Prospective randomized trial of effect of Direct Renin Inhibition in Non-diabetic chronic Kidney disease (DRINK)

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ABSTRACT

BACKGROUND: The potential long-term safety and efficacy of aliskiren in non-diabetic chronic kidney disease (CKD) is unknown. We sought to investigate the renoprotective effect of aliskiren on non-diabetic CKD patients.

METHODS: In this open-label, parallel, randomized controlled trial, non-diabetic CKD stages 3-4 patients were randomized to receive aliskiren added to an angiotensin II receptor blocker (ARB) at the maximal tolerated dose or ARB alone. Primary outcome was the rate of change in estimated glomerular filtration rate (eGFR). Secondary endpoints included rate of change in protein-to-creatinine ratio (UPCR), cardiovascular events and hyperkalemia. Composite renal outcomes of doubling of baseline serum creatinine (sCr) or a 40% reduction in eGFR or incident end-stage renal disease or death was analysed as post-hoc analysis.

RESULTS: 76 patients were randomized: 37 to aliskiren (mean age 55.1±11.1 y), and 39 to control (mean age 55.0±9.4 y). Their baseline demographics were comparable with eGFR (31.9±9.0 *vs.* 27.7±9.0 ml/min/1.73m^2, P=0.05) and UPCR (30.7±12.6 *vs.* 47.8±2.8 mg/mmol, P=0.33) for treatment *vs.* control subjects. After 144 weeks of follow-up, there was no difference in the rate of eGFR change between groups. Six patients in the aliskiren group and seven in the control group reached the renal composite endpoint (16.2% *vs.* 17.9%, P=0.84). Cardiovascular events rate was 10.8% *vs.* 2.6%, P=0.217. Hyperkalemia rate was 18.9% *vs.* 5.1% with an adjusted hazard ratio of 7.71 (95% CI: 1.14 to 52.3, P=0.04) for the aliskiren arm.

CONCLUSION: Aliskiren conferred neither additional renoprotective benefit nor increased adverse events except for more hyperkalemia in non-diabetic CKD patients.

INTRODUCTION

Aliskiren is an oral direct renin inhibitor and preliminary data suggest that it is safe and effective in hypertensive subjects. (1-3) Among type 2 diabetic subjects with macroalbuminuria, aliskiren added to losartan conferred superior anti-hypertensive and anti-proteinuric effects than losartan alone across various stages of chronic kidney disease (CKD). (4, 5) The antiproteinuric efficacy of aliskiren added to losartan was also observed in IgA nephropathy patients with persistent significant residual proteinuria despite maximal doses of losartan. (6) These data suggest that aliskiren may be potentially beneficial to non-diabetic CKD in which RAS activation plays a key pathogenetic role in driving renal progression. This study was designed to investigate the potential renoprotective efficacy of aliskiren added to an angiotensin receptor blocker (ARB) in non-diabetic patients at risk of developing end-stage renal disease (ESRD), with the rate of change of estimated glomerular filtration rate (eGFR), rate of change of protein-to-creatinine ratio (UPCR) and the time to first renal event over an observation period of 3 years being the primary outcome measure, secondary outcome measure and post hoc analysis, respectively.

ALTITUDE (the Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease Endpoints) study was a multinational, randomized, double-blind, placebo-controlled phase III trial comparing placebo *vs* aliskiren 300 mg once daily, added to background ACE inhibitor or ARB therapy in type 2 diabetics at risk of developing cardiovascular and renal events. (7) After the 7th interim review of data, the DMC concluded that patients were unlikely to benefit from treatment added to standard anti-hypertensives, and reported higher adverse events in the treatment arm, which included increased incidence of non-fatal stroke, renal dysfunction, hyperkalemia and hypotension at 18-24 months. Specifically, the number of patients experiencing a non-fatal stroke

was 85 (2.0%) out of 4,296 patients in the placebo group and 112 (2.6%) out of 4,283 patients in the aliskiren group (nominal, unadjusted, *P*-value 0.04). Nevertheless, in its final published analysis, hyperkalemia and hypotension were the only reported adverse events that were featured more frequently in aliskiren-treated subjects. (8).

