

Cardio-oncology: the new frontier of clinical and preventive cardiology

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Abstract

Even if cancer and cardiovascular diseases are considered two distinct diseases, an intricate interconnection between these conditions has been established. Increased risk of malignancy has been identified in patients with cardiovascular disease, as well as a greater propensity to the development of cardiovascular diseases has been observed in patients with cancer. The development of cardiotoxicity following exposure to certain anticancer drugs only partially explains this relationship. Shared risk factors and common pathogenic mechanisms suggest the existence of a common biology and a complex interplay between these two conditions. Due to improving longevity and therapeutic advances, the number of patients affected or potentially at risk of developing these two diseases is constantly increasing and currently, several drugs against cancer from anthracyclines to checkpoint inhibitors, can also cause a wide range of unexpected cardiovascular side effects. Management of these issues in clinical practice is an emerging challenge for cardiologists and oncologists, and led to the development of a new dedicated discipline called cardio-oncology. Surveillance and prevention strategies as well as interventions to

reduce cardiovascular risk and prevent cardiotoxicities are the primary objectives of cardio-oncology.

In this review, we explore the etiopathogenesis common to cardiovascular disease and cancer and the complex interplay between them. We also report the main characteristics of the drugs responsible for cardiotoxicity, highlighting the available strategies for optimal patient management based on a multidisciplinary approach in the cardio-oncology setting.

Introduction

Cardiovascular disease (CVD) and cancer are the two leading causes of mortality and morbidity worldwide [1]. The burden of both illnesses is expected to increase as the population grows older and therapies enhance longevity.

Emerging evidence [2-6] suggests a bidirectional relationship between CVD and cancer. Shared risk factors, genetics and cellular pathways underpin a common biology, suggesting an overlap between these two entities.

It is estimated that approximately 40% of cancers are linked to common modifiable factors as smoking, alcohol abuse, sedentary lifestyle, obesity, unhealthy diet [7]. The detrimental prognostic importance of such factors, well known in traditional practice of cardiology, has relevance even in the cardio-oncological field. Inadequate management of cardiovascular risk factors increases the risk of cardiotoxicity of cancer therapies and reduces the probability of healing from cancer. The increase in long-term cancer survival also shows that, regardless of the baseline value, some cancer treatment can worsen the CV risk profile thus increasing the chance of a second tumor or a cardiovascular event in the following years [8,9]; therefore strategies to improve their prevention and treatment are global priorities.

Starting from these shared understanding, the collaboration between oncologists and cardiologists is essential, with the goals of balancing the potential adverse influence of one disease on the other, implementing the strategies to reduce the incidence of both CVD and cancer and their clinical impact.

Shared biology, genetic and cellular molecular pathways

Inflammation and oxidative stress

Chronic inflammation is a common thread between a variety of diseases, including both CVD and cancer [10,11]. Inflammation is a unifying mechanism induced by numerous conditions such as obesity, hypertension, hyperglycemia, hypertriglyceridemia,

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microbial and viral infections, allergen exposure, radiation, toxic chemicals, alcohol consumption, tobacco use, and other chronic and autoimmune diseases [12].

It is known that inflammation participates pivotally in the pathogenesis of atherosclerosis and its complications and it could play a major role to trigger plaque rupture/erosion, which is the most common phenomenon responsible for acute coronary syndrome [11,13]. Atherosclerosis, the major cause of CVD, is characterized by a chronic inflammation in large and middle-sized arteries, where activated immune competent cells are abundant [13,14]. Many risk factors for CVD (hypertension, hyperlipidemia, tobacco use, and insulin resistance) trigger atherosclerosis by promoting adhesion of endothelial cells and stimulation of leukocyte attachment to blood vessel walls [11].

It is well known that atherogenesis is characterized by continuous accumulation of lipids and inflammatory cells in the arterial intima. The inflamed microenvironment of the plaque is rich in pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), and interferon- γ (IFN- γ) [15]. The abundance of oxidized low-density-lipoprotein cholesterol (LDL) and reactive oxygen species (ROS) leads to the activation of inflammatory signaling and gene expression cascades including nuclear factor-kB (NF-kB) [16]. Under conditions that favor a state of chronic low-grade inflammation, such as obesity and hypertension, dysregulation of macrophage polarization between the pro-inflammatory M1 and anti-inflammatory M2 phenotypes promotes cardiac injury [17]. In patients with heart failure (HF), inflammation has also been linked to disease development, progression, complications and outcomes [18].

The hypothesis of a relationship between inflammation and cancer arises from the finding of leukocytes within the neoplastic tissue, suggesting that together with gene mutations and DNA instability, chronic inflammation is a necessary process for tumor progression and metastasis [19,20]. Furthermore, the association between some chronic infections and cancer has been established, such as human papilloma virus and cervical cancer [21], *Helicobacter pylori* and stomach cancer [22], Epstein Barr virus and lymphomas [23]. Several cancer types are frequent in chronic inflammatory diseases, among them celiac disease and small bowel lymphomas [24]. Inflammation promotes carcinogenesis and tumor progression, inducing DNA damage and chromosomal instability, enhancing tumor cell proliferation and resistance to apoptosis and stimulating angiogenesis [10]. The interaction between malignant cells and a chronically inflamed extracellular microenvironment activates a wide array of dysregulated intracellular signaling pathways and transcription factors implicated in tumor growth, angiogenesis, and metastasis [25].

High levels of innate cytokines, as evident in chronic inflammation, may promote tumor development [26,27]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) can induce DNA damage and modulate the expression of oncogenes and tumor suppressor genes [28]. Two central pathways of inflammation, Wntless-INT (Wnt) and adenosine 5' monophosphate-activated protein kinase (AMPK), play a role also in the pathogenesis of atherosclerosis and endothelial dysfunction, as well as in cancer [15]. Slug/Snai2 is a transcription factor with a well-described role in cancer progression [29]. New evidence suggests that this factor may contribute to inflammation in dedifferentiated smooth muscle cells and, potentially, atherosclerotic plaque formation and instability. Slug/Snai2 has also been related to impaired cholesterol metabolism [30].

In this setting, biomarkers of inflammation seem to be related to both CVD events and cancer. IL-6 is one of the most important.

This cytokine is related to hypertension and hepatic production of C-reactive protein (CRP) [31]. Moreover, it represents the terminal effector of inflammation in HF [32]. IL-6 has been reported to be involved in the inflammation associated tumorigenesis and may promote tumor growth by inhibiting apoptosis and inducing tumor angiogenesis [33,34]. IL-6 is a strong predictor of all-cause, cardiovascular and cancer-related mortality [35]. IL-1 β signaling is correlated with cardiac remodeling and dysfunction. For this reason, this mediator is particularly important in HF [32]. IL-1 β generated in the course of chronic inflammation supports tumor development [26]. In particular, it could play a role in case of clonal hematopoiesis of indeterminate potential (CHIP), as described below [36].

Common *genetic factors* in the pathophysiology of both disease have also been identified, such as aberrant activation of LRP6, TCF7L2 polymorphism, DYRK1B mutations, methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism [15].

