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Effect of spironolactone on the risks of mortality and hospitalization for heart failure in pre-dialysis advanced chronic kidney disease: A nationwide population-based study

Wei-Cheng Tseng [a,b,d], Jia-Sin Liu [f], Szu-Chun Hung [e], Ko-Lin Kuo [e], Yu-Hsin Chen [b], Der-Cherng Tarng [a,b,c,d,*], Chih-Cheng Hsu [d,f,g,**]

[a] Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan
[c] Department and Institute of Physiology, National Yang-Ming University, Taipei, Taiwan
[d] Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan
[e] Division of Nephrology, Taipei Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, Taipei, Taiwan
[f] Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan
[g] Department of Health Services Administration, China Medical University, Taichung, Taiwan

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ABSTRACT

Background: Spironolactone has been shown to reduce cardiovascular death in patients with mild-to-moderate chronic kidney disease (CKD), but its risks and benefits in advanced CKD remain unsettled. We aimed to assess whether spironolactone reduces cardiovascular mortality and morbidity in pre-dialysis stage 5 CKD patients.
Methods: Using Taiwan's National Health Insurance Research Database from January 2000 to June 2009, we enrolled 27,213 pre-dialysis stage 5 CKD adult patients, in whom 1363 patients were treated with spironolactone (user) and 25,850 were not (nonuser). Outcomes were all-cause mortality, hospitalization for heart failure (HHF) and major adverse cardiac event (MACE, the composite of acute myocardial infarction and ischemic stroke). Patients were followed up till December 31, 2009.
Results: Over 85,758 person-years of follow-up, spironolactone users had higher incidence for all-cause mortality (24.7/100 person-years vs. 10.6/100 person-years), infection-related death (4.4/100 person-years vs. 1.7/100 person-years) and HHF (4.0/100 person-years vs. 1.4/100 person-years). Multivariable Cox hazards model showed that spironolactone users were associated with higher risks of all-cause mortality (adjusted hazard ratio [aHR] 1.35, 95% confidence interval [CI] 1.24–1.46), infection-related death (aHR 1.42, CI 1.16–1.73) and HHF (aHR 1.35, CI 1.08–1.67) as compared to nonusers. The risks for cardiovascular mortality, MACE and hyperkalemia-associated hospitalization were similar between two groups. After matching users and nonusers (1:3 ratio) by propensity scores, the results were consistent in matched cohort and across subgroups.
Conclusions: Spironolactone may be associated with higher risks for all-cause and infection-related mortality and HHF in pre-dialysis stage 5 CKD patients. Spironolactone should be used with caution in advanced CKD patients.

1. Introduction

Chronic kidney disease (CKD), an emerging global health issue with the prevalence of 10% ~ 12% worldwide, is a significant risk factor for cardiovascular disease [1]. The risks for death and cardiovascular events could remarkably increase as the stages of CKD progress [1]. Patients with stage 5 CKD (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73m^2) carry highest risks for all-cause and cardiovascular mortality with the life expectancy shortened by 21.3 years [1]. This excess cardiovascular risk is not only mediated by traditional risk factors (hypertension, diabetes, smoking, and dyslipidemia) but also attributable to unique factors from advanced CKD (acidosis, anemia, uremic toxin and endothelial dysfunction), which further accelerate coronary vascular calcification, cardiac fibrosis and left ventricular hypertrophy [2]. Current interventions targeted at traditional risk factors to reduce cardiovascular mortality in CKD are unsatisfying [3–6] and potentially even harmful [6]. Therefore, alternative treatment to decrease mortality and cardiovascular events in CKD is still urgently needed.

* Correspondence to: D.-C. Tarng, Department and Institute of Physiology, National Yang-Ming University; Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 11217, Taiwan.
** Correspondence to: C.-C. Hsu, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, 35, Keyan Road, Zhunan Town, Miaoli County 35053, Taiwan.
E-mail addresses: dctarng@vghtpe.gov.tw (D.-C. Tarng), cch@nhri.org.tw (C.-C. Hsu).

