


Outcomes of diuretics in rheumatic heart disease with compensated chronic heart failure: a retrospective study

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Abstract

Aims The purpose of this retrospective propensity score-matched study was to evaluate the superiority of different application approaches [continuous diuretics use (CDU) vs. intermittent diuretics use (IDU)] and types [loop diuretics (LDs) vs. thiazide diuretics (TDs)] of diuretics on long-term outcomes for rheumatic heart disease (RHD) patients with compensated chronic heart failure (CHF).

Methods and results A total of 494 RHD patients with compensated CHF were analysed after propensity score matching. Cox proportional hazards regression model was used to investigate the associations of different diuretic application approaches and types with all-cause mortality, cardiovascular death (CVD), and cerebrovascular death. Binary logistic regression analyses were used to evaluate the associations of different diuretic application approaches and types with 1-, 3-, and 5-year heart failure (HF) re-hospitalization as well as new-onset atrial fibrillation (AF). In the comparison between IDU and CDU strategies for RHD patients with compensated CHF, CDU was associated with increased risks of all-cause mortality [adjusted hazard ratio (HR) = 2.47, 95% confidence interval (CI): 1.54–3.97, $P < 0.001$] and CVD (adjusted HR = 3.67, 95% CI: 1.95–6.89, $P < 0.001$) except cerebrovascular death (adjusted HR = 1.07, 95% CI: 0.34–3.41, $P = 0.905$). CDU was also associated with increased risks of 3-year [adjusted odds ratio (OR) = 1.80, 95% CI: 1.09–2.96, $P = 0.022$] and 5-year (adjusted OR = 2.02, 95% CI: 1.18–3.45, $P = 0.010$) HF re-hospitalization risk and new-onset AF (adjusted OR = 2.34, 95% CI: 1.31–4.20, $P = 0.004$) except 1-year HF re-hospitalization risk (adjusted OR = 1.54, 95% CI: 0.88–2.70, $P = 0.130$). In the comparison between TDs and LDs among study participants receiving IDU strategy, LDs were only associated with decreased 1-year HF re-hospitalization risk (adjusted OR = 0.30, 95% CI: 0.12–0.77, $P = 0.012$) rather than all-cause mortality, CVD, cerebrovascular death, 3- and 5-year HF re-hospitalization, and new-onset AF (all adjusted $P > 0.05$). In the comparison between TDs and LDs among study participants receiving CDU strategy, LDs were not associated with cerebrovascular death and 1-year HF re-hospitalization (both adjusted $P > 0.05$) but with increased risks of all-cause mortality (adjusted HR = 1.80, 95% CI: 1.09–2.99, $P = 0.023$), CVD (adjusted HR = 1.89, 95% CI: 1.04–3.44, $P = 0.037$), 3-year (adjusted OR = 1.91, 95% CI: 1.06–3.43, $P = 0.031$) and 5-year (adjusted OR = 2.16, 95% CI: 1.12–4.19, $P = 0.022$) HF re-hospitalization, and new-onset AF (adjusted OR = 2.66, 95% CI: 1.25–5.68, $P = 0.012$).

Conclusions Continuous diuretics use (especially LDs) was associated with increased risks of all-cause mortality, CVD, medium-term/long-term HF re-hospitalization, and new-onset AF in RHD patients with compensated CHF.

Keywords Rheumatic heart disease; Diuretic; Outcomes; Heart failure; Atrial fibrillation

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Introduction

Rheumatic heart disease (RHD) resulting from rheumatic fever is characterized by permanent heart valve damage associated with valvular stenosis and/or valvular insufficiency of mitral, tricuspid, and/or aortic valves. RHD is virtually eliminated in most developed regions, but the burden of morbidity and mortality still remains high in developing countries and under-developed regions and is still a major health problem in these countries and regions based on accumulating data on subclinical RHD.^{1,2} Chronic heart failure (CHF) is recognized as the leading cause of complication and re-hospitalization in RHD patients, especially with advanced RHD that may not be amenable to surgery. CHF can be 'compensated' or 'decompensated'. The classic clinical feature of RHD with decompensated CHF is congestion,³ which is defined as signs and symptoms of extracellular fluid accumulation that result from increased left and/or right cardiac filling pressures. Removal of excess fluid overload with diuretics is one of the mainstays in volume management of CHF (Class I recommendation).⁴ Diuretic therapy is generally continued indefinitely for fluid control in RHD patients with decompensated CHF unless cardiac function improves, but a significant proportion is still in state of persistent congestion (including subclinical hyperaemia) at the time of discharge or after discharge, associated with increased mortality.⁵ Basing on which, a long-standing perception has attributed a beneficial effect to continuous diuretics use (CDU) in the setting of CHF, even after congestion has been eliminated. However, few clinical trials have studied the impact of CDU on clinical outcomes in RHD patients with compensated CHF.

Conventional diuretics appear to reduce the risk of death and heart failure (HF) re-hospitalization in patients with CHF compared with placebo,⁶ although only small trials were available. However, observational data have raised safety concerns about CDU of CHF. Many cross-sectional studies have linked diuretic use to increased mortality,⁷ manifesting the characteristics in a dose-dependent manner.^{8–10} A small and exploratory study indicated that short-term HF medication (e.g. diuretics) omission among outpatients with stable HF and a left ventricular ejection fraction <45% led to increasing congestion but it was good for increasing blood pressure and improving renal function, suggesting that short-term discontinuation of diuretics may not cause HF progression.¹¹ Post hoc analysis of the HF-ACTION study showed that the initiation or discontinuation of diuretics was not associated with a difference in mortality, HF readmission, and exercise capacity in a 6-month timeframe.⁷ Two small prospective pilot studies showed that long-term maintenance of lower-dose diuretics for stable CHF patients was feasible and did not worsen the clinical situation.¹² Further, in a prospective,

randomized, and double-blind study on the safety and tolerability of withdrawing low-dose furosemide in stable HF outpatients in Brazil, Rohde *et al.*¹³ recently found that short-term diuretic withdrawal may be feasible in outpatients with compensated HF after receiving optimal medical therapy. These results suggested that the diuretics use in patients with CHF is dynamic and vary according to the state of congestion, which means that application approaches and dose of diuretics in CHF patients with euvolaemia should be adjusted as early as possible using a careful, de-escalation therapy [defined as intermittent diuretics use (IDU)] after achieving successful decongestion with diuretic therapy.⁵ The relationship between this strategy and outcome of CHF remains poorly defined.

