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Impact of SGLT2 inhibitors plus standard treatment on atrial remodeling and recurrence risk in elderly individuals with persistent atrial fibrillation

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Abstract: **Background**: Atrial fibrillation (AF) represents the most common type of persistent arrhythmia in older adults. This research assesses the impact of integrating sodium-glucose cotransporter 2 inhibitors (SGLT2i), specifically dapagliflozin, into standard care on atrial remodeling and the recurrence of AF in elderly patients with multiple co-existing conditions. **Objective**: The findings aim to inform improved treatment strategies for this patient population. **Method**: The study enrolled 174 elderly persistent AF (PAF) patients, comparing 88 (research group) who received dapagliflozin plus standard care against 86 controls on standard care only. The primary endpoints were the incidence of AF recurrence and the magnitude of change in left atrial diameter (LAD) at the 12-month mark. Secondary outcomes included levels of myocardial fibrosis biomarkers (PIIINP, PICP, TGF-β1), inflammation markers (hs-CRP, IL-6), cardiac function tests (NT-proBNP, LVEF), quality of life (6MWT, ADL) and safety monitoring. **Results**: The research group showed a lower rate of AF recurrence at 12 months than the control group ($P<0.05$); this benefit was even greater in patients with diabetes ($P<0.05$). LAD decreased after treatment in both groups and the decrease was greater in the research group ($P<0.001$). The research group also achieved greater reductions in serum PIIINP, PICP, TGF-β1, hs-CRP and IL-6 compared to the control group ($P<0.05$). Furthermore, a more substantial drop in NT-proBNP was observed ($P<0.05$). LVEF remained stable in the research group but declined slightly in the control group ($P<0.05$). Quality of life metrics also favored the research group, which showed superior gains in both 6MWT distance and ADL scores ($P<0.05$). The safety profile was similar between groups, with no statistically significant difference in adverse effects ($P>0.05$). **Conclusion**: These results indicate that adding dapagliflozin to standard care is a promising treatment option for PAF.

Keywords: Atrial remodeling; Elderly patients; Persistent atrial fibrillation; Recurrence rate; SGLT2 inhibitors

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INTRODUCTION

Atrial fibrillation (AF), a highly prevalent global arrhythmia, affects over 30 million people, with incidence rising markedly with age (Sagris *et al.*, 2021). The persistent form of AF (PAF) is identified in 40 to 50% of patients. It is a significant contributor to disability and death in the elderly, as it often progresses to permanent AF and carries high risks of thromboembolism and heart failure (HF) (Zhang *et al.*, 2025; Hu *et al.*, 2025). Atrial remodeling, encompassing electrical and structural alterations, as well as the activation of inflammatory pathways, is central to PAF pathogenesis (Bizhanov *et al.*, 2023). Managing elderly PAF patients is particularly challenging due to frequent comorbidities like hypertension, diabetes and HF. Current mainstays of treatment, namely rhythm control (e.g., catheter ablation, amiodarone) and ventricular rate control (e.g., beta-blockers), are often hampered by poor drug tolerance and high recurrence rates (around 40-60% within one year) (Chen *et al.*, 2024). This underscores the critical need for more effective adjuvant therapies. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have gained recognition for their cardiovascular benefits in diabetes and HF, notably in the form of preserved ejection fraction (HFpEF) (Tang *et al.*, 2025). Multiple large-scale randomized controlled trials (RCTs) attribute their efficacy in reducing HF hospitalizations to mechanisms that counteract ventricular remodeling, such as facilitating weight loss, improving insulin resistance and curbing the overactivation of the sympathetic nervous and the renin-angiotensin-aldosterone system (RAAS) (Wing *et al.*, 2025; Xie *et al.*, 2023). Furthermore, preclinical animal studies point to a more direct cardioprotective mechanism. By targeting the transforming growth factor-β1 (TGF-β1)/Smad3 axis, SGLT2i slows down fibroblast growth in the atria, leading to less collagen deposition and improved electrical conduction across the atria (Daud *et al.*, 2021). Current knowledge of SGLT2i benefits in AF is largely extrapolated from studies involving young animals or non-AF-affected individuals (Wang *et al.*, 2024). Consequently, it is unclear if these benefits translate to elderly PAF patients or positively impact atrial remodeling. No clinical study has yet been conducted to

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comprehensively examine the intervention effects of SGLT2i combined with standard treatment on atrial size, fibrotic biomarkers and rates of AF recurrence in geriatric populations, particularly those with concomitant comorbidities, lacking long-term follow-up evidence.

