups with regard to change in high-density lipoprotein cholesterol or triglyceride levels between baseline and year 6. Changes in lipid profiles in the 3 strata of eGFR were consistent with the overall population, although numbers in individual strata with lipid measures in follow-up were small (Fig S1).

Use of angiotensin-converting enzyme inhibitors (per antihypertensive treatment trial randomized assignment and open label) was slightly more common in the usual-care group than the pravastatin group at year 2 (6.4% v 4.8%; $P = 0.001$), but not at year 4 (11.3% v 11%; $P = 0.7$) or year 6 (17.3% v 18.3%; $P = 0.5$). Similar trends were seen in the 3 baseline eGFR strata (data not shown).

There were no statistically significant differences in systolic and diastolic blood pressures at baseline or year 2, 4, or 6 in the total group or stratified by baseline eGFR between the usual-care and pravastatin groups.

Table 1. Baseline Characteristics Stratified by Estimated Baseline GFR and Treatment Group

	Normal or Increased Baseline GFR (≥ 90 mL/min/1.73 m ²)		Mildly Decreased Baseline GFR (60-89 mL/min/1.73 m ²)		Moderate or Severe Decrease in GFR (< 60 mL/min/1.73 m ²)		Total	
	Pravastatin	Usual Care	Pravastatin	Usual Care	Pravastatin	Usual Care	Pravastatin	Usual Care
Patients randomly assigned	1,342 (26.7)	1,298 (25.8)	2,903 (57.8)	2,960 (58.8)	779 (15.5)	778 (15.5)	5,170 (49.9)	5,185 (50.1)
Age at lipid randomization (y)	63.3 \pm 6.4	63.1 \pm 6.2	67.0 \pm 7.4	67.0 \pm 7.4	70.7 \pm 7.9	70.6 \pm 7.8	66.7 \pm 7.7	66.6 \pm 7.6
Ethnicity						*		
White non-Hispanic	360 (26.8)	392 (30.2)	1,301 (44.8)	1,290 (43.6)	399 (51.2)	391 (50.3)	2,116 (40.9)	2,133 (41.1)
Black non-Hispanic	598 (44.6)	561 (43.2)	883 (30.4)	896 (30.3)	235 (30.2)	210 (27.0)	1,781 (34.5)	1,739 (33.5)
White Hispanic	185 (13.8)	165 (12.7)	471 (16.2)	501 (16.9)	89 (11.4)	128 (16.5)	759 (14.7)	803 (15.5)
Black Hispanic	105 (7.8)	88 (6.8)	89 (3.1)	84 (2.8)	14 (1.8)	8 (1.0)	210 (4.1)	181 (3.5)
Other	94 (7.0)	92 (7.1)	159 (5.5)	189 (6.4)	42 (5.4)	41 (5.3)	304 (5.9)	329 (6.4)
Women	667 (49.7)	638 (49.2)	1,347 (46.4)	1,404 (47.4)	427 (54.8)	420 (54.0)	2,511 (48.6)	2,540 (49.0)
Body mass index (kg/m ²)	30.5 \pm 6.2	30.6 \pm 6.6	29.7 \pm 5.8	29.7 \pm 5.9	29.1 \pm 5.7	29.1 \pm 6.0	29.8 \pm 5.9	29.9 \pm 6.1
Baseline systolic blood pressure (mm Hg)	142.3 \pm 17.3	141.8 \pm 17.9	142.8 \pm 17.7	142.7 \pm 17.4	145.8 \pm 19.6	145.7 \pm 20.7	143.1 \pm 17.9	142.9 \pm 18.2
Baseline diastolic blood pressure (mm Hg)	83.6 \pm 10.5	83.2 \pm 10.5	82.8 \pm 10.3	83.0 \pm 10.2	82.5 \pm 11.3	82.1 \pm 11.2	82.9 \pm 10.6	82.9 \pm 10.4
History of coronary heart disease at baseline	151 (11.3)	163 (12.6)	406 (14.0)	436 (14.7)	119 (15.3)	155 (19.9)*	695 (13.4)	780 (15.0)*
Eligibility risk factors†								
Current cigarette smoking	368 (27.4)	360 (27.7)	662 (22.8)	659 (22.3)	134 (17.2)	157 (20.2)	1,193 (23.1)	1,208 (23.3)
Atherosclerotic CVD	376 (28.0)	390 (30.1)	1,082 (37.3)	1,115 (37.7)	349 (44.8)	353 (45.4)	1,866 (36.1)	1,929 (37.2)
History of MI or stroke	179 (13.3)	179 (13.8)	505 (17.4)	514 (17.4)	164 (21.1)	179 (23.0)	880 (17.0)	908 (17.5)
History of coronary revascularization	63 (4.7)	74 (5.7)	212 (7.3)	211 (7.1)	65 (8.3)	80 (10.3)	349 (6.8)	378 (7.3)
Other atherosclerotic CVD	213 (15.9)	212 (16.3)	607 (20.9)	632 (21.4)	188 (24.1)	200 (25.7)	1,043 (20.2)	1,090 (21.0)
ST depression on electrocardiogram	132 (9.9)	133 (10.4)	347 (12.1)	334 (11.4)	97 (12.6)	95 (12.4)	604 (11.8)	579 (11.3)
Type 2 diabetes	602 (44.9)	561 (43.2)	942 (32.5)	930 (31.4)	249 (32.0)	231 (29.7)	1,855 (35.9)	1,783 (34.4)
Low HDL cholesterol	114 (8.5)	117 (9.0)	325 (11.2)	327 (11.0)	102 (13.1)	87 (11.2)	549 (10.6)	548 (10.6)
LVH by electrocardiogram	256 (19.1)	250 (19.3)	546 (18.8)	593 (20.0)	158 (20.3)	153 (19.7)	992 (19.2)	1,016 (19.6)
LVH by echocardiogram	48 (3.6)	43 (3.4)	151 (5.3)	148 (5.1)	44 (5.7)	49 (6.4)	252 (4.9)	251 (4.9)
Estimated GFR (mL/min/1.73 m ²)	101.8 \pm 12.9	102.4 \pm 12.3	75.3 \pm 8.0	75.2 \pm 8.1	50.8 \pm 8.2	50.6 \pm 8.4	78.6 \pm 19.0	78.4 \pm 19.0
Lipid baseline lipid profile								
Total cholesterol	223.0 \pm 26.2	224.5 \pm 26.8	223.2 \pm 27.3	223.3 \pm 26.1	226.2 \pm 26.3	224.1 \pm 28.5	223.7 \pm 26.9	223.7 \pm 26.7
LDL cholesterol	145.2 \pm 20.9	146.3 \pm 21.3	145.4 \pm 21.6	145.4 \pm 21.2	146.5 \pm 21.2	144.5 \pm 21.4	145.6 \pm 21.4	145.5 \pm 21.3
Fasting triglycerides	143.9 \pm 71.6	149.5 \pm 70.6	150.4 \pm 68.4	151.6 \pm 68.4	164.5 \pm 74.5	164.0 \pm 90.5	150.6 \pm 70.4	152.8 \pm 73.0

