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EDITORIAL
Cardio-oncology

Navigating cardiotoxicity risk in cancer therapy: the importance of the HFA-ICOS score

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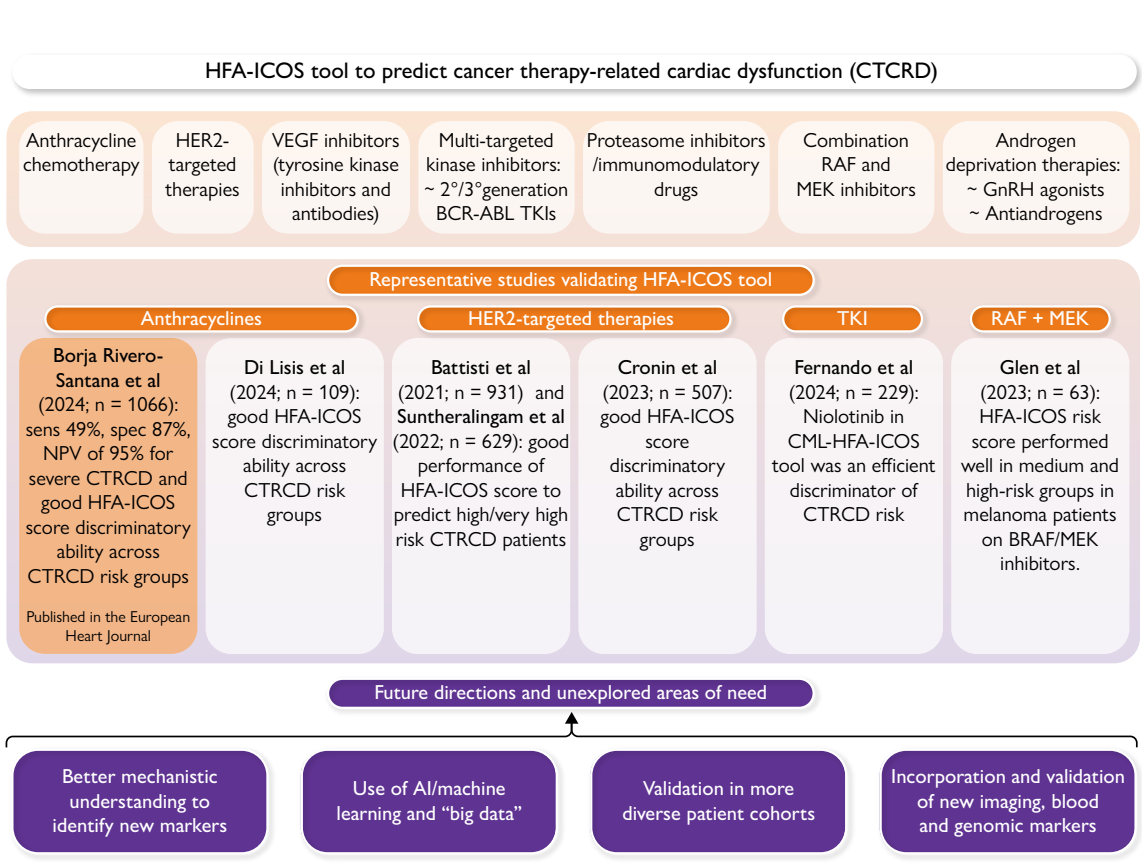
Graphical Abstract



Validation of HFA-ICOS tool: current evidence and future directions.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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The integration of oncology and cardiology has become increasingly critical as advances in cancer therapies introduce new challenges for cardiovascular health. Cardiotoxic effects of cancer therapies have been recognized for over five decades, particularly with anthracycline-based regimens. These therapies, while effective against malignancies, are linked to short- and long-term cardiac damage, including left ventricular dysfunction and heart failure, arrhythmias, vascular disease, systemic and pulmonary hypertension, thromboembolic events to name a few.[1] The advent of more targeted cancer treatments has expanded the spectrum of cardiotoxicity, necessitating more detailed, comprehensive, and individualized cardiovascular care for patients undergoing such therapies.