Further, loop diuretics (LDs) are the cornerstone of decongestion therapy in decompensated HF; however, is this drug established as the best option? The majority of patients with CHF receive long-term treatment with LDs, but LDs not only had no significant superiority with respect to all-cause mortality and also increased the risk of death as mentioned earlier. On the other hand, thiazide diuretics (TDs) are not prescribed because of its weak diuretic effects, especially in the advanced stage of HF. Compared with long-acting TDs (e.g. chlorthalidone), short-acting TDs (e.g. hydrochlorothiazide) may be preferred in CHF patients with acute decompensation related to its better bioavailability, short half-life, and lower risk of electrolyte imbalance.¹⁴ In addition, a meta-analysis showed a significant beneficial effect on TD in decreasing the risk for HF in hypertension patients.¹⁵ These suggest that compensated CHF patients may benefit from using TDs for maintaining decongestion. Yet now there remains a lack of head-to-head comparison trials examining the effect of different diuretics (LDs vs. TDs) on long-term prognosis in patients with compensated CHF.

Current guidelines state diuretics as a treatment for the clinical signs and symptoms of congestion mainly based on non-valvular heart diseases. However, there is no evidence that it affects progression of RHD. RHD patients with CHF who are more symptomatic are likely to receive higher doses of diuretics and to receive LDs rather than TDs, and more symptomatic/congested patients have a worse prognosis.¹⁶ In fact, in RHD patients with compensated CHF, prescription of diuretics remains, to a large extent, subjective and evidence free,⁴ lacking of conclusive supporting data derived from large-scale, randomized studies with 'hard' clinical endpoints. It is not clear whether the de-escalation therapy can improve the prognosis of RHD. Here, we conducted a retrospective propensity score-matched study to examine the effects of diuretic application approaches (CDU vs. IDU) on long-term outcomes in RHD patients with compensated CHF as well as diuretics types (LDs vs. TDs).

Methods

Study participants

The retrospective propensity score-matched study was reviewed and approved by the Ethics Committee of Guangzhou First People's Hospital, South China University of Technology, Guangzhou, China (K-2018-136-1). RHD was diagnosed according to echocardiographic diagnostic criteria of the World Heart Federation.¹⁷ Patients were entered into the study from the date of first diagnosis of RHD with different types of valve damage (any location and condition). Patients' missing/invalid clinical data and any contraindication to use of diuretics were excluded from the study. All RHD patients with first hospitalization for HF were followed up since the date of the first post-discharge when euvolaemia has been achieved. Patient survival time was calculated from date of their first discharge for HF to date of death or last follow-up. The final follow-up date was 31 December 2018. Clinical data were collected from patient interviews, review of medical records, and contact with treating physicians. The CDU group was defined as the group that RHD patients with CHF had persistent prescription and administration of diuretics during compensated HF period. The IDU group was defined as the group that RHD patients with CHF were not prescribed any diuretics during compensated HF period. However, the types and modes (e.g. intravenous or oral) of diuretic administration were not limited when RHD patients were in acute decompensated HF during the follow-up, regardless of whether in the CDU or IDU group. RHD patients in the CDU group were divided into two subgroups according to the type of diuretic used: (i) the LDs subgroup, which represented the patients who only receive furosemide, and (ii) the TDs subgroup, which represented the patients who only receive hydrochlorothiazide. In addition, RHD patients with combination therapy of LDs and TDs were excluded from the study.

Rheumatic heart disease surgical treatment was defined as surgical or percutaneous intervention for valve repair or replacement of any affected valve(s) (e.g. mitral, aortic, and tricuspid) using tissue or mechanical prosthesis according to the updated guidelines during the follow-up. HF at baseline and during the study (recurrent HF) was diagnosed according to Framingham HF criteria. Atrial fibrillation (AF) was diagnosed according to prior history of AF or electrocardiographic findings at baseline plus follow-up examinations. Coexisting medical conditions (e.g. hypertension, coronary heart disease, type 2 diabetes mellitus, and stroke) were evaluated according to relevant guidelines (details guidelines information was presented in Methods section of supporting information). Cardiac standard chamber quantification was determined by echocardiography according to recommendations from the European Association of Echocardiography.¹⁸ Biochemical tests were performed using standard chemical lab methods.

Propensity score matching

Because the IDU group was much smaller than the CDU group, an imbalance in crucial covariates related to outcomes could have biased the estimation of the CDU effect. To adjust for other baseline factors, we performed a 1:2 propensity score matching (PSM) using R Statistical Software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). The propensity score was generated through logistic regression to predict the probability of effectiveness of CDU as a function of baseline factors as follows: age, sex, course, smoking, drinking, waiting time for surgery, cardiac valve damage, surgical intervention, New York Heart Association (NYHA) functional classification, medical condition (e.g. hypertension, coronary heart disease, type 2 diabetes mellitus, AF, and stroke), combined medication [e.g. antiplatelet drugs, warfarin, digoxin, nitrates, renin-angiotensin system inhibitors (RSIs), beta-receptor blockers (BBs), mineralocorticoid receptor antagonists (MRAs), calcium channel blockers, and statin], and level of partial blood biochemical index (e.g. white blood cell count, haemoglobin, alanine aminotransferase, creatinine, C-reactive protein, B-type natriuretic peptide, and serum potassium). The calliper width for PSM was 0.1. After PSM, a total of 494 RHD patients finally entered the study.

Long-term follow-up endpoints

Primary endpoints were all-cause mortality, cardiovascular death (CVD), and cerebrovascular death (details definition was presented in Methods section of supporting information). Secondary endpoints were the risks of HF re-hospitalization and new-onset AF. In particular, the cerebrovascular death was defined as death due to cerebral infarction or cerebral haemorrhage. HF re-hospitalization was defined as a hospital re-hospitalization (including at least one overnight admission to emergency) for which HF was the primary cause, requiring treatment with diuretics, intravenous inotropes, or nitrates. Three information sources were queried to identify primary and secondary endpoints: participants and their families, medical records, and the Center for Disease Control and Prevention.

