

# 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

**Alexander R. Lyon<sup>1\*</sup>, Susan Dent<sup>2</sup>, Susannah Stanway<sup>3</sup>, Helena Earl<sup>4</sup>, Christine Brezden-Masley<sup>5</sup>, Alain Cohen-Solal<sup>6</sup>, Carlo G. Tocchetti<sup>7</sup>, Javid J. Moslehi<sup>8</sup>, John D. Groarke<sup>9</sup>, Jutta Bergler-Klein<sup>10</sup>, Vincent Khoo<sup>11,12</sup>, Li Ling Tan<sup>13</sup>, Markus S. Anker<sup>14</sup>, Stephan von Haehling<sup>15,16</sup>, Christoph Maack<sup>17</sup>, Radek Pudil<sup>18</sup>, Ana Barac<sup>19</sup>, Paaladinesh Thavendiranathan<sup>20</sup>, Bonnie Ky<sup>21</sup>, Tomas G. Neilan<sup>22</sup>, Yury Belenkov<sup>23</sup>, Stuart D. Rosen<sup>1</sup>, Zaza Iakobishvili<sup>24</sup>, Aaron L. Sverdlov<sup>25</sup>, Ludhmila A. Hajjar<sup>26</sup>, Ariane V.S. Macedo<sup>27</sup>, Charlotte Manisty<sup>28</sup>, Fortunato Ciardiello<sup>29</sup>, Dimitrios Farmakis<sup>30,31</sup>, Rudolf A. de Boer<sup>32</sup>, Hadi Skouri<sup>33</sup>, Thomas M. Suter<sup>34</sup>, Daniela Cardinale<sup>35</sup>, Ronald M. Witteles<sup>36</sup>, Michael G. Fradley<sup>21</sup>, Joerg Herrmann<sup>37</sup>, Robert F. Cornell<sup>38</sup>, Ashutosh Wechelaker<sup>39</sup>, Michael J. Mauro<sup>40</sup>, Dragana Milojkovic<sup>41</sup>, Hugues de Lavallade<sup>42</sup>, Frank Ruschitzka<sup>43</sup>, Andrew J.S. Coats<sup>44,45</sup>, Petar M. Seferovic<sup>46</sup>, Ovidiu Chioncel<sup>47,48</sup>, Thomas Thum<sup>49</sup>, Johann Bauersachs<sup>50</sup>, M. Sol Andres<sup>1</sup>, David J. Wright<sup>51</sup>, Teresa López-Fernández<sup>52</sup>, Chris Plummer<sup>53</sup>, and Daniel Lenihan<sup>54</sup>**

<sup>1</sup>Cardio-Oncology Service, Royal Brompton Hospital and Imperial College, London, UK; <sup>2</sup>Duke Cancer Institute, Duke University, Durham, NC, USA; <sup>3</sup>Breast Unit, Royal Marsden Hospital, Surrey, UK; <sup>4</sup>Department of Oncology, University of Cambridge and NIHR Cambridge Biomedical Research Centre, Cambridge, UK; <sup>5</sup>Division of Medical Oncology, Sinai Health System, Mount Sinai Hospital, Toronto, Canada; <sup>6</sup>UMR-S 942, Paris University, Cardiology Department, Lariboisiere Hospital, AP-HP, Paris, France; <sup>7</sup>Department of Translational Medical Sciences and Interdepartmental Center for Clinical and Translational Research (CIRCET), Federico II University, Naples, Italy; <sup>8</sup>Cardio-Oncology Program, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; <sup>9</sup>Cardio-Oncology Program, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA; <sup>10</sup>Department of Cardiology, Medical University of Vienna, Vienna, Austria; <sup>11</sup>Department of Clinical Oncology, Royal Marsden Hospital and Institute of Cancer Research, London, UK; <sup>12</sup>Department of Medical Imaging and Radiation Sciences, Monash University and Department of Medicine, Melbourne University, Melbourne, Australia; <sup>13</sup>Department of Cardiology, National University Heart Centre, Singapore, National University Health System, Singapore, Singapore; <sup>14</sup>Division of Cardiology and Metabolism, Department of Cardiology, Charité and Berlin Institute of Health Center for Regenerative Therapies (BCRT) and DZHK (German Centre for Cardiovascular Research), partner site Berlin and Department of Cardiology, Charité Campus Benjamin Franklin, Berlin, Germany; <sup>15</sup>Department of Cardiology and Pneumology, University of Goettingen Medical Center, Goettingen, Germany; <sup>16</sup>German Center for Cardiovascular Research (DZHK), partner site Goettingen, Goettingen, Germany;

\*Corresponding author. Cardio-Oncology Service, Royal Brompton Hospital, Sydney Street, London SW3 6NR, UK. Tel: +44 20 7352 8121, Email: a.lyon@ic.ac.uk

<sup>17</sup>Comprehensive Heart Failure Center, University Clinic Würzburg, Würzburg, Germany; <sup>18</sup>First Department of Medicine – Cardioangiology, Charles University Prague, Medical Faculty and University Hospital Hradec Kralove, Prague, Czech Republic; <sup>19</sup>MedStar Heart and Vascular Institute, Georgetown University, Washington, DC, USA; <sup>20</sup>Ted Rogers Program in Cardiotoxicity Prevention and Joint Division of Medical Imaging, Peter Munk Cardiac Center, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Canada; <sup>21</sup>University of Pennsylvania, Philadelphia, PA, USA; <sup>22</sup>Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; <sup>23</sup>Sechenov Medical University, Moscow, Russia; <sup>24</sup>Department of Community Cardiology, Tel Aviv Jaffa District, Clalit Health Fund and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; <sup>25</sup>School of Medicine and Public Health, University of Newcastle and “Cancer and the Heart” Program, Hunter New England LHD, Newcastle, Australia; <sup>26</sup>Cardio-Oncology, Department of Cardio-Pneumology, University of São Paulo, São Paulo, Brazil; <sup>27</sup>Santa Casa Cardio-Oncology, Santa Casa de São Paulo and Rede Dor São Luiz, São Paulo, Brazil; <sup>28</sup>Barts Heart Centre and University College London, London, UK; <sup>29</sup>Department of Precision Medicine, Luigi Vanvitelli University of Campania, Naples, Italy; <sup>30</sup>University of Cyprus Medical School, Nicosia, Cyprus; <sup>31</sup>Cardio-Oncology Clinic, Heart Failure Unit, “Attikon” University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece; <sup>32</sup>Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; <sup>33</sup>Cardiology Division, Internal Medicine Department, American University of Beirut Medical Center, Beirut, Lebanon; <sup>34</sup>Department of Cardiology, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland; <sup>35</sup>Cardioncology Unit, European Institute of Oncology, IRCCS, Milan, Italy; <sup>36</sup>Stanford University School of Medicine, Stanford, CA, USA; <sup>37</sup>Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA; <sup>38</sup>Vanderbilt University Medical Center, Nashville, TN, USA; <sup>39</sup>National Amyloidosis Centre, University College London, London, UK; <sup>40</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA; <sup>41</sup>Department of Haematology, Hammersmith Hospital, Imperial College, London, UK; <sup>42</sup>Department of Haematological Medicine, King’s College Hospital, London, UK; <sup>43</sup>University Heart Center, Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; <sup>44</sup>University of Warwick, Warwick, UK; <sup>45</sup>Pharmacology, Centre of Clinical and Experimental Medicine, IRCCS San Raffaele Pisana, Rome, Italy; <sup>46</sup>Faculty of Medicine and Serbian Academy of Sciences and Arts, University of Belgrade, Belgrade, Serbia; <sup>47</sup>Emergency Institute for Cardiovascular Diseases ‘Prof. C.C. Iliescu’, Bucharest, Romania; <sup>48</sup>University of Medicine Carol Davila, Bucharest, Romania; <sup>49</sup>Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hannover, Germany; <sup>50</sup>Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; <sup>51</sup>Liverpool Centre for Cardiovascular Science, Liverpool Heart and Chest Hospital, Liverpool, UK; <sup>52</sup>Cardiology Service, Cardio-Oncology Unit, La Paz University Hospital and IdiPAZ Research Institute, Ciber CV, Madrid, Spain; <sup>53</sup>Department of Cardiology, The Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle, UK; <sup>54</sup>Cardio-Oncology Center of Excellence, Washington University in St Louis, St Louis, MO, USA

Received 5 January 2020; revised 13 May 2020; accepted 25 May 2020

This position statement from the Heart Failure Association of the European Society of Cardiology Cardio-Oncology Study Group in collaboration with the International Cardio-Oncology Society presents practical, easy-to-use and evidence-based risk stratification tools for oncologists, haemato-oncologists and cardiologists to use in their clinical practice to risk stratify oncology patients prior to receiving cancer therapies known to cause heart failure or other serious cardiovascular toxicities. Baseline risk stratification proformas are presented for oncology patients prior to receiving the following cancer therapies: anthracycline chemotherapy, HER2-targeted therapies such as trastuzumab, vascular endothelial growth factor inhibitors, second and third generation multi-targeted kinase inhibitors for chronic myeloid leukaemia targeting BCR-ABL, multiple myeloma therapies (proteasome inhibitors and immunomodulatory drugs), RAF and MEK inhibitors or androgen deprivation therapies. Applying these risk stratification proformas will allow clinicians to stratify cancer patients into low, medium, high and very high risk of cardiovascular complications prior to starting treatment, with the aim of improving personalised approaches to minimise the risk of cardiovascular toxicity from cancer therapies.

