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Effect of statin therapy on the progression of autosomal dominant polycystic kidney disease. A secondary analysis of the HALT PKD trials

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Abstract

Background—Autosomal dominant polycystic kidney disease (ADPKD) commonly results in end-stage renal disease (ESRD), yet a long-term treatment that is well tolerated is still lacking. In a small randomized trial in children and adolescents pravastatin administration for 3 years was associated with reduced renal cyst growth, but no large trial has tested the effect of statins in adults.

Methods—We performed a post-hoc analysis of the HALT PKD trials to compare outcomes of participants who never used statins with those who used statin for at least 3 years. Because statins were not randomly allocated we used propensity score models with inverse probability of treatment weighting to account for imbalances between the groups. For subjects in Study A (preserved renal function, n=438) relevant outcomes were percent change in total kidney and liver volume and the rate of decline in estimated glomerular filtration rate (eGFR); for those in Study B (reduced renal function, n=352) we compared time to the composite endpoint of death, ESRD or 50% decline in eGFR. Follow-up was 5–8 years.

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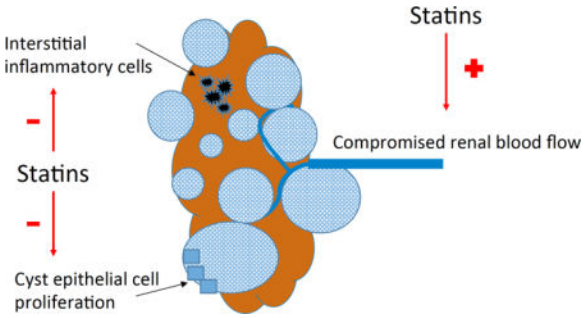
Results—There was no difference in any outcome between the 2 groups. However, limitations of this analysis are the small number of statin users in Study A, different statin drugs and doses used, non-randomized allocation and advanced disease stage in Study B.

Conclusions—Although this post-hoc analysis of the HALT PKD trials does not demonstrate a benefit of statin therapy, conclusions remain preliminary. A larger randomized trial in young people with ADPKD is necessary to answer the question whether statins can slow renal cyst growth and preserve kidney function.

Graphical abstract

Statins have pleiotropic effects which include inhibition of cell proliferation and inflammation. Statins have been shown to improve endothelial dysfunction and increase renal blood flow. We tested the hypothesis that statins prevent progression of ADPKD, by performing a secondary analysis of the HALT PKD Trials.



Keywords

Autosomal dominant polycystic kidney disease; end-stage renal disease; glomerular filtration rate; HALT PKD trials; hydroxymethylglutaryl-CoA reductase inhibitors; total kidney volume

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic and potentially fatal disease, with an estimated prevalence of 1 in 400 to 1 in 2,500 in populations worldwide[1–3]. Progressive development and enlargement of renal cysts eventually destroys the normal parenchyma, leading to end-stage renal disease (ESRD) in the majority of afflicted patients. Despite recent progress in understanding the genetic basis and pathophysiological mechanisms of this disease, the incidence of ESRD and age at onset of ESRD may not have changed significantly[4–6].

Several new medications have been tested in interventional trials. Some may slow but not halt the progression of ADPKD and all have substantial side effects[7–10]. Although tolvaptan has been approved in Japan, Canada and Europe for rapidly progressive ADPKD, it is not approved in the United States for this indication, and the mainstay of therapy remains control of hypertension to prevent left ventricular hypertrophy and cardiovascular complications[11–13]. Additional well tolerated therapies to slow the progression of ADPKD are urgently needed.

Studies in animal models of ADPKD have shown that statin treatment decreases cyst formation, preserves renal blood flow and mitigates interstitial inflammation[14–16]. In a randomized placebo-controlled trial in 110 young (age 8–22 years) patients with ADPKD, treatment with pravastatin for 3 years reduced the increase in height-adjusted total kidney volume (TKV) measured by magnetic resonance imaging (MRI)[17]. No statin treatment trial with sufficient statistical power has been performed in adults with preserved renal function. Although the SHARP (Study of Heart and Renal Protection) trial included 675 patients with polycystic kidney disease, the mean estimated glomerular filtration rate (eGFR) at randomization was 27 ml/min/1.73 m^2, reflecting disease too far advanced for any intervention to alter the course[18].

Therefore we undertook a secondary analysis of the HALT PKD trials which involved 1044 adult subjects participating for 5–8 years (ClinicalTrials.gov numbers NCT00283686 for Study A and NCT01885559 for Study B, see below)[19,20]. The primary objective of these trials was to compare aggressive blood pressure (BP) control and intensive blockade of the renin-angiotensin-aldosterone system (RAAS) with less rigorous therapy[21]. We examined whether subjects who took a statin drug for at least 3 years had slower progression of ADPKD compared to those who did not, the cutoff being based on the pravastatin trial in children and young adults.

SUBJECTS AND METHODS

The HALT PKD trials were randomized, double-blind, multicenter trials to test the hypothesis that intensive BP control using single or double RAAS blockade can retard the progression of kidney disease in hypertensive patients with ADPKD[19–21]. The 2 trials involved individuals at different disease stages: Study A randomized 558 young (15–49 years, mean age 36 years) subjects with preserved renal function (eGFR > 60 mL/min/1.73 m^2) in a 2×2 factorial design to either a low BP goal (95/60–110/75 mm Hg) or standard BP goal (120/70–130/80 mm Hg) using either lisinopril (an angiotensin converting enzyme inhibitor) and placebo or the combination of lisinopril and telmisartan (an angiotensin-2 receptor blocker), with other medications added as needed to achieve the BP goal. Study B randomized 486 older (18–64 years, mean age 48 years) patients with reduced renal function (eGFR 25–60 mL/min/1.73 m^2) to either lisinopril and placebo or lisinopril and telmisartan to achieve a single BP goal of 120–130/70–80 mm Hg. Known coronary artery disease and diabetes were exclusion criteria for HALT, therefore subjects with a strong indication for statin use were excluded from both Study A and B.

All participants gave informed consent and the trials were conducted according to the principles of the Helsinki Declaration.

Cardiac and renal MRI was obtained at baseline and after 2, 4 and 5 years in Study A participants using methods established by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)[22]. Estimated GFR (eGFR) was calculated for both Study A and B using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, based on centralized serum creatinine determinations by isotope dilution mass spectrometry (IDMS)[23].

The primary outcome for Study A was percent change in TKV, for Study B the composite of time to ESRD, death, or 50% reduction in eGFR. Secondary outcomes were rate of change in eGFR, and for Study A change in height-adjusted total liver volume (htTLV) and in left ventricular mass index (LVMI). Follow-up time was 5–8 years.

