REVIEW   **Open Access**

A new classification of cardio-oncology syndromes

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Abstract

Increasing evidence suggests a multifaceted relationship exists between cancer and cardiovascular disease (CVD). Here, we introduce a 5-tier classification system to categorize cardio-oncology syndromes (COS) that represent the aspects of the relationship between cancer and CVD. COS Type I is characterized by mechanisms whereby the abrupt onset or progression of cancer can lead to cardiovascular dysfunction. COS Type II includes the mechanisms by which cancer therapies can result in acute or chronic CVD. COS Type III is characterized by the pro-oncogenic environment created by the release of cardiokines and high oxidative stress in patients with cardiovascular dysfunction. COS Type IV is comprised of CVD therapies and diagnostic procedures which have been associated with promoting or unmasking cancer. COS Type V is characterized by factors causing systemic and genetic predisposition to both CVD and cancer. The development of this framework may allow for an increased facilitation of cancer care while optimizing cardiovascular health through focused treatment targeting the COS type.

Keywords: Cardio-oncology, Cancer, Cardiac Tumours, Prevention, Cardiotoxicity, Inflammation, Cardiovascular disease, Immune system, Heart failure, Prognostic biomarkers, Medical diagnostic radiation

Introduction

With 2 million new cancer diagnoses per year, improvements in cancer therapies has led to an increasing prevalence of cancer survivorship [1]. There are close to 17 million cancer survivors in the United States today, representing 1 in 20 people [1, 2]. In the next 10 years, there is a projected 31% increase in survivors, with more than 22 million cancer survivors estimated for 2030 [1]. In the last decade, cardiologists and oncologists have provided clinical and experimental evidence that cancer, as well as cancer treatments, result in detrimental effects on the cardiovascular system, a consequence that imposes clinical challenges for patient management. In parallel, the captivating notion that CVD can represent a pre-oncogenic condition has gained growing awareness [3]. Among survivors, CVD is the leading cause of non-cancer related mortality [4, 5]. Interestingly, the relationship is not unidirectional [6]. Epidemiologic data have reported an increased cancer risk in patients with CVD [7–9]. This relationship may be intuitive, given that both disease processes share common risk factors and pathogenesis.

In this manuscript, we propose a 5-tier classification system to better characterize the intersection between cardiology and oncology (Fig. 1). Types I and II of our classification systems address how cancer and cancer therapies affect the cardiovascular system, while Types III and IV incorporate how cardiovascular diseases, monitoring strategies, and therapies may contribute to unmasking cancer or fostering a tumorigenic environment (Fig. 2). Type V addresses systemic and genetic

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Cardio-Oncology Syndrome (COS): Neoplastic disorders and Cardiovascular disease whereby direct or indirect mechanisms associated with the one condition induces acute or chronic presence of the other
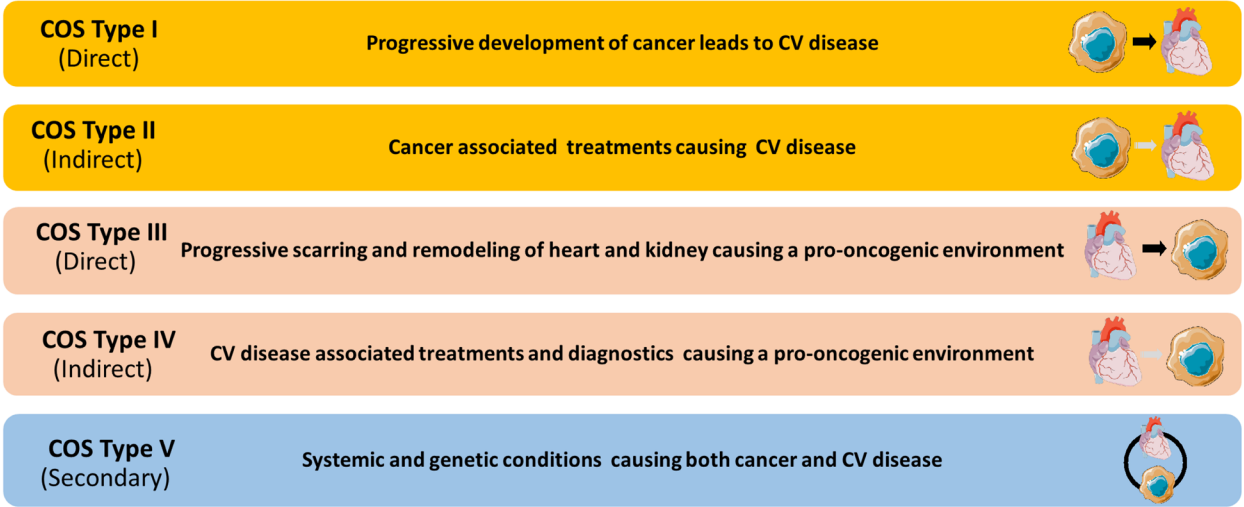
COS Type I (Direct) — Progressive development of cancer leads to CV disease

COS Type II (Indirect) — Cancer associated treatments causing CV disease

COS Type III (Direct) — Progressive scarring and remodeling of heart and kidney causing a pro-oncogenic environment

COS Type IV (Indirect) — CV disease associated treatments and diagnostics causing a pro-oncogenic environment

COS Type V (Secondary) — Systemic and genetic conditions causing both cancer and CV disease

Fig. 1 Cardio-Oncology Syndromes in Precision Cardio-Oncology. The five types of Cardio-Oncology Syndromes are listed, along with a description of whether they are direct (black arrows), indirect (grey arrows), or secondary and how they are defined. A few examples are given for each type. CHiP, clonal haematopoiesis of indeterminate potential; COS, Cardio-Oncology Syndromes; CV, cardiovascular; TKI, Tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor

Link between Cancer and CVD

Direct   Indirect

Effect of Cancer/Therapies on CVD Development

Effect of CVD/Management on Cancer Development

Effect of Systemic Factors on CVD & Cancer
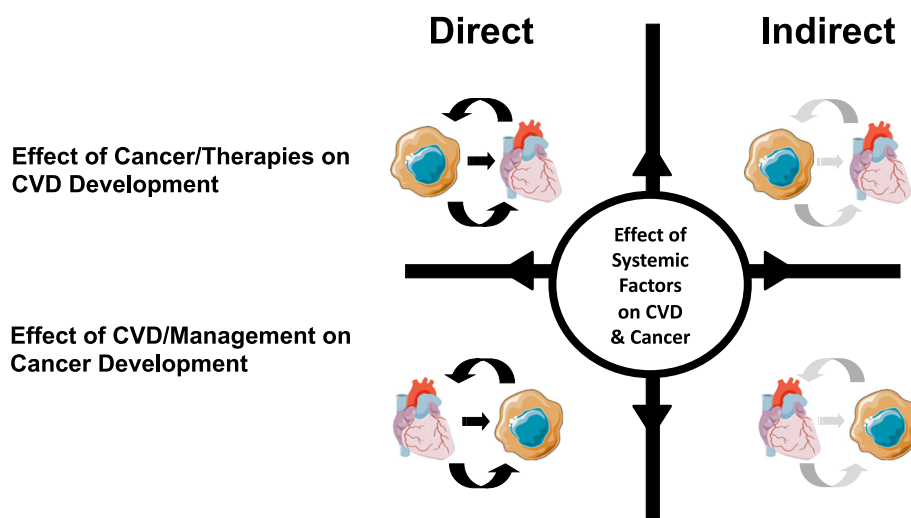
Fig. 2 Relationships between CVD and cancer. This schematic demonstrates the multifaceted relationship that exists between CVD and cancer. While CVD is the leading cause of non-cancer related mortality among cancer survivors, there is also a known increased risk for cancer in patients with CVD. Additionally, CVD and therapies for CVD can have both a direct (curved black arrows) and indirect (curved grey arrows) impact on cancer; while cancer and therapies for cancer can have both a direct (curved black arrows) and indirect (curved grey arrow) impact on cardiac function and health. CVD, cardiovascular disease

conditions that can lead to both CVD and cancer. We also emphasize the need for medical communities in both cardiology and oncology to raise awareness of these aetiologies and related challenges to maximize collaboration among medical scientists and clinicians. Such interdisciplinary partnerships will help advance the clinical care, research, and education needed in Cardio-Oncology to advance the field and optimize the care landscape for our patients.