Metabolic disorders promoting both CVD and cancer

Obesity and metabolic syndrome

According to epidemiologic data, up to 20% of malignancies could be related to weight, weight gain and obesity [37]. The risk of cancer appears to rise with increasing BMI, where cancer risk was increased by 12% with a BMI of 27.5 to 29.9 and up to 70% in those with a BMI greater than 40 kg/m² [38]. Each 1 kg/m² of excess weight increases the risk of cancer by 21% [39]. Bariatric surgery for severe obesity is associated with long-term weight loss and reduced overall mortality; in particular, cancer mortality is reduced by approximately 60% [40]. Evidence supports a causal link between overweight and obesity and risk of cancer incidence at several sites, including pancreas, esophagus, colorectum, renal cell, liver and cholangiocarcinoma, thyroid, postmenopausal breast and endometrial cancers, among others [41]. Recent epidemiological evidence, furthermore, highlights that obesity in the first decades of life is associated with the anticipation of obesity-related cancer (colon, pancreas) in the following decades of early adult life (40-50 yrs) emphasizing the important role of this treatable risk factor [42-45].

Obesity, and visceral obesity in particular, is a condition characterized by a proinflammatory and prothrombotic state, insulin resistance and atherogenic dyslipidemia [46-48]. Adipose tissue becomes dysfunctional, promoting a pro-inflammatory, hyperlipidemic and insulin resistant environment that also contributes to type 2 diabetes mellitus (T2DM) [49,50]. Accordingly, obesity has been classified as an independent risk factor for CVD [51,52]. The increased cardiovascular risk has also been established in young people [53]. Furthermore, there is a well-documented association between obesity and heart failure [32]. In addition, different hormones and pro-inflammatory cytokines, also referred to as adipokines, are produced by the adipose tissue, several of which have antiapoptotic and proangiogenic properties. Obesity alters the expression of adipokines, such that predominantly proinflammatory cytokines are released, including TNF- α , IL-6, IL-1 β and Monocyte chemoattractant protein-1 (MCP-1) [49]. These, in addition to promoting fat storage, also have oncogenic properties [12]. High concentrations of estrogen are commonly seen in obese people. Estrogen signaling and aromatase expression in the breast of obese women are often impaired, promoting cancer formation and pro-

gression [54]. Leptin is an adipocyte-derived hormone. Increased circulating leptin is frequent in obesity and independently associated with insulin resistance and CVD [55]. The mitogenic and anti-apoptotic effects of leptin have been described in various cancer types. Leptin also induces cancer progression, cell migration and invasion [56]. It is closely related to hepatocellular carcinoma [57], but also prostate cancer [58], breast and gynecologic cancer [59]. There is also a plausible hypothesis that the huge adverse effect of obesity on cancer burden might be mediated largely by insulin [60]. High levels of insulin-like growth factor-1 (IGF-1) are often found in obesity and in the metabolic syndrome and are associated with tumor growth, as outlined below [61,62].

In addition to biochemical mechanism linking obesity to cancer incidence, obesity may indirectly worsen cancer mortality through the effect of chemotherapy on cardiovascular system. The risk of developing cardiotoxicity from cancer therapy in obese patients is higher due to reduced cardiac reserve and associated cardiovascular morbidities (Figure 1) [39].

Diabetes mellitus

The close correlation between diabetes and CVD is well-known. Diabetes is associated with an early, accelerated and widespread atherosclerosis. Hyperglycemia and insulin resistance are the two major hallmarks of diabetes responsible for CVD. The common underlying mechanism appears to be the increased ROS production in diabetic cardiomyocytes [63]. Hyperglycemia may trigger smooth muscle cells proliferation and migration through the expression of many growth factors, especially IGF-1 [64].

Diabetes may influence the neoplastic process by several mechanisms, including hyperinsulinemia (either endogenous due to insulin resistance or exogenous due to administered insulin or insulin secretagogue), hyperglycemia, or chronic inflammation [65]. Insulin-like signaling systems are important to control cell proliferation and survival [60]. Tumor cells express both insulin and IGF receptors and multiple signaling pathways are activated after insulin receptors or IGF-I receptors interact with their ligands [65]. Once activated, these signaling pathways may induce proliferation, protection from apoptotic stimuli, invasion, and metastasis. It has been reported a modestly increased risk of prostate cancer, premenopausal breast cancer and colorectal cancer in people with high circulating levels of IGF-1 [66,67]. Hyperinsulinemia could also promote carcinogenesis indirectly, reducing hepatic production of IGF binding protein and consequently increasing the levels of circulating free bioactive IGF-I [68]. Moreover, elevated circulating insulin causes a reduction in the hepatic synthesis and blood levels of sex hormone binding globulin, leading to increases in bioavailable endogenous sex steroid [69].

Accordingly, the risk of postmenopausal breast, endometrial, and possibly other cancers is incremented [65]. Inflammation further helps through enhancing insulin resistance to the complex interplay of cancer and CVD [70].

Hyperlipidemia

Hypercholesterolemia, in particular high level of LDL associated cholesterol, fulfills all criteria required to consider a traditional risk factor as a causative agent of atherosclerosis [71]. In fact,

