Original Article
DOI: https://doi.org/10.70749/ijbr.v2i02.411

INDUS JOURNAL OF BIOSCIENCES RESEARCH
https://induspublisher.com/IJBR
ISSN: 2960-2793/ 2960-2807

Frequency and Factors Leading to Non-Adherence to SGLT-2 Inhibitors in Patients with Ischemic Heart Disease

Atta ur Rehman URF Saleem[1], Navedullah Khan[1], Gulzar Ali Buriro[1], Mukesh Kumar[1], Amin Ullah[1], Jibran ul Haq[1], Hassan Ali[1]

[1]Department of Adult Cardiology, National Institute of Cardiovascular Diseases (NICVD), Karachi, Sindh, Pakistan.

ARTICLE INFO

Keywords

SGLT-2 Inhibitors, Non-adherence, Ischemic Heart Disease, Patient Education, Side Effects.

Corresponding Author: Atta ur Rehman URF Saleem,
Department of Adult Cardiology, National Institute of Cardiovascular Diseases (NICVD), Karachi, Sindh, Pakistan.
Email: saleemkundi@yahoo.com

Declaration

Author's Contributions: All authors contributed to the study and approved the final manuscript.
Conflict of Interest: The authors declare no conflict of interest.
Funding: No funding received.

Article History

Received: 28-11-2024
Revised: 17-12-2024
Accepted: 26-12-2024

ABSTRACT

Objective: To evaluate the frequency of non-adherence to sodium-glucose cotransporter-2 (SGLT-2) inhibitors in patients with ischemic heart disease (IHD) and identify factors contributing to non-adherence at National Institute of Cardiovascular Diseases Karachi, Pakistan. **Methodology:** A prospective descriptive study was conducted on 171 IHD patients prescribed SGLT-2 inhibitors at the National Institute of Cardiovascular Diseases, Karachi. Adherence was assessed using the MMAS-8© scoring system, categorizing patients into high adherence (score = 8), medium adherence (score 6–7), and low-adherence (score < 6), we will take a score of <6 as Non-adherence. Factors influencing adherence, including patient education about SGLT2 inhibitors, side effects, and cost, were analyzed. Statistical analysis was performed using chi-square tests with a significance level of $P \leq 0.05$. **Results:** Among 171 patients, 58 (33.91%) demonstrated high adherence, 42 (24.56%) had medium adherence, and 71 (41.53%) were non-adherent ($P = 0.003$). The primary factors influencing non-adherence included lack of patient education (24 patients, 14.03%, $P = 0.001$), side effects (19 patients, 11.11%, $P = 0.001$), and cost barriers (15 patients, 8.77%, $P = 0.001$). Dizziness was the most frequently reported side effect (12 patients, 63.16%). **Conclusion:** The study highlights significant non-adherence to SGLT-2 inhibitors, driven by education gaps, side effects, and cost issues. Addressing these factors through patient education about SGLT2 inhibitors, affordable access programs, and proactive side effect management can enhance adherence and improve cardiovascular outcomes in IHD patients.

INTRODUCTION

The use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors (Empagliflozin, Dapagloflozin) in managing patients with ischemic heart disease (IHD) represents a breakthrough in cardiovascular and diabetic care. These agents, initially developed for type 2 diabetes mellitus, have demonstrated significant cardiovascular benefits, including a reduction in heart failure and cardiovascular mortality.[1] Despite these benefits, adherence to SGLT-2 inhibitors remains suboptimal, posing challenges for achieving desired health outcomes in IHD patients. This study focuses on understanding the frequency of non-adherence and the factors influencing it among patients at the National Institute of Cardiovascular Diseases (NICVD), Karachi.