Participants were evaluated at 7 study centers at baseline, at 4, 7 and 12 months, and then every 6 months until the end of the trial in 2014 (Study A) or until a subject met an endpoint (Study B). At each study visit all concomitant medications were documented and entered into the database. Statin use was defined by the presence of any hydroxymethylglutaryl-CoA-reductase inhibitor on the medication list at any time point of follow up. The duration of statin use was calculated by adding up the number of 6-month periods (regardless whether consecutive or not) where participants reported their use. The HALT study protocol did not make any recommendation regarding statin therapy, and serum cholesterol measurements were not obtained. Prescription of a statin drug was at the discretion of the patient's private physician.

Statistical analysis

For this post-hoc analysis of the HALT PKD trials we categorized participants into 2 groups based on statin use: 1) No Use (never used) and 2) Statin Use (at least 3 years of use, based on the pravastatin trial in children and young adults[17]), which led to the exclusion of 113 participants (37 for Study A; 76 for Study B) who used statins for less than 3 years (mean years of use for Study A and B: 0.9 ± 0.8 and 1.1 ± 0.8, respectively). We compared demographic and clinical baseline characteristics between the 2 groups using analysis of variance and Chi-square tests of significance, or their nonparametric counterparts when necessary. Several variables such as TKV, htTLV and urine albumin were log-transformed in order to normalize. Because of imbalances in baseline characteristics between the 2 groups we utilized a propensity score model with inverse probability of treatment weighting (IPTW) to create a cohort of participants who were well-balanced on all baseline covariates[24]. For both Study A and B, the propensity of taking statins for at least 3 years was calculated for each participant using logistic regression as a function of the following baseline predictors: age, gender, body mass index (BMI), eGFR, urine albumin, home systolic and diastolic BP, and study drug arm. For Study A only, LVMI, TKV, and BP arm were also included. Because not all participants provided their home BP measurements at baseline, we used the first non-missing value as long as it occurred prior to their first statin use. For each participant, the estimated propensity score was weighted by the inverse probability of being in the No Use or Statin Use group. In order to assess for balance between groups, we calculated weighted standardized mean differences for each of the baseline covariates included in the model and compared the magnitude of imbalance to the unweighted differences.

For Study A, linear mixed models were used to assess whether changes in outcomes (TKV and eGFR) were different between the 2 groups after accounting for the inverse probability of treatment weights. Predictors included month, statin use group, and their interaction. Of interest was whether the interaction was significant, which would indicate differences in

annual percent increase of TKV or rate of decline in eGFR. In addition, we examined whether statin use had any effect on htTLV using similar linear mixed models.

For Study B a Cox proportional hazards model was used to investigate whether statin use was a predictor of time to composite endpoint after accounting for the inverse probability of treatment weights. The only predictor was statin use group.

RESULTS

The most commonly prescribed statins were simvastatin (36%) and atorvastatin (35.6%), followed by pravastatin (11%), rosuvastatin (10.4%), and lovastatin (6%). Fluvastatin and pitavastatin were used by one individual each. Unfortunately the doses of each drug were not adequately documented.

In Study A only 59 of 558 (10.5%) of participants used a statin for at least 3 years (mean 5.3 ± 1.5 years), whereas 462 (83%) were in the No Use group. Statin users were more often male and significantly older than non-users, had higher baseline (or first non-missing) systolic BP, and lower baseline eGFR (Table 1), but after accounting for the propensity weights the standardized mean differences between statin use groups were attenuated, with all below 0.20 (Figure 1 a). Average home systolic and diastolic BPs during the trial were similar in the 2 groups (data not shown). Due to missing data on any of the covariates used in the propensity score model, 83 Study A participants were not included in the IPTW analyses. These participants were similar to those 438 included, with the exception that the latter group had a higher baseline BMI (25.8 ± 4.7 kg/m^2 vs. 27.3 ± 5.2 kg/m^2; p=0.02; Table 2).

The rate of increase in TKV (Figure 2) and htTLV (Figure 3) was not significantly different between the 2 groups after accounting for the propensity weights. TKV growth was 6.5% vs. 6.2% per year in the Statin Use and No Use groups, respectively (p=0.51). Increase in htTLV was 0.8% and 1.0% per year in the Statin Use and No Use groups (p=0.54). eGFR declined slightly faster (3.06 ml/min/year) in the Statin Use group than the No Use group (2.87 ml/min/year), but this was not significant (p=0.57) (Figure 4).

In Study B, 118 of 486 (24%) participants used a statin for at least 3 years (mean 5.0 ± 1.3), and 292 (60%) were in the No Use group. Statin users were more often men and were older than never users (Table 3); after accounting for the propensity weights, standardized mean differences between statin use groups were attenuated with all below 0.20 (Figure 1 b). Average home systolic and diastolic BPs during the trial were similar in the 2 groups (data not shown). Due to missing data on any of the covariates used in the propensity score model, 58 Study B participants were not included in the IPTW analyses. These participants were similar to the 352 who were included (Table 4).

There was no difference in time to the composite endpoint of death, ESRD or 50% decline in eGFR between the 2 groups (HR=0.99; p=0.96) in Study B (Figure 5).

DISCUSSION

ADPKD is a common genetic disease with high morbidity and premature mortality, for which a treatment is desperately needed. Due to the slow progression, from birth to the 5th or 6th decade of life when ESRD ensues, treatment will need to be given for many years starting at a young age, requiring a drug with a low side effect profile and no serious toxicity. Statins have been used in millions of people worldwide for lipid lowering and prevention of cardiovascular events, and are generally well tolerated. Statins exert pleiotropic effects besides decreasing serum cholesterol levels[25,26]. By inhibiting the enzyme hydroxymethylglutaryl-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, and other mechanisms such as cell cycle arrest and induction of apoptosis, statins inhibit cell proliferation, shown in several cancer cell lines and in clinical studies of malignancies[27,28]. Tubular epithelial cell proliferation is required for cyst growth, and both simvastatin and pravastatin inhibited proliferation of an immortalized ADPKD cyst cell line in a dose dependent manner [abstract Wang W et al: Statin effect on human ADPKD tubular epithelial cell proliferation. J Am Soc Nephrol 2014; 25: 412A]. In the Han:SPRD rat model of ADPKD, lovastatin treatment resulted in decreased cystic kidney size, decreased volume density of cysts and improved renal function[14,15]. Most importantly, a randomized controlled trial in pediatric patients with ADPKD showed that treatment with pravastatin (20 mg daily if age 8–12 years and 40 mg daily if age 13–22 years) was associated with slower increase in height-adjusted TKV compared to placebo[17]. GFR did not change in either group at this early stage of ADPKD.

In contrast, the current post-hoc analysis of the HALT PKD trials does not confirm a beneficial effect of statins on renal volume growth in adults. Although participants in HALT Study A had preserved renal function (baseline eGFR 91.5 ± 17.5 ml/min/1.73 m^2), they were significantly older (mean age 36.2 ± 8.3 years)[29] than the pediatric patients (mean age 16 ± 4 years), suggesting that antiproliferative treatments may be most effective in early-stage ADPKD. Likewise, in the animal models statins were administered after weaning, a very young age.

