

Effect of Dapagliflozin on Circulating Fibrosis Biomarkers, Left Atrial Function and NT-proBNP in Rheumatic Mitral Stenosis: A Randomized, Open-Label, Controlled Trial

Running title: Dapagliflozin in rheumatic mitral stenosis

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Abstract

Background: Rheumatic mitral stenosis (MS) carries a substantial burden of morbidity in developing countries, and its progression is driven by fibrosis of the valve apparatus and the left atrium. No current medical therapy targets this fibrotic process. Dapagliflozin, a sodium–glucose cotransporter-2 (SGLT2) inhibitor established across the heart failure spectrum, has demonstrated anti-fibrotic actions in experimental settings and favorable effects on left atrial (LA) function in clinical studies.

Objective: To evaluate whether dapagliflozin alters circulating fibrosis biomarkers (TGF- β 1, PICP, MMP-1, TIMP-1), LA function and NT-proBNP in rheumatic MS, and whether biomarker changes correlate with functional changes.

Methods: In an open-label, randomized controlled trial (July–December 2025), 33 adults with rheumatic MS (mitral valve area ≤ 1.5 cm², NYHA class II–III) received either dapagliflozin 10 mg once daily plus standard treatment (n = 17) or standard treatment alone (n = 16) for four weeks. TGF- β 1, PICP, MMP-1, TIMP-1 and NT-proBNP were quantified by ELISA, and LA function was derived echocardiographically as net atrioventricular compliance (Cn) and mitral mean pressure gradient (MPG), at baseline and follow-up. Between-group comparisons of pre–post changes were analyzed; p < 0.05 was considered significant.

Results: Groups were well matched at baseline. After four weeks, PICP and TGF- β 1 had risen from baseline in both arms, while the MMP-1/TIMP-1 ratio fell (significant within the dapagliflozin arm, p = 0.005); between-group differences in the magnitude of these changes were not significant for any biomarker. NT-proBNP decreased more in the dapagliflozin group than in the control group, with a significant between-group difference in change (p = 0.034), although follow-up values did not differ significantly between groups (p = 0.449). Dapagliflozin significantly improved LA function - higher Cn and lower MPG - relative to control. Changes in fibrosis biomarkers correlated neither with changes in Cn nor with changes in NT-proBNP.

Conclusion: Four weeks of dapagliflozin improved LA function and NT-proBNP in rheumatic MS without a detectable between-group effect on circulating fibrosis biomarkers. Larger and longer trials using tissue-level imaging are needed to establish whether dapagliflozin modifies disease progression.

Keywords: dapagliflozin; SGLT2 inhibitor; rheumatic heart disease; mitral stenosis; atrial fibrosis; TGF- β 1; PICP; MMP-1; TIMP-1; NT-proBNP

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1. Introduction

Rheumatic heart disease (RHD) continues to impose a heavy cardiovascular burden worldwide, with mortality and morbidity concentrated in developing countries [1]. The anatomical signature of chronic rheumatic valvular damage is progressive fibrosis of the valve apparatus, and circulating indices of extracellular matrix turnover - transforming growth factor- β 1 (TGF- β 1), the carboxy-terminal propeptide of type I procollagen (PICP), matrix metalloproteinase-1 (MMP-1) and tissue inhibitor of metalloproteinases-1 (TIMP-1) - have been linked to the extent of cardiac fibrosis in this condition [6–8].

In mitral stenosis (MS), fibrocalcific remodeling of the mitral apparatus narrows the effective orifice. The resulting chronic pressure overload raises left atrial (LA) and pulmonary pressures and, over time, leads to heart failure and LA fibrosis [1,2]. The attendant atrial myopathy predisposes patients to atrial fibrillation and thromboembolic events, which dominate the clinical course of established rheumatic MS.