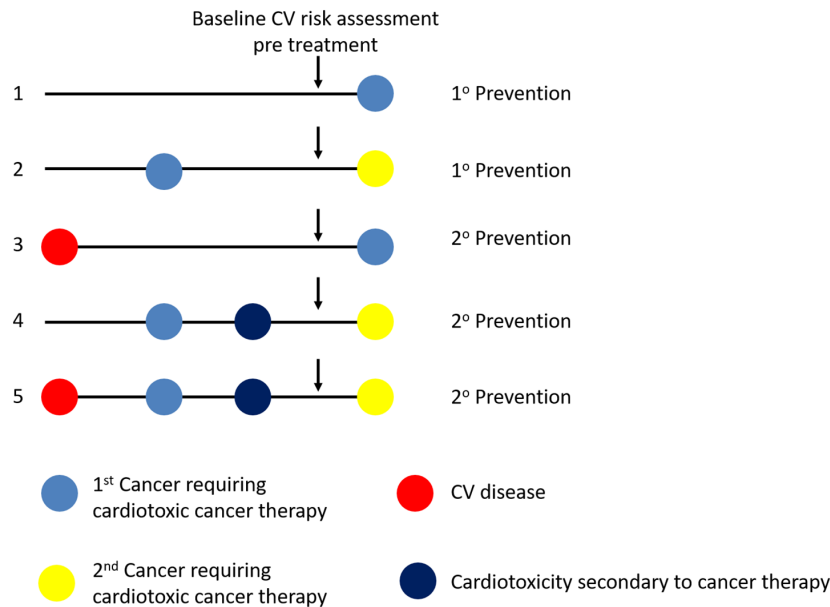
## Keywords

Risk factors • Cardio-oncology • Cardiotoxicity • Heart failure • Risk prediction

## Introduction

There is a growing epidemic of cardiovascular disease (CVD) in cancer patients during and after cancer treatment. Improved cancer-related survival and the development of more targeted molecular therapies, in addition to the continued use of anthracycline chemotherapy, have resulted in a significant increase in both current and previously treated cancer patients presenting to cardiology services with CVD.<sup>1</sup> The frequency of cardiovascular (CV) problems is higher in cancer patients who are receiving or who have previously received cancer treatments with a known CV toxicity profile. The average age of oncology patients is also increasing with the general ageing of the population, which is in part due to improved survival from CVD. Therefore, there are a rising number of patients who present to oncology and haemato-oncology services not only with a new cancer diagnosis but also with pre-existing CVD or risk factors for CVD.<sup>1</sup> This poses a particular challenge when considering evidence-based oncology treatments that improve survival but impart a higher risk of CV toxicity.

Current oncology practice, including treatment planning and protocols for cancer treatments with potentially CV toxicity, provides unique opportunities to comprehensively assess CV health before initiation of cancer treatment. This allows cardiologists and other healthcare professionals, working in partnership with oncologists and haemato-oncologists, to optimise the management of pre-existing CVD and modifiable CV risk factors with the aim of reducing the risk of CV complications during and after cancer treatment. The assessment occurring prior to the initiation of cancer treatment and in patients without overt CVD or previous cardiotoxicity can be considered a *primary prevention* strategy while interventions in patients with pre-existing CVD or evidence of prior CV toxicity fall into the category of *secondary prevention* (Figure 1). Specialist care of CVD in cancer patients is now offered by dedicated cardio-oncology services which have emerged over the last 10 years.<sup>2,3</sup> This multidisciplinary approach has the potential not only to reduce morbidity and mortality from CVD, but also to improve cancer outcomes by reducing interruptions in cancer treatment due to CV events and facilitate treatment options with greater potential CV risk.



**Figure 1** Examples of five different patients and primary or secondary prevention based on the history of pre-existing cardiovascular (CV) disease and/or prior cardiotoxicity from treatment of a previous malignancy.

The aim of a multidisciplinary cardio-oncology approach is to support best practice, guideline-directed cancer care by maintaining cancer patients on effective therapies for as long as recommended, and increase the proportion of cancer patients who complete their cancer treatment without interruption for CVD.

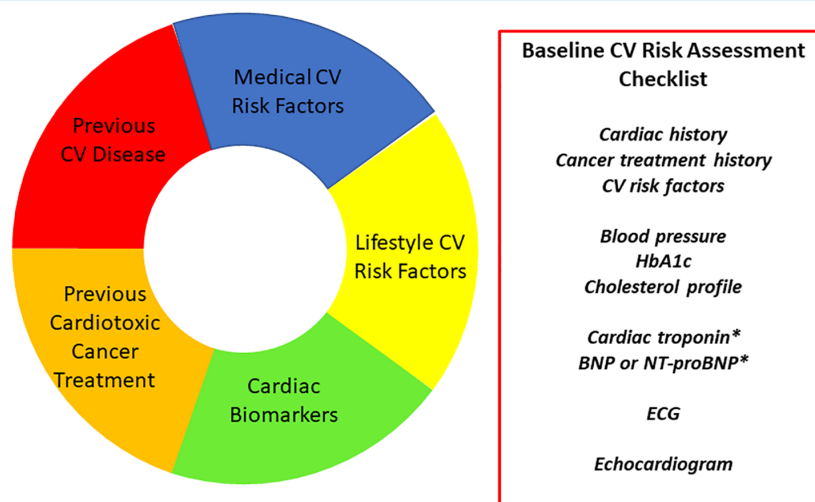
Many studies have identified a range of parameters that contribute to CVD risk, but these risk factors are not routinely and systematically assessed in oncology and haemato-oncology units at the time of cancer diagnosis or during cancer treatment (Figure 2). Several guidelines and expert position statements have been published by professional societies of cardiology, oncology and cardio-oncology focussed on CVD in cancer patients and all recommend baseline CV risk assessment in cancer patients prior to starting potentially cardiotoxic cancer treatments.<sup>1,4–6</sup> However, there is no standardised system or risk assessment tool to facilitate CV risk stratification in oncology and haemato-oncology services.

The Cardio-Oncology Study Group from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) hosted a workshop in collaboration with the International Cardio-Oncology Society (ICOS) dedicated to the development of 'Baseline CV risk stratification proformas' that can be used by oncology and haemato-oncology teams to stratify cancer patients for CV risk before initiation of potentially cardiotoxic cancer therapies (Table 1). This position statement summarises the evidence reviewed at the workshop and subsequently by the co-authors of this paper, and proposes new HFA-ICOS baseline CV risk stratification proformas for seven classes of cancer therapies which are associated with significant risk of CVD, including but not limited to heart failure (HF).

## General principles

The assessment of baseline CV risk in cancer patients before starting potentially CV toxic cancer therapies is based on the following core principles:

- Risk is a continuous variable.
- Multiple CV risk factors may co-exist in an individual cancer patient and they have an additive or synergistic contribution to CV risk.
- Evidence or expert consensus exists that a parameter contributes to future risk of CVD and justifies its inclusion in the baseline CV risk assessment proforma.
- Increased absolute risk (rather than relative risk) is the most relevant for individual patient-based treatment decisions and the relative importance attributed to these risk factors.
- Cancer patients identified at increased risk of cancer treatment-related CV toxicity using these baseline CV risk assessment proformas should not have their evidence-based cancer treatment withheld unless they are identified at high or very high risk and after multidisciplinary discussion between the treating oncologist/haematologist and cardiologist.
- Baseline CV risk stratification should be completed promptly and should not delay starting cancer treatment (unless high or very high risk or pre-existing CVD is present).
- Decisions to withhold effective but potentially cardiotoxic cancer treatments in cancer patients at high or very high risk of CVD should only be made after multidisciplinary team discussion between the treating oncologist/haematologist and cardiologist balancing treatment efficacy vs. safety and CV risk for a particular individual.



**Figure 2** The different risk factors which contribute to baseline cardiovascular (CV) risk in a cancer patient scheduled to receive a cardiotoxic cancer treatment, and a checklist of the clinical history and investigations required at baseline prior to starting a cardiotoxic cancer therapy. \*Cardiac biomarkers (troponin and natriuretic peptides) should be measured where available. BNP, brain natriuretic peptide; ECG, electrocardiogram; HbA1c, glycated haemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide.

- Decisions regarding switching to alternative less cardiotoxic cancer treatments in cancer patients identified at high or very high risk of CVD should only be made after multidisciplinary team discussion between the treating oncologist/haematologist and cardiologist, balancing treatment efficacy vs. safety and CV risk for a particular individual.
- The cancer patient should be informed and participate in the decision making process and be informed of their baseline CV risk level.
- Cardiovascular treatment interventions should be considered to mitigate CV risk in cancer patients when identified.
- Pathways of care should exist within an institution using these proformas so that patients with increased CV risk (medium, high or very high) have their pre-existing CVD and modifiable CV risk factors reviewed and optimised by a suitable healthcare professional (e.g. cardio-oncology service, cardiologist or primary care/family physician) depending on the nature of the risk, the cardiotoxic treatment planned and healthcare system.
- Baseline CV risk assessment proformas should be easy to understand and implement in oncology and haemato-oncology services.
- The application and impact of baseline CV risk assessment proformas can be assessed using an appropriate clinical audit and review.

## Design and application of baseline cardiovascular risk proformas

Several cancer drug therapies associated with clinically important rates of CV toxicity during or after treatment exposure are summarised in *Table 1*. The authors acknowledge that other cancer

therapies are associated with CV risks (e.g. radiation therapy, stem cell transplantation); however, these are beyond the scope of this article. There is growing use of immune therapies in oncology, and there is now considerable evidence of CV toxicities from immune checkpoint inhibitors (ICIs) and emerging information of HF complicating cytokine release syndrome following chimeric antigen receptor T (CAR-T) cell therapies for various cancers.<sup>7–9</sup> Whilst no evidence currently exists regarding which clinical, imaging and laboratory parameters may identify patients at higher risk, given the severity of these complications we recommend all patients scheduled to receive ICI or CAR-T therapy have a baseline echocardiogram, electrocardiogram (ECG) and measurement of cardiac troponin and a natriuretic peptide, which serve as a baseline reference if new cardiac complications develop.

