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ORIGINAL ARTICLE

Effects of aliskiren on blood pressure and humoral factors in hypertensive hemodialysis patients previously on angiotensin II receptor antagonists

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Abstract

Background: A direct renin inhibitor (DRI), aliskiren, may be effective for blood pressure (BP) control in hemodialysis patients. However, it is unclear whether aliskiren has a greater beneficial effect on BP and humoral factors than angiotensin II receptor antagonists (ARBs) in hypertensive patients on hemodialysis.

Methods: Eighteen hemodialysis patients (58 ± 14 years) on the recommended dose of an ARB were prospectively randomized into two groups: ARB and DRI groups. Patients in the ARB group continued taking their previous ARB, whereas those in the DRI group switched to aliskiren (150 mg/day) for 12 weeks. Baseline measurements of BP and humoral factors such as plasma renin activity (PRA), plasma aldosterone concentration (PAC) and brain natriuretic peptide (BNP) were performed. Measurements were repeated every 4 weeks.

Results: At baseline, no differences were observed in age, gender or BP between the two groups. Systolic BP was unaffected by treatment in either groups (group effect, $p = 0.26$; time effect, $p = 0.38$; group × time effect, $p = 0.24$). PRA decreased in DRI ($p \leqq 0.02$, group effect, $p = 0.65$; time effect, $p = 0.13$; group × time effect, $p = 0.048$), but not in ARB ($p \geqq 0.94$). PAC increased only in DRI ($p \leqq 0.03$), whereas BNP was unaffected in either group.

Conclusion: Aliskiren at a dose of 150 mg/day had a similar effect on BP compared with ARBs, but significantly lowered PRA.

Keywords

Aliskiren, angiotensin II receptor antagonists, direct renin inhibitor, hemodialysis, hypertension

History

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Introduction

Renin is the upstream substance in the renin angiotensin system (RAS), and RAS inhibition is effective in lowering blood pressure (BP). Direct renin inhibitor (DRI), angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (also known as angiotensin receptor blockers, ARBs) all generally lowered BP in patients with hypertension (1,2). ACEIs and ARBs also have antihypertensive effects on patients who undergo hemodialysis (3,4). However, there are few clinical reports on the antihypertensive effects and safety of DRI in hemodialysis patients. There have been no clinical trials conducted to date that directly compare the effects of DRI with ARBs on BP and humoral factors in dialysis patients. Our purpose was to examine the effects of a treatment change from the recommended dose of ARBs to DRI, aliskiren (150 mg/day), on BP and humoral factors in hemodialysis patients with hypertension.

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Subjects

Eighteen hypertensive patients (age: 58 ± 14 years; 12 men and 6 women) on regular hemodialysis were enrolled in the present study. All patients met the following inclusion criteria: hospital outpatients on hemodialysis; 20 years of age, taking the recommended dose of an ARB, with pre-dialysis systolic BP between 130 and 170 mmHg, and confirmed to have proper fluid volume. The pre-hemodialysis systolic BP was the average of pre-hemodialysis BP values measured three times a week. Arm BP was measured in the supine position at rest before hemodialysis. ''Proper fluid volume'' was defined as human atrial natriuretic peptide (hANP) $\leqq$200 pg/ml in a blood sample taken post-hemodialysis, or a cardiothoracic ratio (CTR) of $\leqq$55% on a post-hemodialysis chest X-ray. Patients were excluded from the study if they were on ACEIs or if they were deemed unsuitable by their attending physician. This trial was performed from April 2010 to March 2011. This study, which conformed to the Declaration of Helsinki, was approved by the Yamamoto General Hospital ethics committee. Written informed consent was obtained from all subjects before they were enrolled. This trial was registered on the UMIN: http://www.umin.ac.jp/ (UMIN000003551).

Methods

The study design was an open-label, randomized, parallel-group comparison. The subjects were randomly assigned to an ARB group or a DRI group and tracked for 12 weeks. The envelope method was used to randomly assign patients to the two groups. All patients had been taking the recommended dose of their ARB for at least 4 weeks prior to the start of the trial. Patients in the ARB group continued taking the same dose of their ARB, whereas patients assigned to the DRI group switched from their ARB to 150 mg/day of aliskiren. Patients taking additional antihypertensive agents, other than ACEIs, continued taking those drugs (Figure 1).

