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The year in cardiovascular medicine 2022: the top 10 papers in cardio-oncology

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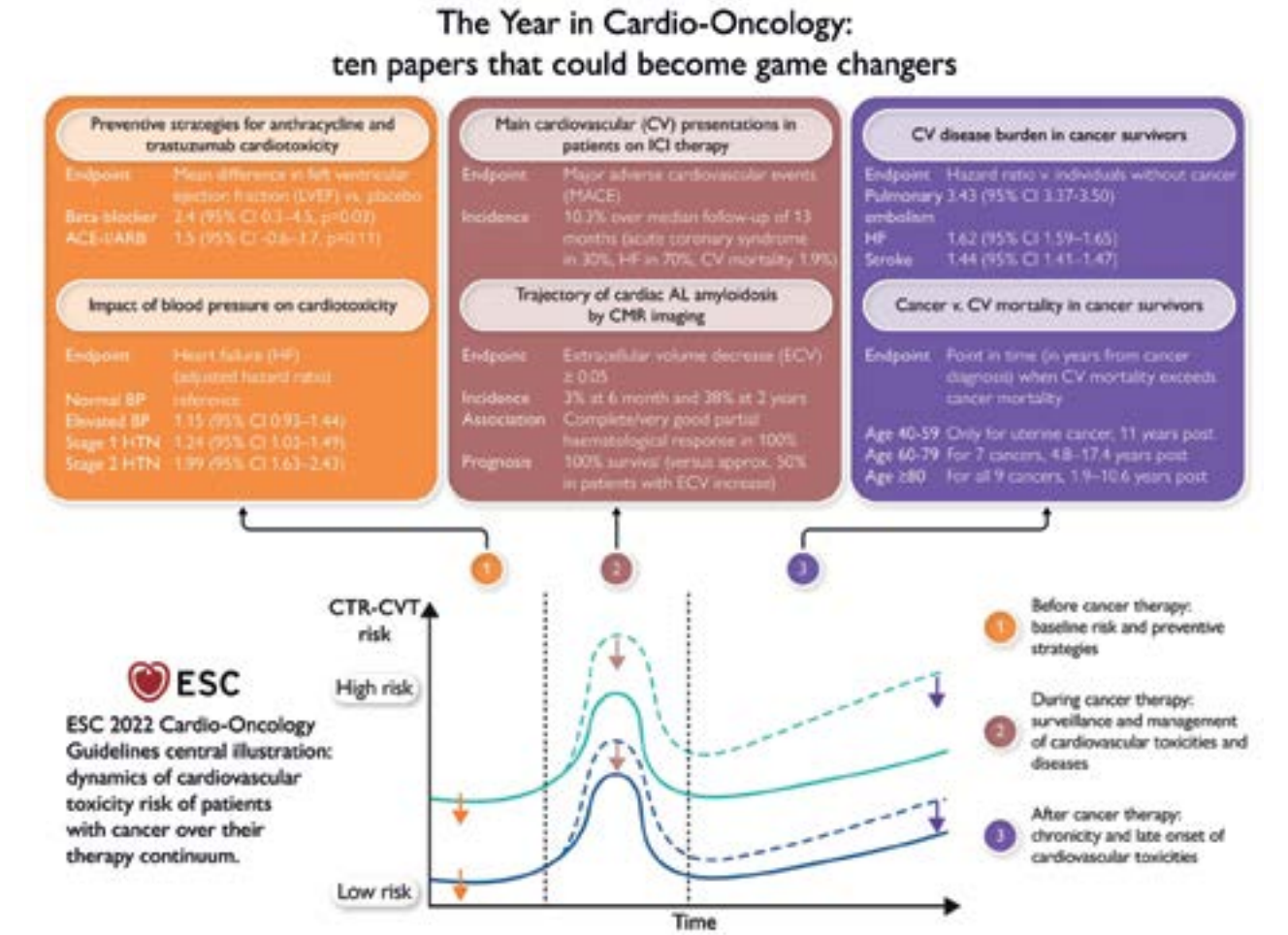

GRAPHICAL ABSTRACT Cardio-oncology through the continuum of cancer care: key publications in 2022. ACC, American College of Cardiology; ACE-I, angiotensin converting enzyme-inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; CI, confidence interval; HTN, hypertension