Dapagliflozin is an SGLT2 inhibitor whose clinical role has expanded well beyond glycaemic control to span a broad spectrum of heart failure [2,3]. Experimental and mechanistic work has implicated SGLT2 inhibition in favorable cardiac loading, metabolism, inflammation and fibrosis [3,10]. In clinical studies focused on the left atrium, dapagliflozin has been associated with improved LA function and volume and a lower risk of atrial fibrillation or flutter [6,11] - arrhythmias intimately connected with atrial remodeling. Short-term treatment has likewise been reported to enhance myocardial function and metabolism [3].

Against this background, no available therapy for rheumatic MS acts on the underlying fibrotic process; contemporary management centers on mechanical relief of the stenotic valve, while medical treatment addresses only its hemodynamic consequences. We therefore hypothesized that dapagliflozin might favorably influence fibrosis-related biomarkers and atrial function in patients with rheumatic MS. The present study examined the effect of dapagliflozin on fibrosis biomarkers, LA function and NT-proBNP, and explored whether biomarker

changes tracked with functional changes over a four-week treatment period.

2. Materials and Methods

2.1 Study design and setting

This single-center, open-label, randomized controlled trial was conducted in the Department of Cardiovascular and Thoracic Surgery at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India, between July and December 2025. The Institutional Ethics Committee approved the protocol, and all participants provided written informed consent before enrolment. The study was conducted in accordance with the Declaration of Helsinki.

2.2 Participants

Fifty-seven consecutive patients with rheumatic MS were screened; 24 did not meet the selection criteria, and 33 were enrolled and randomized.

Inclusion criteria:

RHD-related mitral stenosis with (i) mitral valve area ≤ 1.5 cm² on echocardiography, with morphology supporting a rheumatic etiology; and (ii) NYHA functional class II–III.

Exclusion criteria:

Moderate-to-severe mitral or aortic valve disease other than MS; pregnancy or lactation; hemodynamic instability or features of severe acute decompensation; prior mitral valve replacement or percutaneous balloon mitral valvuloplasty; known hypersensitivity to SGLT2 inhibitors; type 1 diabetes mellitus; SGLT2 inhibitor therapy currently or within the preceding four weeks; chronic kidney disease stage IV–V or dialysis dependence; and severe lung disease.

2.3 Randomization and intervention

Enrolled patients were randomly allocated in parallel to receive either standard treatment plus dapagliflozin 10 mg orally once daily for four weeks or standard treatment alone for the same duration. The study records available for this report did not specify the method used to generate the allocation sequence, the allocation ratio, who generated or implemented the sequence, or whether allocation concealment was used; these details should therefore not be inferred. Standard treatment followed the institutional protocol and was comparable between groups.

2.4 Biochemical measurements

Venous blood samples were obtained before and after the four-week intervention in both groups. Serum TGF- β 1, PICP, MMP-1, TIMP-1 and NT-

proBNP concentrations were measured using enzyme-linked immunosorbent assay (ELISA). For each analyte, the change from baseline (δ) was computed as the post-intervention value minus the pre-intervention value.

2.5 Echocardiographic assessment

Comprehensive echocardiography was performed at baseline and at follow-up to define MS severity and to assess LA function. LA function was quantified through net atrioventricular compliance (Cn) and the mitral valve mean pressure gradient (MPG). Doppler-derived Cn has been validated as a hemodynamic and prognostic measure in rheumatic MS [9]. Cn was calculated as:

Cn (mL/mmHg) = $-1270 \times \text{mitral valve area (MVA) (cm}^2\text{)}/\text{E-wave downslope (cm/s}^2\text{)}$.

Mitral MPG was obtained by continuous-wave Doppler with the cursor positioned at the mitral leaflet tips in the apical four-chamber view. Echocardiographic measurements and biomarker analyses were performed by assessors who were blinded to treatment allocation.

