Published in final edited form as:
Am J Kidney Dis. 2008 September ; 52(3): 412–424. doi:10.1053/j.ajkd.2008.05.027.

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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Abstract

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

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Trial registration: www.clinicaltrials.gov; study number: NCT00000542.

Descriptive Text for Online Delivery
Hyperlink: Supplementary Figure S1 (PDF)
About: Statin use and lipid levels over the course of the study by baseline eGFR. To convert GFR in mL/min/1.73m^2 to mL/s/1.73m^2, multiply by 0.01667.

Study Design—Prospective randomized clinical trial, *post hoc* analyses.

Setting and participants—10,060 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (lipid-lowering component) stratified by baseline eGFR: <60, 60–89, ≥90 mL/min/1.73 m^2. Mean follow-up was 4.8 years.

Intervention—Randomized, pravastatin 40 mg/day or usual care.

Outcomes and measurements—Total cholesterol, HDL- and LDL-cholesterol; end stage renal disease (ESRD), estimated glomerular filtration rate (eGFR).

Results—Through year six, total cholesterol declined in the pravastatin (−20.7%) and usual care groups (−11.2%). No significant differences were seen between the groups for rates of ESRD (1.36 vs 1.45/100 patient years, P=0.9), composite endpoints of ESRD and 50% or 25% decline in eGFR, or rate of change of eGFR. Findings were consistent across eGFR strata. In patients with eGFR≥90 mL/min/1.73 m^2, 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 reduced 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 degree of cholesterol reduction achieved.

Keywords

hyperlipidemia; glomerular filtration rate; pravastatin

Introduction

It is estimated that more than 10 million Americans have chronic kidney disease (CKD) and are at high risk for 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. Epidemiologic studies show that higher cholesterol levels are associated with a more rapid decline in kidney function.[3;4] Statins have physiologic actions beyond lipid lowering, such as improvement in vascular compliance[5] and reduction in chronic inflammation[6] that may have a beneficial effect in 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 CKD patients with modest dyslipidemia slows decline in kidney function remains 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 reduced mortality in older, moderately hypercholesterolemic, hypertensive participants with at least one 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 two groups. The purpose of this paper is to report a post hoc analysis of the effect of pravastatin therapy compared to 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) vs. usual care. Participants were drawn from ALLHAT, a 4-armed antihypertensive trial in which a calcium channel blocker (amlodipine), an angiotensin converting enzyme (ACE) inhibitor (lisinopril), and an alpha-adrenergic blocking agent (doxazosin) were each compared with a thiazide-like diuretic (chlorthalidone). The 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 LDL-C 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 levels lower than 350 mg/dL (3.9 mmol/L). Participants were excluded who were currently using prescribed lipid-lowering agents or large doses (≥500 mg/day) of nonprescription niacin; were known to be intolerant of statins or to have significant liver dysfunction (serum alanine aminotransferase [ALT] >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, i.e., at 3, 6, 9, and 12 months following 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 pre-selected 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 lab 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: $(186.3 * \text{Serum Creatinine}^{-1.154} * \text{Age in Years}^{-0.203} * 1.212$ (If Black)*0.742 (If Female)).[13] Patients were classified into categories of baseline eGFR (mL/min per 1.73 m^2): normal or increased (≥ 90), mild reduction (60–89), and moderate-severe reduction (<60) (≥1.50, 1.00–1.48, <1.00 mL/s/1.73 m^2, respectively).

The following kidney disease outcomes were assessed: (1) development of ESRD, defined as a combined end point of start of long-term dialysis, death due to 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% decline in eGFR from baseline; 3) composite end point of ESRD or ≥25% decline in eGFR from baseline (4) mean eGFR during study follow-up; and (5) rate of change of 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 using the *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 using mixed-effects linear regressions of eGFR against time, treatment group, and baseline eGFR variables. The Cox proportional hazards model was used to obtain hazard ratios (hereafter called *relative risks* [RRs]) and 95% confidence intervals (CIs) for time to ESRD as well as for the composite outcomes. To assess possible bias from censoring due to competing causes of death, vital status (non–kidney disease deaths, unknown vital status, known alive) was tabulated for those without renal end points, and the composite end points was analyzed using methods already described. Estimated GFR rate of change estimates were obtained as linear combinations of coefficients of the appropriate time and time-interaction variables following mixed-effects linear regressions of eGFR versus treatment and time. The appropriateness of the proportional hazards assumption was assessed using Schoenfeld residuals,[14] as well as log-log survival plots.15 The appropriateness of the linear mixed-effects models were confirmed 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 Figure 1. At baseline, 2640 participants (26%) had normal or increased eGFR, 5863 (58%) had mild reduction in eGFR and 1557 (16%) had moderate or severe reduction in eGFR. In the moderate-severe stratum, the vast majority of participants (97.3%) were in the stage 3 CKD category (eGFR 30–59 mL/min/1.73m^2 [0.50–0.98 mL/s/1.73m^2]). There were no differences in the baseline characteristics of participants randomized to pravastatin compared with usual care, except for ethnicity (higher Black non-Hispanic in the pravastatin group, and higher white Hispanic in the usual care group) and history of CHD (higher in the usual care group) at baseline in the patients with moderate to severe reduction in eGFR (Table 1).