Other effects of statins include improvement of endothelial dysfunction by upregulating endothelial and vascular smooth muscle cell production of nitric oxide[25,30,31]. Endothelial dysfunction is an early feature of ADPKD[32–37] and may account for the decreased renal blood flow observed in young people with ADPKD[38,39]. In fact, a double-blind cross-over study among young (mean age 35 years) normotensive ADPKD patients demonstrated an increase in effective renal plasma flow after 4 weeks of simvastatin treatment (40 mg daily), accompanied by improvement in endothelium-dependent vasodilatation in the forearm[40]. In contrast, an increase in renal blood flow or GFR was not seen with the same treatment in older (mean age 47 years) patients with more advanced ADPKD[41], consistent with the notion that statin benefits may be limited to early stages of this disease[42].

Because statins have anti-inflammatory and anti-oxidant effects[25,31,43], they have been studied for the prevention of acute kidney injury after cardiac surgery, a state of an intense systemic inflammatory response, with mixed results[26,44]. Renal interstitial inflammation and oxidative stress are prominent features of ADPKD, resulting in dense fibrosis, tubular

atrophy and glomerulosclerosis[45–48]. Statin treatment was associated with less renal interstitial and systemic inflammation in the Han:SPRD rat model[14,16]; likewise in the pediatric ADPKD trial, plasma levels of inflammatory and oxidative stress biomarkers declined during pravastatin treatment but not with placebo[49]. However, any anti-inflammatory effects did not translate into slower decline of eGFR in our post-hoc analysis of either Study A or Study B. Similarly, a small (n = 49) open-label trial of pravastatin 20 mg for 2 years in advanced ADPKD (mean age 51 years) also did not show a benefit[50], consistent with the SHARP trial results in very advanced disease[18].

Limitations of this study are the small numbers of participants who used a statin for at least 3 years, particularly in Study A, and the nonrandomized allocation to statins. The variety of statin drugs used and the fact that doses were not documented also contribute to uncertainty. Lipid-soluble statins may have better antiproliferative effects than water-soluble ones that do not readily penetrate into epithelial cells. Low-potency statins may not have the same pleiotropic effects as high-potency statins and/or high doses. Clinical trials showing a benefit of pre-angiography statin administration to prevent contrast-induced acute kidney injury typically used high doses of a high-potency statin[51–53]. A meta-analysis of trials examining statin therapy to prevent progression of chronic kidney disease did not find a benefit of low-intensity statins, but subjects in the high-intensity study arms did have a significantly slower decline in eGFR compared to controls[54]. Among high-potency statins, atorvastatin may have better renoprotective effects than rosuvastatin, based on a direct comparison in the PLANET (Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease) trials[55].

KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend the use of statins in all patients with chronic kidney disease who are older than 50 years and not receiving dialysis, regardless of serum cholesterol levels, for prevention of cardiovascular disease[56]. Therefore, the question whether a high-potency statin drug reduces renal cyst growth and preserves kidney function is relevant mainly for young (age 16–40 years) individuals with ADPKD, who are the most likely to benefit from any intervention. A randomized controlled trial of sufficient size, similar to HALT Study A, is necessary, using a high-potency lipid-soluble statin drug for young people with ADPKD and preserved renal function.

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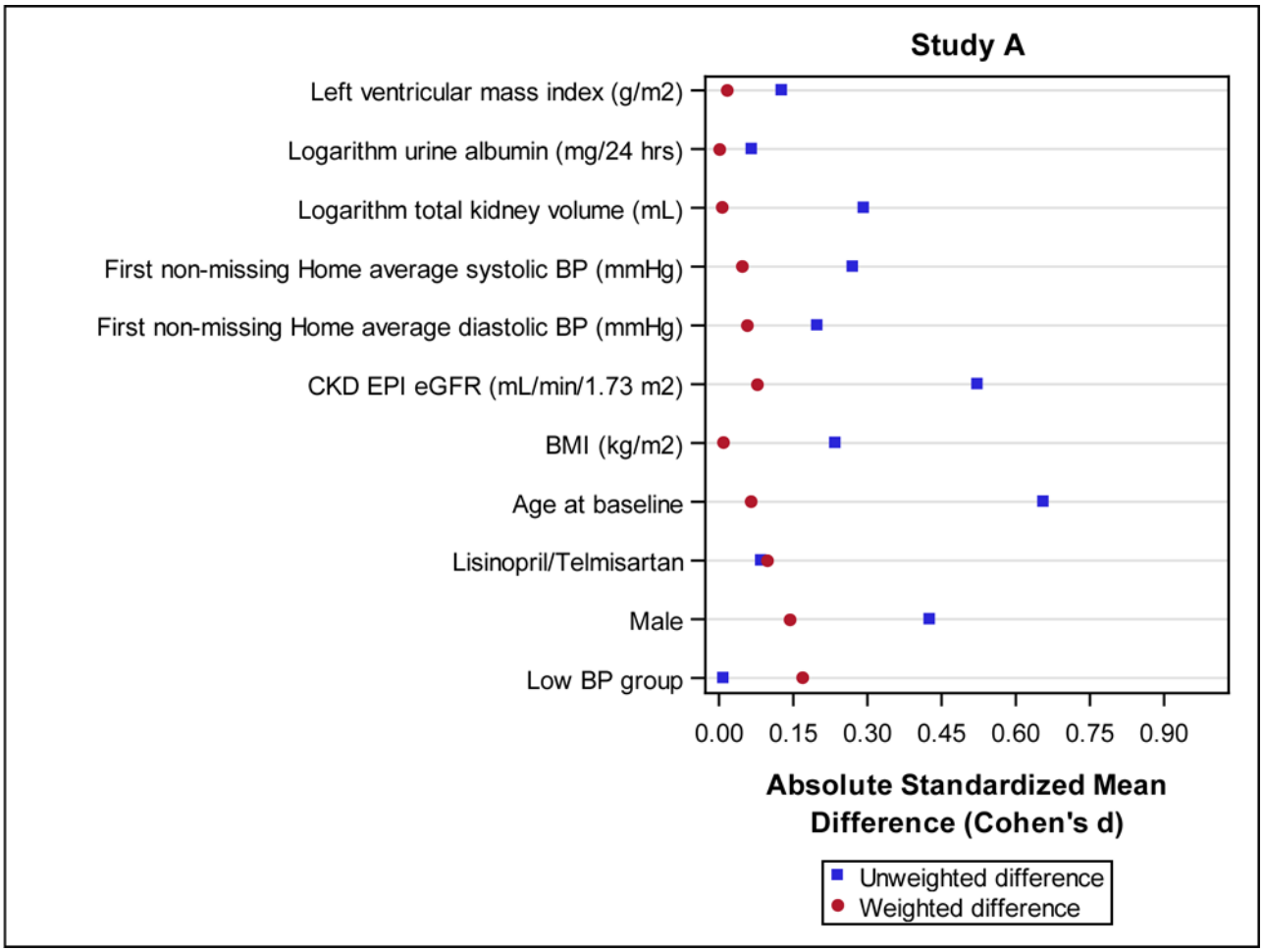
Short summary

Autosomal dominant polycystic kidney disease (ADPKD) is a common disorder, yet other than blood pressure control, treatment that is well tolerated for long-term use is still lacking. Studies in animal models and a small randomized trial in adolescents have shown benefits of statin therapy for reducing the progression of ADPKD, but no large trial has been undertaken in adults with early to moderately advanced disease. Therefore we performed a secondary analysis of the recently completed HALT PKD trials (1044 participants) to examine whether statin use for at least 3 years, compared to no use, was associated with slower renal and liver cyst growth, or with less decline in renal function.



