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Special article

The year in cardiovascular medicine 2021: cardio-oncology

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Introduction

Publications in cardio-oncology have increased exponentially over the past two decades. The *Year in Cardiovascular Medicine: Cardio-Oncology 2020–2021* covers the most recent and relevant studies in this field over the outlined timeframe. Several consensus documents have been released, a number of population-based studies outlined the burden and uniqueness of cardiovascular diseases (CVD) in patients with cancer, and clinical and basic science work provided important new data on mechanisms, diagnostics, surveillance, and management of cancer therapy-specific cardiovascular toxicities.

Consensus documents, position papers, and guidelines

The year 2020–2021 has witnessed several consensus documents and position papers by various professional societies on the topic of cardio-oncology, four of these by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). The first, in collaboration with the International Cardio-Oncology Society (IC-OS), focuses on baseline cardiovascular risk assessment in cancer patients scheduled to receive cancer therapies with the potential to cause heart failure.[1] This paper includes risk assessment proformas, which can be downloaded for clinical use. The HFA Cardio-Oncology Study Group, in conjunction with the ESC Council of Cardio-Oncology, also published a position paper on the role of cardiac imaging (furthermore in collaboration with the European Association of Cardiovascular Imaging) and a paper on the role of cardiac biomarkers, describing how cardiac imaging or biomarkers can be used in risk assessment, surveillance, and follow-up in cancer patients before, during, and after cardiotoxic cancer therapies (*Figure 1 – see in original*).[2,3] The fourth position paper from HFA focuses on the common mechanistic pathways underlying the pathophysiology of cancer and cardiovascular disease and provides insights into new treatment targets.[4]

A very timely and important consensus statement entitled 'Cardio-oncology care in the era of the coronavirus disease 2019 (COVID-19) pandemic' was written by IC-OS.[5] This document refines some of the recommendations outlined earlier in the year by the European Society of Medical Oncology in the consensus document on the 'Management of cardiac disease in cancer patients throughout oncological treatment'.[6] The IC-OS COVID-19 document reinforces primary prevention, simplifies surveillance recommendations, and emphasizes the continued need for the assessment and management for acute, urgent, and emergent CVDs with appropriate precautions in place. Further insight and recommendations on the acute cardiovascular emergencies in cancer patients are outlined in the position paper 'Evaluation and management of cancer patients presenting with acute cardiovascular disease' by the Acute CardioVascular Care Association in collaboration with the ESC council of Cardio-Oncology.[7]

A Scientific Statement from the American Heart Association (AHA) focuses on the 'Recognition, Prevention, and Management of Arrhythmias and Autonomic Disorders in Cardio-Oncology'.[8] Another Scientific Statement from the AHA covers the 'Impact of Hormonal Therapies for Treatment of Hormone-Dependent Cancers (Breast and Prostate) on the Cardiovascular System'.[9] The second expert consensus on a specific cancer therapy in the past year is the IC-OS document on 'Cardiovascular Manifestations from Therapeutic Radiation'.[10] Last but not least, the IC-OS consensus document on 'Defining cardiovascular toxicities of cancer therapies' provides harmonized definitions of the five cardiovascular toxicities of cancer therapies most frequently published upon in the last 5 years: cardiomyopathy and heart failure, myocarditis, vascular toxicity, hypertension, and arrhythmias.[11]

Burden and uniqueness of cardiovascular diseases in cancer patients

Several population-based studies have provided new data and insight on the burden of CVD in patients with cancer, its unique characteristics, as well as its implications. Along these lines, the report from the CardioTox registry is a milestone.[12] First, it proposed a new grading of cardiotoxicity from mild to severe. Second, it shows that most cardiotoxicities are of mild degree. Third, only severe cardiotoxicities have a measurable prognostic impact. Another seminal publication outlines that adolescent and young adult cancer survivors have a cardiac mortality risk that is higher not only than the general population but also than childhood cancer survivors, and persisting over a lifetime.[13] The highest risk group were Hodgkin lymphoma survivors.