Cardio-oncology, as a specialty focussed on the cardiovascular health of people living with and beyond cancer, has only come to prominence in the last 10 to 15 years. And only 2 years ago, the first international cardio-oncology guidelines were published by the European Society of Cardiology (ESC), in association with the European Hematology Association, the European Society for Therapeutic Radiology and Oncology, and the International Cardio-Oncology Society (IC-OS).[1] These guidelines provide a pivotal framework for prevention, surveillance/detection, management, and long-term care for patients from cancer diagnosis and into survivorship. The breadth of the guidelines, containing over 270 recommendations is representative of the complexities of cardio-oncological patient care, which must consider not only patient-specific factors, but also those related to cancer and cancer therapies past and present.

One of the key recommendations in these guidelines is the focus on the baseline cardiovascular risk assessment of patients starting their cancer journey.[1] To assist with that, the ESC Cardio-Oncology guidelines recommend the use of the ESC Heart Failure Association—IC-OS (HFA-ICOS) Baseline risk assessment score, published in 2020.[2] That publication presented baseline risk stratification pro formas for patients prior to receiving several classes of anti-cancer therapies, including anthracyclines, HER2-targeted therapies, vascular endothelial growth factor inhibitors, BCR-ABL multi-targeted kinase inhibitors, multiple myeloma therapies, RAF and MEK inhibitors, and androgen deprivation therapies.[2] These tools consider various patient-related and therapy-related factors to classify patients into low-, medium-, high-, or very high-risk categories. The guidelines rely heavily on these risk categories to advise consideration of preventative strategies as well as ongoing surveillance algorithms,[1] and thus validity of these risk scores is of critical clinical relevance. One of the primary criticisms of the HFA-ICOS risk assessment tools was their reliance on expert opinion with very limited validation at the time of their publication.[3] The tools have mainly been tested in breast cancer populations, raising questions about their applicability to other cancer types.

There have been a few studies that have provided validation of different aspects of the HFA-ICOS baseline risk assessment tools. These have largely focussed on patients treated with HER2 therapies,[4–6] some tyrosine kinase inhibitors,[7,8] anthracyclines,[9] and BRAF/MEK inhibitors.[10] Most of these studies have found reasonably good ability to predict those at high risk, yet their ability to accurately identify those at low risk was variable. For example, a study involving 629 women with HER2 + breast cancer who received trastuzumab, with or without anthracyclines, found that the HFA-ICOS risk assessment outperformed other risk scores, but still fell short in accurately identifying patients at low absolute risk of cancer therapy-related cardiac dysfunction (CTRCD).[6] These findings were echoed in a study of 931 HER2+ breast cancer patients:[4] a challenge remained in pinpointing a truly low-risk subgroup using the HFA-ICOS pro forma. A retrospective study of 507 breast cancer patients reported better negative predictive values based on the HFA-ICOS risk pro forma. The study demonstrated significant differences in incidence of cardiac events between the groups: 3.3% in both low- and medium-risk groups, 4.4% in the high- and 38% in the very high-risk groups, though the overall incidence of CTRCD remained low in this study.[5]

Beyond HER2 therapies, a study of 63 melanoma patients treated with BRAF/MEK inhibitors demonstrated good performance of the HFA-ICOS risk score for the medium- and high-risk groups, but almost 50% of study patients were in the low HFA-ICOS risk group.[10] A study by Fernando *et al.* retrospectively looked at 229 chronic myeloid leukaemia (CML) patients treated with nilotinib over a 15-year period to assess the incidence of all cardiovascular events with a secondary endpoint of ischaemic events and a survival analysis to evaluate risk stratification by baseline HFA-ICOS risk category.[8] The study demonstrated that HFA-ICOS was an effective risk stratification tool in nilotinib-treated patients with significant correlation of increased cardiovascular events in the high-/very high-risk groups (HR 3.57) and medium-risk groups (HR 2.51) compared with the lower risk patient subgroup.[8] An earlier and smaller retrospective study of 54 CML patients treated with TKI therapy demonstrated a significantly higher sensitivity of the HFA-ICOS risk stratification tool vs. the older Systematic Coronary Risk Evaluation (SCORE) for identifying patients at higher risk of CTRCD.[7]

In a recent prospective study of 109 breast cancer patients treated with anthracyclines with or without trastuzumab, there was a significantly higher incidence of overall CTRCD (100%) in the very high-risk group vs. the medium- (29%) and low-risk groups (13%).[9] Although smaller, this prospective study supports the validity of HFA-ICOS in anthracycline-treated patients.