Cardio-oncology syndrome type I (COS 1; direct): effect of the presence of cancer itself on the cardiovascular system

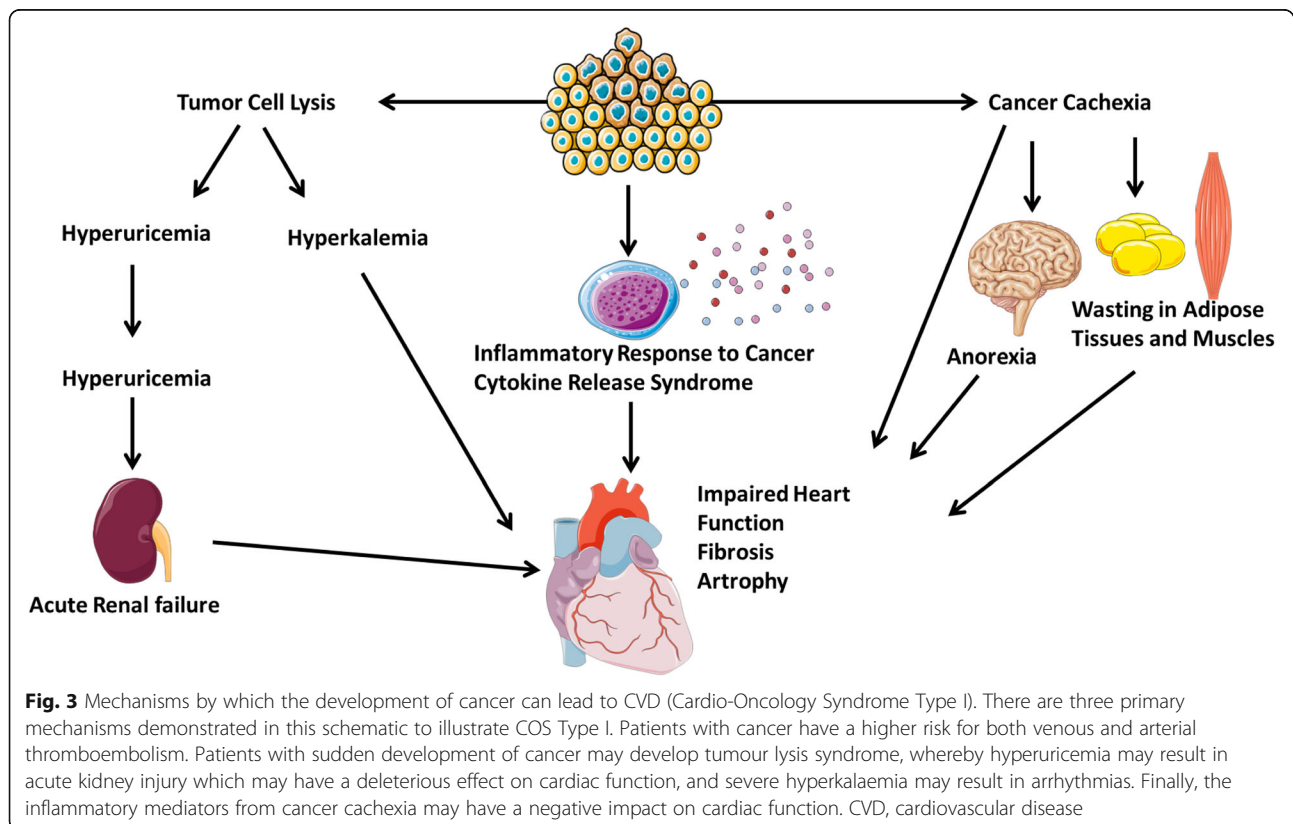### Arterial thromboembolism due to cancer

Patients with cancer are at higher risk of developing venous and arterial thromboembolic events. The risk of arterial thromboembolism varies by cancer type [10, 11]. Particularly lung, gastric, and pancreatic cancers demonstrate the higher risk. Evidence for this statement is substantial, while the mechanism remains less clear. It has been suggested that tumour cells present tissue factors and are therefore able to bind with coagulation factors. Concurrently, they also produce inflammatory cytokines and cancer procoagulant factors [12]. These mechanisms are responsible for the activation of the coagulation-cascade, promotion of the platelet activation and consequentially increased thrombus formation. Furthermore,

patients with cancer often present with lymphocytosis, neutrophilia, and thrombocytosis, which are known to promote hypercoagulability (Fig. 3) [13].

Cancer-associated cachexia and anorexia

Cachexia is a state of involuntary weight loss and is commonly observed in patients with cancer - predominantly pancreatic, colon, lung, head, and neck as well as in gastro-oesophageal cancer. Depending on the cancer type, the prevalence of cachexia varies between 40 to 70%. Though this condition impacts several organ systems, skeletal muscle is the first to be affected by body wasting (Fig. 3) [14]. The cardiac manifestations, as shown primarily in animal studies, results in altered heart function, cardiac atrophy, and fibrosis, and reduced cardiac weight [15].

The mechanisms by which malignancies induce cardiac wasting are not fully elucidated. It has been proposed the ubiquitin-proteasome system, autophagy, and myocyte apoptosis contribute to cardiac wasting [16]. Also, cancer-associated cachexia is characterized by the secretion of inflammatory mediators and hormonal factors from tumours and their microenvironment [15]. These factors demonstrate diagnostic value and may serve as biomarkers for the identification of cancer-induced cardiac alterations.

Fig. 3 Mechanisms by which the development of cancer can lead to CVD (Cardio-Oncology Syndrome Type I). There are three primary mechanisms demonstrated in this schematic to illustrate COS Type I. Patients with cancer have a higher risk for both venous and arterial thromboembolism. Patients with sudden development of cancer may develop tumour lysis syndrome, whereby hyperuricemia may result in acute kidney injury which may have a deleterious effect on cardiac function, and severe hyperkalaemia may result in arrhythmias. Finally, the inflammatory mediators from cancer cachexia may have a negative impact on cardiac function. CVD, cardiovascular disease

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Anorexia is a major component of cancer cachexia. Tumours cause dysphagia and alter the gut function resulting in nutritional deficiencies. In addition, some cancer patients experience depression and pain, further decreasing the desire to eat [17]. Eating disorders have multiple medical consequences, such as potentially life-threatening cardiovascular complications characterized by hemodynamic and structural changes, cardiomyopathy, and premature death [18].
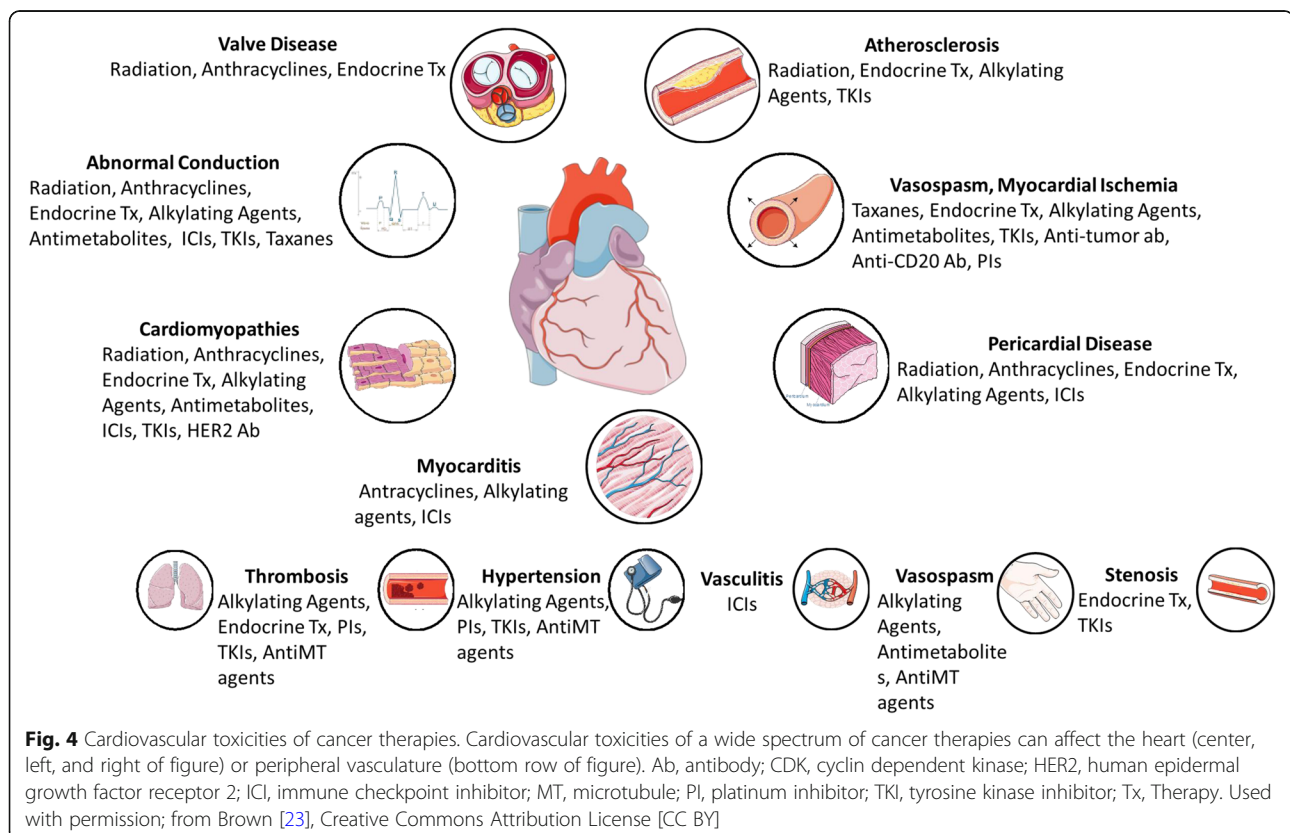
Tumour lysis syndrome