(Continued)

Table 1 (Cont'd). Baseline Characteristics Stratified by Estimated Baseline GFR and Treatment Group

	Normal or Increased Baseline GFR (≥ 90 mL/min/1.73 m ²)		Mildly Decreased Baseline GFR (60–89 mL/min/1.73 m ²)		Moderate or Severe Decrease in GFR (< 60 mL/min/1.73 m ²)		Total
	Pravastatin	Usual Care	Pravastatin	Usual Care	Pravastatin	Usual Care	
Randomly assigned to ACE inhibitor	306 (29.2)	261 (25.7)	598 (25.9)	627 (26.9)	158 (25.7)	156 (25.6)	1,094 (26.8)
Randomly assigned to calcium channel blocker	276 (26.3)	286 (28.1)	654 (28.3)	633 (27.2)	160 (26.0)	164 (26.9)	1,122 (27.5)
Randomly assigned to diuretic	466 (44.5)	470 (46.2)	1,057 (45.8)	1,067 (45.9)	298 (48.4)	290 (47.5)	1,872 (45.8)

Note: Values expressed as number (percent) or mean \pm SD. Estimated GFR derived from the application of the Modification of Diet in Renal Disease Study equation based on serum creatinine level, age, race, and sex.¹³ Body mass index calculated as weight in kilograms divided by the square of height in meters. To convert total, LDL, and HDL cholesterol to mmol/L, multiply by 0.02586; to convert triglycerides to mmol/L, multiply by 0.01129; to convert GFR in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

Abbreviations: CVD, cardiovascular disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction; ACE, angiotensin-converting enzyme.

* $P < 0.05$, comparison between pravastatin and usual care.

†For trial eligibility, participants had to have at least 1 other risk factor in addition to hypertension. Thus, the indicated risk factors are not mutually exclusive or exhaustive and may not represent prevalence.

