VOL. 3, NO. 3, 2024
ISSN 2772-963X

Letters

RESEARCH LETTER

Impact of Sodium-Glucose Cotransporter 2 Inhibitors on Mortality in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic heart disease that can result in heart failure (HF) symptoms with associated increased mortality.[1] While outflow obstruction is the most visible etiology for symptoms in HCM, other factors such as impaired cardiac energetics can contribute. Additionally, there is no proven medical therapy for nonobstructive HCM with limiting HF symptoms, underscoring an important unmet treatment need.[1,2]

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have recently emerged as an important therapeutic option for non-HCM HF patients to reduce mortality, HF hospitalizations, and improve quality of life, regardless of ejection fraction or diabetes mellitus (DM) status.[3,4] One potential mechanism for the cardioprotective effects of SGLT2i is improving cardiac energetics, which might also benefit HCM patients.[3] In a recent small open-label study, SGLT2i were noted to improve symptoms in diabetic HCM patients.[5] However, there remains a paucity of data on SGLT2i on safety and impact on clinical outcomes in HCM.

The TriNetX Global Research Network, which provides deidentified electronic health records from >80 health care organizations for >115 million patients, was interrogated. Using the International Classification of Diseases-10th Revision codes, patients diagnosed with HCM (I42.1 or 142.2 for obstructive and nonobstructive HCM, respectively) from 2013 to 2021 were subdivided into 2 groups: those receiving SGLT2i (dapagliflozin, empagliflozin, canagliflozin, or ertugliflozin) and those who were not. To minimize potential inclusion of other common causes of left ventricular hypertrophy, patients with International Classification of Diseases-10th Revision code for HCM combined with aortic stenosis or systemic hypertension were excluded.

HCM patients were followed for 2 years, either from the first encounter when SGLT2i was initiated or from HCM diagnosis (for patients not treated with SGLT2i). The primary endpoint was all-cause mortality, and secondary endpoints were acute HF exacerbation, all-cause hospitalization, documented cardiovascular symptoms (chest pain, abnormal breathing, palpitations, and/or lower extremity edema), and potential SGLT2i-related adverse events (hypotension, syncope, urinary tract infection, and acute renal failure).

To control for differences, 1:1 propensity score matching was performed using the greedy nearest neighbor matching algorithm. ORs with 95% CIs were calculated. Kaplan-Meier survival curve for all-cause mortality was created using log-rank test.

We identified a total of 28,661 HCM patients: 511 (1.8%) on SGLT2i and 28,150 (98.2%) not. HCM patients on SGLT2i were older (55 $\pm$ 15 years vs 48 $\pm$ 19 years, $P < 0.01$), had a higher prevalence of obstructive HCM (43% vs 25%, $P < 0.01$) and comorbidities, including a nearly 6-fold higher prevalence of DM (42% vs 7%, $P < 0.01$) and HF (65% vs 11%, $P < 0.01$). After propensity score matching, each group consisted of 436 patients with similar demographics, including prevalence of obstructive HCM (42% vs 41%, $P = 0.63$), age, sex, and baseline comorbidities (body mass index, HF, cardiovascular symptoms, DM, chronic kidney disease, and insulin use) ($P > 0.05$ for each).

Over a 2-year follow-up period, HCM patients on SGLT2i had lower rates of all-cause mortality (OR 0.24, $P < 0.01$). Additionally, HCM patients on SGLT2i had lower rates of all-cause hospitalization (OR 0.69,