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Spironolactone, a mineralocorticoid receptor antagonist, protects against cardiac fibrosis, left ventricular remodeling and endothelial dysfunction [7]. By contrast, spironolactone may also result in acidosis and life-threatening hyperkalemia, especially in CKD patients [8]. In stage 2 and 3 CKD patients without heart failure (HF), spironolactone reduces left ventricular mass, decreases arterial stiffness and improves left ventricular function when added to the blockers of renin-angiotensin system [9]. In HF patients with reduced ejection fraction and serum creatinine level ≤ 221 μmol/L, spironolactone can effectively decrease overall mortality and hospitalization for HF (HHF) [10]. Furthermore, low-dose spironolactone treatment is well-tolerated even in oligo-anuric hemodialysis patients [11]. Therefore, spironolactone may hold the promise for reducing mortality, preventing new-onset HF and protecting against cardiovascular events in pre-dialysis stage 5 CKD patients. However, little is known regarding the risks and benefits of spironolactone in pre-dialysis stage 5 CKD, and therefore the current guidelines for the management of heart failure do not support or refute the use of spironolactone in this patient group [12,13]. Inampudi et al. recently analyzed 106 HHF patients with pre-dialysis stage 5 CKD and found that prescribed spironolactone at discharge was not associated with reduction of all-cause mortality, and even with a higher all-cause readmission rate [14], raising the safety concern of spironolactone use in pre-dialysis stage 5 CKD. Nonetheless, small patient numbers in Inampudi's study precluded definitive conclusions. Therefore, the risks and benefits of spironolactone remain unsettled in these high-risk stage 5 CKD patients.

Till now, there is no large-scale study addressing the role of spironolactone on mortality and cardiovascular events in pre-dialysis stage 5 CKD patients. To bridge this knowledge gap, we aimed to assess whether spironolactone use decreased the risks of all-cause mortality, HHF, major adverse cardiac events (MACE, the composite of acute myocardial infarction and ischemic stroke), and hyperkalemia-associated hospitalization in a nationwide cohort of patients with pre-dialysis stage 5 CKD.

2. Methods

2.1. Data source

The present study used the data derived from the Taiwan's National Health Insurance Research Database (NHIRD), which contained healthcare utilization information for >99% of its entire 23 million population [15,16]. The NHIRD has been described in prior studies and the accuracy of diagnoses has been validated before [15,16]. The study was approved by the institutional review board at Taipei Veterans General Hospital.

2.2. Design and study participants

The study was designed as a population-based longitudinal cohort study. From January 1, 2000, through June 30, 2009, we selected individuals who had a primary diagnosis of CKD (Appendix Table A1) and received erythropoiesis-stimulating agent (ESA) treatment as potential study subjects. ESA is to be initiated when pre-dialysis CKD patients have their serum creatinine levels ≥530.4 μmol/L (approximately eGFR <15 mL/min/1.73 m^2) and hematocrit levels <28% in Taiwan by the reimbursement regulations of national health insurance in Taiwan. The selected cohort in this study was the most representative of pre-dialysis stage 5 CKD patients in Taiwan and has been validated previously [15,16]. We excluded patients younger than 20 years or older than 100 years and those who had undergone dialysis or renal transplantation before the ESA treatment. Because we used prescription information within 90 days after the first ESA treatment to ascertain spironolactone use, the 91st day after the ESA prescription was defined as the index date. Patients who died, who commenced renal replacement therapy, or who had not been prescribed any anti-hypertensive agents from the first ESA treatment to the index date were also excluded. The dosage of ESA was calculated by the sum of all doses used within 90 days after the first ESA treatment. Ultimately, we selected 27,213 patients as the study subjects (Fig. 1). Comorbidities were defined as the respective diseases diagnosed within 3 years before the index date (Appendix Table A1). Patients with history of prior HF were categorized as mild (merely treated in an outpatient setting or had length of hospital stay ≤7 days) and severe HF (length of hospital stay >7 days) as the mean length of stay for HHF in Taiwan were 6–9 days from 1999 to 2008 [17]. Charlson comorbidity index was used to quantify patient comorbidity profiles.