Numbers of renal clinical events in each treatment group during each period are listed in Table 2. Of 114 ESRD events, 30 were deaths caused by kidney disease. No significant difference was seen in 6-year rates of ESRD between those randomly assigned to receive pravastatin (1.36/100 patients) or usual care (1.45/100 patients; $P = 0.9$; Figs 3 and 4). In both groups, 3.5% of participants reached the composite end point of ESRD or a 50% or greater decrease in eGFR ($P = 0.9$). There was no significant difference in 6-year event rates for the composite end point of ESRD or a 25% decrease in eGFR (relative risk, 0.95; 95% confidence interval, 0.86 to 1.04; $P = 0.3$). These overall findings were similar in the 3 strata of baseline eGFR. No significant treatment group by eGFR interaction was seen (Figs 3 and 4). There was also no statistically significant interaction between randomization to pravastatin/usual care and randomization to any of the antihypertensive arms.

There were no statistically significant differences in eGFR in the pravastatin group compared with the usual-care group in the overall population at years 2, 4, and 6 (Table 3; Fig 5). In the overall population and stratified by baseline eGFR, there was a trend for a greater eGFR in the pravastatin group. However, this was statistically significant in only the baseline eGFR of 60 to 89 mL/min/1.73 m² (1.00 to 1.48 mL/s/1.73 m²) stratum at years 4 and 6, and there was no significant interaction of baseline eGFR and treatment group. Because of the multiple comparisons involved, these data have to be interpreted with caution.

There were no statistically significant differences in rates of change in eGFRs between pravastatin and usual care in the overall population and stratified by baseline eGFR (Table 4).

All outcome analyses were repeated with an alternate eGFR stratification (< 45 , 45 to 59, 60 to 89 and ≥ 90 mL/min/1.73 m² [< 0.75 , 0.75 to 0.98, 1.00 to 1.48, and ≥ 1.50 mL/s/1.73 m²]). In the eGFR less than 45 mL/min/1.73 m² (< 0.75 mL/s/1.73 m²) stratum, 166 participants were assigned to pravastatin (mean eGFR, 37.8 mL/min/1.73 m² [0.63 mL/s/1.73 m²]) and 157 participants were assigned to usual care (mean eGFR, 37 mL/min/1.73 m² [0.62 mL/s/1.73 m²]). There was no significant difference in risk of ESRD

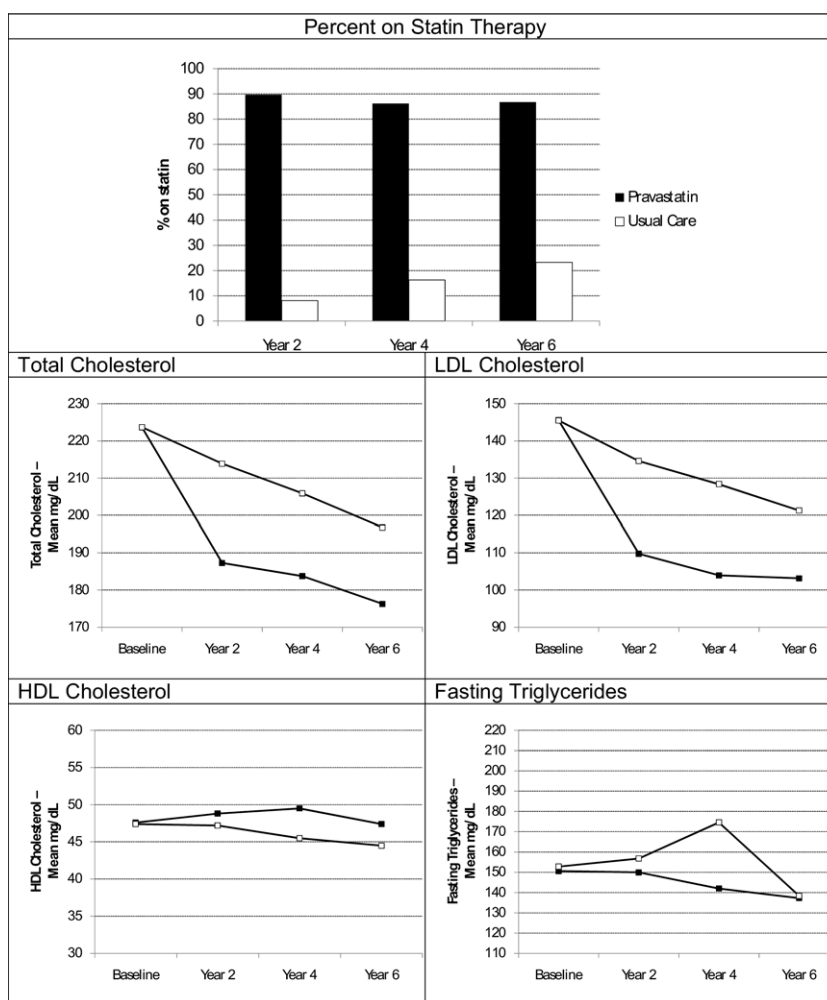


Figure 2. Statin use and lipid levels during the course of the study. Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein. To convert total, LDL, and HDL cholesterol in mg/dL to mmol/L, multiply by 0.02586; triglycerides in mg/dL to mmol/L, multiply by 0.01129.