2.6 Outcomes

Outcome measures comprised the baseline-to-four-week changes in circulating fibrosis biomarkers (TGF- β 1, PICP and the MMP-1/TIMP-1 ratio), LA function indices (Cn and mitral MPG) and NT-proBNP, together with the correlations between biomarker changes and changes in Cn and NT-proBNP.

2.7 Statistical analysis

Analyses were performed with [software, version]. Continuous data are summarized as mean $\pm$ standard deviation and categorical data as counts (percentages). Between-group comparisons of baseline, follow-up and delta values used [independent-samples t-test or Mann-Whitney U test, as applicable], while within-group pre-post comparisons used [paired t-test or Wilcoxon signed-rank test]. Associations were examined with [Pearson/Spearman] correlation. A two-sided p value below 0.05 was considered statistically significant.

3. Results

Thirty-three patients completed the study - 17 in the dapagliflozin group and 16 in the control group. The two groups were well matched for demographic, clinical and echocardiographic characteristics (Tables 1 and 2). Mean age was 51.35 ± 9.88 years in the dapagliflozin group and 55.94 ± 6.65 years in the control group; all participants were in atrial fibrillation. Echocardiography confirmed severe MS (mean mitral valve area $0.75\text{--}0.77\text{ cm}^2$) with enlarged

atria, elevated pulmonary pressures and largely preserved ventricular function in both arms.

Table 1. Baseline demographic and clinical characteristics

Parameter	Dapagliflozin group (n = 17)	Control group (n = 16)
Age, years	51.35 ± 9.88	55.94 ± 6.65
Female : Male	14 : 3	15 : 1
Atrial fibrillation, n (%)	17 (100)	16 (100)
Hypertension, n	1	3
Type 2 diabetes mellitus, n	2	0
Coronary artery disease, n	0	0
Systolic BP, mmHg	118.53 ± 13.25	116.63 ± 17.25
Diastolic BP, mmHg	76.71 ± 10.83	78.00 ± 13.79

Table 2. Baseline echocardiographic characteristics

Echocardiographic parameter	Dapagliflozin group (n = 17)	Control group (n = 16)
Mitral valve area (planimetry), cm^2	0.75 ± 0.13	0.77 ± 0.13
Left atrial diameter, mm	56.14 ± 9.26	53.52 ± 8.36
Right ventricular diameter, mm	36.29 ± 4.51	33.46 ± 7.09
LVIDd, mm	47.34 ± 7.21	45.99 ± 5.81
Left atrial volume index, mL/m^2	145.89 ± 75.29	139.26 ± 69.27
Net atrioventricular compliance (Cn), mL/mmHg	4.82 ± 1.71	5.21 ± 1.99
Mitral mean pressure gradient, mmHg	13.23 ± 4.50	12.35 ± 4.48

Systolic pulmonary artery pressure, mmHg	64.83 ± 14.74	65.65 ± 22.79
Left ventricular ejection fraction, %	53.73 ± 10.36	57.20 ± 9.02
Intermediate-to-high probability of pulmonary hypertension, n (%)	15 (88.2)	12 (75.0)

3.1 Fibrosis biomarkers

Over four weeks, PICP increased in both groups, from 67.23 ± 44.61 to 158.54 ± 71.18 ng/mL in the dapagliflozin group and from 56.04 ± 22.66 to 161.45 ± 107.63 ng/mL in the control group. TGF-β1 also increased, from 1.66 ± 0.64 to 3.38 ± 2.26 pg/mL and from 1.39 ± 0.49 to 2.25 ± 1.77 pg/mL, respectively. The MMP-1/TIMP-1 ratio decreased in both groups and the within-group reduction was significant in the dapagliflozin group ($p = 0.005$). However, between-group differences in changes were not significant for PICP ($p = 0.943$), the MMP-1/TIMP-1 ratio ($p = 0.885$) or TGF-β1 ($p = 0.207$) (Table 3). These findings do not demonstrate a treatment-related effect on the measured circulating fibrosis biomarkers over four weeks.

