JACC: CARDIOONCOLOGY VOL. 5, NO. 1, 2023

VIEWPOINT

The European Society of Cardiology Cardio-Oncology Guidelines

Evidence Base, Actionability, and Relevance to Clinical Practice

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The newly published 2022 European Society of Cardiology (ESC) Guidelines on Cardio-Oncology[1] are a major milestone in the field. They represent an enormous undertaking, necessary for a highly nuanced and diverse field. A previous milestone in the field was the inaugural issue of this journal in September 2019.[2] Although there had clearly been important pieces of research in cardio-oncology well before this milestone, it reminds us that cardio-oncology is a young specialty that has grown rapidly. The first time the word *cardio-oncology* appears in PubMed is in 2008.[3] From then until the date of release of the ESC guidelines, there were 1,295 papers indexed in PubMed using this moniker.

The first sentence of the ESC guidelines begins, "Guidelines summarize and evaluate available evidence"— a statement that, given the relative newness of cardio-oncology, might appear somewhat incongruous with the 133-page length of the document. In this context, the purpose of this Viewpoint is to provide our perspective on the guidelines' evidence base, actionability, and relevance to daily clinical practice, especially in Canada. To accomplish this, we first apply an analytic approach to the guidelines. We then discuss several specific clusters of recommendations. Finally, we describe the implementation of the guidelines in Canada.

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Richard K. Cheng, MD, MSc, served as Guest Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Integral to a description of the evidence base underpinning the guidelines is the level of supporting evidence. Level of Evidence: A evidence consists of multiple randomized, controlled trials or meta-analyses; Level of Evidence: B evidence includes a single randomized, controlled trial or a large, non-randomized study; and Level of Evidence: C evidence includes expert opinion, small or retrospective studies, or registries. These levels of evidence are fundamental to how we interpret data and the resulting clinical recommendations. Medical history is full of examples where inferences made based on a lower level of evidence have been unsupported or proven incorrect by further studies that constitute a higher level of evidence. Therefore, this hierarchy in levels of evidence should be regarded as sacrosanct when evaluating an evidence base.

There were 272 explicit recommendations made in the guidelines. Of these, 208 (76%) were supported by Level of Evidence: C evidence. There were 156 (57%) Class I recommendations, indicating that these strategies are indicated and should be implemented in clinical practice. However, of the Class I recommendations, 5 (3%) were supported by Level of Evidence: A evidence; 33 (21%) by Level of Evidence: B evidence; and 118 (76%) by Level of Evidence: C evidence. This is only a superficial representation of the recommendations, and in many circumstances, expert opinion is all that may be required. However, the risk with Class I recommendations supported by Level of Evidence: C evidence is that they may hinder research to address the limited existing evidence, because clinicians, ethics committees, and patients may be reluctant to trial strategies that run counter to the guidelines. In addition, Class I recommendations impose expectations with respect to clinical practice. These expectations can exert pressure on health care systems to invest

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.10.009

JACC: CARDIOONCOLOGY, VOL. 5, NO. 1, 2023
FEBRUARY 2023:137–140

resources to adhere to the guidelines as a measure of quality of care. This is reasonable when the guidelines are founded on high-quality evidence. However, in the absence of Level of Evidence: A or B evidence, the case for health care systems to invest the funding needed to adhere to the guidelines is less compelling.

The guidelines' length is a 2-edged sword. Its great strength is how comprehensive it is in scope. It has tackled all the key issues in cardio-oncology. This will be an extremely valuable resource as a reference to clinicians managing these patients. However, an important limitation of the document's length is that the most important or robust recommendations may not be readily apparent among the many recommendations with limited supportive data.

Several specific recommendations merit particular attention. First, those recommendations supported by Level of Evidence: A evidence should be highlighted because these might be considered the most robust. There is 1 diagnostic, 1 surveillance, and 2 therapeutic recommendations. Diagnostically, cardiac magnetic resonance is recommended in patients with suspected amyloid light chain (AL) cardiac amyloidosis. For cardiotoxicity surveillance, it is notable that the only recommendation supported by Level of Evidence: A evidence is to monitor the QTc interval at baseline and days 14 and 28 in patients starting ribociclib. The only therapies supported by Level of Evidence: A evidence relate to anticoagulation. Prophylactic low-molecular weight heparin is recommended for patients with multiple myeloma and risk factors for venous thromboembolism; direct oral anticoagulants (or low-molecular weight heparin) are recommended for the treatment of venous thromboembolism in patients with cancer.