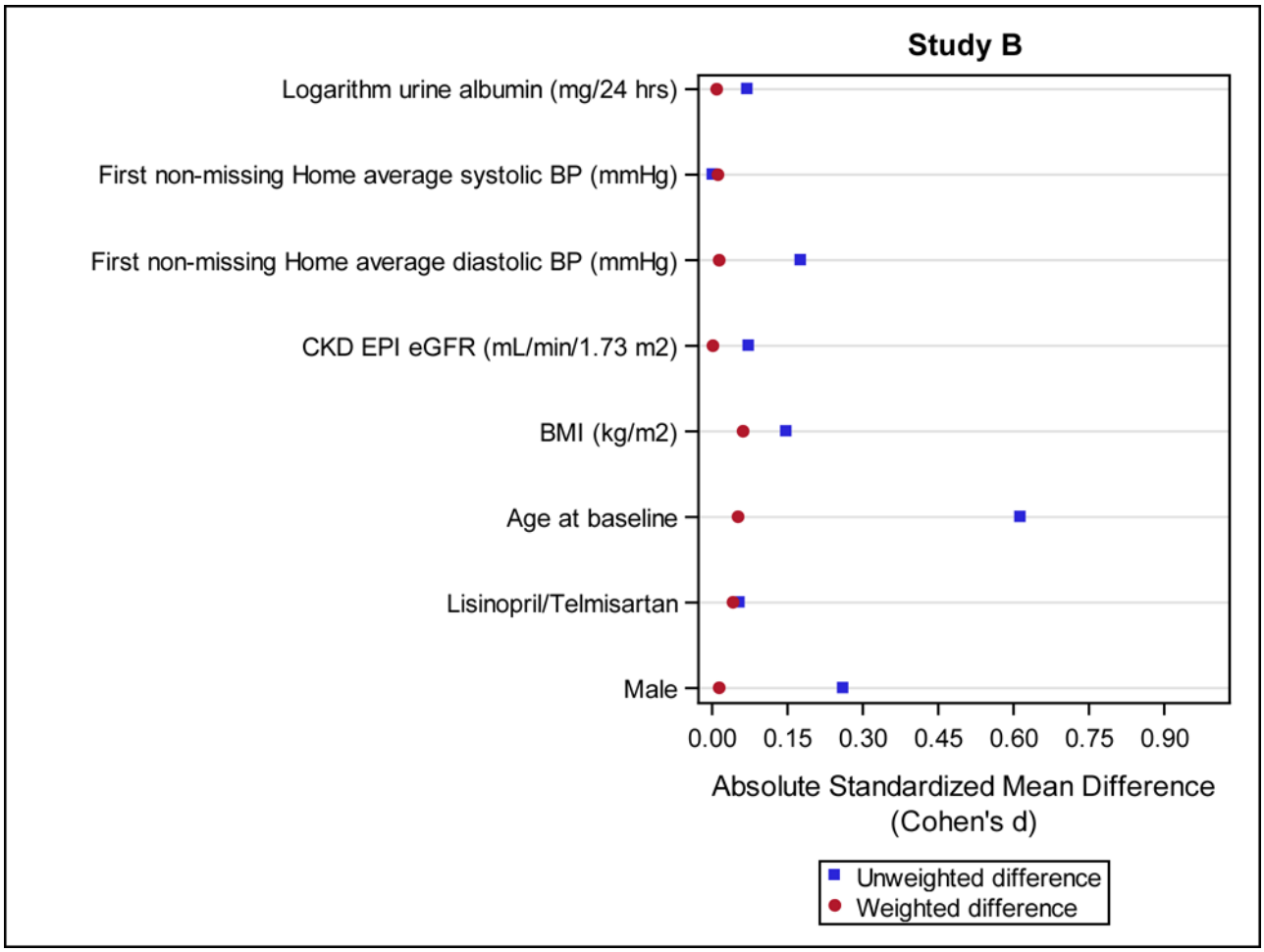


Figure 1.

Standardized mean differences with (weighted differences) and without (unweighted differences) accounting for the inverse probability of treatment weight (IPTW). Baseline characteristics which were used in the propensity score models are shown for Study A (Fig. 1 a) and Study B (Fig. 1 b).