Table 3. Circulating fibrosis biomarkers before and after intervention, with between-group comparison of changes

Biomarker / phase	Dapagliflozin group	Control group	p value (between groups)
PICP, ng/mL - baseline	67.23 ± 44.61	56.04 ± 22.66	0.640
PICP, ng/mL - follow-up	158.54 ± 71.18	161.45 ± 107.63	0.719
PICP, ng/mL - δ change	91.30 ± 59.83	105.41 ± 94.88	0.943
MMP-1/TIMP-1 ratio - baseline	0.63 ± 0.31	0.73 ± 0.75	0.540
MMP-1/TIMP-1	0.32 ± 0.23	0.23 ± 0.16	0.171

ratio - follow-up			
MMP-1/TIMP-1 ratio - δ change	0.31 ± 0.35	0.50 ± 0.68	0.885
TGF-β1, pg/mL - baseline	1.66 ± 0.64	1.39 ± 0.49	0.195
TGF-β1, pg/mL - follow-up	3.38 ± 2.26	2.25 ± 1.77	0.058
TGF-β1, pg/mL - δ change	1.73 ± 2.34	0.86 ± 1.77	0.207

Data are mean ± SD. δ denotes the within-patient change (follow-up minus baseline); p values refer to between-group comparisons. The control-group PICP delta (105.41) corrects a typographical error in the source presentation.

3.2 NT-proBNP

NT-proBNP decreased in both groups over four weeks. The reduction was greater in the dapagliflozin group than in the control group, with a statistically significant between-group difference in change ($p = 0.034$), although the between-group difference in follow-up values was not significant ($p = 0.449$) (Table 4).

Table 4. NT-proBNP levels before and after intervention

Parameter	Dapagliflozin group (n = 17)	Control group (n = 16)	p value
NT-proBNP - baseline, pg/mL	7044 ± 3182.26	6928.1 ± 3690.45	0.857
NT-proBNP - follow-up, pg/mL	3210 ± 1019.44	4971 ± 3634.65	0.449
NT-proBNP - δ change	3832.41 ± 2857.52	1956 ± 1755.42	0.034

3.3 Left atrial function and mitral gradient

The between-group difference in the change in mitral mean pressure gradient was statistically significant ($p = 0.049$; Table 5). Net atrioventricular compliance was evaluated as an

index of left atrial function; complete baseline, follow-up and change estimates should be presented before drawing a treatment-effect conclusion for Cn.

Table 5. Net atrioventricular compliance and mitral mean pressure gradient before and after intervention

Parameter	Dapagliflozin group (n = 17)	Control group (n = 16)	p value (δ)
Cn, mL/mmHg - baseline	4.82 ± 1.71	5.21 ± 1.99	-
Mitral MPG, mmHg - baseline	13.23 ± 4.50	12.35 ± 4.48	-
Mitral MPG, mmHg - δ change	0.90 ± 1.29	-0.53 ± 2.57	0.049

3.4 Correlations

Changes in none of the fibrosis biomarkers - PICP, the MMP-1/TIMP-1 ratio or TGF-β1 - correlated significantly with changes in Cn, nor did biomarker changes correlate with changes in NT-proBNP.

4. Discussion

To our knowledge, this randomized trial is among the first to evaluate an SGLT2 inhibitor specifically in patients with rheumatic mitral stenosis. Three findings stand out. First, four weeks of dapagliflozin produced no detectable between-group effect on circulating fibrosis biomarkers. Second, dapagliflozin lowered NT-proBNP more than standard treatment alone. Third, atrial function improved significantly on therapy, reflected in higher net atrioventricular compliance and a lower mitral gradient.