This study investigates the novel addition of SGLT2i (dapagliflozin) to standard rhythm/rate control therapy in elderly, comorbid patients with PAF. Through follow-up observation, we will assess its impact on multifaceted atrial remodeling and arrhythmia recurrence in a real-world setting. Should our findings demonstrate a significant delay in atrial remodeling and a consequent reduction in AF recurrence, it would offer a compelling rationale for drug repurposing, thereby informing more personalized treatment strategies for this growing patient demographic.

MATERIALS AND METHODS

Research design

This was an open-label prospective cohort study, approved by the local ethics committee, used the 12-month AF recurrence rate as the primary endpoint. Sample size calculation, based on pilot data and published estimates (El-Harasis *et al.*, 2024) (assuming 30% recurrence in controls, Hazard rate (HR)=0.6, two-sided alpha [α]=0.05, power [1-β]=80%), indicated a need for 70 patients per group. To ensure robustness against an estimated 20% dropout (including loss to follow-up, voluntary withdrawal, or adverse events), we planned to enroll at least 84 subjects in each study arm.

Patient selection criteria

Inclusion criteria required all the following: Age ≥65 years; Diagnosis of PAF with left atrial enlargement. *Exclusion Criteria* included any of the following: Severe hepatic or renal dysfunction [epidermal growth factor receptor (eGFR) <30 mL/min/1.73m^2]; Recent (within 3 months) use of SGLT2i, AF ablation, or new oral anticoagulants; Life expectancy <1 year; Severe arrhythmias; Allergy to dapagliflozin or history of diabetic ketoacidosis; Active urinary/genital tract infection; Psychiatric/cognitive impairment affecting compliance; Inability to complete the follow-up period.

Study participants

The study included patients with 174 patients with PAF admitted to our hospital from May 2023 to June 2024. 86 patients constituted the control group and received standard therapy and the other 88 constituted the research group and received additional dapagliflozin. All participants provided informed consent.

Treatment methods

Routine therapeutic interventions were provided to each patient, including measures for both rhythm and ventricular rate management. Rhythm control was achieved through amiodarone, prescribed at a maintenance dose of 0.2 g per day (qd). For ventricular rate control, a beta-blocker-metoprolol-was used, with the daily dosage set at 25-50 mg taken twice (bid). The research group had dapagliflozin added to this conventional treatment plan. Dapagliflozin was administered orally at 10 mg prior to breakfast daily; in cases where the baseline estimated glomerular filtration rate (eGFR was between 30 and 45 ml/min/1.73m²), the dose was modified to 5 mg once daily. All treatments were continued for an extended period.

Prognostic follow-up

A 12-month follow-up was completed for all participants, with monthly evaluations until July 1, 2025. Dapagliflozin was administered continuously throughout the 12-month study period without dose adjustment unless eGFR fell below 30 mL/min/1.73m^2.

Endpoints

Primary endpoints focused on AF recurrence during the follow-up period (defined as the first detected AF episode >30 seconds, validated through Holter or symptom diaries and absent acute triggers such as infection/surgery) and the pre- to post-treatment (12-month) change in left atrial diameter (LAD). All patients received identical monitoring intensity.

For secondary endpoint assessment, several parameters were evaluated. Fasting venous blood was drawn at baseline and post-treatment for laboratory analysis of Procollagen Type III N-Terminal Propeptide (PIIINP), Procollagen Type I C-Terminal Propeptide (PICP), Transforming Growth Factor-β1 (TGF-β1), High-Sensitivity C-Reactive Protein (hs-CRP), Interleukin-6 (IL-6) and N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP). Assays were performed using ELISA kits (Wuhan Huamei Biotechnology, China) with intra- and inter-assay coefficients of variation <10%. Additionally, each patient underwent a 6-minute walk test (6MWT) (Zeren *et al.*, 2022) and an activities of daily living (ADL) assessment (Militaru *et al.*, 2021). The 6MWT measures the distance an individual can walk quickly on a flat, hard surface in six minutes, with a longer distance indicating better cardiopulmonary capacity. The ADL questionnaire evaluates the patient's functional abilities in terms of basic life skills (e.g., eating, dressing, moving) and tool-using capabilities; a higher score in this questionnaire reflects a better quality of life. Adverse events that emerged during treatment (e.g., hypoglycemia or genitourinary infection) were also counted. Adverse events were adjudicated by a blinded endpoint committee unaware of group allocation.