The mean duration of follow up was 4.8 years. Adherence to statin therapy in those randomized to pravastatin declined over the course of the study from 89.8% at year 2, 86.2% at year 4, to 86.6% at year 6. (Figure 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 declined 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 (Figure 2). The changes and differential in total cholesterol between the pravastatin and usual care groups followed a similar pattern in the three eGFR subgroups (Figure S1). During the follow up period, LDL, HDL and triglyceride measurements were available only in a small subset of patients (5% of the usual care group and 10% of the pravastatin group). LDL-cholesterol levels declined 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 HDL-cholesterol or triglyceride between baseline and year six. Changes in lipid profiles in the 3 strata of eGFR were consistent with the overall population, though numbers in individual strata with lipid measures in follow up were small (Figure S1).

Use of ACE-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% vs 4.8%, p=0.001), but not at year 4 (11.3 % vs 11%, p=0.7) or year 6 (17.3 vs 18.3, p=0.5). Similar trends were seen in the three baseline eGFR strata (data not shown).

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

The number of renal clinical events in each treatment group, over each time period is shown in table 2. Of 114 ESRD events, 30 were deaths due to kidney disease. No significant difference was seen in the 6-year rates of ESRD between those randomized to receive pravastatin (1.36/100 patient years) or usual care (1.45/100, P=0.9) (Figures 3 and 4). In both groups, 3.5% of participants reached the composite endpoint of ESRD or a ≥50% decline in eGFR (p=0.9). There was no significant difference in the six year event rates for the composite end point of ESRD or a 25% decline in eGFR (RR 0.95 (0.86 – 1.04, p=0.3). These overall findings were similar in the three strata of baseline eGFR. No significant treatment group by eGFR interaction was seen (Figures 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 to the usual care group in the overall population at years 2, 4 and 6 (table 3 and figure 5). In the overall population, and when stratified by baseline eGFR, there was a trend for a higher eGFR in the pravastatin group. However, this was statistically significant only in the baseline eGFR 60–89 mL/min/1.73m^2 (1.00–1.48 mL/s/1.73m^2) stratum at years 4 and 6, and there was no significant interaction of baseline eGFR and treatment group. Due to the multiple comparisons involved, these data have to be interpreted with caution.

There were no statistically significant differences in rate of change of eGFR 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, 45–59, 60–89 and ≥90 mL/min/1.73m^2)(<0.75, 0.75–0.98, 1.00–1.48, ≥1.50 mL/s/1.73 m^2). In the eGFR <45 mL/min/1.73m^2 (<0.75 mL/s/1.73 m^2) stratum 166 participant were assigned to pravastatin (mean eGFR 37.8 ml/min/1.73 m^2 [0.63 mL/s/1.73 m^2]) and 157 participants were assigned to usual care (mean eGFR 37 ml/min/1.73 m^2 [0.62 mL/s/1.73 m^2]); there was no significant difference in risk of ESRD (RR 0.77, 95% CI 0.41–1.45,) and rate of change of eGFR (−0.23 vs −0.37 mL/min/1.73m^2/yr, p=0.3 [−0.004 vs −0.006 ml/s/1.73 m^2/yr).

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 higher eGFR in the pravastatin group which was not statistically significant.

Previous studies that have examined the effect of statin therapy on progression of kidney disease have yielded inconsistent results, perhaps due to their heterogeneity with regard to patient population studied, baseline kidney function and proteinuria, the criteria used to measure kidney function, and the type of statin used.[17] Several studies have shown no benefit of statin therapy on slowing decline in GFR,[9;10;18–24] others,[8;25–27] particularly in patients with high levels of proteinuria[28] have shown that statin therapy is associated with slower decline in GFR. In the Cholesterol and Recurrent Events trial (CARE), decline in

GFR in the pravastatin group was slower than that in the placebo group only in those with GFR <40 ml mL/min per 1.73 m^2 (0.67 mL/s/1.73 m^2).[29] In the Pravastatin Pooling Project, using data obtained from three large trials (West of Scotland Coronary Prevention Study, Cholesterol and Recurrent Events, and Long-term Intervention with Pravastatin in Ischemic Disease), there was a modestly (0.2 ml/min/year) slower decline in GFR in patients with an eGFR <60 mL/min per 1.73 m^2 (<1.00 mL/s/1.73 m^2) who were treated with pravastatin compared to the control group, but there was no significant reduction in the frequency of a 25% decline 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 m^2/year [0.02 mL/s/1.73 m^2]); 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 decline in GFR. Finally, a recent meta-analysis of 11 trials by Strippoli and colleagues also showed no benefit of statin therapy on decline in kidney function. [32]

