Aswan University Medical Journal, volume 5 / No.3/ September 2025 (126-134) Online ISSN: **2735-3117**

ORIGINAL ARTICLE

Efficacy of adding Glucose Co-transporter 2 -Inhibitors in Treatment of Non-Valvular Paroxysmal Atrial Fibrillation

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ABSTRACT

Keyword: AF, SGLT2, MACE, Efficacy.

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Background: In individuals with type 2 diabetes mellitus, SGLT2 inhibitors have been demonstrated to lower blood pressure, decrease weight, improve left ventricular remodeling, and decrease hospitalization for heart failure and cardiovascular death. **Objectives:**The aim of this study was to evaluate the efficacy of SGLT2 inhibitors on the AF cardiovascular outcome. **Methodology:**This single-blinded randomized controlled trial was carried out on 60cases with non-valvular paroxysmal atrial fibrillation at the cardiology department, Aswan University Hospitals. **Results:**the change in LAD% and LAV-i% was significantly lower in group A (those who received SGLT2 inhibitors) compared to group B (those who did not receive SGLT2 inhibitors), both in absolute terms and relative terms. In the same way, LAS absolute and relative % change showed a significant improvement in the study group compared to control**.** After adjusting for all correlates, it was found that adding SGLT-2 to the standard treatment resulted in reduction of the risk of MACE by 32% (AOR= 0.678, 95% CI; 0.071 – 0.984, p=0.043) compared with those treated with the standard regimen.**Conclusion:**the addition of SGLT-2I to patients' existing guideline-directed medical therapy for non-valvular paroxysmal AF was found to be independently associated with reduction in the short-term adverse effects of the disease.

INTRODUCTION

With an estimated prevalence of about 3% in adults aged ≥20, atrial fibrillation (AF) is the most prevalent arrhythmia in the world. It is considerably more common in those with diseases including hypertension, valvular heart disease, or chronic kidney disease**(1)**.

In order to prevent glucose reabsorption, increase urine glucose excretion, and lower blood glucose levels, sodium glucose cotransporter-2 (SGLT-2) inhibitors were created to specifically inhibit these transporters, which are only present in the kidneys' proximal convoluted tubule**(2)**.Several trialshad demonstrated the cardiovascular benefits of these medications on management of AF **(3-8)**. In individuals with type 2 diabetes mellitus, SGLT2 inhibitors have been demonstrated to lower blood pressure, decrease weight, improve left ventricular remodeling, and decrease hospitalization for heart failure and cardiovascular death**(9)**.

A post-hoc analysis of the DECLARE-TIMI 58 study revealed that dapagliflozin decreased the incidence of AF and atrial flutter-related events in type 2 DM patients, irrespective of their prior history of AF or atrial flutter. This finding pertains to the direct effects of SGLT2 inhibitors on AF**(9)**.

SGLT2 inhibitors may lower atrial fibrillation and atrial flutter as well as all-cause mortality in patients with type 2 diabetes, according to a meta-analysis of 16 trials. These results imply that by decreasing and/or reversing structural and electrical remodeling, SGLT2i may have anti-arrhythmic benefits**(10)**. The direct impact of SGLT2 inhibitors on left atrial remodeling in non-valvular paroxysmal atrial fibrillation, independent of diabetic status, has not yet been investigated.
The aim of this study was to evaluate the efficacy of SGLT2 inhibitors (dapagliflozin) on LA remodeling in non-valvular paroxysmal AF and on AF cardiovascular outcome.