Baseline CV risk assessment proformas have been developed for seven cardiotoxic cancer therapy classes known to cause a range of CV toxicities including left ventricular dysfunction (LVD) and HF (*Tables 2–8*).<sup>10–68</sup> The risk is estimated for all CV complications from the drug class, e.g. left ventricular dysfunction, QTc prolongation and arrhythmias, vascular events including myocardial infarction (MI) and hypertension:

- **Anthracycline chemotherapy:** the main CV complications of anthracycline chemotherapy are LVD and HF, and atrial and ventricular arrhythmias.<sup>19,69</sup>
- **HER2 targeted therapies:** the main CV complications of HER2 targeted therapies are LVD and HF, and systemic hypertension.<sup>44,70,71</sup>
- **Vascular endothelial growth factor (VEGF) inhibitors [these agents are also known as angiogenesis inhibitors or VEGF tyrosine kinase inhibitors (TKIs) as many act via multi-targeted inhibition of tyrosine kinases]:** the main CV complications of VEGF inhibitors are

**Table 1** Cancer therapy classes identified for cardiovascular baseline risk assessment and associated cardiovascular toxicity

Cancer treatment class	Cancer indication	Treatment-related CV toxicity
<b>Anthracycline chemotherapy</b> (doxorubicin, epirubicin, daunorubicin, idarubicin)	Breast cancer, lymphoma, acute leukaemia, sarcoma	Heart failure Asymptomatic LVSD Atrial and ventricular arrhythmias
<b>HER2-targeted therapies</b> (trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1), lapatinib, neratinib, tucatinib)	HER2+ breast cancer HER2+ gastric cancer	Heart failure Asymptomatic LVSD Hypertension
<b>VEGF inhibitors</b> TKIs (sunitinib, pazopanib, sorafenib, axitinib, tivozanib, cabozantinib, regorafenib, lenvatinib, vandetinib) and antibodies (bevacizumab, ramucirumab)	VEGF TKIs: renal cancer, hepatocellular cancer, thyroid cancer, colon cancer, sarcoma, GIST Antibodies: breast cancer, ovarian cancer, gastric cancer, gastro-oesophageal cancer, colon cancer	Hypertension Heart failure Asymptomatic LVSD Myocardial ischaemia and infarction QTc prolongation
<b>Multi-targeted kinase inhibitors: second and third generation BCR-ABL TKIs</b> (ponatinib, nilotinib, dasatinib, bosutinib)	Chronic myeloid leukaemia	Arterial thrombosis (myocardial infarction, stroke and PAOD <sup>a</sup> ) Venous thromboembolism Hypertension Heart failure and asymptomatic LVSD Atherosclerosis <sup>b</sup> QTc prolongation <sup>b</sup> Pulmonary hypertension <sup>c</sup> Heart failure <sup>d</sup> Asymptomatic LVSD <sup>d</sup>
<b>Proteasome inhibitors</b> (carfilzomib, bortezomib, ixazomib)	Multiple myeloma	Myocardial ischaemia and infarction Atrial and ventricular arrhythmias Venous thromboembolism Arterial thrombosis Hypertension
<b>Immunomodulatory drugs</b> (lenalidomide, pomalidomide)		Heart failure and asymptomatic LVSD Hypertension QTc prolongation <sup>e</sup>
<b>Combination RAF and MEK inhibitors</b> (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib)	Raf mutant melanoma	Atherosclerosis Myocardial ischaemia and infarction Diabetes mellitus Hypertension
<b>Androgen deprivation therapies</b> <b>GnRH agonists</b> (goserelin, leuprorelin) <b>Antiandrogens</b> (abiraterone)	Prostate cancer ER+ breast cancer <sup>f</sup>	Myocarditis including fulminant myocarditis Pericarditis Non-inflammatory heart failure Ventricular arrhythmias AV block Acute coronary syndromes including atherosclerotic plaque rupture and vasculitis
<b>Immune checkpoint inhibitors: anti-programmed cell death 1 inhibitors</b> (nivolumab, pembrolizumab) <b>anti-cytotoxic T-lymphocyte-associated protein 4 inhibitor</b> (ipilimumab) <b>anti-programmed death-ligand 1 inhibitors</b> (avelumab, atezolizumab, durvalumab)	Melanoma (metastatic and adjuvant) Metastatic renal cancer, non-small cell lung cancer, small cell lung cancer, refractory Hodgkin's lymphoma, metastatic triple negative breast cancer, metastatic urothelial cancer, liver cancer, MMR-deficient cancer	

AV, atrio-ventricular; CV, cardiovascular; ER, oestrogen receptor; GIST, gastro-intestinal stromal tumour; GnRH, gonadotropin release hormone; LVSD, left ventricular systolic dysfunction; MMR, mismatch repair; PAOD, peripheral arterial occlusive disease; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

<sup>a</sup>Associated with ponatinib.

<sup>b</sup>Associated with ponatinib and nilotinib.

<sup>c</sup>Associated with dasatinib.

<sup>d</sup>Associated with carfilzomib.

<sup>e</sup>Associated with vemurafenib and cobimetinib.

<sup>f</sup>The risk scores for androgen deprivation therapies in this position statement relate to androgen deprivation therapies for prostate cancer only.

**Table 2** Baseline cardiovascular risk stratification proforma for anthracycline chemotherapy

Risk factor	Score	Level of evidence	References
Previous cardiovascular disease			
Heart failure or cardiomyopathy	Very high	B	10,11
Severe valvular heart disease	High	C	11
Myocardial infarction or previous coronary revascularisation (PCI or CABG)	High	C	10–12
Stable angina	High	C	10–12
Baseline LVEF <50%	High	B	10
Borderline LVEF 50–54%	Medium <sup>2</sup>	C	
Cardiac biomarkers (where available)			
Elevated baseline troponin <sup>a</sup>	Medium <sup>1</sup>	C	13–15
Elevated baseline BNP or NT-proBNP <sup>a</sup>	Medium <sup>1</sup>	C	16,17
Demographic and cardiovascular risk factors			
Age ≥80 years	High	B	10,12,18
Age 65–79 years	Medium <sup>2</sup>	B	10,18–20
Hypertension <sup>b</sup>	Medium <sup>1</sup>	B	11,12,21
Diabetes mellitus <sup>c</sup>	Medium <sup>1</sup>	C	10–12
Chronic kidney disease <sup>d</sup>	Medium <sup>1</sup>	C	
Previous cardiotoxic cancer treatment			
Previous anthracycline exposure	High	B	18–20,22–25
Prior radiotherapy to left chest or mediastinum	High	C	20,22,23,26,27
Previous non-anthracycline-based chemotherapy	Medium <sup>1</sup>	C	24,25,28
Lifestyle risk factors			
Current smoker or significant smoking history	Medium <sup>1</sup>	C	23
Obesity (BMI >30 kg/m <sup>2</sup> )	Medium <sup>1</sup>	C	20,29,30
<b>Risk level</b>			

BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention.

Low risk = no risk factor OR one medium<sup>1</sup> risk factor; Medium risk = medium risk factors with a total of 2–4 points; High risk = medium risk factors with a total of ≥5 points OR any high risk factor; Very high risk = any very high risk factor.

<sup>a</sup>Elevated above the upper limit of normal for local laboratory reference range.

<sup>b</sup>Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or on treatment.

<sup>c</sup>Glycated haemoglobin >7.0% or >53 mmol/mol, or on treatment.

<sup>d</sup>Estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>.

Please see online supplementary Table S2 for the 1 page printable version for clinical use.

systemic hypertension, LVD and HF, QTc prolongation and arterial thrombosis including MI.<sup>48,53,57,72</sup>

- **Multi-targeted kinase inhibitors for chronic myeloid leukaemia (CML) targeting BCR-ABL (often called BCR-ABL TKIs):** the main CV complications of multi-targeted kinase inhibitors for CML targeting BCR-ABL include arterial thrombosis leading to MI, stroke and peripheral arterial occlusive disease (ponatinib), venous thromboembolism, systemic hypertension, LVD and HF, accelerated atherosclerosis (ponatinib and nilotinib), QTc prolongation (nilotinib) and pulmonary hypertension (dasatinib).<sup>59,62,73–78</sup>
- **Proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs):** the main CV complications of PIs and IMiDs in combination are LVD and HF, ischaemia and MI, atrial and ventricular arrhythmias, venous thromboembolism and arterial thrombosis.<sup>66,67,79</sup>
- **Combination RAF and MEK inhibitor treatment:** the main CV complications of RAF and MEK inhibitors are LVD, HF and systemic

hypertension for all combinations and QTc prolongation for one combination (vemurafenib and cobimetinib).<sup>80,81</sup>

- **Androgen deprivation therapies (ADT) for prostate cancer treatment including gonadotropin release hormone (GnRH) agonists:** ADT are associated with an increased risk of diabetes mellitus, hypertension and atherosclerosis (see below).<sup>82–84</sup>
- **Immune checkpoint inhibitors:** myocarditis including fulminant myocarditis, non-inflammatory HF, ventricular arrhythmias, atrio-ventricular block, sudden cardiac death, acute coronary syndromes including atherosclerotic plaque rupture and vasculitis.

The first six proformas each comprise of a single table with five columns on one page. This can be printed or accessed electronically, completed by the appropriate oncology or haemato-oncology healthcare professional with the patient, and filed in the patient's medical records (paper or digital):

- Column 1 lists the CV risk factors

**Table 3** Baseline cardiovascular risk stratification proforma for HER2-targeted cancer therapies (trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib)

Risk factor	Score	Level of evidence	References
Previous cardiovascular disease			
Heart failure or cardiomyopathy	Very high	C	31
Myocardial infarction or CABG	High	B	31,32
Stable angina	High	B	31–34
Severe valvular heart disease	High	C	31
Baseline LVEF <50%	High	C	
Borderline LVEF 50–54%	Medium <sup>2</sup>	B	35–37
Arrhythmia <sup>a</sup>	Medium <sup>2</sup>	C	31,32
Cardiac biomarkers (where available)			
Elevated baseline troponin <sup>b</sup>	Medium <sup>2</sup>	B	38,39
Elevated baseline BNP or NT-proBNP <sup>b</sup>	Medium <sup>2</sup>	C	17
Demographic and cardiovascular risk factors			
Age ≥80 years	High	B	32,33
Age 65–79 years	Medium <sup>2</sup>	B	35,36,40,41
Hypertension <sup>c</sup>	Medium <sup>1</sup>	B	32–36,42,43
Diabetes mellitus <sup>d</sup>	Medium <sup>1</sup>	C	31,32,42
Chronic kidney disease <sup>e</sup>	Medium <sup>1</sup>	C	32
Current cancer treatment regimen			
Includes anthracycline before HER2-targeted therapy	Medium <sup>1f</sup>	B	32,40,41,43–45
Previous cardiotoxic cancer treatment			
Prior trastuzumab cardiotoxicity	Very high	C	
Prior (remote) anthracycline exposure <sup>g</sup>	Medium <sup>2</sup>	B	42
Prior radiotherapy to left chest or mediastinum	Medium <sup>2</sup>	C	41,46,47
Lifestyle risk factors			
Current smoker or significant smoking history	Medium <sup>1</sup>	C	34
Obesity (BMI >30 kg/m <sup>2</sup> )	Medium <sup>1</sup>	C	29,34,43,45

**Risk level**

BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Low risk = no risk factor OR one medium<sup>1</sup> risk factor; Medium risk = medium risk factors with a total of 2–4 points; High risk = medium risk factors with a total of ≥5 points OR any high risk factor; Very high risk = any very high risk factor.

