Management of Cardiac Rhythm Disorders in Cardio-oncology

Letizia Rosa Romano [1,2] Alberto Polimeni [1,2] Ciro Indolfi [2,3] and Antonio Curcio [1,2]

1. Department of Pharmacy, Health and Nutritional Sciences, Università della Calabria, Rende, Italy; 2. Division of Cardiology, Annunziata Hospital, Cosenza, Italy; 3. Division of Cardiology, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy

Abstract

Arrhythmias and cancer are two pathological conditions that often coexist due to a patient's pre-existing comorbidities, or toxicity linked to anti-neoplastic drugs, and both are often characterised by poor prognosis. Cardio-oncology is a new interdisciplinary field that focuses on the cardiovascular health of cancer patients, especially those undergoing cancer treatment. Furthermore, cardiotoxicity can cause arrhythmias through primary and secondary mechanisms. Chemotherapy drugs have been shown to directly affect molecular pathways associated with arrhythmia development, as well as indirectly through mechanisms involving ischaemia or inflammatory injury to the heart. Understanding how to prevent and to treat these electrophysiological issues in cancer is an important challenge for cardio-oncologists. This review explores the intersection between cardio-oncology and electrophysiology, the various cardiac cell types implicated in the development of arrhythmias during cancer, the interplay between arrhythmias and cancer pathogenesis, and the need for the implantation of electronic devices along with their associated risks.

Keywords

VF, AF, tumour, anti-neoplastic drug, cancer-related cardiovascular disease

Received: 14 April 2024 **Accepted:** 16 August 2024 **Citation:** *Arrhythmia & Electrophysiology Review* 2025;14:e05. **DOI:** https://doi.org/10.15420/aer.2024.20
Disclosure: The authors have no conflicts of interest to declare.
Correspondence: Antonio Curcio, Division of Cardiology, Department of Pharmacy, Health and Nutritional Sciences, Università della Calabria, Via Pietro Bucci, 87036 Rende CS, Italy. E: antonio.curcio.cardio@unical.it

Cardiovascular disease (CVD) is the leading cause of death in Western countries. The significant improvements in cardiovascular therapy, both pharmacological and device-based, have extended lifespans. However, chronic conditions, such as ischaemic cardiomyopathy and heart failure (HF), often coincide with additional comorbidities, including cancer. This overlap presents patients with multiple evolving challenges stemming from the underlying cardiovascular condition, the cancer itself, or combined complications, such as thromboembolism or cardiotoxicity from anti-neoplastic agents.

Furthermore, an increasing trend of CVD burden among cancer patients hospitalised between 2003 and 2014 has been observed.[1] This uptrend underscores the importance of monitoring and addressing cardiovascular risk factors in cancer patients to improve overall treatment outcome and patient survival, and underlines the need for integrated care approaches to manage both cancer and cardiovascular health.

Chemotherapy can induce cardiac remodelling more frequently if anthracycline and tyrosine kinase inhibitors are part of the protocol. Specifically, anti-neoplastic drugs can cause fibrosis and dilatation, worsen both left ventricular (LV) and right ventricular systolic and diastolic function, and, finally, generate pulmonary hypertension.[2] Beavers et al. highlighted the increasing necessity to better understand cardiac and cancer drug interactions due to the evolving treatment scenario in these fields.[3]

Biomarker assessment has proven to be a valuable tool for the early detection of worsening prognosis and for ongoing patient monitoring. The advancements in chemotherapy, radiotherapy and surgical procedures may also heighten thromboembolic risk. Biological agents are emerging as the next frontier in cancer treatment, offering promising oncological outcomes with fewer cardiovascular side-effects.[4]

Herrmann et al. additionally emphasised the critical relationship between cancer treatment and the occurrence of arrhythmia.[5] Cancer therapy-related cardiovascular toxicity (CTR-CVT) can manifest as several forms of cardiac arrhythmia, including bradycardia, which can range from benign and asymptomatic cases to more severe forms such as complete heart block, sinus tachycardia, supraventricular tachycardia (SVT), AF or flutter, ventricular arrhythmia (VA) and other abnormalities that include QT segment prolongation (QT interval corrected using the Fridericia formula [QTc] >500 ms), ST-segment and T wave alterations. More specifically, arrhythmias in cancer patients may arise from cardiomyopathies caused by drugs or radiation, electrolyte imbalance (notably potassium loss) due to renal complications from anti-neoplastic and antibiotic drugs, and hypoxia due to underlying pulmonary disease, pulmonary or pleural tumour involvement, or infections resulting in significant pleural and pericardial effusion.[6] Involvement of the cervical lymph nodes can also, although rarely, lead to carotid sinus syncope.[7]

The aim of this review is to outline the interplay between cardio-oncology and electrophysiology, the primary cell populations implicated in both

Table 1: Level of Risk of Oncologic Treatments in AF Development or Worsening

Class or Drugs	Specific Agents Responsible for CTRCD	Risk
Alkylating agents	Cyclophosphamide Busulfan Melphalan	Moderate
Anthracyclines	Doxorubicin	High
Anti-metabolites	Capecitabine Gemcitabine 5-fluorouracil	Moderate
Anti-microtubule agents	Paclitaxel	Low
Immunomodulatory drugs	Lenalidomide Thalidomide	Moderate
Platinum compounds	Cisplatin	High
Proteasome inhibitors	Bortezomib Carfilzomib	Very low

CTRCD = cancer therapy-related cardiac dysfunction.

tumour development and the maintaining of arrhythmic circuits, the connection between arrhythmias and cancer pathogenesis, and the benefits and risks associated with the use of electronic devices.

