

## EDITORIAL COMMENT

# Cancer Therapy–Related Cardiac Dysfunction



## Expanding the Horizon of Cardiac Troponin in Clinical Practice\*

Laura De Michieli, MD,<sup>a,b</sup> Allan S. Jaffe, MD<sup>b,c</sup>

Cardiac troponin (cTn) is the biomarker of choice to detect myocardial injury and for the evaluation of possible acute myocardial infarction.<sup>1</sup> High-sensitivity cardiac troponin (hs-cTn) assays are recommended,<sup>2</sup> and it is now established that these assays can assist in assessing morbidity and mortality risks in the healthy population<sup>2</sup> as well as in patients with cardiomyopathies<sup>3</sup> or coronavirus disease-2019 infection.<sup>4</sup> The use of sex-specific 99th percentile upper reference limits (URLs) is recommended by the Fourth Universal Definition of Myocardial Infarction Task Force.<sup>1</sup>

The 2022 European Society of Cardiology cardiology guidelines<sup>5</sup> advocate for the use of cTn and N-terminal pro-B-type natriuretic peptide (NT-proBNP) to assess baseline cardiovascular (CV) risk, to define cancer therapy-related CV toxicity, and to aid in monitoring and follow-up. In this issue of *JACC: CardioOncology*, Mecinaj et al<sup>6</sup> evaluate the impact of the guidelines on the incidence of cancer therapy-related cardiac dysfunction (CTRCD) in a modest-sized cohort of 120 low-risk patients from the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial. The authors

provide useful information based on guideline definitions of CV toxicity.<sup>5</sup>

Their main findings are that the incidence of mild CTRCD is high, primarily driven by increased cTn concentrations above the 99th percentile URL. These biomarker elevations were not associated with short-term (2-year) reductions in left ventricular systolic function or other forms of CTRCD. The authors also report differences in the incidence of CTRCD assessed by cardiac troponin I (cTnI) compared to cardiac troponin T (cTnT) and between sex-specific and sex-neutral thresholds. They also report that neither metoprolol nor candesartan therapy changed the frequency of CTRCD.

These findings deserve some discussion. First, although the frequency of mild CTRCD was high (nearly 50%), it could have been even higher. As suggested by the guidelines,<sup>5</sup> the 99th percentile URL was used as a criterion. This threshold is predicated on the evaluation of patients with possible myocardial infarction. One could argue that using the reference change interval might be better. The reference change interval is a way of determining for a given value that the conjoint analytical and biological variation of the assay has been exceeded. If so, the frequency of increases might be higher given the very low values of both high-sensitivity cardiac troponin T (hs-cTnT) and high-sensitivity cardiac troponin I (hs-cTnI) in this cohort (median 3 [3-5] ng/L for hs-cTnT and median 0.8 [0.8-1.4] ng/L for hs-cTnI). In general, when hs-cTn values increase, this indicates an adverse prognosis.<sup>7</sup>

Second, patients with known heart disease were not included in this study. This reduces the generalizability of the findings and reinforces the need for longer follow-up to determine late effects. Previous studies in pediatric and adolescent and young adult populations suggest that cTnT elevations (with less

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From the <sup>a</sup>Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy; <sup>b</sup>Cardiovascular Department, Mayo Clinic and Medical School, Rochester, Minnesota, USA; and the <sup>c</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic and Medical School, Rochester, Minnesota, USA.

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sensitive assays) were associated with an increased incidence of heart failure during long-term follow-up, some of which was reduced by dexrazoxane.<sup>8</sup> Cardinale et al<sup>9</sup> reported that in patients receiving high-dose chemotherapy, increases in cTnI (with a contemporary assay) were associated with a higher incidence of cardiac events at 3 years. Thus, an increase in cTn values might be considered a risk factor to be reported in patients' records.

Accordingly, we should not be overly reassured by findings observed in a low-risk cohort with a short duration of follow-up. The results might have been very different if a less selected group had been included. Those at higher risk before cancer therapy are also likely to be at higher risk after treatment.<sup>9</sup> However, studying patients at higher risk also raises the question of how best to consider the interaction between elevated baseline cTn values because of cardiac comorbidities and the potential subsequent increased risk of CTRCD. The guidelines<sup>5</sup> suggest applying the criteria of a "new significant rise from baseline beyond the biological and analytical variation of the assay used" to identify CTRCD in patients with elevated baseline cTn values. One could, as mentioned previously, advocate for this approach. In unselected patients with cancer, increased hs-cTnT values are associated with increased mortality independent of age, sex, tumor entity and stage, and the presence of cardiac comorbidities.<sup>10</sup> Elevated hs-cTnI and hs-cTnT at baseline are also associated with a greater risk of trastuzumab-related cardiac dysfunction.<sup>11</sup> Further studies addressing the appropriate management of patients with increased baseline values and subsequent changes in cTn would be of value.

Third, cTnI and cTnT are not clinically interchangeable either diagnostically or prognostically.<sup>12</sup> Not only are there preanalytical issues that differ, but also many hs-cTnI assays measure lower concentrations than can be achieved by hs-cTnT assays,<sup>13</sup> contributing to variable detection rates in patients with low baseline concentrations. In addition, hs-cTnI increases are larger after myocardial infarction,<sup>13</sup> but hs-cTnT is more frequently increased in patients with nonischemic etiologies of myocardial injury, such as renal failure.<sup>1</sup> Prognostically, cTnI elevations are more strongly associated with CV events, whereas cTnT is more strongly related to non-CV death.<sup>1</sup>

Moreover, the definition of the 99th percentile URL is potentially problematic; 99th percentile URLs tend

to be overestimated<sup>14</sup> and highly variable. Thus, the criteria used might have a significant effect and should result in an insistence by the field that the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine on normal range studies<sup>15</sup> be followed more precisely.

We applaud the use of sex-specific thresholds. The metrics for males and females are different in the general population and in patients with heart failure.<sup>16</sup> In this study, sex-neutral thresholds would have lowered the frequency of CTRCD for both assays so that some of the women at potential risk might not have been detected. This might become important during longer-term follow-up. Women have lower cTn values both in the presence and absence of overt CV comorbidities.<sup>16</sup> Until further studies are available involving older patients with more CV comorbidities and with longer follow-up, sex-specific thresholds should be applied. Similar arguments are appropriate for NT-proBNP. Although the threshold of 125 ng/L is commonly used, there are substantial differences in NT-proBNP values according to sex.<sup>17</sup>

Similar considerations to those indicated earlier should be applied when considering therapy for primary and secondary prevention of CTRCD. Previous studies and meta-analysis suggest that neurohormonal therapies including renin-angiotensin-aldosterone system blockers, beta-blockers, and mineralocorticoid receptor antagonists might have cardioprotective benefit;<sup>5</sup> in some cases, they reduced cTn levels.<sup>18</sup>

In conclusion, every journey, no matter how exciting or perilous, begins with the first step. The work of Mecinaj et al<sup>6</sup> is a good step toward better definitions for patients at risk of CTRCD. However, as with all good research, it raises additional questions that require more data and additional research.

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**ADDRESS FOR CORRESPONDENCE:** Dr Allan S. Jaffe, Department of Cardiology, Gonda 5, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA. E-mail: [jaffe.allan@mayo.edu](mailto:jaffe.allan@mayo.edu).

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