<sup>a</sup>Atrial fibrillation, atrial flutter, ventricular tachycardia, or ventricular fibrillation.

<sup>b</sup>Elevated above the upper limit of normal for local laboratory reference range.

<sup>c</sup>Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or on treatment.

<sup>d</sup>Glycated haemoglobin >7.0% or >53 mmol/mol, or on treatment.

<sup>e</sup>Estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>.

<sup>f</sup>High risk if anthracycline chemotherapy and trastuzumab delivered concurrently.

<sup>g</sup>Previous malignancy (not current treatment protocol).

Please see online supplementary Table S3 for the 1 page printable version for clinical use.

- Column 2 is the box to complete if present (yes/no)
- Column 3 is the weighting of the risk factor (medium, high or very high)
- Column 4 has the level of evidence (LoE) supporting the inclusion and weighting based on the standard LoE definitions used in professional cardiology and oncology guidelines; and
- Column 5 has references for the publications providing evidence for the risk factor having predictive value pre-treatment for future CV adverse events which supports inclusion and level of risk weighting.

The conceptual background of these recommendations is that both patient-related as well as therapy-related factors contribute to

the CV risk.<sup>1,85</sup> The clinical and demographic variables contributing to increased CV risk can be divided into risk factor classes which are similar for the six cancer-related treatments associated with CVD and HF in particular. The CV risk factor classes included in the first six proformas are:

- Pre-existing CVD
- Elevated circulating cardiac biomarkers pre-treatment (if measured)
- Demographic and co-existing medical conditions recognised as CV risk factors
- Previous cardiotoxic cancer treatment
- Lifestyle-related CV risk factors.

**Table 4** Baseline cardiovascular risk stratification proforma for vascular endothelial growth factor inhibitors

Risk factor	Score	Level of evidence	References
Previous cardiovascular disease			
Heart failure or cardiomyopathy	Very high	C	48–50
Arterial vascular disease (IHD, PCI, CABG, stable angina, TIA, stroke, PVD)	Very high	C	50–52
Venous thrombosis (DVT or PE)	High	C	
Baseline LVEF <50%	High	C	
Borderline LVEF 50–54%	Medium <sup>2</sup>	C	
QTc ≥480 ms	High	C	
450 ms ≤ QTc <480 ms (men) 460 ms ≤ QTc <480 ms (women)	Medium <sup>2</sup>	C	
Arrhythmia <sup>a</sup>	Medium <sup>2</sup>	C	50
Cardiac biomarkers (where available)			
Elevated baseline troponin <sup>b</sup>	Medium <sup>1</sup>	C	50
Elevated baseline BNP or NT-proBNP <sup>b</sup>	Medium <sup>1</sup>	C	53
Demographic and cardiovascular risk factors			
Age ≥75 years	High	C	54–56
Age 65–74 years	Medium <sup>1</sup>	C	48,54,56
Hypertension <sup>c</sup>	High	C	48,50–52,54,55
Diabetes mellitus <sup>d</sup>	Medium <sup>1</sup>	C	50
Hyperlipidaemia <sup>e</sup>	Medium <sup>1</sup>	C	49,50
Chronic kidney disease <sup>f</sup>	Medium <sup>1</sup>	C	57
Proteinuria	Medium <sup>1</sup>	C	
Previous cardiotoxic cancer treatment			
Prior anthracycline exposure	High	C	
Prior radiotherapy to left chest or mediastinum	Medium <sup>1</sup>	C	
Lifestyle risk factors			
Current smoker or significant smoking history	Medium <sup>1</sup>	C	50
Obesity (BMI >30 kg/m <sup>2</sup> )	Medium <sup>1</sup>	C	50,54,58

**Risk level**

BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; DVT, deep vein thrombosis; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

Low risk = no risk factor OR one medium<sup>1</sup> risk factor; Medium risk = medium risk factors with a total of 2–4 points; High risk = medium risk factors with a total of ≥5 points OR any high risk factor; Very high risk = any very high risk factor.

<sup>a</sup>Atrial fibrillation, atrial flutter, ventricular tachycardia, or ventricular fibrillation.

<sup>b</sup>Elevated above the upper limit of normal for local laboratory reference range.

<sup>c</sup>Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or on treatment.

<sup>d</sup>Glycated haemoglobin >7.0% or >53 mmol/mol, or on treatment.

<sup>e</sup>Non-high-density lipoprotein cholesterol level >3.8 mmol/L (>145 mg/dL).

<sup>f</sup>Estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>.

Please see online supplementary Table S4 for the 1 page printable version for clinical use.

Each risk factor class includes a range of risk factors or variables identified as contributing to CV risk for patients receiving the specific cancer therapy according to the evidence available and expert opinion.

Once completed, a risk level can be calculated from the summary using the following simple rules:

- 1 Patients with no risk factors are 'low risk'
- 2 Patients with one or more risk factors are categorised according to the highest risk factor present:
  - Patients with one or more very high risk factors—their risk level is 'very high'
  - Patients with one or more high risk factors—their risk level is 'high'

3 Medium risk factors are given a point weighting as medium<sup>1</sup> or medium<sup>2</sup>

- Patients with one medium<sup>1</sup> risk factor only are 'low risk'
- Patients with a single medium<sup>2</sup> risk factor or more than one medium<sup>1</sup> risk factor with points totalling 2–4 are 'medium risk'
- Patients with several medium risk factors with points totalling 5 or more points are 'high risk'

Evidence for defining the absolute risk is limited or absent for each risk factor for every drug class. Based on discussion and expert opinion, the risk of future cardiotoxicity for each of the risk groups can be considered as follows: low risk <2%, medium



**Table 5** Baseline cardiovascular risk stratification proforma for multi-targeted kinase inhibitors for chronic myeloid leukaemia including second and third generation BCR-ABL tyrosine kinase inhibitors

Risk factor	Score	Level of evidence	References
<b>Previous cardiovascular disease</b>			
Arterial vascular disease (IHD, PCI, CABG, stable angina, TIA, stroke, PVD)	Very high	C	59,60
Arterial thrombosis with TKI	Very high	C	
Heart failure or LVSD	High	C	
BCR-ABL TKI-mediated LVSD	High	C	
Abnormal ABPI <sup>f</sup>	High	C	
Pulmonary arterial hypertension <sup>g</sup>	High	C	
Baseline LVEF <50%	High	C	
Venous thromboembolism (DVT/PE)	Medium <sup>2</sup>	C	60,61
Arrhythmia <sup>a</sup>	Medium <sup>2</sup>	C	
QTc ≥ 480 ms	High	C	
450 ms ≤ QTc < 480 ms (men) 460 ms ≤ QTc < 480 ms (women)	Medium <sup>2</sup>	C	
<b>Demographic and other cardiovascular risk factors</b>			
Cardiovascular disease 10-year risk score >20%	High	B	62
Hypertension <sup>b</sup>	Medium <sup>2</sup>	B	59–61
Diabetes <sup>c</sup>	Medium <sup>1</sup>	B	63
Hyperlipidaemia <sup>d</sup>	Medium <sup>1</sup>	B	60,61
Age ≥75 years	High	C	
Age 65–74 years	Medium <sup>2</sup>	B	61
Age ≥60 years	Medium <sup>1</sup>	B	61
Chronic kidney disease <sup>e</sup>	Medium <sup>1</sup>	C	
Family history of thrombophilia	Medium <sup>1</sup>	C	
<b>Lifestyle and other factors</b>			
Current smoker or significant smoking history	High	B	60
Obesity (BMI >30 kg/m <sup>2</sup> )	Medium <sup>1</sup>	C	
<b>Risk level</b>			

ABPI, ankle–brachial pressure index; BMI, body mass index; CABG, coronary artery bypass graft; DVT, deep vein thrombosis; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; PCI, percutaneous coronary intervention; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PVD, peripheral vascular disease; TIA, transient ischaemic attack; TKI, tyrosine kinase inhibitor.

Low risk = no risk factor OR one medium<sup>1</sup> risk factor; Medium risk = medium risk factors with a total of 2–4 points; High risk = medium risk factors with a total of ≥5 points OR any high risk factor; Very high risk = any very high risk factor.

<sup>a</sup>Atrial fibrillation, atrial flutter, ventricular tachycardia, or ventricular fibrillation.

<sup>b</sup>Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or on treatment.

<sup>c</sup>Glycated haemoglobin >7.0% or >53 mmol/mol, or on treatment.

<sup>d</sup>Non-high-density lipoprotein cholesterol level >3.8 mmol/L (>145 mg/dL).

<sup>e</sup>Estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>.

<sup>f</sup>ABPI ≤0.9.

<sup>g</sup>Peak systolic pulmonary artery pressure at rest ≥35 mmHg when estimated non-invasively on echocardiography.

Please see online supplementary Table S5 for the 1 page printable version for clinical use.

risk 2–9%, high risk 10–19%, very high risk ≥20%. These should be considered a guide and future studies are needed to validate and refine these ranges and risk weighting.