PATIENTS AND METHODS

This study adopted a double-blinded Randomized Controlled Clinical Trial (RCT)and was carried out on 60cases with non-valvular paroxysmal atrial fibrillation at the cardiology department, Aswan University Hospitals. Sample size was calculated using G Power software version 3.1**(11)**. The alpha error = 0.05, power 80%, and the effect size was 0.4 in the mean of echocardiographic parameters **(2)**. The minimum required sample was60cases (30 cases treated with standard regimen plus SGLT-2and 30 treated with standard regimen only as control).
Non-valvular paroxysmal AF cases aged 18-60 years with Glomerular Filtration Rate (GFR) > 45 ml/min/1.73 m2and with normal or slightly dilated left atrium were included. In contrast, those with valvular heart diseases, hugely dilated LA, GFR <45 ml/min/1.73 m2, ischemic heart disease, or with ischemic stroke were excluded.

Randomization:

Random numbers were generated at the computer center. Eligible cases were randomly assigned into two equal groups i.e., **Group-I (Study group)**: included30patients with AF were treated with rhythm control, anticoagulants based on their CHADs VASc score, plus SGLT2 inhibitors (dapagliflozin), for six months and **Group-II (Control group):** included30patients with AF were treated with rhythm control, anticoagulants based on their CHADs VASc score only. Allocation was contained in opaque, sequentially numbered sealed envelopes.

Procedure

Every visit includes a comprehensive clinical evaluation that includes heart rate, rhythm, and full cardiac examination at baseline and at 6-months, as well as demographic data, other risk factors, past or current medication treatment history, history of an AF attack, and any new complaints or indications of decompensating HF. Thyroid function, serum electrolytes, PT, PC, INR, ECG, laboratory evaluation of diabetic condition and renal functions, and any other research required given the patient's clinical circumstances

Non-invasive Imaging(Transthoracic Echocardiography was performed before treatment and at 6-months follow-up to detect the following i.e., Left atrium antero-posterior diameter in parasternal long axis view, Indexed LAV (LAV-i)**.**

Speckle tracking (STE) analysis of LA was performed to calculate LA strain (LAS)**.**

Following patient evaluation, a block randomization procedure was used to randomly assign the patients to receive medication containing dapagliflozin 10 mg once day. Patients were given one blinded tablet of the experimental drug, dapagliflozin, once daily for six months. Every month, 30 blinded dosages were administered to each participant. To monitor compliance, pill counts were conducted every three months. Both groups were followed up for 6-months to assess LA remodeling, recurrent presentation by paroxysmal AF, mortality rate and HF at hospital.

Statistical analysis: Shapiro-Wilk test and histograms were used to evaluate the normality of the data distribution. Quantitative parametric data, represented as mean and standard deviation (SD),

were evaluated using the unpaired student t-test. Quantitative non-parametric data, represented as the median and interquartile range (IQR), were assessed using the Mann Whitney test. The qualitative data, which were presented as frequency and percentage (%), were evaluated using the Chi-square test or Fisher's exact test as applicable. A p-value below 0.05 was considered statistically significant. The software utilized was SPSS version 26 (IBM Inc., Armonk, NY, USA) **(12)**.

Ethical Consideration: IRB approval was given by the Faculty of Medicine's Medical Ethic Committee at Aswan University (IRB 693/11/22). The study was prospectively registered using clinical trial.gov (NCT05993897). The study was carried out in compliance with the CONSORT checklist for research ethics**(13)**and the guidelines provided in the Helsinki Declaration**(14)**. Before the study began, each patient's informed consent was obtained, and the study's purpose and title were thoroughly stated. All collected data was kept confidential and used only for scientific research. The quality of the medical care that each research participant received was unaffected by their decision to withdraw from the study at any time.

RESULTS

Sixty cases with non-valvular paroxysmal AF participated in this RCT. They were randomly allocated into two equal groups.

As shown in **Fig. 1-3**, both groups were matched for demographic characteristics (age [p=0.694] and sex [p=0.573])**(Fig. 1)**, the main risk factors (smoking [p=0.260], DM [p=452], renal disease [1.000] and HTN [p=0.573])**(Fig. 2)** and Restoration of sinus rhythm (p=0.612).