Non-adherence to prescribed therapies is a significant issue in managing chronic diseases. Globally, adherence rates for SGLT-2 inhibitors in cardiovascular patients vary, with studies reporting adherence rates around 67% during the first year.[2] Factors contributing to non-adherence include side

effects, cost, lack of awareness, and complex medication regimens.[3]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have proven transformative in managing ischemic heart disease (IHD) and heart failure, with benefits extending beyond glycemic control. These drugs significantly reduce hospitalizations and improve cardiovascular outcomes, making them critical in cardiology.[4,5] Mechanistic studies reveal that SGLT-2 inhibitors enhance myocardial energy efficiency and reduce systemic inflammation, which are pivotal for cardiovascular benefits.[6] Additionally, renal protection provided by these agents further complements their role in managing cardiovascular and renal comorbidities.[7]

Adherence rates remain suboptimal globally, with studies showing that only 67–80% of patients maintain adequate adherence within the first year. This is often driven by side effects and cost barriers.[8] In low- and middle-income countries like Pakistan, socioeconomic factors and limited awareness exacerbate adherence challenges.[9] Side effects such as dizziness and urogenital infections, though mild, significantly contribute to discontinuation rates. Addressing these through patient education and monitoring can substantially improve adherence.[10] Recent clinical trials confirm the robust cardiovascular benefits of SGLT-2 inhibitors across populations with and without diabetes.[11]

In Pakistan, cardiovascular diseases, including IHD, are among the leading causes of morbidity and mortality.[12] SGLT-2 inhibitors, such as dapagliflozin and empagliflozin, have been pivotal in reducing healthcare burdens associated with cardiovascular complications. However, adherence data specific to the Pakistani population is scarce, underscoring the need for localized studies.

SGLT-2 inhibitors have shown efficacy in improving cardiac outcomes in patients with diabetes and IHD. They reduce hospitalization rates, improve ejection fraction, and lower mortality, making them essential in managing these comorbidities.[13] Furthermore, their ability to reduce adverse cardiac events in acute coronary syndrome patients has been validated through systematic reviews.[14]

Adherence to medications like SGLT-2 inhibitors is influenced by several factors, including patients' perceptions of medication benefits, socioeconomic barriers, and adverse effects.[15] In Pakistani clinical settings, financial constraints and lack of awareness are prominent barriers.[16] Studies emphasize the need for patient education and financial support mechanisms to improve adherence.

The high prevalence of IHD in Pakistan and the proven benefits of SGLT-2 inhibitors highlight the importance of addressing adherence. Identifying factors leading to non-adherence will guide interventions to optimize the use of these medications in local settings.[17]

The objective of this study is to determine the frequency of non-adherence to SGLT-2 inhibitors in patients with ischemic heart disease and to identify the factors leading to non-adherence in the population served by the Department of Cardiology, NICVD, Karachi.

MATERIALS AND METHODS

This prospective descriptive study was conducted in the Department of Cardiology at the National Institute of Cardiovascular Diseases (NICVD), Karachi. The data collection period spanned from June 2024 to November 2024.

The sample size was calculated to include 171 patients, using the WHO formula for sample size determination. The calculation was based on a non-adherence proportion of 32%, with a 95% confidence interval and a 7% margin of error. The reference for the non-adherence proportion was a study by Sara Denicolò et al., which highlighted medication non-adherence and its impact on renal and cardiovascular outcomes.[18]

All patients diagnosed with ischemic heart disease (IHD) and prescribed SGLT-2 inhibitors during the study period were included. Eligible participants were adults of either gender, aged between 18 and 75 years. Patients with comorbidities such as liver cirrhosis, chronic kidney disease, or immunosuppression, and those with contraindications to SGLT-2 inhibitors (including documented allergies, type 1 diabetes, or secondary causes of diabetes such as steroid-induced diabetes), were excluded. Pregnant or lactating women, individuals with a history of severe psychiatric disorders, those currently abusing illicit drugs, and patients unwilling to participate were also excluded.

Data were collected prospectively through direct patient interactions during outpatient visits to the Cardiology Outpatient Department (OPD) at NICVD. Information on patient demographics, clinical history, and adherence to prescribed SGLT-2 inhibitors was gathered through structured interviews and validated questionnaires. Variables such as age, gender, BMI, disease duration, ejection fraction (measured by transthoracic echocardiography), and socioeconomic status were recorded. Factors contributing to non-adherence, including perceived side effects, financial constraints, lack of accessibility, and lack of education about SGLT2 inhibitors were documented based on recorded patient interactions.