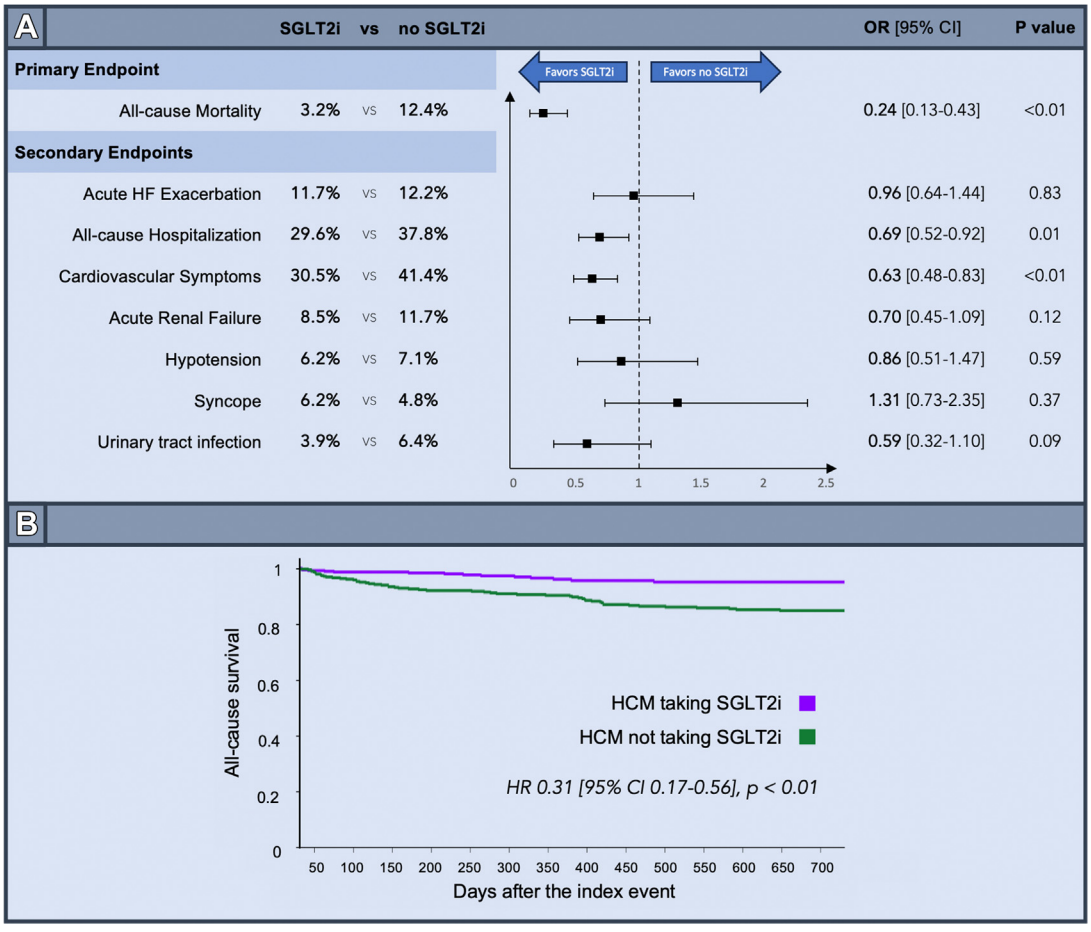
What is the clinical question being addressed?

Can SGLT2i improve clinical outcomes in HCM?

What is the main finding?

In a large real-world dataset, derived from electronic health records, the use of SGLT2i in a subset of HCM patients was safe and associated with improved survival, decreased hospitalizations, and less cardiovascular symptoms. These data justify randomized clinical trials to evaluate the efficacy of SGLT2i in HCM.

FIGURE 1 Outcomes in Propensity Matched HCM Patients on SGLT2i Compared to Those Not on SGLT2i



(A) Forest plot of ORs for 2-year outcomes in HCM patients taking SGLT2i compared to propensity-matched HCM patients not taking SGLT2i. (B) Kaplan Meier curve for all-cause survival in the same groups. HCM = hypertrophic cardiomyopathy; HF = heart failure; SGLT2i = sodium-glucose cotransporter 2 inhibitors.

$P = 0.01$) and cardiovascular symptoms (OR 0.63, $P < 0.01$) compared to propensity-matched HCM patients not on SGLT2i. There was no difference in the incidence of acute HF exacerbations ($P = 0.83$) or potential SGLT2i adverse events ($P > 0.09$ for each) (Figure 1).