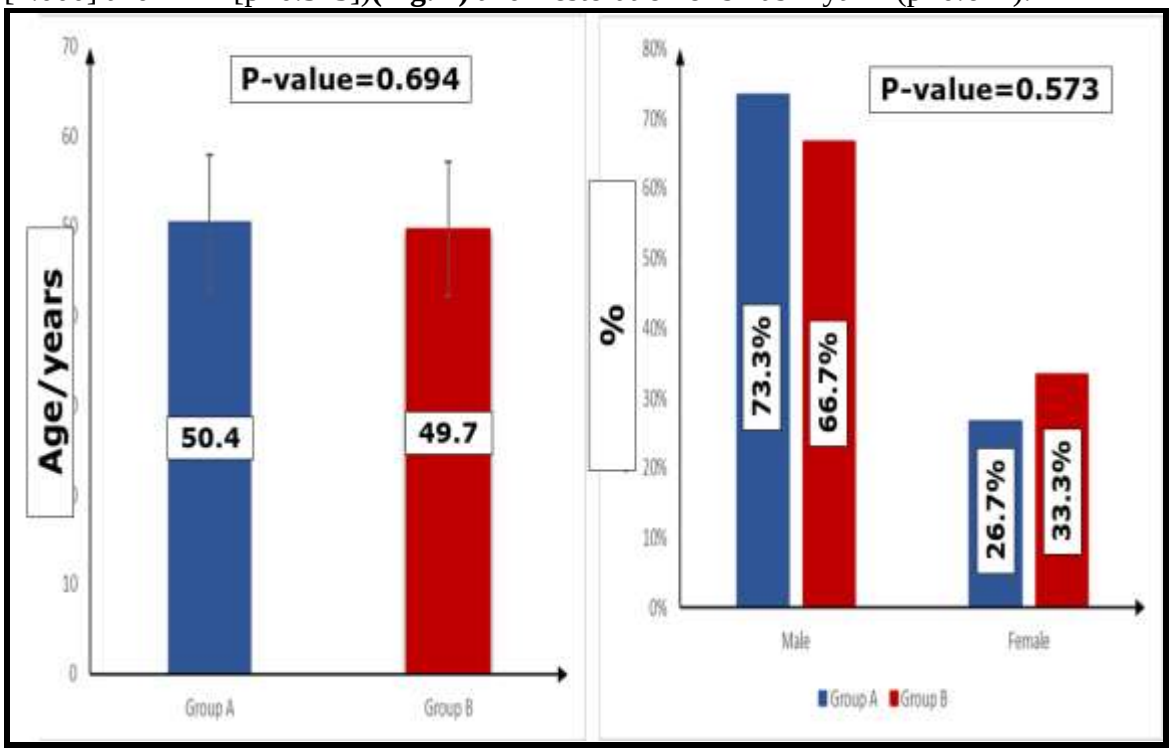

Fig. 1: Age and Sex Distribution of the studied groups

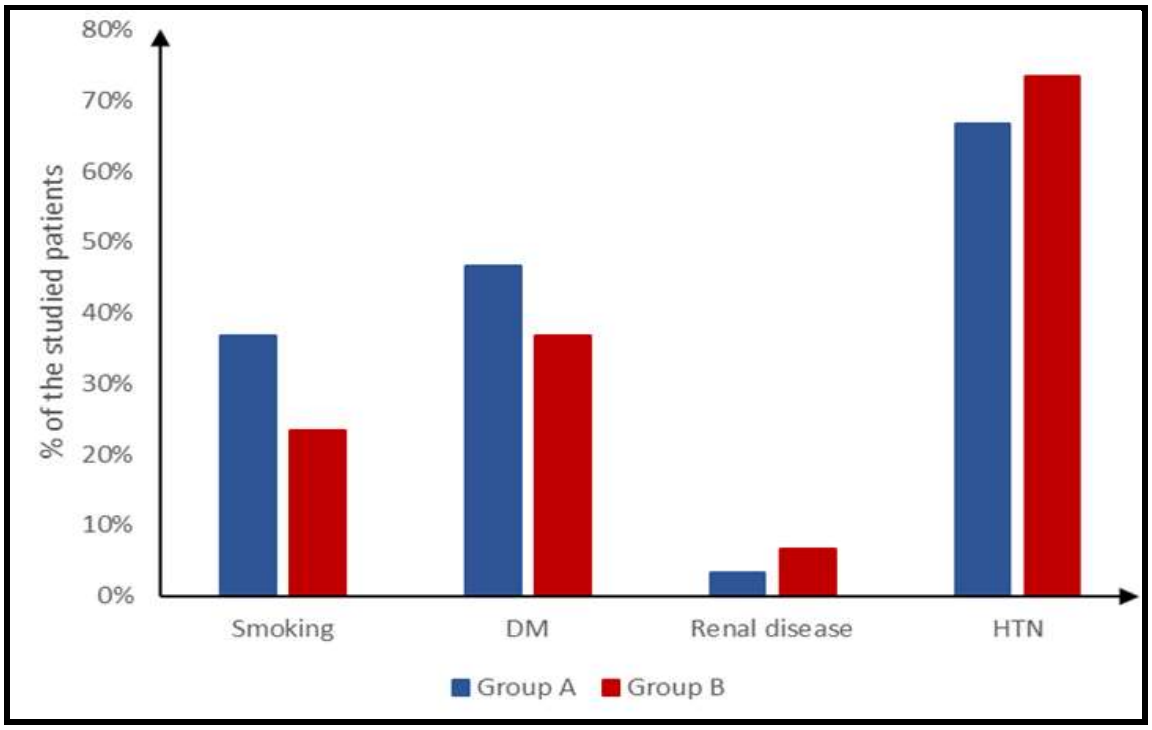

Fig. 2: Distribution of the studied groups according to Risk Factors

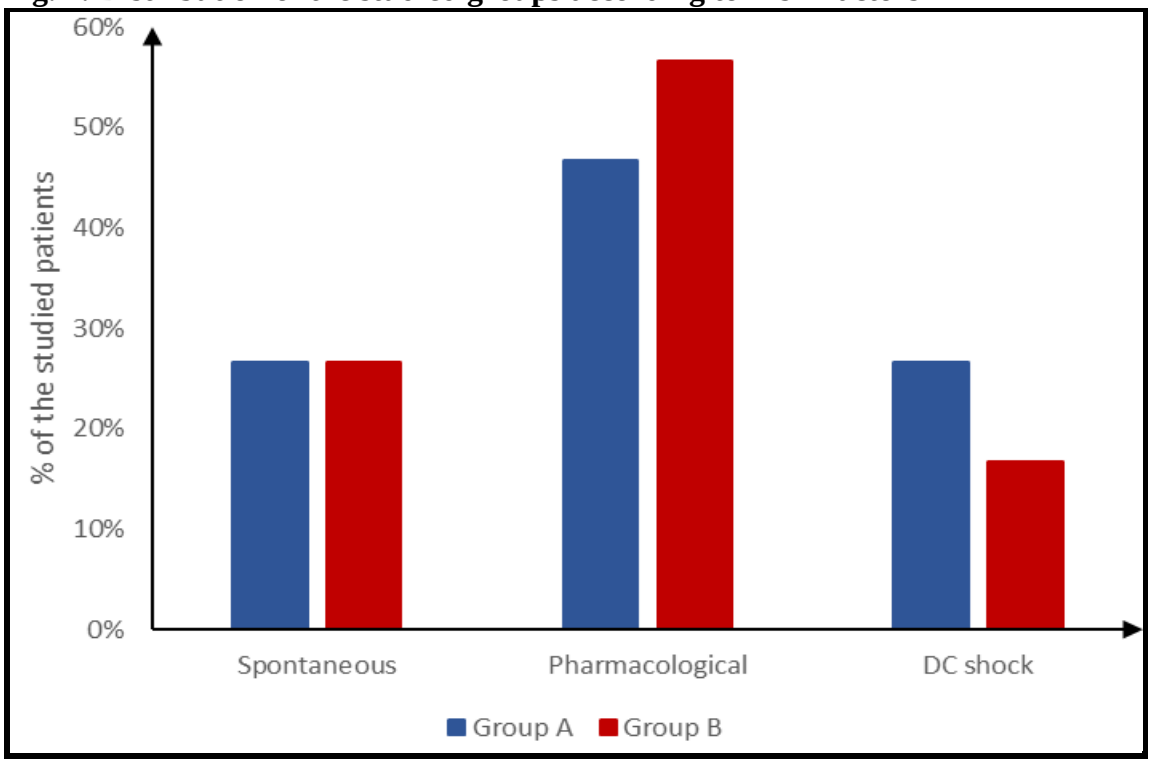

Fig. 3: Distribution of the studied groups according to Rhythm resolution

Table 1 showed the history of treatment of the studied groups. Non-significant difference was observed regarding medications (rhythm control [p=00000] and anticoagulant [p=0.821]) and

different anticoagulant therapy [p=0.638]. Contrarily, the study group had significantly (p=0.004) lower rate of recurrent AF history (90% [n=9] than control (66.7% [n=20]).

Table 1: Treatment history Differences of the studied groups

	Group A (n=30)	Group B (n=30)	P value*
Medications			
• **Rhythm control**	30 (100%)	30 (100%)	----
• **Anticoagulants**	24 (80%)	21 (70%)	= 0.821
