Efficacy and Safety of Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) in Cardiac Amyloidosis: A Systematic Review : Study protocol

Efficacité et sécurité des Inhibiteurs du Sodium-Glucose Cotransporteur 2 dans l'amylose cardiaque: Protocole d'une revue systématique

Rim Bourguiba[1], Saoussen Antit[2], Sarra Ben Rejab[3], Syrine Bellakhal[1], Lilia Zakhama[2]

1. Université Tunis EL Manar, Faculté de medecine de Tunis, Department of internal medicine, Hopital des Forces de sécurité de l'intérieur, La Marsa, Tunisia
2. Université Tunis EL Manar, Faculté de medecine de Tunis, Department of cardiology Hopital des Forces de sécurité de l'intérieur, La Marsa, Tunisia
3. Université Tunis EL Manar, Faculté de medecine de Tunis, Department of Anatomopathology, Hôpital des Forces de sécurité de l'intérieur, La Marsa, Tunisia

Abstract

Background: Sodium-glucose transport protein 2 inhibitors (SGLT2i) have revolutionized the management of heart failure and renal dysfunction. Cardiac amyloidosis, an underdiagnosed cause of heart failure, primarily results from light-chain (AL) or transthyretin (ATTR) deposition. Emerging evidence suggests that SGLT2i may improve cardiac and renal outcomes in these patients. However, data on their efficacy and safety in cardiac amyloidosis remain limited. This study aimed to conduct a systematic review to evaluate the efficacy and safety of SGLT2i in cardiac amyloidosis.

Methods: This systematic review and meta-analysis followed PRISMA guidelines and was registered on PROSPERO (CRD42024584183). A comprehensive search was performed across PubMed, Embase, Google Scholar, ScienceDirect, and Cochrane Library databases, including studies involving adult patients with AL or ATTR cardiac amyloidosis. Outcomes analyzed included cardiovascular mortality, heart failure hospitalizations, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), NT-proBNP, renal parameters, and adverse events. Data were synthesized using a random-effects model to account for heterogeneity, with effect measures expressed as risk ratios (RR) or mean differences (MD) and 95% confidence intervals (CIs).

Results: Preliminary findings indicate that SGLT2i use in cardiac amyloidosis is associated with significant improvements in LVEF, NT-pro BNP levels, and renal parameters such as eGFR and albuminuria progression. A reduction in heart failure hospitalizations and stabilization of NYHA functional class were also observed. Adverse events, including genitourinary infections and orthostatic hypotension, were reported but were consistent with known SGLT2i safety profiles. However, heterogeneity in study designs and small sample sizes limit definitive conclusions.

Conclusion: This systemic review highlights the potential of SGLT2i to improve functional and cardiovascular outcomes in cardiac amyloidosis while maintaining an acceptable safety profile. Despite these promising results, further randomized controlled trials are necessary to confirm the findings and define the role of SGLT2i in managing cardiac amyloidosis. Until then, clinicians should cautiously integrate SGLT2i into treatment strategies based on individual patient characteristics and clinical context.

Key words: cardiac amyloidosis Sodium-glucose transport protein 2 inhibitors

Résumé

Introduction: Les inhibiteurs du cotransporteur sodium-glucose de type 2 (iSGLT2) ont révolutionné la prise en charge de l'insuffisance cardiaque et rénale. L'amylose cardiaque, cause sous-diagnostiquée d'insuffisance cardiaque, résulte principalement de dépôts de chaînes légères (AL) ou de transthyrétine (ATTR). Des données émergentes suggèrent que les iSGLT2 pourraient améliorer le pronostic cardiaque et rénale chez ces patients. Toutefois, les données concernant leur efficacité et leur tolérance dans l'amylose cardiaque restent limitées. Cette étude avait pour objectif de réaliser une revue systématique afin d'évaluer l'efficacité et la sécurité des iSGLT2 dans l'amylose cardiaque.

Méthodes: Cette revue systématique et méta-analyse a été conduite selon les recommandations PRISMA et enregistrée sur PROSPERO (CRD42024584183). Une recherche exhaustive a été menée dans les bases de données PubMed, Embase, Google Scholar, ScienceDirect et Cochrane Library, incluant les études portant sur des patients adultes atteints d'amylose cardiaque AL ou ATTR. Les critères de jugement analysés comprenaient la mortalité cardiovasculaire, les hospitalisations pour insuffisance cardiaque, la classification NYHA, la fraction d'éjection ventriculaire gauche (FEVG), les taux de NT-proBNP, les paramètres rénaux, ainsi que les effets indésirables. Les données ont été synthétisées à l'aide d'un modèle à effets aléatoires afin de tenir compte de l'hétérogénéité, avec des mesures d'effet exprimées en ratios de risque (RR) ou en différences moyennes (DM) avec des intervalles de confiance (IC) à 95 %.

