Impact of Two Commonly Used Doses of Tolvaptan on Prognosis in Very Elderly Patients with Chronic Heart Failure (Postprint)

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Date: 2022-08-12T00:00:00+00:00

Abstract

Background Tolvaptan is widely used in elderly patients with chronic heart failure, but whether there is a difference in the impact of two doses of tolvaptan, 7.5 mg/day and 15 mg/day, on heart failure prognosis remains unclear. Objective To investigate the effects of two commonly used doses of tolvaptan on the prognosis of very elderly patients with chronic heart failure. Methods A retrospective analysis was conducted on 212 very elderly patients with chronic heart failure who were treated in the geriatric ward of the 960th Hospital of the People' s Liberation Army from February 2016 to February 2022 and received tolvaptan. Patients were divided into 7.5 mg/day and 15 mg/day groups according to the administered dose. Baseline characteristics, comorbidities, concomitant medications, and laboratory test indicators were compared between the two groups. Kaplan-Meier survival curves were plotted to compare differences in all-cause mortality and cardiovascular mortality between the two groups, and a multivariate Cox proportional hazards regression model was used to analyze the impact of the two tolvaptan doses on endpoint events. Results A total of 212 very elderly patients with chronic heart failure were included, with a follow-up period of 374.5 (155.5, 940.5) days. There were 124 cases of all-cause death (58.5%) and 53 cases of cardiovascular death (25%). Kaplan-Meier survival analysis showed that both all-cause mortality and cardiovascular mortality were higher in the tolvaptan 15 mg/day group compared with the tolvaptan 7.5 mg/day group (P=0.0043, P=0.0012). Multivariate Cox proportional hazards regression model analysis demonstrated that after adjusting for age, NYHA cardiac function classification, chronic kidney disease, diabetes mellitus, hypertension, coronary heart disease, diuretics, ALB, NT-proBNP, and eGFR, the risk of all-cause death and cardiovascular death in the 15 mg/day group increased by 1.03-fold and 1.51-fold, respectively, compared with the 7.5 mg/day group

(HR=2.03, 95%CI: 1.34-2.99 and HR=2.51, 95%CI: 1.4-4.5). After stratification by eGFR, age, albumin, and NT-pro BNP, the tolvaptan 15 mg/day group remained associated with increased risks of all-cause death and cardiovascular death. Conclusion In very elderly patients with chronic heart failure, tolvaptan 15 mg/day is associated with increased risks of all-cause death and cardiovascular death compared with tolvaptan 7.5 mg/day, and low-dose tolvaptan is recommended.

Full Text

Preamble

Effect of Two Commonly Used Doses of Tolvaptan on Prognosis in Very Elderly Patients with Chronic Heart Failure

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Abstract

Background: Tolvaptan is widely used in elderly patients with chronic heart failure, yet whether the two doses of 7.5 mg/day and 15 mg/day differentially affect heart failure prognosis remains unclear.

Objective: To investigate the effects of two commonly used doses of tolvaptan on prognosis in very elderly patients with chronic heart failure.

Methods: We retrospectively analyzed 212 very elderly chronic heart failure patients treated in the health care ward of the 960th Hospital of the People' s Liberation Army between February 2016 and February 2022 who received tolvaptan. Patients were divided into two groups based on dose (7.5 mg/day vs. 15 mg/day). Baseline characteristics, comorbidities, concomitant medications, and laboratory parameters were compared between groups. Kaplan-Meier survival curves were constructed to compare all-cause and cardiovascular mortality, and multivariate Cox proportional hazards regression was used to analyze the effect of tolvaptan dose on endpoint events.

Results: Among 212 included patients followed for a median of 374.5 days (IQR: 155.5–940.5), 124 all-cause deaths (58.5%) and 53 cardiovascular deaths (25.0%) occurred. Kaplan-Meier analysis showed that both all-cause and cardiovascular

mortality were higher in the 15 mg/day group compared to the 7.5 mg/day group (P = 0.0043 and P = 0.0012, respectively). After adjusting for age, NYHA functional class, chronic kidney disease, diabetes, hypertension, coronary artery disease, diuretic use, albumin, NT-proBNP, and eGFR, the 15 mg/day group exhibited a 1.03-fold and 1.51-fold increased risk of all-cause and cardiovascular death, respectively, compared with the 7.5 mg/day group (HR = 2.03, 95% CI: 1.34–2.99; and HR = 2.51, 95% CI: 1.40–4.5). This association persisted across strata of eGFR, age, albumin, and NT-proBNP levels.