Electrophysiology and Cardio-oncology

In July of 2021, the American Heart Association released a scientific statement regarding the recognition, management and prevention of autonomic disorders and arrhythmias in cardio-oncology.[8] AF has been described as the most encountered arrhythmia, but ventricular repolarisation abnormalities and QT prolongation, VAs and bradycardia, including heart block, can also occur. These arrhythmias may be electrophysiological signs of cardiotoxicity caused by cancer treatment or of the cancer's pathogenesis and progression.[9]

In particular, AF is linked to significant morbidity and mortality in both the general population and in cancer patients, even when accounting for traditional risk factors.[9,10] Case–control studies have reported a correlation between AF and malignancy, particularly colon and breast cancer.[11] Chronic cancer-related inflammation plays a pivotal role in the increased incidence of AF in this population.[12,13] Chemotherapy is also associated with atrial arrhythmias (*Table 1*).[12]

Chemotherapeutic Drugs and Mechanisms Associated with Arrhythmias

Fluorouracil

Fluorouracil is an anti-metabolite in which the hydrogen at the uracil C-5 position is replaced with fluorine. It primarily inhibits thymidylate synthase, which disrupts the intracellular deoxynucleotide pools necessary for DNA replication and has anti-cancer effects. Other potential modes of action include incorporation into RNA, where it may replace uracil causing RNA disruption; similarly, inclusion into DNA may cause fragmentation. Fluorouracil is used to treat gastrointestinal, head and neck cancers. It is known to possibly cause coronary vasospasm and AF as a consequence of ischaemia. Fluoropyrimidine-treated patients may also experience arrhythmias, including SVT, such as AF and atrial flutter, VA and VF.[14]

Anthracyclines

Anthracyclines are common anti-neoplastic drugs used to treat various malignancies, including breast cancer, leukaemia and lymphoma. This group destroys the process of redox cycling, which leads to the creation of reactive oxygen species (ROS) and, consequently, to damage to the DNA. Cardiomyopathy and congestive HF are the most frequent cardiovascular complications due to their use, and arrhythmias may occur as a consequence of indirect effects such as LV dysfunction.[15] Anthracyclines are widely used chemotherapy drugs but are limited by dose-dependent cardiotoxicity. Recent studies[16-18] have identified topoisomerase 2β (Top2β) as a key factor in this toxicity, given that it induces DNA damage and mitochondrial dysfunction. Therefore, Top2β is emerging as a promising target in the prevention of anthracycline-induced cardiotoxicity.[16] In addition, these chemotherapeutic agents prolong the action potential of Purkinje fibres, increasing the risk of arrhythmias. AF has also been observed at a prevalence of 10.3%; although the exact mechanism is unclear, it could be the result of the accumulation of toxic metabolites or the effect of anthracyclines on ion channels.[19,20]

Tyrosine Kinase Inhibitors

Ibrutinib is an irreversible tyrosine kinase inhibitor that increases B-cell adhesion and reduces chemokine production through Bruton's tyrosine kinase (BTK) inhibition, which lessens chemokine-mediated homing and retention of chronic lymphocytic leukaemia cells in lymph nodes, blood and bone marrow. It is associated with a significant increase in the incidence of SVT and AF (range, 3.5–10.8%).[21] Ibrutinib also targets BTK and Tec protein kinase that affect phosphatidylinositol 3-kinase (PI3K) – protein kinase B (AKT) signalling and, in several studies, the inhibition of the PI3K–AKT pathway and/or BTK proteins increased the risk for AF.[22] Treatment with this drug also shows increased bleeding rates, therefore, caution is needed in the use of anticoagulants.[23–25]

Arrhythmia management is based on either rate control (β-adrenergic receptor blockers and calcium channel blockers) or rhythm control strategies (anti-arrhythmic drugs [AADs] or transcatheter ablation; *Supplementary Figure 1*).[26–28]

Role of Anti-arrhythmic Drugs

Amiodarone, the most preferred AAD, is characterised by its large volume of distribution, which contributes to potential drug interactions, and increased risk of skin and mucosal damage with radiation. Additional AADs used in the cancer setting include flecainide, the application of which is curtailed by chemotherapy-induced structural heart disease, and ibutilide, which may exacerbate ECG issues when used with other QT-prolonging medications.

Risk of QT Interval Prolongation

Multiple cancer treatments have been associated with QT prolongation. The incidence in patients with cancer in general is up to 22% across a variety of drug classes.[29] Nonetheless, the risk of developing a life-threatening VA, including torsade de pointes, is generally quite low. Arrhythmia complications are usually observed when the QT interval is greater than 500 ms or changes more than 60 ms, and in this situation, according to recommendations from the Food and Drug Administration[30] and the European Medicines Agency[31], treatment should be discontinued or given at a lower dose.

Arsenic trioxide is associated with the highest risk of QTc prolongation and the consequent torsades de pointes, with reported cases of sudden death.[32] Other high-risk drugs include the histone deacetylase inhibitor panobinostat, various tyrosine kinase inhibitors, such as nilotinib, pazopanib, sunitinib and vemurafenib, and selective oestrogen receptor

modulators, such as tamoxifen, that inhibit the ion channel responsible for the delayed rectifier K^+ current in the heart (IKr or KV11.1), which then causes IKr channel block, which in turn causes prolongation of the QT interval.[33,34] Moreover, various supportive therapies, such as anti-emetics, antihistamines and antidepressants, can also cause QT prolongation, and their co-administration has an additive effect on this condition (*Table 2*).[35]

Chemotherapy-induced Ventricular and Bradyarrhythmias

The incidence of VA in patients receiving chemotherapy is rare, except in the case of advanced metastatic disease. Mechanisms cited include a direct or indirect effect of the chemotherapeutic agent on cardiomyocytes, prolongation of the QT interval and concomitant ischaemia. Other causes are LV systolic dysfunction and electrolyte abnormalities.[36] When VA occurs, correction of electrolyte imbalance, use of IV magnesium sulphate, and trying to keep the heart rate above 100 BPM using transvenous pacing or isoproterenol are necessary. Lidocaine and advanced cardiac life support measures ought to be started in refractory/emergency cases related to QT interval prolongation.[29] According to emerging results, mexiletine may also help to reduce recurring torsade de pointes and arsenic-induced QT prolongation; however, the overall safety and efficacy of mexiletine with chemotherapy agents are yet to be established. General VA management principles should be followed in the treatment of VA caused directly by anti-cancer therapies. Given their lower propensity for drug interactions, β-blockers and class IB anti-arrhythmics are currently recommended as the safest options for VA treatment.[37]

