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EDITORIAL COMMENT

SGLT2 Inhibitors in Mitigating Cancer Therapy-Related Cardiac Dysfunction

Expanding the Evidence

Mohamed S. Dabour, MS,[a,b] Anne H. Blaes, MD, MS,[c] Bhavadharini Ramu, MD,[d] Beshay N. Zordoky, MS, PhD[a]

Over the past decade, sodium-glucose cotransporter 2 (SGLT2) inhibitors have become cornerstone therapies for type 2 diabetes mellitus (T2DM), as well as for cardiovascular and kidney diseases. One area that has recently attracted significant attention is the potential role of SGLT2 inhibitors in mitigating cancer therapy-related cardiac dysfunction (CTRCD). CTRCD encompasses a range of cardiovascular complications, including left ventricular dysfunction, myocarditis, vascular toxicity, hypertension, arrhythmias, and coronary ischemia, posing serious challenges for affected patients. Current cardioprotective strategies for CTRCD remain limited, with dexrazoxane being the only Food and Drug Administration-approved agent for preventing anthracycline-induced cardiac dysfunction. As such, the search for new cardioprotective agents continues.

Emerging preclinical evidence suggests that SGLT2 inhibitors may hold promise in this area.[1] At the clinical level, 5 retrospective studies have suggested a potential benefit of SGLT2 inhibitors in mitigating CTRCD in patients with diabetes.[2-6] The use of SGLT2 inhibitors has been consistently associated with a reduction in heart failure hospitalizations and improved cardiovascular outcomes. These studies included patients with cancer and T2DM, particularly those treated with anthracyclines, with only 1 study investigating the effect of SGLT2 inhibitors against other potentially cardiotoxic therapies.[6]

In this issue of *JACC: CardioOncology*, Bhatti et al[7] provide valuable insights into the protective role of SGLT2 inhibitors in reducing the risk of CTRCD in patients with cancer and T2DM receiving potentially cardiotoxic antineoplastic therapies. The investigators leveraged the TriNetX research platform, which aggregates electronic health record-derived clinical data on more than 110 million patients across U.S. health care institutions. They identified 95,203 adult patients (≥18 years of age) with cancer and T2DM, exposed to potentially cardiotoxic antineoplastic agents, and without a prior documented history of cardiomyopathy or heart failure. The cohort was then divided based on baseline SGLT2 inhibitor use before cancer therapy: 9,403 patients were on SGLT2 inhibitors, while 85,800 were not. Using propensity score matching (PSM), the investigators created 2 well-matched cohorts (n = 8,675 for each group), ensuring a reduced likelihood of significant unmeasured confounders using sensitivity analysis. The study included different malignancies including breast malignancies, lymphomas, gastrointestinal malignancies, multiple myeloma, and genitourinary malignancies. A notable strength of this study, compared with prior observational studies, is the inclusion of patients exposed to multiple potentially cardiotoxic antineoplastic agents, including anthracyclines, alkylating agents, antimetabolites, monoclonal antibodies, tyrosine kinase inhibitors, and proteasome inhibitors.

In the primary outcome analysis (incident CTRCD), patients on SGLT2 inhibitors had a significantly lower risk of developing CTRCD within a 12-month

From the [a]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, USA; [b]Department of Clinical Pharmacy, Faculty of Pharmacy, Tanta University, Tanta, Egypt; [c]Division of Hematology/Oncology/Transplantation, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA; and the [d]Division of Cardiology, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA.

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follow-up period (HR: 0.76; 95% CI: 0.69-0.84). In addition to its primary endpoint, the study examined several secondary outcomes, including heart failure exacerbations, all-cause mortality, all-cause hospitalization or emergency room visit, new onset atrial fibrillation/flutter, new onset metastatic cancer, and need for further systemic antineoplastic therapy, which were all significantly lower in the SGLT2 inhibitor group compared with those not on SGLT2 inhibitors. These findings suggest that the cardioprotective effects of SGLT2 inhibitors may extend beyond CTRCD prevention, and enhance overall cardiovascular health and raise intriguing possibilities regarding the previously reported anticancer properties of SGLT2 inhibitors in preclinical studies.[1]

In a subgroup analysis based on different classes of antineoplastic treatments, SGLT2 inhibitors were consistently associated with a reduced risk of CTRCD in those treated with anthracyclines, monoclonal antibodies, antimetabolites, tyrosine kinase inhibitors, and alkylating agents, though the effect with proteasome inhibitors was not statistically significant. The investigators performed another subgroup analysis to examine the effects of different SGLT2 inhibitors on CTRCD. Notably, empagliflozin was associated with a significantly lower risk of developing CTRCD, while dapagliflozin and canagliflozin did not show statistically significant reductions. However, the investigators advised that the findings of these subgroup analyses should be interpreted with caution, as the sample size may have been insufficient to detect statistically significant differences.