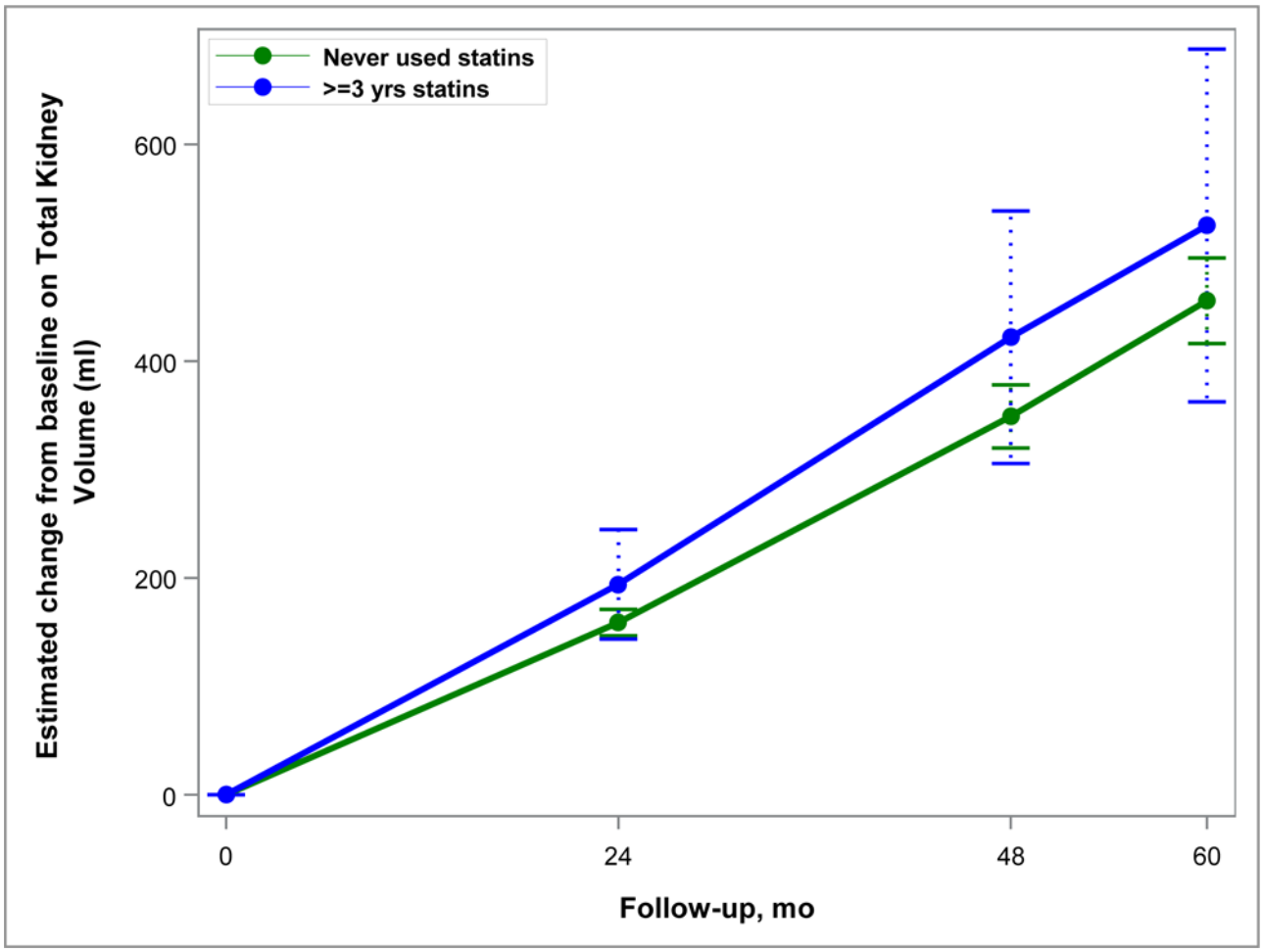


Figure 2.

Model-based estimates of change in total kidney volume (TKV) from baseline over 60 months in Study A. Point estimates and 95% confidence intervals derived from linear mixed models accounting for the inverse probability of treatment weights and including predictors for month, statin use group, and their interaction. The difference between statin users (for at least 3 years) and never users was not significant (p=0.51).

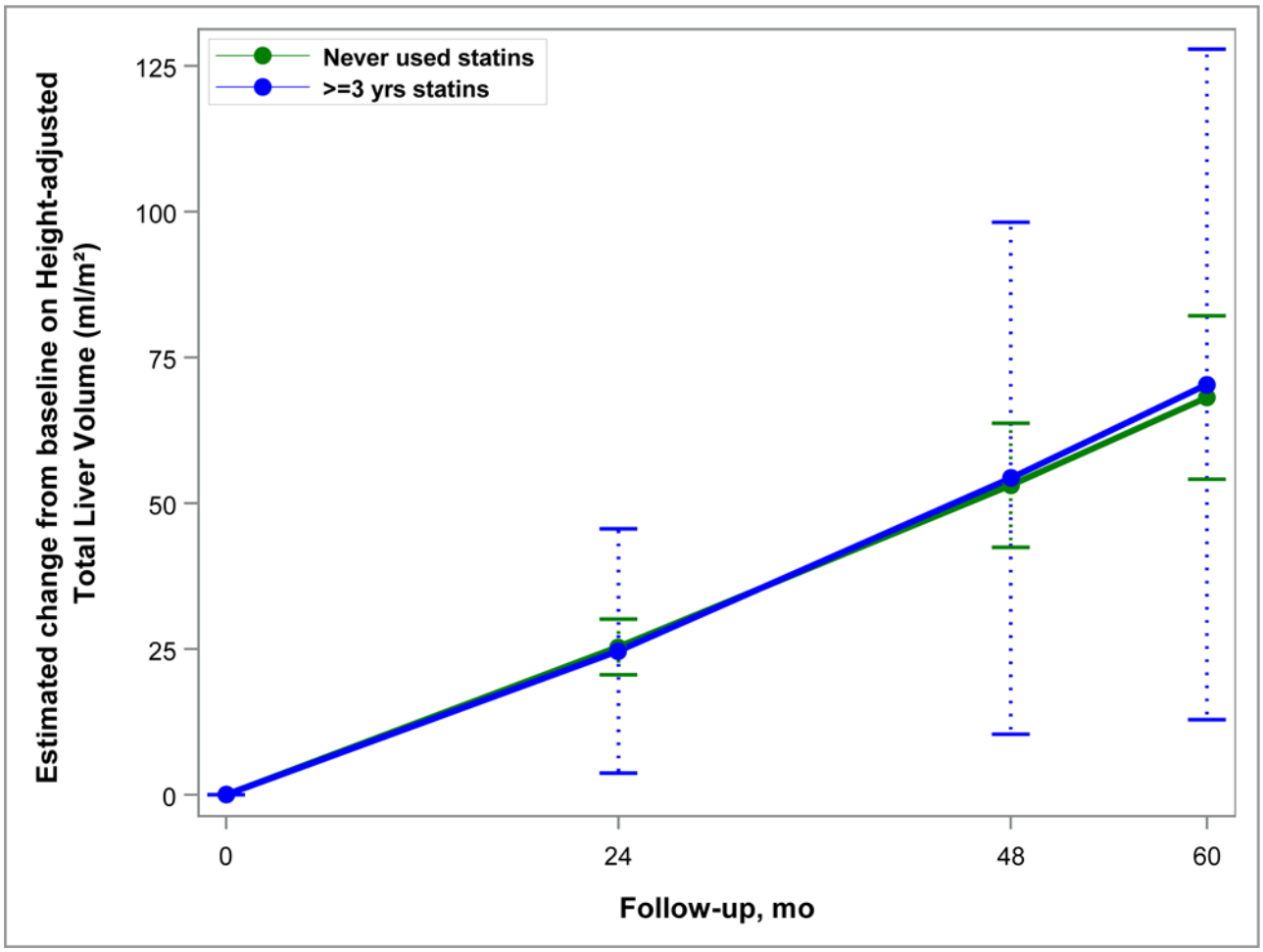


Figure 3.

Model-based estimates of change in height-adjusted total liver volume (htTLV) from baseline over 60 months in Study A. Point estimates and 95% confidence intervals derived from linear mixed models accounting for the inverse probability of treatment weights and including predictors for month, statin use group, and their interaction. The difference between statin users (for at least 3 years) and never users was not significant (p=0.54).

