Long-Term Effects of Spironolactone in Peritoneal Dialysis Patients

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ABSTRACT
ESRD treated with dialysis is associated with increased left ventricular hypertrophy, which, in turn, is related to high mortality. Mineralocorticoid receptor antagonists improve survival in patients with chronic heart failure; however, the effects in patients undergoing dialysis remain uncertain. We conducted a multicenter, open-label, prospective, randomized trial with 158 patients receiving angiotensin-converting enzyme inhibitor or angiotensin type 1 receptor antagonist and undergoing peritoneal dialysis with and without (control group) spironolactone for 2 years. As a primary endpoint, rate of change in left ventricular mass index assessed by echocardiography improved significantly at 6 (P=0.03), 18 (P=0.004), and 24 (P=0.01) months in patients taking spironolactone compared with the control group. Rate of change in left ventricular ejection fraction improved significantly at 24 weeks with spironolactone compared with nontreatment (P=0.02). The benefits of spironolactone were clear in patients with reduced residual renal function. As secondary endpoints, renal Kt/V and dialysate-to-plasma creatinine ratio did not differ significantly between groups during the observation period. No serious adverse effects, such as hyperkalemia, occurred. In this trial, spironolactone prevented cardiac hypertrophy and decreases in left ventricular ejection fraction in patients undergoing peritoneal dialysis, without significant adverse effects. Further studies, including those to determine relative effectiveness in women and men and to evaluate additional secondary endpoints, should confirm these data in a larger cohort.


ESRD treated by hemodialysis or peritoneal dialysis (PD) is associated with a high prevalence of increased left ventricular (LV) mass (left ventricular hypertrophy [LVH]), fibrosis, and capillary loss.1,2 CKD exposes the heart to three major mechanisms that facilitate the development of cardiomyopathy and induce LV failure: pressure overload, volume overload, and CKD-related nonhemodynamic factors that alter the myocardium.3 The persistence and severity of LVH are closely associated with cardiovascular and all-cause mortality.3–6 Terminal events in LVH are known to include pump failure and sudden arrhythmic death.3,7–9 Furthermore, ischemic disease, as exemplified by coronary atherosclerosis, is a less important factor in cardiovascular mortality and morbidity from CKD and ESRD.1 Therefore, a new paradigm of therapy for ESRD that prioritizes prevention and reversal of LVH and cardiac fibrosis is needed.1

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Mineralocorticoid receptor (MR) antagonists are reported to improve the survival of patients with chronic heart failure and heart failure that occurs after myocardial infarction\textsuperscript{10–12} and to reduce LV mass\textsuperscript{13}, however, in patients undergoing dialysis, the few reports on the effects of MR blockade have typically focused on small cohorts that were underpowered to allow conclusions to be drawn.\textsuperscript{14–17} We explored the effects of concurrent spironolactone and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin type 1 receptor blocker (ARB) on cardiac complications (LV mass index [LVMI] and LV ejection fraction [LVEF]), peritoneal membrane, and residual renal functions in a multicenter, open-label, prospective controlled trial of patients undergoing PD.

RESULTS

Patient Characteristics at Baseline

A total of 158 patients under treatment with ACEI or ARB and undergoing peritoneal dialysis were randomly assigned to receive spironolactone (\(n=78\)) or not receive spironolactone (control group, \(n=80\)) (Figure 1). None of the patients were receiving both an ACEI and an ARB at the start of the study. Primary causes of renal failure were as follows: diabetes mellitus (39.2%), chronic GN (31.5%), nephrosclerosis (21.5%), other (3.8%), or unknown (4.4%). Patients were younger than the mean age of 66.2 years seen in Japanese dialysis patients (mean age \(\pm SD, 57.4 \pm 12.27\) and 55.6 \(\pm 14.37\) years in the treatment and control groups, respectively).\textsuperscript{18} Duration of PD treatment at baseline was relatively short (6 and 7.5 months, respectively), and urine volume was preserved (1000 and 955 ml, respectively). Baseline values for rate of use of icodextrin solution, LVMI, LVEF, BP, dialysate-to-plasma creatinine ratio (D/P Cr) by peritoneal equilibration test, renal Kt/V urea, urine volume, serum brain natriuretic peptide, and aldosterone levels were similar between the groups. Other demographic and baseline characteristics in the randomized population were similar, except for the rate of furosemide use (Table 1).