Vascular disease is being increasingly recognized as a major contributor to cardiovascular mortality in patients with cancer. A nationwide study from Austria pointed out a nearly seven-fold and a nearly 15-fold increased risk of arterial thrombotic event (ATE) and venous thrombotic event (VTE), respectively, in cancer patients relative to the general population.[14] A prominent age-related gradient in relative risk was seen: highest in the youngest age group (12 years and under) and lowest in the oldest group (80–90 years), attributable to the (relatively) low prevalence of vascular disease in the young. However, even in the oldest age group, the risk of ATE and VTE remained higher than in the age-matched general population. As demonstrated in acute stroke patients undergoing thrombectomy, arterial thrombi are more fibrin- and platelet-rich in patients with than in those without cancer.[15] Fibrin–platelet-rich thrombi are also characteristic of stent thrombosis, and a seminal study in patients who underwent percutaneous coronary intervention (PCI) outlined a nearly three times higher stent thrombosis (ST) and two times higher myocardial infarction (MI) risk in those with cancer than in patients without cancer over 5 years of follow-up (as well as a 1.7 times higher bleeding risk).[16] In patients with malignancies, the ST risk was particularly high in the first year after PCI, whereas the increased risk for MI was more continuous and the risk of both could be predicted by a high DAPT score (2 or higher). These data have been reproduced in the report from the US nationwide readmission database, indicating that patients with cancer have two and three times higher readmission risk

for MI and bleeding, respectively, than patients without cancer in the first 90 days after PCI.[17]

Recognition of increased ventricular arrhythmias in cancer patients and with cancer therapies is expanding. A pharmacovigilance study outlined an increase in reports of drug-induced long QT syndrome, torsades de pointes, or ventricular arrhythmia from 580 reports over 17 years in the late 1960s to early 1980s to 15 070 reports in just 5 years in the current era (2014–2018).[18] The contribution of anticancer drugs to these numbers has increased substantially, from 0.9% (5/580) to 14.0% (2115/15 070). Forty-nine anticancer drugs accounted for drug-induced long QT syndrome or ventricular arrhythmias, nearly 50% were associated with sudden death and 40% were tyrosine kinase inhibitors (TKIs). Careful evaluation of the arrhythmogenic profile of kinase inhibitors in another study defined one with a predominantly ventricular arrhythmia risk (nilotinib), two with a predominantly bradycardia risk (alectinib and crizotinib), and seven with a predominantly atrial fibrillation (AF) risk (ibrutinib, ponatinib, ribociclib, trametinib, osimertinib, and idelasib).[19] The AF risk was highest for ibrutinib, and an elegant experimental study identified C-src kinase as the prime target of AF risk with ibrutinib.[20,21] In addition to kinase inhibitors, immunomodulatory agents (lenalidomide, pomalidomide), antimetabolites (azacytidine, clofarabine), taxanes (docetaxel), and binutuzumab, an anti-CD20 monoclonal antibody, were found to be associated with a higher reported rate of AF in another pharmacovigilance database study.[22] Three quarters of the identified associations were with drugs used in haematological malignancies. This matches the results of a nationwide population-based study that found the risk of AF to vary across cancer subtypes, being highest in multiple myeloma patients [adjusted subdistribution hazard ratio (aHR) 3.3].[23] Among solid tumours, AF risk was highest in oesophageal cancer and lowest in gastric cancer patients (aHR: 2.69 and 1.27; respectively). An analysis from the SEER Medicare database found that breast cancer patients had a two-fold increased risk of developing AF compared with a propensity-matched control cohort. The risk was highest among patients with the most advanced breast cancer stages.[24] Beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and spironolactone/eplerenone lowered the risk of new-onset AF in patients with breast cancer across all grades. Patients developing AF within the first 30 days after breast cancer diagnosis had a two-fold increased 1-year all-cause mortality rate. This risk was reduced by nearly 60% in breast cancer patients with new-onset AF on anticoagulation. This is an interesting observation considering that the main cause of cardiovascular death (nearly two-thirds) in breast cancer patients with new-onset AF was heart failure; systemic embolism and ischaemic stroke accounted only for one-third collectively.