The imbalance in cardiovascular events was not observed in the subsequent ATMOSTPHERE trial on heart failure patients and could well represent a true or a chance finding as reasoned elsewhere. (9, 10) Patients in ALTITUDE were quite different from those in the present study. Regardless of the negative findings in diabetic subjects, the present study went on to investigate the potential effect of add-on direct renin inhibition in the non-diabetic CKD cohort which the effect of aliskiren has been well-characterized.

METHODS

Study Design and Participants

This is an open-label, prospective, parallel, randomized, controlled trial on the renoprotective efficacy and safety of aliskiren in patients with non-diabetic CKD in a major teaching hospital in Hong Kong. The study was approved by an Institutional Review Board and Ethics Committee of the Hong Kong Hospital Authority and the University of Hong Kong. All participating patients gave written, informed consent. Eligible subjects from August 2009 to October 2011 were randomized in a 1:1 ratio using a computer-generated allocation sequence sealed with opaque envelope to continue with conventional treatment using ARB or receive add-on aliskiren for a period of 3 years (144 weeks). The inclusion criteria were as follows: *(1)* male or female age ≥ 18 years; *(2)* CKD stage 3 or 4 as defined by an eGFR 15-59 ml/min/1.73 m^2 body surface area; *(3)* receiving treatment with the maximum dose of ARB for at

least 3 months. The major exclusion criteria were: *(1)* eGFR < 15 or $\geq$ 60 ml/min/1.73 m^2 body surface area; *(2)* clinical evidence of acute kidney injury as a contributing factor to reduced eGFR; *(3)* serum K^+ > 5.2 mmol/l while taking an ARB; *(4)* presence of diabetes mellitus or bilateral renal artery stenosis; *(5)* receiving ACEi/ARB combination within 3 months of study entry; *(6)* concurrent treatment with immunosuppressive agent; *(7)* female of child-bearing age who are unwilling to practice effective contraception and female who are pregnant or intending to conceive; *(8)* patients who have previously participated in another study examining the effect of aliskiren added to losartan in IgA nephropathy. (6) The recruitment flow is presented in Figure 1.

Treatment Protocol and Follow-up

The study was designed to investigate the renoprotective effect of aliskiren added to maximum recommended dose of losartan (100 mg/day) for a period of 3 years (144 weeks). All eligible subjects were treated with aliskiren at a starting dose of 150 mg/day for 4 weeks, followed by 300 mg/day for the remaining duration to maintain a target blood pressure under 130/80 mmHg. The choice of other anti-hypertensive agents to achieve the target blood pressure included calcium channel blocker (CCB), beta-blocker, and thiazide diuretic, but the use of ACEi was prohibited.

Upon study entry, full medical histories and physical findings were documented during medical consultation at the Queen Mary Hospital. Baseline investigations included full blood count, renal and liver biochemistries, eGFR (assessed using the abbreviated 4-variable Modification of Diet in Renal Disease study equation), (11) 24-hour urine protein excretion, early morning urinary

protein-to-creatinine ratio, fasting blood glucose, serum lipid profile, aldosterone level, and plasma renin activity. At each clinic visit at 6, 12, 24, 36, 48, 64, 80, 96, 112, 128 and 144 weeks after randomization, blood pressure, body weight, blood count, eGFR and electrolytes, and early morning urinary protein-to-creatinine ratio were monitored. At yearly intervals, measurement of all baseline parameters was repeated. All adverse events and other medications including anti-hypertensives used during the study period were recorded.

Assay of Plasma Renin Activity and Serum Aldosterone

PRA was measured by the GammaCoat Plasma Renin Activity (PRA) ^{125}I RIA kit (DiaSorin Inc., USA) in EDTA plasma at the renal laboratory of S.C.W.. The assay involved the measurement by radioimmunoassay of the angiotensin I generated *in vitro* from the incubation of the chilled plasma sample with phenylmethylsulfonyl fluoride and the angiotensin maleate generation buffer. The background renin activity was determined by the difference between the angiotensin I concentration generated at 37^0C and 4^0C. Serum aldosterone was measured by solid-phase radioimmunoassay with the DPC Coat-A-Count® Aldosterone Radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, CA, USA) in accordance with the manufacturer's specifications.