In our present analysis, we demonstrate a favorable association of SGLT2i use in HCM with decreased mortality compared to HCM patients not on SGLT2i. Additionally, HCM patients on SGLT2i had lower hospitalization rates and less cardiovascular symptoms, suggesting improvement in HF-related quality of life.

The precise mechanism for the benefits of SGLT2i in HCM is unknown. However, their positive effect on myocardial bioenergetics and left ventricular remodeling in other forms of HF may explain their potential effectiveness for HCM.[1,2] While we did not find a difference in documented acute HF exacerbations with SGLT2i use in HCM, it is notable that acute HF exacerbation is uncommon in this disease.[1] The decrease in hospitalizations and documented cardiovascular symptoms supports a potential meaningful symptom improvement in addition to mortality. Moreover, we found low rates of potential SGLT2i adverse events including hypotension and syncope, supporting potential safety of SGLT2i use in HCM patients with other indications for initiation including DM and chronic kidney disease.

The subset of patients on SGLT2i was highly selective, representing only 1.8% of HCM patients in

this dataset. Nearly 45% of HCM patients on SGLT2i had DM, which is 6-fold higher than in the general HCM population and likely explains the rationale for SGLT2i initiation. Conversely, SGLT2i were likely initiated in the remaining HCM patients based on observed benefits in other forms of HF. Nevertheless, despite the older age and higher comorbidity burden in HCM patients on SGLT2i, a clear mortality benefit was demonstrated when propensity-matched to other HCM patients. The TriNetX database does not include detailed HCM phenotyping information with cardiac imaging; therefore, it is not possible to exclude the possibility for residual confounding. Additional prospective studies are necessary to determine if this observed benefit of SGLT2i remains consistent across a broader, well-phenotyped, and more traditional HCM patient population.

In conclusion, the favorable association of SGLT2i with reduced all-cause mortality, hospitalizations, and cardiovascular symptoms in HCM in this dataset supports the need for future randomized clinical trials to confirm their efficacy in HCM before routine clinical use can be recommended.

Amro Aglan, MD[a,*]
Ayman R. Fath, MD[b,*]
Abdullah S. Eldaly, MD[c]
Allen S. Anderson, MD[b]
Jason S. Phillips, MD[b]
Barry J. Maron, MD[a]
Martin S. Maron, MD[a]
***Ethan J. Rowin, MD**[a]

*Hypertrophic Cardiomyopathy Center
67 S. Bedford Street, Suite 302W
Burlington, Massachusetts 01803, USA
E-mail: Ethan.Rowin@lahey.org

From the [a]Hypertrophic Cardiomyopathy Center, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA; [b]University of Texas Health Science Center at San Antonio, Texas, USA; and the [c]Houston Methodist Hospital, Houston, Texas. USA.

https://doi.org/10.1016/j.jacadv.2024.100843

*Drs Aglan and Fath contributed equally to this work. Dr Maron is a consultant for Cytokinetics, iRhythm (with grant), Imbria Pharmaceuticals, TAKEDA Pharmaceuticals (with grant). Dr Rowin has received research funding from Pfizer, iRhythm. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Maron BJ, Rowin EJ, Udelson JE, Maron MS. Clinical spectrum and management of heart failure in hypertrophic cardiomyopathy. *J Am Coll Cardiol HF*. 2018;6:353-363.

2. Ranjbarvaziri S, Kooiker KB, Ellenberger M, et al. Altered cardiac energetics and mitochondrial dysfunction in hypertrophic cardiomyopathy. *Circulation*. 2021;144:1714-1731.

3. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 inhibitors. *J Am Coll Cardiol Basic Trans Science*. 2020;5:632-644.

4. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451-1461.

5. Subramanian M, Sravani V, Krishna SP, et al. Efficacy of SGLT2 inhibitors in patients with diabetes and nonobstructive hypertrophic cardiomyopathy. *Am J Cardiol*. 2023;188:80-86.