Tumour lysis syndrome (TLS) describes a state of a massive tumour cell death resulting in the development of metabolic imbalances and organ dysfunction. TLS can occur spontaneously when cancer cells die without preceding chemotherapy, embolization, or radiation therapies, or as a result of antineoplastic treatments. The majority of TLS cases are reported in haematological malignancies, such as leukaemia and lymphomas with marked sensitivity to cell lysis with chemotherapy. The prevalence of TLS is lower in patients with solid cancer. The pathogenesis of TLS is explained by the fact that cells, particularly malignant cells, contain high levels of potassium, phosphorus, and uric acid. The release of these intracellular substances facilitates the development and progression of TLS and its complications [19].
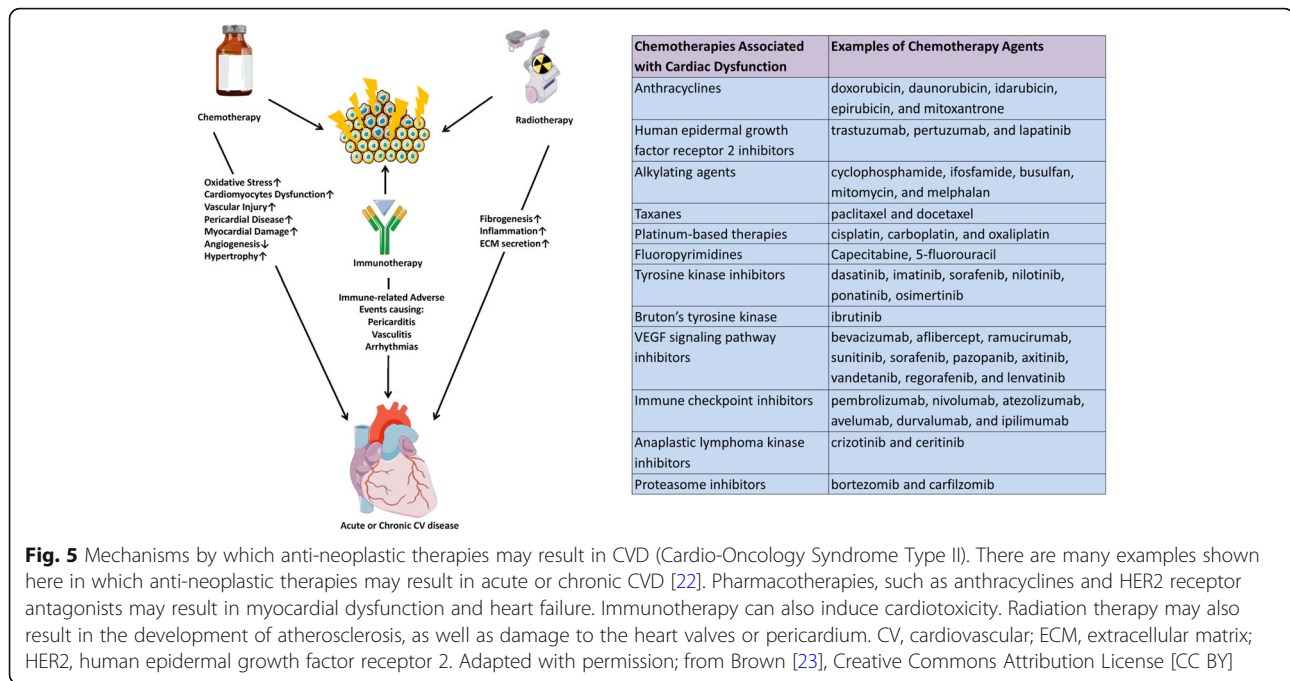
Cancer cell lysis is associated with a significant release of nucleic acids, purines, and eventually uric acid. The latter can crystalize and block the flow in the renal tubules, which consequently leads to acute kidney injury (Fig. 3) [20]. Hyperuricemia is associated with impaired endothelium-mediated relaxation, vascular stiffness and hampering left ventricular filling pattern. Additionally, serum levels of uric acid are linked to the progression of heart failure (HF). Excessive phosphorus binds to calcium and forms a calcium-phosphorus product called calcium phosphate. This product is deposited in kidneys and cardiac tissue resulting in acute kidney injury and cardiac arrhythmia, respectively. Also, the decline in free calcium concentration, caused by phosphorus binding, is associated with prolongation of the QT interval on ECG and muscle tetany. This may lead to arrhythmias if drugs that prolongate the QT interval are administrated [20].

Cardio-oncology syndrome type II-(COS 2; indirect): anti-neoplastic treatments cause acute or chronic CV disease

Cancer treatments-induced cardiotoxicity

Modern cancer therapies can lead to CV structural and functional dysfunction [21]. Cardiotoxicity is one of the most concerning side effects of chemotherapy. The classification and segregation of toxicities by type of therapy have been discussed extensively elsewhere [22] and are

Fig. 4 Cardiovascular toxicities of cancer therapies. Cardiovascular toxicities of a wide spectrum of cancer therapies can affect the heart (center, left, and right of figure) or peripheral vasculature (bottom row of figure). Ab, antibody; CDK, cyclin dependent kinase; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; MT, microtubule; PI, platinum inhibitor; TKI, tyrosine kinase inhibitor; Tx, Therapy. Used with permission; from Brown [23], Creative Commons Attribution License [CC BY]

Chemotherapies Associated with Cardiac Dysfunction	Examples of Chemotherapy Agents
Anthracyclines	doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone
Human epidermal growth factor receptor 2 inhibitors	trastuzumab, pertuzumab, and lapatinib
Alkylating agents	cyclophosphamide, ifosfamide, busulfan, mitomycin, and melphalan
Taxanes	paclitaxel and docetaxel
Platinum-based therapies	cisplatin, carboplatin, and oxaliplatin
Fluoropyrimidines	Capecitabine, 5-fluorouracil
Tyrosine kinase inhibitors	dasatinib, imatinib, sorafenib, nilotinib, ponatinib, osimertinib
Bruton's tyrosine kinase	ibrutinib
VEGF signaling pathway inhibitors	bevacizumab, aflibercept, ramucirumab, sunitinib, sorafenib, pazopanib, axitinib, vandetanib, regorafenib, and lenvatinib
Immune checkpoint inhibitors	pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, and ipilimumab
Anaplastic lymphoma kinase inhibitors	crizotinib and ceritinib
Proteasome inhibitors	bortezomib and carfilzomib

Fig. 5 Mechanisms by which anti-neoplastic therapies may result in CVD (Cardio-Oncology Syndrome Type II). There are many examples shown here in which anti-neoplastic therapies may result in acute or chronic CVD [22]. Pharmacotherapies, such as anthracyclines and HER2 receptor antagonists may result in myocardial dysfunction and heart failure. Immunotherapy can also induce cardiotoxicity. Radiation therapy may also result in the development of atherosclerosis, as well as damage to the heart valves or pericardium. CV, cardiovascular; ECM, extracellular matrix; HER2, human epidermal growth factor receptor 2. Adapted with permission; from Brown [23], Creative Commons Attribution License [CC BY]

largely catalogued in Fig. 4. This section highlights a few examples of cancer therapy-related cardiac dysfunction. A broad list of commonly used chemotherapies is provided in Fig. 5.

Several classes of commonly used chemotherapy agents are known to have myocardial dysfunction and HF as important consequences, most notoriously anthracyclines and human epidermal growth factor receptor 2 (HER2) receptor antagonists [24]. While both agents can cause reversible myocardial dysfunction, irreversible myocyte damage is classically reported with anthracyclines and can lead to HF years after drug administration. Even "targeted" therapy such as vascular endothelial growth factor inhibitors can exert off-target effects causing hypertension, thromboembolism, QT prolongation, and atrial fibrillation (AF), as well as cardiomyopathy [24–27]. Other targeted tyrosine kinase inhibitors such as ibrutinib, sorafenib, and mammalian target of rapamycin complex (mTORC) inhibitors also have a wide range of CV effects including AF, QTc prolongation, and HF [28]. Cancer patients can face an increase in venous thromboembolism compared to the general public, depending on the type of cancer or specific treatments, among other factors [10]. The pharmacokinetics of several chemotherapeutic agents, coalescing with drug interactions, frequent surgical procedures, and reduced mobility of patients during treatment also contribute to the risk for thromboembolism.

Different conditions can be induced by immunotherapies for onco-hematological disorders. As an example, chimeric antigen receptor T (CAR-T) cell therapy is used in the treatment of haematological malignancies,

including acute leukaemia, lymphoma and multiple myeloma. In spite of the remarkable clinical effectiveness, this treatment shows serious side effects that cannot be underrated. Cytokine release syndrome (CRS) is one of the most clinically important and potentially harmful toxicities. When CAR-T cells are activated by malignant cell antigen, they in turn activate monocytes and macrophages, causing the release of proinflammatory cytokines and chemokines including IL-6, IL-8, IL-10, interferon-gamma (INF-γ), monocyte chemoattractant protein-1b, and granulocyte-macrophage colony-stimulating factor [29, 30]. Consequently, the IL-6 receptor antagonist Tocilizumab is used to treat CRS in cancer patients as first-line treatment [31–34]. While cardiac dysfunction caused by CRS is largely reversible, tocilizumab is used in more severe cases, which can include lethal cardiac dysfunction [35, 36]. Consequently, tocilizumab, an IL-6 receptor antagonist, is indicated when patients demonstrate significant left ventricular dysfunction [37]. Corticosteroid therapy is applied in certain acute cases that do not respond to tocilizumab. When a patient may not respond to tocilizumab or a steroid, other agents such as anakinra (an IL-1R inhibitor) and etanercept (an anti-TNF) can be used to block inflammatory pathways [29, 38]. Indeed, immunotherapy can trigger native immune-system mediated cardiotoxicity, such as myocarditis, pericarditis, HF, and arrhythmias [10]. In general, these events are uncommon, occurring in < 3% of patients who receive immune checkpoint inhibitors, but carry a high risk of morbidity and mortality [39].