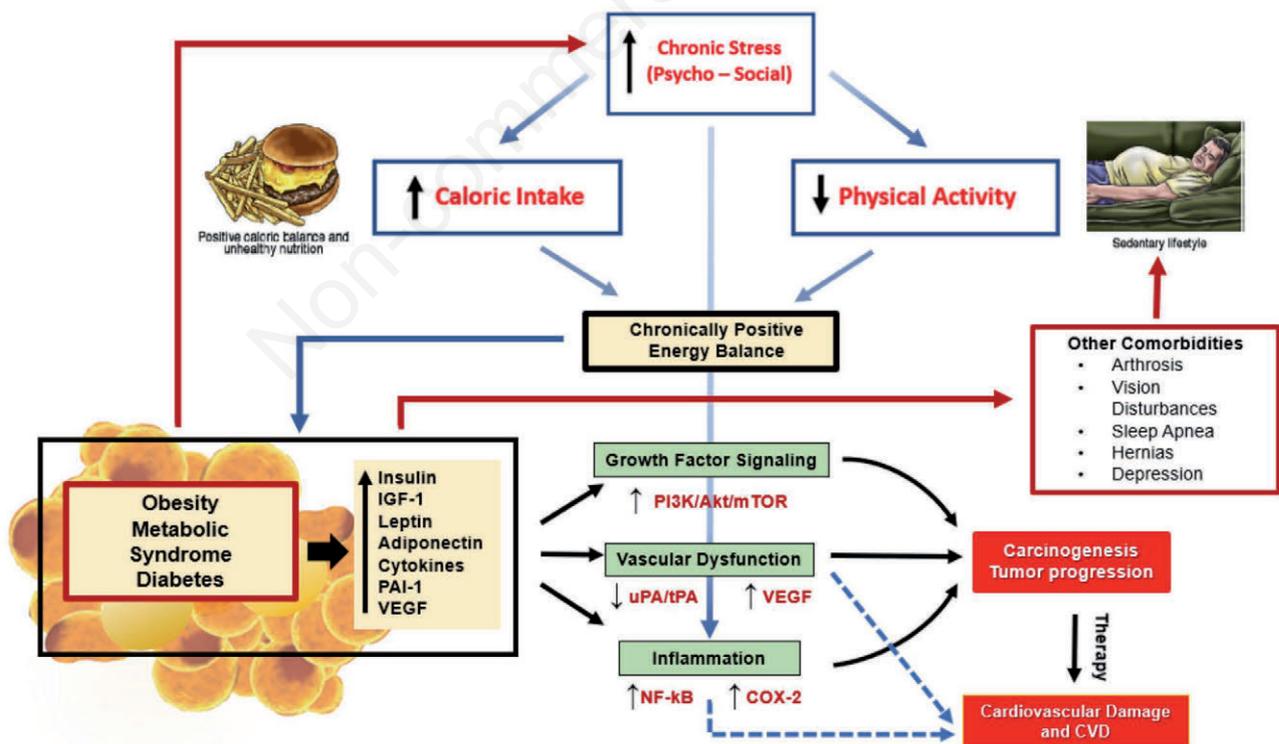


Figure 1. Obesity, sedentary behavior and unhealthy diet: a vicious circle promoting the development of cancer and cardiovascular diseases. IGF-1, insulin like growth factor-1; PAI-1, Plasminogen activator inhibitor-1; VEGF, vascular endothelial growth factor; PI3K/AKT/mTOR, pathway involving phosphatidylinositol 3-kinases, AKT serine-threonine kinase, and the mammalian target of rapamycin; uPA/tPA, urokinase-type (uPA) and the tissue-type (tPA) activators of plasminogen; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; COX-2, Cyclooxygenase-2; CVD, cardiovascular disease. See the text for details.

several mechanisms, including oxidative modification of the lipoprotein and formation of foam cells, contribute to atherogenesis; oxidized LDL was found to have biological effects on the vessel wall, including stimulation of cytokine production, inhibition of endothelial cell vasodilator function, and stimulation of growth factor production [72].

Several epidemiological studies suggested that high cholesterol levels are associated with increased risk of developing cancer [73]. Cholesterol is metabolized to active derivatives including cholesterol oxidation products (COP), known as oxysterols, which have been shown to alter cellular proliferation [73]; 27-hydroxycholesterol (27-OHC) is the most abundant oxysterol in the plasma and has been shown to be involved in the pathogenesis of several cancers including breast [74], and prostate cancer [75]. In contrast, 27-OHC reduces cell proliferation in colorectal cancer cells, suggesting a variable effect according to organ affected [73]. Moreover, it has been described a relation with atherosclerosis via proinflammatory processes mediated by estrogen receptor alpha [76].

Hypertension

In case of high blood pressure, the presence of inflammation, oxidative stress, neurohormonal activation and autonomic influences contributes to CVD and to cancer as well. The increase in oxidative stress may activate genes involved in generating an inflammatory response that, in the presence of hyperlipidemia, leads to the formation of atherosclerotic plaque [72].

In hypertensive subjects an increase in vascular endothelial growth factor (VEGF) levels is observed, due to angiotensin II [77]. VEGF plays a crucial role for new blood vessel formation, a fundamental step for the development and growth of the tumor [78]. Elevated blood pressure (BP) was significantly associated with incident cancer in men (hazard ratio per 10 mmHg increment: 1.07 [95% CI: 1.04-1.09]) and with cancer mortality in both sexes (HRs per 10-mmHg increment of 1.12 [95% CI: 1.08-1.15] for men and 1.06 [95% CI: 1.02-1.11] for women) [79]. Again, hypertension increases the risk of kidney cancer in both sexes [80]. In particular, it has been described a close connection with an increased risk of mortality from renal cell carcinoma [81]. In men, hypertension is related to prostate cancer as part of the metabolic syndrome. Higher risk for developing endometrial and breast cancer has been described in hypertensive women [80].

Unhealthy lifestyle

Figure 2 shows the proportions of cancers attributable to the modifiable causes described below [7]. The population attributable fraction (PAF) represents the contribution of a risk factor to the burden of disease or death and corresponds to the proportional reduction in population disease or mortality burden that would occur if exposure to a risk factor was eliminated [7].

Tobacco

Smoking is a well-known shared risk factor for CVD and cancer. Tobacco usage promotes atherosclerosis through exposition to cigarette smoke causing endothelial cell activation, dysfunction, injury, and death, leading to storage of lipids and inflammatory cells, as well as reducing the nitric oxide. Activated inflammatory cells, adhesion molecules and spontaneous platelet aggregation support the shift toward a procoagulant state and consequently the formation of rupture-prone plaques [82]. On the other hand, repetitive injury to squamous cell epithelium enhances carcinogenic

effect. Nicotine, a highly addictive substance, can inhibit apoptosis and enhance angiogenesis [82]. There is broad agreement that cigarette smoking causes cancers at a minimum of 12 different sites, including lung, oral cavity, pharynx, esophagus, pancreas, larynx, urinary bladder [83]. Mortality among current smokers is 2 to 3 times as high as that among persons who never smoked. Moreover, it has been described that male smokers are at higher risk for death from prostate cancer and female smokers are at higher risk for death from breast cancer [84].

Alcohol

Moderate alcohol consumption seems to have a cardioprotective effect in subjects free from CVD. The linkage is described by a J-shaped dose effect-curve: in case of excessive alcohol intake all-cause mortality and cardiovascular events are increased [12]. Larger amounts can cause dilated cardiomyopathy and heart failure [85]. Several potential cardioprotective effects of low alcohol doses have been hypothesized, such as decreased inflammation, decreased platelet aggregation and function, reduced myocardial ischemia-reperfusion damage, effects on coagulation factors, endothelial events, elevated high-density lipoprotein (HDL) cholesterol levels and effect on anti- and proapoptotic pathways [12].

The effect of alcohol on cancer development appears to be modulated by polymorphisms in genes encoding enzymes for ethanol metabolism (*e.g.*, alcohol dehydrogenases, aldehyde dehydrogenases, and cytochrome P450 2E1), folate metabolism, and DNA repair [86,87]. Moreover, acetaldehyde, the main metabolite of ethanol, may exert genotoxic effect [86]. Alcohol intake has been linked to hepatocellular carcinoma (HCC). The relationship could be a direct toxic effect, or an indirect one, mediated by cirrhosis, a predisposing factor for HCC [88]. Causal link has been established also between alcohol and cancers of the oral cavity, pharynx, larynx, esophagus (squamous cell carcinoma), colorectum and breast (pre- and post-menopause) [89,90].

Unhealthy diet

Increased cardiac risk has been established for an unhealthy diet, which is common in western countries, and is characterized by a high amount of saturated fat, red meat, sugar and processed food [39,91]. Evidences indicate that higher intake of most dietary saturated fatty acids (SFAs) increases blood levels of LDL cholesterol and the LDL to HDL ratio, resulting in an increased risk of coronary heart disease (CHD) [92,93]. Replacing 5% of energy intake from saturated fats with equivalent energy intake from either polyunsaturated fatty acids (PUFAs), monounsaturated fats (MUFAs), or carbohydrates from whole grains was associated with 25%, 15%, and 9% lower risk of CHD, respectively [92]. Excessive intake of dietary trans fatty acids (TFA) is an important risk factor for cardiovascular events as well as a risk factor for cancer and diabetes [94]. Direct carcinogens, such as aflatoxins and nitrosamines, may be present in food and can act directly on DNA, causing mutations, deletions and insertions [31].