Résultats: Les résultats préliminaires indiquent que l'utilisation des iSGLT2 dans l'amylose cardiaque est associée à une amélioration significative de la FEVG, des taux de NT-proBNP, et des paramètres rénaux tels que le débit de filtration glomérulaire estimé (DFGe) et la progression de l'albuminurie. Une réduction des hospitalisations pour insuffisance cardiaque et une stabilisation de la classe fonctionnelle NYHA ont également été observées. Des effets indésirables, incluant des infections génito-urinaires et une hypotension orthostatique, ont été rapportés, mais restent cohérents avec le profil de tolérance connu des iSGLT2. Cependant, l'hétérogénéité des protocoles d'étude et les faibles tailles d'échantillon limitent la portée des conclusions.

Conclusion: Cette revue systématique vise à étudier le rôle des iSGLT2 dans l'amylose cardiaque ainsi que le profil de sécurité. Malgré ces résultats prometteurs, des essais contrôlés randomisés supplémentaires sont nécessaires pour confirmer ces observations et définir clairement la place des iSGLT2 dans la prise en charge de l'amylose cardiaque. En attendant, les cliniciens doivent intégrer prudemment ces agents dans leurs stratégies thérapeutiques, en tenant compte des caractéristiques individuelles et du contexte clinique.

Mots-clés : amylose cardiaque, inhibiteurs du cotransporteur sodium-glucose de type 2 (iSGLT2)

Correspondance

Rim Bourguiba

Department of internal medicine. Hôpital des forces de sécurité intérieure. La Marsa, Tunisia
Email: rim.bourguiba@fmt.utm.tn

LA TUNISIE MEDICALE-2025; Vol 103 (05): 550-552 DOI: 10.62438/tunismed.v103i5.5709

Background

Sodium-glucose transport protein 2 inhibitor (SGLT2i) represents a revolutionary treatment in the management of heart failure and kidney dysfunction. Cardiac amyloidosis is novel cause of heart failure that remains underdiagnosed[1] . Cardiac amyloidosis is mainly secondary to light chain deposition (AL amyloidosis) or Transthyrethin deposition (ATTR). SGLT2i seems to be a promising treatment to improve cardiac and renal outcome[2]. Few retrospective studies about safety and efficacity of SGLT2i in cardiac amyloidosis have been published[3–9].
The objective of this study is to conduct a systematic review to assess the efficacy and safety of SGLT2 inhibitors in cardiac amyloidosis, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Methods

Study design and context

This study is a systematic review and meta-analysis conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10]. The objective was to evaluate the efficacy and safety of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with cardiac amyloidosis. To ensure the robustness of our analysis, we established a detailed protocol prior to initiating the study. The protocol was registered in PROSPERO under the number CRD42024584183 to ensure transparency and reproducibility. This study synthesizes evidence from randomized controlled trials (RCTs), observational studies, and case series to provide a comprehensive assessment of the potential role of SGLT2i in this unique patient population.
The context of this study is driven by the increasing recognition of cardiac amyloidosis as a significant contributor to heart failure and the growing interest in repurposing SGLT2i for cardiovascular conditions beyond diabetes. While SGLT2i have demonstrated efficacy in heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), their role in cardiac amyloidosis remains underexplored.
Through this systemic review, we aim to provide clinicians and researchers with a consolidated understanding of the therapeutic potential of SGLT2i in cardiac amyloidosis, focusing on key outcomes such as functional improvement, cardiac remodeling, hospitalization rates, and safety profiles.

Search strategy: A comprehensive search will be conducted in electronic databases including PubMed, Embase, Google Scholar, ScienceDirect, and Cochrane Library, from inception to the present.
Keywords will include: "cardiac amyloidosis", "Transthyretin Amyloid Cardiomyopathy", "amyloid light-chain cardiomyopathy", "SGLT2 inhibitors" or its subclasses such as "Canagliflozin", "Dapagliflozin", "Empagliflozin", "Ertugliflozin", and "Sotagliflozin", "efficacy", "safety", "clinical outcomes", and "Heart failure".
Reference lists of relevant articles will also be hand-searched for additional studies. There will be no restriction on publication year. No language restrictions will be applied; however, non-English studies will be translated when necessary.
Search equation for PubMed: ("cardiac amyloidosis" OR "ATTR cardiomyopathy" OR "AL cardiomyopathy") AND ("SGLT2 inhibitors" OR "Canagliflozin" OR "Dapagliflozin" OR "Empagliflozin" OR "Ertugliflozin" OR "Sotagliflozin") AND ("efficacy" OR "safety" OR "clinical outcomes" OR "heart failure").

Participants/population

The study will include asymptomatic and symptomatic adults diagnosed with cardiac amyloidosis. The types of cardiac amyloidosis considered are: Amyloid light-chain cardiomyopathy (AL-CM), Transthyretin amyloid cardiomyopathy (ATTR-CM), including both acquired (ATTRwt-CM) and hereditary (ATTRv- CM) forms.

Comparator(s)/control

The comparator group will include patients with cardiac amyloidosis who do not receive SGLT2 inhibitors. These patients may be treated with placebo or may receive standard care without SGLT2 inhibitors. The standard care may include other amyloid-specific medications (e.g., Tafamidis) or heart failure treatments such as ACE inhibitors (ACE-i), angiotensin II receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), and beta-blockers.