There are numerous recommendations on the use of echocardiography and the measurement of natriuretic peptides and cardiac troponins before cardiotoxic therapies. These are recommended at baseline for patients treated with anthracycline-based chemotherapy, HER2-targeted therapies, fluoropyrimidines, VEGF inhibitors, dasatinib, Bruton tyrosine kinase inhibitors, combined RAF and MEK inhibitors, immune checkpoint inhibitors, osimertinib, chimeric antigen receptor T-cell therapy, hematopoietic stem cell transplantation; and in those with AL cardiac amyloidosis. The rationale for the baseline use of echocardiography and plasma biomarker measurement is to: 1) establish levels against which future measurements can be compared; and 2) identify patients at high risk of cardiotoxicity who may benefit from closer surveillance and/or cardioprotective treatment.

During follow-up, echocardiography and plasma biomarkers also receive Class I or IIa recommendations for cardiotoxicity surveillance in many patients receiving anthracycline, HER2-targeted therapies, VEGF-inhibitors, dasatinib or ponatinib, carfilzomib or bortezomib, and hematopoietic stem cell transplantation; whereas serial QTc monitoring is recommended in androgen deprivation therapy recipients, and serial troponin measurements are recommended in immune checkpoint inhibitor recipients. Importantly, the yield and cost effectiveness of these strategies have not been evaluated with a few exceptions.

Support for serial monitoring of left ventricular ejection fraction during cancer therapy is strongest for HER2-targeted therapies. Landmark clinical trials required such monitoring per protocol,[4] and so this approach has been translated to clinical guidelines. The measurement of global longitudinal strain may enhance the use of cardioprotective therapies in individuals treated with cardiotoxic treatments.[5] A single-center, open-label randomized trial suggests that the use of an angiotensin-converting enzyme inhibitor in individuals with elevated troponin following (predominantly anthracycline-based) chemotherapy could help preserve left ventricular ejection fraction.[6] It remains unclear whether this approach will reduce the development of heart failure. Thus, even the best available evidence to support serial imaging or biomarker measurement is not definitive and requires demonstration of improved clinical outcomes. Moreover, the cost and resource implications of implementing these recommendations are substantial. These include both the direct cost of the surveillance test and the indirect cost of acting on abnormal test results. Delays in delivering ongoing cancer treatments may arise while awaiting the evaluation of abnormal surveillance test results, which is particularly undesirable if some of these abnormalities are either false positives or where there is no evidence-based strategy to address the abnormal result.

Many of the other recommendations relate to the management of cardiovascular disease in patients with cancer. Generally, these guidelines cite respective European Society of Cardiology Guidelines for Acute Coronary Syndromes, Valvular Heart Disease, and Atrial Fibrillation, respectively. However, the

various guidelines in turn are based on evidence that did not include many individuals with advanced or active cancers. Therefore, the generalizability of these guidelines to patients with active, advanced cancer is limited.

In Canada, health care is managed on a provincial level. Therefore, there is variability across the country in health care resources available, including physicians, infrastructure, and budget to be able to implement many of the recommendations made in the guidelines. Collaboration among oncologists, cardiologists, primary care physicians, and nonphysician health care providers is critical to deliver comprehensive and timely care; however, there are often challenges with respect to wait times to see a cardiologist before starting treatment, due to the busy nature of their clinical practice or where the number of cardiologists is limited. Many centers in Canada do not have dedicated cardio-oncology clinics, so many patients with cardio-oncology issues are currently being managed by general cardiologists, especially in the community setting. Several of the guideline recommendations involve a baseline cardiovascular risk assessment to determine whether referral to a cardiologist is indicated at baseline. However, it is unclear whether oncologists have the capacity or familiarity needed to complete a cardiovascular risk assessment. Additional challenges are likely to remain, especially in carrying out some of the ESC guideline recommendations related to referral of all cancer patients at higher risk of developing cardiac complications to cardiologists as well as obtaining timely echocardiography before starting treatment. Although the measurement of cardiac serum biomarkers in cancer patients at higher risk of cardiovascular toxicity from various systemic therapies was recommended, these tests are not routinely funded in all centers across Canada at present. Access to cardiac magnetic resonance for the purposes of diagnosing immune checkpoint inhibitor myocarditis or pericarditis as suggested (Level of Evidence: B recommendation) in the guidelines may be limited in some centers in Canada as well.