Anti-coagulant			
• **NOACs**	21 (87.5%)	19 (90.5%)	= 0.638
• **Warfarin**	3 (12.5%)	2 (9.5%)	
Recurrent AF	9 (30%)	20 (66.7%)	**= 0.004**

***Chi-square test was used to compare Frequency between groups**

The mean values of baseline vital parameters were insignificantly different between groups i.e., HR (p=0.472), SBP (p=0.496) and DBP (p=0.418). Likewise, all basic laboratory investigations were comparable between groups (p>0.05). Parallel to that, both groups were matched for the Baseline Echocardiography findings (p>0.05).

Table 2: Treatment history Differences of the studied groups

	Group A (n=30)	Group B (n=30)	P value*
HR (beat/min)			
• **Mean ± SD**	131.97 ± 27.36	136.83 ± 24.58	= 0.472
• **Range**	76 - 159	72 - 158	
SBP (mm/hg)			
• **Mean ± SD**	123.2 ± 37.3	129.73 ± 36.64	= 0.496
• **Range**	65 - 179	68 - 176	
DBP (mm/hg)			
• **Mean ± SD**	79.1 ± 31.01	85.5 ± 29.77	= 0.418
• **Range**	46 - 132	48 - 130	

***Independent t-test was used to compare mean between groups**

HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure

As shown in **Fig.4**, The absolute and relative changes in LAD% were significantly (p<0.001) lower inthe study group compared withcontrol (relative% change: -8.8% vs. 3.5%, and absolute% change: -3.9 vs. 1.54 mm.). Likewise, there was a significant (p<0.001) decrease in the LAVI absolute and relative % change in the study group than control i.e. absolute% change: -4.04 vs 2.07 mm and relative% change: -9.7% vs 5.1%. As well, Group A, which got SGLT2 inhibitors, showed a substantial (p<0.001) improvement in the absolute and relative percentage change of the LA strain compared to group B, which did not receive SGLT2 inhibitors (relative% change was 18.7% versus -7.8% and absolute% change was 4.01 versus 0.16 mm).