Anticoagulation is a core element in the management of AF but challenging in the cancer population. A single-centre study reported that nearly one-half of patients with cancer and AF had an elevated risk for stroke but did not receive anticoagulation.[25] Thrombocytopenia, coagulopathy, or a history of major bleeding were factors associated with a lower utilization rate of anticoagulation as were concerns for drug–drug interactions. Active chemotherapy was an independent predictor for the lack of anticoagulant use. Concerns for bleeding risk and drug–drug interactions were also found to be the main reasons for not utilizing anticoagulation for stroke prevention in patients with active cancer in a web-based survey of nearly 1000 physicians.[26] CHA_2DS_2-VASc and HAS-BLED scores were considered appropriate aids in decision-making by two-thirds and just over a half, respectively, although not specifically validated in cancer patients. Most decisions on anticoagulation (75%) were taken in a team or cardiologist–oncologist approach and patients were involved in the decision-making in ~60%. If anticoagulation was pursued, two-thirds group of practitioners (80% cardiologists, 75% from Europe) preferred direct oral anticoagulants (DOACs), and nearly half indicated that DOACs should be used in all types of cancers other than non-operable gastrointestinal (GI) cancers. GI malignancies pose a bleeding risk, and any GI bleed should be evaluated as an indicator for the presence of GI malignancy in patients with AF on anticoagulation. A large population-based study confirms this notion, indicating a higher risk of colorectal cancer among patients with lower GI bleed on anticoagulation (85% warfarin).[27] The absolute risk was two times higher in the elderly, whereas the relative risk was two times higher in the group <65 years of age.

Finally, on structural heart disease, studies on the management of aortic stenosis in patients with cancer and prior chest radiation continue to define the advantages and disadvantages of transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR). SAVR is associated with a lower stroke and permanent pacemaker risk, whereas TAVR yields a lower mortality, bleeding, and AF risk, and length of stay.[28,29] This is a general view, and a more differential analysis indicates that worse survival outcomes with SAVR are confined to those with intermediate and high surgical risk.[30] In patients with a malignant pericardial effusion who underwent pericardiocentesis, utilization of colchicine 0.6 mg twice a day for 2 months is associated with a one-third reduction in all-cause mortality and need for repeat pericardiocentesis or pericardial window placement.[31] These results persisted on propensity score matching; in fact, the effect size became even more noticeable: colchicine was associated with a nearly 50% reduction in all-cause death and repeat pericardiocentesis or pericardial window placement for recurred pericardial effusion.

Therapy-specific cardiovascular toxicities

Chemotherapeutics and targeted therapies

Studies on anthracyclines continue to reveal less well-defined aspects such as abnormal vasoreactivity secondary to vascular oxidative stress.[32,33] Among therapeutic options, sacubitril/valsartan was found to attenuate anthracycline cardiotoxicity in an experimental model.[34] Further, mitochondria-rich extracellular vesicles were shown to rescue patient-derived cardiomyocytes from doxorubicin injury.[35] These patients were enrolled in the Cardiovascular Cell Therapy Research Network (CCTRN) SENECA Trial for

Allogeneic Mesenchymal Cell Therapy in Anthracycline-Induced Cardiomyopathy/Heart Failure Patients, which successfully completed its Phase 1 study goals.[36] In the meantime, data are mounting on the protective effects of statins for cardiotoxicity. A propensity score-matched cohort study demonstrated that statins reduced the risk of heart failure after anthracycline more so than after trastuzumab exposure.[37] In the first randomized clinical trial to evaluate the merit of strain imaging in breast cancer patients receiving anthracycline therapy ± trastuzumab, the strain surveillance of chemotherapy for improving cardiovascular outcomes (SUCCOUR) trial did not see a difference in left ventricular ejection fraction (LVEF) change over 1 year using an 3D-LVEF or global longitudinal strain (GLS)-based approach.[38] However, patients commenced on ramipril and carvedilol based on an abnormal GLS dynamic (12% relative increase) had less of a decline in LVEF than those commenced on these therapies based on an abnormal 3D-LVEF dynamic. These data support the notion that early recognition and early intervention is more favourable. However, as a secondary analysis of a trial that missed its primary endpoint, these data are still to be viewed as hypothesis-generating.

Three-monthly LVEF monitoring remains the recommended standard cardiac surveillance protocol for patients on trastuzumab therapy. While adherence to this guideline was not associated with lower risk of HF in a single-centre study, an LVEF <55% at any timepoint or during the final surveillance timepoint was found to be associated with HF with remarkable odds ratios of 27.0 and 25.6, respectively.[39] Eighty percent of patients had received anthracyclines, and these data reinforce the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines, which list a 'borderline' LVEF of 50–55% as a risk factor for cancer therapy-related cardiac dysfunction, especially in patients undergoing cancer therapy with anthracyclines.