(RR, 0.77; 95% CI, 0.41 to 1.45) and rate of change in eGFR (-0.23 v -0.37 mL/min/1.73 m²/y [-0.004 v -0.006 mL/s/1.73 m²/y]; $P = 0.3$).

DISCUSSION

In older hypertensive patients with moderate dyslipidemia, pravastatin was not superior to usual care in preventing clinical kidney disease outcomes. This was consistent across the strata of baseline eGFR. There was a trend for a greater eGFR in the pravastatin group, which was not statistically significant.

Previous studies that examined the effect of statin therapy on progression of kidney disease have yielded inconsistent results, perhaps because of their heterogeneity with regard to patient population studied, baseline kidney function and protein-

uria, criteria used to measure kidney function, and type of statin used.¹⁷ Several studies have shown no benefit of statin therapy on slowing the decrease in GFR,^{9,10,18-24} and others,^{8,25-27} particularly in patients with high levels of proteinuria,²⁸ have shown that statin therapy is associated with a slower decrease in GFR. In the Cholesterol and Recurrent Events (CARE) trial, the decrease in GFR in the pravastatin group was slower than that in the placebo group only in those with GFR less than 40 mL/min/1.73 m² (<0.67 mL/s/1.73 m²).²⁹ In the Pravastatin Pooling Project, using data obtained from 3 large trials (West of Scotland Coronary Prevention Study, CARE, and Long-term Intervention with Pravastatin in Ischemic Disease), there was a modestly (0.2 mL/min/y) slower decrease in GFR in patients with an eGFR less than 60 mL/min/1.73 m² (<1.00 mL/s/1.73 m²) who were treated

Table 2. Number of Kidney Disease Events by Treatment Group and Time Period

	No. of Patients	Cumulative No. of Events			Total Events
		2 Years	4 Years	6 Years	
ESRD					
Total	10,355	29	81	109	114
Pravastatin	5,170	14	40	55	56
Usual care	5,185	15	41	54	58
ESRD or 50% decrease in eGFR					
Total	8,996	80	211	290	316
Pravastatin	4,535	39	103	143	159
Usual care	4,461	41	108	147	157
ESRD or 25% decrease in eGFR					
Total	8,996	800	1,377	1,713	1,803
Pravastatin	4,535	373	650	824	881
Usual care	4,461	427	727	889	922

Abbreviations: ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate.

with pravastatin compared with the control group, but there was no significant decrease in the frequency of a 25% decrease in GFR.³⁰ In a meta-analysis of 27 randomized trials, statin therapy had an overall modest beneficial effect on change in GFR (1.22 mL/min/1.73 m²/y [0.02 mL/s/1.73 m²]); however, there was substantial variability across the studies.³¹ Specifically, in the hypertensive and diabetic cohorts, likely the ones most similar to ALLHAT-LLT, there was no beneficial effect of statin therapy on decrease in GFR. Finally, a recent meta-analysis of 11 trials by Strippoli et al³² also showed no benefit of statin therapy on decrease in kidney function.

Our study makes an important contribution to this literature. In the ALLHAT-LLT, there was no consistent benefit of pravastatin therapy compared with usual care with regard to a variety of kidney disease outcomes. This is consistent with the findings in the CARE study,²⁹ the meta-analyses of Strippoli et al,³² and diabetic and hypertensive cohorts in the meta-analyses of Sandhu et al.³¹ Although there was a trend for eGFR to be greater in the pravastatin group at some points in time, this finding was not consistent and has to be interpreted with caution because of the multiple comparisons involved.