Statistical analysis

All statistical analyses were performed using SPSS version 24 (SPSS, Chicago, IL), R Statistical Software version 3.6.1 (R Foundation for Statistical Computing), and PASS version 15 (Statistical Solution Ltd, Cork, Ireland). Categorical variables were presented as numbers and percentages. Continuous variables with non-normal variables were reported as median (interquartile range). Significant differences among categori-

cal variables were determined by χ^2 test or Fisher's test. Significant differences among continuous variables were analysed by Mann-Whitney *U* test, independent-sample *t*-test, or two-way ANOVA. Patient survival time was determined based on the clinical information. The Cox proportional hazards regression model for survival analysis was fit to estimate the crude hazard ratios (HRs), adjusted HRs, and their 95% confidence intervals (CIs) with adjustments for potential confounders. Binary logistic regression analysis was used to evaluate the odds ratio (OR) of HF re-hospitalization (1, 3, and 5 years) and new-onset AF. *P* values of less than 0.05 were considered as statistically significant. All probabilities are two-tailed estimated.

Results

Characteristics of study participants

Baseline clinical and echocardiographic characteristics of the study patients before PSM are listed in *Table S1*. More than half of study participants had a combination of valve damage (54.4%, predominantly mitral valve), NYHA functional Classes II–IV (87.2%), surgical treatment (54.2%), and AF (65.0%). After PSM, there was no significant difference between the CDU and IDU groups on baseline clinical characteristic (*Table 1*). A total of 494 RHD patients were included in the study with median follow-up of 5.1 years, a median age of 47 years, and 69.2% were female.

Effect of different diuretic application approaches (intermittent diuretics use vs. continuous diuretics use) on all-cause mortality, cardiovascular death, and cerebrovascular death

Compared with IDU, CDU was associated with increased risks of all-cause mortality (adjusted HR = 2.47, 95% CI: 1.54–3.97, *P* < 0.001) and CVD (adjusted HR = 3.67, 95% CI: 1.95–6.89, *P* < 0.001) in RHD patients with compensated CHF except cerebrovascular death (adjusted HR = 1.07, 95% CI: 0.34–3.41, *P* = 0.905), as shown in *Figure 1*.

Effects of different diuretic application approaches (intermittent diuretics use vs. continuous diuretics use) on the risks of heart failure re-hospitalization and new-onset atrial fibrillation

As shown in *Table 2*, CDU was associated with increased risk of 3-year (adjusted OR = 1.80, 95% CI: 1.09–2.96, *P* = 0.022) and 5-year (adjusted OR = 2.02, 95% CI: 1.18–3.45,

P = 0.010) HF re-hospitalization with exception of 1 year (adjusted OR = 1.54, 95% CI: 0.88–2.70, *P* = 0.130). CDU was also associated with increased new-onset AF risk (adjusted OR = 2.34, 95% CI: 1.31–4.20, *P* = 0.004).

Effects of different diuretic types (thiazide diuretics vs. loop diuretics) on the risks of all-cause mortality, cardiovascular death, and cerebrovascular death

As shown in *Table 3*, in the IDU group of RHD patients with compensated CHF, there was no significant difference between the LDs and TDs subgroups on all-cause mortality (adjusted HR = 0.31, 95% CI: 0.09–1.13, *P* = 0.076), CVD (adjusted HR = 0.16, 95% CI: 0.02–1.57, *P* = 0.116), and cerebrovascular death (adjusted HR = 0.22, 95% CI: 0.03–1.95, *P* = 0.175). But in the CDU group, LDs were associated with higher risk of all-cause mortality (adjusted HR = 1.80, 95% CI: 1.09–2.99, *P* = 0.023) and CVD (adjusted HR = 1.89, 95% CI: 1.04–3.44, *P* = 0.037) except cerebrovascular death (adjusted HR = 1.14, 95% CI: 0.16–8.02, *P* = 0.896).

Effects of different diuretic types (thiazide diuretics vs. loop diuretics) on the risks of heart failure re-hospitalization and new-onset atrial fibrillation

As shown in *Table 4*, in the IDU group of RHD patients with compensated CHF, LDs were only associated with lower risk of 1-year (adjusted OR = 0.30, 95% CI: 0.12–0.77, *P* = 0.012) HF re-hospitalization rather than the risks of 3-year (adjusted OR = 0.58, 95% CI: 0.25–1.33, *P* = 0.197) and 5-year (adjusted OR = 0.57, 95% CI: 0.23–1.44, *P* = 0.233) HF re-hospitalization and new-onset AF (adjusted OR = 1.56, 95% CI: 0.48–5.09, *P* = 0.466). In contrast, in the CDU group, LDs were associated with higher risk of 3-year (adjusted OR = 1.91, 95% CI: 1.06–3.43, *P* = 0.031) and 5-year (adjusted OR = 2.16, 95% CI: 1.12–4.19, *P* = 0.022) HF re-hospitalization and new-onset AF (adjusted OR = 2.66, 95% CI: 1.25–5.68, *P* = 0.012) except 1-year (adjusted OR = 1.24, 95% CI: 0.68–2.27, *P* = 0.481) HF re-hospitalization.

Discussion

Association of different diuretic application approaches with mortality, and heart failure re-hospitalization and new-onset atrial fibrillation

To the best of our knowledge, this is the only study relating diuretic application approaches to long-term clinical hard

Table 1 Baseline characteristics of study participants after propensity score matching