The primary endpoint was the change in the pre-hemodialysis BP at 12 weeks after the start of the trial. Secondary endpoints included changes in plasma renin activity (PRA), plasma aldosterone concentration (PAC) and brain natriuretic peptide (BNP) during the trial. To assess safety during the trial, blood samples were taken every 4 weeks to assess the following biochemical parameters: potassium (K), hemoglobin (Hb), urea nitrogen (UN), creatinine (Cre), uric acid (UA), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG) and hemoglobinA1c (HbA1c). Serum levels of K, Hb, UN, Cre, UA, HDL, LDL, TG and HbA1c were measured pre-hemodialysis at the beginning of the week (Monday or Tuesday). Since it is not clear how interdialytic weight gain or hemodialysis therapy affects PRA or PAC, PRA, PAC and BNP were measured post-hemodialysis in the middle of the week (Wednesday or Thursday) when patients were at the same body weight (dryweight).

To maintain proper fluid volume, dry weight was decreased if there was an increase in hANP of $\geqq$100 or in CTR of $\geqq$3%. Dry weight was increased if there was a decrease in hANP of $\geqq$100 or in CTR of $\geqq$3%. During the trial, antihypertensive medications and hemodialysis conditions, other than dry weight, were not modified.

Statistical analysis

Data are expressed as mean $\pm$ SD in the tables and mean $\pm$ SE in the figures. Baseline data were compared by an unpaired *t*-test or a non-parametric Mann–Whitney rank sum test. A two-way repeated measures ANOVA was used as a primary analysis to evaluate the effects of ARB and DRI on the variables in the two groups (group effect, time effect, and group $\times$ time effect). When either the main effect of group or time or an interaction effect between group and time was statistically significant in ANOVA ($p<0.05$), post-hoc analysis was used for comparisons before and during treatment. Statistical significance was set at $p<0.05$. SPSS statistical software (IBM Japan, Tokyo, Japan) was used for all analyses.

Results

Patient characteristics

The trial included 12 men and 6 women (38–78 years old; mean age, 58 ± 14 years; mean hemodialysis duration, 111 ± 94 months). At baseline, no differences were observed between the DRI and ARB groups in age, gender, body surface area, systolic BP (148.9 ± 23.3 versus 135.3 ± 3.3, $p=0.11$), diastolic BP (77.1 ± 10.2 versus 71.8 ± 10.4, $p=0.28$) or medications use (Table 1). The types and doses of ARBs taken prior to the trial were 80 mg/day of valsartan (five subjects in the DRI group and seven in the ARB group), 40 mg/day of telmisartan (four subjects in the DRI group and one in the ARB group) and 20 mg/day of olmesartan (no subjects in the DRI group and one in the ARB group) a day (Table 1). All 18 patients completed the 12 weeks of follow-up, and no patient showed any change in dry weight. No cardiovascular adverse events such as