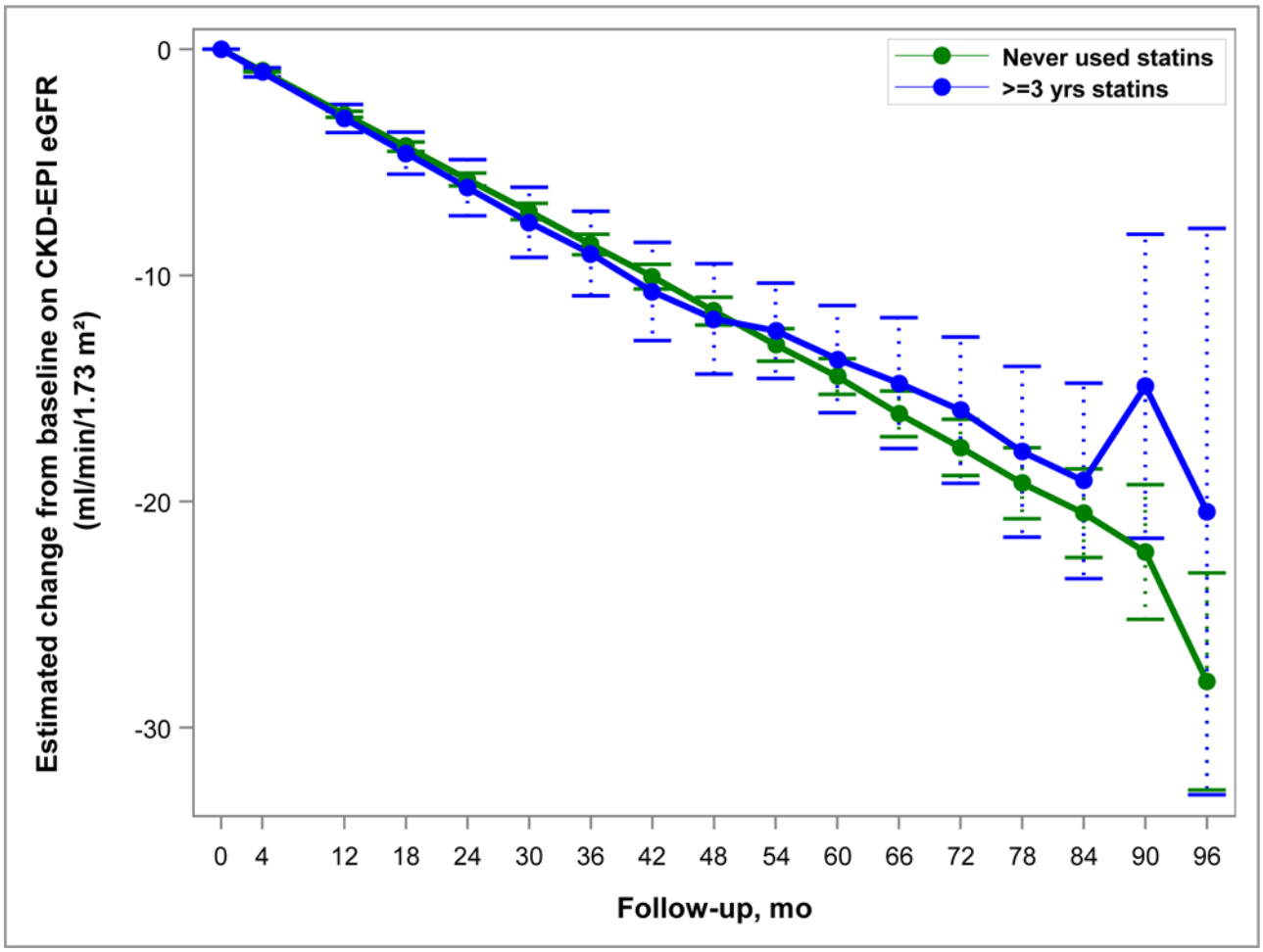


Figure 4.

Model-based estimates of change in eGFR over 60 months in Study A. Point estimates and 95% confidence intervals derived from linear mixed models accounting for the inverse probability of treatment weights and including predictors for month, statin use group, and their interaction. The difference between statin users (for at least 3 years) and never users was not significant (p=0.57).

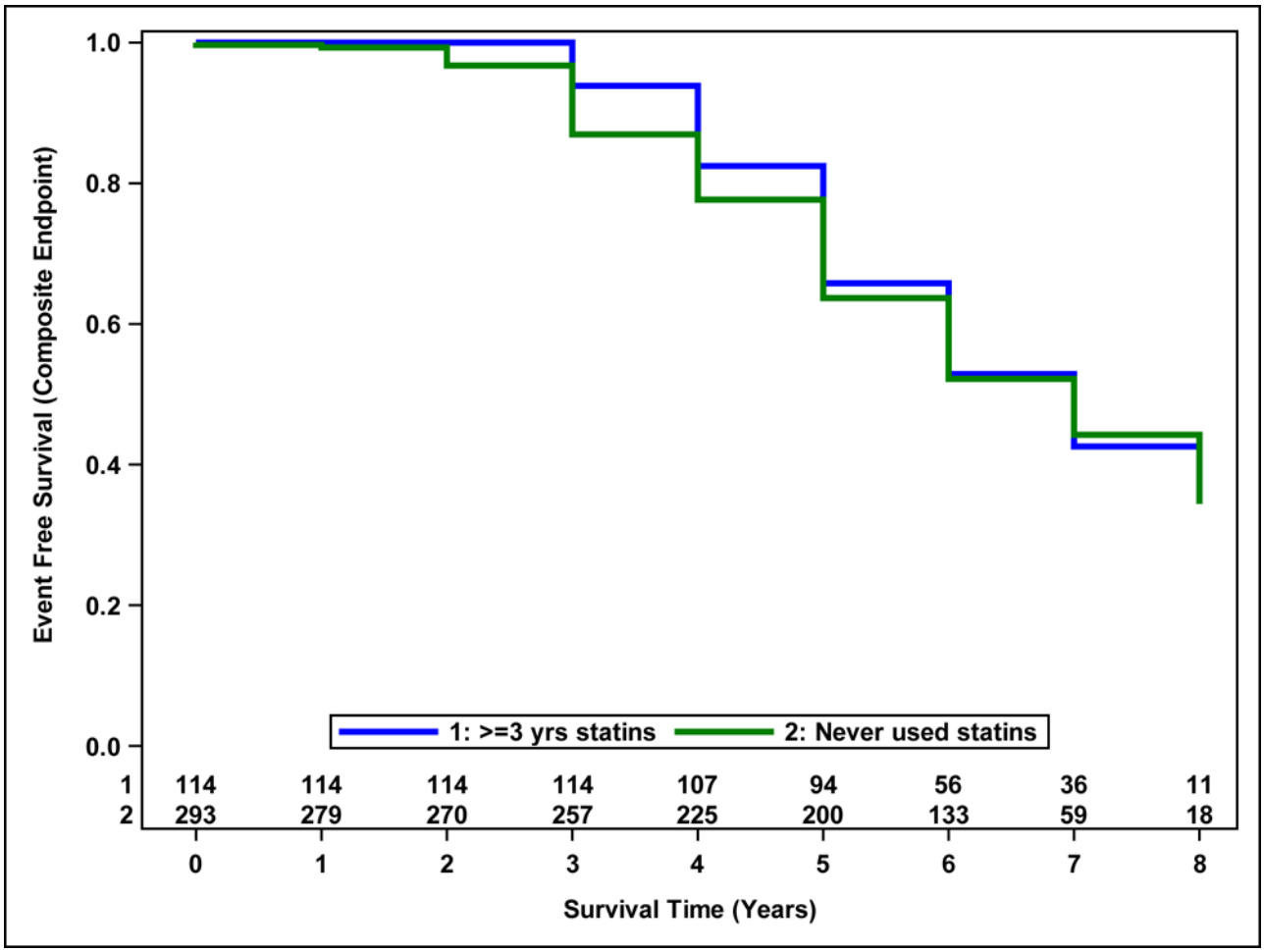


Figure 5.

