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Authors

Agarwal, Siddharth
Qamar, Usama
Fujiwara, Yu
et al.

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Brief Report

The Effect of Sodium-Glucose Cotransporter-2 Inhibitors on Cardiovascular Outcomes in Patients With Cancer: A Systematic Review and Meta-Analysis

Siddharth Agarwal, MD[a], Usama Qamar, MD[b], Yu Fujiwara, MD[c], Avirup Guha, MD, MPH[d], Abdul Rafeh Naqash, MD[a], Eric H. Yang, MD[e], Daniel Addison, MD[f], Ana Barac, MD, PhD[g], and Zain Ul Abideen Asad, MD, MS[a,*]

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Clinical practice guidelines recommend the use of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) to improve outcomes in patients with heart failure (HF).[1,2] Patients receiving certain cancer therapies are at increased risk of developing HF, which is associated with worse health-related quality-of-life metrics and clinical outcomes.[3] In patients receiving anthracyclines, the incidence of developing clinical HF can range from anywhere between 5% and 48%, depending on the cumulative anthracycline dose.[4] At present, there are limited data to support the use of HF therapies as a broad pharmacologic prevention strategy for patients with cancer who are at risk of developing HF, and the only class I recommendation as per the American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines for these patients includes the need for a multidisciplinary care discussion involving the patient about the risk/benefit ratio of cancer therapy interruption, discontinuation, or continuation.[1,4]

It is important to note that the clinical trials that established the benefits of SGLT-2i therapy in preventing HF and other cardiovascular outcomes had excluded patients with cancer.[1] A recent observational study suggested that SGLT-2i was associated with improved clinical outcomes in patients with cancer receiving cardio-toxic therapies.[5] However, given the paucity of published data, examining the totality of evidence on this subject is essential, and therefore, in this systematic review and meta-analysis, we examined the effects of SGLT-2i on the prevention of mortality and cardiovascular events in patients with active cancer receiving cardio-toxic cancer therapies.

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A systematic database search of EMBASE/Ovid, PubMed/MEDLINE, SCOPUS, and the Cochrane Library from inception until October 2023 using the search terms "SGLT2 inhibitors," "sodium-glucose transporter 2 inhibitors," "cardiotoxicity," "cancer," "chemotherapy," and "anthracycline" was performed. In addition, we manually reviewed the bibliography of included studies to identify other potential trials of interest. The primary outcome was all-cause mortality. The secondary outcomes included HF hospitalizations, clinically significant arrhythmias, and overall drug-related adverse events (Table 1). We also performed a subgroup analysis based on the nature of adverse events (infectious or noninfectious). The Mantel-Haenszel method was used to calculate the pooled risk ratio (RR) with a 95% confidence interval (CI). A random-effects model approach was used. The proportion of total variability in the estimates was summarized with the I^2 index. Heterogeneity was considered large when I^2 >50%. Statistical analysis was performed using the Review Manager (Version 5.4, Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The outcomes were compared in SGLT-2i and no SGLT-2i as the control group.

Overall, 4,097 patients (SGLT-2i = 1,649, no SGLT-2i = 2,448) from 4 observational studies were identified through a comprehensive database search of 242 studies.[5–8] No randomized controlled trials were identified. The mean age of patients included in the meta-analysis was 65.9 years, with 49.7% women, and a mean follow-up of 1.6 years. The characteristics of included patient populations are reported in Table 1.

In follow-up, 200 of 1,550 patients (12.9%) receiving an SGLT-2i died, compared with 599 of 1,614 patients (37.1%) who did not receive an SGLT-2i. The pooled estimate showed a statistically significant smaller risk of all-cause mortality with SGLT-2i use than with no SGLT-2i (RR 0.35, 95% CI 0.30 to 0.40, p <0.001, I^2 = 0%) (Figure 1).

A total of 91 of 1,649 patients (5.5%) receiving an SGLT-2i had an HF hospitalization, compared with 216 of 2,448 patients (8.8%) who did not receive an SGLT-2i. The

[a]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; [b]Department of Medicine, King Edward Medical University, Lahore, Pakistan; [c]Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, New York; [d]Cardio-Oncology Program, Medical College of Georgia at Augusta University, Augusta, Georgia; [e]UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, California; [f]Cardio-Oncology Program, The Ohio State University, Columbus, Ohio; and [g]Inova Schar Cancer Institute and Inova Heart and Vascular Institute, Fairfax, Virginia. Manuscript received December 24, 2023; revised manuscript received and accepted January 28, 2024.