	IDU	CDU	P value
N	190	304	—
Male:female	59:131	93:211	0.914
Age of onset (years)	47.0 (37.0, 56.0)	47.0 (34.0, 59.0)	0.917
Age of surgery (years)	48.0 (41.0, 55.0)	48.0 (40.0, 55.0)	0.718
Follow-up (years)	5.2 (2.6, 8.1)	5.1 (2.7, 9.5)	0.224
Disease duration (years)	10.0 (5.0, 18.0)	11.5 (4.3, 20.0)	0.716
Smoking (%)	19 (10.0)	30 (9.9)	0.962
Drinking (%)	21 (11.1)	30 (9.9)	0.674
Types of diuretics (thiazine:loop)	61:129	122:182	0.072
Average daily dose of TD (mg)	25 (12.5, 25)	25 (25, 25)	0.085
Cumulative use time of TD (years)	1.7 (0.9, 2.9)	4.8 (1.8, 7.1)	<0.001
Average daily dose of LD (mg)	40 (20, 60)	40 (20, 60)	0.169
Cumulative use time of LD (years)	1.7 (1.2, 2.8)	5.1 (2.0, 8.5)	<0.001
SBP at initial diagnosis (mmHg)	120 (115, 128)	120 (114, 127)	0.402
DBP at initial diagnosis (mmHg)	75 (68, 80)	73 (67, 81)	0.509
Heart rate at initial diagnosis (b.p.m.)	80 (75, 91)	81 (76, 96)	0.462
Cardiac valve damage			
(A-I) MS			
No	56 (29.5)	81 (26.6)	0.494
Yes	134 (70.5)	223 (73.4)	
(A-II) MS degree			0.094
Mild	85 (63.4)	120 (53.8)	
Moderate	33 (24.6)	58 (26.0)	
Severe	16 (11.9)	45 (20.2)	
(B-I) MR			0.103
No	84 (44.2)	112 (36.8)	
Yes	106 (55.8)	192 (63.2)	
(B-II) MR degree			0.654
Mild	42 (39.6)	66 (34.4)	
Moderate	27 (25.5)	55 (28.6)	
Severe	37 (34.9)	71 (37.0)	
(C-I) AS			0.764
No	146 (76.8)	230 (75.7)	
Yes	44 (23.2)	74 (24.3)	
(C-II) AS degree			0.627
Mild	26 (59.1)	37 (50.0)	
Moderate	12 (27.3)	24 (32.4)	
Severe	6 (13.6)	13 (17.6)	
(D-I) AR			0.929
No	122 (64.2)	194 (63.8)	
Yes	68 (35.8)	110 (36.2)	
(D-II) AR degree			0.840
Mild	29 (42.6)	49 (44.5)	
Moderate	30 (44.1)	44 (40.0)	
Severe	9 (13.2)	17 (15.5)	
(E-I) TR			0.117
No	146 (76.8)	214 (70.4)	
Yes	44 (23.2)	90 (29.6)	
(E-II) TR degree			0.078
Mild	21 (47.7)	27 (30.0)	
Moderate	14 (31.8)	30 (33.3)	
Severe	9 (20.5)	33 (36.7)	
(F-I) PAH			0.080
No	64 (33.7)	80 (26.3)	
Yes	126 (66.3)	224 (73.7)	
(F-II) PAH degree			0.076
Mild	83 (65.9)	120 (53.6)	
Moderate	27 (21.4)	69 (30.8)	
Severe	16 (12.7)	35 (15.6)	
Cardiac valve damage (stenosis or regurgitation)			0.155
MV	76 (40.0)	128 (42.1)	
AV	4 (2.1)	8 (2.6)	
TV	1 (0.5)	2 (0.7)	
MV + AV	66 (34.7)	78 (25.7)	
MV + TV	31 (16.3)	50 (16.4)	
MV + AV + TV	12 (6.3)	38 (12.5)	

(Continues)

Table 1 (continued)

	IDU	CDU	P value
Surgical intervention			
(A) Valve replacement (tissue or mechanical prosthesis)			
MV	64 (66.0)	101 (68.2)	0.835
AV	3 (3.1)	7 (4.7)	
MV + AV	29 (29.9)	38 (25.7)	
MV + TV	1 (1.0)	2 (1.4)	
(B) Valve repair			
MV	9 (64.3)	10 (45.5)	0.468
TV	5 (35.7)	9 (40.9)	
AV	0 (0.0)	2 (9.1)	
MV + TV	0 (0.0)	1 (4.5)	
NYHA			
I	40 (21.1)	38 (12.5)	0.089
II	58 (30.5)	106 (34.9)	
III	72 (37.9)	124 (40.8)	
IV	20 (10.5)	36 (11.8)	
Medical condition			
HT	38 (20.0)	81 (26.6)	0.093
CHD	17 (8.9)	18 (5.9)	0.202
T2D	14 (7.4)	28 (9.2)	0.475
AF	79 (41.6)	118 (38.8)	0.542
Stroke	18 (9.5)	31 (10.2)	0.793
Combined medication			
Antiplatelet drugs	27 (14.2)	47 (15.5)	0.705
Warfarin	120 (63.2)	167 (54.9)	0.072
Digoxin	93 (48.9)	169 (55.6)	0.150
Nitrates	17 (8.9)	29 (9.5)	0.826
RSIs	78 (41.1)	130 (42.8)	0.708
BBs	69 (36.3)	105 (34.5)	0.688
MRAs	97 (51.1)	178 (58.6)	0.103
CCBs	19 (10.0)	33 (10.9)	0.763
Statins	25 (13.2)	24 (7.9)	0.057
Blood biochemical index			
WBC ($\times 10^9/L$)	6.94 (5.57, 9.26)	7.15 (5.58, 9.24)	0.598
HGB (g/L)	124.0 (113.0, 135.0)	121.0 (108.0, 134.0)	0.115
PLT ($\times 10^9/L$)	186.5 (139.5, 239.5)	182.0 (143.0, 234.5)	0.885
FBG (mmol/L)	4.98 (4.39, 5.98)	5.10 (4.30, 6.20)	0.849
ALT (U/L)	18.0 (12.0, 23.0)	18.0 (11.0, 28.0)	0.241
AST (U/L)	25.0 (20.0, 33.0)	23.0 (18.0, 34.7)	0.642
Cr ($\mu\text{mol/L}$)	77.5 (64.8, 94.0)	82.0 (68.0, 96.0)	0.234
CRP (mg/L)	3.7 (1.7, 10.7)	5.9 (2.0, 15.9)	0.144
ASO (U/mL)	50.3 (0.0, 101.7)	40.0 (0.0, 78.4)	0.445
RF (U/mL)	10.0 (0.0, 11.3)	9.2 (0.0, 11.3)	0.613
ESR (mm/h)	16.0 (9.0, 26.0)	20.0 (10.0, 34.0)	0.054
BNP (pg/mL)	218.3 (84.7, 914.9)	209.5 (56.2, 817.0)	0.322
TRIG (mmol/L)	1.07 (0.76, 1.40)	0.96 (0.70, 1.36)	0.169
TC (mmol/L)	4.30 (3.48, 5.05)	4.25 (3.46, 5.02)	0.671
HDL-C (mmol/L)	1.10 (0.90, 1.33)	1.09 (0.86, 1.35)	0.717
LDL-C (mmol/L)	2.37 (1.89, 2.97)	2.30 (1.81, 2.90)	0.411
Na ⁺ (mmol/L)	140.4 (137.5, 142.1)	139.3 (136.3, 142.1)	0.157
K ⁺ (mmol/L)	3.90 (3.65, 4.20)	4.00 (3.68, 4.22)	0.213
Echocardiography			
LVD (cm)	4.50 (4.15, 4.94)	4.57 (4.23, 4.99)	0.466
LAD (cm)	4.58 (3.97, 5.09)	4.69 (4.04, 5.09)	0.676
RVD (cm)	1.90 (1.43, 2.39)	2.00 (1.63, 2.42)	0.066
RAD (cm)	3.46 (3.22, 3.97)	3.40 (3.15, 3.96)	0.097
LVEF (%)	54.0 (48.0, 59.0)	53.0 (48.0, 58.0)	0.660