Immune therapies

The utilization of immune therapies continues to expand and with this the recognition of their cardiovascular side effects. A nationwide study from Denmark showed a 1-year absolute risk of cardiac events (arrhythmia, peri-/myocarditis, or heart failure, based on administrative national databases using ICD-10 codes) of nearly 10% in lung cancer patients, of nearly 7% in melanoma patients on PD-1 inhibitor therapy, and of 7.5% in melanoma patients on CTLA-4 inhibitor therapy.[40] No cardiovascular deaths and half of non-cardiovascular deaths were seen in melanoma patients on PD-1 inhibitor therapy; 3–4% cardiovascular and 50% non-cardiovascular 1-year mortality rates in the other groups. Compared with non-immune checkpoint inhibitor (ICI) therapy, the risk of CV events was two times higher in patients on PD-1 inhibitor therapy with no differential over 1 year in lung cancer patients. In melanoma patients, the CV event risk was twice as high (4 times higher risk) in the first 6 months of PD-1 inhibitor therapy. Melanoma patients on CTLA-4 inhibitor therapy had the highest relative risk of CV events (hazard ratios 5 and 3.5 in the first 6 and 12 months, respectively).

The diagnostic criteria (or definition) of ICI myocarditis continue(s) to evolve. Cardiac magnetic resonance imaging has been a vital part of confirming the diagnosis; however, an international registry-based study cautions on sole reliance on this technique. Late gadolinium enhancement (LGE) was present in only 35% of cases with biopsy-confirmed pathological fibrosis and elevated T2-weighted short tau inversion recovery (STIR) in only 26% of cases with biopsy-confirmed lymphocytic infiltration.[41] A critically important aspect is time; the rate of LGE+ CMRs increased from 21.6% within 4 days of admission to 72.0% thereafter. The presence of LGE, LGE pattern, or elevated T2-weighted STIR was not associated with major adverse cardiovascular events (MACE).

A separate study from the same international registry found that lower GLS was strongly associated with MACE (composite of cardiogenic shock, arrest, complete heart block, and cardiac death) in ICI myocarditis.[42] After adjustment for LVEF, each percent point reduction in GLS was associated with a 1.5-fold increase in MACE among patients with a reduced EF (hazard ratio: 1.5; 95% confidence interval: 1.2–1.8) and a 4.4-fold increase in patients with a preserved EF (hazard ratio: 4.4; 95% confidence interval: 2.4–7.8). Patients without ICI myocarditis had no change in GLS on ICI therapy versus baseline, unlike patients with ICI myocarditis who showed a change from –20 to –14%. Global longitudinal strain was lower in ICI myocarditis patients with reduced compared with preserved EF (12 vs. 15%).

A very interesting preclinical study reported the development of a new model of ICI myocarditis using different degrees and combinations of *Ctla4* and *Pdcd1* (PD-1) knockout mice. A graded survival response was noted based on the level of gene loss. Mice without *Ctla4* cannot survive, monoallelic loss of *Ctla4* is sustainable but approximately half of mice with concomitant complete genetic loss of *Pdcd1* (PD-1) face premature death with prominent infiltration of the myocardium by T cells and macrophages. The therapeutic merit of CTLA4–Ig (abatacept) was confirmed in this model, opening perspectives for mechanistic investigations.[43] In a second, novel melanoma model, anti-PD1 therapy promoted CD4+ and CD8+ T-cell infiltration of the myocardium with marked CD8+ T-cell activation.[44] A decline in LV function could be seen in association with dysregulation of myocardial metabolism and could be attenuated by tumour necrosis factor alpha (TNFα) blockade. The translational aspect of this study is the impaired LV functional response to stress in patients with metastatic melanoma on anti-PD1 therapy.