Conclusion: In very elderly chronic heart failure patients, tolvaptan 15 mg/day is associated with increased risks of all-cause and cardiovascular mortality compared with 7.5 mg/day. Low-dose tolvaptan is recommended for this population.

Keywords: tolvaptan; elderly; chronic heart failure; prognosis; cohort study

Study Value

This study demonstrates that in very elderly heart failure patients, both the 7.5 mg/day and 15 mg/day doses of tolvaptan significantly improve volume overload and increase serum sodium levels without affecting potassium levels or eGFR. However, the 15 mg/day group exhibited higher all-cause and cardiovascular mortality than the 7.5 mg/day group. After adjusting for age, comorbidities, concomitant medications, and baseline renal function, albumin, and NT-proBNP levels, the 15 mg/day dose was associated with significantly higher risks of all-cause and cardiovascular death. These findings suggest that 7.5 mg/day tolvaptan provides comparable symptomatic improvement in very elderly heart failure patients while offering better outcomes for endpoint events.

Heart failure (HF) represents a leading cause of morbidity and mortality among elderly patients, with the total number of HF patients continuing to rise due to population growth and aging [1]. Controlling volume overload is paramount in HF management. Tolvaptan, a selective vasopressin-2 receptor antagonist and novel diuretic, increases urine output, reduces volume load, elevates serum sodium levels, alleviates dyspnea, and improves symptoms in patients with acute and chronic congestive HF. Early inpatient use of tolvaptan can shorten hospital stays, while continued outpatient use extends time to readmission, demonstrating efficacy in both elderly and younger patients, though its impact on all-cause mortality remains controversial [2-4]. The 2018 Chinese Expert Consensus on Volume Management in Heart Failure recommends a tolvaptan dose of 7.5–15 mg/day [5]. Some reports suggest that long-term use of $ $7.5 mg/day tolvaptan in elderly HF patients can reduce HF readmission rates [6]. However, the differential effects of 7.5 mg/day versus 15 mg/day tolvaptan on all-cause and cardiovascular outcomes in elderly HF patients remain unclear. Therefore, this study aimed to investigate the relationship between these two tolvaptan doses and the risks of all-cause and cardiovascular mortality in very elderly HF patients.

Methods

Study Design

This retrospective cohort study examined the effects of 7.5 mg/day versus 15 mg/day tolvaptan on endpoint events in very elderly patients with chronic heart failure. The study adhered to the principles of the Helsinki Declaration and was approved by the hospital ethics committee (2022 Research Ethics Review No. 29), with a waiver of informed consent.

Patient Population

The study population comprised very elderly chronic heart failure patients treated in the health care ward of the 960th Hospital of the People' s Liberation Army between February 2016 and February 2022 who received tolvaptan.

Data Collection

Inclusion and Exclusion Criteria **Inclusion criteria:** (1) Patients hospitalized in the health care department of the 960th Hospital between February 1, 2016, and February 28, 2022, with a primary diagnosis of chronic heart failure according to ICD-10 code I50, including discharge or outpatient diagnoses of heart failure, cardiac insufficiency, or NYHA functional class II-IV; (2) age $ $80 years; (3) cumulative tolvaptan use $ $7 days per hospitalization and $ $2 hospitalizations (tolvaptan duration was the sum of multiple courses); and (4) complete endpoint event records available through February 1, 2022.

Exclusion criteria: (1) History of malignant tumors; and (2) tolvaptan use <7 days with only one hospitalization.

