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EDITORIAL COMMENT

Metformin to Prevent Anthracycline Cardiotoxicity?

That Would Be Sweet!*

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Despite the emergence of novel therapies, anthracyclines remain a cornerstone of treatment for many malignancies but increase the risk of heart failure (HF).[1] This has generated interest in the primary prevention of anthracycline cardiotoxicity, with limited success for most approaches except dexrazoxane,[2,3] where use is limited by availability, cost, and need for intravenous administration. Diabetes mellitus (DM) is associated with a more than 2-fold increased risk of HF and cardiovascular death in anthracycline-treated patients.[4] DM is also associated with worse prognosis after HF onset.[5] Metformin, the most commonly used first-line therapy for type 2 DM,[6] is associated with improved HF outcomes in observational studies outside the cancer setting.[7] Mouse models suggest adenosine monophosphate-activated protein kinase activation by metformin is protective against anthracycline-mediated apoptosis and cardiotoxicity.[8] However, there are little data on the use of metformin as a cardioprotective strategy in patients with DM treated with anthracyclines.

In this issue of *JACC: CardioOncology*, Takeshi et al[9] report on a retrospective cohort study of patients with DM and malignancy who were treated with anthracyclines at their hospital between 2008 and 2021. They examine the association of metformin use with new-onset HF (primary outcome) and all-cause mortality (secondary outcome). Breast cancer and lymphoma were the most common malignancies. Propensity scores (PSs) were used to match 175 metformin-treated patients to 175 patients treated for DM without metformin. The PS model included risk factors for the development of HF, and the matched sample was well-balanced on important characteristics. The cumulative anthracycline dose was not meaningfully different between groups (median dose = 231 mg/m^2 [quartile (Q)1-Q3: 148-297] in metformin-treated patients and 220 mg/m^2 [Q1-Q3: 130-250] in controls). The use of sulfonylureas (which potentially increase the risk of HF) and sodium-glucose cotransporter 2 inhibitors (protective in HF) was similar between groups. Participants were followed for a median of 1.7 years.

The resulting matched cohorts had an overall high incidence of HF (7.1% at 1 year), which is higher than typically observed in anthracycline-treated patients (<5% per year).[1] This incidence of HF likely reflects the higher risk incurred by DM and other cardiovascular risk factors within the cohort. After PS matching, metformin-treated patients had a lower incidence of HF compared to patients not treated with metformin at 1 year (3.6% vs 10.5 %; P = 0.022) and at 5 years (8.1 vs 15.7%;

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$P = 0.026$). This translated to a HR of 0.35 (95% CI: 0.14-0.90) at 1 year and 0.44 (95% CI: 0.21-0.93) at 5 years for HF in favor of metformin use. These observations suggest that metformin may be protective against symptomatic HF in higher-risk patients with DM undergoing anthracycline therapy. Metformin use was also associated with a lower incidence of all-cause mortality during the follow-up period (HR: 0.71; 95% CI: 0.50-1.00; $P = 0.049$).

The study has several strengths, including the incorporation of a comprehensive list of relevant variables and the use of objective criteria for the definition of HF after review by 2 cardiologists. However, enthusiasm should be tempered by the retrospective and observational nature of the study, which carries the potential for residual confounding. There are likely important systematic differences underlying the reason for people to be treated for DM with or without metformin. It is hard to envision the profile of the patients who are treated for DM without metformin while remaining comparable to their metformin-treated counterparts. Metformin is recommended as the first-line therapy in patients with type 2 DM by all major treatment guidelines given its long track record of efficacy, tolerability, safety, and cost-effectiveness.[6] The proportion of patients with type 1 DM in the nonmetformin group was not specified.

Although the groups were balanced in measured risk factors at baseline, it is possible that metformin may have been avoided in people with a history of contraindication in the past that was not captured in the baseline demographics or those perceived by clinicians to be at higher risk for a future contraindication. The most common reason for avoidance of metformin is renal failure, but baseline creatinine levels were similar in the 2 groups in the matched sample (0.86 mg/d, standardized difference = 0.08) as were age and sex, making it unlikely that the renal function was systematically different at baseline. It is possible that those patients unexposed to metformin may have had resolved acute kidney injury in the past leading to its avoidance. The study excluded patients with a known prior history of HF, but it is possible that metformin may have been avoided in patients with an unrecognized history of HF or cardiac dysfunction (eg, if treated with recovery outside the institution). More broadly, metformin intolerance (most commonly caused by gastrointestinal symptoms) may be a marker of patients who are more likely to be frail and therefore at higher risk of HF and death than patients who were not on metformin therapy. The healthy user effect[10] wherein healthier people are more likely to start medications than those with comorbidities is well-documented in several other settings. If such systematic differences existed within this group, they may explain the lower risk of HF and death associated with metformin.

Nonetheless, the results of the study are intriguing, suggesting a large benefit (HR: 0.35-0.44) for metformin in reducing the incidence of HF in patients with DM treated with anthracyclines. These findings will need to be confirmed with randomized controlled trials (RCTs) before these data can be incorporated clinically. Recently, Serageldin et al[11] reported an RCT (NCT04170465) of 70 women without DM who were treated for breast cancer in the adjuvant setting with 240 mg/m^2 of doxorubicin and who were randomized to metformin (1,700 mg/d) or control. The baseline left ventricular ejection fraction was similar in both groups, whereas the left ventricular ejection fraction at treatment end was minimally numerically higher in the metformin arm, although statistically significant (65.9% vs 62.2%; $P = 0.0007$).

We also note that several RCTs have yielded mixed results regarding the efficacy of metformin for either the prevention of cancer recurrence or improvement in progression-free survival[12] despite observational data suggesting benefit with metformin. This would prompt skepticism about the mortality benefit observed in this trial because early mortality is expected to be driven by cancer outcomes unless there is a high contribution from cardiovascular disease in this higher-risk cohort with DM. These RCTs with prospectively collected data may provide an opportunity to pool available adverse cardiovascular event data to further study the impact of metformin on cardiotoxicity. A review of available adverse events data from these studies suggests frequent gastrointestinal side effects in cancer patients receiving metformin. Therefore, caution is warranted regarding the use of metformin for cardioprotection in the absence of an established indication because it may adversely impact the delivery of cancer therapy despite the perception that it is a low-risk intervention. If new RCTs are pursued, it may be wise to begin with populations at high risk of HF and/or those receiving high doses of anthracyclines given the limited success of prior studies of cardioprotection in all-comers.

Furthermore, future studies will need to address whether the potential protective role of metformin can be applied to patients without DM.

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