Several different classes of chemotherapeutic agents have also been associated with benign sinus bradycardia; and, although rare, symptomatic bradycardia and late atrioventricular block can also occur.[36] Paclitaxel provokes asymptomatic and reversible sinus bradycardia in up to 30% of patients, while more severe bradyarrhythmias are atypical. In contrast, thalidomide has been reported to cause sinus bradycardia in up to 40% of patients, with dizziness and syncope[36,38]. Fluorouracil causes both symptomatic and asymptomatic bradycardia in 12% of patients due to reversible damage to the conduction system provoked by transient coronary artery vasospasm.[38] However, the best-known chemotherapy drugs that may cause bradycardia are the anaplastic lymphoma kinase inhibitors, such as crizotinib or ceritinib[39]. They are mainly used to treat non-small cell lung cancer. A retrospective analysis of 1,053 patients, including those who had at least one heart rate measurement before treatment and who subsequently received crizotinib, found that 41.9% of patients had at least one documented episode of sinus bradycardia, with an average maximum decrease in heart rate of 30 BPM.[39] Crizotinib directly suppresses the Pacemaker current (I_f) in the sinoatrial node cells, lowers the spontaneous beating rate, and inhibits the rapid delayed rectifier potassium (Ikr), sodium (INa), and L-type calcium (ICa,L) ion channels. Other tyrosine kinase inhibitors similarly inhibit the ICa,L and outward rectifier K^+ currents, which results in a slowing of the heart rate. Moreover, they prolong the cardiac action potential by blocking the PI3K–AKT pathway, which raises the late sodium current (Ina,L) and lowers the fast currents (INa, ICa,L, IKr and IKs).[40]

In the case of severe bradycardia related to anti-cancer drugs, a multidisciplinary team should weigh the risks and advantages of continuing the medication at a reduced dose and investigate alternative therapies. When there is no other course of treatment available, pacemaker implantation is recommended.[41]

Table 2: Level of Risk of Oncologic Treatments in ECG QT Segment Prolongation

Class or Drugs	Specific Agents Responsible for CTRCD	Risk
Anthracyclines	Aclarubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone	Very low
Anti-metabolites	5-Fluorouracil Capecitabine Gemcitabine Pentostatin	High
Anti-microtubule agents	Docetaxel Paclitaxel Vinblastine Vincristine	Low
Cyclin-dependent kinase inhibitor	Ribociclib	High
HER2 inhibitors	Lapatinib Pertuzumab Trastuzumab	Low
Immune checkpoint inhibitors	Ipilimumab Nivolumab Pembrolizumab	Low
Other anti-neoplastic agents	Arsenic trioxide	High
Platinum-based anti-neoplastic class	Oxaliplatin	High
Proteasome inhibitors	Bortezomib Carfilzomib	Low
Selective oestrogen receptor modulator	Toremifene	
Tyrosine kinase inhibitor	Nilotinib Pazopanib Sorafenib Sunitinib Vandetanib Vemurafenib	High

CTRCD = cancer therapy-related cardiac dysfunction; HER2 = human epidermal growth factor receptor 2.

Differential Cardiac Cell Involvement in Arrhythmia Development in Cancer

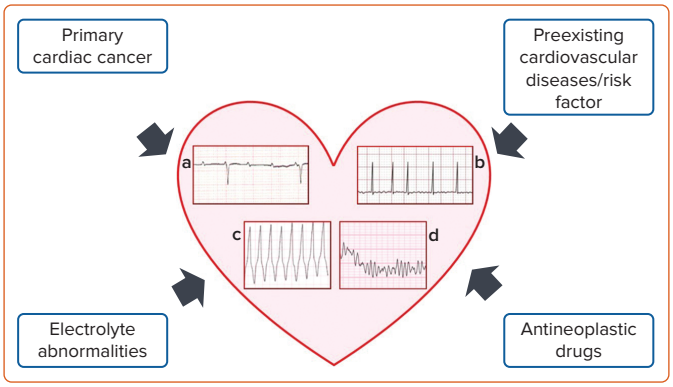
The principal mechanisms of cancer-provoked arrhythmia include the structural and electrical effects of chemotherapy, immune system involvement, and oxidative stress (*Figure 1*). Various cell types are involved in the adult human heart, such as cardiomyocytes, fibroblasts, vascular and endothelial cells, and pericytes. These cells can be influenced by the aforementioned pathological conditions and play distinct roles in the development of arrhythmias.

Cardiomyocytes

Cardiomyocytes represent ~70–85% of the cardiac volume but account for only 30–40% of the cells in the heart.[42] The myocytes are connected to each other via gap junctions, which enable synchronous contraction such that they can function as a syncytium.[43] Cardiomyocyte contraction is also commensurate with its calcium (Ca^{2+}) transient.[44]

Chronic doxorubicin treatment induced arrhythmic activity in a neonatal rat cardiomyocyte culture setting, mostly by inducing premature beats with compensatory pauses, sometimes with a bigeminal pattern; however, arrhythmogenicity was demonstrated in a dose-dependent fashion.[45] The primary triggering mechanism of doxorubicin cardiac toxicity involves Ca^{2+}

Figure 1: Main Causes of Cardiac Arrhythmia That Could Affect Cancer Patients



ECGs represent: complete atrioventricular block (A), AF (B), sustained ventricular tachycardia (C) and (D) VF (D).

homeostasis with significant changes in Ca^{2+} transients.[46] Nevertheless, good β-adrenergic responsiveness was maintained under these conditions.[47] Furthermore, doxorubicin can induce Calcium/calmodulin-dependent protein kinase II (CaMKII)-mediated Ca^{2+} leakage from the sarcoplasmic reticulum, which affects intracellular Ca^{2+} homeostasis and enhances the genesis of cardiac-triggered activity and AF arrhythmogenesis. In contrast, CaMKII inhibition can reduce doxorubicin-induced cardiotoxicity.[48] Selective oestrogen receptor modulators mimicking oestrogen on cardiomyocytes were associated with torsade de pointes because of QTc interval prolongation. Mechanisms include inhibition of the rapidly activating delayed rectifier potassium channel (IKr) and interaction with other channels (IK1, ICa,L, IKs). However, aromatase inhibitors reduce circulating oestrogen levels, potentially shortening the QTc interval.[49]

