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EDITORIAL COMMENT

How Common Is Pre-Existing Cardiovascular Disease in Cancer Patients

What Do We Know? Does It Matter?*

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Advances in treatments have extended the life expectancy of patients with cancer through a reduction of cancer-related deaths. Patients with cancer have a significant burden of cardiovascular disease (CVD) due to shared risk factors,[1] similar pathophysiological processes, and adverse cardiovascular effects of chemoradiotherapy and other targeted treatments[2] with significant differences in the types of CVD among different cancer types.[3] Cancer patients have a >2-fold increase in the risk of CVD mortality compared with the general population,[4] with CVD the second most common cause of death after cancer itself.[5] Understanding the patterns of CVD burden in different cancer types is important for appropriate risk stratification, informing treatment planning, and understanding the evolving health care needs of this growing high cardiovascular risk population.

In this issue of *JACC: CardioOncology*, Battisti et al[6] have undertaken an analysis of 634,240 patients from the National Cancer Registration Dataset of England, linked to 4 national cardiac audits (myocardial Infarction, heart failure, cardiac surgery, and percutaneous coronary intervention) and hospital admissions administrative data to determine the prevalence of pre-existing CVD in a national cohort of cancer patients. The investigators restricted the analysis to potentially curable cancers (stage I to III breast cancer, stage I to III colon/rectal cancer, stage I to III prostate cancer, stage I to IIIA non-small cell lung cancer [NSCLC], stage I to IV diffuse large B-cell lymphoma [DLBCL], and stage I to IV Hodgkin lymphoma) and reported prevalent CVD within 5 years before their cancer diagnosis. The investigators reported CVD prevalence by cancer type, and within each cancer group by age, sex, race, comorbidity burden, deprivation, and cancer stage. Using this methodology, the reported prevalence of CVD was 16.2% in the overall cancer cohort and 7.7% in the breast cancer cohort, 22.1% in the colon cancer cohort, 16.8% in the rectal cancer cohort, 15.4% in the prostate cancer cohort, 36.1% in the NSCLC cohort, 21.7% in the DLBCL cohort, and 11.6% in the Hodgkin lymphoma cohort. Unsurprisingly, the prevalence of CVD increased with age in all cancer types and was greater in males compared with females. Patients that were the most deprived (as determined by household income) had a greater prevalence of CVD, and racial differences were noted with the odds of CVD in Asian patients 20% greater than White patients after multivariable adjustment (odds ratio [OR]: 1.21; 95% CI: 1.16-1.27) with the greatest odds seen in DLBCL (OR: 1.52; 95% CI: 1.29-1.80), and prostate cancer (OR: 1.47; 95% CI: 1.35-1.61).

The investigators are to be congratulated; the use of a cancer registry linked to longitudinal multisource cardiovascular and administrative data provides more granular cancer-specific data than previous work using administrative datasets has allowed, and provides a more accurate measure of CVD prevalence than what is possible using cross-sectional data at a single point in time. This work provides important information around the burden of CVD across different cancer types and highlights important

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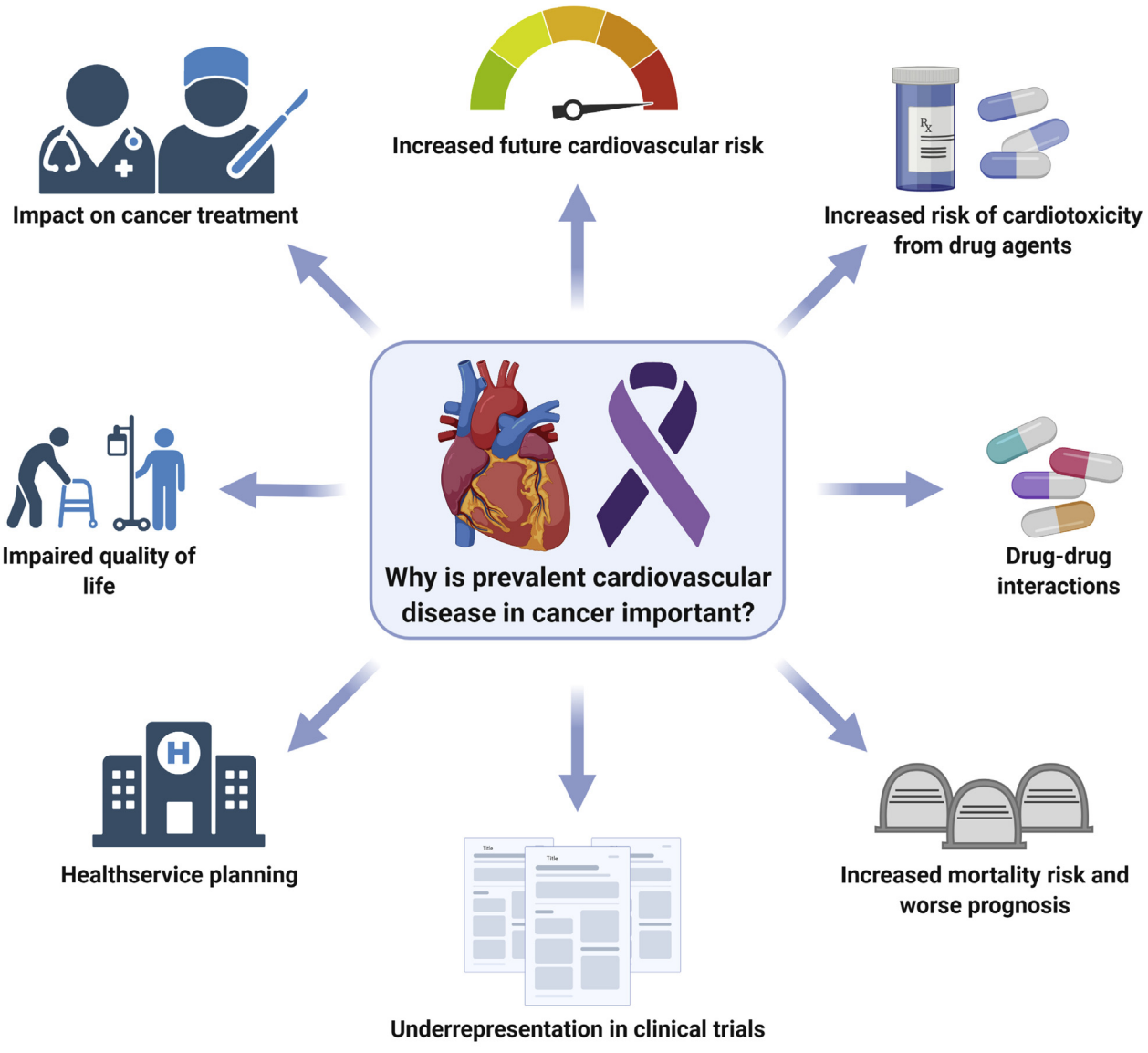
FIGURE 1 Why Is Prevalent Cardiovascular Disease in Cancer Important?