Several factors may have a bearing on the interpretation of our findings. First, the rate of decrease in GFR in patients with an eGFR less than 60 mL/min/1.73 m² (<1.00 mL/s/1.73 m²) was very slow in both the pravastatin and usual-care groups. Although this may relate to overall excellent levels

of blood pressure control in ALLHAT, the slow rate of progression decreases the ability to detect a difference between the 2 randomized groups. In addition, mean eGFR at baseline in patients in the moderate-severe group (50 mL/min/1.73 m² [0.83 mL/s/1.73 m²]) was greater than in studies that showed a beneficial effect of statin therapy (most marked in the <40-mL/min/1.73 m² [<0.67-mL/s/1.73 m²] group in CARE). However, results in the smaller subset of participants with eGFR less than 45 mL/min/1.73 m² (<0.75 mL/s/1.73 m²) did not suggest improved outcomes with pravastatin. Second, although proteinuria measurements were not obtained, we speculate that based on the inclusion criteria, the ALLHAT patient population profile is associated with relatively low levels of proteinuria. In addition, patients were excluded if they had a specific indication for angiotensin-converting enzyme-inhibitor therapy, such as proteinuria. The LLT results are consistent with studies that showed no beneficial effects of statin therapy in patients with minimal proteinuria compared with a marked benefit in those with high-grade proteinuria. Finally, because of the significant drop-in during the course of the study, the difference in total and LDL cholesterol levels between the randomized groups was modest compared with traditional lipid-lowering trials and did not achieve the 30% to 40% decrease in LDL cholesterol levels recommended in current lipid guidelines.³³

The achieved LDL cholesterol levels in patients in the group with a moderate to severe decrease in eGFR in the ALLHAT-LLT (102 mg/dL [2.64 mmol/L] at year 2) was similar to