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

Several factors may have a bearing on the interpretation of our findings. First, the rate of decline in GFR in patients with a eGFR<60 mL/min per 1.73 m^2 (<1.00 mL/s/1.73 m^2) was very slow in both pravastatin and the usual care groups. While 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 two randomized groups. In addition, the mean eGFR at baseline in patients in the moderate-severe group (50 mL/min per 1.73 m^2 [0.83 mL/s/1.73 m^2) was higher than in studies that have shown a beneficial effect of statin therapy (most marked in the <40 mL/min per 1.73 m^2 [0.67 mL/s/1.73 m^2] group in CARE). However, results in the smaller subset of participants with eGFR<45 ml/min/1.73 m^2 (0.75 mL/s/1.73 m^2) did not suggest improved outcomes with pravastatin. Secondly, while 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 ACE inhibitor therapy, such as proteinuria. The LLT results are consistent with studies that show no beneficial effects of statin therapy in patients with minimal proteinuria, compared to a marked benefit in those with high grade proteinuria. Finally, due to the significant drop-in during the course of the study, the difference in the total and LDL-cholesterol between the randomized groups was modest when compared to traditional lipid lowering trials, and did not achieve the 30–40% reduction in LDL-C recommended in current lipid guidelines.[33]

The achieved LDL-cholesterol in the patients in the moderate to severe reduction in eGFR group in the ALLHAT-LLT (102 mg/dL [2.64 mmol/L] at year 2) was similar to the achieved LDL-cholesterol 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 decrement in LDL-cholesterol in the ALLHAT –LLT with a net difference of 30 mg/dL (0.78 mmol/L) at year 2, compared to 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 may contribute to the lack of statistically significant benefit seen with statin therapy in our study. It is also possible that level of LDL- and total cholesterol achieved in the ALLHAT-LLT are still too high for CKD patients; 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 two groups may be due 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% decline in eGFR. However, the study did have adequate power to detect a 10% difference in the composite end point of ESRD and 25% decline in eGFR.

The effect of statin therapy on kidney function may depend on the population studied. In the Sandhu meta-analyses, statin therapy was associated with improved kidney function in patients with cardiovascular disease, but not in diabetic or hypertensive patients. It can be speculated that reduction in cardiovascular events in high risk patients with statins results in fewer catheterization/interventional procedures with lower burden of contrast exposure, and atheroemboli. This effect would not be marked in patients at lower risk for cardiovascular disease.

Our study has several strengths. With more than 1500 patients with moderately reduced eGFR, this is one of the largest individual studies to address the issue of statins in 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 lab minimizes issues of variability of 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 per 1.73 m^2 [0.83 mL/s/1.73 m^2] in the moderate-severe reduction stratum); though the results were consistent in the subgroup with eGFR < 45 mL/min per 1.73 m^2 (0.75 mL/s/1.73 m^2) whether similar results are seen in more advanced CKD needs additional study.

There are important limitations to our analyses. Several studies have shown beneficial effects of statin therapy on proteinuria;[35] however, others have shown increase in tubular proteinuria.[36] Since proteinuria data are not available in 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 per 1.73 m^2 [1.50 mL/s/1.73 m^2]) has not been confirmed. Therefore, the relatively rapid decline 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 two groups. Decreasing sample size over time is another possible limitation. Such a decrease happens in all trials for a number of reasons, including deaths, end-of-study censoring, and losses to follow-up, and participants who remain in the study but who are missing laboratory analyses. The average follow-up time in the ALLHAT lipid-lowering trial was 4.8 years, and the minimum potential follow-up time 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 reinforces the importance of achieving target LDL- and total cholesterol reduction 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 (SHARP) study will be eagerly awaited to guide clinical practice in this area.[37]

In summary, this post-hoc analysis of the ALLHAT-LLT demonstrates that in hypertensive patients with moderate dyslipidemia, 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 of degree of reduction achieved in total and LDL-cholesterol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The National Heart, Lung, and Blood Institute sponsored the study and was involved in all aspects other than direct operations of the study centers. This included collection, analysis, and interpretation of the data plus the decision to submit the manuscript for publication.

Support: This study was supported by contract NO1-HC-35130 with the National Heart, Lung, and Blood Institute. The ALLHAT investigators acknowledge contributions of study medications supplied by Pfizer (amlodipine and doxazosin), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin), and financial support provided by Pfizer. Dr Barzilay and Dr Sastrasinh received grant support from Boehringer Ingelheim.