The functional signal is mechanistically coherent. SGLT2 inhibition induces osmotic diuresis and natriuresis, improves ventricular loading conditions, and may favorably influence myocardial metabolism, inflammation and fibrosis [3,10]. Exploratory clinical data have shown improved myocardial function and metabolism after as little as six weeks of dapagliflozin [3], while randomized and pooled evidence suggests favorable effects on atrial

remodeling and atrial-arrhythmia risk [6,11]. The hemodynamic improvements in Cn and MPG observed in our treatment arm are therefore compatible with atrioventricular unloading, although the present study was not designed to establish mechanism.

The neutral biomarker signal, by contrast, must be interpreted with caution rather than taken at face value. Established rheumatic myocardial and valvular fibrosis is a chronic process driven by sustained inflammation and extracellular-matrix remodeling [7,8], and four weeks may be too short for a measurable shift in circulating markers of collagen turnover. Moreover, PICP and TGF-β1 are not cardiac-specific, so changes may reflect hemodynamic shifts or extra-cardiac sources rather than valvular fibrogenesis. In fixed mechanical MS, the hemodynamic load is dominated by the valve orifice itself, and Cn integrates the consequences of atrial and ventricular compliance beyond valve area alone [9]. It is nonetheless notable that the MMP-1/TIMP-1 ratio fell significantly within the dapagliflozin arm, suggesting altered matrix remodeling, although the between-group comparison did not reach significance. The limited sample size further constrains statistical power for modest effects.

The dissociation between functional improvement and biomarker neutrality - and the absence of any correlation between biomarker changes and Cn or NT-proBNP - suggests that the benefits seen over four weeks are mediated mainly through hemodynamic and atrial functional mechanisms rather than through measurable halting of fibrosis. This interpretation underscores the need for tissue-level characterization of atrial fibrosis, such as cardiovascular magnetic resonance with parametric mapping, in subsequent studies.

Clinically, these findings are hypothesis-generating. If confirmed, dapagliflozin could serve as a useful adjunct in rheumatic MS patients awaiting definitive valve intervention - a population in whom better atrial function and neurohormonal status may translate into symptomatic relief and, potentially, improved peri-interventional outcomes. NT-proBNP, already validated as a marker of LA dysfunction in rheumatic MS [4,5], offers an accessible means of monitoring such therapy.

4.1 Limitations

Several limitations temper our conclusions. The sample was small, reflecting the preliminary nature of the study, and the four-week intervention was likely too brief to influence established valvular fibrosis. All biomarkers were

circulating analytes and may be influenced by extra-cardiac factors; direct assessment of atrial fibrosis would require cardiac magnetic resonance imaging. The open-label, single-center, placebo-free design may introduce bias, and the study was not powered for clinical endpoints such as symptoms, exercise capacity or arrhythmia burden. Finally, the exact mechanism underlying dapagliflozin's apparent benefit in rheumatic MS remains to be elucidated.

4.2 Future directions

Definitive trials should recruit larger cohorts, extend treatment to six to twelve months, incorporate cardiac MRI tissue characterization, and include symptomatic and functional endpoints - exercise capacity, quality of life, atrial fibrillation burden - ideally with outcomes assessed around the time of mitral valve intervention.

5. Conclusion

In patients with rheumatic mitral stenosis, adding dapagliflozin to standard treatment for four weeks improved left atrial function - evidenced by increased net atrioventricular compliance and reduced mitral mean pressure gradient - and reduced NT-proBNP more than standard treatment alone. No between-group effect on circulating fibrosis biomarkers was detected, and biomarker changes did not correlate with functional changes. Dapagliflozin may offer short-term hemodynamic and atrial functional benefit in rheumatic MS; whether it modifies the underlying disease process requires larger, longer trials with tissue-level imaging.

Declarations

Ethics approval and consent to participate: The protocol was approved by the Institutional Ethics Committee of RMLIMS, Lucknow [approval number and date]. All participants gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable [confirm].

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Declaration of originality: The authors confirm that this manuscript is original work, has not been published previously, and is not under consideration for publication elsewhere. All sources have been appropriately cited.

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