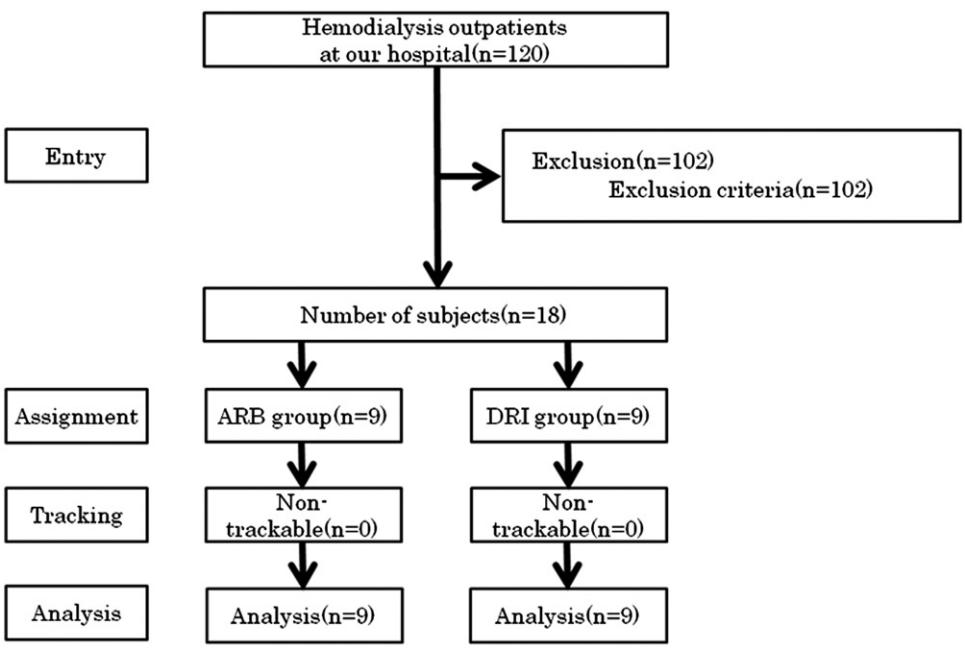

Figure 1. Patient flowchart.

Table 1. Patient baseline characteristics.

	DRI group ($n=9$)	ARB group ($n=9$)	p
Men (n)	7 (77.8%)	5 (55.6%)	NS
Diabetes complication (n)	3 (33.3%)	1 (11.1%)	NS
Age (years)	57 ± 14	60 ± 13	NS
Dialysis history (months)	89 ± 91	122 ± 100	NS
Dialysis time (hours)	4.2 ± 0.5	3.8 ± 0.6	NS
Kt/V	1.4 ± 0.3	1.5 ± 0.5	NS
Access			
AVG	2	0	
AVF	7	9	
Systolic BP (mmHg)	148.9 ± 23.3	135.3 ± 3.3	NS
Diastolic BP (mmHg)	77.1 ± 10.2	71.8 ± 10.4	NS
ARB at start of experiment			
Valsartan 80 mg	5	7	
Telmisartan 40 mg	4	1	
Olmesartan 20 mg	0	1	
With CCBs	3 (33.3%)	6(66.7%)	NS
With beta-blockers	1 (11.1%)	2(22.2%)	NS
With diuretics	3 (33.3%)	4(44.4%)	NS
With alpha-blockers	1 (11.1%)	1(11.1%)	NS
Potassium (mEq/l)	5.2 ± 0.7	5.2 ± 0.8	NS
Hemoglobin (g/dl)	11.0 ± 1.3	11.0 ± 0.9	NS
Urea nitrogen (mg/dl)	64.4 ± 13.0	62.6 ± 14.8	NS
Creatinine (mg/dl)	11.5 ± 3.5	11.9 ± 2.3	NS
Uric acid (mg/dl)	7.9 ± 1.9	7.4 ± 1.1	NS
High-density lipoprotein (mg/dl)	50.1 ± 10.6	56.4 ± 15.7	NS
Low-density lipoprotein (mg/dl)	80.9 ± 22.1	85.7 ± 21.3	NS
Triglyceride (mg/dl)	106.1 ± 56.7	98.3 ± 33.6	NS
HbA1c (%)	5.6 ± 1.3	5.1 ± 0.7	NS
Comorbidity			
CVD	2	0	
Stroke	0	1	
PAD	0	0	
Arrhythmia	0	0	
History of malignant disease	0	2	

AVG, arteriovenous graftfistula; AVF, arteriovenous fistula; BP, blood pressure; ARB, angiotensin II receptor antagonist; CCB, calcium channel blocker; CVD, cardiovascular disease; PAD, peripheral artery disease; NS, non-significant.

myocardial infarction or cardiovascular death were observed during the trial.

Changes in BP during the trial

Figure 2 shows changes in systolic and diastolic BP every 4 weeks. Changing drug treatment from an ARB to aliskiren had no significant effect on systolic BP (group effect, $p=0.25$; time effect, $p=0.38$; group × time effect, $p=0.24$) or diastolic BP (group effect, $p=0.25$; time effect, $p=0.17$; group × time effect, $p=1.00$). Systolic BP appeared to be slightly higher after 12 weeks compared with baseline, especially in the ARB group (135.3 ± 3.3 versus 142.2 ± 14.2 mmHg, $p=0.11$). During the course of the study, an intradialytic SBP < 90 mmHg was observed in 2.3% (8 of 351) of the sessions in the DRI group and 5.4% (19 of 351) in the ARB group. Except for intradialytic hypotension, no other events that could be considered side effects in any of the 18 patients throughout the trial.