Quality control

The study was open-label due to logistical constraints. To minimize performance bias, objective endpoints (e.g., LAD, biomarkers) were assessed by blinded staff, while subjective endpoints (e.g., symptom recurrence) were verified by independent adjudicators unaware of group assignment.

Statistical analysis

All data were double-entered for accuracy and complete follow-up was achieved with no missing values. Analyses were performed in SPSS 30.0. The Shapiro-Wilk test determined the distribution of continuous variables. Data following a normal distribution (expressed as $\bar{\chi}\pm s$) were evaluated with independent or paired t-tests for between- and within-group comparisons, respectively. Non-normal data employed the Mann-Whitney U test (between groups) and Wilcoxon test (within groups). Categorical variables [n (%)] were compared using the chi-square (χ^2) test. A P-value<0.05 was considered statistically significant.

RESULTS

Baseline data of research participants

Initial analysis of participant baseline data—such as age, sex and disease course—showed no significant intergroup differences (P>0.05). The standardized mean differences (SMD) for all variables were below 0.2, further confirming minimal intergroup disparities. Subgroup analyses for diabetes mellitus were pre-specified in the study protocol. Comparative statistics for all key comorbidities (diabetes, heart failure, coronary artery disease, hypertension) showed no significant differences (P>0.05, Table 1), ensuring group comparability.

Comparison of recurrence rates

All enrolled participants completed the follow-up. Recurrence was observed in 15.91% of the research group and 29.07% of the control group, demonstrating a significantly better outcome in the research group (P<0.05). This advantage was particularly evident in the diabetic subgroup, where the research group showed a more pronounced reduction in recurrence (P=0.037). With respect to LAD, although both groups showed decreased values after treatment (P=0.021), the research group maintained a significantly lower LAD than the control group post-treatment (P<0.001) (Table 2).

Comparison of myocardial fibrosis and inflammatory reaction

At baseline, serum levels of PIIINP, PICP, TGF-β1, hs-CRP and IL-6 did not differ significantly between the groups (P>0.05). After treatment, the research group exhibited marked reductions in all measured markers compared to both baseline values and the control group (P<0.05). In contrast, the control group demonstrated a reduction only in hs-CRP and IL-6 (P<0.05), with PIIINP, PICP and TGF-β1 remaining statistically unchanged (P>0.05) (Fig. 1).

Comparison of cardiac function

Comparative analysis of cardiac function demonstrated that both groups achieved reduced NT-proBNP levels following treatment, with the research group exhibiting a greater decrease than the control group (P<0.05). Regarding left ventricular ejection fraction (LVEF), no significant pre-post difference was detected within the research group (P>0.05). However, the control group showed a slight post-treatment decrease in LVEF, with values significantly lower than those in the research group (P<0.05) (Fig. 2).

Comparison of quality of life

Pre-treatment assessments revealed no intergroup disparities in 6MWT or ADL metrics (P>0.05). Subsequent to therapeutic intervention, both cohorts exhibited enhanced performance on both measures (P<0.05), with the research group (6MWT: 269.00±27.18 m, ADL: 68.76±6.63) demonstrating significantly greater improvement than the control group (6MWT: 243.60±238.65 m, ADL: 62.05±6.14) (P<0.05) (Fig. 3).

Comparison of treatment safety

During the treatment period, adverse events including hypoglycemia and aggravated lower limb edema were observed in both groups. The research group also reported three cases of urogenital infection and two cases of abnormal blood potassium. However, statistical analysis revealed no intergroup differences in adverse reaction rates (P=0.132). It is important to note that all reported events resolved subsequent to clinical management (Table 3).