Non-adherence was defined as Intentional medication non-adherence whereby the patient chooses to deviate from the treatment regimen or Unintentional medication non-adherence whereby the patient may be careless or forgetful about adhering to treatment regimen. Non-adherence was ascertained by interviewing the patient using Morisky medication adherence scale-8 (MMAS-8©). Factors influencing non-adherence, such as cost, forgetfulness, lack of education about SGLT2 inhibitors and perceived side effects, were assessed based on patient interview.

Data were analyzed using statistical software. Descriptive statistics were calculated for continuous variables (mean ± standard deviation or median with interquartile range) and categorical variables (frequencies and percentages). The association between non-adherence and demographic or clinical factors was evaluated, with p-values ≤ 0.05 considered statistically significant. Specific statistical tests were applied based on the distribution and nature of the data.

The study protocol was reviewed and approved by the Ethical and Research Committee of NICVD, Karachi. All procedures adhered to the Declaration of Helsinki concerning research involving human subjects.

RESULTS

Overview and Patient Count

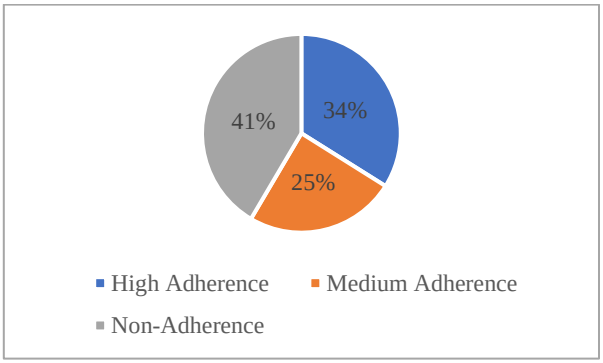
The study included a total of 171 patients to evaluate the frequency and factors contributing to non-adherence to SGLT2 inhibitors. Adherence levels were categorized into High Adherence, Medium Adherence, and Non-Adherence based on the MMAS-8© scoring system. Among these patients, 58 (33.91%) were highly adherent (score = 8), 42 (24.56%) exhibited medium adherence (score 6–7), and 71 (41.53%) were non-adherent (score < 6).

Adherence Levels

The adherence levels showed that a significant proportion of patients, 71 out of 171 (41.53%), were non-adherent, scoring below 6 on the MMAS-8© scale. Meanwhile, 58 patients (33.91%) demonstrated high adherence, and 42 patients (24.56%) had medium adherence. These results, analyzed using a chi-square test, were statistically significant (P-value: 0.003). Figure 1 provides a visual representation of the distribution of adherence levels. The pie chart emphasizes the significant proportion of non-adherence among the cohort.

Figure 1

Adherence Levels to SGLT2 Inhibitors



Non-Adherence Factors

The analysis of non-adherence factors identified a lack of patient education about SGLT2 inhibitors as the most common issue, affecting 24 patients (14.03%), followed by side effects in 19 patients (11.11%). Cost and accessibility were significant barriers for 15 patients (8.77%). These factors were found to be statistically significant (P-value: 0.001). Table 1 provides a detailed outline of these factors.

Table 1

Factors Contributing to Non-Adherence

Factors	Count (%)
Forgetfulness	3 (1.75)
Poly-Pharmacy	10 (5.84)
Cost & Accessibility Issues	15 (8.77)
Side Effects	19 (11.11)
Lack of Patient Education	24 (14.03)
P-value	0.001

Side Effects Among Non-Adherent Patients

Of the 19 patients reporting side effects, dizziness was the most common complaint (12 patients, 63.16%), followed by itching/allergy (3 patients, 15.79%) and burning micturition (2 patients, 10.53%). Statistical analysis confirmed significance with a P-value of 0.05. The distribution of side effects is shown in Table 2.

Table 2

Reported Side Effects Among Non-Adherent Patients

Side Effect	Count (%)
Dizziness	12 (63.16%)
Itching/Allergy	3 (15.79%)
Burning Micturition	2 (10.53%)
Non-Specific	2 (10.53%)
P-value	0.05

Statistical Analysis

The statistical analysis revealed significant links between adherence and certain non-adherence factors ($P < 0.05$). These results suggest that enhancing patient education about SGLT2 inhibitors, reducing cost barriers, and managing side effects could improve adherence rates. A chi-square test was employed for categorical variables to ensure a thorough evaluation of the dataset.

