EDITORIAL COMMENT

Interpreting Nonrandomized Evidence for Clinical Decision Making in Cardio-Oncology*

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Over the last decade, advances in cancer care have dramatically improved the longevity of patients with various cancers. However, cardiotoxicity including the development of arrhythmias, thrombotic complications, subclinical cardiac dysfunction, and clinical heart failure (HF) remains a major impediment to the broader use of potentially life-saving cancer therapies such as anthracyclines. In the absence of powered randomized clinical trials to guide many clinical care decisions in cardio-oncology, there has been a large increase over time in nonrandomized evidence generated to fill key data gaps regarding medication safety and effectiveness. We offer critical perspectives on the role and interpretation of these nonrandomized evidence streams with anthracycline-induced cardiotoxicity offered as an example.

The toolbox to mitigate anthracycline-induced cardiotoxicity is limited to dose reduction, the use of adjunctive chelation therapies, or switching to a different chemotherapy.[1] Concomitant administration of neurohormonal therapies such as inhibitors of the renin-angiotensin system and β-blockers has been the subject of the evaluation of a number of studies to evaluate a possible cardioprotective benefit.[2] These studies have been limited by small sample sizes, substantial heterogeneity in the patient population, the lack of a standardized definition of cardiotoxicity, and modest treatment effects. Although the available data suggest that these therapies are likely to modestly attenuate a decline in left ventricular function, it is uncertain whether these effects are clinically meaningful. Accordingly, the most recent American Heart Association/American College of Cardiology/Heart Failure Society of America HF guidelines state that the use of these neurohormonal therapies as cardioprotective agents is of uncertain benefit.[3]

Exposure to a cardiotoxin, including anthracyclines, is now included in the universal definition of HF of patients at risk for HF (Stage A). At present, the only Class I recommendation in this population is the need for engagement of multidisciplinary care discussions, especially when faced with decisions related to potential interruption or discontinuation of cancer therapies.[3] However, it seems plausible that evidence-based HF prevention approaches recommended in the care of other at-risk patient subsets might also be useful after exposure to cardiotoxic chemotherapy.[4] The sodium-glucose co-transporter-2 (SGLT2) inhibitors are the only specific drug class that are recommended for any Stage A HF condition (in this case, among those with type 2 diabetes and established or high risk for cardiovascular disease).[4] These therapies are actively being tested to determine if they have a role in reducing risk in patients faced with more time-limited forms of cardiac injury such as early after myocardial infarction (NCT04509674, NCT04564742). It seems plausible that the cardioprotective effects of SGLT2 inhibitors may extend to other at-risk populations such as those exposed to cardiotoxic chemotherapy, including anthracyclines.

TABLE 1   Select Principles for the Design and Analysis of Observational Pharmacoepidemiologic Studies in Cardio-Oncology

Select Biases and Threats to Validity	Design Elements Less Prone to Bias
Multiple hypothesis testing	Registration on a public registry and prespecification of key design elements
Immortal time, lead time, and depletion of susceptible biases	Develop a target trial protocol, which mirrors a theoretical randomized trial Ensure start of follow-up is aligned with treatment initiation
Prevalent user bias	Incident user design with selection of patients newly initiated on therapy
Confounding by indication	Active comparator design
Unmeasured or residual confounding and healthy user bias	Multivariable regression, standardization, or propensity score methods Complete adjustment for confounders or proxies of confounders including measures of heathy behaviors Assess its impact via quantitative bias analysis, negative controls, or benchmarking with trial results
Missing covariate data	Appropriate accounting with multiple imputation

In this issue of *JACC: CardioOncology*, Abdel-Qadir and colleagues[5] report on the association between SGLT2 inhibitor use and the development of cardiovascular outcomes including HF after anthracycline-containing chemotherapy. The investigators examined cardiovascular outcomes after anthracycline initiation for cancer in a large sample of older adults from Ontario. The key exposure variable of interest was an SGLT2 inhibitor, which had to be used in the 365 days preceding the anthracycline start date. The 99 patients classified as being "exposed" to SGLT2 inhibitor therapy within that time frame did not experience any HF hospitalizations in follow-up compared with a modest risk observed in the 933 "unexposed" patients. Previous users of SGLT2 inhibitors did not appear to face any excess in safety events including diabetic ketoacidosis.