On the contrary, fruit and vegetable intakes are associated with reduced risk of CVD, cancer and all-cause mortality [95]. Higher whole grain intake is associated with a reduced mortality, especially deaths due to CVD [96].

Dietary fiber and fruit and vegetable intakes have been shown to lower blood pressure, cholesterol levels, inflammation and platelet aggregation, and to improve vascular and immune function [95]. Antioxidant, antibacterial, and antiviral effects as well as positive modulation on steroid hormone concentrations and hormone metabolism have also been observed [97]. High-fiber foods may

have a beneficial effect on gut microbiota [98]. Antioxidants in fruit and vegetables may neutralize reactive oxygen species and reduce DNA damage [97]. In this regard, a diet rich in vegetables and whole grains such as the Mediterranean diet is associated with a lower incidence and mortality from breast cancer [99,100].

Sedentary lifestyle

Several large studies have demonstrated that mortality is inversely related to the level of physical activity [101,102]. In particular, physical activity is associated with a 20% to 30% lower risk of CHD [103]. Regarding the amount of physical activity required to reduce CVD risk, it has been reported that 150 min of

weekly moderate activity reduces mortality by 14%, 300 min by 20% [104]. A similar inverse dose-dependent association between physical exercise and risk of HF has also been described [105]. In addition to cardioprotective effects, exercise promotes a modest reduction in the incidence of prostate, breast, bladder, esophageal, kidney, and endometrial cancers [31,106]. Physical activity also reduces cancer mortality and recurrence in cancer survivors [107,108]. For each 15-min increment of daily physical activity, cancer mortality decreases by 1% [109]. The underlying mechanisms likely relates to reduction in obesity, metabolic syndrome, diabetes, hypertension and hyperlipidemia. Furthermore, in patients with cancer, exercise prevents cardiac-related drug toxic-

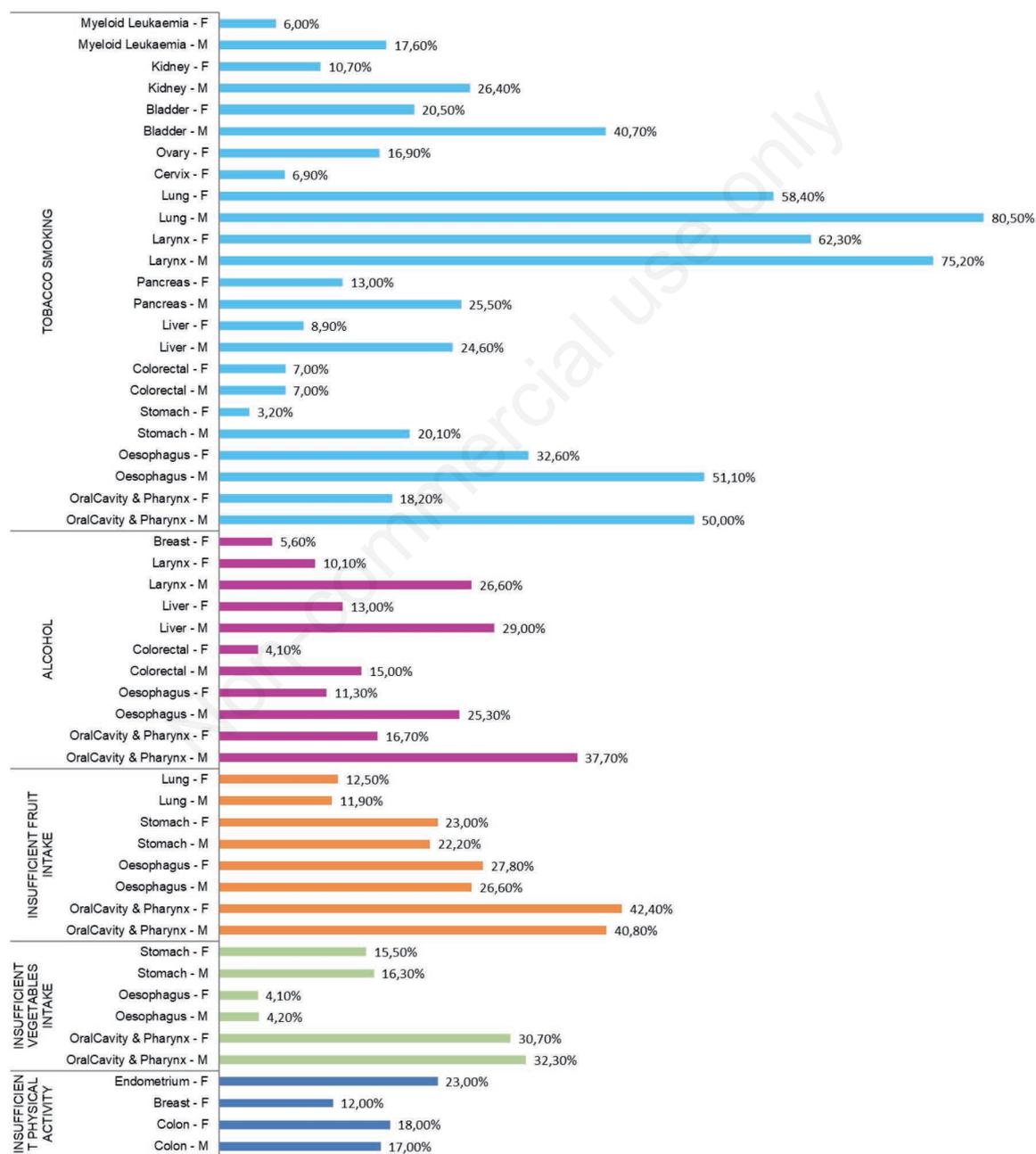


Figure 2. Median of population attributable fractions, expressed as a percentage (PAF%), reported for modifiable risk factors associated with specified cancers. F, female; M, male. See the text for details.

ty thanks to better cardiovascular health and greater cardiac reserve [39].

Development of malignancy in patients with CVD: “the Reverse Cardio-Oncology”

Due to advancements in management of ischemic heart disease and chronic heart failure, the prognosis of patients affected has improved significantly, with more patients surviving for an extended time, thus increasing the importance of detection and treatment of non-cardiac diseases. It has been described that patients with HF have an increased risk of cancer and their prognosis is worse compared with that of cancer patients without HF [2,3]. Moreover, increased risk of malignancy was identified in patients with HF after myocardial infarction (this trend was seemingly more evident among patient with reduced left ventricular ejection fraction) [110], patients undergoing cardiac interventions or procedures, and patients after a thrombotic event [111]. The specific mechanism for this relationship has not been established.