Baseline Data Collection and Definitions Clinical data were extracted from the electronic medical record system, including sex, age, comorbidities, concomitant medications, serum BUN and creatinine before and after treatment, eGFR (calculated using the Cockcroft-Gault formula) [7], NT-proBNP, troponin I (cTnI), serum sodium, and potassium. Chronic HF diagnosis followed the 2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure [8], requiring HF symptoms and/or signs with BNP >35 ng/L and/or NT-proBNP >125 ng/L plus at least one of: (1) left ventricular hypertrophy and/or left atrial enlargement, or (2) abnormal cardiac diastolic function. Hypertension, diabetes, and chronic kidney disease were identified from admission or discharge diagnoses in the electronic record system. Concomitant medications included nitrates, antiplatelet agents, β-blockers, renin-angiotensin system (RAS) inhibitors, calcium channel blockers, and diuretics (oral furosemide or hydrochlorothiazide, intravenous furosemide or torsemide), recorded at tolvaptan initiation. Laboratory values were collected within one week before and seven

days after tolvaptan initiation. Echocardiographic results obtained within three months before drug initiation were recorded, with the most recent result used if multiple studies were available.

Follow-up and Endpoint Determination Follow-up began at the time of first tolvaptan administration during hospitalization between February 1, 2016, and February 28, 2022, and ended at the time of tolvaptan discontinuation. For patients with multiple hospitalizations, tolvaptan duration was calculated as the cumulative sum. The follow-up endpoint for all-cause and cardiovascular mortality was the occurrence of death or the end of the follow-up period (February 28, 2022). Endpoint events were ascertained through annual hospitalization records or by contacting nursing home physicians. Data were independently extracted by two trained clinicians, with key information regarding tolvaptan duration and endpoints verified through duplicate review.

Primary endpoint: All-cause mortality during follow-up. **Secondary endpoint:** Cardiovascular death, defined as death from ischemic heart disease, sudden cardiac death, myocardial infarction, heart failure, valvular disease, arrhythmia, ischemic stroke, or peripheral vascular disease.

Efficacy assessment: 24-hour urine volume before and after tolvaptan administration, and NT-proBNP and cTnI levels reassessed at 7 days. Objective measures were used because >40% of these very elderly patients could not accurately report symptom improvement.

Safety assessment: Changes in hepatic and renal function and electrolytes after tolvaptan administration, including liver and kidney function tests and electrolytes at 7 days. If 7-day liver function data were unavailable, results within one month were included [9].

Statistical Analysis

Statistical analysis was performed using FengRui Statistical Software version 1.5. Normally distributed continuous variables are presented as mean ± standard deviation and compared using t-tests; non-normally distributed variables are expressed as median (P25, P75) and compared using nonparametric tests. Missing data were handled according to variable type and missingness mechanism. For normally distributed continuous variables like body weight, stratified mean imputation was used (by sex). For skewed continuous variables such as cTnI, NT-proBNP, and liver function parameters, median imputation was applied. Changes in laboratory parameters from baseline to after treatment were compared using paired t-tests. Categorical variables are expressed as frequencies and percentages and compared using ^{2} tests. Kaplan-Meier survival curves were used to compare endpoint events between the two tolvaptan dose groups. Multivariate Cox proportional hazards regression models were constructed with tolvaptan dose as the independent variable and all-cause or cardiovascular death as dependent variables, adjusting for age, NYHA functional class, chronic kidney

disease, diabetes, hypertension, coronary artery disease, diuretic use, albumin, NT-proBNP, and eGFR. Subgroup analyses were performed by eGFR, age, albumin, and NT-proBNP levels, with HRs (95% CIs) calculated for each stratum. A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

No significant differences were observed between groups in sex, age, weight, NYHA class, LVEF, left ventricular posterior wall thickness, left atrial diameter, comorbidities (coronary artery disease, hypertension, diabetes, chronic kidney disease), or concomitant medications (nitrates, antiplatelet agents, β-blockers, RAS inhibitors, calcium channel blockers, trimetazidine, oral and intravenous diuretics) (all $P > 0.05$). The median tolvaptan treatment duration was 99 days, with 77.8% of patients receiving treatment for >30 days. The median follow-up duration was 374.5 days, with no significant difference between groups ($P > 0.05$). However, 24-hour urine volume before treatment was significantly lower in the 15 mg/day group compared to the 7.5 mg/day group ($P < 0.05$) .