Fibroblasts

Fibroblasts are the predominant cell type of myocardial tissue. They surround myocytes and are found throughout all of the cardiac tissue, with a main involvement in pathological conditions, such as myocardial remodelling and fibrosis. Fibroblasts are 'non-excitable' cells but can affect electrophysiology indirectly by slowing or blocking the orderly propagation of electrical impulses. Interstitial fibrosis and collagen accumulation generate local anisotropy which enhances the predisposition to cardiac arrhythmogenesis.[50] Anthracyclines increase ROS formation and enhance the expression of matrix metalloproteinase 2 (MMP2) and MMP9, thereby altering the activity of cardiac fibroblasts and the turnover of the myocardial extracellular matrix. This causes weakening of the collagenous matrix and contributes to myocardial remodelling.[51] ROS-activated transforming growth factor-β, in turn, increases *NOX4* and *NOX2* gene expression and mediates the downregulation of antioxidant enzymes, such as catalase and glutathione peroxidase. Cardiac fibroblasts act as amplifiers of oxidative stress induced by anthracycline exposure and contribute to a profibrotic phenotype in this setting. Therefore, fibroblasts could be the first cellular target of oxidative stress induced by cancer and anti-neoplastic drugs, while triggering cardiomyocyte dysfunction through proarrhythmic crosstalk.[52]

Vascular and Endothelial Cells

Endothelial cells and vascular smooth muscle cells (ECs and VSMCs, respectively) are the protagonists of ischaemic damage caused by coronary artery vasospasm and vascular coronary endothelial injury. Furthermore, cardiac arrhythmias can result from these circumstances. Anthracyclines decrease nitric oxide production, which has a central role in endothelial homeostasis. They also affect VSMCs, leading to a senescence phenotype and impairment of contractility. This latter effect is the result of a downregulation of α-adrenergic receptors and an increase in oxidative stress.[53] Alkylating agents cause direct severe endothelial injury because of the extravasation of toxic metabolites. They also generate ROS, which impair the antioxidant defence system of the cell, causing oxidative stress, EC dysfunction and HF.[54] Anti-metabolites, such as 5-fluorouracil, could induce heart damage by coronary vessel spasm, direct damage to the myocardium, activation of coagulation leading to coronary thrombosis or an autoimmune mechanism. 5-Fluorouracil also exerts a direct toxic effect on ECs through an increase in the circulating levels of endothelin-1, a potent vasoconstrictor, thereby leading to coronary spasm and endothelium-independent vasoconstriction via protein kinase C.[55]

Pericytes

Cardiac pericytes are abundant in the heart but remain the most enigmatic and underappreciated of cell types. They are embedded in the basement membrane of microvessels, which is formed by pericytes and ECs. Similar to the VSMCs of larger vessels, pericytes can produce vasoconstriction and vasodilation and regulate vascular diameter and capillary blood flow.[56] They are known to play a key role in vascular tone as well as in angiogenesis. However, their dysfunctional presence and/or absence is critical in the mechanisms leading to cardiac pathologies such as MI, fibrosis and thrombosis.[57] Pericyte loss and cardiac dysfunction associated with sunitinib are mediated by the inhibition of platelet-derived growth factor receptor β (PDGFR-β) signalling, an essential pro-survival signalling pathway for pericytes.[58] As evidence suggests, pericytes are directly involved in cardiovascular complications such as coronary vasospasm, no reflow, and cancer drug-induced cardiotoxicity.[59] All of these conditions, as mentioned above, play a key role in arrhythmogenesis.

Arrhythmia Related to Cancer Pathogenesis

All cancer types increase the risk of cardiac arrhythmia. Patients with cardiovascular risk factors, prior cardiotoxic therapy, or those who have already had CVD are undoubtedly more likely to develop cancer-related arrhythmias.[60] Older age is another significant risk element. It causes complicated changes in the heart that affect the extracellular matrix and cellular composition. In the elderly, the rate of cardiomyocyte death is often enhanced, and fibrosis occurs as a result of oxidative stress brought on by an increase in ROS generation.[61]

Ventricular Arrhythmias

Non-sustained ventricular tachycardias have been observed in unselected patients with colorectal, pancreatic and non-small cell lung cancer, often leading to fatal outcomes during the first 5 years.[62]

In another study, 6–7% of patients with an ICD developed a diagnosis of cancer, and approximately one-third of cases developed VA.[63] The incidence of VAs is particularly high in patients with advanced disease with systemic dissemination. One possible mechanism for this association is inflammation: inflammation promotes all stages of carcinogenesis, and key inflammatory mediators in cancer include interleukin-1β, interleukin-6, tumour necrosis factor-α, chemokines and the transcription factor NF-KB.[64]

Atrial Fibrillation

Furthermore, there is an increased incidence of AF 1 year after a breast cancer diagnosis in women and is associated with increased 1-year cardiovascular mortality not related to breast cancer.[65] It should be noted that the important factors in the development of AF are the severity of the

cancer and the anatomical location of the tumour; indeed, the strongest association between oncology and AF is that for lung cancer, with a poor prognosis, while the association between prostate cancer and AF is the weakest, despite a relatively good prognosis.[66]

Bradyarrhythmias

Regarding bradyarrhythmias, several studies have suggested an influence of the temporal lobe of the brain on autonomic cardiovascular regulation and progressive reduction of the heart rate, followed by asystole as the first sign of a left medial temporal cerebral neoplasm.[67]

Role of Cardiac Implantable Electronic Devices in Oncology

The indication for ICD and CRT requires a life expectancy of at least 1 year and good functional status both for primary and secondary prevention of life-threatening VAs.[68,69]

Studies evaluating the effect of cancer on the severity of VAs in patients with ICD are weak and mostly retrospective; the majority reported an increase in arrhythmia burden after the diagnosis of cancer and noted the usefulness of the ICD.[70] In exceptional cases, the application of a wearable cardioverter defibrillator or implantation of a subcutaneous ICD may be considered.[71]

Bradyarrhythmias associated with syncope and/or chronotropic incompetence that does not resolve with the discontinuation of anti-cancer treatment or in the absence of alternative strategies are reasonable indications for implantation of a permanent pacemaker.[72]

In contrast, CRT, left bundle branch area pacing, and cardiac contractility modulation can improve cardiac function and enable the use of therapies with newer anti-neoplastic agents that otherwise cannot be given (*Table 3*).