AF, atrial fibrillation; ALT, alanine aminotransferase; AR, aortic regurgitation; AS, aortic stenosis; ASO, antistreptolysin O; AST, aspartate aminotransferase; AV, aortic valve; BBs, beta-receptor blockers; BNP, B-type natriuretic peptide; CCBs, calcium channel blockers; CDU, continuous diuretics use; CHD, coronary heart disease; Cr, creatinine; CRP, C-reactive protein; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HGB, haemoglobin; HT, hypertension; IDU, intermittent diuretics use; K⁺, serum potassium; LAD, left atrial end-systolic diameter; LD, loop diuretic; LDL-C, low-density lipoprotein cholesterol; LVD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRAs, mineralocorticoid receptor antagonists; MS, mitral stenosis; MV, mitral valve; Na⁺, serum sodium; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PLT, platelet count; RAD, right atrial end-systolic diameter; RF, rheumatoid factor; RSIs, renin-angiotensin system inhibitors; RVD, right ventricular end-diastolic diameter; SBP, systolic blood pressure; T2D, type 2 diabetes mellitus; TC, total cholesterol; TD, thiazide diuretic; TR, tricuspid regurgitation; TRIG, triglyceride; TV, tricuspid valve; WBC, white blood cell count.

Figure 1 Effect of different diuretic application approaches (IDU vs. CDU) on all-cause mortality, cardiovascular death, and cerebrovascular death. Model 1: adjusting for baseline adjustment covariates, including age, gender, smoking, drinking, rheumatic heart disease course, New York Heart Association functional classification, cardiac valve damage, surgical intervention, medical condition (hypertension, coronary heart disease, type 2 diabetes mellitus, atrial fibrillation, and stroke), combined medication (antiplatelet drugs, warfarin, digoxin, nitrates, renin-angiotensin system inhibitors, beta-receptor blockers, mineralocorticoid receptor antagonists, calcium channel blockers, and statins), types of diuretics, cumulative use time, blood biochemical index (white blood cell count, haemoglobin, serum sodium, serum potassium, creatinine, haemoglobin A1C, and C-reactive protein), and echocardiography (left atrial end-systolic diameter, left ventricular end-diastolic diameter, right ventricular end-diastolic diameter, and right atrial end-systolic diameter). CI, confidence interval; CDU, continuous diuretics use; HR, hazard ratio; IDU, intermittent diuretics use.

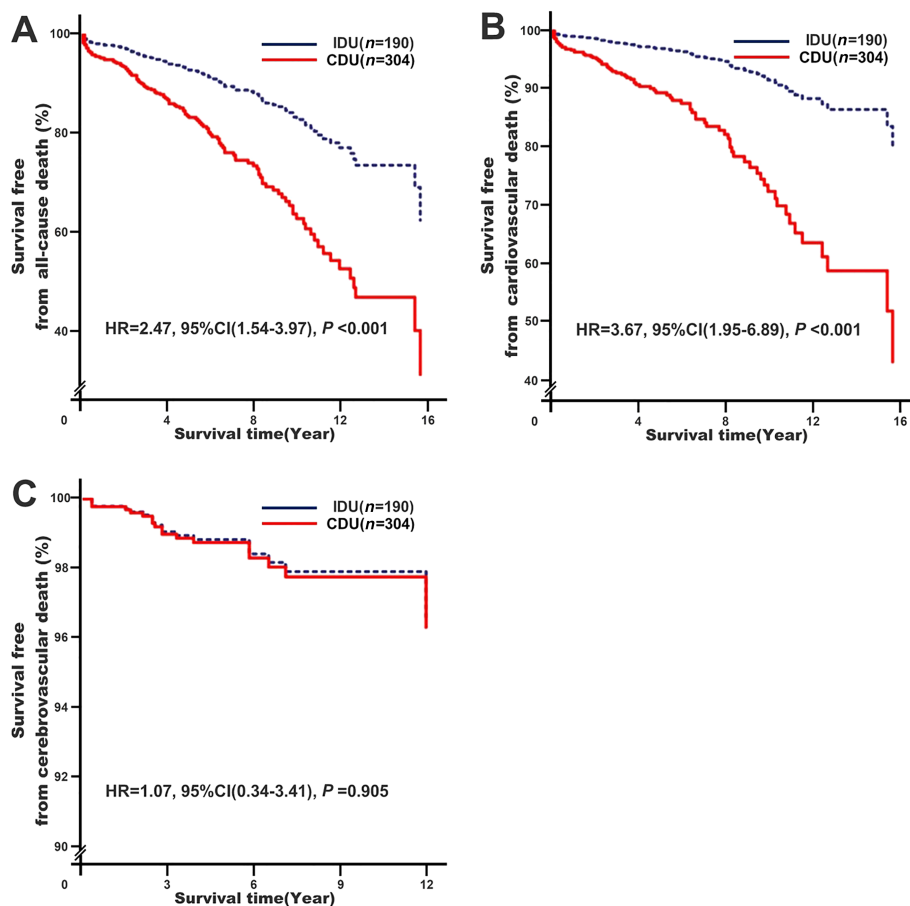


Table 2 Effects of different diuretic application approaches (intermittent diuretics use vs. continuous diuretics use) on the risks of heart failure re-hospitalization^a and new-onset atrial fibrillation^b in rheumatic heart disease patients