Changes in humoral factors during the trial

Changes in PRA, PAC, and BNP are shown in Figure 3. PRA significantly decreased in the DRI group, but not in the ARB group (group effect, $p=0.65$; time effect, $p=0.13$; group × time effect, $p=0.048$). In the DRI group, PRA at baseline was significantly higher than the values at 4th, 8th or 12th week ($p \leqq 0.023$), whereas PRA were unaffected over 12 weeks in the ARB group ($p \geqq 0.94$). PRA at 12th week appeared to be lower in the DRI group compared with the ARB group (1.6 ± 2.5 versus 4.4 ± 7.9 ng/ml/h, $p=0.24$), although the difference did not reach statistical significance. This may have been due to the small number of patients in each group and a large variability in PRA levels.

PAC increased in the DRI group, while no change was observed in the ARB group (group effect, $p=0.19$; time effect, $p=0.02$; group × time effect, $p=0.16$). In the DRI group, PAC at baseline was significantly lower than the values at 4th, 8th or 12th weeks ($p \leqq 0.031$). No changes were observed in PAC over time in the ARB group ($p \geqq 0.91$).

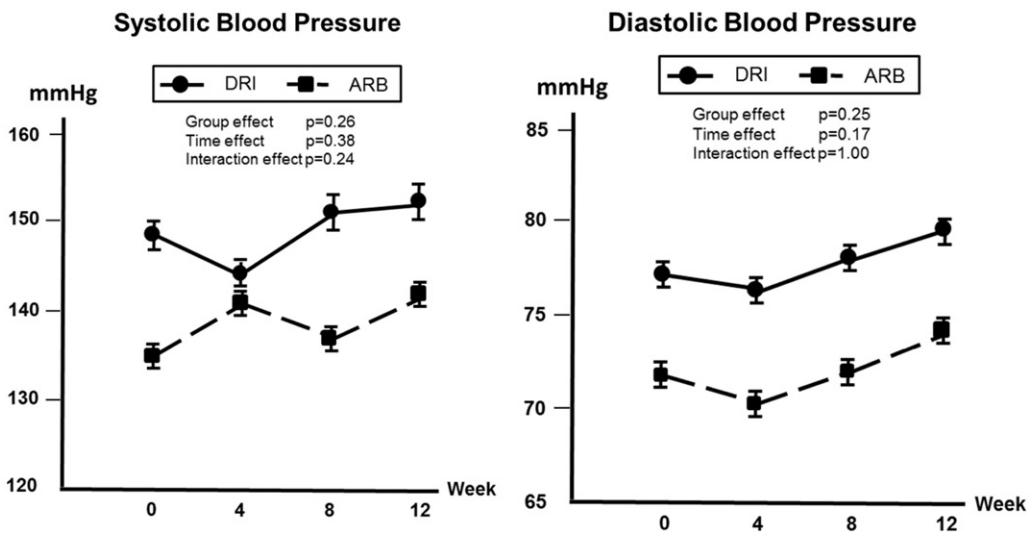

Figure 2. Changes in systolic and diastolic blood pressures every 4 weeks in the DRI and ARB groups. There was no significant difference between the DRI group and the ARB group in the change of blood pressure 12 weeks after the start of the study for either systolic pressure or diastolic pressure.