DISCUSSION

This study evaluated the adherence rates to sodium-glucose cotransporter-2 (SGLT-2) inhibitors among ischemic heart disease (IHD) patients at a tertiary care center in Pakistan. Key findings revealed that 41.53% of patients were non-adherent to SGLT-2 inhibitors, with lack of patient education about SGLT2 inhibitors (14.03%), side effects (11.11%), and cost and accessibility issues (8.77%) as the primary factors. Notably, dizziness was the most common side effect leading to non-adherence (63.16%). These findings emphasize the need for patient-centric interventions to address barriers to adherence.

Globally, adherence to SGLT-2 inhibitors in cardiovascular patients has been explored, with adherence rates ranging from 67% to 80% in the first year, as reported by multiple studies.[19,20] For example, research conducted in Europe and North America has consistently shown that factors such as side effects, cost, and complex medication regimens impact adherence rates. These findings align with our study, underscoring universal challenges in adherence to these medications.

Despite the widespread adoption of SGLT-2 inhibitors in managing IHD, limited data exist on adherence rates specific to the Pakistani population. While a few local studies have addressed the clinical efficacy of these medications in diabetic populations,[12] there is a scarcity of research focusing on adherence in the context of IHD. This study fills this critical gap by providing localized insights into the factors influencing adherence.

Local literature has extensively documented the burden of cardiovascular diseases, with a strong emphasis on preventive strategies and treatment outcomes.[7] However, adherence to advanced pharmacotherapies like SGLT-2 inhibitors has not been adequately explored. The few available studies have primarily focused on general medication adherence without specific attention to SGLT-2 inhibitors, highlighting the originality and significance of this research.

Our study identified a lack of patient education about SGLT2 inhibitors as the leading factor for non-adherence, affecting 14.03% of patients. This finding echoes international studies, which have highlighted the role of patient awareness in improving adherence rates.[21] Educational interventions, including counseling and structured follow-ups, have been proven effective in mitigating this barrier. Implementing similar strategies in local healthcare settings could significantly improve adherence.

Side effects, particularly dizziness, were another major contributor to non-adherence in our cohort. This is consistent with previous research, which has documented mild but impactful side effects of SGLT-2 inhibitors.[22] While these adverse effects are generally manageable, proactive monitoring and patient counseling are essential to address patient concerns and improve treatment persistence.

Cost and accessibility challenges were significant barriers for 8.77% of patients. These findings align with studies from other low- and middle-income countries, where financial constraints often limit access to advanced therapies.[2] Policymakers and healthcare providers must prioritize affordable access to these medications, particularly for socioeconomically disadvantaged populations.

The study's findings underscore the multifaceted nature of medication adherence. While pharmacological benefits of SGLT-2 inhibitors are well-established, real-world challenges such as patient education about SGLT2 inhibitors, side effects, and socioeconomic factors critically influence their effective utilization. Addressing these barriers requires a holistic approach that integrates patient-centric care, affordable healthcare policies, and continuous monitoring.

Study Limitations and Future Directions

This study has some limitations. First, the prospective design involved direct patient interactions, which, while comprehensive, may introduce interviewer biases. Second, the single-center setting may limit the generalizability of the findings to other regions of Pakistan. Additionally, self-reported adherence measures, such as the MMAS-8© scale, are subjected to recall and social desirability biases.

Future research should focus on multi-center prospective studies to validate these findings across diverse populations. Additionally, intervention-based studies exploring the effectiveness of educational and financial support programs in improving adherence to SGLT-2 inhibitors would provide actionable insights for healthcare providers.

CONCLUSION

This prospective study evaluated frequency of non-adherence to sodium-glucose cotransporter-2 (SGLT-2) inhibitors among ischemic heart disease (IHD) patients and identified key barriers to adherence, including lack of patient education, side effects, and cost challenges. Through direct patient interactions, 41.53% of patients were found to be non-adherent, highlighting critical areas for intervention to optimize clinical outcomes.