Radiation therapy is also taxing on the CV system. Radiotherapy may lead to both short and long-term

epicardial coronary artery and microcirculatory damage, may cause regurgitation related to valve retraction and stenosis, and can induce fibrotic changes in the parietal pericardium [24].

Cardio-oncology syndrome type III (COS 3; direct): CVD promotes a pro-oncogenic environment
Epidemiological evidence demonstrating higher cancer risk in CVD patients

Emerging epidemiological data has suggested an increased cancer risk in patients with prevalent CVD compared to subjects without CVD [3, 7–9]. Even though most studies attempt to account for surveillance bias, this remains a potential concern with many observational studies. In a Danish study, all age groups demonstrated higher incidence rates of cancer after 1 year from the diagnosis of MI [40]. The association of CVD with increased cancer risk is further supported by a long-term prospective study that evaluated the clinical features and prevalence of malignant neoplasia in patients with acute coronary syndrome (ACS) during a 17-year follow-up. The incidence rate was 17.8 cases per 1000 person-years in patients with ACS, which was three times higher than that observed in the general population. Those who developed malignancies after the ACS diagnosis demonstrated a worse prognosis [41].

Earlier, data of the Swedish Inpatient Register were collected from patients who were admitted to the hospital between the years 1965 and 1983 for venous thromboembolism. The enrolled patients did not have cancer at the start of the study. The authors stated that venous thromboembolism could be a potential indicator of cancer as 4% of these patients were diagnosed with cancer within the first year after admission and the risk of all cancers was higher than expected with a standardised incidence rate of 4.4 (95% CI 4.2–4.9) [42].. Based on data collected for the Vitamin Intervention for Stroke Prevention study, the investigators revealed that ischemic stroke survivors had a higher annual rate of age-adjusted cancer risk compared to the general population at 1 year (581.8/100,000 persons vs. 486.5/100,000 persons, SIR 1.2, 95% CI 1.16–1.24) and 2 years (1301.7/100,000 vs. 911.5/100,000, SIR 1.4, 95% CI 1.2–1.6) after recruitment [43]. In these instances, the temporal presentation of events helps to define the sequence of risk.

Based on 13 prospective studies, a meta-analysis found patients with hypertension were more susceptible to develop breast cancer [44, 45]. The prevalence of colorectal cancer was 11% higher in patients with hypertension and renal cell carcinoma was also shown to be associated with high blood pressure [44].

Interestingly, AF may be also associated with cancer. The RE-LY (Randomized Evaluation Long-Term Anticoagulant Therapy Study) revealed that malignant tumours were the main non-CV cause of mortality in AF patients [46, 47]. Also, the Women's Health Study (WHS) showed that 10% of patients who had new-onset AF developed subsequent cancer [47]. Yet, most evidence stems from retrospective analyses with mostly non-causal relationships. Also, available data tend to show positive associations due to publication bias. Thus, these findings should be examined and evaluated critically by the reader.
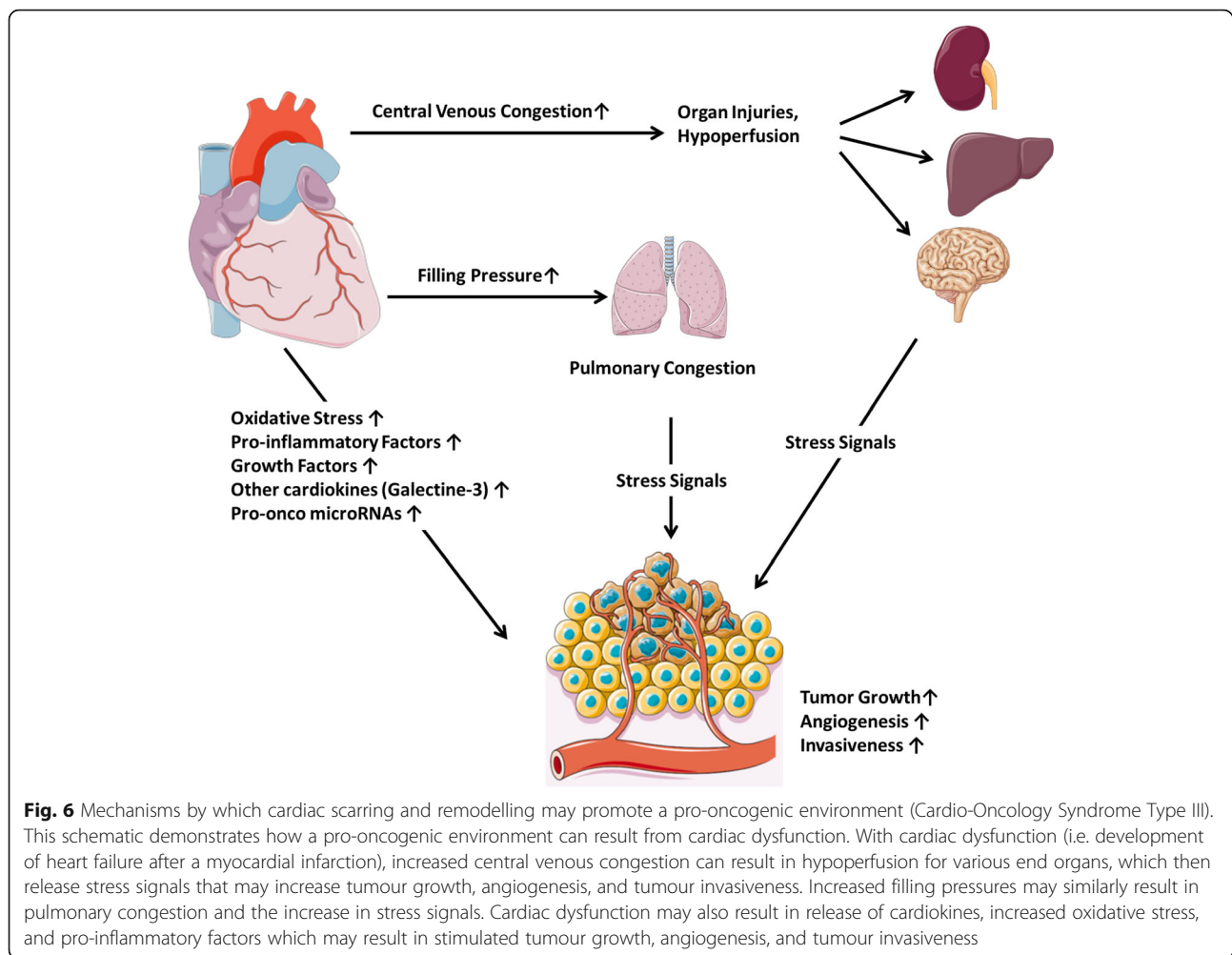
An additional consideration is potential survivor bias in cardiovascular trials. Participants that receive and survive focused cardiac treatment or intervention will accrue exposure-time for risk of developing subsequent cancer. However, since most studies compared those with CVD compared to those without CVD when assessing the association of CVD with subsequent risk for cancer, it is unlikely the association seen between CVD and cancer is driven by survivor bias, since those with CVD even with treatment, are less likely to accrue more time at risk than the non-CVD comparator.

The effect of CVD-induced hypoxia on cancer

Evidence suggests that tissue hypoxia in atherosclerosis may accelerate cancer progression (Fig. 6). Endothelial abnormalities and insufficient blood flow induce tissue hypoxemia in CVD patients. Hypoxia subsequently induces hypoxia-inducible factor 1-alpha (HIF-1α) [48]. The latter is commonly overexpressed in many cancers and has many functions such as, increasing glucose metabolism, alteration of apoptotic pathways, stimulating angiogenesis and tumour growth, and invasion [49]. Studies in animal xenograft models revealed that tumour growth and angiogenesis were repressed by the loss of HIF-1 activity and stimulated by HIF-1α overexpression. Also, cancer biopsies from patients indicated that HIF-1α is overexpressed in several tumours and showed that its level of expression correlated with prognosis and mortality [49]. Based on these findings, the activation of HIF-1α in CVD constitutes a potential pro-oncogenic element that may lead to subsequent cancer and constitutes a common therapeutic target for both diseases. However, the presented evidence provides better support to HIF-1α increasing tumour growth rather than causing cancer. Therefore, adequate study design and preclinical models are needed to determine whether the HIF-1α initiates cancer.

Cardiokines stimulate tumour growth

A recent experimental study indicated that factors secreted by failing hearts stimulate tumour growth by releasing pro-oncogenic factors into the circulation [50] (Fig. 6). In the setting of MI, mice genetically predisposed to the development of intestinal tumours,

Fig. 6 Mechanisms by which cardiac scarring and remodelling may promote a pro-oncogenic environment (Cardio-Oncology Syndrome Type III). This schematic demonstrates how a pro-oncogenic environment can result from cardiac dysfunction. With cardiac dysfunction (i.e. development of heart failure after a myocardial infarction), increased central venous congestion can result in hypoperfusion for various end organs, which then release stress signals that may increase tumour growth, angiogenesis, and tumour invasiveness. Increased filling pressures may similarly result in pulmonary congestion and the increase in stress signals. Cardiac dysfunction may also result in release of cardiokines, increased oxidative stress, and pro-inflammatory factors which may result in stimulated tumour growth, angiogenesis, and tumour invasiveness

exhibited a higher number of intestinal polyps compared to sham mice. The authors suggested that the oncogenic activity of the failing heart was mediated by secreted factors such as SerpinA3, a factor regulating tumour cell survival pathways and apoptosis [50]. Treating colon cancer cell lines (HT-29) with a selection of proteins that were overexpressed in the myocardium of failing hearts, resulted in a higher proliferative rate. Further, the investigators showed that HF and inflammation biomarkers were associated with new onset cancer incidence among participants with HF from the PREVEND (Prevention of Renal and Vascular End-Stage Disease) study [50]. Comparable outcomes were validated in a recent study showing that MI-induced HF accelerates breast cancer progression in mice. Further, prospective studies showed that cancer prevalence is higher in patients with CV events [51]. Cardiokines may represent a new biological pathway by which CVD induces cancer development and progression. However, these findings require further investigation in larger clinical studies.