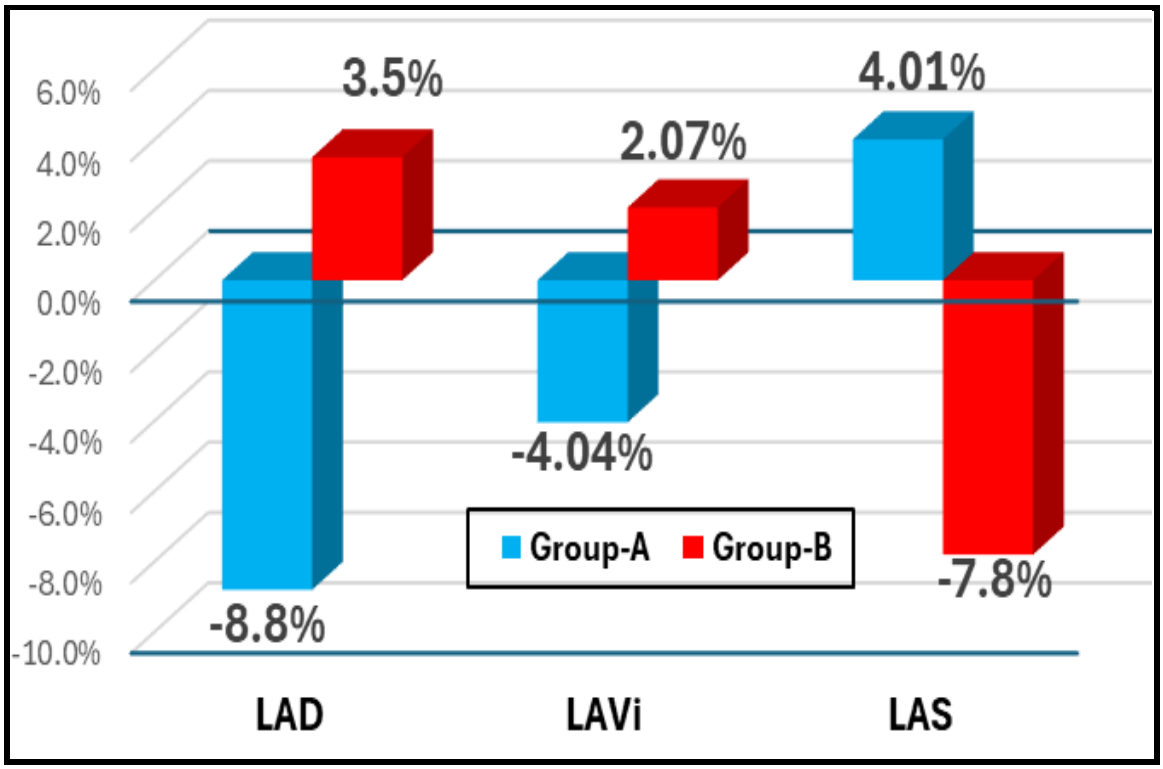

Fig.4: Percent Change in Echocardiography Parameters

The main outcome measures (total mortality, vascular mortality, heart failure hospitalization, and cerebrovascular stroke) showed insignificant difference between the two studied groups **(Fig. 5)**.