The seventh baseline CV risk assessment proforma relates to ADT including GnRH agonists and other anti-androgens (e.g. 17 $\alpha$ -hydroxylase inhibitors) used for prostate cancer. The risks relate to the development of atherosclerotic vascular disease, and there are several established CV risk calculators for MI and stroke associated with atherosclerosis (Table 9 and ADT baseline CV risk assessment proformas).<sup>86–88</sup> The risk categories are different from those for the other oncology drugs as they are based on the 10-year risk of events. Several studies have shown that, particularly for prostate cancer patients who have a mean age >60 years and frequently have concomitant coronary artery disease, that GnRH

agonists given as ADT increase CV risk and mortality, and preventative strategies are needed.<sup>89</sup> Whilst these CV risk calculators were not specifically developed for cancer patients receiving GnRH agonists or other ADT, and frequently excluded patients with active cancer, they are established from large population studies and included in the ESC guidelines for CVD prevention and are also included in many national cardiology society guidelines. The risk calculators collect various parameters associated with future risk of atherosclerosis-related CVD, although the specific parameters required vary between the different risk calculators (online supplementary Table S1). It was the consensus of the authors to recommend the use of these established CV risk calculators specifically for patients receiving ADT including GnRH agonists for prostate cancer which have an increased risk of MI

**Table 6** Baseline cardiovascular risk stratification proforma for proteasome inhibitors and immunomodulatory agents for multiple myeloma

Risk factor	Score	Level of evidence	References
Previous cardiovascular disease			
Heart failure or cardiomyopathy	Very high	C	64
Prior proteasome inhibitor cardiotoxicity	Very high	C	
Venous thrombosis (DVT or PE)	Very high	C	64
Cardiac amyloidosis	Very high	C	
Arterial vascular disease (IHD, PCI, CABG, stable angina, TIA, stroke, PVD)	Very high	C	64
Prior immunomodulatory drug CV toxicity	High	B	65
Baseline LVEF <50%	High	C	
Borderline LVEF 50–54%	Medium <sup>2</sup>	C	
Arrhythmia <sup>a</sup>	Medium <sup>2</sup>	C	64
Left ventricular hypertrophy <sup>b</sup>	Medium <sup>1</sup>	C	
Cardiac biomarkers (where available)			
Elevated baseline troponin <sup>c</sup>	Medium <sup>2</sup>	C	
Elevated baseline BNP or NT-proBNP <sup>c</sup>	High	B	66
Demographic and cardiovascular risk factors			
Age ≥75 years	High	C	
Age 65–74 years	Medium <sup>1</sup>	C	
Hypertension <sup>d</sup>	Medium <sup>1</sup>	C	64,67
Diabetes mellitus <sup>e</sup>	Medium <sup>1</sup>	C	
Hyperlipidaemia <sup>f</sup>	Medium <sup>1</sup>	C	64
Chronic kidney disease <sup>g</sup>	Medium <sup>1</sup>	C	
Family history of thrombophilia	Medium <sup>1</sup>	C	
Previous cardiotoxic cancer treatment			
Prior anthracycline exposure	High	C	68
Prior thoracic spine radiotherapy	Medium <sup>1</sup>	C	68
Current myeloma treatment			
High-dose dexamethasone >160 mg/month	Medium <sup>1</sup>	C	
Lifestyle risk factors			
Current smoker or significant smoking history	Medium <sup>1</sup>	C	67
Obesity (BMI >30 kg/m <sup>2</sup> )	Medium <sup>1</sup>	C	
<b>Risk level</b>			

BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; DVT, deep vein thrombosis; IHD, Ischaemic heart disease; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

Low risk = no risk factor OR one medium<sup>1</sup> risk factor; Medium risk = medium risk factors with a total of 2–4 points; High risk = medium risk factors with a total of ≥5 points OR any high risk factor; Very high risk = any very high risk factor.

<sup>a</sup>Atrial fibrillation, atrial flutter, ventricular tachycardia, or ventricular fibrillation.

<sup>b</sup>Left ventricular wall thickness >1.2 cm.

<sup>c</sup>Elevated above the upper limit of normal for local laboratory reference range.

<sup>d</sup>Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or on treatment.

<sup>e</sup>Glycated haemoglobin >7.0% or >53 mmol/mol or on treatment.

<sup>f</sup>Non-high-density lipoprotein cholesterol level >3.8 mmol/L (>145 mg/dL).

<sup>g</sup>Estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>.

Please see online supplementary Table S6 for the 1 page printable version for clinical use.

and stroke. The coronary heart disease risk level can then be calculated using the online web-based calculator for the risk score as follows:

- <10% 10-year risk = low risk level
- 10–19% 10-year risk = medium risk level
- ≥20% 10-year risk = high risk level

The result should be communicated to the patient and to the appropriate healthcare professionals (primary care physician,

cardiologist, cardio-oncologist) to address modifiable CV risk factors according to ESC guidelines for CVD prevention.<sup>86</sup> These are primary prevention CV risk calculators and are only suitable for cancer patients scheduled to receive ADT who have not previously presented with the clinical manifestations of atherosclerotic disease. Any prostate cancer patient with a previous history of CVD is high risk and should be evaluated by an appropriate healthcare professional to review their symptom status and CV risk factor control. These CV risk calculators are not suitable for other cardiotoxic cancer therapies where there is an increased

**Table 7** Baseline cardiovascular risk stratification proforma for combination RAF and MEK inhibitors (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib)

Risk factor	Score	Level of evidence
Previous cardiovascular disease		
Heart failure or cardiomyopathy	Very high	C
Myocardial infarction or CABG	High	C
Stable angina	High	C
Severe valvular heart disease	High	C
Borderline LVEF 50–54%	Medium <sup>2</sup>	C
Arrhythmia <sup>a</sup>	Medium <sup>1</sup>	C
Cardiac biomarkers (where available)		
Elevated baseline troponin <sup>b</sup>	Medium <sup>2</sup>	C
Elevated baseline BNP or NT-proBNP <sup>b</sup>	Medium <sup>2</sup>	C
Demographic and cardiovascular risk factors		
Age ≥65 years	Medium <sup>1</sup>	C
Hypertension <sup>c</sup>	Medium <sup>2</sup>	C
Diabetes mellitus <sup>d</sup>	Medium <sup>1</sup>	C
Chronic kidney disease <sup>e</sup>	Medium <sup>1</sup>	C
Previous cardiotoxic cancer treatment		
Prior anthracycline exposure <sup>f</sup>	High	C
Prior radiotherapy to left chest or mediastinum	Medium <sup>2</sup>	C
Lifestyle risk factors		
Current smoker or significant smoking history	Medium <sup>1</sup>	C
Obesity (BMI >30 kg/m <sup>2</sup> )	Medium <sup>1</sup>	C
<b>Risk level</b>		

BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Low risk = no risk factor OR one medium<sup>1</sup> risk factor; Medium risk = medium risk factors with a total of 2–4 points; High risk = medium risk factors with a total of ≥5 points OR any high risk factor; Very high risk = any very high risk factor.

<sup>a</sup>Atrial fibrillation, atrial flutter, ventricular tachycardia, or ventricular fibrillation.

<sup>b</sup>Elevated above the upper limit of normal for local laboratory reference range.

<sup>c</sup>Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or on treatment.

<sup>d</sup>Glycated haemoglobin >7.0% or >53 mmol/mol, or on treatment.

<sup>e</sup>Estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>.

<sup>f</sup>Previous malignancy.

Please see online supplementary Table S7 for the 1 page printable version for clinical use.

risk of HF, hypertension, QT prolongation and other CVDs. In addition, data on the increased CV risk in women receiving GnRH agonists for breast or ovarian cancer are lacking and therefore this proforma is currently only applicable to men with prostate cancer scheduled to receive a GnRH agonist.

We recommend completion of the baseline CV risk assessment proformas in all patients scheduled to receive one of the seven oncology drug classes with potential cardiotoxicity listed in Table 1. This can be performed after the decision has been made by the treating oncologist or haematologist to start a potentially cardiotoxic cancer treatment. It is important to emphasise that this needs to be completed promptly so that cancer treatment is not delayed and can be commenced safely. In emergency scenarios, guideline-based cancer treatment should be commenced and the baseline CV risk assessment proformas can be completed once clinical stability has been achieved (e.g. CML presenting with blast crisis, solid tumours presenting with acute oncological emergencies).

Following completion of the baseline CV risk assessment proformas the risk level should be recorded in the patient's medical records, reviewed by the treating oncologist or haemato-oncologist and communicated to the patient and their primary care physician. The specific treatment pathways for each of the drug categories and risk levels is beyond the scope of this position statement and will be addressed in a future HFA position statement, but the authors recommend, conceptually, the following general principles until more detailed guidance is available:

- *Low risk* level cancer patients continue with treatment with CV surveillance as appropriate according to local, national and international guidelines.
- *Medium risk* cancer patients require closer monitoring of CV health during treatment or consideration for referral for a cardio-oncology or cardiology assessment.
- *High* and *very high risk* level patients are referred for a cardio-oncology or cardiology assessment, ideally in a specialist

**Table 8** Baseline cardiovascular risk stratification proforma for androgen deprivation therapies including gonadotrophin-releasing hormone agonists (goserelin, leuprolide) and anti-androgen therapies (abiraterone) for prostate cancer

Clinical risk score <sup>a</sup>	Score
Known pre-existing cardiovascular disease (CVD) <sup>b</sup> or CVD 10-year risk score $\geq 20\%$	High
CVD 10-year risk score $\geq 10\%$ to $< 20\%$	Medium
CVD 10-year risk score $< 10\%$	Low

CVD, cardiovascular disease.

Risk factors and variables required: age, gender, ethnic group, height, weight, social class indicator (Townsend quintile), smoking status (current, ex- or non-smoker), total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (mmHg), diabetes status (yes/no), family history of premature CVD (before 60 years) (yes/no), chronic kidney disease (yes/no), atrial fibrillation (yes/no), systemic inflammatory disease (e.g. rheumatoid arthritis, psoriasis) (yes/no).

<sup>a</sup>For validated CVD risk scores, see Table 9.

<sup>b</sup>Prior symptomatic coronary artery disease, carotid artery disease or peripheral artery disease, e.g. stable angina, acute myocardial infarction, transient ischaemic attack/stroke, ischaemic claudication.

**Table 9** Atherosclerosis-related cardiovascular risk calculators

Risk score	Website
ESC HeartScore	<a href="http://www.heartscore.org">www.heartscore.org</a>
QRISK®3	<a href="https://qrisk.org/three">https://qrisk.org/three</a>
JBS3 risk score (2014)	<a href="http://www.jbs3risk.com">http://www.jbs3risk.com</a>
ACC/AHA pooled cohort CV risk calculator (2013)	<a href="http://www.cvriskcalculator.com">http://www.cvriskcalculator.com</a>

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; JBS, Joint British Societies.

cardio-oncology service (if available) to optimise management of their pre-existing CVD and modifiable CV risk factors, and provide a personalised management plan for surveillance during cancer treatment.