Hypercoagulability promotes cancer

It is already acknowledged that cancer induces a hypercoagulable state through the production of pro-coagulant factors. However, emerging data indicate that thrombosis can also promote cancer (Fig. 6). Higher cancer prevalence was reported in patients after stroke and venous thromboembolism [42, 52]. Moreover, shorter duration of anticoagulation with warfarin (6 weeks) treatment was associated with a higher risk of incident cancer compared with long-duration treatment (6 months) [53]. Studies indicated that thrombin promotes metastasis and induces vascular growth factors and angiogenesis [54, 55]. Also, thrombin boosts the proliferation of dormant cancer cells and promotes progression to clinical disease [48].

Cardio-oncology syndrome type IV- (COS 4; indirect): the association between CVD treatments and diagnostics and cancer diagnosis
Cardiovascular diagnostic radiation
Studies have suggested some indication of an association of cumulative cardiovascular diagnostic radiation with

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subsequent development of cancer [56–58]. Cancer prevalence attributed to the exposure to cardiovascular diagnostic radiation has been extensively investigated and existing data suggest that children and adolescents are more prone to developing radiation-associated malignancies than older individuals [56–58]. Consequently, there has been a debate regarding the optimal type of imaging modalities that should be used for specific indications in young patients with a focus on reducing radiation-exposing imaging studies.

A retrospective cohort study aimed to evaluate the prevalence of leukaemia and brain tumours after CT scans in children and young adults [56]. The investigators noted a positive link between the radiation dose from CT scans and both leukaemia and brain tumours. However, these cancers are rare, thus, the cumulative absolute risks are small. It has also been estimated that one excess case of leukaemia and one excess case of brain tumour per 10 000 head CT scans will occur within the 10 years after the first CT scan in patients younger than 10 years [56].

Another population-based cohort study compared cancer incidence in young individuals exposed to a CT scan, more than 1 year before cancer diagnosis, with cancer incidence rates in unexposed individuals. Among individuals exposed to a CT scan before the age of 19 years, the overall cancer incidence was 24% higher in comparison to unexposed individuals. The proportional increase in cancer risk was obvious at short intervals of exposure and was greater for patients exposed at younger ages [57]. Further, cancer prevalence in young patients exposed to radiation from cardiac catheterizations is relatively low: below 50 per 100,000 for males and 200 per 100,000 for females [58].

Although clinical benefits should compensate for the low absolute risks, radiation doses should be kept as low as possible and alternative methods, which do not involve ionizing radiation, should be considered if suitable. As an example, ejection fraction can be determined by echocardiography (no ionizing radiation) instead of multigated acquisition scan. Moreover, when considering the annual frequency of CVD requiring examination with CT scans and cardiac catheterization, the overall attributable cancer risk may become important. Therefore, cautious consideration by treating physicians is needed before pursuing any potentially carcinogenic diagnostic or therapeutic options.

Cardiovascular medications

The safety of CVD treatments concerning cancer development is still an active topic of investigation (Fig. 7), with equivocal results. Several studies reported a higher rate of diagnosis of lung cancer in patients treated with angiotensin-converting enzyme inhibitors, especially in individuals treated for more than 5 years [59]. Yet, the outcomes of a large cohort study did not link cancer incidence to angiotensin receptor blocker (ARB)

treatment. Interestingly, a subgroup analysis showed a significant association between ARB and cancers in male genital organs [60]. Nevertheless, randomized clinical trials with irbesartan, valsartan, and losartan did not detect any rise in the overall or site-specific cancer risk in patients taking ARB [61]. The inconsistencies among these findings may be due to bias (e.g., selection bias), which can lead to inaccurate conclusions. Evaluating the link between CVD drugs and carcinogenesis is important to consider, given the millions of patients treated with CVD drugs.

Surveillance bias

Patients with CVD are typically under closer medical surveillance than the general population. Thus, the heightened risk of cancer in CVD might be partially explained by observation bias. Frequent chest X rays and CT scans, as well as PET scans and MRI scans, may unmask pre-existing cancers. Also, repeated lab tests may also raise concern for malignancies, which allows the detection of cancer at early stages. Clinicians have long been aware that bleeding, which is frequently observed in AF patients treated with oral anticoagulants, could potentially unmask occult cancer. Predominantly, evidence of the association between bleeding and cancer diagnosis emerges from small retrospective analyses of databases intended to address other queries. However, a nationwide Danish retrospective study involving patients with AF treated with anticoagulants reported a 15-fold higher hazard of a new colorectal cancer diagnosis with lower gastrointestinal bleeding in patients older than 75 years [62]. A recent study analysed data from the Retrospective observational registry of patients with atrial fibrillation from Vigo's health area (CardioCHUVIAF). The authors found that gastrointestinal bleeding was associated with a 13-fold higher hazard of a new gastrointestinal cancer diagnosis. In the same study, genitourinary bleeding was associated with an 18-fold higher hazard of new genitourinary cancer diagnosis [63]. A large population of CVD patients is treated with anticoagulants and is at higher bleeding risk. Hence, they are more exposed to clinical management and screening (e.g., colonoscopies), which unmasks occult cancers. To conclude, anticoagulants are likely related to the unmasking of prevalent GI cancers rather than a causative mechanism.

Survivor bias

An additional source of potential bias is survivor bias for CVD patients that are randomized to a procedure as compared to no procedure. CVD patients that undergo the procedure or receive a study drug may have benefit and live longer, thus leading to increased exposure time at risk for development of subsequent cancer. A classic example of this would be with the use of implantable
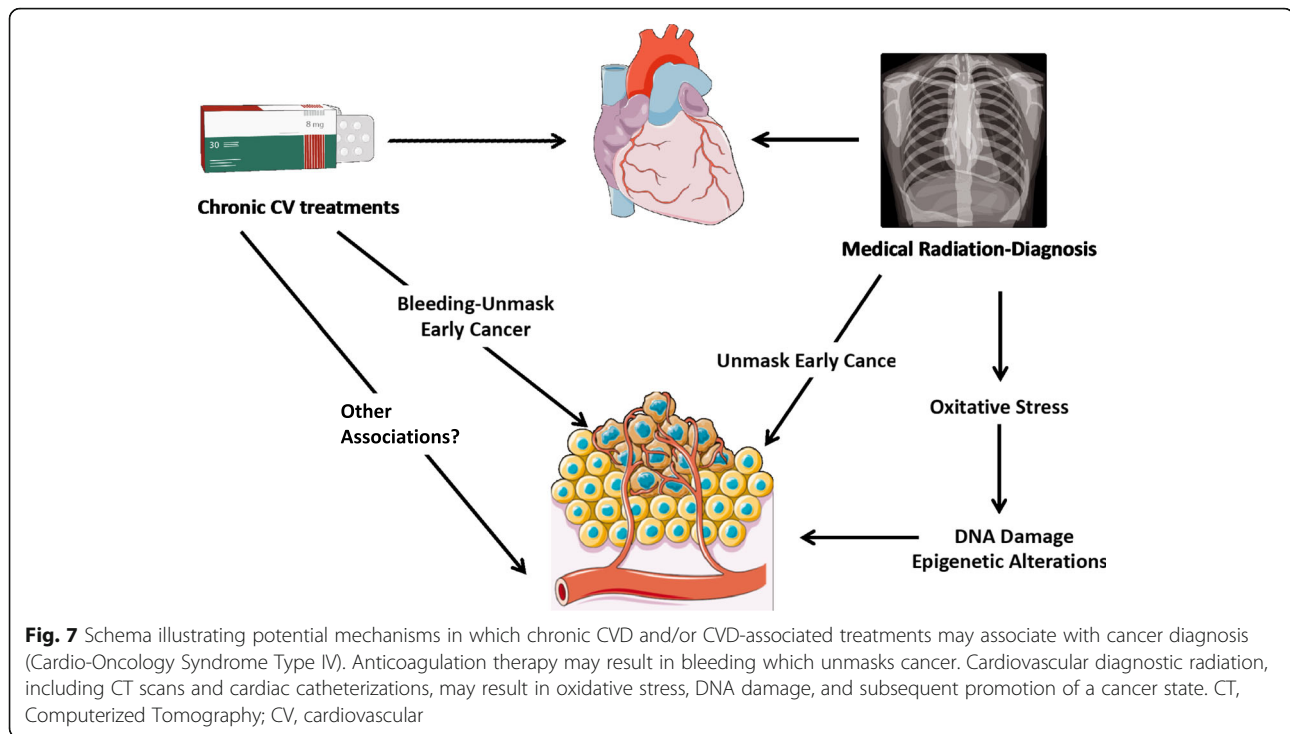
Fig. 7 Schema illustrating potential mechanisms in which chronic CVD and/or CVD-associated treatments may associate with cancer diagnosis (Cardio-Oncology Syndrome Type IV). Anticoagulation therapy may result in bleeding which unmasks cancer. Cardiovascular diagnostic radiation, including CT scans and cardiac catheterizations, may result in oxidative stress, DNA damage, and subsequent promotion of a cancer state. CT, Computerized Tomography; CV, cardiovascular

cardiac defibrillators (ICD) in heart failure with reduced LVEF. Those that receive an ICD may live longer than those without an ICD, leading to increased rates of observed cancer in those with ICDs.