Changes in Renal Function, NT-proBNP, and Electrolytes

No significant differences were observed between groups at baseline in BUN, creatinine, eGFR, NT-proBNP, cTnI, serum sodium, or potassium levels (all $P > 0.05$), though baseline 24-hour urine volume was lower in the 15 mg/day group ($P < 0.05$). After 7 days of tolvaptan treatment, both groups showed significant increases in 24-hour urine volume and serum sodium ($P < 0.001$). The 15 mg/day group exhibited significantly higher BUN and creatinine at 7 days compared to the 7.5 mg/day group ($P < 0.01$). Potassium levels remained unchanged in both groups. NT-proBNP levels decreased after treatment, though the difference was not statistically significant ($P > 0.05$). No significant changes were observed in eGFR, cTnI, ALT, AST, γ-GT, or bilirubin levels in either group .

Mortality Outcomes

During a median follow-up of 375 days (IQR: 155.5–940.5) and median tolvaptan treatment duration of 99 days (IQR: 39.5–321.8), 124 all-cause deaths occurred (58.5%), including 59 (52.7%) in the 7.5 mg/day group and 65 (65%) in the 15 mg/day group. All-cause mortality was significantly higher in the 15 mg/day group ($P = 0.0043$) [Figure 1: see original paper]A. Cardiovascular death occurred in 54 patients (25.5%), with 33 (33%) in the 15 mg/day group versus 21 (18.8%) in the 7.5 mg/day group ($P = 0.0012$) [Figure 1: see original paper]B.

Cox Proportional Hazards Regression Analysis

After adjusting for age, NYHA functional class, chronic kidney disease, diabetes, hypertension, coronary artery disease, diuretic use, albumin, NT-proBNP, and eGFR, multivariate Cox regression revealed that the 15 mg/day group had a 2.04-fold higher risk of all-cause mortality compared with the 7.5 mg/day group (HR = 2.04, 95% CI: 1.38–3.01). BUN and creatinine were collinear with eGFR, so only eGFR was included in the model. CKD diagnosis was based on discharge records rather than eGFR criteria, thus both were included. Compared with NYHA class II, class IV was associated with a 2.15-fold increased all-cause mortality risk (HR = 2.15, 95% CI: 1.21–3.83). β-blocker and RAS inhibitor use were protective factors, while concomitant oral furosemide use increased all-cause mortality risk by 1.27-fold (HR = 2.27, 95% CI: 1.08–4.76). Higher albumin levels were associated with reduced all-cause mortality risk .

Cox regression models demonstrated that after adjusting for age (Model 1), the 15 mg/day group had 0.73-fold and 1.5-fold increased risks of all-cause and cardiovascular death, respectively (HR = 1.73, 95% CI: 1.19–2.5; HR = 2.5, 95% CI: 1.41–4.45). Model 2 additionally adjusted for hypertension, coronary artery disease, NYHA class, chronic kidney disease, and diabetes, yielding HRs of 1.76 and 2.75 for all-cause and cardiovascular mortality. Model 3 further adjusted for eGFR, albumin, NT-proBNP, and oral diuretic use, showing that the 15 mg/day group had 1.03-fold and 1.51-fold increased risks of all-cause and cardiovascular death (HR = 2.03, 95% CI: 1.34–2.99; HR = 2.51, 95% CI: 1.40–4.5) .

Subgroup and Interaction Analyses

Given the cohort' s mean age of 91 years and the protective effect of higher albumin levels identified in multivariate analysis, we performed stratified analyses using albumin <35 g/L (a predictor of adverse HF outcomes) [10], NT-proBNP \$ $1800 pg/mL (the diagnostic threshold for acute decompensated HF in patients > 75 years)$[8], $and eGFR cutoffs of 30 and 45 mL/min/1.73 m^{2}$\$ (below which HF prognosis worsens and safety risks increase) [11]. The increased mortality risk with 15 mg/day tolvaptan persisted across all age and albumin strata (P < 0.05) and remained consistent across eGFR and NT-proBNP strata, with statistically significant differences observed in the eGFR <30 mL/min/1.73 m^2 subgroup (P < 0.05). No significant interactions were found between tolvaptan dose and eGFR, albumin, age, or NT-proBNP for either all-cause or cardiovascular mortality [Figure 2: see original paper].