Treatment Characteristics

Systolic and diastolic BP pressure did not significantly differ between the groups during the study period (\(P=0.65\) and \(P=0.76\) at 24 months, respectively) (Supplemental Figure 1).

Primary Outcomes

Changes in LVMI

Rate of change in LVMI assessed by echocardiography was significantly improved in the spironolactone group at 6 (\(P=0.03\) versus control), 18 (\(P=0.004\) versus control), and 24 (\(P=0.01\) versus control) months compared with the nontreatment control group (Figure 2A). Because we observed interactions between women and men (\(P=0.01\)), we separately analyzed the effects of spironolactone. The effect of spironolactone on rate of changes in LVMI was similar in men with LVMI \(< 50\) g/m\(^2\) (normal range for men) and LVMI \(> 50\) g/m\(^2\) (LVH)\textsuperscript{19,20} at baseline (\(P\) for interaction=0.21). The rate of change in LVMI for men with LVMI \(< 50\) g/m\(^2\) (normal range) at baseline did not change
during the follow-up period in the group given spironolactone but increased significantly in the control group at 12 (P=0.02 versus baseline; P=0.01 versus spironolactone treatment group), 18 (P<0.001 versus baseline; P<0.001 versus spironolactone treatment group), and 24 (P<0.001 versus baseline; P<0.001 versus spironolactone treatment group) months (Figure 2B). The rate of change in LVMI for men with LVMI>50 g/m²² (LVH) at baseline did not significantly change during the observation period in the control group, but decreased significantly after 6 months when compared with baseline, and was further suppressed at 18 (P=0.001 versus baseline; P=0.003 versus control) and 24 (P<0.001 versus baseline; P=0.02 versus control) months by spironolactone (Figure 2C). In contrast, in women, rate of change in LVMI did not differ significantly during the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spironolactone Group (n=78)</th>
<th>Control Group (n=80)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57.4±12.7</td>
<td>55.6±14.37</td>
<td>0.40&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>23 (29.5)</td>
<td>22 (27.5)</td>
<td>0.86&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>33 (42.3)</td>
<td>29 (36.3)</td>
<td>0.52&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Use of icodextrin, n (%)</td>
<td>22 (28.2)</td>
<td>23 (28.8)</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Time receiving PD (mo)</td>
<td>6 (2.0–21.0)</td>
<td>7.5 (2.0–22.5)</td>
<td>0.57&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>NYHA-FC, n (%)</td>
<td>77 (98.7)</td>
<td>80 (100)</td>
<td>0.49&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Height (m²²)</td>
<td>3.8±0.55</td>
<td>3.8±0.47</td>
<td>0.69&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>137.4±15.42</td>
<td>135±16.56</td>
<td>0.16&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76.3±10.39</td>
<td>78.7±11.60</td>
<td>0.18&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.4±1.31</td>
<td>10.3±1.24</td>
<td>0.85&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.3±0.64</td>
<td>6.3±0.60</td>
<td>0.66&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.3±0.51</td>
<td>3.4±0.49</td>
<td>0.36&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>184 (162.0–200.0)</td>
<td>182.5 (152.5–209.0)</td>
<td>0.74&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>106 (87.0–125.0)</td>
<td>106 (81.5–135.0)</td>
<td>0.59&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>137.8±6.65</td>
<td>138.4±3.40</td>
<td>0.33&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.3±0.66</td>
<td>4.3±0.65</td>
<td>0.69&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>P (mg/dl)</td>
<td>5.4±1.54</td>
<td>5.2±1.28</td>
<td>0.44&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ca (mg/dl)</td>
<td>8.8±0.88</td>
<td>8.7±1.13</td>
<td>0.58&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood urea (mg/dl)</td>
<td>52.9 (42.9–64.9)</td>
<td>54 (45.7–63.6)</td>
<td>0.58&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>8.3 (6.6–10.8)</td>
<td>8.5 (6.7–11.2)</td>
<td>0.67&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>β₂-MG (µg/ml)</td>
<td>20.6±5.66</td>
<td>22.6±8.02</td>
<td>0.08&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Urine volume (ml/d)</td>
<td>1000 (500.0–1650.0)</td>
<td>955 (550.0–1400.0)</td>
<td>0.30&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weekly renal Kt/V urea</td>
<td>0.81 (0.41–1.08)</td>
<td>0.66 (0.41–1.06)</td>
<td>0.45&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weekly PD Kt/V urea</td>
<td>1.13 (0.70–1.40)</td>
<td>1.17 (0.75–1.53)</td>
<td>0.39&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>D/P Cr 4 h</td>
<td>0.66 (0.59–0.75)</td>
<td>0.66 (0.58–0.76)</td>
<td>0.57&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum aldosterone (pg/ml)</td>
<td>53.6 (20.0–100.0)</td>
<td>58.1 (24.4–120.0)</td>
<td>0.58&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum BNP (pg/ml)</td>
<td>83.1 (27.6–233.0)</td>
<td>68.6 (29.0–214.1)</td>
<td>0.62&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>64.9±10.77</td>
<td>65.5±9.89</td>
<td>0.70&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVMI (g/m²²)</td>
<td>51.6±21.08</td>
<td>52.3±18.10</td>
<td>0.82&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women</td>
<td>45.4±19.7</td>
<td>51.2±14.28</td>
<td>0.30&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Men</td>
<td>53.9±21.26</td>
<td>52.8±19.41</td>
<td>0.79&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are expressed as number (percentage), mean±SD, and median (interquartile range). TC, total cholesterol; LDL-C, LDL cholesterol; β₂-MG, β₂-macroglobulin; BNP, brain natriuretic peptide; EPO, erythropoietin.