The possibility of CRT should be considered in HF patients with reduced ejection fraction and left bundle branch block and QRS>130 ms, even in mildly symptomatic status. Interestingly, a cancer diagnosis in the previous 3 years did not rule out CRT in the Swedish Contemporary Heart Failure Cohort, suggesting that cardiologists are not guided by a history of malignancy when considering CRT.[73,74] In this regard, a significant improvement in ejection fraction was observed only 6 months after CRT implantation in symptomatic HF patients with chemotherapy-induced cardiomyopathy[74]. Similarly, patients with doxorubicin-induced cardiomyopathy and HF refractory to maximal pharmacologic therapy may achieve benefit from CRT.[75] However, further studies on the effective role of cardiac implantable devices in HF related to cancer therapy are needed when HF with preserved ejection fraction is diagnosed in oncology patients (*Figure 2*).

Cardiac Implantable Electronic Device-related Infections in Cancer Patients

The improved prognosis of patients with malignancies has resulted in an increased number of candidates with cancer for implantation of devices for cardiac rhythm management. Patients with a current diagnosis of malignancy had significantly higher rates of mortality and postoperative complications, including major bleeding, chest and cardiac complications, and device-related infections, compared with patients without cancer.[76] Cancer patients are often at greater risk of device-related infections due to a possible immunocompromised state. The rate of device infection is approximately 4%, with a notable increase over time.[77] The most common

Table 3: Level of Risk of Oncologic Treatments in Heart Failure

Class or Drugs	Specific Agents Responsible for CTRCD	Risk
Anthracycline	Doxorubicin Idarubicin Epirubicin	High
BCR-ABL inhibitors	Bosutinib Dasatinib Nilotinib Ponatinib	Very high
HER2-targeted therapies	Trastuzumab Lapatinib Pertuzumab	Very high
Multiple myeloma therapies	Bortezomib Carfilzomib	Very high
RAF and MEK inhibitors	Dabrafenib Encorafenib Vemurafenib	High
VEGF inhibitors	Axitinib Bevacizumab Pazopanib Regorafenib Sorafenib Sunitinib Vandetanib	Very high

BCR-ABL = breakpoint cluster region – Abelson murine leukaemia; CTRCD = cancer therapy-related cardiac dysfunction; HER2 = human epidermal growth factor receptor 2; MEK = mitogen-activated extracellular signal-regulated kinase; RAF = rapidly accelerated fibrosarcoma; VEGF = vascular endothelial growth factor.

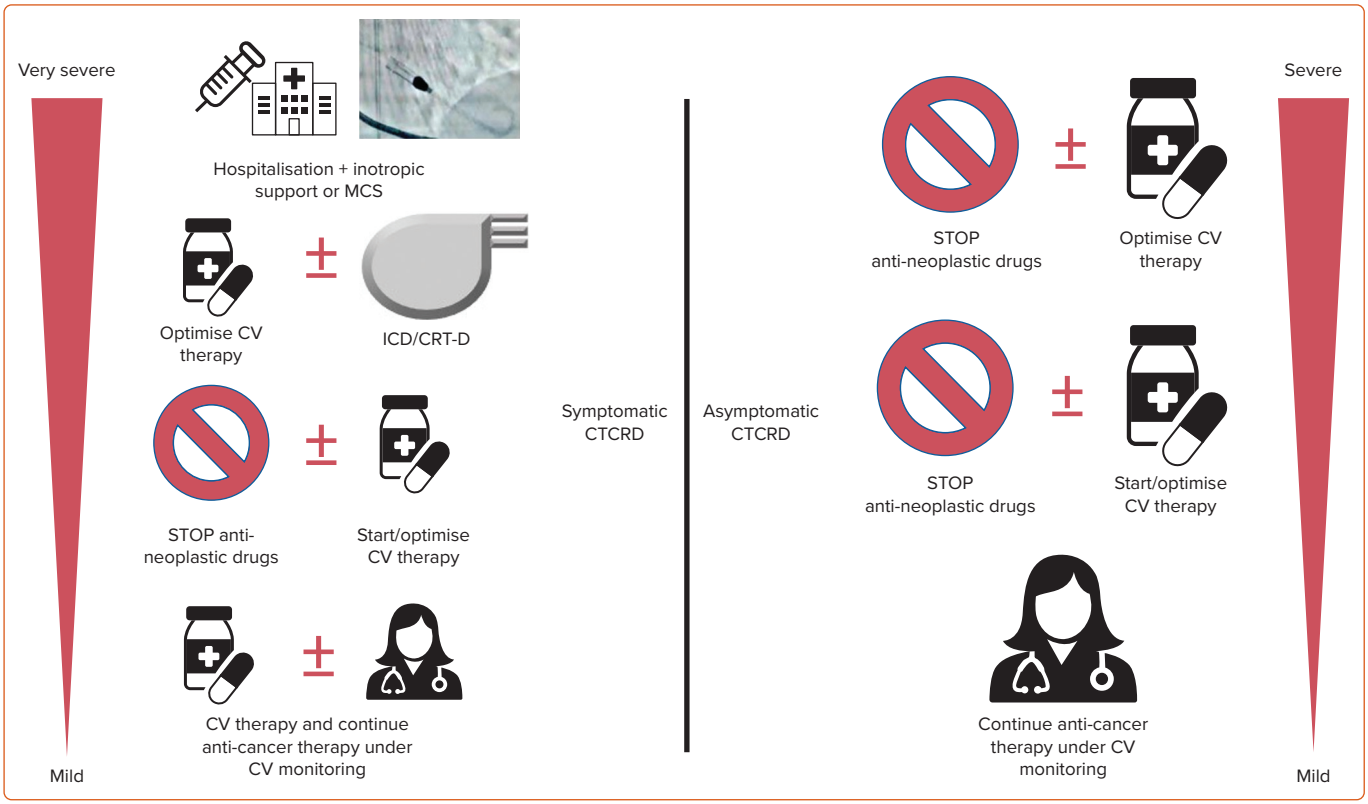
microorganisms causing device-related infections are skin flora, such as coagulase-negative staphylococci (38%), *Staphylococcus aureus* (31%), Gram-negative bacteria and others (9%).[78] Total removal of the entire device system (generator and leads) is often necessary, and this intervention increases the mean hospitalisation cost and the overall in-hospital mortality rates.[79,80] The evaluation of modifiable risk factors for infection is crucial in the oncologic setting, and these risk factors include use of perioperative systemic antimicrobials, absence of infection or fever in the previous 24 hours, discontinuation of antiplatelet medications 5–7 days before the procedure, and, if possible, avoidance of bridging with low-molecular-weight heparin.[80,81] Moreover, the combination of preoperative vancomycin, intraoperative pocket irrigation with polymyxin B and bacitracin, envelopes with special antimicrobial mesh, and postoperative oral minocycline 100 mg twice daily for 5 days was found to be associated with an infection rate of the implanted devices similar to that of non-cancer patients.[82]