Probability of event-free survival from the composite outcome in Study B. Survival curves estimated from a Cox proportional hazards model accounting for the inverse probability of treatment weights and including statin use group as a predictor. Number of participants at risk are shown above the x-axis. There was no difference between statin users (for at least 3 years) and never users (p=0.96).

Table 1

Baseline demographic and clinical characteristics of Study A participants by use of statin drugs, before and after IPTW

a. ***Categorical measures:***

		BEFORE IPTW			AFTER IPTW		
		Never used (n=462)	**Used 3 or more years (n=59)**		**Never used (n=382)**	**Used 3 or more years (n=56)**	
Characteristic	**Category**	**n (%)**	**n (%)**	**p value**	**%**	**%**	**p value**
Sex	Male	218 (47.2%)	40 (67.8%)	0.0029	49.6%	42.4%	0.5059
	Female	244 (52.8%)	19 (32.2%)		50.4%	57.6%	
PKD genotype	NMD	35 (8.4%)	6 (10.2%)	0.8975	7.9%	6.9%	0.4952
	PKD1	312 (74.8%)	43 (72.9%)		74.8%	81.8%	
	PKD2	70 (16.8%)	10 (16.9%)		17.2%	11.3%	
Treatment group	Lisinopril/Telmisartan	223 (48.3%)	31 (52.5%)	0.5363	49.7%	44.9%	0.6747
	Lisinopril/Placebo	239 (51.7%)	28 (47.5%)		50.3%	55.1%	
Blood pressure group	Standard BP	237 (51.3%)	30 (50.8%)	0.9479	50.3%	41.9%	0.4388
	Low BP	225 (48.7%)	29 (49.2%)		49.7%	58.1%	
CAD or Angina	Yes	2 (0.4%)	0 (0.0%)	0.6122	0.7%	0%	–
	No	459 (99.6%)	59 (100.0%)		99.3%	100.0%	

b. Continuous measures:

	Before IPTW					After IPTW		
		Never used (n=462)		**Used 3 or more years (n=59)**		**Never used (n=382)**	**Used 3 or more years (n=56)**	
Measure	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**p value**	**Mean (SE)**	**Mean (SE)**	**p value**
Age at baseline (years)	462	35.8 ± 8.5	59	40.7 ± 6.2	<.0001	36.6 (0.4)	35.3 (3.3)	0.6935
BMI (kg/m^2)	453	27.0 ± 5.2	58	28.2 ± 5.2	0.0907	27.3 (0.3)	27.2 (1.2)	0.9323
Home average systolic BP (mmHg) *	430	120.8 ± 10.4	59	123.5 ± 9.0	0.0649	121.2 (0.6)	122.1 (1.1)	0.4882
Home average diastolic BP (mmHg) *	430	80.6 ± 8.2	59	82.2 ± 7.8	0.1595	80.7 (0.4)	79.7 (1.7)	0.5698
CKD EPI eGFR (mL/min/1.73m^2)	461	93.0 ± 17.7	59	84.3 ± 15.3	0.0004	91.4 (0.9)	94.9 (7.2)	0.6345
Urine albumin (mg/24 hrs) *Median (p25, p75)*	448	18.5 (12.1, 32.8)	58	16.4 (12.6, 34.0)	0.6158 **	34.8 (2.6)	35.9 (8.2)	0.9839 **

b. Continuous measures:								
	Before IPTW					**After IPTW**		
		Never used (n=462)		**Used 3 or more years (n=59)**		**Never used (n=382)**	**Used 3 or more years (n=56)**	
Measure	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**p value**	**Mean (SE)**	**Mean (SE)**	**p value**
Total kidney volume (mL)	456	1187.4 ± 722.2	58	1393.2 ± 788.5	0.0437	1228 (38.8)	1224 (122.2)	0.9746
Logarithm total kidney volume (mL)	456	6.9 ± 0.6	58	7.1 ± 0.6	0.0352	7.0 (0.0)	7.0 (0.1)	0.9324
Height-adjusted TKV (mL/m)	448	679.9 ± 400.7	57	786.4 ± 434.5	0.0617	701.5 (21.2)	703.3 (65.1)	0.9788
Renal blood flow (mL/min/1.73m^2)	309	607.4 ± 208.8	44	608.5 ± 212.0	0.9752	599.3 (12.5)	722.2 (93.1)	0.1919
Left ventricular mass index (g/m^2)	446	63.7 ± 12.8	58	65.5 ± 15.4	0.3264	63.8 (0.7)	63.2 (2.5)	0.8222
CKD EPI eGFR at F5 (mL/min/1.73m^2)	422	90.4 ± 18.6	59	81.9 ± 16.6	0.0009	89.5 (1.0)	93.4 (7.6)	0.6207
Statin Use (# years of any use)	462	N/A	59	5.3 ± 1.5	—	—	4.9 (0.4)	—

BP: blood pressure; CAD: coronary artery disease; IPTW: inverse probability of treatment weighting; NMD: no mutation detected.

*At the visit a participant first reported a home systolic and diastolic BP reading (for 96% of participants, this was at the baseline (71%) or 4 month (25%) visit)

**p value from log transformed variable

BMI: body mass index; BP: blood pressure; CKD EPI eGFR: estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; F5: Follow-up visit 5 (after 4 months in the study); IPTW: inverse probability of treatment weighting; *p25*: 25th percentile.