Study End Points

The primary outcome measure was pre-specified as the rate of change in estimated glomerular filtration rate (eGFR). Secondary outcome measures included cardiovascular events (including fatal and nonfatal myocardial infarction, heart failure, stroke, and peripheral vascular disease), hyperkalemia events (moderate to severe

hyperlalemia defined as plasma potassium ≥ 5.5 mmol/L) and changes in proteinuria, plasma renin activity and serum aldosterone levels. Composite renal outcome of a doubling of baseline serum creatinine (sCr), 40% reduction in eGFR,(12, 13) ESRD or death was analysed as post-hoc analysis.

Statistical Analysis

The original power calculation was based on the rate of GFR decline (0.25 ± 0.08 ml/min/1.73 m^2/month) reported in the REIN study (14) for patients with CKD and creatinine clearance in the range 20–70 ml/min/1.73 m^2 and proteinuria below 3 g/ 24 h, we estimated that the enrollment of 70 patients will achieve 80.9% power to detect a 22% difference in the final rate of eGFR decline between aliskiren-treated and control subjects with a significance level (α) of 0.05 using a two-sided two-sample *t*-test. Assuming a dropout rate of 15%, the study was designed to enroll 80 patients. In the end, 76 (37 *vs*. 39) subjects were recruited, yielding a study power of 84.1% to detect the pre-defined differences in the rate of eGFR decline. In the light of the results of ALTITUDE using event-free survival as the primary outcome, the current study is therefore further analysed using the same outcome parameters as a post-hoc analysis considering its clinical relevance. (15) The renoprotective effect on composite outcomes was also analysed.

Data are presented as means ± standard deviation unless otherwise specified. The main efficacy analysis was performed on an intention-to-treat basis and included all patients who underwent randomization. No patients were excluded after randomization until they reached observation endpoints.

Estimated glomerular filtration rate was calculated using the abbreviated 4-variable MDRD study equation, where eGFR = 186.3 x (serum creatinine,

mg/dl)$^{-1.154}$ x (age upon follow-up, y)$^{-0.203}$ x (0.742 for female) x 1.21 for black race. The rates of change in eGFR and UPCR over the study period with repeated measures were analysed by mixed models with unstructured covariance and adjusted for baseline value, treatment, trial visit, interaction between baseline value and visit, and interaction between treatment and visit. The slope of change was analysed with a linear growth model with sensitivity analyses on quadratic growth model. The change in the mean of eGFR and geometric mean of UPCR were analysed further with change score approach as sensitivity analyses. The slope for patients who developed ESRD requiring renal replacement therapy was computed to the time point when such therapy was initiated.

Intergroup and intragroup differences in other quantitative variables between baseline and study endpoint were compared with t-test. Cumulative survival and incidence of composite renal outcome, cardiovascular survival and hyperkalemia were visualized with the Kaplan-Meier method and compared with log-rank test. Cox proportional-hazards model were used to adjust confounding factors including gender, age, BMI and diastolic blood pressure and low-density lipoprotein on survival outcomes.

All statistical analyses were performed with R version 3.0.2 and Stata version 15.0. This trial is registered at ClinicalTrials.gov with the Identifier NCT01150201.

RESULTS

Baseline characteristics

Seventy-six patients were enrolled into the study, with 37 in the aliskiren arm and 39 in the control arm. The baseline demographic and clinical characteristics of the study subjects in each group were summarized in Table 1. There were no significant

differences in these characteristics except that the aliskiren group had a higher eGFR and lower HDL-cholesterol level.

Primary Outcome

At the end of 3 years, all subjects were alive. From the mixed model, both the trends of eGFR decline in both groups were linear. There was no demonstrable difference in the annual change of eGFR between the aliskiren group (-1.67 ml/min/1.73m^2, 95% CI: -1.99 to -1.36) and control group (-1.53 ml/min/1.73m^2, 95% CI: -1.85 to -1.20) over the study period (P=0.52) as shown in Figure 2a. The eGFR decline over the entire follow-up duration obtained by change score approach was presented in Figure 2b. The change in eGFR over the 144-week study period was -4.06 ml/min/1.73m^2 in the aliskiren group and -4.91 ml/min/1.73m^2 per year in the control group and the decline of eGFR was comparable between groups (P=0.54). .