<sup>a</sup>Welch t test.
<sup>b</sup>Fisher exact test.
<sup>c</sup>Mann–Whitney U test.
observation period in patients with LVMI ≤47 g/m².7 (normal range for women) or in those with LVMI >50 g/m².7 (LVH)¹⁹,²⁰ at baseline (Supplemental Figure 2).

Residual renal function was reported to affect LVMI in patients undergoing PD.²⁰–²² Patients were divided into tertiles according to baseline renal Kt/V: tertile 1, <0.49; tertile 2, ≥0.49 and <0.94; and tertile 3, ≥0.94. The effects of spironolactone were obvious in patients with renal Kt/V <0.49 (tertile 1) (Figure 2D), but were not significant in tertiles 2 and 3.

**Changes in LVEF**
Rate of change in LVEF was significantly improved at 24 weeks compared with the nontreatment control group (P=0.02) (Figure 2E). On analysis of changes of LVEF in tertiles of renal Kt/V, spironolactone improved LVEF at 18 (P=0.02 versus control) and 24 (P=0.002 versus control) months in the patients with Kt/V <0.49 (Figure 2F), but in tertiles 2 and 3, these effects were not detected.

**Secondary Outcomes**
Both urine volume and renal Kt/V decreased with time, but rate of change did not significantly differ between the treatment and control groups (Figure 3, A and B). Significant effects of spironolactone were not detected in the rate of change in D/P Cr ratio between the groups (Figure 3C).

**Adverse Effects**
A total of two patients in the spironolactone group (2.6%) and five patients in the control group (6.3%) died (Figure 1). Kaplan–Meier estimates of mortality and technical survival rate at 24 months were not significantly different (Supplemental Figure 3, A and B; P=0.34 and 0.34, respectively). Kaplan–Meier
values for cardiovascular death and technical survival from cardiovascular causes did not significantly differ between the groups during the study period (Supplemental Figure 3, C and D; \( P = 0.15 \) and 0.71, respectively). There were no significant differences between the two groups in occurrence of cerebral bleeding (\( P > 0.99 \)), cerebral infarction (\( P > 0.99 \)), myocardial infarction (\( P > 0.76 \)), and hypotension (\( P = 0.76 \)) (Table 2).