As already described above, CVD and cancer both share proinflammatory pathways or impaired cellular metabolic profiles [12]. It has also been hypothesized that impairment in immunity after HF development predisposes to higher cancer risk [110]. In the context of myocardial infarction, necrotic cells release danger sig-

nals, resulting in an intense inflammatory response [112]. In case of cardiac damage, tissue hypoxia and shear stress may trigger epigenetic response. Epigenetic mechanisms, such as DNA methylation, histone modifications, and RNA-based mechanisms, are also extensively associated with cancer, including colorectal, breast, and various other malignancies [113]. Tissue hypoxia in patients with CVD can also stimulate tumor growth and progression *via* HIF-1 pathway [111]. Higher incidence of cancer was reported among ischemic stroke survivors (20% in 1 year and 40% at 2 years) [114]. Hypercoagulability secondary to thrombin activation can promote angiogenesis, tumor growth and the development of metastasis in these patients [111].

Clonal hematopoiesis (CHIP), is defined as the presence of an expanded somatic blood-cell clone without other evidence of hematologic malignancy, is a common condition among older persons and is associated with an increased risk of hematologic neoplastic disease [115]. One of the most frequently abnormality encountered in hematopoietic clones is represented by mutation in Ten-Eleven Translocation-2 (TET2) genes. TET2 deficiency is associated with elevated concentration of IL-1 β and with the development and poor prognosis of heart failure [36]. The presence of CHIP in peripheral-blood cells was also linked with almost a doubling of the risk of coronary heart disease in humans and with accelerated atherosclerosis in mice [115]. Somatic mutations in hematopoietic stem cells represent a common path for cancer and CVD [36].

Regarding the pharmacological treatment of CVD and cancer

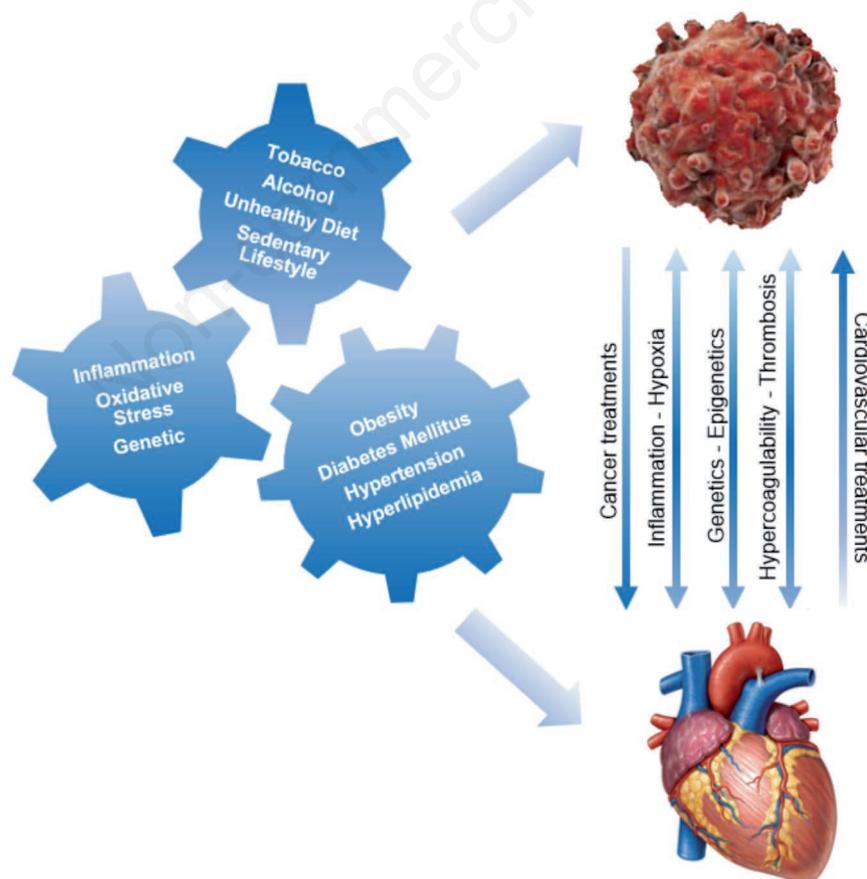


Figure 3. Dynamic interplay between cancer and cardiovascular disease. See the text for details.

development, data are inconclusive and conflicting. There is currently no evidence that cardiovascular medications are closely linked to an increased risk of cancer. It has been suggested an increased risk of cancer development in case of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) combination [116]. Individually, the use of ACE-Is or ARBs has been linked to a 6% decreased incidence of colon cancer [117]. Instead, in the Life After Cancer Epidemiology (LACE) Study cohort, ACE-Is exposure was associated with breast cancer recurrence [118]. Although still limited, evidence suggests that increasing exogenous insulin dose is associated with an increased cancer risk in people with type 2 diabetes treated with insulin monotherapy [119].

Thus, need exists to update the current understanding of the potential effect on risk of future cancer of cardiovascular medications.

Development of CVD in patients with cancer

On the basis of shared risk factors, the prevalence of heart disease in patients with cancer could be increased also at the time of cancer diagnosis, before treatment begins. It has been observed that calcium scores of the coronary arteries are higher in a cohort of patients with breast cancer pre-radiotherapy than in age-matched healthy controls, suggesting that breast cancer patients may also bear a higher risk of developing coronary heart disease independently from treatment [120]. Cancer cells can induce a proatherosclerotic, prothrombotic and hypercoagulable state, due to production of various pro-inflammatory cytokines, increased concentration of LDL into vascular intima, and increased levels of coagulation molecules, leading to newly unstable formed plaques [121]. On the other hand, cancer is also a prothrombotic disease, favoring thromboembolic events as deep vein thrombosis and pulmonary embolism [122].

Cardiotoxicity is defined as the 'toxicity that affects the heart', including a direct effect of cancer drugs on the heart but also an indirect effect due to enhancement of hemodynamic flow abnormalities or due to thrombotic events [123,124]. As a consequence, cardiac adverse events, such as HF, hypertension, myocardial infarction, thromboembolism, pericardial effusion, QT prolongation, and bradycardia, may cause premature discontinuation of effective oncologic treatments, thus becoming an obstacle in the battle against cancer [125]. Genetic and epigenetic factors may influence the cardiotoxicity susceptibility (Figure 3) [123].

Management strategies

Prevention of CVD and cancer: better safe than sorry

In 2010 the American Heart Association has defined the concept of *ideal cardiovascular health*, according to 7 health behaviors, including nonsmoking, physical activity at goal levels, body mass index <25 kg/m², healthy dietary intake, untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm Hg, and fasting blood glucose <100 mg/dL [126]. It has been demonstrated that achieving the goals for a higher number of ideal health parameters is associated with more favorable health outcomes [127]. In this regard, in the Atherosclerosis Risk in Communities (ARIC) Study, a strong inverse relationship was identified between the number of ideal health metrics met at baseline and incident CVD over 20 years of follow up [128]. Additionally, obedience to the 7 ideal health metrics resulted also linked with lower cancer incidence. Participants

meeting goals for at least 6 of the 7 health metrics had 51% lower risk of incident cancer [129]. Accordingly, the identification and management of risk factors allow to reduce both CVD and cancer. As is well known, prevention is better than cure.