ICI therapy may induce not only cardiomyopathy and myocarditis but also vascular events. An increased rate of atherosclerotic cardiovascular events (MI, coronary revascularization, and ischaemic stroke, individually and combined) has been recognized from 1.37 per 100 person-years before to 6.55 per 100 person-years 2 years after initiation of ICI therapy. This calculated into an overall 3.3-fold higher risk for cardiovascular events after starting ICI therapy.[45] Analyses of aortas by computed tomography in a substudy of 40 patients indicated an increase in total aortic atherosclerotic plaque volume after initiation of ICI therapy, unless concomitant statin and steroid

use, which had an attenuating effect. Interestingly, an increase in plaque volume was not seen in an experimental study in atherosclerotic *Ldlr*$^{-/-}$ mice with combined anti-CTLA-4 and anti-PD-1 antibody therapy twice a week for 4 weeks. However, in this model, endothelial activation and plaque progression towards a lymphoid-based inflammatory phenotype was noted (nearly three-fold increase of CD8^{+} T cells and nearly four-fold increase in necrotic core size).[46]

CAR-T cell therapy is the second major expanding immune therapy. Cardiovascular events, in particular cardiac dysfunction and heart failure, have been described. In a new report on 145 patients enrolled at a single centre, 45 MACE (including cardiovascular death, symptomatic heart failure, acute coronary syndrome, ischaemic stroke, and *de novo* cardiac arrhythmia) occurred in 31% of patients.[47] Baseline creatinine (HR 15.5 for each 1 mg/dL increase) and cytokine release syndrome (CRS) grade 3 (HR 8.4) and 4 (HR 29.9) were independent predictors of MACE. Of note, CRS preceded MACE by 5 days on average and nearly all MACE occurred within 20 days from start of therapy. Most events were heart failure (15%), followed by atrial fibrillation (7.5%). Supraventricular tachycardia and non-sustained ventricular tachycardia were seen in one patient each, and ACS and cardiac death in two patients each. A pharmacovigilance study likewise found that (after hypotension) cardiomyopathy was the most frequently overreported cardiovascular adverse event followed by tachyarrhythmias, mainly atrial fibrillation followed by ventricular tachycardia.[48] Tachyarrhythmias were reported more often following axicabtagene-ciloleucel than tisagenlecleucel use and venous thromboembolic events were noted only for patients receiving axicabtagene-ciloleucel. Respiratory failure was the second most common adverse event, and no lag time was seen between cardiopulmonary adverse effects and CRS. The fatality rate of cardiopulmonary adverse effects was 31%.

Reverse cardio-oncology

In addition to an increase in the risk of CVD and cardiovascular events as a consequence of cancer or cancer therapies, an increase in the risk of cancer can be seen after cardiovascular events and development of CVD. This has become known as reverse cardio-oncology and was first shown for patients with heart failure but then for various cohorts of CVD patients. An elegant experimental and translational study in the past year found that MI accelerates breast cancer outgrowth and cancer-specific mortality. In mouse models of breast cancer, it was found that MI epigenetically reprogrammed monocytes to an immunosuppressive phenotype in the bone marrow and increased their level in both the circulation and tumour. Depletion of these cells abrogated MI-induced tumour growth, supporting their causal role.[49]

Future directions

Emerging developments relate to artificial intelligence (AI), and a number of initiatives are under way using various imaging and other techniques. One of the first and most important advancements in this field is that of AI-enhanced and fully automated detection of cardiac amyloidosis using echocardiograms and electrocardiograms (ECGs).[50] Two more studies have confirmed the utility of AI-enhanced ECGs for the early detection of cardiac amyloidosis.[51,52] Another important development is training and education in cardio-oncology; the ACC council on cardio-oncology provides a first outline of standards in this area.[53]

Summary and conclusions

The publications in cardio-oncology in 2020–2021 reflect a growing interest in this field and reinforce the commitment of the scientific community to this new discipline. Improving our knowledge on the pathophysiological mechanisms and the prognostic impact of CV toxicities of cancer therapies is crucial for evidence-based management strategies in clinical practice. Societal consensus documents continue to summarize these aspects and more is to come in this very area.

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References

1. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail* 2020;22:1945–1960.
2. Celutkiene J, Pudil R, Lopez-Fernandez T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;22:1504–1524.
3. Pudil R, Mueller C, Celutkiene J, Henriksen PA, Lenihan D, Dent S, et al. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. *Eur J Heart Fail* 2020;22:1966–1983.
4. de Boer RA, Hulot JS, Tocchetti CG, Aboumsallem JP, Ameri P, Anker SD, et al. Common mechanistic pathways in cancer and heart failure. A scientific roadmap on behalf of the Translational Research Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;22:2272–2289.
5. Lenihan D, Carver J, Porter C, Liu JE, Dent S, Thavendiranathan P, et al. Cardio-oncology care in the era of the coronavirus disease 2019 (COVID-19) pandemic: an International