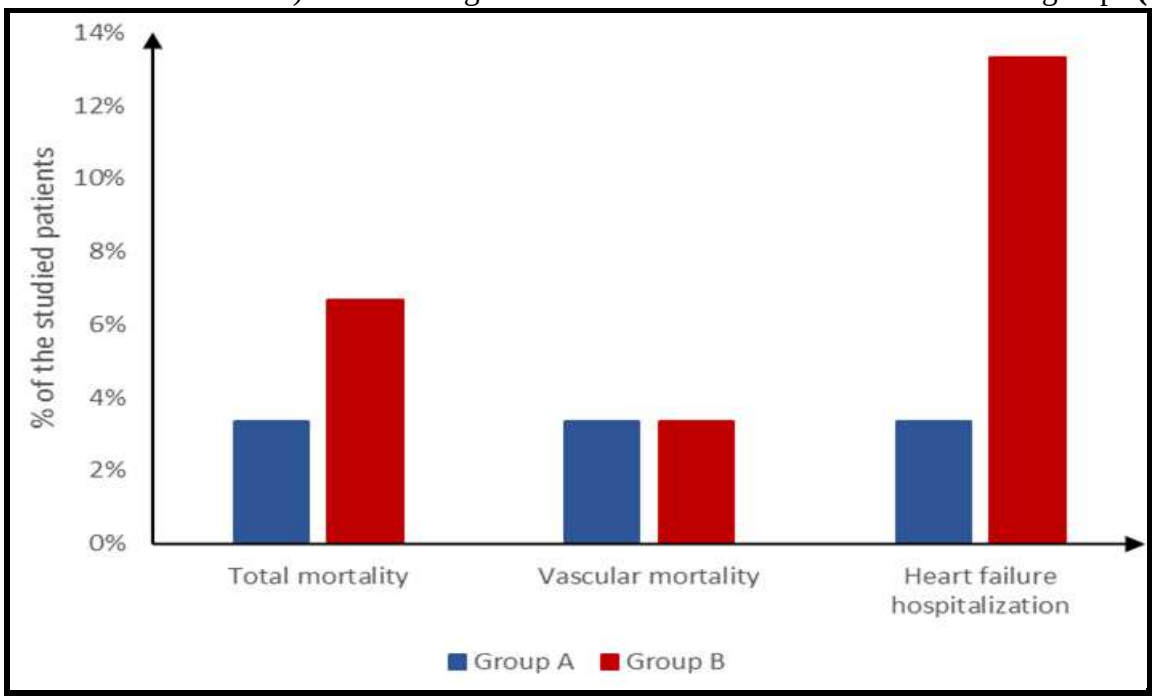

Fig.5: Outcomes of the studied groups

Table 3 showed the multivariable logistic regression model for the predictors of MACEamong the studied cohort. After adjusting for all correlates, it was found that adding SGLT-2 to the standard

treatment resulted in reduction of the risk of MACE by 32% (AOR= 0.678, 95% CI; 0.071 – 0.984, p=0.043) compared with those treated with the standard regimen.

Table 3: Predictors of MACE among the studied groups

Variable	Univariate		Multivariate	
	Unadjusted OR (95% CI)	**P-value**	**AOR (95% CI)**	**P-value**
Treatment (Study)	0.286 (0.53 – 1.549)	= 0.146	0.678 (0.071 – 0.984)	= **0.043**
Age/years	1.039 (0.927 – 1.165)	= 0.511		
Sex (Male)	1.447 (0.292 – 7.166)	= 0.651		
Hypertension	1.224 (0.188 – 7.959)	= 0.832		
DM	5.674 (0.668 – 22.260)	= 0.762	6.107 (1.044 – 9.924)	= **0.043**
Smoking	1.664 (0.811 – 14.718)	= 0.342		
Renal Disease	1.007 (0.934 – 1.084)	= 0.861		
Recurrent AF	2.906 (1.091 – 5.060)	= **0.002**	1.903 (1.011 – 6.343)	= **0.039**
LAD (post-)	1.441 (1.071 – 2.128)	= **0.008**	1.213 (1.045 – 1.408)	= **0.011**
LAV-i (post-)	2.084 (1.064 – 4.678)	= **0.016**		
LAS (post-)	1.597 (1.011 – 5.052)	= **0.027**		

AOR, Adjusted Odds Ratio; CI, Confidence Interval

DISCUSSION

The current study included 60 at Aswan University Hospitals' cardiology department who had non-valvular paroxysmal atrial fibrillation.The current study aimed to assess the effects of dapagliflozin (an SGLT2 inhibitor) on the CV outcome of AF and left atrial remodeling in non-valvular paroxysmal AF. AF is thought to be the most common persistent cardiac arrhythmia causing mortality all over the world.