Cardio-oncology syndrome type V (COS 5): systemic and genetic conditions

Cardiac tumours

Cardiac tumours fall within COS Type V (Secondary) due to shared systemic and genetic conditions leading to concurrent cancer and CVD (Fig. 8). The degree of environmental and genetic contribution is largely variable depending on the exact cardiac tumour subtype. Some tumours may occur due to genetic predisposition, but this is not always the case. Perhaps one of the best-known examples of genetically driven cardiac tumours is tuberous sclerosis, an autosomal dominant disorder that is associated with cardiac rhabdomyomas [64]. Another well-known genetic disorder is the Carney complex, which is associated with myxomas [65].

Cardiac tumours can be metastatic and spread via haematogenous seeding (e.g., melanoma, lymphoma), lymphatic spread (e.g., breast cancer), venous extension (e.g., renal cancer), or direct extension (e.g., lung cancer) [66]. Regardless of tumour type, any cardiac mass can have hemodynamic effects depending on the location, by impairing valvular function or obstructing normal blood flow. Additionally, tumours may serve as a nidus for arrhythmias and result in sudden death. Embolic complications can be seen either from the tumour itself or due

to thrombus formation on the tumour. More aggressive malignant tumours can also have a direct myocardial or pericardial extension.
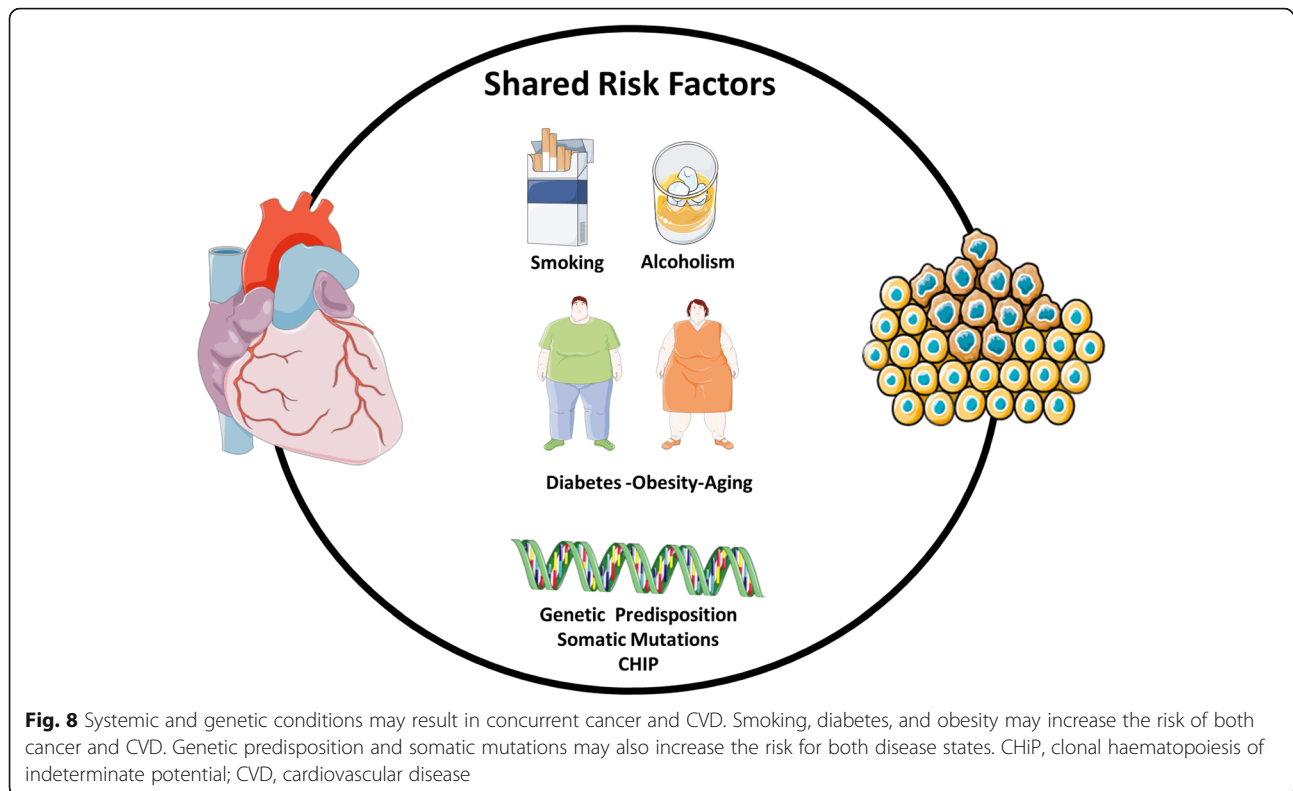
Shared risk factors

Extensive research over the decades has established risk factors associated with the development of cancer and CVD. These factors have been previously interpreted as discrete entities associated with either cancer or CVD. More recently however, an appreciation of a shared overlap model has come to light in regard to risk factors common to both CVD and cancer [67–70].

Smoking

Worldwide, smoking accounts for nearly 30% of all cancer-related deaths and increases the risk of CVD 2- to 3-fold. Smoking stimulates pro-inflammatory pathways through irritants, carcinogens, and oxidative stress present in the development of CVD and smoking-related cancer. Impaired nitric oxide bioavailability and endothelial damage caused by smoking are key mediators in the development of atherosclerosis and subsequent CVD [71]. Tobacco is strongly associated with incident lung, oesophageal, pancreatic, and bladder cancer.

Alcoholism

Studies over the last several decades have consistently shown a J- or U-shaped relationship between alcohol use and CVD [72]. Compared to non-drinkers, alcohol use increases the risk of colorectal, oropharynx, oesophageal,

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Fig. 8 Systemic and genetic conditions may result in concurrent cancer and CVD. Smoking, diabetes, and obesity may increase the risk of both cancer and CVD. Genetic predisposition and somatic mutations may also increase the risk for both disease states. CHiP, clonal haematopoiesis of indeterminate potential; CVD, cardiovascular disease

liver, and breast cancer [73, 74]. Even moderate alcohol use has been associated with an increased risk of overall cancer [75]. Acetaldehyde, an ethanol metabolite, is considered carcinogenic through reactive oxidative stress, altered DNA methylation, and changes in oestrogen pathways [76].

Type 2 diabetes Mellitus

Type 2 diabetes mellitus has long been identified as a risk factor for the development of CVD through deleterious effects on the micro- and microvasculature [77]. A consensus report released by the American Diabetic Association found convincing evidence of an association between type 2 diabetes mellitus and cancer [78]. Medications used in the treatment of diabetes also provide insight into the interplay between CVD and cancer. The use of metformin has been reported in several systematic reviews and meta-analyses to reduce the risk of cancer incidence and all-cancer mortality compared to other traditional regimens [79]. More recently, sodium-dependent glucose transporter 2 (SGLT2) inhibitors have become first-line agents in metformin-resistant diabetes and are recommended for secondary CVD prevention due to their cardioprotective effects. In a recent study by Claudio et al., SGLT2 inhibition in early-stage lung adenocarcinoma reduced tumour progression and prolonged survival in mice with SGLT2 expression [80]. Conversely, pioglitazone - a thiazolidinedione - improves

glycaemic control in patients with type 2 diabetes but has been shown to have detrimental CV effects and an increased risk of bladder cancer [81].

Obesity

This association between CVD and obesity is likely mediated indirectly through factors related to the metabolic syndrome including dyslipidaemia, insulin resistance, sedentary lifestyle, but also a pro-thrombotic and inflammatory state [82, 83]. In a dose-response meta-analysis of observational studies, every 5% increase in body mass index (BMI) was associated with a 10% greater risk of death related to cancer. The risk of cancer associated with obesity is higher in women compared to men and may be attributable to excess adipose tissue producing elevated oestrogen levels, a known risk factor for breast and endometrial cancer [84].

Physical inactivity

A dose-response relationship was observed in a pooled meta-analysis, finding 2.5 h/week of moderate-intensity activity led to a significant 13% reduction in cancer mortality [85]. Sedentary behaviour, irrespective of activity level, has also been shown by several meta-analyses to be associated with CVD and certain types of cancer [86]. The shared biological mechanism in reducing CVD and cancer is likely multifactorial through beneficial effects

on blood pressure, insulin sensitivity, and reduced adipose tissue [87].

Shared pathophysiology

While mechanisms involved in the development of CVD in cancer patients have been extensively elucidated, pathways driving the increased prevalence of malignancies in CVD patients have not been equally explored [88]. In this section, we highlight common molecular pathways central to CVD and cancer, namely inflammation and clonal haematopoiesis of indeterminate potential (Fig. 8).