Clinical outcomes		IDU (ref., N/%)	CDU (N/%)	Crude OR (95% CI)	Crude P value	Adjusted OR (95% CI)	Adjusted P value
1-year HF re-hospitalization	No	154 (84.2)	212 (73.9)	1.88 (1.17–3.02)	0.009	1.54 (0.88–2.70)	0.130 ^a
	Yes	29 (15.8)	75 (26.1)				
3-year HF re-hospitalization	No	104 (68.4)	132 (52.6)	1.95 (1.28–2.98)	0.002	1.80 (1.09–2.96)	0.022 ^a
	Yes	48 (31.6)	119 (47.4)				
5-year HF re-hospitalization	No	69 (53.9)	77 (33.3)	2.33 (1.50–3.64)	<0.001	2.02 (1.18–3.45)	0.010 ^a
	Yes	59 (46.1)	154 (66.7)				
New-onset AF	No	80 (73.0)	90 (48.4)	2.88 (1.73–4.79)	<0.001	2.34 (1.31–4.20)	0.004 ^b
	Yes	30 (27.0)	96 (51.6)				

AF, atrial fibrillation; CDU, continuous diuretics use; CI, confidence interval; HF, heart failure; IDU, intermittent diuretics use; OR, odds ratio.

^aModel 2: it is the same as Model 1, and also including new-onset AF.

^bModel 3: it is the same as Model 2 with exception of those covariates, including new-onset AF, left ventricular end-diastolic diameter, right ventricular end-diastolic diameter, and right atrial end-systolic diameter.

Table 3 Effects of different diuretic types (thiazide diuretics vs. loop diuretics) on the risks of all-cause mortality, cardiovascular death, and cerebrovascular death in rheumatic heart disease patients with different diuretic application approaches (intermittent diuretics use or continuous diuretics use)^a

Clinical outcomes	Effect size for a change of	IDU		CDU	
		Effect size (95% CI)	<i>P</i> value	Effect size (95% CI)	<i>P</i> value
All-cause mortality	TDs (ref.) vs. LDs	0.31 (0.09–1.13)	0.076	1.80 (1.09–2.99)	0.023
CVD	TDs (ref.) vs. LDs	0.16 (0.02–1.57)	0.116	1.89 (1.04–3.44)	0.037
Cerebrovascular death	TDs (ref.) vs. LDs	0.22 (0.03–1.95)	0.175	1.14 (0.16–8.02)	0.896

CDU, continuous diuretics use; CI, confidence interval; CVD, cardiovascular death; IDU, intermittent diuretics use; LDs, loop diuretics; TDs, thiazide diuretics.

^aModel 4: it is the same as Model 1 with exception of types of diuretics.

Table 4 Effects of different diuretic types (thiazide diuretics vs. loop diuretics) on the risks of heart failure re-hospitalization^a and new-onset atrial fibrillation^b in rheumatic heart disease patients with different diuretic application approaches (intermittent diuretics use or continuous diuretics use)

Group	Clinical outcomes	TDs (ref., N/%)	LDs (N/%)	Crude OR (95% CI)	Crude <i>P</i> value	Adjusted OR (95% CI)	Adjusted <i>P</i> value	
IDU	1-year HF re-hospitalization	No	44 (75.9)	110 (88.0)	0.43 (0.19–0.96)	0.040	0.30 (0.12–0.77)	0.012 ^a
		Yes	14 (24.1)	15 (12.0)				
	3-year HF re-hospitalization	No	31 (62.0)	73 (71.6)	0.65 (0.32–1.33)	0.235	0.58 (0.25–1.33)	0.197 ^a
		Yes	19 (38.0)	29 (28.4)				
	5-year HF re-hospitalization	No	18 (46.2)	51 (57.3)	0.64 (0.30–1.36)	0.246	0.57 (0.23–1.44)	0.233 ^a
		Yes	21 (53.8)	38 (42.7)				
	New-onset AF	No	23 (79.3)	58 (70.7)	1.59 (0.57–4.38)	0.374	1.56 (0.48–5.09)	0.466 ^b
		Yes	6 (20.7)	24 (29.3)				
CDU	1-year HF re-hospitalization	No	86 (78.2)	126 (71.2)	1.45 (0.83–2.53)	0.191	1.24 (0.68–2.27)	0.481 ^a
		Yes	24 (21.8)	51 (28.8)				
	3-year HF re-hospitalization	No	52 (59.1)	80 (49.1)	1.50 (0.89–2.53)	0.130	1.91 (1.06–3.43)	0.031 ^a
		Yes	36 (40.9)	83 (50.9)				
	5-year HF re-hospitalization	No	34 (43.0)	43 (28.3)	1.92 (1.09–3.38)	0.025	2.16 (1.12–4.19)	0.022 ^a
		Yes	45 (57.0)	109 (71.7)				
	New-onset AF	No	50 (62.5)	40 (37.7)	2.75 (1.51–5.01)	0.001	2.66 (1.25–5.68)	0.012 ^b
		Yes	30 (37.5)	66 (62.3)				

AF, atrial fibrillation; CDU, continuous diuretics use; CI, confidence interval; HF, heart failure; IDU, intermittent diuretics use; LDs, loop diuretics; OR, odds ratio; TDs, thiazide diuretics.

^aModel 5: it is the same as Model 2 with exception of types of diuretics.