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See page 90 for Declaration of Competing Interest.

*Corresponding author: Tel: 405-271-8001; fax: 405-271-2619.
E-mail address: drzainasad@gmail.com (Z.U.A. Asad).

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Table 1
Baseline characteristics of the studies included in the meta-analysis

Study	Sample size (n) (SGLT-2i/No SGLT-2i)	Type of cancer (%)	Age (years)	Female (%)	SGLT-2i (%)	Study Outcomes	Chemotherapy (%)	Radiation therapy (%)	CAD (%)	HF (%)	Other cardiac medications (%)	Adverse events (%)	Follow up (years)
Gongora et al,[8] 2022	32/96	Lymphoma (34/34), Breast (28/23), Genitourinary (9/19), Gastrointestinal (16/7), Sarcoma (6/7), Leukemia (3/3), Other (3/6)	60/60	50/43	Empagliflozin (50), Canagliflozin (34), Dapagliflozin (16)	Composite of cardiac events (heart failure incidence, heart failure admissions, new cardiomyopathy [>10% decline in ejection fraction to <53%], and clinically significant arrhythmias), Overall mortality	Anthracyclines (100/100) (Mostly Doxorubicin)	-	6/10	6/7	Statins (62/55), RAAS inhibitors (44/46), Aspirin (38/28), Beta-blockers (31/28), Calcium channel blocker (19/14), Diuretics (16/14)	Sepsis (12/27), Neutropenic fever (9/20), Urinary tract infection (9/28), Genital yeast (9/3)	1.5
Abdel-Qadir et al,[6] 2023	99/834	Breast cancer (50/50), Lymphoma (25/24), Other (25/26)	70/71	65/62	Empagliflozin, Canagliflozin, Dapagliflozin	Hospitalization for HF, Incident HF diagnoses (in- or out-of-hospital), and Documentation of any CVD in future hospitalizations	Doxorubicin (78), Epirubicin (14), Others (8)	-	12/10	0/0	Angiotensin antagonists (79/72), Beta-blockers (27/26), Statins (90/75)	Diabetic ketoacidosis or Hyperosmolar hyperglycemic state or Hyperglycemia (0/1.8)	1.6
Chiang et al,[7] 2023	878/878	Gastrointestinal (36/35), Genitourinary (19/17), Thoracic (12/13), Head and neck (10/11), Breast (12/11), Hematologic (4/6), Skin (1/2), Others (19/18)	65/65	46/48	Empagliflozin (49), Dapagliflozin (38)	Hospitalization for incident heart failure, All-cause mortality	Antimetabolites (18/17), Platinum (12/13), Plant alkaloids (10/11), Anthracyclines (8/8), Others (14/13)	3/3	4/3	5/5	ACEI/ARB (55/58), Beta-blockers (58/60), Diuretics (42/44), Calcium channel blockers (54/55), Statins (57/56), Aspirin (21/23)	Diabetic ketoacidosis (0.4/0.6) Urosepsis (1/4), Sepsis (5/15), Hypoglycemia (1/3), Acute kidney injury (5/7), Fournier's gangrene (0.1/0)	1.6
Avula et al,[5] 2024	640/640	Breast (15/16), Lymphomas (25/24), Myelodysplastic syndromes (40/34), Gastrointestinal (18/22), Neoplasms of unspecified behavior (22/22), Metastatic malignancy (30/30), Others (17/16)	68/68	42/42	Empagliflozin, Canagliflozin, Dapagliflozin	HF exacerbations, All-cause mortality	Alkylating agents (32/31, Anthracyclines (19/21), Anti-metabolites (41/40), Monoclonal antibodies (34/36), Others (32/34)	11/12	-	-	Antiarrhythmics (88/89), Antilipemic agents (88/86)	Urinary tract infection (9/16), Lower extremity amputation (1.6/1.6)	2

CAD = coronary artery disease; HF = heart failure; RAAS = renin angiotensin aldosterone system; SGLT-2i = sodium-glucose cotransporter-2 inhibitor.