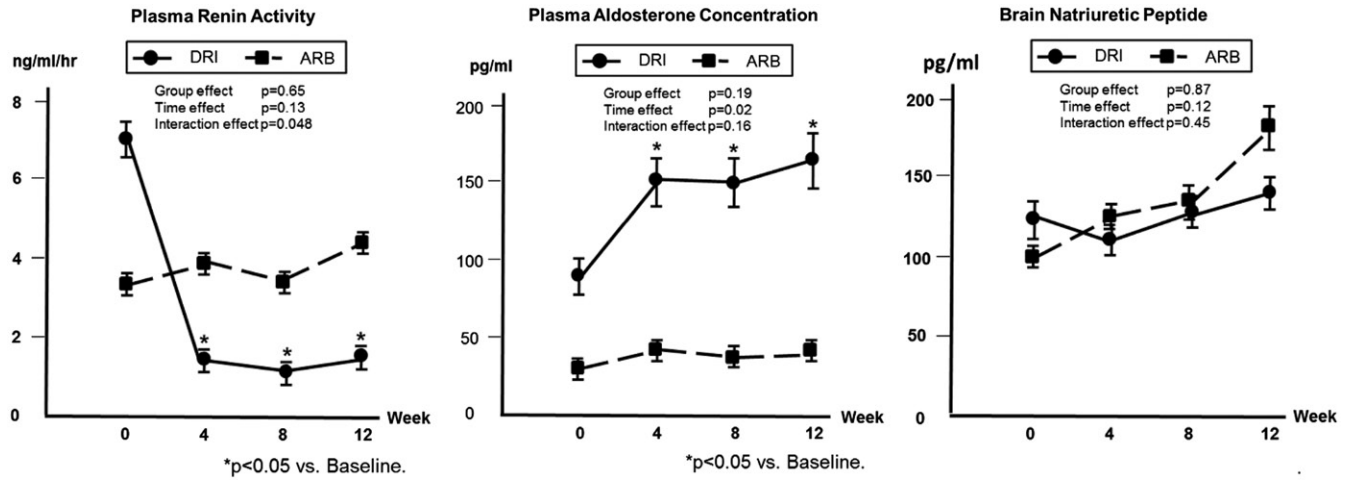

Figure 3. Change in PRA, PAC, and BNP every 4 weeks in the DRI and ARB groups. PRA decreased and PAC increased significantly in DRI group, but not in ARB group. *$p < 0.05$ versus baseline.

No significant changes were observed in BNP in either group during the trial (group effect, $p = 0.87$; time effect, $p = 0.12$; group × time effect, $p = 0.45$).

Changes in biochemical parameters during the trial

Serum K levels showed a tendency to decrease in some patients in the DRI group after 12 weeks, but no significant changes were seen in either group. Serum K levels in the DRI group were 5.5 ± 0.7 mEq/l at baseline and 4.6 ± 0.8 mEq/l after 12 weeks.

Discussion

Our study demonstrated that a treatment change from the recommended dose of an ARB to a 150 mg daily dose of aliskiren had no additive antihypertensive effect on pre-hemodialysis BP in hemodialysis patients with hypertension. However, PRA was significantly decreased and PAC increased by aliskiren from the 4th week until the end of the trial. Furthermore, aliskiren could be safely administered to our hemodialysis patients.

Effects of treatment change from ARB to DRI on BP

Recently, Morishita et al. (5) reported that aliskiren was effective for BP control in hemodialysis patients with hypertension. Therefore, aliskiren might have potential for providing the same degree of antihypertensive benefits as the recommended dose of an ARB and can be administered safely to hemodialysis patients. A previous study showed that the addition of aliskiren (150 mg/day for 8 weeks) significantly decreased BP, PRA, PAC and BNP levels in hypertensive patients on hemodialysis (6). In the present study, switching patients from an ARB to aliskiren did not affect BP but significantly decreased PRA. These findings may suggest that aliskiren could replace the recommended dose of an ARB in hemodialysis patients with hypertension.

The BP on the first hemodialysis day of the week may be different from that on the last hemodialysis day of the week, as the BP in hemodialysis patients is dependent on their circulating blood volume. Therefore, we used the mean of BP on the three hemodialysis days of a week as the pre-dialysis baseline BP. No significant differences in pre-dialysis BP was observed before and after the 12 weeks of aliskiren treatment, which may be due in part to the variability in BP. We also evaluated the change in BP on the last hemodialysis day of a week, such as Friday or Saturday. No significant difference in BP on the last day of the week was observed before and after the trial in both groups (data not shown). Interdialytic body weight gain was unchanged in ARB group (1.9 versus 1.9 kg), while it increased in DRI group (2.0 versus 2.3 kg). It is possible that this small gain in body weight may have contributed to the increase in BP in the DRI group.