^bModel 6: it is the same as Model 3 with exception of types of diuretics.

outcomes in RHD patients with real and complex valve damage during compensated HF period. In this study, the difference between the two diuretic application approaches (IDU vs. CDU) was whether or not to receive diuretics treatment among RHD patients with CHF during their compensated HF period. The daily routine dose of diuretics was not different between the two treatment options, but the cumulative use time in patients with CDU was about three times higher than that with IDU, which was associated with worse prognosis. Similar results were found as follows: Ahmed *et al.*¹⁹ reported that diuretics use increased all-cause mortality and CVD by 36–51% while the risks reported by Hamaguchi *et al.*²⁰ are even higher, up to 50–72%. Interestingly, we also found that CDU had no effect on short-term (within 1 year) HF re-hospitalization risk but was significantly associated with increased risk of the medium-term/long-term (over 3 years) HF re-hospitalization (approximately increased by at least 80%) and had tendency to longer diuretics use time and higher HF re-hospitalization risk. This was consistent with the

observation by Domanski *et al.*,²¹ who reported that diuretics use increased HF readmission risk by 31–66% in post hoc analysis of SOLVD and DIG study. Recent studies by Miura *et al.*²² and Damman *et al.*²³ confirmed that diuretics use increased the compound endpoint (e.g. all-cause mortality, CVD, and HF re-hospitalization) by 28–63%. In addition, Schartum-Hansen *et al.*²⁴ found that the use of diuretics in suspected coronary artery disease patients without systolic HF was associated with increased risk of all-cause mortality. These results suggest that diuretic strategy of CDU should be discouraged when RHD patients are under decongested status.²⁵ In contrast, Grinstead *et al.*²⁶ found that the probability of remaining off diuretics at 6 weeks was 71% in a 12-week clinical trial of 41 patients with stable HF. Damman *et al.*²³ insightfully evaluated the feasibility for trials randomizing euvoalaemic patients with CHF to withdrawal or dose reduction of diuretics. It was shown that lower dose of diuretics (compared with continuous use or use of higher doses of diuretics) was associated with lower risk of CVD and

HF readmission. Similar benefits on diuretic reduction were observed in patients with cardiac resynchronization therapy.²⁷ Studies have shown that the adverse effect of persistent diuretic use was associated with age, haemoglobin concentration, worsening renal function, imbalance of serum electrolytes (e.g. hypokalaemia, hyponatraemia, and hypomagnesaemia), and thiamine deficiency^{12,16,19,28,29} and contributed to increased sympathetic tone³⁰ and renin-angiotensin-aldosterone system activation,³¹ which is the potential mechanism for a poor prognosis triggered by long-term CDU. It is well established that diuretics activate the sympathetic nervous system and the renin-angiotensin-aldosterone system in HF. This occurs as a response to diuretic treatment rather than as a result of the disease process itself,⁷ manifesting the characteristics of a dose-dependent manner.²⁸ Higher dose of diuretics use leads to a higher risk of cardiovascular events,¹⁶ even after triple blockade with RSIs, BBs, and MRAs.²² On the contrary, the activation of renin-angiotensin-aldosterone system (e.g. plasma renin levels) decreases with diuretic reduction.³²

In this study, our result also showed that CDU was associated with increased new-onset AF risk in RHD patients with compensated CHF (approximately increased by 1.34-fold), which was similar to the observation by Jong *et al.*,³³ who reported that diuretics use increased non-valvular AF risk by 39%, and an observation showed increased mortality in hypertensive patients with AF treated with diuretics.²⁴ This may explain that diuretics increase the risk of HF and mortality at least partially. The underlying mechanism may be related to persistent left atrial structural and electrical remodelling.³⁴ As expected, the size of left atrial end-systolic diameter was enlarged more obviously in those RHD patients with CDU (Supporting Information, *Table S2*). In addition, diuretic-induced hypokalaemia and hypomagnesaemia were also linked to the risk of AF, especially in the presence of severe myocardial fibrosis and digoxin use.²⁸

Valvular AF (especially caused by RHD) is associated with increased risk of stroke, which is the leading cause of cerebrovascular death. However, there are limited prospective data to assess the effect of diuretic use on risk of cerebrovascular death from RHD. In this study, we also found that there was no significant difference on cerebrovascular death risk between IDU and CDU in RHD patients with compensated CHF. This was inconsistent with previously reported association of diuretic use with hypertension-related cerebrovascular death. In the HYVET and SHEP study, diuretics (e.g. indapamide and chlorthalidone) caused a 30–36% reduction in the incidence of stroke while in the PROGRESS study, the stroke risk was lowered by 43% in combination with diuretics (e.g. indapamide) on the basis of RSIs (e.g. perindopril) treatment.^{35,36} This difference might result from hypertension and RHD-related cerebrovascular death, which are mainly caused by stroke. The former is more common in large-artery atherosclerosis stroke and small-artery occlusion

lacunar stroke. The latter, however, is mostly attributed to cardioembolism.³⁷ RHD-related cardioembolism is associated with left atrial enlargement, which is an independent predictor of stroke even after adjustment by types of AF (paroxysmal or sustained) and valvular heart diseases.³⁸ Furthermore, our study showed that both IDU and CDU did not reverse left atrial remodelling but made it more serious (Supporting Information, *Tables S2* and *S3*). The explanation of the effect could be partly attributed to this observation.

Effect of diuretic types on mortality, and heart failure re-hospitalization and new-onset atrial fibrillation

Rheumatic heart disease patients in the IDU group were not prescribed any diuretics during non-congestion but still received LDs or TDs when acute decompensated HF occur, which was no difference on the treatment for RHD patients with acute decompensated HF in the CDU group. In this study, we found that there was no significant difference on all-cause mortality, CVD, cerebrovascular death, medium-term/long-term HF readmission, and new-onset AF in RHD patients with acute decompensated HF between the LDs and TDs subgroups (*Table 3*). These results suggested that the prognosis is related to diuretics use for eliminating congestion and has nothing to do with the choice of diuretic types. Our findings were similar to the observation by Trullas *et al.*³⁹ on different types of TDs on patients with acute compensated HF. Multicentre PSM analysis of different LDs use (e.g. bumetanide, furosemide, and torasemide) on mortality in CHF patients showed that mortality was not affected by the choice of individual LDs⁴⁰ as well as the mode of administration (oral vs. subcutaneous injection).⁴¹ However, LDs treatment decreased the short-term (within 1 year) HF readmission by 70% compared with TDs treatment (*Table 4*). This was consistent with a recent observation by Brisco-Bacik *et al.*,²⁹ who reported that LDs rather than early introduction of TDs (e.g. metolazone) may be the preferred strategy in clinical practice for acute decompensated HF. Compared with short-acting LDs (e.g. furosemide), the long-acting LDs (e.g. azosemide) significantly reduced CVD risk,³⁰ but there was no significant difference in HF-associated arrhythmias between these two diuretics.⁴² In the TORIC study, torasemide rather than furosemide was reported to improve NYHA functional classification,⁴³ and the effect of torasemide on improving the prognosis, however, depends on the upcoming results of the TRANSFORM-HF study (a large-scale, pragmatic, randomized, unblinded clinical effectiveness study comparing torasemide vs. furosemide as treatment for HF on clinical outcomes over 12 months, NCT03296813).