In this issue of the *European Heart Journal*, Rivero-Santana *et al.* present the largest cohort validation of the HFA-ICOS risk assessment tool to date, utilizing the European-based CARDIOTOX real-world registry data,[11] which provides crucial insights into the practical application of the HFA-ICOS risk score in a real-world setting. In a cohort of 1066 anthracycline-treated patients followed up for over 54 months the authors established a significant correlation between the HFA-ICOS score categories and the incidence of symptomatic or moderate-severe CTRCD and all-cause mortality.[11] The patient cohort appears to be an accurate reflection of patients seen in cardio-oncology centres with a small number of patients with severe underlying cardiovascular conditions at baseline. Yet, interestingly 19% of the patients in the study had abnormal cardiac biomarkers at baseline representing a larger portion of cardio-oncology patients with milder or even asymptomatic underlying cardiovascular issues at the time of cancer diagnosis, posing an interesting and more complex question of how well our risk factor stratification tools capture these patients with subclinical disease.

The authors should be congratulated on the efforts made to ensure a thorough statistical validation including calibration of their predictive model with time-dependent Brier scores and calibration plots of observed vs. expected survival probabilities. Assessment of the discriminative ability of the HFA-ICOS score was also detailed using Uno's C statistic and receiver operating characteristic (ROC) area under the curve (AUC) assessment providing further validity to the study's findings. Expectedly, the HFA-ICOS tool categorized a small numbers of patients as very high risk (0.9% $n = 10$) and high risk (14% $n = 152$), with both groups showing significantly higher incidence of symptomatic and moderate-severe asymptomatic CTRCD and all-cause mortality.[11] The HFA-ICOS risk prediction models performance appeared accurate demonstrating a sensitivity of 49.3%, and specificity of 87.9% with a

positive predictive value of 23.3%.[11] The negative predictive value of 95.6% for the development of symptomatic or severe/moderate asymptomatic CTRCD suggests that patients classified as low-moderate risk could avoid unnecessary investigations, which would have significant economic benefits for smaller cardio-oncology centres,[11] and allow for appropriate channelling of resources into higher risk groups, potentially mitigating the adverse cardiovascular effects of cancer treatments.

However, the study also highlights the need for ongoing refinement and validation of the HFA-ICOS scores. The complex interplay between patient factors, cancer type/stage, cancer treatments and their combinations, doses and duration, and lack of validation across the majority of treatment types so far create a fertile ground for further research, focusing on more personalized and precise risk stratification and early detection tools, across diverse patient populations (*Graphical Abstract*).

This further research can focus on:

- Improved mechanistic understanding of cardiotoxicity and cardioprotection, allowing us to develop more precise and robust markers of risk and early disease.
- Discovery, validation, and incorporation of novel imaging, blood and genomic biomarkers, enabling more precise risk stratification and early intervention.
- Validating the HFA-ICOS scores across diverse patient populations and anti-cancer therapies.
- Utilizing AI/machine learning technologies applied to 'big data' registries to understand 'unseen' risk predictors and create better algorithms for risk stratification.

While no risk assessment strategy is perfect, we should strive for the most precise calculation of risk, especially in medium- and high-risk categories where potential clinical impact is the greatest, but also in low-risk groups where there is potential for health cost savings to avoid unnecessary screening. The incorporation of advanced cardiovascular imaging techniques, proteomics, genomics, AI/machine learning and *ex vivo* biological platforms could enhance the accuracy and predictive value of these risk assessment tools. Importantly, increasing awareness by both healthcare providers and patients that reducing CVD risk has a direct correlation to improved cancer survivorship and vice versa, that history of cancer represents a definitive CV risk factor (despite its absence from all major general cardiovascular risk calculators) is paramount.[12,13]

Enhancing national and international collaborations in cardio-oncology with a view of addressing multiple gaps in our knowledge is critical for this emerging field and importantly for our patients, who stand to benefit from more individualized approaches that can only be developed collaboratively.

Declarations

Disclosure of Interest

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