DISCUSSION

As the most common form of sustained arrhythmia in the elderly, PAF is characterized by a high recurrence rate closely associated with atrial remodeling (Khan *et al.*, 2023). This study is the first to investigate the effects of combining SGLT2i (dapagliflozin) with standard therapy on atrial remodeling and recurrence in older adults with PAF, offering new perspectives for optimizing management strategies in this population.

This study shows that combining dapagliflozin with standard care significantly lowered AF recurrence over 12 months in elderly patients, highlighting two key benefits. Firstly, it exhibits a direct antiarrhythmic property: SGLT2i appears to attenuate the generation of arrhythmogenic substrates by suppressing atrial fibrosis (shown by drops in PIIINP, PICP, TGF-β1). The reduction in fibrotic biomarkers to near-normal levels suggests that dapagliflozin may reverse pro-fibrotic pathways, potentially delaying structural remodeling. Animal studies note improved electrical homogeneity by SGLT2i via lowering the dispersion of atrial effective refractory periods (Huang *et al.*, 2023), providing a plausible mechanistic basis for the observed decline in AF recurrence. Secondly, the indirect metabolic modulation of SGLT2i likely plays a role—particularly in diabetic patients, who experienced greater AF risk reduction. It indicates that the glucose-lowering properties of dapagliflozin may work synergistically by ameliorating insulin resistance and reducing oxidative stress (e.g., decreased serum malondialdehyde levels), thereby suppressing the activity of AF triggers (Anson *et al.*, 2023).

Table 1: Baseline data in the two groups of subjects

Groups	Control group	Research group	Statistical	P	SMD
n	86	88	(t or χ^2)		
Sex			χ^2=0.645	0.422	0.122
male	54 (62.79)	50 (56.82)			
female	32 (37.21)	38 (43.18)			
Age	69.35±2.77	68.42±7.50	t=1.082	0.281	0.164
BMI (kg/m^2)	23.30±2.09	23.19±1.52	t=0.419	0.676	0.060
Duration of AF (months)	5.19±1.87	5.11±1.78	t=0.262	0.794	0.044
Coexisting diseases					
diabetes mellitus	46 (53.49)	52 (59.09)	χ^2=0.555	0.456	0.120
heart failure	34 (39.53)	38 (43.18)	χ^2=0.239	0.625	0.061
coronary heart disease	24 (27.91)	20 (22.73)	χ^2=0.618	0.432	0.114
hypertension	50 (58.14)	47 (53.41)	χ^2=0.395	0.530	0.100
History of smoking			χ^2=0.209	0.648	0.060
yes	41 (47.67)	45 (51.14)			
no	45 (52.33)	43 (48.86)			
History of drinking			χ^2=0.307	0.580	0.087
yes	25 (29.07)	29 (32.95)			
no	61 (70.93)	59 (67.05)			
LAVI (mL/m2)	44.97±5.15	45.05±5.64	t=0.094	0.925	0.015
eGFR (mL/min/1.73m^2)	68.57±10.91	69.26±10.41	t=0.428	0.669	0.065
HbA1c (%)	7.14±1.07	7.31±0.99	t=1.120	0.264	0.165

Table 2: Recurrence in the two groups of subjects

	Status of recurrence					LAD (mm)	
	Total	Subgroup				Baseline	After treatment
		Diabetes mellitus	Heart failure	Coronary heart disease	Hypertension		
Control group (n=86)	25 (29.07)	14 (30.43)	4 (11.76)	7 (29.17)	17 (14.00)	42.60±2.96	39.95±3.74*
Research group (n=88)	14 (15.91)	6 (11.54)	6 (15.79)	3 (15.00)	8 (6.38)	43.00±2.96	37.51±3.25*
Statistical (t or χ^2 or Fisher's exact)	χ^2=4.332	χ^2=5.366	-	-	-	t=0.881	t=4.603
P	0.037	0.021	0.740	0.306	0.320	0.380	<0.001

Note: * indicates P<0.05 for intra-group comparisons.

These observations align with previous reports linking SGLT2i to reduced cardiovascular mortality in diabetic populations (Neuen *et al.*, 2024). Notably, the considerable (30%) recurrence rate in controls indicates that traditional rate/rhythm control has limited efficacy in the elderly, multimorbid population. Potential explanations for this include drug-related adverse effects, such as beta-blocker-induced atrial fibrosis due to negative inotropic actions, or amiodarone-associated thyrotoxicity with prolonged administration, which can precipitate AF recurrence.