In this study, demographic data, comorbidities, baseline echocardiography, and biochemistry results between the two groups in this study did not differ significantly. This was consistent with El-Saied et al., who found similar results across the groups**(15)**.

The present work showed that in the study group, there was a significant reduction in LAD and LAV-i. In contrast, the study group showed a significant improvement in LA average strain.Furthermore, the change in LAD% and LAV-i% was significantly lower in group A (those who received SGLT2 inhibitors) compared to group B (those who did not receive SGLT2 inhibitors), both in absolute terms and relative terms. In the same way, LAS absolute and relative % change showed a significant improvement in the study group compared to control. This was in agreement withEl-Saied et al.**(15)**.

In the present work, MACE parameters (total/vascular mortality, HF hospitalization, and CVS were insignificantly different between the studied groups. In line with this, a meta-analysis by Li et al. revealed consistent results **(16)**. Also, Zinman et al. conducted a study in which patients were randomly assigned to receive either a placebo or 10 mg or 25 mg of empagliflozin once daily. The findings indicated that the rates of hospitalization for heart failure, all-cause mortality, and cardiac mortality were insignificantly lower in the empagliflozin group compared to the placebo group**(3)**.

The efficacy of adding SGLT2 in the treatment of AF was shown in the multivariable model i.e., after adjusting for all factors, there was independently better results in the study group regarding the adverse outcomes (there was 32% (AOR= 0.678, 95% CI; 0.071 – 0.984, p=0.043) reduction in the

risk of MACE in cases treated with rhythm control in addition to anticoagulant according CHADs VASc score and SGLT2 inhibitors (Dapagliflozin) compared with those treated with the standard regimen.

Alongside our research, Böhm et al. found that the incidence of outcomes was lower with empagliflozin than with placebo. The frequencies of new-onset AF as determined by the electrocardiogram were low (1.6% for placebo and 2.3% for empagliflozin)**(17)**. In consistent, according to Zhao et al., 2023, AF recurred in 33 patients (23.9%) from the SGLT2i group, while in total, it occurred in 150 patients (38.7%)**(18)**.This aligned with that of Peters, 2021 in a meta-analysis discovered that the incidence of cerebrovascular events was similar across groups (RR: 1.06; 95% CI 0.85–1.32; p = 0.59) **(19)**.

This could be explained by that empagliflozin and other sodium glucose co-transporter-2 (SGLT2) inhibitors are anti-hyperglycemic medications that enhance the kidneys' excretion of glucose. In patients with T2DMat high CVrisk, empagliflozin has been demonstrated to lower CV and all-cause mortality, HF hospitalizations, and halt the course of kidney disease **(20)**. Similar outcomes have been shown with various SGLT2 inhibitors in T2 DM at high CV risk, including individuals with and without a history of heart failure, with the exception of mortality advantages. In the HF population, AF is quite common and linked to higher rates of morbidity and death **(21)**.

Study Limitations

There were some limitations to the current study. Firstly, this was a single-center study which limits the study's external validity (generalization). Secondly, the limited follow-up duration and the incomplete MACE parameter examinations.

CONCLUSION AND RECOMMENDATION

In conclusion,the addition of SGLT-2I to patients' existing guideline-directed medical therapy for non-valvular paroxysmal AF was found to be independently associated with reduction in the short-term adverse effects of the disease.

In recommendation, further studies are needed with multicenter cooperation and larger sample sizes to validate our findings. Interpretation and correlation ofSGLT2 cardiovascular benefits on cardiac mechanics by different conventional echo- cardio graphic parameters should be thoroughly studied. Longer follow-up periods are needed to support our study's findings.

Acknowledgement:

The authors wish to thankthe medical and administrative staff of the cardiology departments, Aswan University Hospital for the consistent help and support. It was not possible to complete this work without the help and support of the recruited patients.

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