Secondary Outcomes

From the log-linked mixed generalized linear model, the change of mean UPCR demonstrated linear and quadratic properties. There was a statistically significant increase in the annual change of mean UPCR in the aliskiren group (9.41 mg/mmol, 95% CI: 5.52 to 13.3) when compared to the control group (-1.68 mg/mmol, 95% CI: -7.23 to 3.87) over the study period (P=0.002) as shown in Figure 3a. The difference between group remained robust when analysed with a quadratic growth model (P=0.003). However, the difference in the change of geometric mean of UPCR between groups did not reach statistical difference when analysed with change-score approach as presented in Figure 3b and Table 2 (P=0.06). There was also no appreciable difference in the survival of composite renal endpoint of a doubling of

baseline serum creatinine, 40% reduction of eGFR, ESRD or death as shown in Figure 4 (P=0.93). No significant between-group difference for other major clinical and biochemical parameters were detected as summarized in Table 2.

There was no significant difference between the two groups in the composite endpoint of morbidity and mortality from cardiovascular causes (Figure 5). There were four (10.8%) cardiovascular events in the aliskiren group. These comprised acute myocardial infarction and onset of fast atrial fibrillation, angina pectoris, hypotension, congestive heart failure and pulmonary edema each in one subject. In the control group, one patient (2.5%) developed acute myocardial infarction during follow-up.

Plasma renin activity (PRA) was markedly suppressed in the aliskiren group, but not the control group (Figure 6a). After the initiation of aliskiren, the geometric mean of PRA significantly decreased by 1.87 ng/ml/h in aliskiren group ($P<0.01$) and the difference in reduction between groups was statistically significant ($P<0.01$) throughout the study period. The response in serum aldosterone level to aliskiren treatment was less predictable and did not show any intragroup or intergroup differences at any time point during follow-up (Figure 6b).

All subjects achieved target blood pressure control throughout follow-up, and there was no significant difference in systolic and diastolic blood pressures between groups (Figure 6c). Also, there were no appreciable intergroup differences in serum albumin, fasting glucose, low-density-lipoprotein cholesterol, and body weight throughout the study (data not shown).

Adverse events

Seven (18.9%) aliskiren-treated patients and two (5.1%) control subjects developed hyperkalemia with serum potassium ≥ 5.5 mmol/L during follow-up

(Figure 7). Add-on aliskiren was associated with 6 times higher relative risk of moderate to severe hyperkalemia (adj-hazard ratio: 7.71, 95% CI: 1.14 to 52.3, P=0.04) after adjusted gender, age and baseline BMI, eGFR, diastolic blood pressure, fasting glucose, low density lipoprotein and potassium level with Cox regression. Five (71.4%) of these episodes occurred within the first 36 weeks of commencing aliskiren therapy, whereas in the two control subjects, hyperkalemia occurred at 48 and 112 weeks of follow-up, respectively. In all these subjects, hyperkalemia was successfully normalized with the use of diuretic or polystyrene sulphonate, and none required withdrawal of study medications. Higher low-density lipoprotein level was associated with the onset of moderate to severe hyperkalemia (adj-hazard ratio: 2.69, 95% CI: 1.19 to 6.11, P=0.02) in the exploratory analysis. Two patients in the aliskiren group developed colonic cancer, and one patient in the control group had colonic polyps. Two *De novo* diabetes mellitus were reported in both groups, dermatoses and impotence were reported each in one patient in the aliskiren group. Gouty arthritis, obstructive sleep apnea and myopathy were reported in one patient each in the control group.

DISCUSSION

Our first finding, obtained by following aliskiren- and losartan-treated CKD subjects for a median follow-up of 3 years, was that there was no significant difference in both the rate of change in eGFR and the combined risk of doubling of serum creatinine, 40% reduction in eGFR, ESRD or death between the two groups analysed by different statistical approach. While these findings are limited by the relatively short duration of follow-up, they may also signify the lack of additional

clinical benefits of inhibiting renin in the face of maximal blockade of the angiotensin II receptor, similar to the diabetic population.