It is important that pathways exist to minimise the time delay from risk assessment and referral to cardiology clinical assessment, and the decision and management plan are communicated to the referring oncology or haemato-oncology team promptly to prevent any delay in starting cancer treatment, following the core principles of a cardio-oncology service.<sup>2</sup> The timing and nature of CV surveillance recommendations will depend upon various factors including the cardiotoxicity profile of the cancer therapy required (Table 1), the risk factors contributing to the risk level calculation and patient preference. CV imaging and cardiac biomarkers are available for surveillance and detection of early cardiotoxicity, and their role in cancer patients receiving potentially cardiotoxic cancer

therapies and surveillance algorithms are the topic of two HFA position statements (in preparation).

We recommend that following implementation of these risk proformas, which could be digital or paper-based depending upon local medical records, an audit and review of the risk stratification process is performed to identify the frequency of application, percentage of risk assessments completed, the actions taken from the assessment and how that conforms to local pathways and standards of care. Oncologists and haemato-oncologists should identify cardiologists with whom to collaborate in setting up pathways of care for their high risk and very high risk patients. If cardiology support is not available locally, then whilst identifying regional or national options these risk proformas should provide a guide for oncologists to consider alternative, non-cardiotoxic cancer therapies in patients identified as high risk or very high risk where alternative treatment options are available. In the long term collection of outcome data, and comparison to retrospective datasets regarding CV events, could be considered. We suggest collaborative studies between centres implementing these risk stratification proformas to assess their impact in reducing CV complications of cancer therapies as well as changes in the overall cancer and CV outcomes. Large datasets can also serve to refine the weighting of risk for the different parameters for each cancer drug class, with the ultimate aim to improve the sensitivity and predictive value.

## Conclusions and future directions

Cardiology and oncology professional society guidelines and expert position statements on CVD in cancer patients uniformly recommend baseline CV risk assessment for oncology patients scheduled to receive potentially cardiotoxic cancer therapies.<sup>1,4-6</sup> Here we present proformas for baseline CV risk assessment which can be employed by oncology and haemato-oncology services for patients scheduled to receive one of seven cardiotoxic cancer therapies. Assessment of baseline CV risk is part of a personalised approach to care for cancer patients. The identification of cancer patients who are at an increased risk of CV complications in a timely manner is important so that appropriate measures can be implemented to eliminate or at least mitigate their CV risk and ensure, where possible, that cancer patients receive their treatment safely. There is the potential for these proformas to be electronic with semi-automated population of the fields from the electronic patient record if a suitable platform exists. Future studies are required to validate and refine these proformas, including the specific weighting of each risk factor and the addition of new risk factors as they are identified. The impact of proformas upon overall survival and both CV-related and cancer-related outcomes and mortality needs to be assessed as well. The long-term goal is to improve both oncology and CV outcomes for this patient population through a personalised approach to CV risk, which should allow cancer patients to complete their evidence-based cancer treatments free from CV toxicity and CVD, leading to an improvement in overall survival.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Cardiovascular risk calculators and parameters included in risk calculations for various international risk calculators.

**Table S2.** Baseline cardiovascular risk stratification proforma for anthracycline chemotherapy.

**Table S3.** Baseline cardiovascular risk stratification proforma for HER2-targeted cancer therapies (trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib).

**Table S4.** Baseline cardiovascular risk stratification proforma for vascular endothelial growth factor inhibitors.

**Table S5.** Baseline cardiovascular risk stratification proforma for multi-targeted kinase inhibitors for chronic myeloid leukaemia including second and third generation BCR-ABL tyrosine kinase inhibitors.

**Table S6.** Baseline cardiovascular risk stratification proforma for proteasome inhibitors and immunomodulatory agents for multiple myeloma.

**Table S7.** Baseline cardiovascular risk stratification proforma for combination RAF and MEK inhibitors (dabrafenib+trametinib, vemurafenib+cobimetinib, encorafenib+binimetinib).

## Funding

A.R.L. is supported by the Fondation Leducq Network of Excellence in Cardio-Oncology. C.G.T. is supported by the grant 'Ricerca di Ateneo Federico II 2017'. A.L.S. is supported by the Heart Foundation of Australia Future Leader Fellowship (Award ID 101918). J.M. is supported by R01 HL141466. R.A.d.B. is supported by the European Research Council (ERC CoG 818715, SECRETE-HF), and furthermore by the Netherlands Heart Foundation (CVON DOSIS, grant 2014-40, CVON SHE-PREDICTS-HF, grant 2017-21; CVON RED-CVD, grant 2017-11; and CVON PREDICT2, grant 2018-30); and the Innovational Research Incentives Scheme program of the Netherlands Organization for Scientific Research (NWO VIDI, grant 917.13.350). C.M. is supported by the German Research Foundation (DFG; SFB-894, TRR-219; Ma 2528/7-1) and the German Ministry of Education and Research (BMBF; 01EO1504). M.S.A. has received research support from the German Cardiovascular Research Center.

**Conflict of interest:** A.R.L. has received speaker, advisory board or consultancy fees and/or research grants from Pfizer, Novartis, Servier, Amgen, Takeda, Roche, Janssens-Cilag Ltd, Clinigen Group, Eli Lilly, Eisai, Bristol-Myers Squibb, Ferring Pharmaceuticals and Boehringer Ingelheim. S.D. has received speaker, advisory board or research funding from Novartis, Eli Lilly, Genetech and Pfizer. S.S. has received speaker, advisory board or consultancy fees from Roche, Clinigen and Eli Lilly. H.E. has received grants from Roche and Sanofi-Aventis, and advisory board or speaker fees from Daiichi-Sankyo, AstraZeneca, INTAS Pharmaceuticals, Pfizer, Amgen and Prime Oncology. A.C.S. has received speaker, advisory board or consultancy fees and/or research grants from Novartis, Servier, Amgen, Abbott, Vifor, AstraZeneca, MSD, Roche, Takeda and Bristol-Myers Squibb. J.M. has served as a consultant for Novartis, Pfizer, Bristol-Myers Squibb, Takeda, Pharmacyclis,

Regeneron, Myokardia, Audentes Pharmaceuticals, AstraZeneca, Deciphera, Ipsen, and Intrexon and has received grant funding from Pfizer and Bristol-Myers Squibb. J.D.G. receives research funding from Amgen. T.G.N. has received speaker, advisory board or consultancy fees from Parexel, Intrinsic Imaging, Bristol-Myers Squibb, H3 Biomedicine, Aprea Therapeutics. A.L.S. has received speaker fees, advisory board and/or research grants from Bayer, Biotronik, Novartis and Vifor. B.K. has received consultancy fees from Bristol-Myers Squibb. C.G.T. received speaking fees from Alere. H.S. received honoraria for presentations from Servier, Novartis, AstraZeneca, Abbott and Boehringer Ingelheim. C.M. has received speak fees from Pfizer. R.F.C. has received advisory board or consultancy fees from Karyopharm Therapeutics, Takeda and Janssen. V.K. has participated in advisory boards, conferences and educational meetings for Accuray, Astellas, Bayer, Janssen and Boston Scientific. T.L.F. has received speaker fees from Janssen, Amgen, Servier, Daiichi-Sankyo, MSD, and Philips. A.B. serves on DSMB for CTI Biopharma and has received honoraria from Bristol-Myers Squibb. P.T. has received speaker fees from Boehringer Ingelheim, Takeda, Amgen. M.S.A. has received personal fees from Servier. D.F. has received consultation fees, speaker honoraria and/or travel grants from Abbott, Boehringer Ingelheim, Daiichi-Sankyo, Menarini, Novartis, Pfizer, Roche and Servier. C.M. has received speaker, advisory board or consultancy fees from Servier, Amgen, Boehringer Ingelheim, Astra, Novartis, Bayer, Berlin Chemie, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer. S.D.R. has received speaker and advisory board consultancy fees from Servier, Novartis and Clinigen Group. M.G.F. has received advisory board fees from Novartis and research funding from Medtronic. Z.I. has received advisory board or speaker fees from Novartis, AstraZeneca, Boehringer Ingelheim, Pfizer, Bayer, Eli Lilly. T.T. is founder and shareholder of Cardior Pharmaceuticals, served in an advisory board of Novo Nordisk and received honoraria from Amicus Therapeutics and Sanofi-Genzyme. J.B. has received speaker, advisory board or consultancy fees and/or research grants from Novartis, Vifor, Bayer, Servier, Abiomed, Boehringer Ingelheim, Daiichi-Sankyo, AstraZeneca, CVRx, BMS, Pfizer, MSD, Abbott, Medtronic and Zoll not related to this manuscript. C.P. has received travel expenses and honoraria for speaking at educational meetings or advisory boards from Amgen, Bayer, Celgene, Ferring, Incyte, Novartis, Pfizer and Roche.

## References

- Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:2768–2801.
- Lancellotti P, Suter TM, Lopez-Fernandez T, Galderisi M, Lyon AR, Van der Meer P, Cohen Solal A, Zamorano JL, Jerusalem G, Moonen M, Aboyans V, Bax JJ, Asteggiano R. Cardio-oncology services: rationale, organization, and implementation: a report from the ESC Cardio-Oncology Council. *Eur Heart J* 2019;**40**:1756–1763.
- Pareek N, Cevallos J, Moliner P, Shah M, Tan LL, Chambers V, Baksi AJ, Khattar RS, Sharma R, Rosen SD, Lyon AR. Activity and outcomes of a cardio-oncology service in the United Kingdom – a five-year experience. *Eur J Heart Fail* 2018;**20**:1721–1731.

4. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, Dent S, Douglas PS, Durand JB, Ewer M, Fabian C, Hudson M, Jessup M, Jones LW, Ky B, Mayer EL, Moslehi J, Oeffinger K, Ray K, Ruddy K, Lenihan D. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2017;**35**:893–911.
5. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhaes A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2014;**15**:1063–1093.
6. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, Crisciello C, Goldhirsch A, Cipolla C, Roila F; ESMO Guidelines Working Group. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012;**23** Suppl 7:vii155–166.
7. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol* 2018;**19**:e447–e458.
8. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Awadalla M, Hassan MZ, Moslehi JJ, Shah SP, Ganatra S, Thavandiranathan P, Lawrence DP, Groarke JD, Neilan TG. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;**71**:1755–1764.
9. Alvi RM, Frigault MJ, Fradley MG, Jain MD, Mahmood SS, Awadalla M, Lee DH, Zlotoff DA, Zhang L, Drobnik ZD, Hassan MZ, Bassily E, Rhea I, Ismail-Khan R, Mulligan CP, Banerji D, Lazaryan A, Shah BD, Rokicki A, Raje N, Chavez JC, Abramson J, Locke FL, Neilan TG. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol* 2019;**74**:3099–3108.
10. Wang L, Tan TC, Halpern EF, Neilan TG, Francis SA, Picard MH, Fei H, Hochberg EP, Abramson JS, Weyman AE, Kuter I, Scherrer-Crosbie M. Major cardiac events and the value of echocardiographic evaluation in patients receiving anthracycline-based chemotherapy. *Am J Cardiol* 2015;**116**:442–446.
11. Salz T, Zabor EC, de Nully Brown P, Dalton SO, Raghunathan NJ, Matar MJ, Steingart R, Vickers AJ, Svenssen Munksgaard P, Oeffinger KC, Johansen C. Preexisting cardiovascular risk and subsequent heart failure among non-Hodgkin lymphoma survivors. *J Clin Oncol* 2017;**35**:3837–3843.
12. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 2007;**25**:3808–3815.
13. Cardinale D, Sandri MT, Martinoni A, Tricca LabTech A, Civelli M, Lamantia G, Ciniere S, Martinelli G, Cipolla CM, Fiorentini C. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol* 2000;**36**:517–522.
14. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, Civelli M, Peccatori F, Martinelli G, Fiorentini C, Cipolla CM. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation* 2004;**109**:2749–2754.
15. Ky B, Butt M, Sawaya H, French B, Januzzi JL Jr, Sebag IA, Plana JC, Cohen V, Banchs J, Carver JR, Wieggers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol* 2014;**63**:809–816.
16. Lenihan DJ, Stevens PL, Massey M, Plana JC, Araujo DM, Fanale MA, Fayad LE, Fisch MJ, Yeh ET. The utility of point-of-care biomarkers to detect cardiotoxicity during anthracycline chemotherapy: a feasibility study. *J Card Fail* 2016;**22**:433–438.
17. De Iulius F, Salerno G, Taglieri L, De Biase L, Lanza R, Cardelli P, Scarpa S. Serum biomarkers evaluation to predict chemotherapy-induced cardiotoxicity in breast cancer patients. *Tumour Biol* 2016;**37**:3379–3387.
18. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozenzweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979;**91**:710–717.
19. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003;**97**:2869–2879.
20. Hequet O, Le QH, Moullet I, Pauli E, Salles G, Espinouse D, Dumontet C, Thieblemont C, Arnaud P, Antal D, Bouafia F, Coiffier B. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol* 2004;**22**:1864–1871.
21. Szmít S, Jurczak W, Zaucha JM, Drozd-Sokolowska J, Spychalowicz W, Joks M, Długosz-Danecka M, Torbicki A. Pre-existing arterial hypertension as a risk factor for early left ventricular systolic dysfunction following (R)-CHOP chemotherapy in patients with lymphoma. *J Am Soc Hypertens* 2014;**8**:791–799.
22. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL, Leisenring WM. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ* 2009;**339**:b4606.
23. van Nimwegen FA, Schaapveld M, Janus CP, Krol AD, Petersen EJ, Raemaekers JM, Kok WE, Aleman BM, van Leeuwen FE. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. *JAMA Intern Med* 2015;**175**:1007–1017.
24. Gianni L, Dombrowsky P, Sledge G, Martin M, Amadori D, Arbuck SG, Ravdin P, Brown M, Messina M, Tuck D, Weil C, Winograd B. Cardiac function following combination therapy with paclitaxel and doxorubicin: an analysis of 657 women with advanced breast cancer. *Ann Oncol* 2001;**12**:1067–1073.
25. Volkova M, Russell R. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. *Curr Cardiol Rev* 2011;**7**:214–220.
26. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;**368**:987–998.
27. van der Pal HJ, van Dalen EC, van Delden E, van Dijk IW, Kok WE, Geskus RB, Sieswerda E, Oldenburger F, Koning CC, van Leeuwen F, Caron HN, Kremer LC. High risk of symptomatic cardiac events in childhood cancer survivors. *J Clin Oncol* 2012;**30**:1429–1437.
28. Barrett-Lee PJ, Dixon JM, Farrell C, Jones A, Leonard R, Murray N, Palmieri C, Plummer CJ, Stanley A, Verrill MW. Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk. *Ann Oncol* 2009;**20**:816–827.
29. Guenancia C, Lefebvre A, Cardinale D, Yu AF, Ladoire S, Ghiringhelli F, Zeller M, Rochette L, Cottin Y, Vergely C. Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: a systematic review and meta-analysis. *J Clin Oncol* 2016;**34**:3157–3165.
30. Kotwinski P, Smith G, Cooper J, Sanders J, Ma L, Teis A, Kotwinski D, Mythen M, Pennell DJ, Jones A, Montgomery H; Breast Cancer Early Disease: Toxicity from Therapy with Epirubicin Regimens—Cardiac Assessment and Risk Evaluation (BETTER-CARE) Study Investigators. Body surface area and baseline blood pressure predict subclinical anthracycline cardiotoxicity in women treated for early breast cancer. *PLoS One* 2016;**11**:e0165262.
31. Serrano C, Cortes J, De Mattos-Arruda L, Bellet M, Gomez P, Saura C, Pérez J, Vidal M, Muñoz-Couselo E, Carreras MJ, Sánchez-Ollé G, Tabernero J, Baselga J, Di Cosimo S. Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. *Ann Oncol* 2012;**23**:897–902.
32. Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Heart Assoc* 2014;**3**:e000472.
33. Chavez-MacGregor M, Zhang N, Buchholz TA, Zhang Y, Niu J, Elting L, Smith BD, Hortobagyi GN, Giordano SH. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol* 2013;**31**:4222–4228.
34. Gunaldi M, Duman BB, Afsar CU, Paydas S, Erkişi M, Kara IO, Sahin B. Risk factors for developing cardiotoxicity of trastuzumab in breast cancer patients: an observational single-centre study. *J Oncol Pharm Pract* 2016;**22**:242–247.
35. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr, Ewer MS, Rath V, Fehrenbacher L, Brufsky A, Azar CA, Flynn PJ, Zapas JL, Polikoff J, Gross HM, Biggs DD, Atkins JN, Tan-Chiu E, Zheng P, Yothers G, Mamounas EP, Wolmark N. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2012;**30**:3792–3799.
36. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, Martino S, Gralow JR, Dakhil SR, Ingle JN, Winer EP, Gelmon KA, Gersh BJ, Jaffe AS, Rodeheffer RJ. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 Adjuvant Breast Cancer trial. *J Clin Oncol* 2008;**26**:1231–1238.
37. Newshean S, Aziz K, Park JY, Lerman A, Villarraga HR, Ruddy KJ, Herrmann J. Trastuzumab in female breast cancer patients with reduced left ventricular ejection fraction. *J Am Heart Assoc* 2018;**7**:e008637.
38. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, Lamantia G, Colombo N, Cortinovis S, Dessanai MA, Nolè F, Veglia F, Cipolla CM. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol* 2010;**28**:3910–3916.
39. Zardavas D, Suter TM, Van Veldhuisen DJ, Steinsieffer J, Noe J, Lauer S, Al-Sakaff N, Piccart-Gebhart MJ, de Azambuja E. Role of troponins I and T and N-terminal prohormone of brain natriuretic peptide in monitoring cardiac safety of patients with early-stage human epidermal growth factor receptor 2-positive breast cancer receiving trastuzumab: a Herceptin adjuvant study cardiac marker substudy. *J Clin Oncol* 2017;**35**:878–884.

40. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, Murphy M, Stewart SJ, Keeffe D. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002;**20**:1215–1221.
41. Tarantini L, Cioffi G, Gori S, Tuccia F, Boccardi L, Bovelli D, Lestuzzi C, Maurea N, Oliva S, Russo G, Faggiano P; Italian Cardio-Oncologic Network. Trastuzumab adjuvant chemotherapy and cardiotoxicity in real-world women with breast cancer. *J Card Fail* 2012;**18**:113–119.
42. Jawa Z, Perez RM, Garlie L, Singh M, Qamar R, Khandheria BK, Jahangir A, Shi Y. Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: a meta-analysis. *Medicine (Baltimore)* 2016;**95**:e5195.
43. Adamo V, Ricciardi GR, Adamo B, Ferraro G, Franchina T, Rossello R, Zanghi M, Cicero G, Rizzo S, Caristi N, Russo A. The risk of toxicities from trastuzumab, alone or in combination, in an elderly breast cancer population. *Oncology* 2014;**86**:16–21.
44. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buysse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;**365**:1273–1283.
45. Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C, Perren T, Passalacqua R, Bighin C, Klijn JG, Ageev FT, Hitre E, Groetz J, Iwata H, Knap M, Gnant M, Muehlbauer S, Spence A, Gelber RD, Piccart-Gebhart MJ. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol* 2007;**25**:3859–3865.
46. Guglin M, Hartlage G, Reynolds C, Chen R, Patel V. Trastuzumab-induced cardiomyopathy: not as benign as it looks? A retrospective study. *J Card Fail* 2009;**15**:651–657.
47. Huszno J, Les D, Sarzynski-Slota D, Nowara E. Cardiac side effects of trastuzumab in breast cancer patients – single center experiences. *Contemp Oncol (Pozn)* 2013;**17**:190–195.
48. Ewer MS, Suter TM, Lenihan DJ, Niculescu L, Breazna A, Demetri GD, Motzer RJ. Cardiovascular events among 1090 cancer patients treated with sunitinib, interferon, or placebo: a comprehensive adjudicated database analysis demonstrating clinically meaningful reversibility of cardiac events. *Eur J Cancer* 2014;**50**:2162–2170.
49. Hurley PJ, Konety S, Cao Q, Oertli C, Vankina S, Blaes AH. Frequency and risk factors for tyrosine kinase inhibitor-associated cardiotoxicity. *J Clin Oncol* 2016;**34**(15 Suppl):6596.
50. Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, Ruhsam M, Hejna M, Schmidinger H. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2008;**26**:5204–5212.
51. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, Woulfe K, Pravda E, Caciola F, Desai J, George S, Harris DM, Ismail NS, Chen JH, Schoen FJ, van den Abbeele AD, Demetri GD, Force T, Chen MH, Morgan JA. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007;**370**:2011–2019.
52. Di Lorenzo G, Autorino R, Bruni G, Carteni G, Ricevuto E, Tudini M, Fiorella C, Romano C, Aieta M, Giordano A, Giuliano M, Gonnella A, De Nunzio C, Rizzo M, Montesarchio V, Ewer M, De Placido S. Cardiovascular toxicity following sunitinib therapy in metastatic renal cell carcinoma: a multicenter analysis. *Ann Oncol* 2009;**20**:1535–1542.
53. Hall PS, Harshman LC, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. *JACC Heart Fail* 2013;**1**:72–78.
54. Hamnvik OP, Choueiri TK, Turchin A, McKay RR, Goyal L, Davis M, Kaymakalan MD, Williams JS. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. *Cancer* 2015;**121**:311–319.
55. Kozloff M, Yood MU, Berlin J, Flynn PJ, Kabbinnar FF, Purdie DM, Ashby MA, Dong W, Sugrue MM, Grothey A; Investigators of the BRiTE Study. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. *Oncologist* 2009;**14**:862–870.
56. Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinnar F, Bergsland E, Ngai J, Holmgren E, Wang J, Hurwitz H. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* 2007;**99**:1232–1239.
57. Touyz RM, Herrmann J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. *NPJ Precis Oncol* 2018;**2**:13.
58. Neiman V, Gottfried M, Hammers HJ, Eisenberger MA, Carducci MA, Sinibaldi VJ, Rosenbaum E, Sarid D, Gez E, Peer A, Neumann A, Kovel S, Sella A, Mermerstain W, Rouvinov K, Berger R, Keizman D. Clinicopathologic factors associated with the development of sunitinib-induced hypertension (HTN) in patients (pts) with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2014;**32**(15 Suppl):508 (abstr).
59. Dahlen T, Edgren G, Lambe M, Hoglund M, Bjorkholm M, Sandin F, Sjalander A, Richter J, Olsson-Strömberg U, Ohm L, Bäck M, Stenke L; Swedish CML Group and the Swedish CML Register Group. Cardiovascular events associated with use of tyrosine kinase inhibitors in chronic myeloid leukemia: a population-based cohort study. *Ann Intern Med* 2016;**165**:161–166.
60. Lipton JH, Chuah C, Guercci-Bresler A, Rosti G, Simpson D, Assouline S, Etienne G, Nicolini FE, le Coutre P, Clark RE, Stenke L, Andorsky D, Oehler V, Lustgarten S, Rivera VM, Clackson T, Haluska FG, Baccarani M, Cortes JE, Guilhot F, Hochhaus A, Hughes T, Kantarjian HM, Shah NP, Talpaz M, Deininger MW; EPIC investigators. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *Lancet Oncol* 2016;**17**:612–621.
61. Aghel N, Lipton JH, Atenafu EG, Kim DD, Delgado DH. Cardiovascular events after exposure to nilotinib in chronic myeloid leukemia: long-term follow-up. *Clin Lymphoma Myeloma Leuk* 2017;**17**:870–878.e1.
62. Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, le Coutre PD, Etienne G, Dorthiac-Llacer PE, Clark RE, Flinn IW, Nakamae H, Donohue B, Deng W, Dalal D, Menssen HD, Kantarjian HM. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia* 2016;**30**:1044–1054.
63. Castagnetti F, Breccia M, Gugliotta G, Martino B, D'Adda M, Stagno F, Carella AM, Avanzini P, Tiribelli M, Trabacchi E, Visani G, Gobbi M, Salvucci M, Levato L, Binotto G, Capalbo SF, Bochicchio MT, Soverini S, Cavo M, Martinelli G, Alimena G, Pane F, Saglio G, Rosti G, Baccarani M; GIMEMA CML Working Party. Nilotinib 300 mg twice daily: an academic single-arm study of newly diagnosed chronic phase chronic myeloid leukemia patients. *Haematologica* 2016;**101**:1200–1207.
64. Chen JH, Lenihan DJ, Phillips SE, Harrell SL, Cornell RF. Cardiac events during treatment with proteasome inhibitor therapy for multiple myeloma. *Cardiooncology* 2017;**3**:4.
65. Gov.UK. Lenalidomide: risk of thrombosis and thromboembolism. February 2011. <https://www.gov.uk/drug-safety-update/lenalidomide-risk-of-thrombosis-and-thromboembolism> (3 June 2020).
66. Cornell RF, Ky B, Weiss BM, Dahm CN, Gupta DK, Du L, Carver JR, Cohen AD, Engelhardt BG, Garfall AL, Goodman SA, Harrell SL, Kassim AA, Jadhav T, Jagasia M, Moslehi J, O'Quinn R, Savona MR, Slosky D, Smith A, Stadtmayer EA, Vogl DT, Waxman A, Lenihan D. Prospective study of cardiac events during proteasome inhibitor therapy for relapsed multiple myeloma. *J Clin Oncol* 2019;**37**:1946–1955.
67. Libourel EJ, Sonneveld P, van der Holt B, de Maat MP, Leebeek FW. High incidence of arterial thrombosis in young patients treated for multiple myeloma: results of a prospective cohort study. *Blood* 2010;**116**:22–26.
68. Danhof S, Schreder M, Rasche L, Striffler S, Einsele H, Knop S. 'Real-life' experience of preapproval carfilzomib-based therapy in myeloma – analysis of cardiac toxicity and predisposing factors. *Eur J Haematol* 2016;**97**:25–32.
69. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, Civelli M, Lamantia G, Colombo N, Curigliano G, Fiorentini C, Cipolla CM. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015;**131**:1981–1988.
70. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;**344**:783–792.
71. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, Castro G Jr, Untch M, Smith I, Gianni L, Baselga J, al-Sakaff N, Lauer S, McFadden E, Leyland-Jones B, Bell R, Dowsett M, Jackisch C; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;**389**:1195–1205.
72. Motzer RJ, McCann L, Deen K. Pazopanib versus sunitinib in renal cancer. *N Engl J Med* 2013;**369**:1970.
73. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre PD, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DeAngelo DJ, Abruzzese E, Rea D, Baccarani M, Müller MC, Gambacorti-Passerini C, Lustgarten S, Rivera VM, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes TP, Shah NP, Kantarjian HM. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood* 2018;**132**:393–404.
74. Giles FJ, Mauro MJ, Hong F, Orlowski CE, McNeill C, Woodman RC, Hochhaus A, le Coutre PD, Saglio G. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia* 2013;**27**:1310–1315.
75. Cacci G, Mulas O, Bonifacio M, Abruzzese E, Galimberti S, Orlandi EM, Iurlo A, Annunziata M, Luciano L, Castagnetti F, Gozzini A, Stagno F, Binotto G, Prego P,

- Albano F, Martino B, Fozza C, Scaffidi L, Trawinska MM, Baratè C, Elena C, Cattaneo D, Scalzulli E, la Nasa G, Foà R, Breccia M. Recurrent arterial occlusive events in patients with chronic myeloid leukemia treated with second- and third-generation tyrosine kinase inhibitors and role of secondary prevention. *Int J Cardiol* 2019;**288**:124–127.
76. Fox LC, Cummins KD, Costello B, Yeung D, Cleary R, Forsyth C, Tatarczuch M, Burbury K, Motorna O, Shortt J, Fleming S, McQuillan A, Schwarzer A, Harrup R, Holmes A, Ratnasingam S, Chan KL, Hsu WH, Ashraf A, Putt F, Grigg A. The incidence and natural history of dasatinib complications in the treatment of chronic myeloid leukemia. *Blood Adv* 2017;**1**:802–811.
77. Shah NP, Wallis N, Farber HW, Mauro MJ, Wolf RA, Mattei D, Guha M, Rea D, Peacock A. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. *Am J Hematol* 2015;**90**:1060–1064.
78. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. *J Clin Oncol* 2015;**33**:4210–4218.
79. Xiao Y, Yin J, Wei J, Shang Z. Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: a systematic review and meta-analysis. *PLoS One* 2014;**9**:e87671.
80. Gogas HJ, Flaherty KT, Dummer R, Ascierto PA, Arance A, Mandala M, Liskay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R, Sileni VC, Dutriaux C, de Groot JW, Yamazaki N, Loquai C, Gollerkeri A, Pickard MD, Robert C. Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: incidence, course and management. *Eur J Cancer* 2019;**119**:97–106.
81. Mincu RI, Mahabadi AA, Michel L, Mrotzek SM, Schadendorf D, Rassaf T, Totzeck M. Cardiovascular adverse events associated with BRAF and MEK inhibitors: a systematic review and meta-analysis. *JAMA Netw Open* 2019;**2**:e198890.
82. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst* 2010;**102**:39–46.
83. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;**24**:4448–4456.
84. Gandaglia G, Sun M, Popa I, Schiffmann J, Abdollah F, Trinh QD, Saad F, Graefen M, Briganti A, Montorsi F, Karakiewicz PI. The impact of androgen-deprivation therapy (ADT) on the risk of cardiovascular (CV) events in patients with non-metastatic prostate cancer: a population-based study. *BJU Int* 2014;**114**:E82–E89.
85. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. *Mayo Clin Proc* 2014;**89**:1287–1306.
86. Piepoli MF, Hoes AV, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM, ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
87. Martinez-Quintana E, Miranda-Garcia C, Gopar-Gopar S, Saiz-Udaeta B, Rodriguez-Gonzalez F. Transient apical ballooning syndrome during dobutamine stress echocardiography. *Clin Investig Arterioscler* 2014;**26**:200–203.
88. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* 2017;**357**:j2099.
89. Bhatia N, Santos M, Jones LW, Beckman JA, Penson DF, Morgans AK, Moslehi J. Cardiovascular effects of androgen deprivation therapy for the treatment of prostate cancer: ABCDE steps to reduce cardiovascular disease in patients with prostate cancer. *Circulation* 2016;**133**:537–541.