Although additional data on this intriguing clinical question are certainly welcome, we believe several issues pose a threat to the validity of the design and major findings of the present study. For broader context, we summarize key general principles in the interpretation of nonrandomized evidence (Table 1). At the planning stage, target trial emulation is a helpful approach that attempts to recreate or emulate each of the elements of an ideal randomized trial (the "target trial") addressing the same clinical question.[4] This design framework encourages investigators pursuing observational data analyses to select patient populations, assign treatment exposure status, and determine windows of follow-up that closely mirror that of a target trial. In the present example, because anthracycline initiation was chosen as the index date, there is a potential for study participants to have initiated treatment with an SGLT2 inhibitor well before the start of follow-up, introducing prevalent user bias. As such, potential clinical events or safety issues occurring early after treatment initiation are unaccounted for, which might be of particular

relevance in the study of SGLT2 inhibitors that appear to afford very rapid clinical benefits. The selection of incident users (rather than prevalent users) of SGLT2 inhibitors at the time of or within a shorter time frame before anthracycline exposure would be more optimal in future observational studies and would more closely align with the target trial of interest.

However, even observational pharmacoepidemiologic studies that are structured and designed to specifically emulate a theoretical target trial remain at risk for residual or unmeasured confounding. Thus, minimizing this confounding with rigorous statistical methodology and the selection of appropriate comparators is critically important. Assigning treatment groups as "exposed" and "unexposed" as was the case in the present example is prone to confounding by indication. The identification of an active comparator therapy known to be neutral in cardiovascular risk and which has similar local access, affordability, and indication for use lessens the potential for this type of confounding. Indeed, in the present study, patients treated with an SGLT2 inhibitor systematically differed from those unexposed in having longer durations of diabetes and worse glycemic profiles but better kidney function and entered the cohort more often in the latter part of the study time frame. An active comparator design would facilitate the selection of similar pairs of individuals who were initiated on therapies for similar reasons. Additional statistical accounting for proxies of confounders such as previous vaccinations or screening behaviors may further account for healthy user bias. After these analyses, assessment for the presence of these biases should be employed by including a comparison of the estimated treatment effects against those of known findings from randomized trials (even if from adjacent populations or settings). In the present study, the large estimated treatment effect sizes exceed the plausible treatment effects

seen in pivotal trials of SGLT2 inhibitors in any other patient population, suggesting the presence of unaccounted bias. Further evaluation of negative control outcomes (that are known not to be associated with the treatment under study) might serve as another bias assessment.

In the case of anthracycline-induced cardiotoxicity, we await more definitive evidence, including from the multicenter phase 3 EMPACT (Empagliflozin in the Prevention of Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines; NCT05271162) trial, which will assess whether prophylactic empagliflozin may prevent left ventricular dysfunction in 220 participants receiving high-dose anthracycline therapy. Target trial emulation and rigorous approaches to identify and address confounding might add rigor to future observational pharmacoepidemiologic studies. These studies might be especially informative in estimating event rates necessary for powering subsequent trials and the assessment of safety in broad, less selected populations. Even as new evidence is being generated, as cardio-renal-metabolic comorbidities continue to increase in patients with various cancers,[6] many patients undergoing anthracycline chemotherapy may already have established treatment indications (at-risk type 2 diabetes, chronic kidney disease, and HF) in whom SGLT2 inhibitors should be prioritized. With the application of similarly rigorous bias-resistant methods, we believe randomized and nonrandomized evidence may be complementary and add to the robust composite evaluation of safety and the effectiveness of therapies in cardio-oncology.

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