Importantly, not all RHD patients with CHF can maintain decongested status without diuretics. When diuretics have to be continuously used for maintaining optimal

individualized decongestion, the choice of diuretics types (LDs vs. TDs) is still a dilemma. Compared with TDs, LDs were more likely to be prescribed to maintain euvolaemia due to clinical biases, and higher dose of LDs was generally prescribed for severe or advanced RHD patients with CHF. The difference, however, in efficacy of long-term use of LDs and TDs on clinical outcomes in RHD patients with CHF remains unclear. In this study, we are the first to report that continuous LDs use was associated with increased risks of all-cause mortality (by 80%), CVD (by 89%), medium-term/long-term HF readmission (by at least 91%), and new-onset AF (by 1.66-fold) compared with continuous TDs use. This is consistent with the meta-analysis results obtained by Tager *et al.*, who reported that there was no significant superiority of LDs with respect to mortality and safety endpoints,⁴⁴ and the death risk was positively correlated with the dose of LDs use.²³ As expected, we observed that sub-participants with continuous LDs use had worse renal function, more severe anaemia, and imbalanced serum electrolytes (Supporting Information, Table S4). In contrast, continuous TDs use may be better from the prognostic perspective among RHD patients with CHF for maintaining decongestion status.

Furthermore, it is worth noting that at least 50% of RHD patients with CHF received MRAs treatment in this study, especially in the CDU group (up to 58.1%). MRAs, as one of the neuroendocrine blockers, have become an indispensable drug for HF treatment and are recommended in all patients with symptomatic (NYHA Classes II–IV) HF with reduced ejection fraction. On the other hand, MRAs are also as diuretics. Regular dose of MRAs has relatively weak diuretic effects in patients with HF, but early initiation of MRA therapy with a regular dose might be useful in offsetting the hypokalaemic effect of potassium-wasting LDs and TDs and improving the prognosis of HF with reduced ejection fraction patients being discharged on an optimized disease-modifying therapy regimen.⁵ Larger doses of MRAs can assist LDs or (and) TDs to achieve natriuretic effects, especially when diuretic resistance has developed.⁴⁵ Butler *et al.*⁴⁶ found that adding treatment with high-dose MRAs (e.g. 100 mg spironolactone daily) on the basis of standard LDs therapy for patients with acute HF was well tolerated compared with combined with usual care (e.g. 25 mg spironolactone daily) during 96-h follow-up, as it did not result in hyperkalaemia or worsening of renal function. However, due to the limited long-term safety data of continuous triple diuretic therapy (LDs + TDs + MRAs), it is necessary to be very cautious when using it and closely monitor the volume status and electrolytes to avoid hyperkalaemia.

The findings of this study point to a clear correlation between CDU and increased risk of mortality in RHD patients with compensated CHF. Randomized clinical trials will be necessary to investigate whether CDU is actually a causative

factor of this increase in mortality or merely a sign of compromised neurohormonal status.

Limitations

This study was hurdled by some limitations. Firstly, the design of our study was only a retrospective study that quite possibly limits the value all of its results. Study participants were not randomized to receive either diuretic application strategy. It is not possible to know how many patients in the CDU group would have been impossible to treat as IDU due to inability to discontinue diuretics without fluid retention. Thus, the results of this analysis contain a bias similar to 'per-protocol' analyses present in clinical trials; the mere fact that patients could do without diuretics for extended periods of time may indicate a more favourable neurohumoral profile that may actually be the cause of better outcomes. Secondly, this was not a randomized study, and the decision to either continuous diuretic treatment or not was not study driven. PSM was performed to form comparable groups with similar a priori risks for mortality, and this matching procedure was obviously successful because the major differences between the unmatched populations vanished. However, the matching method utilized in this study was especially vulnerable to magnifying hidden confounding variables so that the bias may be exacerbated by the fact that there are still no guidelines regarding when to use and when to discontinue diuretics. What motivates the clinician to prescribe diuretics (and which diuretic) to any given RHD patient is a complete unknown. Thus, it is utterly incapable of eliminating the bias introduced by physician decision as well as a potentially favourable neurohormonal profile. Thirdly, because the sample size of this study is not big enough ($N = 494$), large-scale prospective studies will help to further verify those findings. Finally, due to the lack of knowledge on optimal medical therapy among RHD patients with HF, basic HF medications (e.g. RSIs, BBs, and MRAs) were used not enough among participants in this retrospective study. Therefore, results must be interpreted carefully.

Conclusions

Continuous diuretics use was associated with higher risks of all-cause mortality, CVD, re-hospitalization, and new-onset AF. Our analysis suggests that de-escalating diuretic therapy is often feasible in euvolaemic patients with RHD and is associated with better outcomes. Whether this observed relationship is causal due to an unnecessary persistence with diuretic therapy or just reflects the expected association between greater severity of HF and more intensive diuretic therapy is uncertain. These alternative hypotheses should be investigated in randomized trials.

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Conflict of interest

None declared.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethics guidelines of the

institutional and with the principles of the Declaration of Helsinki.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of study participants before PSM.

Table S2. Effect of different diuretic application approaches on heart remodeling in RHD participants with compensated CHF at the end of follow-up.

Table S3. Effect of different application approaches and types of diuretics on heart remodeling in RHD participants with compensated CHF at the end of follow-up.

Table S4. Effect of different types of diuretics on partial biochemical indicators in RHD participants with compensated CHF at the end of follow-up.

Figure S1. Causes of death among study participants before PSM.

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