The second major finding was that aliskiren-treated subjects did not experience more adverse cardiovascular events. Although the DMC of ALTITUDE cautioned a possible increase in the risk of nonfatal strokes in the aliskiren group and terminated the study prematurely, it must be remembered that the reported numbers in its interim analysis do not represent the final number of events in the study, as it was estimated that approximately a third of events remained to be collected and adjudicated at the time of its recommendation. Therefore, while the imbalance in stroke risk (absolute difference of 0.6% between treatment and the control groups) may persist or increase, it may also attenuate had ALTITUDE been allowed to continue. Three additional explanations may account for the absence of increased stroke risk in DRINK. First, our cohort comprises non-diabetic CKD subjects, who understandably may pose a lower cardiovascular risk than their diabetic counterparts with a similar level of renal function (or dysfunction). Secondly, patient demographics are different in that ALTITUDE subjects were predominantly Caucasians who were 10 years older (65 *vs.* 55 y) and had higher body mass indices (29.1 *vs.* 25.4 kg/m^2). Finally, DRINK was not powered to detect differences in cardiovascular risk and is at risk of a type II statistical error.

An unexpected finding in the present study is the lack of additional anti-proteinuric efficacy of aliskiren when added to losartan, which was previously reported to achieve further proteinuria reduction at 6 months by 20% in diabetic subjects in AVOID (4) and by 22% in IgA nephropathy. (6) This discrepancy may stem from the lower baseline proteinuria and GFR levels in DRINK (mean eGFR 31.9 $ml/min/1.73m^2$, geometric mean UPCR 30.7 mg/mmol) than in AVOID (mean eGFR

68.5 ml/min/1.73m^2, geometric mean UACR 58 mg/mmol) or IgAN (mean eGFR 40.3 ml/min/1.73m^2, geometric mean 167 mg/mmol). This finding is consistent with the notion that patients with greater levels of proteinuria and GFR at baseline tend to benefit more from anti-proteinuria treatment than those with lower levels of proteinuria before treatment. (18)

Plasma renin activity fell dramatically by over 80% from baseline after the initiation of aliskiren. This observation is in agreement with reports by others and our group on human subjects. (2, 6, 19) Aliskiren has been shown to reduce the renin-mediated complement activation and the subsequent intensified intrarenal renin blockade is hypothesized to protect against progressive tubulointerstitial fibrosis. (20, 21) Although such robust and consistent reductions in PRA can be expected to confer renoprotection due to the interruption of a rate-limiting step of the RAS cascade (22) and the prevention of a reactive elevation of PRA following ARB therapy, (2) such theoretical phenomenon did not translate into a tangible clinical benefit. This may in part be related to the lack of suppression of the more downstream molecule, aldosterone, the level of which displayed unpredictable levels without a trend towards reduction. Further work is required to delineate why there is an overall lack of suppressive effect of renin inhibition on circulating aldosterone levels.

A consistent finding in clinical trials to date regarding the use of combined DRI and ARB treatment is a relatively high incidence of hyperkalemia. This appears to correlate inversely with the level of eGFR. In AVOID (mean eGFR 68.5 ± 25.7 ml/min/1.73 m^2), 14% of study subjects had serum potassium > 5.5 mmol/l. In DRINK (31.9 ± 9.0 ml/min/1.73 m^2) and our previous IgAN cohort (40.3 ± 21.2 ml/min/1.73 m^2), the incidence was 19% and 24%, respectively. Nevertheless, in none of these subjects was there a necessity to withdraw aliskiren as hyperkalemia could be

effectively controlled with diuretic and/or simple resin therapy. Furthermore, the high incidence of hyperkalemia may be related to a more advanced CKD cohort recruited in DRINK and aliskiren's long terminal half-life and persistence in kidney tissue. (23)

There are several shortcomings in this study. First, the survival analyses on the cardiovascular outcomes and rate of change in proteinuria was not powered to detect statistical difference in the sample size calculation. Type II statistical error may arise in detecting the differences in these outcomes. Second, the sample size was calculated based on the progression rate reported by REIN study which recruited patients with higher level of proteinuria (mean 5.6 g/24h). Our study had recruited a cohort with a lower level proteinuria that could have progressed more slowly than expected and hence this could undermine the power of the study. Third, the low number of subjects renders this study underpowered for the secondary hard endpoints.

