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EDITORIAL COMMENT

Pumping Up the Standards

A Call for Improved Cardiovascular Event Reporting in Oncology Trials*

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Cardiovascular disease (CVD) is the leading competing cause of mortality in patients with cancer.[1] Cancer and CVD have shared risk factors that independently increase the incidence of both conditions. The expected impact of cardiovascular (CV) toxicity is higher in people with pre-existing CVD and associated risk factors.

As a result of immune checkpoint inhibitor (ICI) and vascular endothelial growth factor receptor inhibitor (VEGFi) combination therapies, overall survival has increased across several disease types with medians exceeding 4 years. Accordingly, acute and long-term cardiovascular adverse events (CVAEs) are increasingly relevant as competing risks for survival and determinants of quality of life. ICI toxicities are relatively unpredictable, and we cannot extrapolate natural history and treatment approaches of the resulting CVD from its correlates in the general population. Myocarditis may be the most clinically relevant of these; typically manifests 2 to 6 weeks from treatment onset; and although uncommon, can portend a high risk of morbidity and mortality.[2]

In this issue of *JACC: CardioOncology*, Rankin et al[3] report a scoping review of phase II to IV randomized trials in solid tumor cancers with ICI/VEGFi combinations. The data analyzed included trial CV eligibility (inclusion and exclusion) criteria and methods of defining, collecting, and reporting on CVAEs. Seventeen trials (10,313 participants) with 8 different ICI/VEGFi combinations were included. Most trials (n = 15) had multiple CV exclusion criteria, typically prior heart failure, myocardial infarction/unstable angina, hypertension, and stroke. All trials used the Common Terminology Criteria for Adverse Events definitions and severity grading to report on CVAEs. Follow-up for CV events was for at least 30 days past the last treatment dose in all trials, longer (90-120 days) for adverse events of special interest (AEOSIs) in some but shorter than the duration of the trials in all. The most common threshold for reporting any adverse events was ≥10% (n = 6 trials) but was higher in 5 trials at ≥20% to 25%. AESOIs included myocarditis, arrhythmias, heart failure, arterial thromboembolism, and left ventricular systolic dysfunction; these AEOSIs had a lower incidence threshold for reporting of >1%. The authors did not provide a summary of the reported incidences of CVAEs or AEOSIs; these data could help inform the more common CVAEs to focus future research and reporting efforts. However, the review demonstrates heterogeneity in CV eligibility criteria and CVAE reporting, limiting any pooling of results or conduction of meta-analyses.

In oncology randomized controlled trials (RCTs), participant eligibility criteria play a pivotal role in determining which populations gain federal approval for drug use, funding, and use by clinicians in clinical practice. Increased eligibility specificity and restriction provide clinicians with a clear understanding of the degree of benefits and harms within that specific population. However, it may limit generalizability to those with comorbidities commonly encountered in routine clinical practice. It may also lead to

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underestimation of CVAEs when the interventions are used in people with a greater burden of CV comorbidities. This leads to the efficacy-effectiveness gap whereby patients in the "real world" have overall less benefit and more toxicities than the average trial population.[4] Balancing the need for specificity (within trials) and homogeneity (across trials) in inclusion criteria with inclusivity of a more typical population is essential for conducting ethical and meaningful RCTs that contribute to both scientific knowledge and improved standard clinical practice.

The *Common Terminology Criteria for Adverse Events* criteria, although standardized, do not adequately characterize the nature of CVAEs in a manner that can inform clinical use of newer anticancer therapies. The Hicks criteria are a set of standardized definitions for CV and stroke outcomes endorsed by the Food and Drug Administration intended to be used in clinical trials to enhance the ability to aggregate data and facilitate meta-analyses.[5] The authors highlight that none of the trials used these criteria, except for the reporting of hypertension. No trials classified deaths related to CVAEs as a specific CV death despite 10 trials with events meeting the Hicks criteria for CV death. These data are crucial to appropriately counsel patients.

We believe trialists can learn from the shortcomings identified in this review when designing future oncology trials with the following considerations. First, although it is unlikely feasible to power studies specifically for CV events, un-necessary exclusion of patients with CV risk factors should be avoided. These patients should be included with a robust protocol for defining and recording CVAEs. Second, trials should consider longer follow-up for AEOSIs. With ICI therapy, late CV events (>90 days) are less well characterized but generally have a higher risk of noninflammatory heart failure, progressive atherosclerosis, hypertension, and overall mortality.[5] Third, trialists should consider a consistent approach to reporting CVAEs, such as the incorporation of Hicks criteria. This would allow for incidence pooling and meta-analysis to allow for accurate estimation of potential harms when counseling patients, potentially identify patient subgroups at increased risk for the CV event, and potentially identify situations in which the drug should be contraindicated or discontinued. In the future, subgroups at increased risk could be further studied to identify monitoring and/or intervention strategies to decrease CVAEs. The cardio-oncology community can take a leading role in promoting these developments.

Comprehensive trial reporting can influence real-world clinical decision making. In this review, all studies were in the metastatic/incurable setting. Here, the harm-benefit balance is often in favor of treatment; patients and clinicians are likely willing to accept greater risks of CVAEs when the alternative (no oncologic therapy) leads to cancer death. However, systemic therapy and ICI combinations are tested in the (neo)adjuvant or curative setting where this balance may be less evident. Patients and clinicians must make decisions between a small percentage increase in chances of cure vs a potentially debilitating or fatal toxicity. Here, meta-analyses to identify accurate incidence of CVAEs and their natural history are especially important to inform patient care decisions.

In the 2022 European Society of Cardiology cardio-oncology guidelines, patients receiving combination ICI therapy with other cardiotoxic therapies are classified as high risk for CV toxicity. These recommend that all patients starting ICI treatment should have a baseline electrocardiogram, natriuretic peptide, troponin, and echocardiography (Class 1B). Furthermore, the guideline recommends CV assessment every 6 to 12 months in patients on long-term (>12 months) ICI therapy.[6] Although the guidelines were not in place at the time of these trials, they would apply to all included patients. Notably, only 4 trials required a baseline echocardiogram, none reported on baseline CV risk, and only 2 mandated surveillance echocardiography. Although not all agree with these guidelines, some baseline CV risk assessment for patients receiving 2 cardiotoxic therapies is likely desirable, and further research can inform surveillance strategies.

Because these therapies are used more in clinical practice, more grade 1 events may be detected (ie, elevated cardiac biomarkers or imaging detection of myocarditis in asymptomatic patients). None of the RCTs included in this review reported on grade 1 events, although case series estimate a 11% to 17% prevalence.[7,8] Reporting grade 1 events, although not without increased burden and risks of exacerbating incomplete data capture, might help to inform the natural history of asymptomatic CVAEs.

In conclusion, expanding trial eligibility criteria and developing more rigorous and standardized approaches to assessing/reporting baseline CV risk could improve the utility of clinical trials of medications with a potential for cardiotoxicity. Uniformity and transparency of CVAEs using either the Hicks criteria or other frameworks would allow future pooling and meta-analysis to better characterize CVAEs. Together, this could extend access of potentially efficacious drugs with a focus on clear characterization of the potential benefits and harms of

JACC: CARDIOONCOLOGY, VOL. 6, NO. 2, 2024
APRIL 2024:280–282

treatments so that clinicians and patients can make informed decisions. These are important considerations to move forward in the field of cardio-oncology.

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