Future efforts should focus on enhancing patient education about SGLT-2 inhibitors, addressing cost barriers through affordable access programs, implementing structured counseling initiatives, improving side effect monitoring and management, and leveraging digital health tools to support adherence. These steps, grounded in observations from prospective data collection, will ensure better utilization of SGLT-2 inhibitors and improved cardiovascular outcomes for IHD patients.

REFERENCES

[1] Malik, M., Falkentoft, A., Jensen, J., Andersson, C., Parveen, S. L., Koeber, L., & Schou, M. E. M. (2022). Adherence and discontinuation of sglt2-inhibitors and glp1-r agonists in patients with type 2 diabetes with and without cardiovascular disease. *European Heart Journal*, *43*(Supplement_2). https://doi.org/10.1093/eurheartj/ehac544.2692

[2] Kono, S., Moon, J., Chong, A., Fang, J., Ko, D. T., Austin, P., Atzema, C., Naimark, D., Udell, J. A., Stukel, T., Tu, K., Booth, G., & Jackevicius, C. (2023). Abstract 15684: Adherence and Persistence to SGLT2 Inhibitors in Patients With Heart Failure. *Circulation*, *148*(Suppl_1). https://doi.org/10.1161/circ.148.suppl_1.15684

[3] Khartabil, N., Morello, C. M., & Macedo, E. (2024). Predictive Modeling of Factors Influencing Adherence to SGLT-2 Inhibitors in Ambulatory Care: Insights from Prescription Claims Data Analysis. *Pharmacy*, *12*(2), 72–72. https://doi.org/10.3390/pharmacy12020072

[4] Cowie, M. R., & Fisher, M. (2020). SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nature Reviews Cardiology*, *17*(12), 761–772. https://doi.org/10.1038/s41569-020-0406-8

[5] Saad, M., Mahmoud, A. N., Elgendy, I. Y., Abuzaid, A., Barakat, A. F., Elgendy, A. Y., Al-Ani, M., Mentias, A., Nairooz, R., Bavry, A. A., & Mukherjee, D. (2017). Cardiovascular outcomes with sodium–glucose cotransporter-2 inhibitors in patients with type II diabetes mellitus: A

meta-analysis of placebo-controlled randomized trials. *International Journal of Cardiology*, *228*, 352–358. https://doi.org/10.1016/j.ijcard.2016.11.181

[6] Lopaschuk, G. D., & Verma, S. (2020). Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors. *JACC: Basic to Translational Science*, *5*(6), 632–644. https://doi.org/10.1016/j.jacbts.2020.02.004

[7] Li, X., Zhang, Q., Zhu, L., Wang, G., Ge, P., Hu, A., & Sun, X. (2021). Effects of SGLT2 inhibitors on cardiovascular, renal, and major safety outcomes in heart failure: A meta-analysis of randomized controlled trials. *International Journal of Cardiology*, *332*, 119–126. https://doi.org/10.1016/j.ijcard.2021.03.077

[8] Treewaree, S., Kulthamrongsri, N., Owattanapanich, W., & Krittayaphong, R. (2023). Is it time for class I recommendation for sodium-glucose cotransporter-2 inhibitors in heart failure with mildly reduced or preserved ejection fraction?: An updated systematic review and meta-analysis. *Frontiers in Cardiovascular Medicine*, *10*. https://doi.org/10.3389/fcvm.2023.1046194

[9] Fatima, A., Rasool, S., Devi, S., Talha, M., Waqar, F., Nasir, M., Khan, M. R., Jaffari, S. M. I. A., Haider, A., Shah, S. U., Sapna, F. N. U., Varrassi, G., Khatri, M., Kumar, S., Mohamad, T., Fatima, A., Rasool, S., Devi, S., Talha, M., & Waqar, F. (2023). Exploring the Cardiovascular Benefits of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: Expanding Horizons Beyond Diabetes Management. *Cureus*, *15*(9). https://doi.org/10.7759/cureus.46243