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The 2022 European Society Cardiology (ESC) guidelines on cardio-oncology include 272 recommendations and 48 figures, most of them algorithms, to provide much-needed direction in this field (1). Due to the lack of large-scale, randomized trials, only 3% of the recommendations were level of evidence (LOE) A (21% LOE B and 76% LOE C). The guidelines were composed by a large expert task force and critically reviewed by an equally esteemed panel of reviewers and are the first official guidelines in this area by a major cardiovascular (CV) society. The changing patient perspective with the trajectory of CV disease before, during, and after cancer diagnosis and treatment are key elements. The guidelines emphasize assessment of risk using Heart Failure Association (HFA)-International Cardio-Oncology Society (ICOS) risk assessment tools before initiation of therapy. Based on the stratification of risk, either low, intermediate, or high/very high, different courses of preventive and surveillance strategies are recommended to ensure that CV problems are managed appropriately to enable the most effective and least interfered upon cancer treatment.

Along the central theme of CV care along the continuum of cancer care, we will outline the top articles in cardio-oncology in 2022. Three articles addressed anthracycline cardiotoxicity; one also included breast cancer patients treated with trastuzumab. In a comprehensive meta-analysis including 9 randomized controlled trials and 1362 pa- tients up to 31 March 2021, *Lewinter et al.* (2) reviewed the benefit of beta-blockers and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) for the prevention of left ventricular dysfunction with the following key findings: irrespective of concomitant anthracycline or trastuzumab therapy, ACEI/ARB, and beta-blockers were associated with a higher left ventricular ejection fraction (LVEF), although the absolute differences vs. placebo were small (mean difference 1.5% and 2.4%, respectively) and only significant for beta-blockers. Further, the protection afforded by ACEI/ARB and beta-blockers was clearer for trastuzumab than for anthracyclines.

In a prospective randomized trial, *Hundley et al.* (3) investigated whether statins provided cardio-protection in 279 patients with either breast cancer or lymphoma; the answer was ‘no’. Atorvastatin 40 mg per day initiated 2 days before the start of doxorubicin-based therapy and continued for 2 years thereafter, did not reduce the decline in LVEF overall or in subgroups. Importantly, patients with any indication for statin therapy were excluded from the trial as were those with a pre-treatment LVEF <55%. Eighty-five percent of the patients in the study were women with breast cancer, median age was only 50, and median anthracycline dose was only 240 mg/m^2. Accordingly, caution should be taken in extrapolating these data to patients at higher risk and those with an indication for statins or beyond 2 years.

Innovative cardioprotective strategies beyond standard CV medications are also being investigated. In an elegant set of studies, *Lu et al.* (4) found that doxorubicin leads to the down-regulation of circular RNA derived from the insulin receptor (Circ-INSR) locus in the heart. Circ-INSR binds to the mitochondrial single-stranded DNA-binding protein, preserving mitochondrial DNA stability and replication and ultimately mitochondrial function and structure. Suppression of this functionality leads to metabolic derangement, cardiomyocyte death, and cardiac dysfunction. Conversely, Circ-INSR overexpression by a viral vector or circular ‘RNA-mimics’ prevents doxorubicin-mediated cardiotoxicity in in-vitro and in-vivo models. This research awaits translation to the bedside.

Among CV risk factors that increase the risk of cardiotoxicity, sys- temic hypertension may be the most important. Aiming to define this association in a large population, *Kaneko et al.* (5) analysed hospital administrative data for 34 000 patients with the most common cancer types encountered in Japan (approximately 50% breast cancer, 30% colorectal cancer, and 20% stomach cancer). Patients with stage 1 hypertension [systolic blood pressure (SBP) 130–139 mmHg or diastolic blood pressure (DBP) 80–89 mmHg] according to the 2017 American College of Cardiology/American Heart Association guideline had a 24% risk of newly diagnosed heart failure (HF), a 27% increased risk of angina pectoris (AP), a 32% increased risk of atrial fibrillation (AF), and a 46% increased risk of stroke compared with patients with normal blood pressures (SBP <120 mmHg and DBP < 80 mmHg). Patients with stage 2 hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) had a 99%, 99%, 106%, and 42% increased risk of HF, AF, stroke, and AP, respectively. Using continuous data, an increased risk of HF was observed when SBP exceeded 110 mmHg. Collectively, these data support the diagnostic and therapeutic cut-offs for systemic hypertension defined in the ICOS consensus and ESC guidelines documents. Future studies will need to outline the clinical significance of managing hypertension in patients with cancer in terms of CV events, including HF, and overall outcomes.