In summary, our analysis showed that the addition of aliskiren to losartan in patients with non-diabetic CKD does not provide additional renoprotection over a 144-week period. Our evidence does not support the combined treatment with aliskiren among non-diabetic CKD patients in general. However, given some encouraging short-term results, (4, 6) there might be a chance for a more personalized use of direct renin inhibition as a therapeutic option for targeted subgroups of CKD if responders could be identified. Caution, however, needs to be exercised with regard to the higher incidence of hyperkalemia encountered particularly in subjects with lower GFR in the first year of commencing aliskiren treatment.

DISCLOSURES

This was not an industry supported study. The authors have indicated no financial conflict of interest. Part of the results in the manuscript has been submitted for

presentation in abstract form to the American Society of Nephrology Kidney Week, Washington, D.C., USA, 1-4 Nov, 2019.

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Table 1. Baseline Characteristics of the Randomized Population*

Characteristic	Aliskiren Group (N=37)	Control Group (N=39)	P Value
Age (years)	55.1±11.1	55.0±9.4	0.97
Male:Female	27:10	24:15	0.29
Body mass index (kg/m^2)	25.4±4.4	25.2±5.2	0.85
Renal disease			0.44
Primary glomerular	17 (46%)	17 (44%)	
Hypertensive	13 (35%)	10 (26%)	
Others, unknown	7 (19%)	12 (31%)	
Blood pressure (mmHg)			
Systolic	129±20	131±11	0.49
Diastolic	78±13	81±9	0.35
Mean arterial pressure	95±14	98±9	0.39
Hemoglobin (g/l)	136±20	128±19	0.11
Serum potassium (mmol/l)	4.3±0.5	4.4±0.6	0.23
Serum creatinine (μmol/l)	194±61	215±65	0.15
Estimated GFR (ml/min/1.73 m^2 BSA)*	31.9±9.0	27.7±9.0	0.05
Serum calcium (mmol/l)	2.37±0.11	2.32±0.22	0.24
Serum phosphate (mmol/l)	1.10±0.25	1.17±0.20	0.15
Serum albumin (g/l)	42.6±3.2	43.0±3.6	0.68
Fasting blood glucose (mmol/l)	5.3±0.8	5.3±0.6	0.66
Cholesterol (mmol/l)			
Total	4.9±1.1	4.8±1.0	0.64
Low-density lipoprotein	2.9±1.0	2.8±0.8	0.69
High-density lipoprotein	1.1±0.3	1.3±0.5	0.01
Triglycerides (mg/dl)	2.1±1.4	1.5±1.3	0.07
Urine protein-to-creatinine ratio (mg/mmol)† ‡	30.7±12.6	47.8±2.8	0.33
Urine protein excretion rate (g/24 h)	1.14±1.54	0.77±0.81	0.20
Plasma renin activity (ng/ml/h) ‡	2.27±5.55	2.36±3.60	0.92
Serum aldosterone (pmol/l) ‡	306±2	254±280	0.34
Number of antihypertensive drugs	2.2±1.0	2.1±0.9	0.90
Losartan alone	12 (32%)	12 (31%)	
Losartan + thiazide	3 (8%)	3 (8%)	
Losartan + β-blocker	4 (11%)	6 (15%)	
Losartan + CCB	4 (11%)	3 (8%)	
Losartan + β-blocker + CCB	7 (19%)	9 (23%)	
Losartan + thiazide + CCB	1 (3%)	2 (5%)	
Losartan + thiazide + β-blocker	2 (5%)	3 (8%)	
Losartan + thiazide + β-blocker + CCB	4 (11%)	1 (3%)	

Plus–minus values are means ±SD. To convert the values for serum creatinine to mg/dl, divide by 88.4. To convert the values for triglycerides to mg/dl, divide by 0.0113. To convert the values for cholesterol to mg/dl, divide by 0.0259.
CCB, Ca-channel blocker; BSA, body surface area

*Using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) formula[8]
†Early morning samples, # ±values are standard error of the mean
‡ Geometric mean

Table 2. Comparison of intragroup and intergroup mean differences in clinical and biochemical parameters between baseline and study endpoint.