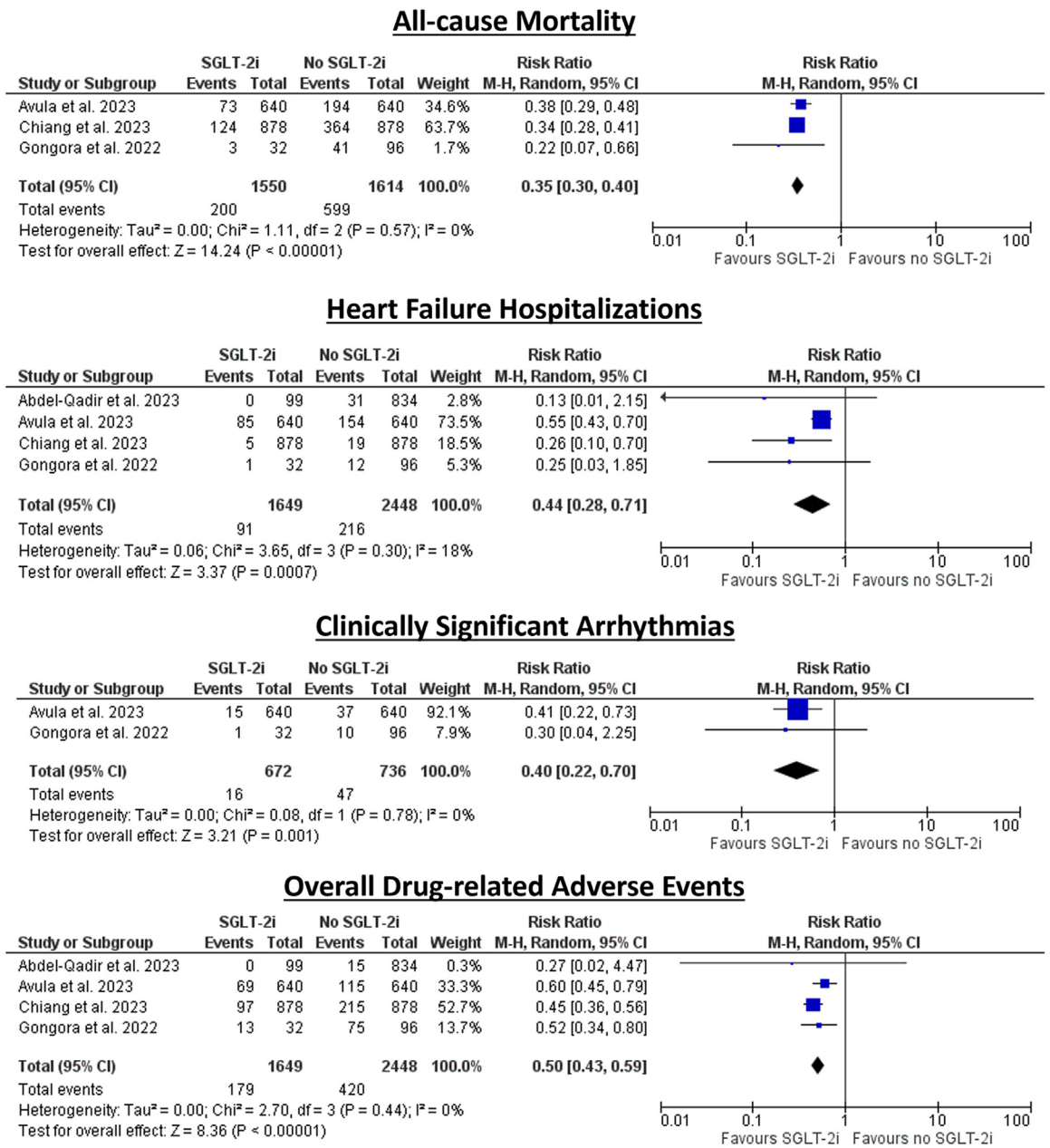

Figure 1. Forest plot for risk of HF hospitalizations, all-cause mortality, clinically significant arrhythmias, and overall drug-related adverse events in patients with cancer receiving SGLT-2i versus no SGLT-2i.

pooled estimate showed a statistically significant smaller risk of HF hospitalization with SGLT-2i use than with no SGLT-2i use (RR 0.44, 95% CI 0.28 to 0.71, p <0.001, I^2 = 18%) (Figure 1).