Financial Disclosure: Mr Baimbridge reports stock holdings in Johnson & Johnson. Dr Basile reports having received consulting fees/honoraria from Astra-Zeneca, Novartis, Pfizer, and Sankyo. Dr Davis reports having received consulting fees/honoraria from Biomarin, GlaxoSmithKline, Proctor & Gamble, and Takeda. Dr Henriquez reports having received consulting fees/honoraria from Astra-Zeneca, Aventis, Boehringer Ingelheim, Novartis, Sankyo, and Sanofi-Synthelabo. Dr Kopyt reports having received consulting fees/honoraria from Amgen, Merck, Novartis, and Pfizer. Dr Rahman reports having received consulting fees/honoraria from Boehringer Ingelheim. Dr Sastrasinh reports stock holdings in Abbott Laboratories, Amylin Pharmaceuticals, AstraZeneca, Barr Pharmaceuticals, Baxter International, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, and Proctor & Gamble. Dr Stanford reports stock holdings in Pfizer.

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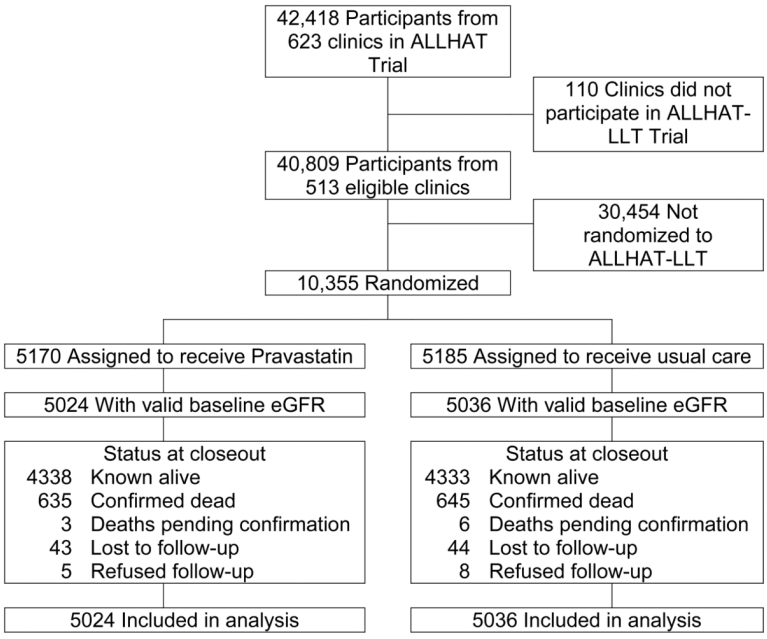


Figure 1.

Randomization and Follow-up of Participants with Valid Baseline Estimated GFR in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