disparities in CVD prevalence observed across race and socioeconomic status like those reported in the general population.

Nevertheless, there are several limitations of the current analysis. Most of the CVD comorbidity data identified was from hospital admissions administrative data (99.8%) with no data linkage to UK primary care datasets that would provide a broader, population-level estimate of CVD prevalence. Identification of prevalent CVD using the methodology used by Battisti et al[6] relies on a hospital admission either with an index cardiovascular condition or a CVD comorbidity coded. This would not capture CVD disease diagnosed in primary care and managed in the community, which is likely to make up a significant contribution to the true CVD burden of patients with cancer, and therefore would result in a significant underestimate of the true prevalence of CVD in this population. Furthermore, although the investigators have included cerebrovascular disease, ischemic heart disease, valvular heart disease, heart failure, peripheral vascular diseases, and hypertensive heart disease in their definition of CVD, they do not consider other important CVDs such as arrhythmias, particularly atrial fibrillation, where the burden in this population is likely to be significant. Our recent

analysis of 5.9 million CVD admissions over 2 years in the United States suggests that atrial fibrillation accounts for 22.4% of CVD admissions in patients with cancer and may account for 31.8% of all CVD admissions in patients with lung cancer.[3] The investigators provide no data on cardiovascular risk factor prevalence in this population or its management, which is important given that the risk of future CVD development in this population is dependent on risk factor burden.[7] Finally, this, like other analyses derived from electronic health care records, does not provide a true measure of CVD prevalence, particularly given that much of the CVD burden may be undiagnosed and clinically silent at the point of cancer diagnosis. Coronary computed tomography studies have demonstrated that coronary artery calcification is present in close to 70% of patients with NSCLC[8] and 26% of breast cancer patients[9] without known coronary heart disease, and is independently associated with a 5-fold increase in future cardiovascular events.[9]

The question that this and other similar studies raise is why is it important to understand the true prevalence of CVD in patients with cancer and does it matter? Understanding differential patterns of CVD prevalence across various cancer types and population groups is important for appropriate risk stratification and for informing treatment planning. Prevalent CVD may represent a contraindication for pursuing specific anticancer treatment options or may require changes in therapy that may influence the potential for curative treatment in individuals with cancer. The current analysis supports this contention, prevalent CVD was associated with reduced odds of receipt of surgery (OR: 0.68; 95% CI: 0.66-0.69), radiotherapy (OR: 0.69; 95% CI: 0.68-0.70), or chemotherapy (OR: 0.74; 95% CI: 0.73-0.76). Prevalent CVD may limit the choice of therapeutic agents in the treatment of cancer. Left ventricular dysfunction is independently associated with future cardiotoxicity risk in a number of cancer therapies, including anti-HER2 compounds such as trastuzumab and pertuzumab, and anthracyclines, which should be avoided where possible in patients with significant left ventricular dysfunction at baseline.[10,11] Significant coronary artery disease is an important risk factor for future cardiotoxicity associated with the use of vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab and ramucirumab,[10] whereas heart failure (with either preserved or reduced left ventricular function), asymptomatic left ventricular dysfunction (ejection fraction <50%), valvular heart disease, hypertensive heart disease, significant cardiac arrhythmias, and evidence of coronary artery disease are highlighted as important risk factors for cardiotoxicity in contemporary cardio-oncology guidelines.[10]

So, where does this leave us? Identification of prevalent cardiovascular disease in patients with cancer is important (**Figure 1**); it has an impact on the longer-term prognosis of cancer survivors, influences treatment choices and provision of therapeutic strategies, and identifies those at greatest risk from cardiotoxicity from the therapeutic interventions we deliver to this at-risk population. Although clinically overt CVD in patients diagnosed with cancer is significant with studies such as the present one suggesting that at least 1 in 6 patients diagnosed with cancer may have CVD, the true burden of CVD is likely to be much greater. Cardiovascular risk assessment using guideline-recommended risk stratification tools and multimodality noninvasive imaging should be used in all patients diagnosed with cancer, to better define prevalent CVD and future cardiovascular risk.[12]

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