Management of cancer patients: the role of cardio-oncology

For many malignancies, the disease has shift from an incurable illness to a chronic condition. Due to the aging of the population, a common occurrence of risk factors, and the administration of cancer therapies to more elderly individuals with pre-existing CVD, it is increasingly likely that a patient may simultaneously have both CVD and cancer [123]. An optimal management of these two diseases is not anymore linked to survival prospects, but also to quality of life during the years earned.

In this setting, cooperation between oncologists and cardiologists is essential to ensure optimal patient management, adopting a holistic and patient-tailored approach.

As previously mentioned, cardiovascular comorbidity can adversely affect cancer outcome. Patients with CVD and/or cardiac risk factors may receive less aggressive cancer treatment. Early identification by the oncologist of patients at risk for cardiotoxicity and optimal management of cardiovascular problems by cardiologists, should be the initial strategy in the development of personalized antineoplastic therapies [123,130].

On the other hand, the appropriate treatment of CVD may also be affected by the presence of cancer. In coronary heart disease patients receiving dual antiplatelet therapy (DAPT), the high risk of bleeding due to the presence of cancer could lead to the withdrawal of aspirin or other antiplatelet drug, with a potential increase of risk of new cardiovascular events. In presence of an acute coronary syndrome, a difficult decision may have to be taken between conservative medical management or early coronary angiography and revascularization [131,132]. In patients with severe symptomatic aortic valve stenosis and cancer, not infrequent in older population, the timing and the choice between aortic valve intervention (surgical or transcatheter) and conservative medical treatment is closely influenced by the type and site of cancer, stage, and outcome [133]. Even in these cases the role of a cardio-oncology team could be decisive. Provide the best treatment with the least possible side effects is always an important task.

Risk stratification and early identification of high-risk patients

The first step is to stratify the risk of cancer patients according to the presence of established atherosclerotic vascular disease, or other cardiac diseases, diabetes mellitus, chronic kidney disease and traditional cardiovascular risk factors (Table 1) [134,135]. HF and/or arrhythmias should also be investigated, especially atrial fibrillation [123]. Identification of high-risk patients is essential in order to apply proper arrangements, including optimization of cardiovascular risk factors and pre-existing disease, planning a more stringent follow up during therapy [136]. Adverse effects may occur even after years, therefore long-term surveillance of cancer survivors is mandatory [137]. Several antineoplastic medications potentially affect the cardiovascular system (Table 2) [123,138-145]. Radiotherapy can also cause cardiovascular damage [146]. Hypertension is the most common comorbidity in cancer patients. As underlined before, pre-existing hypertension is known to increase the risk of other cardiac adverse events, in particular HF [80]. Furthermore, CAD, hypertension, and diabetes are the strongest predictors of left

Table 1. Risk stratification of high risk patients. See the text for details.

Risk factors for developing cardiotoxicity
Young (<18 years) or advanced age (> 50 years for trastuzumab; >65 years for anthracyclines)
Lifestyle risk factors
- Smoking
- High alcohol intake
- Sedentary habit
Established cardiovascular disease
- Arterial hypertension
- Heart failure (with either preserved or reduced ejection fraction)
- Asymptomatic LV dysfunction (LVEF <50% or B-type natriuretic peptide > 100 pg/ml, or N-terminal pro-B-type natriuretic peptide > 400 pg/ml with no alternative cause)
- CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischemia)
- Moderate to severe valvular heart disease with LV hypertrophy or LV impairment
- Hypertensive heart disease with LV hypertrophy
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy Restrictive cardiomyopathy
- Cardiac sarcoidosis with myocardial involvement
- Significant cardiac arrhythmias (<i>e.g.</i> atrial fibrillation, ventricular tachyarrhythmias)
Chronic kidney disease
Diabetes mellitus
Obesity
Hypercholesterolemia
Previous cardiotoxic cancer treatment:
- Prior anthracyclines use
- Prior radiotherapy to chest or mediastinum
Simultaneous chemotherapy with other potential cardiotoxic agents

LV, left ventricular; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

ventricular dysfunction secondary to anthracycline cardiotoxicity [124,136]. Again CAD, hypertension, obesity, and smoking are well-known risk factors for developing left ventricular dysfunction among patients with breast cancer receiving trastuzumab [147]. Smoking cessation is extremely important, so as a tight glycemic control in diabetic patients [146].

Recommended cardiovascular drugs in patients on cancer treatment

Beta-blockers and ACE-Is have been reported to be protective against cardiac toxicity and are recommended in high-risk patients or in patients who develop cardiotoxicity [146]. The prophylactic use of these medications in patient planned for chemotherapy, radiation, or targeted therapy has also been hypothesized [148]. Ivabradine may be a possible additional treatment for selected patients [149]. The effects and possible benefits of sacubitril/valsartan need to be investigated in large scale studies [150].

It is widely recognized that treatment of dyslipidemia is key for cardiovascular prevention, both primary and secondary [151]. In addition to potent LDL-cholesterol lowering, statins have several pleiotropic effects, such as anti-inflammatory and antioxidant properties. A potential anti-cancer role for statins is also emerging, but further studies are needed to identify its therapeutic potential [12,15]. Evidence shows improvement in cancer-specific and overall-survival in cancer patients who are on statins either before or after the time of diagnosis [152,153]. Recently, it has been highlighted that approximately 50% cancer survivors remain untreated although they are eligible for statin therapy. This underlines the need for greater attention to prevent atherosclerotic CVD among these patients [154,155]. Similarly to statin, potential beneficial

effects on cancer recurrence have been identified also for aspirin and for metformin, due to their positive effects on AMPK [15,156]. Randomized dedicated trials are ongoing [156,157]. Anti-inflammatory medications - in particular, statins, colchicine, and aspirin - show also great promise for the prevention of radiation-induced CVD. Nonetheless, direct large-scale studies are called for [158]. In addition to drugs, exercise seems to counteract the negative effects due to chemotherapy, such as fatigue, pulmonary and immune system dysfunction, lymphoedema and toxicity for the heart [159,160]. Furthermore, higher cardiorespiratory fitness (CRF) is independently associated with lower risk of cancer mortality in men with documented CVD who develop cancer, suggesting that tailored exercise rehabilitation programs aimed at encouraging regular physical activity may improve the prognosis of these patients [161,162]. In this regard, mobile health technology, through the use of devices and applications, has the potential to become a powerful healthcare tool [163]. A classification of cancer therapy-induced myocardial toxicity has been proposed by the Royal Brompton Hospital. Depending on the degree of severity, for each of the 6 classes identified, a management strategy has been defined (Table 3) [164].

Previous data have shown that administration of cardiovascular treatments in patients exposed to cardiotoxic drugs can reduce symptomatic CHF and left ventricular ejection fraction (LVEF) and may allow at least partial recovery in whom developing left ventricular systolic dysfunction (LVSD) [165]. In this regard, in a cohort of 2625 patients receiving anthracycline-containing therapy, the overall incidence of cardiotoxicity was 9%. After introduction of HF therapy with ACE-Is and beta-blockers, at least a partial recovery of LVEF was observed in 82% of patients who developed cardiotoxicity [166]. Integrated patient management according to

Table 2. Cardiotoxicity of antineoplastic medications.