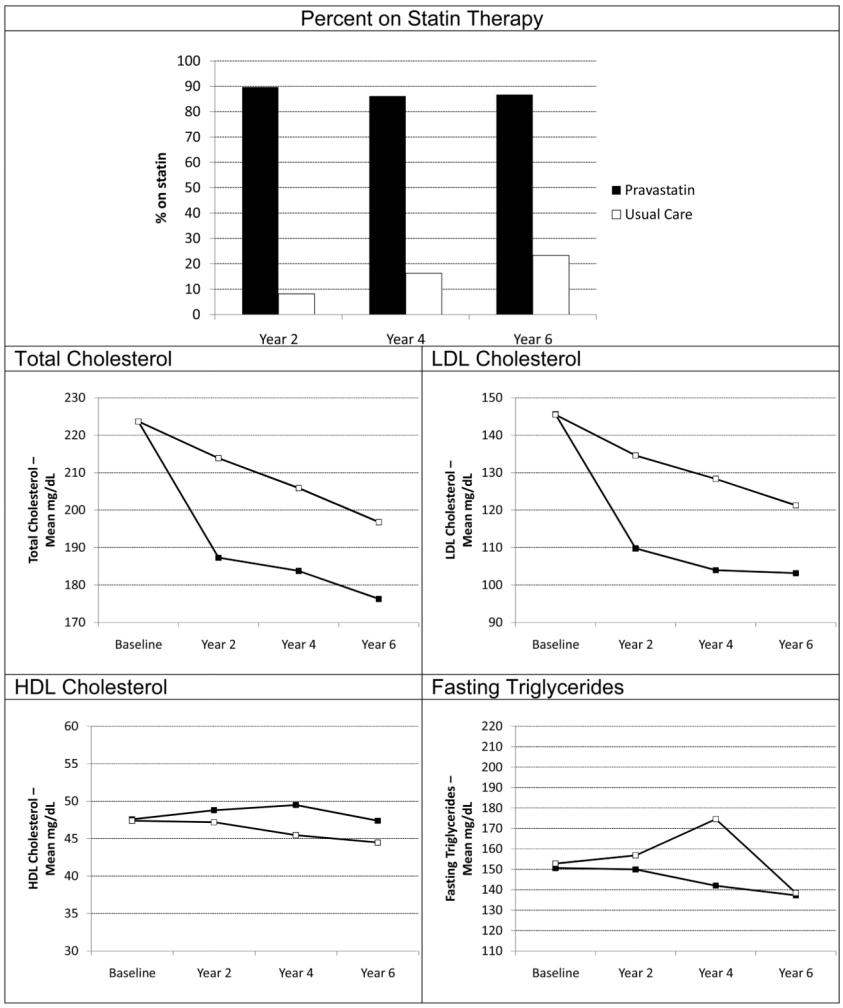
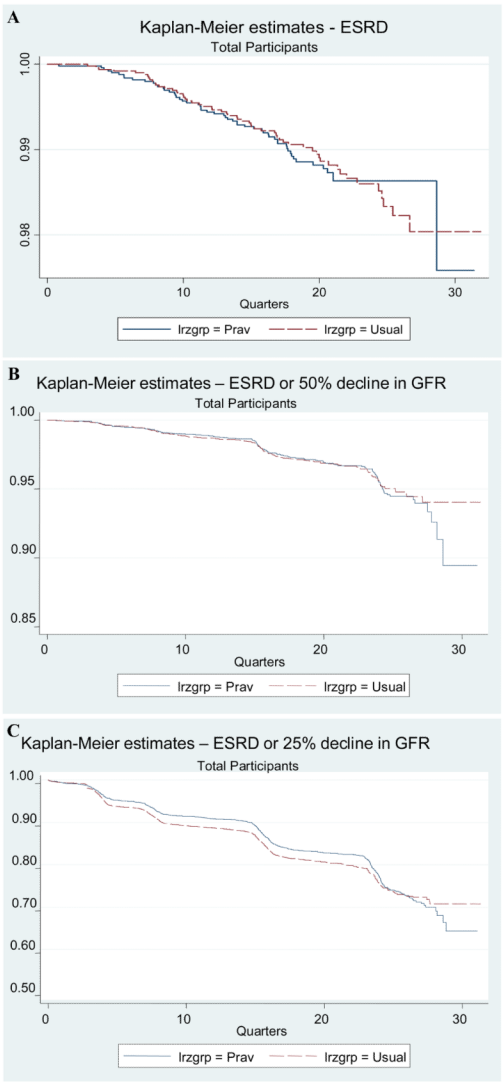


Fig 2.

Statin Use and Lipid Levels Over the Course of the Study. Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein. To convert total cholesterol, LDL-cholesterol, and HDL-cholesterol in mg/dL to mmol/L, multiply by 0.02586. To convert triglycerides in mg/dL to mmol/L, multiply by 0.01129.



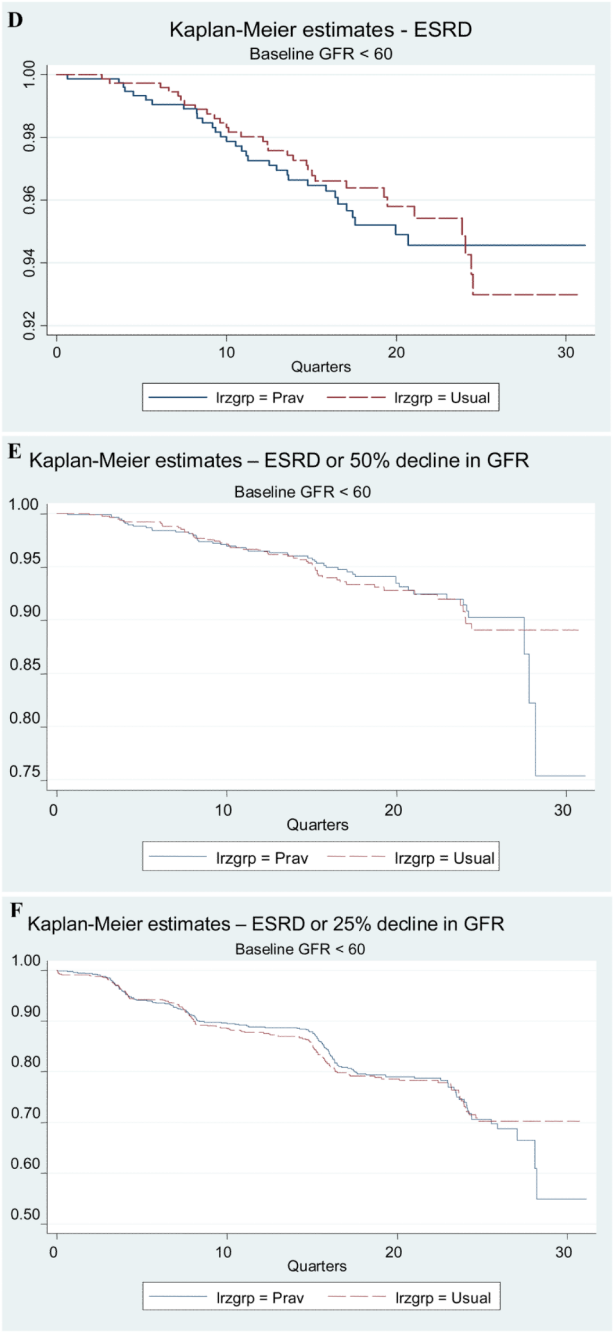


Fig 3.