Serum potassium levels were significantly higher in patients receiving spironolactone at 6 and 12 months (Supplemental Figure 4). Serious hyperkalemia (potassium \( \geq 6.0 \) mEq/L) occurred in two (2.6%) patients (maximum level, 6.0 mEq/L) who received spironolactone and in one (1.3%) (maximum level, 6.2 mEq/L) in the control group during the observation period (\( P = 0.62 \)) (Table 2). Gynecomastia developed in 11 (14.1%) and 2 (2.5%) patients in the spironolactone and control groups, respectively (\( P = 0.01 \)) (Table 2). Spironolactone was switched to eplerenone in two patients, and the doses of spironolactone were reduced from 25 to 12.5 mg/d in two other patients. The remaining seven patients continued with spironolactone. There were no other clinically significant differences between the two groups with respect to laboratory variables, reported adverse events, or adverse events leading to permanent withdrawal of the study medicine.

**DISCUSSION**

Left ventricular hypertrophy is present in almost 75% of patients starting dialysis\(^2\,\,^3\) and is strongly associated with poor outcomes in patients with CKD and ESRD.\(^1\) Recently, much attention has focused on the mediators and signaling pathways for LVH. Activation of the renin-angiotensin system (RAS), oxidative stress, elevated asymmetric dimethyl arginine, low-grade inflammation with increased circulating cytokines, and dyslipidemia are reported to be involved in the pathogenesis of cardiovascular diseases in patients with CKD.\(^2\,\,^4\) Persistent hyperaldosteronemia and/or activation of MR can promote cardiac fibrosis, possibly through generation of signals promoting profibrotic TGF-\( \beta \) production.\(^1\,\,^2\,\,^5\,\,^26\) In animal models, spironolactone ameliorates cardiac fibrosis in nephrectomized uremic rats.\(^2\,\,^7\,\,^28\)
We evaluated the effects of adding spironolactone to ACEI or ARB in patients undergoing PD, and we found that LVMI was significantly suppressed in the spironolactone group (Figure 2). LVMI in patients receiving PD was reported to be linked to a loss of residual renal function\(^2\)\(^{20}\) and to a high peritoneal membrane permeability.\(^{29}\) Thus, the absence of significant effects from spironolactone on renal Kt/V and D/P Cr in this study (Figure 3) supports the notion that these results were mainly due to the effects of spironolactone. In subgroup analysis, the effects of spironolactone were more significant in men (Figure 2). On the other hand, we observed no effect from spironolactone in women (Supplemental Figure 2). In previous studies, in which about 30% of enrolled patients were women, spironolactone was effective in both male and female patients with severe heart dysfunction who were not undergoing dialysis.\(^{10}\) Because of the low number of women in our study, a comparison of the effects of spironolactone between men and women in a larger cohort will be necessary to confirm our data. We did not observe significant interactions between the effect of spironolactone and residual renal functions on rate of changes in LVMI (P for interaction=0.43) or LVEF (P for interaction=0.18); however, we analyzed the relationship with residual renal function on the basis of its clinical importance for PD patients.\(^{20}\)\(^{22}\) Interestingly, the effects of LVMI and LVEF tended to be predominant in PD patients with decreased levels of residual renal function (renal Kt/V\(<0.49\) (Figure 2, D and F). These important points need to be confirmed in future studies.

As for secondary outcomes, we were unable to identify the beneficial effects of spironolactone on residual renal function and peritoneal membrane functions. In most clinical studies on MR blockade in patients with CKD, the primary endpoint has been reduction of proteinuria and/or albuminuria.\(^{30}\)\(^{32}\) The effects of MR blockade in prevention of deterioration of renal function remain unclear.\(^{30}\)\(^{31}\) In our studies, we were unable to identify the effects on prevention of decline in urine volume and residual renal function in patients undergoing PD. MR protein and mRNA were expressed in rat peritoneum, mesothelial cells, and fibroblasts.\(^{33}\)\(^{34}\) Spironolactone and ARB effectively ameliorated the peritoneal thickening and D/P Cr in the rat scraped peritoneal fibrosis model.\(^{33}\) In addition, ARB was reported to suppress the deterioration of peritoneal membrane function in PD patients.\(^{35}\) In this study, RAS was suppressed at baseline in patients by administration of ACEI or ARB for \(>3\) months. Therefore, in these cases, it may be difficult to detect the effects of spironolactone on peritoneal membrane function.