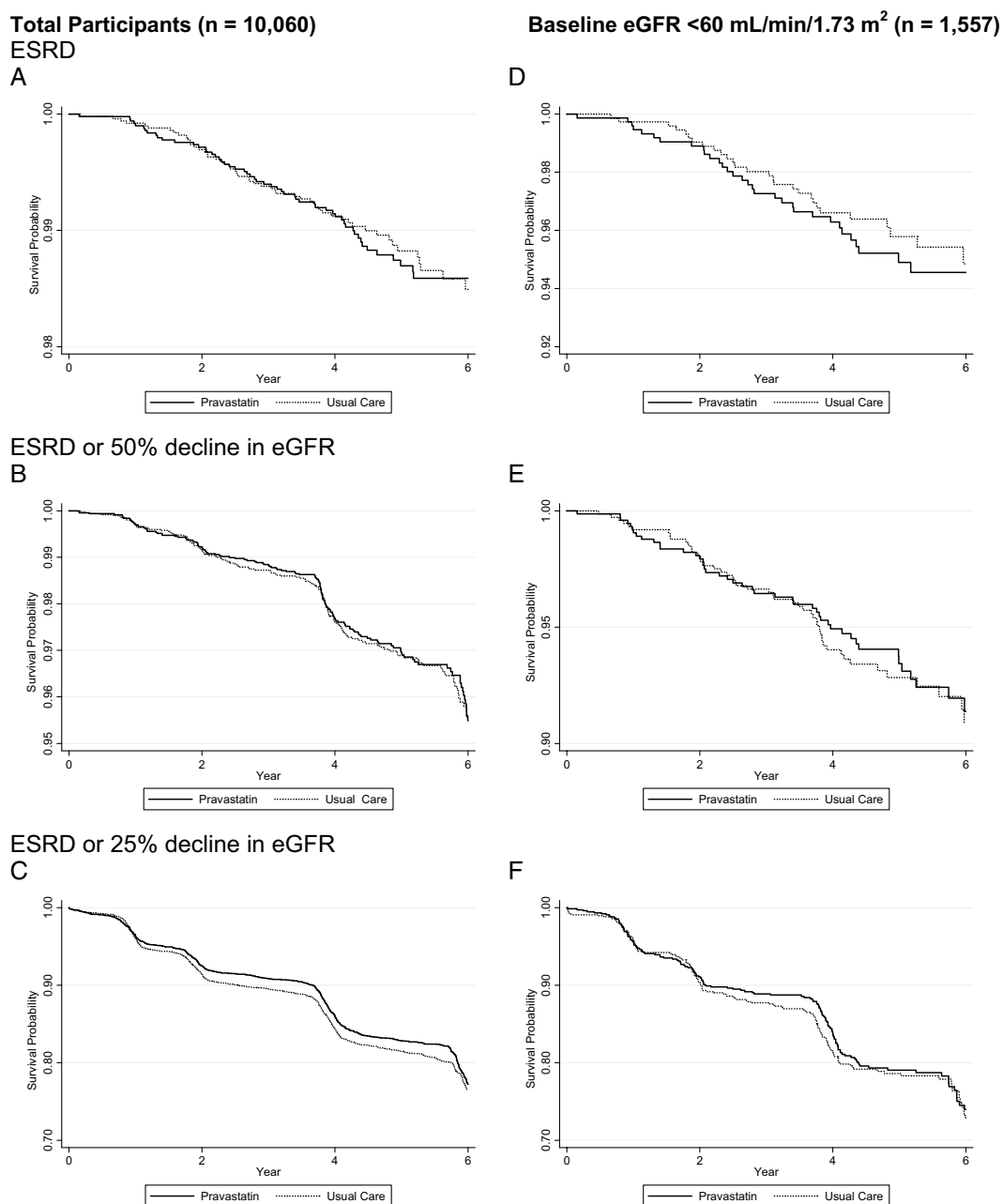


Figure 3. Survival curves for kidney disease events; pravastatin versus usual care. Treatment groups by baseline estimated glomerular filtration rate (eGFR) estimates: (A-C) all participants (n = 10,060), and (D-F) the subgroup of participants with baseline GFR less than 60 mL/min/1.73 m² (n = 1,557). Abbreviation: ESRD, end-stage renal disease. To convert GFR in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

the achieved LDL cholesterol levels in a similar population in the Pravastatin Pooling Project (103.9 mg/dL [2.69 mmol/L] at year 1).³⁴ However, the usual-care group also had a decrease in LDL cholesterol levels in the ALLHAT-LLT, with a net difference of 30 mg/dL (0.78 mmol/L)

at year 2 compared with a difference between pravastatin and placebo of 47 mg/dL (1.22 mmol/L) at year 1 in the Pravastatin Pooling Project. The smaller difference in LDL cholesterol levels may contribute to the lack of statistically significant benefit seen with statin therapy

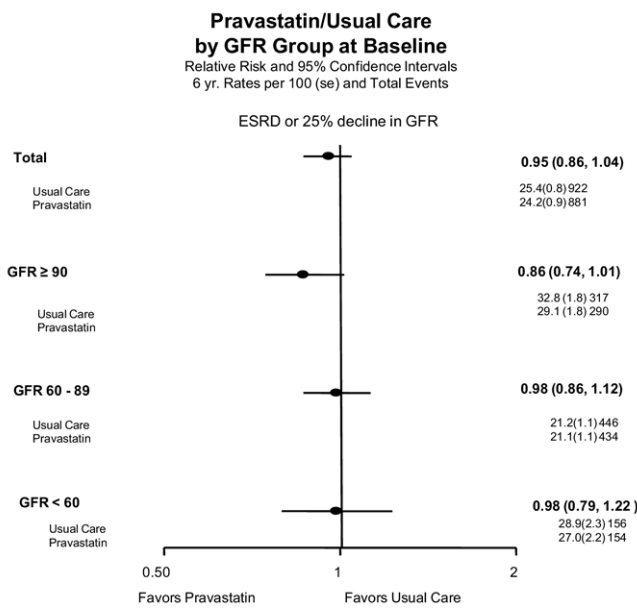
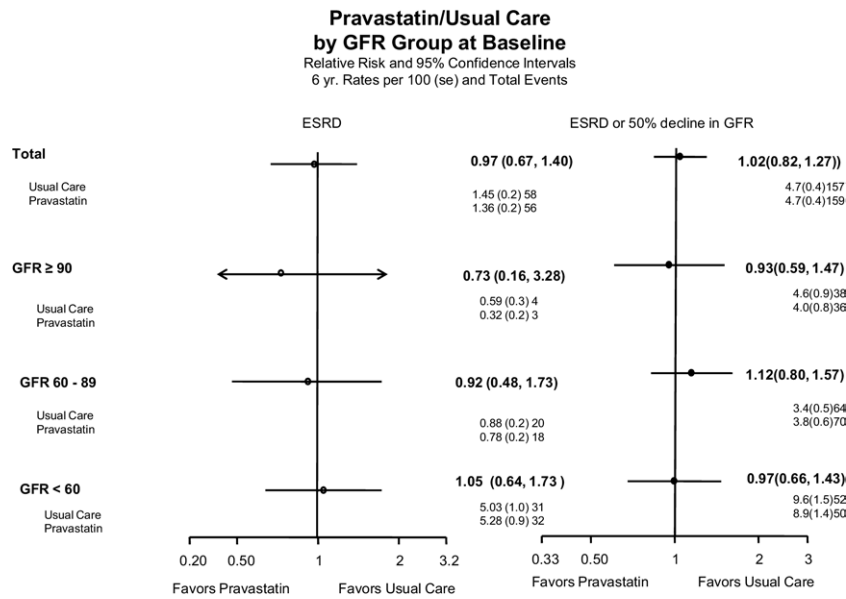