Survival curves for kidney disease events - pravastatin versus usual care. Treatment groups by baseline estimated glomerular filtration rate (eGFR) estimates. Panels A–C: all participants (n=10,060). Panels D–F: the subgroup of participants with baseline GFR <60 mL/min/1.73 m^2 (n=1557). To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

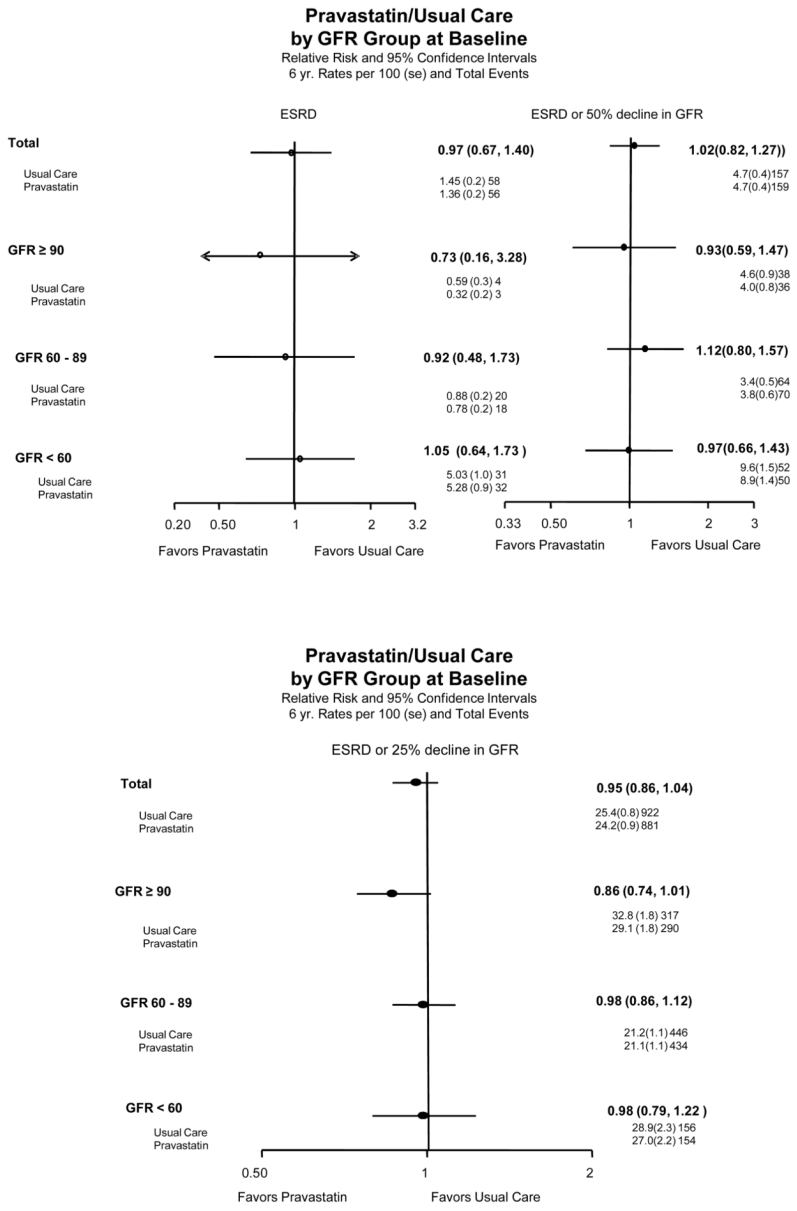


Figure 4.