Cardio-Oncology Society (ICOS) statement. *CA Cancer J Clin* 2020;70:480–504.
6. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol* 2020;31:171–190.
7. Gevaert SA, Halvorsen S, Sinnaeve PR, Sambola A, Gulati G, Lancellotti P, et al. Evaluation and management of cancer patients presenting with acute cardiovascular disease: a Consensus Document of the Acute CardioVascular Care (ACVC) association and the ESC council of Cardio-Oncology-Part 1: acute coronary syndromes and acute pericardial diseases. *Eur Heart J Acute Cardiovasc Care* 2021;10:947–959.
8. Fradley MG, Beckie TM, Brown SA, Cheng RK, Dent SF, Nohria A, et al. Recognition, prevention, and management of arrhythmias and autonomic disorders in cardio-oncology: a scientific statement from the American Heart Association. *Circulation* 2021;144:e41–e55.
9. Okwuosa TM, Morgans A, Rhee JW, Reding KW, Maliski S, Plana JC, et al. Impact of hormonal therapies for treatment of hormone-dependent cancers (Breast and Prostate) on the cardiovascular system: effects and modifications: a scientific statement from the American Heart Association. *Circ Genom Precis Med* 2021;14:e000082.
10. Mitchell JD, Cehic DA, Morgia M, Bergrom C, Toohey J, Guerrero PA, et al. Cardiovascular manifestations from therapeutic radiation: a multidisciplinary expert consensus statement from the International Cardio-oncology Society. *JACC CardioOncol* 2021;3:360–380.
11. Herrmann J, Lenihan D, Armenian S, Barac A, Blaes A, Cardinale D, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J* 2021:ehab674. https://doi.org/10.1093/eurheartj/ehab674. Published online ahead of print.
12. López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, Buño Soto A, Lyon AR, Farmakis D, et al. Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. *Eur Heart J* 2020;41:1720–1729.
13. Wang L, Wang F, Chen L, Geng Y, Yu S and Chen Z. Long-term cardiovascular disease mortality among 160 834 5-year survivors of adolescent and young adult cancer: an American population-based cohort study. *Eur Heart J* 2021;42:101–109.
14. Grilz E, Posch F, Nopp S, Königsbrügge O, Lang IM, Klimek P, et al. Relative risk of arterial and venous thromboembolism in persons with cancer vs. persons without cancer-a nationwide analysis. *Eur Heart J* 2021;42:2299–2307.
15. Fu CH, Chen CH, Lin YH, Lee CW, Tsai LK, Tang SC, et al. Fibrin and platelet-rich composition in retrieved thrombi hallmarks stroke with active cancer. *Stroke* 2020;51:3723–3727.
16. Guo W, Fan X, Lewis BR, Johnson MP, Rihal CS, Lerman A, et al. Cancer patients have a higher risk of thrombotic and ischemic events after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2021;14:1094–1105.
17. Kwok CS, Wong CW, Kontopantelis E, Barac A, Brown SA, Velagapudi P, et al. Percutaneous coronary intervention in patients with cancer and readmissions within 90 days for acute myocardial infarction and bleeding in the USA. *Eur Heart J* 2021;42:1019–1034.
18. Salem JE, Nguyen LS, Moslehi JJ, Ederhy S, Lebrun-Vignes B, Roden DM, et al. Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study. *Eur Heart J* 2021;42:3915–3928.
19. Ye JZ, Hansen FB, Mills RW, Lundby A. Oncotherapeutic protein kinase inhibitors associated with pro-arrhythmic liability. *JACC CardioOncol* 2021;3:88–97.
20. Xiao L, Salem JE, Clauss S, Hanley A, Bapat A, Hulsmans M, et al. Ibrutinib-mediated atrial fibrillation attributable to inhibition of C-terminal Src kinase. *Circulation* 2020;142:2443–2455.
21. Awan FT, Tong D, Zaha VG. Cardio-oncology: a win-win situation: how solving the mystery of an Ibrutinib off-target effect reveals new insights into atrial fibrillation mechanisms. *Circulation* 2020;142:2456–2458. https://doi.org/10.1161/CIRCULATIONAHA.120.052047. Published online ahead of print 21 December 2020.