The guidelines endorse annual optimization of cardiovascular factors in collaboration with primary care, although description of the potential role of the primary care physician in cardio-oncology is otherwise limited. However, empiric evidence suggests that cardiovascular risk factor control in some cancer populations remains suboptimal.[7] Further research, education, and quality improvement is therefore needed to engage primary care physicians in cardiovascular risk assessment in patients with cancer.

Cardio-oncology guidelines have been published over the past few years by several other organizations, including the Canadian Cardiovascular Society, American Society of Clinical Oncology, American College of Cardiology/American Heart Association the European Society of Medical Oncology, and the International Cardio-Oncology Society. The 2022 ESC Cardio-Oncology Guidelines represent the most up-to-date publication covering a very broad range of topics, including identification of cancer patients at risk for developing cardiac toxicity, cardiovascular risk stratification, as well as prevention, monitoring, diagnosis, treatment, and follow-up of cardiovascular toxicities in patients receiving anticancer treatments. Recommendations regarding cardiac management of special populations such as pregnant women with cancer, carcinoid valvular heart disease, and AL cardiac amyloidosis also provide helpful guidance in areas that are challenging to manage in the clinic.

The guideline authors are to be commended for their efforts to make these comprehensive guidelines available in multiple formats for the purposes of various health care practitioners. These include a summary guideline, a slide set for nonspecialists, and a shortened electronic version for digital applications such as smartphones. This will help to facilitate access to the guidelines in real time when facing challenging cardio-oncology issues in clinic. The efforts of this large international multidisciplinary community of scientists and clinicians have resulted in a comprehensive and impressive document that will serve as a valuable resource and reference for clinicians worldwide. However, as we seek to achieve traction and legitimacy for cardio-oncology as a specialty and to provide guidance for clinicians, we must be cautious about making many strong recommendations that are supported by limited data, especially given the challenges and opportunity costs of implementing these recommendations. There may be a role for acknowledging evidence gaps and discussing various clinical strategies that might be considered where such gaps exist, without the need to be assertive in our recommendations. According to William Osler, “medicine is a science of uncertainty and an art of probability,” to which Wellbery adds, “uncertainty is not a necessary evil. On the contrary, for the prepared subject, uncertainty is an opportunity for growth.”[8] The guidelines highlight the evidence gaps in the literature and the need for more high-quality research to enable such growth in cardio-oncology.

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FEBRUARY 2023:137–140

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Leong has received consultancy and speaker fees from Abbvie, Ferring Pharmaceuticals, Janssen, Myovant Sciences, Novartis, Pfizer, Sanofi, Tolmar, AstraZeneca, and Paladin related to prostate and myeloproliferative neoplasm cardio-oncology; and research support from Novartis. Dr Mukherjee has reported that he has no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229–4361. https://doi.org/10.1093/eurheartj/ehac244

2. Ky B. JACC: CardioOncology: poised to serve a maturing, collaborative field. *J Am Coll Cardiol CardioOnc*. 2019;1:131–132.

3. Cardinale D, Colombo A, Lamantia G, et al. Cardio-oncology: a new medical issue. *Ecancermedicalscience*. 2008;2:126. https://doi.org/10.3332/ecancer.2008.126

4. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273–1283.

5. Thavendiranathan P, Negishi T, Somerset E, et al. Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol*. 2021;77:392–401.

6. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006;114:2474–2481.

7. Klimis H, Pinthus JH, Aghel A, et al. The burden of uncontrolled cardiovascular risk factors in men with prostate cancer: a RADICAL-PC analysis. *J Am Coll Cardiol CardioOnc*. 2023;5(1):70–81.

8. Wellbery C. The value of medical uncertainty? *Lancet*. 2010;375:1686–1687.

KEY WORDS epidemiology, guidelines, outcomes