Figure 4. Renal outcomes in the lipid-lowering component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial by treatment group and glomerular filtration rate (GFR) group at baseline (relative risks and 95% confidence intervals, 6-year rates per 100, and total events). Abbreviation: ESRD, end-stage renal disease. To convert GFR in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

in our study. It also is possible that levels of LDL and total cholesterol achieved in the ALLHAT-LLT are still too high for patients with CKD; whether more aggressive lipid lowering will result in improved outcomes in these patients remains to be seen. The lack of a statistically significant difference between the 2 groups may be caused by lack of power given the relatively low event rate. Based on the observed event rates, we estimate that the study was adequately powered (80%) to estimate rate reductions of

41.8% for ESRD or 25.2% for a combined end point of ESRD and 50% decrease in eGFR. However, the study had adequate power to detect a 10% difference in the composite end point of ESRD and 25% decrease in eGFR.

The effect of statin therapy on kidney function may depend on the population studied. In the meta-analyses by Sandhu et al,³¹ statin therapy was associated with improved kidney function in patients with cardiovascular disease, but not in diabetic or hypertensive pa-

Table 3. Estimated GFR by Treatment Group by Time Period*

	Baseline	2 Years	4 Years	6 Years
Estimated† baseline GFR (total mL/min/1.73 m ²)				
Pravastatin	78.6 (78.1-79.2)	75.7 (75.2-76.2)	72.7 (72.1-73.4)	69.8 (69.0-70.6)
Usual care	78.3 (77.7-78.7)	75.1 (74.6-75.6)	71.9 (71.3-72.5)	68.7 (67.9-69.5)
		P = 0.3	P = 0.1	P = 0.06
Estimated* baseline GFR < 60 mL/min/1.73 m ²				
Pravastatin	51.5 (50.8-52.2)	50.7 (49.9-51.5)	49.9 (48.7-51.0)	49.1 (47.6-50.6)
Usual care	51.0 (50.4-51.7)	49.9 (49.1-50.8)	48.8 (47.7-50.0)	47.7 (46.2-49.3)
		P = 0.4	P = 0.2	P = 0.08
Estimated* baseline GFR of 60-89 mL/min/1.73 m ²				
Pravastatin	75.4 (75.1-75.8)	73.3 (72.9-73.7)	71.1 (70.5-71.8)	69.0 (68.1-69.9)
Usual care	75.2 (74.9-75.6)	72.8 (72.3-73.2)	70.3 (69.7-71.0)	67.9 (67.0-68.7)
		P = 0.4	P = 0.09	P = 0.05
Estimated* baseline GFR ≥ 90 mL/min/1.73 m ²				
Pravastatin	101.0 (100.5-101.5)	95.3 (94.7-95.9)	89.6 (88.8-90.5)	84.0 (82.8-85.2)
Usual care	101.2 (100.7-101.7)	95.2 (94.6-95.9)	89.2 (88.3-90.1)	83.3 (82.1-84.5)
		P = 0.6	P = 0.8	P = 0.4

Note: Values in parentheses are 95% confidence intervals. To convert GFR in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

Abbreviation: GFR, glomerular filtration rate.

*Mixed model regression estimates (N = 10,060).

†N = 10,248.

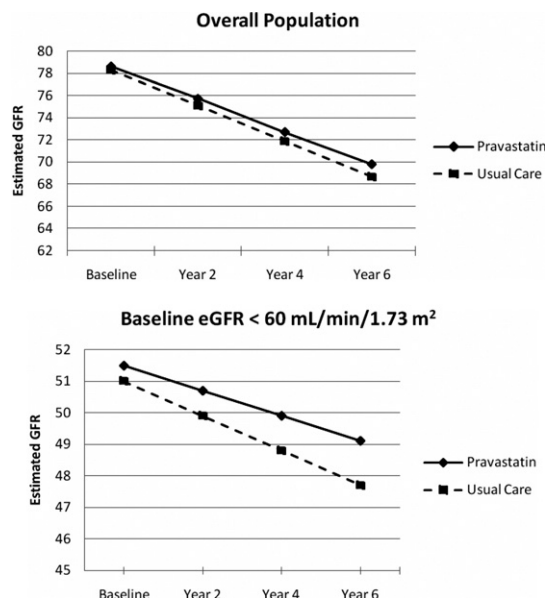


Figure 5. Estimated glomerular filtration rate (eGFR; mL/min/1.73 m²) during the course of the study. To convert GFR in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

tients. It can be speculated that a decrease in cardiovascular events in high-risk patients with statins results in fewer catheterization/interventional procedures with a lower burden of contrast exposure and atheroemboli. This effect would not be marked in patients at lower risk of cardiovascular disease.