Renal Outcomes in the Lipid-Lowering Component of ALLHAT by Treatment Group and GFR Group at Baseline (Relative Risks and 95% Confidence Intervals, 6-Year Rates per 100, and Total Events). To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

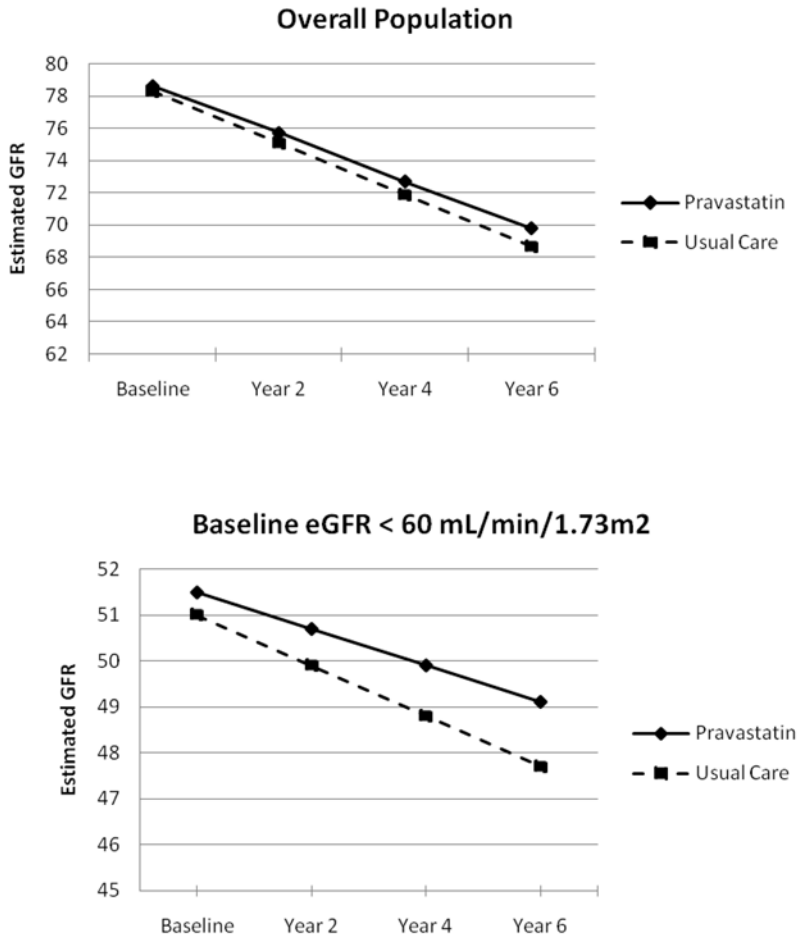


Figure 5.
Estimated GFR (mL/min/1.73 m^2) Over the Course of the Study. To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Am J Kidney Dis. Author manuscript; available in PMC 2010 July 6.

Table 1

Baseline Characteristics Stratified by Estimated Baseline GFR* and Treatment Group

	Normal or Increased Baseline GFR (90+ mL/min per 1.73 m^2)		Mildly Decreased Baseline GFR (60–89 mL/min per 1.73 m^2)		Moderate or Severe Decrease in GFR (<60 mL/min per 1.73 m^2)		Total	
	Pravastatin	**Usual Care**	**Pravastatin**	**Usual Care**	**Pravastatin**	**Usual Care**	**Pravastatin**	**Usual Care**
Number randomized (n, %)	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 – Mean (sd)	63.3 (6.4)	63.1 (6.2)	67.0 (7.4)	67.0 (7.4)	70.7 (7.9)	70.6 (7.8)	66.7 (7.7)	66.6 (7.6)
Ethnicity (n, %)						**		
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, n (%)	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)
BMI (kg/m^2) – mean (sd)	30.5 (6.2)	30.6 (6.6)	29.7 (5.8)	29.7 (5.9)	29.1 (5.7)	29.1 (6.0)	29.8 (5.9)	29.9 (6.1)
Baseline systolic blood pressure (mm Hg) – mean (sd)	142.3 (17.3)	141.8 (17.9)	142.8 (17.7)	142.7 (17.4)	145.8 (19.6)	145.7 (20.7)	143.1 (17.9)	142.9 (18.2)
Baseline diastolic blood pressure (mm Hg) – mean (sd)	83.6 (10.5)	83.2 (10.5)	82.8 (10.3)	83.0 (10.2)	82.5 (11.3)	82.1 (11.2)	82.9 (10.6)	82.9 (10.4)
History of CHD at baseline, n (%)	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, n (%)	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, n (%)	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)