Table 2

Baseline demographic and clinical characteristics of Study A participants by included vs not included in IPTW analysis

a. Categorical measures:				
		Not included (n=85)	**Included (n=438)**	
Characteristic	**Category**	**n (%)**	**n (%)**	**p value**
Sex	Male	41 (48.2%)	217 (49.5%)	0.8253
	Female	44 (51.8%)	221 (50.5%)	
PKD genotype	NMD	6 (15.4%)	35 (8.0%)	0.2528
	PKD1	28 (71.8%)	327 (74.7%)	
	PKD2	5 (12.8%)	76 (17.4%)	
Treatment group	Lisinopril/Telmisartan	38 (44.7%)	217 (49.5%)	0.4142
	Lisinopril/Placebo	47 (55.3%)	221 (50.5%)	
Blood pressure group	Standard BP	48 (56.5%)	220 (50.2%)	0.2920
	Low BP	37 (43.5%)	218 (49.8%)	

b. Continuous measures:					
	Not included (n=85)		**Included (n=438)**		
Measure	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**p value**
Age at baseline (years)	85	35.4 ± 8.7	438	36.6 ± 8.3	0.2158
BMI (kg/m^2)	75	25.8 ± 4.7	438	27.3 ± 5.2	0.0202
Home average systolic BP (mmHg)*	51	120.6 ± 9.4	438	121.2 ± 10.4	0.7095
Home average diastolic BP (mmHg)*	51	81.1 ± 7.1	438	80.7 ± 8.2	0.7641
CKD EPI eGFR (mL/min/1.73 m^2)	84	94.5 ± 17.5	438	91.5 ± 17.6	0.1578
Logarithm urine albumin (mg/24 hrs)	69	3.3 ± 1.0	438	3.0 ± 0.9	0.0833
Logarithm total kidney volume (mL)	78	6.9 ± 0.6	438	7.0 ± 0.6	0.1569
Left ventricular mass index (g/m^2)	68	64.9 ± 12.8	438	63.7 ± 13.2	0.5072

*At the visit a participant first reported a home systolic and diastolic BP reading (for 96% of participants, this was at the baseline (71%) or 4 month (25%) visit)

BMI: body mass index; BP: blood pressure; CKD EPI eGFR: estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; IPTW: inverse probability of treatment weighting; NMD: no mutation detected.

Table 3

Baseline demographic and clinical characteristics of Study B participants by use of statin drugs, before and after IPTW

a. Categorical measures:

		Before IPTW			After IPTW		
		Never used (n=292)	**Used 3 or more years (n=118)**		**Never used (n=249)**	**Used 3 or more years (n=103)**	
Characteristic	**Category**	**n (%)**	**n (%)**	**p value**	**%**	**%**	**p value**
Sex	Male	133 (45.5%)	69 (58.5%)	0.0178	50.1%	50.8%	0.9112
	Female	159 (54.5%)	49 (41.5%)		49.9%	49.2%	
PKD genotype	NMD	12 (4.5%)	10 (8.9%)	0.1343	5.5%	7.4%	0.8154
	PKD1	220 (82.1%)	83 (74.1%)		80.2%	78.2%	
	PKD2	36 (13.4%)	19 (17.0%)		14.3%	14.4%	
Treatment group	Lisinopril/Telmisartan	143 (49.0%)	61 (51.7%)	0.6177	50.7%	52.8%	0.7405
	Lisinopril/Placebo	149 (51.0%)	57 (48.3%)		49.3%	47.2%	
CAD or Angina	Yes	2 (0.7%)	2 (1.7%)	0.3462	1.2%	1.3%	0.9952
	No	290 (99.3%)	116 (98.3%)		98.8%	98.7%	

b. Continuous measures:

	Before IPTW					After IPTW		
		Never used (n=292)		**Used 3 or more years (n=118)**		**Never used (n=249)**	**Used 3 or more years (n=103)**	
Measure	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**p value**	**Mean (SE)**	**Mean (SE)**	**p value**
Age at baseline	292	47.3 ± 8.5	118	52.2 ± 7.3	<.0001	48.9 (0.6)	49.6 (0.9)	0.5425
BMI (kg/m^2)	286	27.4 ± 5.2	115	28.2 ± 5.0	0.1856	27.6 (0.3)	28.1 (0.7)	0.4904
Home average systolic BP (mmHg) *	281	122.9 ± 10.7	118	122.9 ± 11.0	0.9900	122.7 (0.7)	122.9 (1.2)	0.8889
Home average diastolic BP (mmHg) *	281	81.6 ± 8.4	118	80.2 ± 7.3	0.1181	81.0 (0.5)	80.8 (0.9)	0.8757
CKD EPI eGFR (mL/min/1.73m^2)	292	48.8 ± 11.8	118	47.9 ± 11.3	0.5069	48.6 (0.8)	48.6 (1.3)	0.9844
Urine albumin (mg/24 hrs) *Median (p25, p75)*	277	26.8 (16.2, 69.5)	114	31.6 (17.9, 66.0)	0.5351 **	82.3 (9.5)	71.1 (11.7)	0.9013 **
CKD EPI eGFR at F5 (mL/min/1.73m^2)	274	47.3 ± 12.1	116	45.4 ± 11.4	0.1418	46.9 (0.8)	45.6 (1.2)	0.3729
Statin Use (# years of any use)	292	N/A	118	5.0 ± 1.3	—	—	4.9 (0.1	—

CAD: coronary artery disease; IPTW: inverse probability of treatment weighting; NMD: no mutation detected.

*At the visit a participant first reported a home systolic and diastolic BP reading (for 98% of participants, this was at the baseline (78%) or 4 month (19%) visit)

**p value from log transformed variable

BMI: body mass index; BP: blood pressure; CKD EPI eGFR: estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; F5: Follow-up visit 5 (after 4 months in the study); IPTW: inverse probability of treatment weighting; *p25*: 25th percentile.

Table 4

Baseline demographic and clinical characteristics of Study B participants by included vs not included in IPTW analysis

a. Categorical measures:

		Not included (n=57)	Included (n=352)	
Characteristic	**Category**	**n (%)**	**n (%)**	**p value**
Sex	Male	26 (45.6%)	176 (50.0%)	0.5389
	Female	31 (54.4%)	176 (50.0%)	
PKD genotype	NMD	2 (8.0%)	19 (5.4%)	0.8250
	PKD1	20 (80.0%)	282 (80.1%)	
	PKD2	3 (12.0%)	51 (14.5%)	
Treatment group	Lisinopril/Telmisartan	26 (45.6%)	180 (51.1%)	0.4392
	Lisinopril/Placebo	31 (54.4%)	172 (48.9%)	

b. Continuous measures:

	Not included (n=57)		Included (n=352)		
Measure	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**p value**
Age at baseline (years)	57	47.4 ± 9.3	352	48.9 ± 8.3	0.2130
BMI (kg/m^2)	48	28.4 ± 4.7	352	27.5 ± 5.2	0.2499
Home average systolic BP (mmHg)*	44	124.6 ± 10.4	352	122.7 ± 10.8	0.2637
Home average diastolic BP (mmHg)*	44	82.3 ± 8.2	352	81.0 ± 8.1	0.3316
CKD EPI eGFR (mL/min/1.73 m^2)	57	48.9 ± 12.0	352	48.6 ± 11.7	0.8214
Logarithm urine albumin (mg/24 hrs)	38	3.6 ± 1.2	352	3.6 ± 1.2	0.9984

*At the visit a participant first reported a home systolic and diastolic BP reading (for 98% of participants, this was at the baseline (78%) or 4 month (19%) visit)

BMI: body mass index; BP: blood pressure; CKD EPI eGFR: estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; IPTW: inverse probability of treatment weighting; NMD: no mutation detected