Main outcome

Primary Outcomes:
1. Clinical Endpoints:
Cardiovascular death
Hospitalization due to heart failure
Worsening of the NYHA dyspnoea score
6-minute walk test results
2. Improvement in Cardiac , Renal Functions and hematological response :
Left ventricular ejection fraction
Changes in NT-proBNP levels
Troponin levels
Progression of albuminuria
eGFR (estimated Glomerular Filtration Rate)
Creatinine clearance (CrCL)
Hematological response to anti plasma cell therapy : blood and urine Freelight chain kappa and lambda in case of AL amyloidosis

Measure of effect

Cardiovascular death, heart failure hospitalisation: risk ratios (RRs) and 95% confidence intervals (CIs). Left

ventricular ejection fraction, NT-proBNP, eGFR, CrCl, Troponin, Albuminuria progression, 6-minute walk test: mean differences (MDs) and 95% CI's.

Additional outcome(s)

Secondary outcomes will include adverse events related to SGLT2 inhibitors use:
-Genitourinary infections
-Diabetic ketoacidosis
-Bone fractures
-Amputations
-Orthostatic hypotension

Data Extraction

Two independent reviewers will screen titles and abstracts, followed by full-text screening to determine eligibility. Studies not in English will be translated using Google Translate prior to extraction. If applicable, additional data provided by original trial authors will be added. Data extraction will include study characteristics, patient demographics, intervention details, and outcomes. Discrepancies will be resolved through discussion or third-party adjudication.

Risk of bias assessment

The Cochrane Risk of Bias tool will be used for RCTs, and the Newcastle-Ottawa Scale will be used for observational studies. Risk of bias will be independently assessed by two reviewers.

Statistical analysis

A random-effects model will be used to account for potential heterogeneity within and between subgroups. Interaction tests will be performed to determine if there is a statistically significant difference in the effects of SGLT2 inhibitors between subgroups.
For continuous outcomes, we will use mean differences with 95% confidence intervals.
For dichotomous outcomes, we will use relative risk (RR) or odds ratios (OR) with 95% confidence intervals. Subgroup analyses will be reported with p-values for interaction to assess the significance of differences between subgroups.

Software and tools:

- Reference Management: Zotero
- Screening and Selection: Rayyan software
- Statistical Analysis: Easymed stat

Conclusion

This systematic review highlights the potential efficacy and safety of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in the management of cardiac amyloidosis, a condition with significant unmet therapeutic needs. The findings suggest that SGLT2i may improve functional outcomes and cardiovascular parameters in this unique patient population, while maintaining a favorable safety profile. However, the current evidence is limited by the heterogeneity of studies and the relatively small sample sizes, emphasizing the need for well-designed, randomized controlled trials to confirm these results and define the precise role of SGLT2i in cardiac amyloidosis. Until then, clinicians should consider these findings in the context of individual patient profiles and existing treatment protocols. Our study provides a foundation for further research and underscores the importance of exploring innovative therapeutic approaches to improve outcomes in patients with cardiac amyloidosis.

References

1. Bloom MW, Gorevic PD. Cardiac Amyloidosis. Ann Intern Med 2023; 176: ITC33–ITC48.
2. Van Der Aart-van Der Beek AB, De Boer RA, Heerspink HJL. Kidney and heart failure outcomes associated with SGLT2 inhibitor use. Nat Rev Nephrol 2022; 18: 294–306.
3. Lang FM, Teruya S, Cuomo M, et al. Safety and Efficacy of SGLT2 Inhibitors for Amyloid Light-Chain Cardiomyopathy. Journal of Cardiac Failure 2024; 30: 1641–1646.
4. Steinhardt MJ, Cejka V, Chen M, et al. Safety and Tolerability of SGLT2 Inhibitors in Cardiac Amyloidosis—A Clinical Feasibility Study. JCM 2024; 13: 283.
5. Dobner S, Bernhard B, Asatryan B, et al. SGLT2 inhibitor therapy for transthyretin amyloid cardiomyopathy: early tolerance and clinical response to dapagliflozin. ESC Heart Failure 2023; 10: 397–404.
6. Porcari A, Cappelli F, Nitsche C, et al. SGLT2 Inhibitor Therapy in Patients With Transthyretin Amyloid Cardiomyopathy. Journal of the American College of Cardiology 2024; 83: 2411–2422.
7. Lang FM, Teruya S, Weinsaft A, et al. Sodium–glucose cotransporter 2 inhibitors for transthyretin amyloid cardiomyopathy: Analyses of short-term efficacy and safety. European J of Heart Fail 2024; 26: 938–947.
8. Pillai A, Riaz S, Arora S, et al. The Role of Sodium-Glucose Cotransporter-2 Inhibitors in Adults With Transthyretin Cardiac Amyloidosis: A Single-Center Retrospective Cohort Study. Cureus. Epub ahead of print 30 October 2024. DOI: 10.7759/cureus.72725.
9. Sivamurugan A, Byer SH, Grewal US, et al. Impact of SGLT2 inhibitors on the outcomes of patients with cardiac arrhythmias and transthyretin cardiac amyloidosis. Heart Rhythm 2024; S1547527124032922.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; n71.