22. Alexandre J, Salem JE, Moslehi J, Sassier M, Ropert C, Cautela J, et al. Identification of anticancer drugs associated with atrial fibrillation: analysis of the WHO pharmacovigilance database. *Eur Heart J Cardiovasc Pharmacother* 2021;7:312–320.
23. Yun JP, Choi EK, Han KD, Park SH, Jung JH, Park SH, et al. Risk of atrial fibrillation according to cancer type: a nationwide population-based study. *JACC CardioOncol* 2021;3:221–232.
24. Guha A, Fradley MG, Dent SF, Weintraub NL, Lustberg MB, Alonso A, et al. Incidence, risk factors, and mortality of atrial fibrillation in breast cancer: a SEER-Medicare analysis. *Eur Heart J* 2021:ehab745.
25. Fradley MG, Ellenberg K, Alomar M, Swanson J, Kharod A, Nguyen ATH, et al. Patterns of anticoagulation use in patients with cancer with atrial fibrillation and/or atrial flutter. *JACC CardioOncology* 2020;2:747–754.
26. Boriani G, Lee G, Parrini I, Lopez-Fernandez T, Lyon AR, Suter T, et al. Anticoagulation in patients with atrial fibrillation and active cancer: an international survey on patient management. *Eur J Prev Cardiol* 2021;28:611–621.
27. Rasmussen PV, Dalgaard F, Gislason GH, Brandes A, Johnsen SP, Grove EL, et al. Gastrointestinal bleeding and the risk of colorectal cancer in anticoagulated patients with atrial fibrillation. *Eur Heart J* 2020:ehz964.
28. Elbadawi A, Albaeni A, Elgendy IY, Ogunbayo GO, Jimenez E, Cornwell L, et al. Transcatheter versus surgical aortic valve replacement in patients with prior mediastinal radiation. *JACC Cardiovasc Interv* 2020;13:2658–2666.
29. Nauffal V, Bay C, Shah PB, Sobieszczyk PS, Kaneko T, O'Gara P, et al. Short-term outcomes of transcatheter versus isolated surgical aortic valve replacement for mediastinal radiation-associated severe aortic stenosis. *Circ Cardiovasc Interv* 2021;14:e010009.
30. Yazdchi F, Hirji SA, Nohria A, Percy E, Harloff M, Malarczyk A, et al. Transcatheter compared with surgical aortic valve replacement in patients with previous chest-directed radiation therapy. *JACC CardioOncol* 2021;3:397–407.
31. Kim SR, Kim EK, Cho J, Chang SA, Park SJ, Lee SC, et al. Effect of anti-inflammatory drugs on clinical outcomes in patients with malignant pericardial effusion. *J Am Coll Cardiol* 2020;76:1551–1561.
32. Clayton ZS, Brunt VE, Hutton DA, VanDongen NS, D'Alessandro A, Reisz JA, et al. Doxorubicin-induced oxidative stress and endothelial dysfunction in conduit arteries is prevented by mitochondrial-specific antioxidant treatment. *JACC CardioOncol* 2020;2:475–488.
33. Feher A, Boutagy NE, Stendahl JC, Hawley C, Guerrera N, Booth CJ, et al. Computed tomographic angiography assessment of epicardial coronary vasoreactivity for early detection of doxorubicin-induced cardiotoxicity. *JACC CardioOncol* 2020;2:207–219.
34. Boutagy NE, Feher A, Pfau D, Liu Z, Guerrera NM, Freeburg LA, et al. Dual angiotensin receptor-neprilysin inhibition with sacubitril/valsartan attenuates systolic dysfunction in experimental doxorubicin-induced cardiotoxicity. *JACC CardioOncol* 2020;2:774–787.
35. O'Brien CG, Ozen MO, Ikeda G, Vaskova E, Jung JH, Bayardo N, et al. Mitochondria-rich extracellular vesicles rescue patient-specific cardiomyocytes from doxorubicin injury: insights into the SENECA trial. *JACC CardioOncol* 2021;3:428–440.
36. Bolli R, Perin EC, Willerson JT, Yang PC, Traverse JH, Henry TD, et al. Allogeneic mesenchymal cell therapy in anthracycline-induced cardiomyopathy heart failure patients: the CCTRN SENECA trial. *JACC CardioOncol* 2020;2:581–595.
37. Abdel-Qadir H, Bobrowski D, Zhou L, Austin PC, Calvillo-Argüelles O, Amir E, et al. Statin exposure and risk of heart failure after anthracycline- or trastuzumab-based chemotherapy for early breast cancer: a propensity score-matched cohort study. *J Am Heart Assoc* 2021;10:e018393.
38. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, et al. Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol* 2021;77:392–401.