For successful management of device infection, a multidisciplinary approach with a multispecialty team composed of electrophysiologists, infectious disease specialists, oncologists and cardiac surgeons is required for the discussion of patient clinical status, as well as the use of laboratory biomarkers and advanced imaging including trans-oesophageal/transthoracic echocardiography and 18-fluorodeoxyglucose PET/CT for potential device removal, according to patient global risk.[83]

Conclusion

Cardio-oncology has emerged as a vital and evolving subspecialty within cardiology, with significant updates in recent years. The cardiotoxic effects of anti-cancer drugs can be severe and potentially lethal. Accurate

Figure 2: Treatment Options for Cancer Therapy-related Cardiac Dysfunction



In symptomatic cancer therapy-related cardiac dysfunction (CTRCD) the treatment choices range from the starting or uptitration of cardiovascular (CV) therapy ± STOP the anti-neoplastic drugs; to the implantation of heart-failure devices, such as defibrillator (ICD) with or without cardiac resynchronisation therapy (CRT-D), inotropic and/or mechanical cardiovascular support (MCS), depending on the severity of cardiac dysfunction. In asymptomatic patients with mild CTRCD close monitoring could be adequate; in severe cases temporary STOP of anti-neoplastic drugs and CV therapy optimisation is necessary.

assessment of cardiac function and arrhythmia burden represents a complex challenge. In this context, mobile and wearable technologies may be a useful strategy for the real-time detection and management of cardiac issues in cancer patients. Further investigation in this area is needed. According to effective anti-cancer therapies now available, the effect on cardiac rhythm can now be managed with cardiac implantable electronic devices, representing a brand-new discipline of cardio-oncology that might experience an exponential increase in the next few years. As a result, balancing the health of these frail subjects with the current recommendations for device implantation will represent a challenge. Finally, further research is needed to identify novel biomarkers that can predict cardiotoxicity at progressively earlier stages. ❑

Clinical Perspective

- Cardiologists are increasingly involved in the care of cancer patients as a result of improved life expectancy, a decline in cancer mortality, and the emergence of new cancer treatments.
- A growing body of investigation has demonstrated an association between cancer risk factors and cardiovascular disorders, and several serious cardiovascular consequences have been related to cancer therapy.
- Expert cardiologists, or cardio-oncologists, are required to handle the most complicated situations and the necessity of implantation of electronic devices, along with their related risks.

1. Agarwal MA, Aggarwal A, Rastogi S, et al. Cardiovascular disease burden in cancer patients from 2003 to 2014. *Eur Heart J Qual Care Clin Outcomes* 2018;4:69–70. https://doi.org/10.1093/ehjqcco/qcx033; PMID: 29045611.
2. Leiva O, Beaty W, Soo S, et al. Cancer therapy-associated pulmonary hypertension and right ventricular dysfunction: etiologies and prognostic implications. *Rev Cardiovasc Med* 2024;25:87. https://doi.org/10.31083/j.rcm2503087; PMID: 39076943.
3. Beavers CJ, Rodgers JE, Bagnola AJ, et al. Cardio-oncology drug interactions: a scientific statement from the American Heart Association. *Circulation* 2022;145:e811–38. https://doi.org/10.1161/cir.0000000000001056; PMID: 35249373.
4. Giustozzi M, Curcio A, Weijs B, et al. Variation in the association between antineoplastic therapies and venous thromboembolism in patients with active cancer. *Thromb Haemost* 2020;120:847–56. https://doi.org/10.1055/s-0040-1709527; PMID: 32369855.
5. Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J* 2022;43:280–99. https://doi.org/10.1093/eurheartj/ehab674; PMID: 34904661.
6. Sekine Y, Kesler KA, Behnia M, et al. COPD may increase the incidence of refractory supraventricular arrhythmias following pulmonary resection for non-small cell lung cancer. *Chest* 2001;120:1783–90. https://doi.org/10.1378/chest.120.6.1783; PMID: 11742902.
7. Nakahira M, Nakatani H, Takeda T. Syncope as a sign of occult malignant recurrence in the retropharyngeal and parapharyngeal space: CT and MR imaging findings in four cases. *AJNR Am J Neuroradiol* 2002;23:1257–60. PMID: 12169488.
8. Fradley MG, Beckie TM, Brown SA, et al. Recognition, prevention, and management of arrhythmias and autonomic disorders in cardio-oncology: a scientific statement from the American Heart Association. *Circulation* 2021;144:e41–55. https://doi.org/10.1161/cir.0000000000000986; PMID: 34134525.
9. Vizza P, Curcio A, Tradigo G, et al. A framework for the atrial fibrillation prediction in electrophysiological studies. *Comput Methods Programs Biomed* 2015;120:65–76. https://doi.org/10.1016/j.cmpb.2015.04.001; PMID: 25929601.
10. Fradley MG, Gliksman M, Emole J, et al. Rates and risk of atrial arrhythmias in patients treated with ibrutinib compared with cytotoxic chemotherapy. *Am J Cardiol* 2019;124:539–44. https://doi.org/10.1016/j.amjcard.2019.05.029; PMID: 31208701.
11. Guzzetti S, Costantino G, Sada S, Fundarò C. Colorectal cancer and atrial fibrillation: a case-control study. *Am J Med* 2002;112:587–8. https://doi.org/10.1016/s0002-9343(02)01029-x; PMID: 12015256.
12. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003;108:3006–10. https://doi.org/10.1161/01.cir.0000103131.70301.4f; PMID: 14623805.
13. Curcio A, Scalise R, Indolfi C. Pathophysiology of atrial fibrillation and approach to therapy in subjects less than 60 years old. *Int J Mol Sci* 2024;25:758. https://doi.org/10.3390/ijms25020758; PMID: 38255832.
14. Shiga T, Hiraide M. Cardiotoxicities of 5-fluorouracil and other fluoropyrimidines. *Curr Treat Options Oncol* 2020;21:27. https://doi.org/10.1007/s11864-020-0719-1; PMID: 32266582.