On the other hand, although LAD decreased after treatment in both groups, the decrease was greater in the research group. Atrial fibrosis is considered a central mechanism underlying LAD expansion (Wu *et al.*, 2023). Dapagliflozin may mitigate this process by suppressing the TGF-β1/Smad3 signaling pathway, thereby reducing collagen accumulation and promoting atrial structural stability (Xue *et al.*, 2023). Additionally, the greater decrease in NT-proBNP levels in the research group implies that dapagliflozin could reduce left atrial filling pressure via its natriuretic and diuretic actions, indirectly delaying atrial dilatation. These findings are consistent with reported effects of SGLT2i on diastolic function in HFpEF (Patel *et al.*, 2024). Moreover, LVEF remained stable in the research group but declined slightly in the control group. This discrepancy implies that SGLT2i facilitates reverse remodeling, likely by antagonizing volume overload-induced ventricular remodeling via modulation of RAAS activity and sympathetic tone (Scheen & Delanaye, 2022).

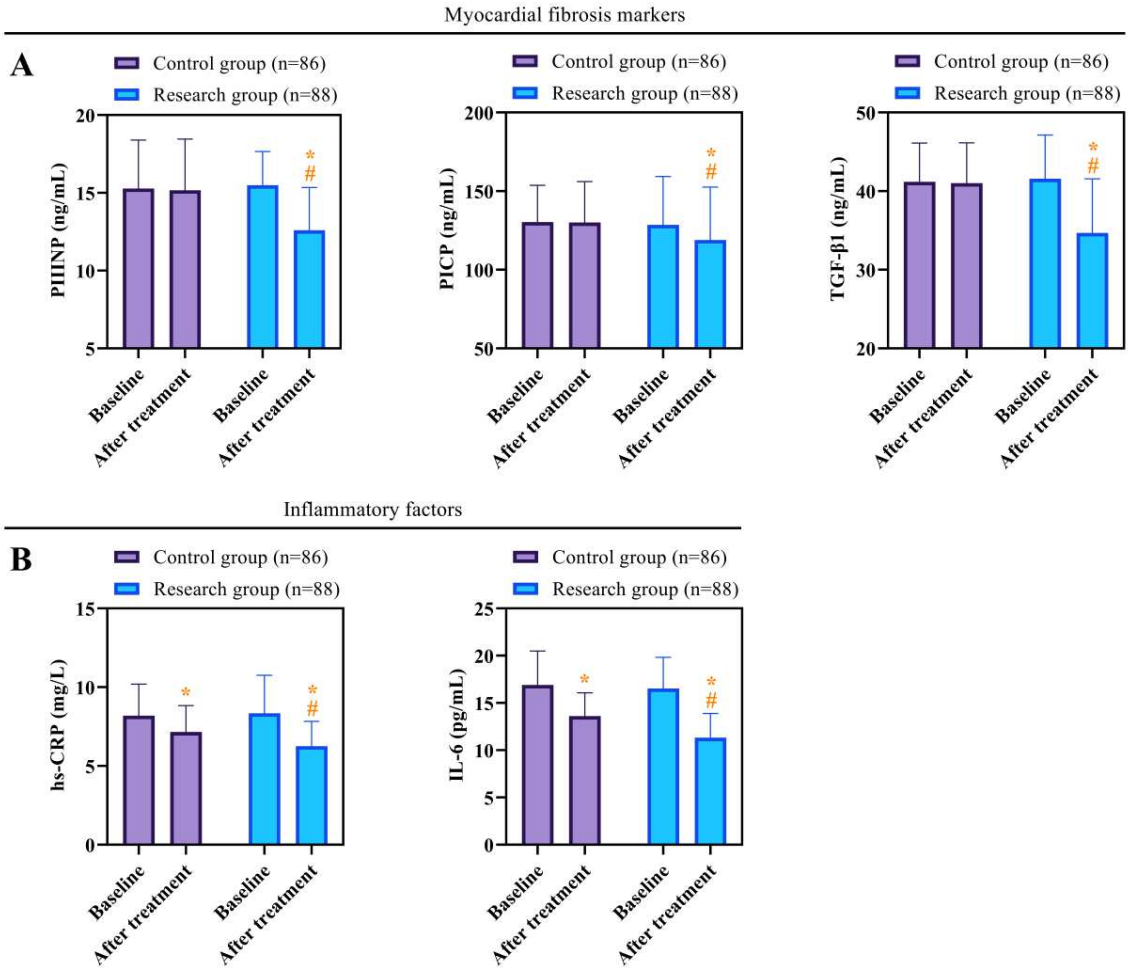

Fig. 1: Comparison of myocardial fibrosis markers and inflammatory factors before and after treatment.
(A) Changes and comparison of myocardial fibrosis markers PIIINP, PICP and TGF-β1 before and after treatment in the two groups. (B) Changes and comparison of inflammatory factors hs-CRP and IL-6 before and after treatment in the two groups. Note: * indicates P<0.05 for intra-group comparisons; # indicates P<0.05 for comparison between groups.

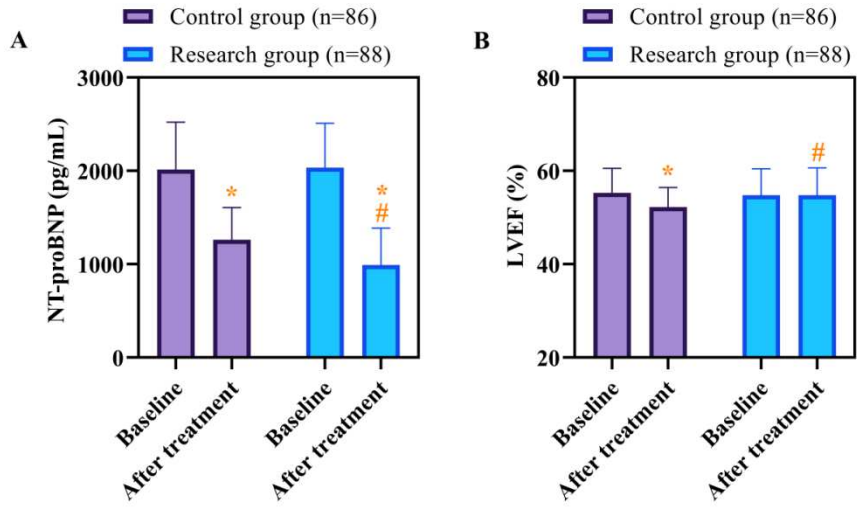

Fig. 2: Comparison of cardiac function before and after treatment.
(A) Changes and comparison of NT-proBNP before and after treatment in the two groups. (B) Changes and comparison of LVEF before and after treatment in the two groups. Note: * indicates P<0.05 for intra-group comparisons; # indicates P<0.05 for comparison between groups.