39. Yu AF, Moskowitz CS, Chuy KL, Yang J, Dang CT, Liu JE, et al. Cardiotoxicity surveillance and risk of heart failure during HER2 targeted therapy. *JACC CardioOncol* 2020;2:166–175.
40. D'Souza M, Nielsen D, Svane IM, Iversen K, Rasmussen PV, Madelaire C, et al. The risk of cardiac events in patients receiving immune checkpoint inhibitors: a nationwide Danish study. *Eur Heart J* 2021;42:1621–1631.
41. Zhang L, Awadalla M, Mahmood SS, Nohria A, Hassan MZO, Thuny F, et al. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. *Eur Heart J* 2020;41:1733–1743.
42. Awadalla M, Mahmood SS, Groarke JD, Hassan MZO, Nohria A, Rokicki A, et al. Global longitudinal strain and cardiac events in patients with immune checkpoint inhibitor-related myocarditis. *J Am Coll Cardiol* 2020;75:467–478.
43. Wei SC, Meijers WC, Axelrod ML, Anang NAS, Screever EM, Wescott EC, et al. A genetic mouse model recapitulates immune checkpoint inhibitor-associated myocarditis and supports a mechanism-based therapeutic intervention. *Cancer Discov* 2021;11:614–625.
44. Michel L, Helfrich I, Hendgen-Cotta UB, Mincu RI, Korste S, Mrotzek SM, et al. Targeting early stages of cardiotoxicity from anti-PD1 immune checkpoint inhibitor therapy. *Eur Heart J* 2021;ehab430.
45. Drobni ZD, Alvi RM, Taron J, Zafar A, Murphy SP, Rambarat PK, et al. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. *Circulation* 2020;142:2299–2311.
46. Poels K, van Leent MMT, Boutros C, Tissot H, Roy S, Meerwaldt AE, et al. Immune checkpoint inhibitor therapy aggravates T cell-driven plaque inflammation in atherosclerosis. *JACC CardioOncol* 2020;2:599–610.
47. Lefebvre B, Kang Y, Smith AM, Frey NV, Carver JR, Scherrer-Crosbie M. Cardiovascular effects of CAR T cell therapy: a retrospective study. *JACC CardioOncol* 2020;2: 193–203.
48. Goldman A, Maor E, Bomze D, Liu JE, Herrmann J, Fein J, et al. Adverse cardiovascular and pulmonary events associated with chimeric antigen receptor T-cell therapy. *J Am Coll Cardiol* 2021;78:1800–1813.
49. Koelwyn GJ, Newman AAC, Afonso MS, van Solingen C, Corr EM, Brown EJ, et al. Myocardial infarction accelerates breast cancer via innate immune reprogramming. *Nat Med* 2020;26:1452–1458.
50. Goto S, Mahara K, Beussink-Nelson L, Ikura H, Katsumata Y, Endo J, et al. Artificial intelligence-enabled fully automated detection of cardiac amyloidosis using electrocardiograms and echocardiograms. *Nat Commun* 2021;12:2726.
51. Grogan M, Lopez-Jimenez F, Cohen-Shelly M, Dispenzieri A, Attia ZI, Abou Ezzedine OF, et al. Artificial intelligence-enhanced electrocardiogram for the early detection of cardiac amyloidosis. *Mayo Clin Proc* 2021;96:2768–2778.
52. Schrutka L, Anner P, Agibetov A, Seirer B, Dusik F, Rettl R, et al. Machine learning-derived electrocardiographic algorithm for the detection of cardiac amyloidosis. *Heart* 2021;42. https://doi.org/10.1136/heartjnl-2021-319846. Published online ahead of print.
53. Alvarez-Cardona JA, Ray J, Carver J, Zaha V, Cheng R, Yang E, et al. Cardio-oncology education and training: JACC council perspectives. *J Am Coll Cardiol* 2020;76:2267–2281.