Class	Cancer control mechanism	Cardiovascular toxicities	Mechanism of cardiotoxicity	Cardiovascular treatment considerations
Anthracyclines				
Doxorubicin, idarubicin, epirubicin, mitoxantrone	DNA damage, lipid peroxidation, p53 activation, induction of apoptosis in response to topoisomerase II inhibition	HF and LVSD (3-48%), bradycardia, sinus tachycardia, atrioventricular block, conduction disturbances, AF, supraventricular tachycardias, ventricular tachycardia/fibrillation, acute pericarditis	<ul style="list-style-type: none"> - DNA damage due to ROS production - Changes in iron metabolism and calcium signaling - Inhibition of topoisomerase 2-β in cardiomyocyte with myocyte destruction 	ACE-Is/ARBs BBs Aldosterone antagonists Statins Sacubitril/valsartan
Antimetabolites				
Cyclophosphamide, ifosfamide, cisplatin, melphalan	Induction of apoptosis due to interaction with DNA	HF, bradycardia, atrioventricular block, AF, supraventricular tachycardias, ventricular tachycardia/fibrillation, pulmonary veno-occlusive disease (cyclophosphamide), acute pericarditis, CAD and ischemic stroke (cisplatin)	<ul style="list-style-type: none"> - Direct endothelial injury; oxidative stress and mitochondrial damage - GSTP deficiency - ↓ expression of heart fatty acid-binding protein and carnitine palmitoyltransferase - Platelet activation and aggregation 	N/A
Antimicrotubule agents				
Paclitaxel Docetaxel	Inhibition of mitosis	HF, bradycardia, atrioventricular block, conduction disturbances, AF, supraventricular tachycardias, ventricular tachycardia/fibrillation (paclitaxel), ischemic stroke (paclitaxel)	<ul style="list-style-type: none"> - Damage on Purkinje system or autonomic control - Induction of histamine release - Enhanced metabolism of doxorubicin toxic species 	Corticosteroids to avoid hypersensitivity reaction
Monoclonal antibody				
Trastuzumab	ErbB2 inhibition	HF and LVSD (1.7-20.1%), arterial hypertension (4%), arrhythmias, thromboembolic events (2-3%)	<ul style="list-style-type: none"> - Impaired ErbB/Neuregulin-1-activated pathway: ↓ cardiomyocyte function and survival - Inhibition of Notch signaling: ↓ cell proliferation and cell survival - Impaired intracellular antioxidant/oxidant balance - ↑ circulating angiotensin II 	Avoid concurrent and sequential administration of anthracycline; ACEIs and/or BBs if reduced LVEF
Pertuzumab	ErbB2 inhibition	HF and LVSD (0.7 - 1.2%), thromboembolic events	Similar to trastuzumab	ACEIs and/or BBs if reduced LVEF
Bevacizumab	VEGF inhibition in tumor vasculature	Arterial hypertension (7.5%), HF (1.6 - 4%), CAD (3.8%), arterial and venous thromboembolic events (3-21%), thrombotic microangiopathy	<ul style="list-style-type: none"> - Disruption of VEGF-mediated angiogenesis, ↓ capillary density, endothelial dysfunction, oxidative stress - Loss of contractile function in cardiomyocyte - ↑ arterial pressure 	Standard antihypertensive medications (first line treatment: ACE-Is). Avoid nondihydropyridine calcium channel blockers (↑ levels of plasma bevacizumab due to cytochrome P450 3A4 inhibition)
Rituximab	Killing CD20+ cells	HF, CAD, Bradycardia, Atrioventricular block, Atrial Fibrillation, Ventricular tachycardia/fibrillation	<ul style="list-style-type: none"> - ↑ Cytokine release, particularly IL-6 - Neurohormonal activation, excessive sympathetic stimulation and microvascular dysfunction - ↑ reticulin fiber formation in cardiomyocytes, ↓ myocardial contractility and conduction 	N/A
Small molecule tyrosine kinase inhibitors				
VEGF inhibitor Cabozantinib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib	VEGF inhibition in tumor vasculature	Arterial Hypertension, HF, QT prolongation > 500 ms, Torsade de pointes (pazopanib, vandetanib), CAD, Vasospasm (sorafenib), AF, thromboembolic events	↓ nitric oxide; microvascular rarefaction; ↑ endothelin-1	ACE-Is/ARBs; dihydropyridine calcium-channel blockers for hypertension

To be continued on next page

Table 2. Continued from previous page.

Class Specific agents	Cancer control mechanism	Cardiovascular toxicities	Mechanism of cardiotoxicity	Cardiovascular treatment considerations
ALK inhibitors Alectinib, crizotinib	Inhibition of ALK activity: ↓ cell proliferation, ↓ angiogenesis	QT prolongation >500 ms, bradycardia	↓ If (pacemaker current) in sinoatrialnodal cells	Avoid nodal blockingagents
BTK inhibitors Acalabrutinib, ibrutinib	Inhibition of the BTK pathway	AF, ventricular arrhythmias; arterial hypertension	- Inhibition of cardiac PI3K–Akt pathway - Atrial fibrosis - Dysregulated calcium handling	Avoid drugs that interact with the CYP 3A4 system and p-glycoprotein
BCR-ABL Imatinib, nilotinib, dasatinib, bosutinib ponatinib	Target BCR-ABL fusionprotein, c-Kit, and PDGF receptors	CAD, HF, arterial hypertension; QT prolongation; pulmonary hypertension (nilotinib, dasatinib); pleural effusion (imatinib, dasatinib); pericarditis and pericardial effusion (bosutinib); PAD (ponatinib, nilotinib); thromboembolic events (ponatinib).	- Accelerated atherosclerosis and endothelial dysfunction - Thrombotic microangiopathy - Hyperlipidemia, hyperglycemia	Statins; antihyperglycemics
BRAF inhibitors Dabrafenib, Vemurafenib	Selective inhibition of B-raf which blockscellular proliferation	QT prolongation > 500 ms (1.6%), Torsade de pointes	- Impaired VEGF signaling and NO production - Cardiomyocyte hypertrophy and pathological remodeling	N/A
MEK inhibitors Binimetinib, Combimetinib, trametinib	Allosteric inhibition of MEK affecting the MAPK pathway	Arterial hypertension; myocardial dysfunction and heart failure; QT prolongation	- Inhibition of ERK1/2 activation in the heart - Impaired VEGF signaling and NO production - Cardiomyocyte hypertrophy and pathological remodeling	N/A
Immunomodulators				
Thalidomide	- ↑ T cell proliferation and NK cell function, ↑ IFN-γ and IL-2 levels, ↓ production of pro-inflammatory cytokines (in particular TNF-α) - ↓ angiogenesis	Bradycardia, atrioventricular block, arterial and venous thromboembolic events (8–22.5%)	- Inhibition of TNF-expression and activity leading to overactivity of the parasympathetic system (dorsal motor neurons of the vagus nerve) - Endothelial cell injury and dysfunction, hypercoagulability	Aspirin or prophylactic LMWH may be considered
Lenalidomide		Arterial and venous thromboembolic events (4–9%), CAD (0–1.9%), arterial hypertension (7–8%), hypotension (7%)	- Endothelial cell injury and dysfunction, hypercoagulability	
Proteasome inhibitors				
Carfilzomib	Irreversible proteasome inhibition by binding to the catalytic site: accumulation of damaged and abnormal proteins	HF (11–25%), CAD, ventricular tachycardia/fibrillation, arterial hypertension (5–27%), pulmonary hypertension (1%)	- ↓ eNOS activity and ↓ NO levels: impaired vasodilation, endothelial dysfunction, oxidative stress - adverse effects on vascular smooth muscle: plaque instability	Traditional heart failure treatment
Immune checkpoint inhibitors (ICIs)				
PD-L1 inhibitors Atezolizumab, avelumab	Binding to host immuneneegative regulation receptors involved in malignancy	Myocarditis, Pericarditis, Takotsubo cardiomyopathy, Dilated cardiomyopathy	- Molecular mimicry (shared antigen between the tumor and myocardium) - Accelerated atherosclerosis	Corticosteroids; standard heart failure therapiesif reduced LVEF; in corticosteroid resistant myocarditis consider infliximab, intravenous immunoglobulin, plasmapheresis, abatacept, alemtuzumab, anti- thymocyte globulin, mycophenolate
PD-1 inhibitors Nivolumab, pembrolizumab				
CTLA4 inhibitor Ipilimumab				
Hormone therapy				
Aromatase inhibitors Anastrozole, letrozole	Inhibition of estrogen synthesis in hormone- dependent tumors	CAD, arterial hypertension, thromboembolic events	↓ Cardioprotective effect mediated by estrogen on serum lipid concentrations, coagulation, fibrinolytic systems, antioxidant systems, NO and prostaglandins production	Statins, BBs and/orACE-Is, metformin to manage hyperlipidemia, hypertension, and diabetesdeveloped during endocrine therapy