Overall, spironolactone therapy was well tolerated. The use of MR antagonists has not been recommended in patients with CKD because of concerns about hyperkalemia, which often occurs when multiple renin-angiotensin-aldosterone blockers are used\(^{30}\)\(^{36}\)\(^{37}\); however, the risk of severe hyperkalemia was not significantly elevated among PD patients assigned to spironolactone (Table 2). Removal of potassium is greater in PD than in hemodialysis. Between 10% and 36% of patients receiving PD are reported to have hypokalemia, and adding potassium tablets is necessary for 10%–20% of PD patients.\(^{38}\)\(^{40}\) In our cohort, hypokalemia (potassium\(<3.0\) mEq/L) was detected in 15.4% of the spironolactone treatment group and in 25% of the control group. On the basis of our findings, MR antagonists do not present serious problems with regard to serum potassium levels in patients undergoing PD. Antian- drogenic adverse effects appeared with high doses of spironolactone\(^{30}\)\(^{41}\) and a significant incidence of gynecomastia was noted in the spironolactone group (14.1%; P=0.01); however, in these cases the spironolactone dose was reduced from 25 mg/d to 12.5 mg/d or the patients were switched to eplerenone. Use of the selective MR blocker eplerenone appears to minimize the risk of gynecomastia.

This study had several limitations. First, this study was open label. Second, we estimated sample size according to the effects of spironolactone on LVMI; thus, analyzing sex effects and other endpoints in this sample may be inappropriate. Third, all patients in the study were Japanese. Japanese patients are reported to have a better prognosis than comparable patients in the United States and Europe, and subclinical atherosclerosis, coronary disease mortality, and risk of coronary calcification are lower in Japanese persons.\(^{42}\) Fourth, an ACEI or ARB was administered for \(>3\) months; therefore, the RAS was already suppressed at the start of this study in patients of both groups. In addition, several types of ACEI and ARB were used, and we did not evaluate their doses. Furthermore, the prescription rate for ARBs was much higher than that for ACEIs in this cohort; this is typical in Japan\(^{43}\) but is very different from patterns in the United States and European countries. The high incidence of cough among Asian individuals\(^{44}\) may be related to the lower use of ACEI in this cohort and in Japanese hypertensive patients. Fifth, most of the patients in this study were classified as New York Heart Association functional class (NYHA-FC) I, which may have contributed to the lower mortality rate. Finally, the effects of spironolactone in women were not studied in detail because the number of female patients enrolled was

### Table 2. Adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Patients, n (%)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spironolactone</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Group (n=78)</td>
<td>Group (n=80)</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>1 (1.3)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>4 (5.1)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2 (2.6)</td>
<td>8 (10.0)</td>
</tr>
<tr>
<td>Hypotension (BP&lt;100 mmHg)</td>
<td>6 (7.7)</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Hyperkalemia (K&gt;6.0 mEq/L)</td>
<td>2 (2.6)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Hypokalemia (P&lt;3.0 mEq/L)</td>
<td>12 (15.4)</td>
<td>20 (25.0)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>11 (14.1)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>16 (20.5)</td>
<td>17 (21.3)</td>
</tr>
</tbody>
</table>
limited (<30%) in this cohort. Furthermore, there was an im-
balance between the two groups with regard to baseline LVMI
in women (Table 1) because randomization was performed
before echocardiography.

In summary, the MR antagonist spironolactone may help to
prevent cardiac hypertrophy and dysfunction in patients
undergoing PD without significant adverse effects. Future
studies are necessary in larger cohorts to confirm the effects
of spironolactone with regard to relative effectiveness in women
and men and the relationship between residual renal function
and secondary endpoints.