Inflammation

Based on the outcomes of the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS), inflammation is a valuable target in both cancer and CVD. In this study, patients with MI and elevated CRP were randomly assigned to receive the canakinumab, an IL-1β-targeting antibody. The authors reported lower rates of CV events in patients treated canakinumab compared to the placebo group. Alongside, canakinumab reduced incident lung cancer and cancer-related mortality. These results demonstrate a promising effect of anti-inflammatory agents, such as canakinumab, in reducing CV and cancer events . Accumulating findings from clinical and preclinical studies highlight the role of inflammation in CVD development and consequential complications and highlight the pathogenic activity of proinflammatory cytokines, mainly TNF (tumour necrosis factor)-α, IL (interleukin)-1β, IL-6, and IL-18 [61]. In the context of cancer, targeting cytokines into the tumour by the fusion of anti-cytokine antibodies represents a novel tool in immunotherapy [89]. The inflammatory response to haematological malignancies is often associated with an overproduction of IL-6, predominantly in B cell-derived and plasma cell tumours. Elevated levels of IL-6 promote myocardial injury and are involved in coronary artery diseases [90, 91]. In general, IL-6 elevation has associated with cardiovascular complications such as atherosclerosis, MI, and heart failure. The pathophysiology of ACS and atherosclerosis comprises adaptive immune response T cells and cytokines [92]. Extensive investigations are needed to tease out what factors are key players in the cancer-CVD axis. However, such elements may 1 day serve as therapeutic targets to improve the outcomes in patients.

Clonal haematopoiesis of indeterminate potential

Age-related genetic mutations in the highly proliferative hematopoietic stem cells of the bone marrow can lead to clonal haematopoiesis of indeterminate potential Early blood cell progenitors contribute to the creation of a genetically distinct subpopulation of blood cells, and successive mutations in the same clone or subpopulation allow the progression to acute myeloid leukaemia [93]. These mutations occur predominantly in genes that encode for key epigenetic regulators of haematopoiesis, such as Ten-Eleven Translocation-2 (TET2), DNA Methyltransferase 3A (DNMT3α), Additional Sex Combs Like 1 (ASXL1), Janus Kinase 2 (JAK2), and tumour protein 53 (TP53) [94, 95].

Some of these somatic mutations in the hematopoietic stem cells (e.g., TET2, JAK2, and ASXL1) are linked to an increased risk of coronary heart disease [95]. Investigators have reported higher expression of pro-inflammatory cytokines in TET2-deficient macrophages, which stimulates the development of the atherosclerotic plaque. In the same study, the authors observed larger atherosclerotic lesions in mice engrafted with bone marrows of TET2-deficient (homozygous and heterozygous) mice compared to a group of mice engrafted with normal bone marrows. Additional studies have linked dysfunctional TET2 to the stimulation of the cytoplasmic supramolecular assembly Nod-like receptor protein 3 inflammasome (NLRP3) [96]. Additionally, somatic mutations in TET2 and DNMT3α were shown to be associated with a poor prognosis in HF patients [97]. Interestingly, the pharmacological inhibition of 3 (NLRP3) prevented the aggravation of cardiac dysfunction in HF mouse models (TET2 or DNMT3αdeficient mouse models) [98]. Based on the data, genetic risk factors and somatic mutations are emerging as common drivers of cancer and CVD. This holds great clinical relevance as these somatic mutations demonstrate predictive values for cancer and CVD. This promising research may help pave the way for personalized medicine that allows optimized prevention, treatments, and management of patients.

Genetic predisposition – monogenetic disease

In this section, we provide instances of common established genetic mutations that may be involved in both diseases. BRCA1/2 mutation carriers are predisposed to breast and ovarian cancer. After the exclusion of deaths due to cancer, the carriers of BRCA1/2 mutations still have lower longevity [99]. Because BRCA1/2 mediates DNA-repair and other vital pathways, it has been previously hypothesized that these genetic variants could be linked to other diseases. Indeed, several studies reported higher levels of proteins or biomarkers associated with elevated thrombotic risk in patients with BRCA1/2 mutations compared to controls with no mutations, independent of breast cancer [100, 101]. These results suggest that the carriers of the mutations are prone to have coagulation-related problems independently of malignancies. Further, low levels of insulin-like growth factor 1 (IGF-1) were detected in individuals carrying BRCA1/2 mutations, while high levels of IGF-1 were detected in BRCA1/2

mutation carriers with breast cancer; abnormal concentrations of IGF-1 have been associated with higher risks to develop insulin resistance, which contributes to the pathophysiology of many CVDs [100, 102].

Titin (TTN) is the largest sarcomeric protein found in the heart and is involved in the pathophysiology of cardiomyopathy. Truncation mutations of TTN are the most frequent mutation observed in dilated cardiomyopathy where most cases are hereditary [103]. TTN mutations, resulting in truncations in the A-band region of the protein, were detected in 25% of patients with dilated cardiomyopathy [104]. Other forms of cardiomyopathies, such as hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy are also linked to TTN mutations [105]. Strikingly, in a cohort that included patients with 34 solid tumours and 7 independent validation cohorts from clinical trials, TTN mutations were detected in ~ 30% of solid tumours. Based on these outcomes, the investigators considered these mutations as potential tools to risk-stratify tumour mutational burden into groups with different clinical responses to immune checkpoint inhibitor monotherapy [106]. These two examples – of what most physicians will consider 'clear cut monogenetic cancer or CVD examples' - further underscore the potential links that exist between cancer and CVD.

Shared prognostic factors

Prognostic markers are hard to objectify because of their either low sensitivity or specificity, unknown thresholds, or difficult reproducibility. Seeing the large overlap in CVD and cancer-related risk factors, it is challenging to find a valuable prognostic biomarker that accurately predicts a patient's prognosis. Several prognostic biomarkers like age and circulatory biomarkers have extensively been studied in both patients with cancer and CVD [107, 108]. However, due to the low sensitivity and specificity, these biomarkers have yet to be utilized in routine clinical practice. Sex-bias presents as another interesting factor in both CVD and cancer [109, 110]. Gender influences not only the overall incidence and shared risk factors, but also the timing and phenotype of disease presentation, the treatment regimen, and the disease prognosis as well [111].

CV biomarkers have been used in patients with cancer to predict the risk and prognosis of cardiotoxicity, showing promising results [112]. The reverse rationale has also been suggested, reporting that certain tumour biomarkers could predict CVD severity and prognosis. CA 125 known as a biomarker for ovarian cancer and several haematological malignancies has been shown as a promising CV biomarker in diverse CVD [113, 114] . Furthermore, other tumour biomarkers, such as CYFRA 21-1, CEA and Ca 19–9, demonstrated a prognostic value, especially in patients with severe HF [115].

The search for the perfect prognostic biomarker in Cardio-Oncology requires extensive resources and a large data pool. Prognostic biomarkers, both positive and negative ones, could help recognize not only the patients at high CV or cancer risks, but also patients with low CV risk that could benefit from more aggressive treatment regimes.

Benefits of the proposed classification

We anticipate that the classification system will guide clinicians to better understanding of the predisposing factors and assist with focusing treatment on removing or tempering the driving cause for each disease state. Additionally, these categories may serve as a tool for classifying cardio-oncology patients into relatively more homogenous cohorts for future trials with targeted interventions. Such an approach would help address an existing issue with the field — heterogeneity of cardio-oncology patients and disease states. By focusing on a single classification at a time, this would align treatments with more consistent underlying drivers of disease and provide more accurate estimates of treatment effect.

By understanding the predisposing factor, treatment may be targeted at removing or tempering the driving cause for the disease state. For example, in those with progressive scarring and remodelling of the heart causing a pro-oncogenic environment (Type III), treatment should be targeted at mitigating this effect. Thus, recognizing that heart failure and myocardial infarction can potentially foster a pro-oncogenic environment may lead to intervention studies in patients with heart failure or myocardial infarction specifically targeting components of the pro-oncogenic environment itself, beyond standard treatment for the predisposing cardiovascular diseases. Conversely, if a pro-oncologic environment was caused by CV disease associated treatments or diagnostic imaging (Type IV), the focus would be on weighing and addressing the risks and benefits of considering alternative treatment or imaging modalities, recognizing that these associations remain under investigation. The classification schematic may therefore help researchers identify focused pathways in appropriately selected and relatively homogenous cohorts for future interventions. Lastly, this novel classification system would harmonize understanding and provide a clinical framework for cardiotoxicity from cancer treatment by providing structured definitions with a "universal language" for cardiologists and oncologists when caring for patients.

The identification and management of CV risk factors in all five types of COS are important because if not recognized and treated, both CVD and cancer pose great burdens for our patients. Yet, in those with cancer, the development of CVD poses a greater risk than cancer itself, and those with heart disease have a greater risk of

developing cancer as well. Thus, to reduce the risk of adverse outcomes, the traditional CV risk factors should be closely managed in this high-risk population. For instance, lowering cholesterol levels via lifestyle changes, medication, or exercise is believed to diminish breast cancer prevalence and slow-down tumour growth [116, 117]. This can be explained by the fact that cholesterol metabolites stimulate oestrogen receptors, which results in tumour growth [118]. Expanding the role of primary care physicians, oncologists, cardiologists, and allied healthcare providers in cancer survivorship will be essential in identifying and managing these five types of COS in a coordinated fashion.

Limitations of the proposed classification

We realize that the enormous number of cancer therapies cannot be easily fit into one syndrome or algorithm. Also, aetiologies of both cancer and CV disease are usually multifactorial, so we recognize that our proposal simplifies a complex truth. Collectively, our approach offers a reasonable and practical first attempt to better categorize these patients. We envision our proposed system to be operationalized in a similar manner to the classifications for cardiorenal syndrome [119] or the WHO groups for pulmonary hypertension [120], in which causes and treatment differ by classification group.