Since the first description of cases with fulminant immune checkpoint inhibitor (ICI) myocarditis in 2016, there has been a vivid interest in iden-tifying the culprit process, if not the nature and molecular target of T cells felt to have ‘gone rogue’. In a genetic mouse model with homozygous knockout of Pdcd1 and heterozygous deletion of Ctla4, Axelrod et al. (6) identified highly activated and clonally expanded CD8+ T cells as the dominant immune population and depletion of CD8+ T cells but not CD4+ T cells nearly completely prevented the 50% mortality rate otherwise seen. In a candidate autoantigen approach, alpha-myosin was identified as one leading target, noted also in three patients with ICI myocarditis. The full translational aspect of these findings needs to be determined.

While myocarditis is important, other CV events are more common in patients on ICI therapy. In a cohort study of nearly 700 patients, *Laenens et al.* (7) found a 10% incidence of HF, acute coronary syndrome, or stroke/transient ischaemic attack within a year of starting ICI therapy, almost two times higher than in cancer patients not on ICIs and more than three times higher than in individuals without cancer [control groups matched to cases for sex, age (within 5 years), history of CV disease, and cancer type in patients with cancer]. The higher event rate was driven by HF rather than vascular events. HF with a preserved LVEF was the most common presentation, accounting for almost 50% of cases, an asymptomatic decline in LVEF was next most common (in 30%); HF with a reduced LVEF accounted for <20%, and fewer than 10% presented as takotsubo syndrome. Half of these events occurred within a few months following completion of treatment. Patients with a prior history of HF or valvular heart disease were more likely to experience HF events. No patient was formally diagnosed with ICI myocarditis in this study.

In patients with cardiac amyloidosis, *Martinez-Naharro et al.* (8) investigated changes in extracellular volume (ECV) on CV magnetic resonance (CMR) in response to haematological treatment. Over the course of treatment, the percentage of patients with regression of cardiac amyloidosis by CMR increased (from 3% at 6 months to 38% at 2 years), and the percentage of those with progression decreased (from 32% at 6 months to 14% at 2 years). All patients with CMR regression had either a complete response or very good partial response, whereas most of those with CMR progression had a partial response or no response. Changes in ECV correlated not only with the haematological response to treatment but also with survival. CMR response at 6 months predicted death and remained prognostic after adjusting for haematological response, N-terminal-pro-brain natriuretic peptide, and longitudinal strain. No patients with a reduction in ECV on CMR 6 months after commencing chemotherapy died over the entire follow-up period (40 ± 15 months). Accordingly, CMR emerges as a potentially very useful imaging biomarker to track burden and response to therapy of cardiac amyloidosis.

In terms of CV disease burden in cancer survivors, a comprehensive (4.5 million) population-based study by *Paterson et al.* (9) from Alberta, Canada, found that patients with cancer have a 44%, 62%, and 243% increased risk of stroke, HF, and pulmonary embolism (PE), respectively, and a 33% higher CV mortality risk than non-cancer patients. The CV risk was highest at the time of diagnosis and declined exponentially over time (most profoundly in the first year). Patients with nervous system malignancies or thoracic cancers had the highest risk of PE and stroke. Patients with thoracic cancer or haematological malignancies had the highest risk of HF and myocardial infarction. Patients with these three cancer entities also had a significantly higher CV mortality.

Another population-based study on 100 000 patients with 9 different types of cancer from England investigated the risk of CV death (10). In patients who were diagnosed with cancer below the age of 60 years, cancer mortality generally exceeded CV mortality except for uterine cancer, for which CV and cancer mortality were similar by 11 years of follow-up. In those aged 60–79 years, CV mortality exceeded cancer mortality for seven cancer types after follow-up ranging from 5 years (bladder cancer) to 17 years (lung cancer). Lastly, in those 80 years or older at the time of cancer diagnosis, CV mortality exceeded cancer mortality for all nine cancer types after follow-up ranging from 1.9 years (melanoma) to 10.6 years (lung cancer). Collectively, these data outline the importance of CV diseases in cancer patients and should stimulate efforts to recognize and manage CV disease effectively.

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Conflict of interest

Pfizer advisory board consultation to J.H. and speak- er fees Janssen and Philips to T.L.-F.

Data availability

This is not an original article, no original data.

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