A total of 16 of 672 patients (2.4%) receiving an SGLT-2i developed clinically significant arrhythmias, compared with 47 of 736 patients (6.4%) who did not receive an SGLT-2i. The pooled estimate showed a statistically significant smaller risk of clinically significant arrhythmias with SGLT-2i use than with no SGLT-2i use (RR 0.40, 95% CI 0.22 to 0.70, p = 0.001, I^2 = 0%) (Figure 1).

A total of 179 of 1,649 patients (10.9%) receiving an SGLT-2i developed a drug-related adverse event, compared with 420 of 2,448 patients (17.2%) who did not receive an SGLT-2i. The pooled estimate showed a statistically significant smaller risk of overall drug-related adverse events with SGLT-2i use than with no SGLT-2i use (RR 0.50, 95% CI 0.43 to 0.59, p <0.001, I^2 = 0%) (Figure 1). On a subgroup analysis based on the nature of adverse events (infectious or noninfectious), patients receiving SGLT-2i had a significantly smaller risk of developing infectious (RR 0.44, 95% CI 0.29 to 0.67, p <0.001, I^2 = 78%), in addition to noninfectious drug-related adverse events (RR 0.62, 95% CI 0.46 to 0.84, p = 0.002, I^2 = 0%), than did those who did not receive SGLT-2i.

In this meta-analysis comprising 4,097 patients, we examined the association between SGLT-2i use and cardiovascular outcomes in patients with cancer and co-morbid type 2 diabetes mellitus (DM). Our significant findings include the following: (1) patients who received SGLT-2i

had a significantly smaller risk of all-cause mortality than did those who did not receive an SGLT-2i; (2) SGLT-2i use was associated with a significantly smaller risk of HF hospitalization, clinically significant arrhythmias, and overall drug-related adverse events than was no SGLT-2i use.

These findings should be considered hypothesis generating given this meta-analysis is based on observational studies, and there are currently no randomized clinical trials (RCTs) studying the cancer population. These findings support the need for multicenter RCTs examining the cardioprotective effects of SGLT-2i in patients with cancer. The ongoing phase 3 RCT Empagliflozin in the Prevention of Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines (EMPACT; NCT05271162) is investigating the effect of prophylactic empagliflozin in preventing left ventricular dysfunction in patients receiving high-dose anthracycline therapy. Translational studies in nondiabetic mice have shown that pretreatment with SGLT-2i can prevent anthracycline-induced cardiotoxicity and reduction in systolic function, likely owing to decreased myocardial fibrosis.[9] The cardioprotective effect in experimental models appears to be through up-regulation of SIRT1, proliferator-activated receptor gamma coactivator 1-α, and FGF21 in the heart.[9]

Our meta-analysis findings should be interpreted in the context of their limitations. First, this is a study-level analysis because aggregate data were extracted from original publications, and we could not access patient-level data. In addition, all patients in the included studies had type 2 DM; therefore, we could not assess the role of SGLT-2i in patients without type 2 DM. Furthermore, we could not differentiate among the effects of the different types of SGLT-2i or among different durations and doses of SGLT-2i use.

In conclusion, this meta-analysis of observational studies suggests that in patients with cancer, the use of SGLT-2i is associated with a significantly smaller risk of all-cause mortality, HF hospitalization, clinically significant arrhythmias, and overall drug-related adverse events than is no SGLT-2i use. Future large randomized controlled trials are needed to validate these findings further and explore the effectiveness and safety of SGLT-2i in this group of patients at great risk.

Declaration of competing interest

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CRediT authorship contribution statement

Siddharth Agarwal: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing − original draft. **Usama Qamar:** Conceptualization, Data curation, Formal analysis, Methodology, Writing − original draft. **Yu Fujiwara:** Conceptualization, Methodology, Supervision, Validation, Writing − review & editing. **Avirup Guha:** Conceptualization, Investigation, Methodology, Supervision, Writing − review & editing. **Abdul Rafeh Naqash:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing − review & editing. **Eric H. Yang:** Conceptualization, Investigation, Software, Supervision, Validation, Writing − review & editing. **Daniel Addison:** Conceptualization, Supervision, Validation, Writing − review & editing. **Ana Barac:** Conceptualization, Methodology, Supervision, Validation, Writing − review & editing. **Zain Ul Abideen Asad:** Conceptualization, Data curation, Investigation, Software, Supervision, Validation, Writing − original draft, Writing − review & editing.

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