Patients who had taken spironolactone within 90 days after the first ESA treatment were defined as the spironolactone user group ($n = 1363$), and the remaining patients were designated as the nonuser group ($n = 25{,}850$). To address confounding by observed covariates, propensity score for the likelihood of receiving spironolactone was calculated using logistic regression analysis, conditional on the baseline covariates listed in Table 1. Thereafter, the spironolactone users were matched to nonuser counterparts on a 1:3 ratio based on the age, sex and propensity score (±0.1). All analyses were conducted in an intention-to-treat fashion.

2.3. Study outcome and follow-up

The outcomes of interest were all-cause mortality, HHF, MACE and hyperkalemia-associated hospitalization. Causes of death (Appendix Table A1) were defined by either the main diagnosis for in-hospital death or the first-listed discharge diagnosis of the last hospitalization within three months before death for out-of-hospital death as indicated previously [18]. We defined HHF as the first hospitalization for new or worsening HF as the primary cause of admission after index date, which was ascertained by the first listed the International Classification of Diseases, Revision 9, Clinical Modification (ICD-9-CM code) (428.x) of the discharge diagnoses. MACE was the composite of acute myocardial infarction (410.x) and ischemic stroke (433.x, 434.x, 436). Hyperkalemia-associated hospitalization was identified by the discharge diagnoses (276.7) or the use of potassium-lowering agents. The follow-up started from the index date to death, the first HHF, the first MACE, or December 31, 2009, whichever occurred first. Death prior to the occurrence of HHF or MACE was considered a competing risk event.

2.4. Pre-specified subgroups

To ascertain the consistency of our results, subgroup analyses were conducted and included different age and gender, and the presence or absence of diabetes mellitus, coronary artery disease, HF history, stroke, atrial fibrillation, cirrhosis, cancer, use of potassium-lowering agents, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and the nephrologist care.

2.5. Statistical analysis

Baseline characteristics of the study population were described as the percentages and means ± SD for categorical and continuous variables, respectively. Differences between the spironolactone user and nonuser groups were compared by the independent *t*-test or χ^2 test where appropriate. Cumulative incidences of all-cause mortality, HHF and MACE were estimated by Kaplan-Meier methods. For all-cause mortality, between-group comparisons of cumulative incidences were assessed by log-rank tests. For HHF and MACE, comparisons were undertaken by the Fine-Gray model, treating mortality as a competing risk.

Multivariable Cox proportional hazards models before and after propensity-scored matching were applied to estimate hazard ratios (HR) of study outcomes after adjusting for age, gender, Charlson comorbidity index, diabetes mellitus, coronary artery disease, prior history of HF, stroke, cirrhosis, cancer, end-stage renal disease (ESRD, necessitating long-term dialysis for at least 90 days) and other covariates in Table 1. Days to events were calculated from the index date. The proportional hazards assumption was confirmed by comparing estimated log-log survival curves for all time-independent covariates. All assessed log-log survival plots indicated no violation of the assumption.

Several additional analyses were also conducted. First, we determined the risk associated with spironolactone treatment for cardiovascular or non-cardiovascular death. Second, association between the spironolactone treatment and outcomes were examined in pre-specified subgroups across baseline characteristics. Third, to test the robustness of our findings, sensitivity analyses were performed by defining spironolactone use at intervals of 30, 60, and 120 days after the first ESA prescription to minimize misclassification bias. Additionally, as-treated model was performed to assess the influence of crossover between user and nonuser groups. A two-tailed *p* value <0.05 was considered significant. Analyses were performed using commercially available software (SAS, version 9.3 [SAS Institute Inc], and Stata SE, version 11.0 [StataCorp]).

3. Results

3.1. Patient characteristics

Table 1 compared baseline patient characteristics classified by spironolactone treatment before and after propensity-score matching. Before matching, the users were older, male predominant, more likely to have comorbidities including diabetes, prior HF and myocardial infarction. They also tended to receive potassium-lowering agents and bicarbonate alkali. After 1 to 3 matching, the distributions of propensity score between the spironolactone users and nonusers were comparable (Appendix Fig. A1) and all 41 baseline characteristics were similar (Table 1). The prescription of spironolactone after the ESA treatment was generally in agreement with their use in the period before the ESA treatment.