	Normal or Increased Baseline GFR (90+ mL/min per 1.73 m^2)		Mildly Decreased Baseline GFR (60–89 mL/min per 1.73 m^2)		Moderate or Severe Decrease in GFR (<60 mL/min per 1.73 m^2)		Total	
	Pravastatin	**Usual Care**	**Pravastatin**	**Usual Care**	**Pravastatin**	**Usual Care**	**Pravastatin**	**Usual Care**
History of MI or stroke, n (%)	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, n (%)	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, n (%)	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 ECG, n (%)	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, n (%)	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-C, n (%)	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 ECG, n (%)	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 echo, n (%)	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/1.73m^2) – mean (sd)*	101.8 (12.9)	102.4 (12.3)	75.3 (8.0)	75.2 (8.1)	50.8 (8.2)	50.6 (8.4)	78.6 (19.0)	78.4 (19.0)
Lipid baseline lipid profile – mean (sd)								
Total cholesterol	223.0 (26.2)	224.5 (26.8)	223.2 (27.3)	223.3 (26.1)	226.2 (26.3)	224.1 (28.5)	223.7 (26.9)	223.7 (26.7)
LDL	145.2 (20.9)	146.3 (21.3)	145.4 (21.6)	145.4 (21.2)	146.5 (21.2)	144.5 (21.4)	145.6 (21.4)	145.5 (21.3)
Fasting triglycerides	143.9 (71.6)	149.5 (70.6)	150.4 (68.4)	151.6 (68.4)	164.5 (74.5)	164.0 (90.5)	150.6 (70.4)	152.8 (73.0)
Randomized to ACE (n, %)	306 (29.2)	261 (25.7)	598 (25.9)	627 (26.9)	158 (25.7)	156 (25.6)	1,094 (26.8)	1,073 (26.3)
Randomized to CCB (n, %)	276 (26.3)	286 (28.1)	654 (28.3)	633 (27.2)	160 (26.0)	164 (26.9)	1,122 (27.5)	1,118 (27.4)
Randomized to diuretic (n, %)	466 (44.5)	470 (46.2)	1,057 (45.8)	1,067 (45.9)	298 (48.4)	290 (47.5)	1,872 (45.8)	1,883 (46.2)

*Derived from the application of the MDRD study equation based on serum creatinine, age, race, and sex.[13]

**$p < 0.05$, comparison between Pravastatin and Usual Care, Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CVD, cardiovascular disease; ECG, electrocardiography; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction.

†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.

To convert total cholesterol, LDL, and HDL to mmol/L, multiply values by 0.02586. To convert triglycerides to mmol/L, multiply values by 0.01129. To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Table 2

Number of Kidney Disease Events by Treatment Group and Time Period

		Cumulative Number of Events			
	N	**2 years**	**4 years**	**6 years**	**Total events**
ESRD					
Total	10355	29	81	109	114
Pravastatin	5170	14	40	55	56
Usual Care	5185	15	41	54	58
ESRD or 50% decline in eGFR					
Total	8996	80	211	290	316
Pravastatin	4535	39	103	143	159
Usual Care	4461	41	108	147	157
ESRD or 25% decline in eGFR					
Total	8996	800	1377	1713	1803
Pravastatin	4535	373	650	824	881
Usual Care	4461	427	727	889	922

Table 3

Estimated Glomerular Filtration Rate by Treatment Group by Time Period

	Baseline		2 Years		4 Years		6 Years	
Estimated Baseline GFR total mL/min/1.73m^2 (95% C.I.); (N=10,248)								
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)	P=0.3	75.1((74.6,75.6)	P=0.1	71.9(71.3, 72.5)	P=0.06	68.7(67.9, 69.5)	P=0.06
Estimated Baseline GFR <60 mL/min/1.73m^2 (95% C.I.)								
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)	P=0.4	49.9(49.1, 50.8)	P=0.2	48.8(47.7, 50.0)	P=0.08	47.7(46.2, 49.3)	P=0.08
Estimated Baseline GFR 60–89 mL/min/1.73m^2 (95% C.I.)								
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)	P=0.4	72.8(72.3, 73.2)	P=0.09	70.3(69.7, 71.0)	P=0.05	67.9(67.0, 68.7)	P=0.04
Estimated Baseline GFR >90 mL/min/1.73m^2 (95% C.I.)								
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)	P=0.6	95.2(94.6, 95.9)	P=0.8	89.2(88.3, 90.1)	P=0.4	83.3(82.1, 84.5)	P=0.3

[1] Mixed model regression estimates.

[2] N=10,060 in the mixed model regressions.

To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Table 4

Time Rate of Change in Estimated Glomerular Filtration Rate by Treatment Group and Baseline Estimated Glomerular Filtration Rate

	Pravastatin			Usual Care			
	Estimated ΔFR[1]	SE	95% C.I.	Estimated ΔGFR[1]	SE	95% C.I.	*p*[2]
Estimated Baseline GFR total	−1.48	0.06	(−1.59, −1.36)	−1.59	0.06	(−1.71, −1.47)	0.2
Estimated Baseline GFR <60	−0.34	0.15	(−0.64, −0.03)	−0.62	0.16	(−0.92, −0.31)	0.2
Estimated Baseline GFR 60–89.9	−1.13	0.08	(−1.28, −0.98)	−1.18	0.08	(−1.33, −1.03)	0.2
Estimated Baseline GFR >90	−2.75	0.12	(−2.97, −2.53)	−3.07	0.12	(−3.31, −2.84)	0.05

[1] mL/min/1.73m^2/yr

[2] *p*-value for comparison of Pravastatin vs. Usual Care

To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.