CONCISE METHODS

Study Design
The Nagoya Spiro Study is a multicenter, open-label, prospective,
randomized controlled trial conducted in 12 hospitals. Patients
were randomly assigned and followed for 2 years. This study was performed
in accordance with the Declaration of Helsinki and Good Clinical
Practice guidelines. The institutional review boards or ethics com-
mittees of all participating institutions approved the protocols.
Written informed consent was obtained from all patients before
enrollment. The trial was monitored by an independent data and
safety monitoring committee. Safety was evaluated by adverse events
reports and clinical laboratory values, including serum potassium
levels. The Nagoya Spiro Study was registered at The University
Hospital Medical Information Network Clinical Trials Registry as
UMIN000492.

Participants
Patients with ESRD undergoing PD were recruited from 12 hospitals
in the Tokai area of Japan, including Nagoya University Hospital
(Nagoya, Japan), Handa Municipal Hospital (Handa, Japan), Daiyukai
Daichi Hospital (Ichinomiya, Japan), Yokkaichi Municipal Hospital
(Yokkaichi, Japan), Anjo Kosei Hospital (Anjo, Japan), Aihoku-
Konankosei Hospital (Konan, Japan), Nagoya Kyoritsu Hospital
(Nagoya, Japan), Gifu Prefectural Hospital (Gifu, Japan), Tosei
General Hospital (Seto, Japan), Ogaki Kita Clinic (Ogaki, Japan),
and Kasugai Municipal Hospital (Kasugai, Japan). Inclusion criteria
were as follows: age 18–80 years, treatment with PD among patients
with NYHA-FC I and II for <5 years, concurrent administration of
ARB or ACEI treatment for >3 months, and treatment with neutral-
pH dialysate and/or icodextrin solution. Patients were excluded if any
of the following criteria were present: severe anemia (hemoglo-
bin<9.0 g/dl), NYHA-FC III and IV heart failure, treatment with
acid-pH fluid dialysate, previous treatment with hemodialysis or
transplantation within the preceding 3 years, and pregnancy or sus-
pected pregnancy.

Treatment Procedures
The 25-mg once-daily dose of spironolactone was selected on the
basis of previous results of clinical trials.10,32 If hyperkalemia or gy-
 necomastia developed, the dose could be decreased to 12.5 mg/d be-
cause spironolactone at a dose 12.5–25 mg/d is reported to be
pharmacologically effective in blocking the aldosterone receptors
and atrial natriuretic peptide concentrations.10,45 In addition, antihy-
pertensive agents, excluding other ACEIs, ARBs, and MR blockers,
were allowed to control systolic BP (<130 mmHg). Doses of ACEIs
and ARBs were not allowed to change unless adverse events occurred.
Following the approval of eplerenone for use in clinical settings in
Japan in July 2007, the Nagoya University Institutional Review Board
approved the change to eplerenone, 50 mg/d, from spironolactone
after demonstration of the safety of spironolactone on serum potas-
sium levels in this study. Follow-up evaluation and laboratory mea-
surements, including serum potassium, were conducted every 4 weeks
for up to 2 years.

Outcome Measures
The primary outcome measures were LVMI and LVEF. Secondary
outcome measures comprised residual renal function and peritoneal
membrane function. We evaluated LVMI and LVEF by echocardiog-
raphy, renal Kt/V, urine volume, and D/P Cr by peritoneal equili-
bration test every 6 months for up to 24 months.