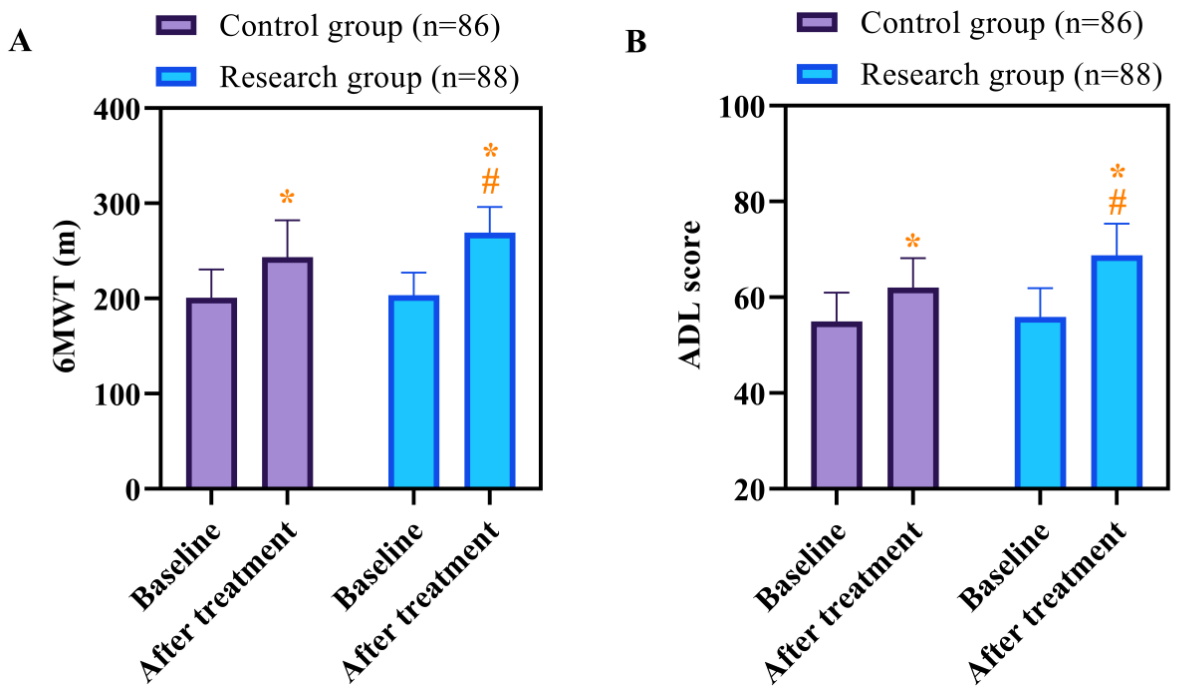

Fig. 3: Comparison of quality of life before and after treatment.
(A) Changes and comparison of 6MWT before and after treatment in the two groups. (B) Changes and comparison of ADL score before and after treatment in the two groups. Note: * indicates P<0.05 for intra-group comparisons; # indicates P<0.05 for comparison between groups.

Table 3: Adverse effects in the two groups of subjects

Groups	Dehydration	Hypoglycemia	Edema of the lower limbs	Genitourinary tract infections	Abnormal blood potassium	Total
Control group (n=86)	1 (1.16)	4 (4.625)	2 (2.33)	1 (1.16)	0 (0.0)	8 (9.30)
Research group (n=88)	2 (2.27)	5 (5.68)	3 (3.41)	3 (3.41)	2 (2.27)	15 (17.05)
χ^2						2.273
P						0.132

Finally, the enhancement in quality of life among research group participants further underscores the positive impact of SGLT2i on patient-reported outcomes. Mechanistically, this may involve improved oxygen uptake in peripheral tissues through facilitated ketone body utilization and fatty acid oxidation. Additionally, reductions in systemic inflammation markers (hs-CRP and IL-6) may help alleviate skeletal muscle injury. Regarding safety, although genitourinary infection rates were higher in the dapagliflozin group (3.41% *vs.* 1.16%), all cases were mild and resolved with standard care. This is consistent with the known safety profile of SGLT2 inhibitors and does not outweigh the net clinical benefit in this elderly population.

We suggest prioritizing dapagliflozin combination therapy in older PAF patients with diabetes, given its potential to concurrently address metabolic dysfunction and decrease AF recurrence. From a clinical feasibility perspective, the addition of dapagliflozin (approximately $4-6/day) should be weighed against potential reductions in hospitalizations. Polypharmacy concerns may be mitigated by its once-daily dosing and low drug interaction profile with standard AF medications. Nevertheless, the non-randomized design may introduce confounding by unmeasured factors (e.g., concurrent use of RAAS blockers or statins, which were not stratified). Second, the single-center sample limits generalizability. Future multi-center randomized trials should control for concomitant medications. Furthermore, surrogate endpoints like PIIINP and LAD changes need verification via cardiac magnetic resonance (CMR). Additionally, since some adverse event data were self-reported and potentially subjective, a more rigorous assessment of the therapy's safety profile is warranted.

CONCLUSION

Adding dapagliflozin (an SGLT2i) to standard therapy not only decreases the likelihood of AF recurrence and

attenuates left atrial dilation but also enhances functional capacity and patient-reported outcomes, potentially by targeting underlying pathways involving fibrosis and inflammatory responses.

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Authors' contributions
N.S. and J.J.: Conceived and designed the study; N.S. and YR.S: Wrote and revised the manuscript; YL.W: Collected and analyzed data; N.S. and YR.S: Made equal contributions in this work as co-first authors. All authors read and approved the final submitted manuscript.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
The ethics committee at Chengdu Shuangliu District First People's Hospital approved the study (l205512).

Conflict of interest
The authors declare no conflict of interest.

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