Discussion

Heart failure is a clinical syndrome caused by cardiac structural and/or functional abnormalities. With population aging and advances in cardiovascular care

prolonging survival in patients with coronary artery disease and hypertension, HF prevalence in China continues to rise [12]. The China-HF registry reported an in-hospital mortality rate of 4.1% [13], yet the 5-year mortality rate remains >50%, with even higher risks in very elderly patients. Diuretics are essential in standard HF therapy for patients with fluid retention. Tolvaptan, a novel oral diuretic, selectively binds to vasopressin V2 receptors in the collecting duct, causing aquaporin-2 internalization and blocking water reabsorption, thereby increasing free water excretion and reducing cardiac preload and myocardial oxygen consumption [14].

The EVEREST [15], TACTICS-HF [16], and SECRET [17] trials demonstrated that tolvaptan effectively reduces volume overload and corrects hyponatremia in acute HF, though its impact on long-term mortality remains controversial [18]. A chronic HF study found that long-term tolvaptan use improved hospitalization-free survival and reduced cardiovascular death or HF readmission [19]. Post-hoc analysis of the SMILE study also showed favorable clinical effects and safety with long-term tolvaptan use, with significantly lower all-cause mortality in responders (those with increased serum sodium and 24-hour urine output) [20]. Notably, 43.6% of SMILE participants received tolvaptan for >2 weeks and 48.6% were >80 years old, suggesting benefit from long-term use in some very elderly patients. The divergent mortality effects across studies may relate to dosing, as TACTICS-HF and SECRET primarily used 30 mg/day—substantially higher than the 7.5–15 mg/day used in SMILE [21].

Our study included 212 very elderly HF patients with a median follow-up of 375 days to examine the prognostic impact of 7.5 mg/day versus 15 mg/day tolvaptan. Key findings include: (1) Both groups had a mean age of 91 years with comparable baseline characteristics, though the 15 mg/day group had lower baseline 24-hour urine volume, likely influencing clinicians to prescribe higher doses in patients with inadequate response to loop diuretics. Nearly 50% of patients were receiving oral or intravenous diuretics before tolvaptan initiation. The median treatment duration was 99 days, with 165 patients (77.8%) receiving tolvaptan for $ 30*daysandonly*9.4^{2}$, the 15 mg/day dose conferred significantly higher mortality risk, indicating that 7.5 mg/day should be preferred in very elderly HF patients with stage 4–5 CKD.

Multivariate analysis identified β-blocker and RAS inhibitor use as protective factors, while NT-proBNP elevation predicted worse outcomes. Although the HR of 1.26 (95% CI: 0.83–1.92) for NT-proBNP was not statistically significant, likely due to sample size, the trend was consistent with established prognostic value. Albumin influences loop diuretic efficacy and HF prognosis [10]; our study confirmed higher albumin as a protective factor without significant interaction with tolvaptan dose. In patients with NT-proBNP $ 1800*pg/mL, the*15*mg/daydosewasassociatedwithsignificantlyhighermortality, likelyreflectingmoresevere* mg) and increased low-dose use (<40 mg), as high-dose loop diuretic combination therapy increases adverse events [21, 22]. Our finding that concomitant

furosemide use increased all-cause mortality risk 2.27-fold (95% CI: 1.08–4.76) suggests that lower loop diuretic doses should be used when combining with tolvaptan in very elderly patients.

Limitations: This retrospective study relied on electronic medical records, potentially missing some confounders. Additionally, sacubitril-valsartan and SGLT2 inhibitors, which have demonstrated efficacy in HF management, were not captured as they were not widely used during the study period (2016–2022). Finally, these results apply specifically to very elderly HF patients and require validation in other age groups.

Conclusion: This study demonstrates that tolvaptan 15 mg/day significantly increases all-cause and cardiovascular mortality risk compared with 7.5 mg/day in very elderly HF patients. The 7.5 mg/day dose effectively improves volume overload with better safety and lower mortality risk, supporting its use as the preferred starting dose in this population. Future studies should expand the sample size and include a non-tolvaptan control group to further clarify its prognostic impact.

Author Contributions

Gao Yan and Liu Kewei conceived the study and designed the protocol. Liang Kun and Luan Mingya implemented the study. Luan Mingya, Zhang Jianxin, Xu Ning, and Liu Nana collected data. Zhang Xiaoping and Shang Gechu organized data and performed statistical analysis. Gao Yan analyzed results and drafted the manuscript. Liu Kewei revised the manuscript, provided quality control, and supervised the project.

Conflict of Interest

The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.