HF, heart failure; LVSD, left ventricular systolic dysfunction; AF, atrial fibrillation; ROS, radical oxygen species; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, Beta-blockers; CAD, coronary artery disease; GSTP, Glutathione S-transferase P; N/A, specific considerations not available; LVEF, left ventricular ejection fraction; ErbB2, erb-b2 receptor tyrosine kinase 2; VEGF, vascular endothelial growth factor; IL, Interleukin; ALK, ALK receptor tyrosine kinase; BTK, Bruton tyrosine kinase; PI3K–Akt, phosphatidylinositol 3-kinases - AKT serine-threonine kinase; BCR-ABL, fusion complex between breakpoint cluster region protein- Abelson murine leukemia viral oncogene homolog 1; PAD, peripheral artery disease; PDGF, platelet-derived growth factor; BRAF, B-Raf proto-oncogene; MEK, Mitogen-activated protein kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinases; TNF, tumor necrosis factor; LMWH, low-molecular-weight heparin; NK, natural killer; IFN-γ, interferon gamma; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PD-L1, Programmed Death-Ligand 1; PD-1, Programmed cell death protein 1; CTLA4, cytotoxic T lymphocyte antigen 4.

the cardio-oncology approach is promising and dedicated cardio-oncology services have been developed across the globe. But despite the growing interest in this emerging field, there is a paucity of data about their structure, activity and impact of such clinics on patient care and clinical outcomes. In the 5-year real-world experience reported by Pareek *et al.* [164] from 128 cancer patients with LVSD referred to the cardio-oncology clinic, 88% of patients were deemed fit for continuation of cancer therapy after cardiovascular optimization, while an improvement of LVSD after 1 year of follow-up was observed in 94% of patients. Similarly, encouraging results have been reported by Kappel *et al.* [167].

On the basis of what has been reported, despite the absence of randomized evidence, the use of a multidisciplinary approach must be supported.

Conclusions

In recent decades we have witnessed significant progress in the therapy of CVD and Cancer. With increasing patient survival, it is now increasingly evident that these two apparently so distant diseases often share the same risk factors having generally a chronic inflammatory state as a unifying element. Seen from this perspective, preventive cardiology is of primary importance: controlling obesity, hypertension, dyslipidemia and diabetes, fighting against smoking, sedentary lifestyle, and the unhealthy diet in patients with cancer may prevent the onset of cardiotoxicity while in patients with CVD helps to prevent cancer. Given the epidemiological relevance of the two morbid conditions, a more stringent control of these risk factors is urgent for the health of the general population. A better collaboration between cardiologists, oncologists and primary care doctors can improve the understanding of this two-way relationship and adopt the most effective and safest prevention strategy.

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Table 3. Management strategies according to Royal Brompton Hospital myocardial toxicity class.

Cardiotoxicity group	Classification	Definition Oncology therapy	Management strategies Cardiology therapy
1 Early biochemical cardiotoxicity	New BNP or troponin I rise but with normal cardiac imaging (If normal at baseline, then any increase above the upper limit of normal. If abnormal at baseline, then 20% rise).	Continue	Cardio-oncology review. Consider closer monitoring, or start low-dose ACE-Is or BBs cardioprotection.
2 Early functional cardiotoxicity	New reduction in GLS or grade III-IV diastolic dysfunction and normal biomarkers.	Continue	Cardio-oncology review. Consider closer monitoring, or start low-dose ACE-Is or BBs cardioprotection.
3 Early mixed cardiotoxicity	Normal LVEF with abnormal biomarkers and GLS/diastolic dysfunction.	Continue	Cardio-oncology review. Start low-dose ACE-Is or BBs cardioprotection.
4 Symptomatic HFpEF	Symptomatic HFpEF.	Interrupt and review risk/benefit*	Cardio-oncology review. Diuretic for fluid congestion. ACE-Is or BBs cardioprotection if continuing cancer therapy.
5 Asymptomatic LVSD	New LVEF reduction to <50%, or a reduction in LVEF >10% to a LVEF <55% [§] .	Review and balance risk/benefit*	Cardio-oncology review. Start ACE-Is and/or BBs and up-titrate to 50-100% target dose for HF as tolerated.
6 Symptomatic LVSD	Symptomatic reduction in LVEF <50%, or a reduction in LVEF >10% to a LVEF <55% [§] .	Interrupt and review risk/benefit*	Cardio-oncology review. Start ACE-Is and/or BBs and up-titrate to 100% target dose for HF as tolerated ^{‡#} .

BNP, brain natriuretic peptide; ACE-Is, angiotensin-converting enzyme inhibitors; BBs, Beta-blockers; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVSD, left ventricular systolic dysfunction. *Continuing cardiotoxic cancer therapy may be suitable in selected cases depending on the risk/benefit ratio, severity of left ventricular impairment, symptoms, cancer stage and response. [§]If LVEF fall is to >50%, then incorporate either biomarker elevation or GLS reduction (<-18% if normal at baseline, or <15% relative reduction of GLS if reduced at baseline).

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