The evidence supporting the statement that CVD represents a pro-oncogenic state is based on retrospective and observational outcomes that cannot establish cause and effect. However, three pre-clinical studies with several combinations of HF aetiologies and cancer types have proven the direct connection between the two syndromes. Also, investigators of these studies found that failing hearts can affect tumour growth and severity independent of CVD risk factors [50, 121, 122].

In the clinical practice, we acknowledge the difficulty in discerning between the CVD itself and the underlying risk factors. Thus, it is more challenging to determine whether detecting incident cancer following CVD is based on shared risk factors such as a history of smoking (Type 5), or if there is truly a link between CVD and cancer (Type 3). Nevertheless, the classification system is essential as it allows clinicians to manage patients and evaluate the predisposition to one or both of the diseases. Different strategies or treatments may be more effective within each defined category. Even in instances where a patient may share more than a single classification (Fig. 9), recognition of which specific categories apply will still guide treatment strategies. Future studies should validate the usefulness of our proposal, and diagnostic and therapeutic studies will be necessary to prove clinical benefit.

Conclusion

In this review, we propose a classification system to categorize Cardio-Oncology syndromes into five distinct groups. The classification system (I-V) can help separate and unmask certain aetiologies of CV damage from cancer and cancer treatment, and vice versa (Fig. 9). Using the classification system, the course of treatment selected by oncologists (COS I, COS II, COS V) or cardiologists (COS III, COS IV, COS V) may help guide surveillance and management pursued by the converse specialty (Fig. 10). This classification has emerged in response to observations of the effects of cancer and its therapies on the CV system, as well as the development or diagnosis of cancers in the setting of heart disease.
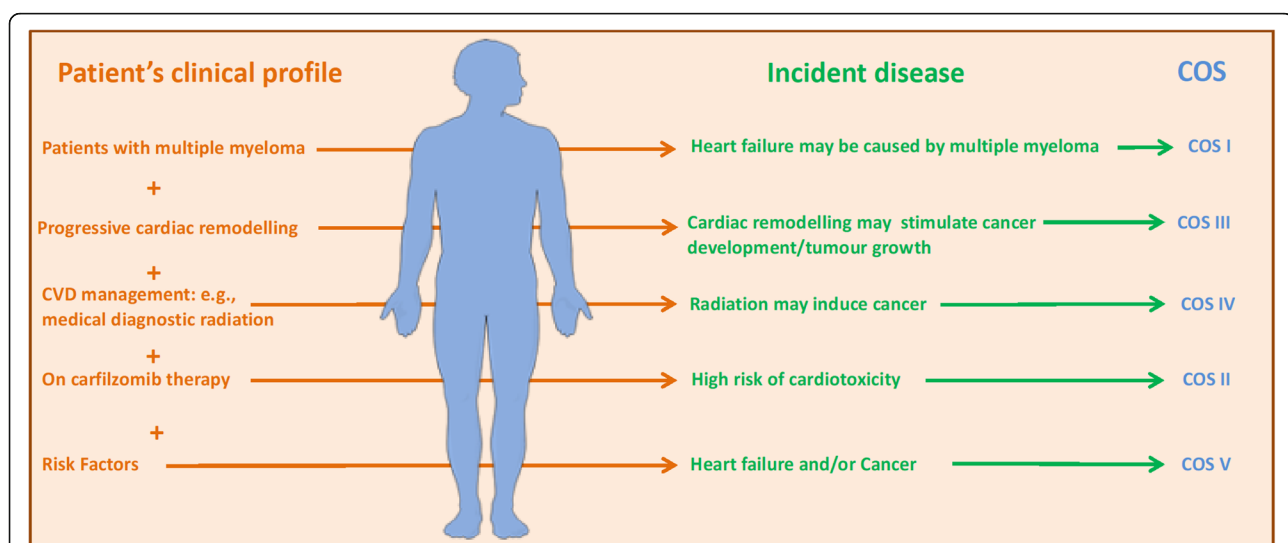

Fig. 9 Theoretical depiction of a clinical situation with a patient consistent with more than a single classification. However, the application of our classification system depends on which disease is diagnosed first and on the available data regarding systemic and genetic predisposition and risk factors [122, 123]
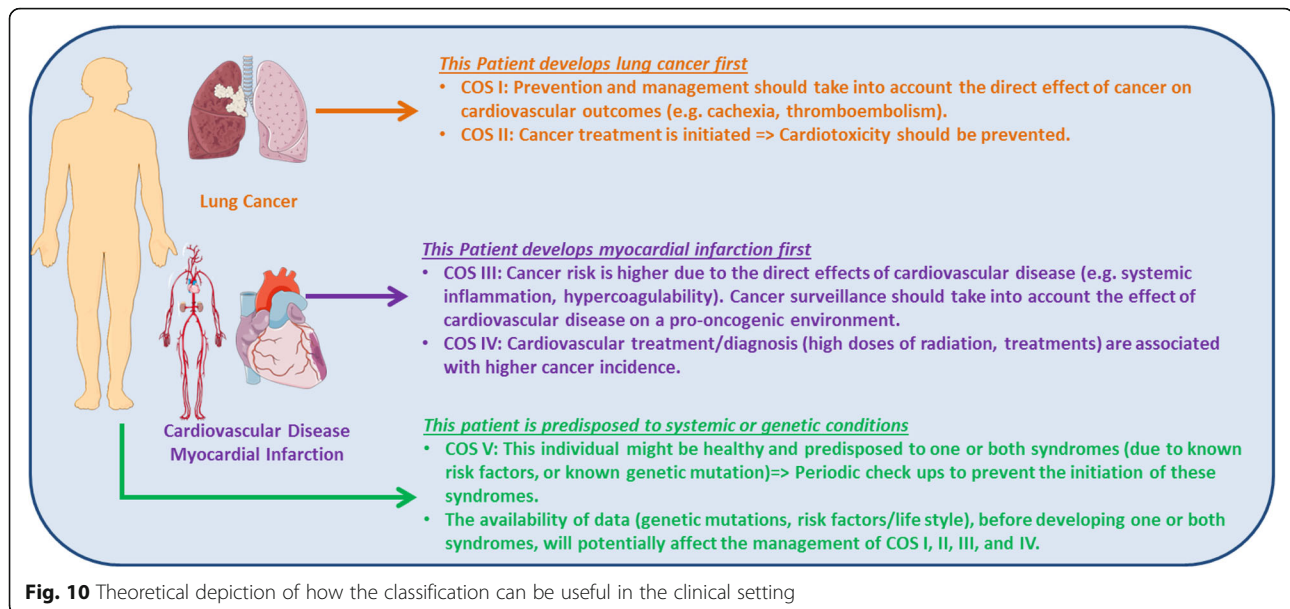
Fig. 10 Theoretical depiction of how the classification can be useful in the clinical setting

These aetiologies include the effects of the tumour itself on the CV system which can have a direct effect on CV dysfunction (COS Type I) from aetiologies including TLS, cardiac cachexia, and arterial thromboembolism; the indirect effects from anti-neoplastic treatments (COS Type II) encompassing traditional chemotherapy, targeted therapies, and immunotherapy, as well as radiation therapy; CVD pro-oncogenic effect (COS Type III), which exerts direct effects from cardiokines, galectin-3 and other factors; chronic CVD and their associated treatments (COS Type IV), which may increase the risk for or enhanced detection of cancer; and lastly shared risk factors, metabolic diseases, and genetic predisposition (COS Type V), which work synergistically to increase the risk of long-term cardiac complications, as well as malignancies. This classification method paves the way for improvements in patient care, research, and education in Cardio-Oncology.. Having such a framework facilitates providing the best cancer care while optimizing CV health, and also being able to pre-empt both CVD and new malignancies based on the recognition of underlying or pre-existing risk and disease.

Abbreviations
COS: Cardio-oncology syndromes; CVD: Cardiovascular disease; TLS: Tumour lysis syndrome; MI: Myocardial infarction; HF: Heart failure; HER2: Human epidermal growth factor receptor 2; AF: Atrial fibrillation; mTORC: Mammalian target of rapamycin complex; CAR-T: Chimeric antigen receptor T; CRS: Cytokine release syndrome; ACS: Acute coronary syndrome; RE-LY: Randomized evaluation long-term anticoagulant therapy study; WHS: Women's Health Study; HIF-1α: Hypoxia-inducible factor 1-alpha; PREV END: Prevention of renal and vascular end-stage disease; ALLHAT: Lipid-lowering treatment to prevent heart attack trial; ACEIs: Angiotensin-converting enzyme inhibitor; CHARM: Candesartan HF assessment of reduction in mortality and morbidity; SGLT2: Sodium-dependent glucose transporter 2; BMI: Body mass index; CANTOS: Canakinumab anti-inflammatory thrombosis outcome study; CAR: Chimeric antigen receptor; TET2: Ten-eleven translocation-2; DNMT3α: DNA Methyltransferase 3A; ASXL1: Additional Sex Combs Like 1; JAK2: Janus Kinase 2; TP53: Tumour protein 53; NLRP3: Nod-like receptor protein 3 inflammasome; IGF-1: Insulin-like growth factor 1

Conflictions of interest
None.

Authors' contributions
Drs. Brown, De Boer, and Aboumsallem conceived the concept. All other authors provided critical intellectual input. The author(s) read and approved the final manuscript.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This is a review so no ethical or approval and/or consent is applicable.

Consent for publication
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