	Aliskiren Group (n=37)		Control group (n=39)		Intergroup
	Mean diff	p-value	Mean diff	p-value	p-value
Body mass index (kg/m^2)	-0.13	0.90	0.11	0.93	0.42
Blood pressure (mmHg)					
Systolic	0.89	0.83	-4.64	0.14	0.22
Diastolic	-0.57	0.83	-4.77	0.03	0.14
Hemoglobin (g/l)	-0.82	0.11	-0.39	0.36	0.14
Serum potassium (mmol/l)	0.21	0.08	0.07	0.61	0.33
Serum creatinine (μmol/l)	43.68	0.06	66.74	<0.01	0.27
Estimated GFR	-4.06	0.09	-4.91	0.03	0.54
Serum calcium (mmol/l)	-0.06	0.14	0.01	0.77	0.12
Serum phosphate (mmol/l)	0.12	0.09	-0.01	0.83	0.01
Serum albumin (g/l)	-0.46	0.52	-0.69	0.40	0.72
Fasting blood glucose (mmol/l)	0.02	0.91	-0.02	0.89	0.78
Cholesterol (mmol/l)					
Total	-0.14	0.58	-0.12	0.53	0.96
Low-density lipoprotein	-0.05	0.80	-0.12	0.47	0.72
High-density lipoprotein	0.06	0.44	0.07	0.48	0.74
Urine protein-to-creatinine ratio (mg/mmol)	15.23	0.45	-10.60	0.46	0.06
Urine protein excretion rate (g/24h)	0.09	0.60	0.03	0.83	0.64
Plasma renin activity (ng/ml/h)	-1.87	<0.01	0.27	0.72	<0.01
Serum aldosterone (pmol/l)	-38.30	0.51	43.23	0.35	0.11

FIGURE LEGENDS

Figure 1. Flow of recruitment

Figure 2a. Adjusted mean of eGFR with 95% CI during follow-up by mixed model. Mean eGFR is adjusted for baseline value, treatment, trial visit, interaction between trial visit and baseline value and interaction between treatment and visit. *P* (χ^2 test) = 0.52 for intergroup difference in slope of change.

Figure 2b. Mean of eGFR with 95% CI during follow-up by change score approach. *P* (paired t-test) = 0.54 for intergroup difference in endpoint mean of eGFR.

Figure 3a. Adjusted mean of urine protein-to-creatinine ratio (UPCR in mg/mmol) with 95% CI during follow-up by mixed model. Mean eGFR is adjusted for baseline value, treatment, trial visit, interaction between trial visit and baseline value and interaction between treatment and visit. *P* = 0.002 for intergroup difference in slope of change.

Figure 3b. Geometric mean of UPCR (mg/mmol) with 95% CI during follow-up by change score approach. *P* (paired t-test) = 0.002 for intergroup difference in endpoint geometric mean of UPCR.

Figure 4. Kaplan-Meier analysis of the overall renal survival with 95% CI during follow-up. Renal events were defined as the composite of a doubling of baseline serum creatinine, 40% reduction in eGFR, ESRD or death. Solid line: control group; dotted line: aliskiren group. *P* (log-rank) = 0.93

Figure 5. Kaplan-Meier analysis of the overall cardiovascular event survival with 95% CI during follow-up. Solid line: control group; dotted line: aliskiren group. *P* (log-rank) = 0.129

Figure 6a. Geometric mean of plasma renin activity during follow-up. The geometric mean values with 95% CI are shown.**P* < 0.01 versus baseline values. The between-group levels were statistically significant at endpoint (*P < 0.01*).

Figure 6b. Geometric mean of serum aldosterone levels during follow-up. The geometric mean values with 95% CI are shown. There were no significant intragroup changes during follow-up, and between-group levels were not statistically significant at each time point.

Figure 6c. Systolic and diastolic blood pressure during follow-up. Mean values with 95% CI are shown. Between-group differences for both systolic and diastolic blood pressures were not statistically significant at each time point.

Figure 7. Kaplan-Meier analysis of the cumulative incidence of developing moderate to severe hyperkalemia with 95% CI during follow-up. Solid line: control group; dotted line: aliskiren group. *P* (log-rank) = 0.04. Adjusted hazard ratio = 7.71 (95% CI: 1.14 to 52.3, *P* = 0.04)