Echocardiography
Standard two-dimensional (2D) and Doppler echocardiography was
performed in each institute using a commercially available echocar-
diographic machine with a 2.0- to 3.5-MHz transducer by a single
experienced echocardiography sonographer. All echocardiographic
data were recorded in accordance with the guidelines of the American
Society of Echocardiography (ASE).46,47

Interventricular septal thickness (IVS), posterior wall thickness
(PWT), and LV internal dimension (LVID) were measured at end-
diastole and end-systole according to the established standards of
ASE. To obtain optimal medial–lateral beam orientation and accu-
rate linear measurements, the protocols recommend recording and
measuring IVS, PWT, and LVID from the parasternal long-axis
acoustic window using 2D-targeted M-mode echocardiography. In
addition, observation from the parasternal short-axis acoustic win-
dow is required. Measurements of LVID and wall thickness are recom-
manded at the level of mitral valve leaflet tips. Scanned images of 2D
long-axis and short-axis views of end-diastolic and end-systolic ventricle
with M-mode scans are required to send to the evaluation center.
LV mass was calculated according to the ASE-recommended
formula:

\[
\text{LV mass (g) = 0.8} \times \left\{1.04 \left[\left(\text{IVS} + \text{LVID} + \text{PWT}\right)^3 - \left(\text{LVID}\right)^3\right]\right\} + 0.6
\]

LV mass was indexed by height to minimize potential distortion by
extracellular volume expansion, and LVMI was defined as LV mass/
height\(^2\).19,20 LVMI was defined as LVMI>50 g/m\(^2\) in men and
47 g/m\(^2\) in women.19,20 LVEF was obtained using the modified
biplane Simpson method from the apical two- and four-chamber
views. Echocardiography sonographers and interpreters were blin-
ded to treatment assignment and protocol. All echocardiographic
data were sent to the evaluation center and were reviewed in a
blinded manner by a cardiologist (T.M.) to confirm the suitability
and validity of echocardiography. In these procedures, data from
four patients were omitted because of poor evaluation.
Sample Size
According to previous studies on LVH regression by eplerenone in hypertensive patients without advanced renal dysfunction, we estimated a 10%–20% reduction in LVMI for 2 years by adding the spironolactone to an ACEI or ARB. It was estimated that a total of 105 patients was necessary to detect significant differences between the two groups with 90% power. The rate of PD dropout from all causes is 10%–20% per year in Japan. To compensate for dropout from this study, we planned to enroll and randomly assigned at least 145 patients.

Statistical Analyses
The trial population in this study is the full analysis set population. Comparison between two groups of continuous variables was performed using the Welch t test or the Mann–Whitney U test. The Fisher exact test was used for categorical variables. Death and technical survival were analyzed by the Kaplan–Meier method and log-rank test. We used estimated marginal means with the linear mixed-effect model with Bonferroni correction to assess group differences in percentage change in LVMI. For the linear mixed-effect model, we included comparison groups and times as fixed effects and patients as random effects. We separately analyzed the effects of spironolactone between men and women, and also between normal LV mass and LVH. Effects of spironolactone were assessed by tertile of residual renal function. Tests of between-subject effects with type III fixed effects were assessed for interactions between spironolactone and LVH. Effects of spironolactone were assessed by tertile of residual renal function. Differences were considered to be statistically significant at P<0.05. All analyses were performed using SPSS Statistics 20 (IBM Corp., Armonk, NY).

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REFERENCES

DISCLOSURES
None.


Supplementary Figures

Long-term effects of spironolactone in peritoneal dialysis patients

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Supplementary Figure 1. Blood pressure in spironolactone treatment and control group.
Systolic and diastolic blood pressure did not differ between groups during the observation period.
Spiro (-): control group; Spiro (+): spironolactone treatment group.
Supplementary Figure 2. Rate of Changes in Left ventricular mass index in females.

In females, rate of changes in left ventricular mass index (LVMI) did not significantly differ during observation period in both patients with LVMI≤47 g/m² (normal range for females) (A) and those with LVMI>47 g/m² (left ventricular hypertrophy) (B) at baseline.

Spiro (-): control group; Spiro (+): spironolactone treatment group.
Supplementary Figure 3. Mortality and technical survival
Kaplan-Meier data for all-cause mortality (A), technical survival rates (B), cardio-vascular death (C) and technical survival for cardio-vascular causes (D)
Supplementary Figure 4. Changes in potassium levels in spironolactone treatment and control groups during the observation period. Spiro (-): control group; Spiro (+): spironolactone treatment group.