Effects of treatment change from ARB to DRI on humoral factors

In non-dialysis patients with hypertension, a higher incidence of cardiovascular events has been observed in those with high PRA levels than those with low PRA levels, suggesting that elevated PRA levels may be a risk factor for cardiovascular events (7). In a sub-analysis of a large-scale trial of RAS inhibitors, a high incidence of cardiovascular events was reported in patients on RAS inhibitors who exhibited high PRA levels (8). PRA levels are generally high in dialysis patients (9). However, an association between PRA level and cardiovascular events including death has not been reported in dialysis patients. In the present study, patients taking aliskiren showed a significant decrease in PRA compared with those taking an ARB. It is not clear if there is also a high incidence of cardiovascular events in dialysis patients who exhibit high PRA levels similar to non-dialysis hypertensive patients. We speculate that the decrease in PRA by aliskiren may reduce the incidence of cardiovascular events and improve the prognosis of dialysis patients. In addition to controlling BP, an important issue for dialysis patients with hypertension is the prevention of fatal cardiovascular events. Even if aliskiren provides the same degree of antihypertensive benefits as other RAS inhibitors, the use of aliskiren may result in an improved prognosis.

In the present study, we measured BNP as one of the predictive biomarkers for cardiovascular events.

No significant decrease was observed in BNP before and after the 12-week study period between the two groups, although the decrease in the DRI group was smaller than in the ARB group. BNP was reported as an independent marker for adverse outcomes in hemodialysis patients (10). In the ALOFT study (11), non-dialysis hypertensive patients showed a significant decrease in BNP levels and improvement in left ventricular diastolic function after taking aliskiren. Another report showed that aliskiren might have cardiovascular protective effects in hemodialysis patients with hypertension (5). In contrast to the previous reports in non-dialysis hypertension patients (11), BNP did not drop in hemodialysis patients that were treated with aliskiren in the present study. The number of hypertensive patients enrolled in the present study was very small. Thus, results on BNP should be interpreted carefully.

PAC levels increased significantly in DRI group. Although it is still unclear whether increased PAC level is associated with poor outcomes in patients with hemodialysis, the increased PAC levels might have a potential to be deleterious. In the present study, we observed no decrease in potassium level in DRI group. Similar to the present results, previous studies reported that aliskiren had the potassium sparing effect (12) and that the incidence of hypokalemia was significantly lower in aliskiren/amlodipine combination therapy than in amlodipine monotherapy (13).

Hyperkalemia is also one of the side effects observed in patients on aliskiren. The risk of hyperkalemia has been shown to increase if a patient is diabetic or is concurrently taking another RAS inhibitor (14). In the present study, no patients exhibited a significant increase in serum K levels. The reason for this might be that few diabetic patients were included and that no concurrent administration of DRI and RAS inhibitors were allowed in the present study. However, diuretics were used in three patients on aliskiren, which might cover potential hyperkalemia under therapy with aliskiren.

Study limitations

There are several limitations in the present study. First, this study had a short follow-up of a small number of patients at a single center. Therefore, no conclusions can be made about the effects of aliskiren on long-term prognosis. A further study with a larger number sample size and longer follow-up is needed to determine the effect of aliskiren on the actual incidence of cardiovascular events. Second, the difference of 10% BP at baseline was observed between two groups although patients were randomly assigned to each arm in the present study. There was great variability among BP in DRI group. Systolic and diastolic BP at week 12 tended to be higher than baseline in both groups. In the DRI group, power analysis showed that the sample size in the present study ($n = 9$, difference 3.39; S.D., 15.67; 95% confidence interval, -15.4 to 8.7) was sufficient to detect a true difference in the mean change of systolic BP of -16.69 or 16.69 with a probability of type II error at less than 20% (power 0.8). This minimal detectable difference is greater than the difference between pre and post in DRI group (3.39 ± 15.67). Therefore, it is possible but unlikely that a physiologically meaningful difference in systolic BP was missed due to a type II error. Although patients in the ARB group did not change their drug therapy, the BP also tended to increase. It is possible that environmental factors such as a seasonal effect or interdialytic body weight gain resulted in the variable elevation of BP during the trial.

Conclusions

The present study showed that there was no significant difference in the change of the BP by switching from the recommended dose of an ARB to a 150 mg/day of aliskiren. In addition, aliskiren significantly decreased PRA levels. These findings suggest that aliskiren might have the potential to reduce the occurrence of cardiovascular events in hypertensive patients on hemodialysis. Aliskiren could be safely administered to hemodialysis patients with hypertension.

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Declaration of interest

All the authors have declared that no conflict of interest exists.

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