Our study has several strengths. With more than 1,500 patients with moderately decreased eGFR, this is one of the largest individual studies to address the issue of statins in patients with kidney disease. In addition, the mean duration of follow-up of 4.8 years is longer than many published studies in this area. Measurement of creatinine in a single central laboratory minimizes issues of variability in creatinine measurement. The methodologic rigor of the study with careful event ascertainment and minimal loss to follow-up enhances the credibility of the study. The results are generalizable to patients with early stage 3 CKD (mean eGFR, 50 mL/min/1.73 m² [0.83 mL/s/1.73 m²] in the moderate-severe reduction stratum). Although results were consistent in the subgroup with eGFR less than 45 mL/min/1.73 m² (<0.75 mL/s/1.73 m²), whether similar results are seen in patients with more advanced CKD needs additional study.

Table 4. Time Rate of Change in Estimated GFR by Treatment Group and Baseline Estimated GFR

Estimated Baseline GFR (mL/min/1.73 m ²)	Pravastatin			Usual Care			P*
	Estimated Δ GFR (mL/min/1.73 m ² /y)	SE	95% Confidence Interval	Estimated Δ GFR (mL/min/1.73 m ² /y)	SE	95% Confidence Interval	
Total	-1.48	0.06	-1.59 to -1.36	-1.59	0.06	-1.71 to -1.47	0.2
<60	-0.34	0.15	-0.64 to -0.03	-0.62	0.16	-0.92 to -0.31	0.2
60-89.9	-1.13	0.08	-1.28 to -0.98	-1.18	0.08	-1.33 to -1.03	0.2
\geq 90	-2.75	0.12	-2.97 to -2.53	-3.07	0.12	-3.31 to -2.84	0.05

Note: To convert GFR in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

Abbreviation: GFR, glomerular filtration rate.

*For comparison of pravastatin versus usual care.

There are important limitations to our analyses. Several studies have shown beneficial effects of statin therapy on proteinuria.³⁵ However, others have shown an increase in tubular proteinuria.³⁶ Because proteinuria data are not available for ALLHAT participants, we cannot study the effects of pravastatin therapy on proteinuria or assess the role of proteinuria level as a predictor of response to statin therapy. In addition, these are post hoc analyses; therefore, these can be hypothesis generating and will await confirmation in other clinical trials. The validity of the MDRD Study equation in predicting change in eGFRs in the normal range (>90 mL/min/1.73 m² [>1.50 mL/s/1.73 m²]) has not been confirmed. Therefore, the relatively rapid decrease seen in this group may represent hyperfiltration or simply a regression to the mean. The substantial drop-in rate in the usual-care group (23% at year 6) coupled with some drop-out in the pravastatin group (13% at year 6) may limit the power of the study to detect a difference between the 2 groups. Decreasing sample size over time is another possible limitation. Such a decrease happens in all trials for a number of reasons, including death, end-of-study censoring, loss to follow-up, and participants who remain in the study, but who are missing laboratory analyses. Average follow-up in the ALLHAT-LLT was 4.8 years, and minimum potential follow-up was less than 4 years. Therefore, the 4-year data to some extent and especially the 6-year data were particularly prone to be missing. Finally, it remains to be seen whether other statins that have greater potency in lipid lowering than pravastatin have a greater impact on clinical outcomes in this population.

Our findings support statin use in accordance with published guidelines and reinforce the im-

portance of achieving target LDL and total cholesterol level decreases with statin therapy.³³ The ALLHAT-LLT, in the context of the inconsistent findings in the literature, does not provide a compelling rationale for routine use of statin therapy specifically to improve GFR in hypertensive patients with CKD. This important question is best resolved by prospective clinical trials specifically designed to address the issue; the results of the ongoing Study of Heart and Renal Protection will be eagerly awaited to guide clinical practice in this area.³⁷

In summary, this post hoc analysis of the ALLHAT-LLT shows in hypertensive patients with moderate dyslipidemia that pravastatin was not superior to usual care in preventing kidney disease outcomes. This was consistent across the strata of baseline eGFR level. However, potential benefit from statin therapy may depend on the degree of decrease achieved in total and LDL cholesterol levels.

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SUPPLEMENTARY MATERIAL

Figure S1: Statin use and lipid levels during the course of the study by baseline estimated glomerular filtration rate (eGFR).

Note: The supplementary material accompanying this article (doi: 10.1053/j.ajkd.2008.05.027) is available at www.ajkd.org.

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