[10] Verma, S. (2019). Potential Mechanisms of Sodium-Glucose Co-Transporter 2 Inhibitor-Related Cardiovascular Benefits. *The American Journal of Cardiology*, *124*, S36–S44. https://doi.org/10.1016/j.amjcard.2019.10.028

[11] Mohebi, R., & Januzzi, J. L. (2021). Cardiovascular benefit of SGLT2 inhibitors. *Critical Reviews in Clinical Laboratory Sciences*, *59*, 1–14. https://doi.org/10.1080/10408363.2021.1993439

[12] Khan, M. S. (2021). SGLT2 inhibitors: A revolution in therapeutics of a major Non-Communicable Disease. *Journal of the Pakistan Medical Association*, 1–3. https://doi.org/10.47391/jpma.1192

[13] Owais, M., Ghulam, N., Yaqoob, N. Y., xMusharaf, M., Wahid, N. A., & x Izat, M. (2024). Role of SGLT2 inhibitors in improving cardiac functions (on Echocardiography) in patients having Diabetes Mellitus and ischemic heart disease. *Journal of University Medical & Dental College*, *15*(3). https://doi.org/10.37723/jumdc.v15i3.942

[14] Sinha, T., Khilji, F., Laraib, F., Fatima, F., Kaur, M., Chaudhari, S. S., Arrey Agbor, D. B., & Khan, A. (2024). The Effectiveness of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors on Cardiovascular Outcomes and All-Cause Mortality in Patients With Acute Coronary Syndrome: A Systematic Review and Meta-Analysis. *Cureus*. https://doi.org/10.7759/cureus.58019

[15] Graversen, C., Valentin, J., Larsen, M., Riahi, S., Holmberg, T., Zinckernagel, L., & Johnsen, S. (2021). Lower perception of pharmacological treatment increases risk of non-adherence to medication. *European Journal of Preventive Cardiology*, *28*(Supplement_1). https://doi.org/10.1093/eurjpc/zwab061.258

[16] Alamgir, M. (2023). Improved treatment for diabetes type 2 associated heart failure. *Journal of Pakistan Medical Association*, *73*(9), 1934–1935. https://doi.org/10.47391/jpma.8085

[17] Ala, M. (2021). SGLT2 inhibition for cardiovascular diseases, chronic kidney disease and NAFLD. *Endocrinology*. https://doi.org/10.1210/endocr/bqab157

[18] Denicolò, S., Perco, P., Thöni, S., & Mayer, G. (2021). Non-adherence to antidiabetic and cardiovascular drugs in

type 2 diabetes mellitus and its association with renal and cardiovascular outcomes: A narrative review. *Journal of Diabetes and Its Complications*, *35*(7), 107931. https://doi.org/10.1016/j.jdiacomp.2021.107931

[19] Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., Mattheus, M., Devins, T., Johansen, O. E., Woerle, H. J., Broedl, U. C., & Inzucchi, S. E. (2015). Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine*, *373*(22), 2117–2128. https://doi.org/10.1056/nejmoa1504720

[20] Neal, B., Perkovic, V., Mahaffey, K. W., de Zeeuw, D., Fulcher, G., Erondu, N., Shaw, W., Law, G., Desai, M., & Matthews, D. R. (2017). Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine*, *377*(7), 644–657. https://doi.org/10.1056/nejmoa1611925

[21] Taibanguay, N., Chaiamnuay, S., Asavatanabodee, P., & Narongroeknawin, P. (2019). Effect of Patient Education on Medication Adherence of Patients with Rheumatoid arthritis: a Randomized Controlled Trial. *Patient Preference and Adherence*, *13*(1), 119–129. https://doi.org/10.2147/ppa.s192008

[22] Perkovic, V., Jardine, M. J., Neal, B., Bompoint, S., Heerspink, H. J. L., Charytan, D. M., Edwards, R., Agarwal, R., Bakris, G., Bull, S., Cannon, C. P., Capuano, G., Chu, P.-L., de Zeeuw, D., Greene, T., Levin, A., Pollock, C., Wheeler, D. C., Yavin, Y., & Zhang, H. (2019). Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *New England Journal of Medicine*, *380*(24), 2295–2306. https://doi.org/10.1056/nejmoa1811744