This research expands our understanding of the potential benefits of SGLT2 inhibitors in mitigating CTRCD in a wide range of cancer types and anticancer medications with distinct mechanisms of toxicity. The investigators should be commended for this important study utilizing the powerful TriNetX platform, enabling the inclusion of a large and diverse cohort of patients with T2DM and cancer. Other strengths include the use of 1:1 PSM to minimize the effect of some confounding factors by balancing baseline characteristics between groups, and the inclusion of various malignancies and cardiotoxic cancer therapies to enhance the generalizability of the study findings. Moreover, the investigators went beyond CTRCD prevention to conduct secondary outcome analyses, providing a broader view of SGLT2 inhibitor benefits. Finally, the subgroup analyses based on different antineoplastic therapies offered valuable insights into the broad-spectrum cardioprotective role of SGLT2 inhibitors.

However, the study has a few limitations. As with all retrospective studies, the findings are subject to potential biases inherent in observational research, given the unmeasured confounders. Unmeasured variables such as lifestyle factors, socioeconomic status, and cancer stage may have influenced the outcomes. Specifically, SGLT2 inhibitor use is associated with higher socioeconomic status.[8] Additionally, the PSM approach estimates the average treatment effect for the matched sample, which may not generalize to the broader population. Although the investigators performed sensitivity analyses, including calculating E-values to test the robustness of their findings, caution is still warranted when interpreting the results. The study considered the need for intravenous loop diuretics as a surrogate for incident CTRCD. However, loop diuretics can be indicated for conditions other than cardiac dysfunction. The cohort was limited to patients with T2DM, raising the question of whether the cardioprotective effects of SGLT2 inhibitors extend to patients with cancer but without diabetes. The study also did not account for variations in dosage, duration, or timing of SGLT2 inhibitor administration or the intensity of cancer treatments. The 12-month follow-up period was appropriate for early CTRCD detection. However, long-term cardiotoxicity can manifest years after cancer treatment, particularly with anthracyclines. Longer follow-up periods are needed to detect not only the long-term CTRCD, but also the incidence of secondary cancers, which was a concern with the early adoption of dexrazoxane. The study utilized new onset metastatic cancer and systemic antineoplastic therapy as surrogate endpoints to evaluate the potential effects of SGLT2 inhibitors on cancer treatment. However, these endpoints are less valid compared with progression-free survival and overall survival.

Looking ahead, randomized clinical trials are warranted to provide unbiased data regarding the efficacy and safety of SGLT2 inhibitors in CTRCD in patients with and without diabetes. These studies should incorporate rigorous clinical and imaging cardiovascular monitoring, along with clinically meaningful oncologic endpoints. Moreover, the trials should have a sufficiently long follow-up period to capture late cardiovascular adverse events associated with cancer therapy and further elucidate the mechanisms by which SGLT2 inhibitors confer cardioprotection. In addition to their cardioprotective

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role, it is crucial to further explore the effects of SGLT2 inhibitors on cancer progression and oncologic outcomes, using valid endpoints such as progression-free survival and overall survival. We eagerly await the results of the ongoing phase 3 EMPACT (Empagliflozin in the Prevention of Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines; NCT05271162) and the phase 2 PROTECT (Potential Protective Role of SGLT-2 Inhibitors for Chemotherapy-Induced Cardiotoxicity; NCT06341842). Early results from prospective studies have already begun to emerge. The EMPACARD-PILOT (EMPAgliflozin in the prevention of CARDiotoxicity) trial, a prospective case-control study involving breast cancer patients scheduled to undergo anthracycline-based chemotherapy, showed that empagliflozin was associated with a reduction in anthracycline-induced cardiac dysfunction in high-risk patients.[9] However, this study is limited by its small sample size of 38 patients per group and a short follow-up period of 6 months, underscoring the need for larger, long-term trials to confirm these findings.

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ADDRESS FOR CORRESPONDENCE: Dr Beshay N. Zordoky, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, 7-115 Weaver-Densford Hall 308 Harvard Street SE, Minneapolis, Minnesota 55455, USA. E-mail: zordo001@umn.edu. X handle: @Zordoky_Lab.

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