15. Mazur M, Wang F, Hodge DO, et al. Burden of cardiac arrhythmias in patients with anthracycline-related cardiomyopathy. *JACC Clin Electrophysiol* 2017;3:139–50. https://doi.org/10.1016/j.jacep.2016.08.009; PMID: 29759386.
16. Vejpongsa P, Yeh ETH. Topoisomerase 2β: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. *Clin Pharmacol Ther* 2014;95:45–52. https://doi.org/10.1038/clpt.2013.201; PMID: 24091715.
17. Mordente A, Meucci E, Martorana GE, Tavian D, Silvestrini A. Topoisomerases and anthracyclines: recent advances and perspectives in anticancer therapy and prevention of cardiotoxicity. *Curr Med Chem* 2017;24:1607–26. https://doi.org/10.2174/0929867323666161214120355; PMID: 27978799.
18. Vejpongsa P, Yeh ETH. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. *J Am Coll Cardiol* 2014;64:938–45. https://doi.org/10.1016/j.jacc.2014.06.1167; PMID: 25169180.
19. Tamargo J, Caballero R, Delpón E. Cancer chemotherapy and cardiac arrhythmias: a review. *Drug Saf* 2015;38:129–52. https://doi.org/10.1007/s40264-014-0258-4; PMID: 25577497.
20. Guglin M, Aljayeh M, Saiyad S, et al. Introducing a new entity: chemotherapy-induced arrhythmia. *Europace* 2009;11:1579–86. https://doi.org/10.1093/europace/eup300; PMID: 19801562.
21. Ganatra S, Sharma A, Shah S, et al. Ibrutinib-associated atrial fibrillation. *JACC Clin Electrophysiol* 2018;4:1491–500. https://doi.org/10.1016/j.jacep.2018.06.004; PMID: 30573111.
22. McMullen JR, Boey EJH, Ooi JYY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood* 2014;124:3829–30. https://doi.org/10.1182/blood-2014-10-604272; PMID: 25498454.
23. Santarpia G, Curcio A, Sibilio G, Indolfi C. Clinical significance of non-vitamin K antagonist oral anticoagulants in the management of atrial fibrillation. *Circ J* 2015;79:914–23. https://doi.org/10.1253/circj.CJ-15-0319; PMID: 25833178.
24. Spaccarotella C, Esposito G, Indolfi C. To anticoagulate or not to anticoagulate to prevent arterial thrombosis during systemic cancer therapy. *JACC CardioOncol* 2023;5:533–5. https://doi.org/10.1016/j.jaccao.2023.05.006; PMID: 37614570.
25. Curcio A, Anselmino M, Di Biase L, et al. The gray areas of oral anticoagulation for prevention of thromboembolic events in atrial fibrillation patients. *J Cardiovasc Med (Hagerstown)* 2023;24(Suppl 2):e97–105. https://doi.org/10.2459/jcm.0000000000001461; PMID: 37186560.
26. Romano LR, Scalzi G, Malizia B, et al. Impact of percutaneous mitral valve repair on left atrial strain and atrial fibrillation progression. *J Cardiovasc Dev Dis* 2023;10:320. https://doi.org/10.3390/jcdd10080320; PMID: 37623333.
27. Santarpino G, Rubino AS, Onorati F, et al. Atrial fibrillation ablation induces reverse remodelling and impacts cardiac function. *Minerva Cardioangiol* 2011;59:17–29. PMID: 21285928.
28. Onorati F, Curcio A, Santarpino G, et al. Routine ganglionic plexi ablation during maze procedure improves hospital and early follow-up results of mitral surgery. *J Thorac Cardiovasc Surg* 2008;136:408–18. https://doi.org/10.1016/j.jtcvs.2008.03.022; PMID: 18692650.
29. Porta-Sánchez A, Gilbert C, Spears D, et al. Incidence, diagnosis, and management of QT prolongation induced by cancer therapies: a systematic review. *J Am Heart Assoc* 2017;6:e007724. https://doi.org/10.1161/jaha.117.007724; PMID: 29217664.
30. Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. 2005. https://www.fda.gov/media/71372/download (accessed 18 February 2025).
31. European Medicines Agency. ICH E14: clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04. 2005. https://www.ema.europa.eu/en/ich-e14-clinical-evaluation-qt-qtc-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic-drugs-scientific-guideline (accessed 10 February 2025).
32. Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. *J Clin Oncol* 2003;21:3609–15. https://doi.org/10.1200/jco.2003.10.009; PMID: 14512391.
33. Shopp GM, Helson L, Bouchard A, et al. Liposomes ameliorate crizotinib- and nilotinib-induced inhibition of the cardiac IKr channel and QTc prolongation. *Anticancer Res* 2014;34:4733–40. PMID: 25202051.
34. Grouthier V, Lebrun-Vignes B, Glazer AM, et al. Increased long QT and torsade de pointes reporting on tamoxifen compared with aromatase inhibitors. *Heart* 2018;104:1859–63. https://doi.org/10.1136/heartjnl-2017-312934; PMID: 29720397.
35. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation* 2010;121:1047–60. https://doi.org/10.1161/circulationaha.109.192704; PMID: 20142454.
36. Buza V, Rajagopalan B, Curtis AB. Cancer treatment-induced arrhythmias: focus on chemotherapy and targeted therapies. *Circ Arrhythm Electrophysiol* 2017;10:e005443. https://doi.org/10.1161/circep.117.005443; PMID: 28798022.
37. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;43:3997–4126. https://doi.org/10.1093/eurheartj/ehac262; PMID: 36017572.
38. Polk A, Vaage-Nilsen M, Vistisen K, Nielsen DL. Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. *Cancer Treat Rev* 2013;39:974–84. https://doi.org/10.1016/j.ctrv.2013.03.005; PMID: 23582737.
39. Ou SHI, Tang Y, Polli A, et al. Factors associated with sinus bradycardia during crizotinib treatment: a retrospective analysis of two large-scale multinational trials (PROFILE 1005 and 1007). *Cancer Med* 2016;5:617–22. https://doi.org/10.1002/cam4.622; PMID: 26823131.
40. Davis MJ, Wu X, Nurkiewicz TR, et al. Regulation of ion channels by protein tyrosine phosphorylation. *Am J Physiol Heart Circ Physiol* 2001;281:H1835–62. https://doi.org/10.1152/ajpheart.2001.281.5.H1835; PMID: 11668044.
41. Gawlik M, Zimodro JM, Gąsecka A, et al. Cardiac arrhythmias in oncological patients: epidemiology, risk factors, and management within the context of the new ESC 2022 guidelines. *Curr Oncol Rep* 2023;25:1107–15. https://doi.org/10.1007/s11912-023-01445-x; PMID: 37589940.
42. Zhou P, Pu WT. Recounting cardiac cellular composition. *Circ Res* 2016;118:368–70. https://doi.org/10.1161/circresaha.116.308139; PMID: 26846633.
43. Dhein S, Salameh A. Remodeling of cardiac gap junctional cell–cell coupling. *Cells* 2021;10:2422. https://doi.org/10.3390/cells10092422; PMID: 34572071.
44. Peters NS, Wit AL. Myocardial architecture and ventricular arrhythmogenesis. *Circulation* 1998;97:1746–54. https://doi.org/10.1161/01.cir.97.17.1746; PMID: 9591770.
45. Gorelik J, Vodyanoy I, Shevchuk AI, et al. Esmolol is antiarrhythmic in doxorubicin-induced arrhythmia in cultured cardiomyocytes: determination by novel rapid cardiomyocyte assay. *FEBS Lett* 2003;548:74–8. https://doi.org/10.1016/S0014-5793(03)00743-9; PMID: 12885410.
46. Varghese E, Samuel SM, Sadiq Z, et al. Anti-cancer agents in proliferation and cell death: the calcium connection. *Int J Mol Sci* 2019;20:3017. https://doi.org/10.3390/ijms20123017; PMID: 31226817.
47. Dodd DA, Atkinson JB, Olson RD, et al. Doxorubicin cardiomyopathy is associated with a decrease in calcium release channel of the sarcoplasmic reticulum in a chronic rabbit model. *J Clin Invest* 1993;91:1697–705. https://doi.org/10.1172/jci116379; PMID: 8386192.
48. Sag CM, Köhler AC, Anderson ME, et al. CaMKII-dependent SR Ca leak contributes to doxorubicin-induced impaired Ca handling in isolated cardiac myocytes. *J Mol Cell Cardiol* 2011;51:749–59. https://doi.org/10.1016/j.yjmcc.2011.07.016; PMID: 21819992.
49. Barber M, Nguyen LS, Wassermann J, et al. Cardiac arrhythmia considerations of hormone cancer therapies. *Cardiovasc Res* 2019;115:878–94. https://doi.org/10.1093/cvr/cvz020; PMID: 30698686.
50. Camelliti P, Borg TK, Kohl P. Structural and functional characterisation of cardiac fibroblasts. *Cardiovasc Res* 2005;65:40–51. https://doi.org/10.1016/j.cardiores.2004.08.020; PMID: 15621032.
51. Octavia Y, Tocchetti CG, Gabrielson KL, et al. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. *J Mol Cell Cardiol* 2012;52:1213–25. https://doi.org/10.1016/j.yjmcc.2012.03.006; PMID: 22465037.
52. Cappetta D, Esposito G, Piegari E, et al. SIRT1 activation attenuates diastolic dysfunction by reducing cardiac fibrosis in a model of anthracycline cardiomyopathy. *Int J Cardiol* 2016;205:99–110. https://doi.org/10.1016/j.ijcard.2015.12.008; PMID: 26730840.
53. Murata T, Yamawaki H, Hori M, et al. Chronic vascular toxicity of doxorubicin in an organ-cultured artery. *Br J Pharmacol* 2001;132:1365–73. https://doi.org/10.1038/sj.bjp.0703959; PMID: 11264228.
54. Dugbartey GJ, Peppone LJ, De Graaf IAM. An integrative view of cisplatin-induced renal and cardiac toxicities: molecular mechanisms, current treatment challenges and potential protective measures. *Toxicology* 2016;371:58–66. https://doi.org/10.1016/j.tox.2016.10.001; PMID: 27717837.
55. Albini A, Tosetti F, Li VW, et al. Cancer prevention by targeting angiogenesis. *Nat Rev Clin Oncol* 2012;9:498–509. https://doi.org/10.1038/nrclinonc.2012.120; PMID: 22850752.
56. Rucker HK, Wynder HJ, Thomas WE. Cellular mechanisms of CNS pericytes. *Brain Res Bull* 2000;51:363–9. https://doi.org/10.1016/S0361-9230(99)00260-9; PMID: 10715555.
57. Armulik A, Abramsson A, Betsholtz C. Endothelial/pericyte interactions. *Circ Res* 2005;97:512–23. https://doi.org/10.1161/01.RES.0000182903.16652.d7; PMID: 16166562.
58. Chintalgattu V, Rees ML, Culver JC, et al. Coronary microvascular pericytes are the cellular target of sunitinib malate-induced cardiotoxicity. *Sci Transl Med* 2013;5:187ra69. https://doi.org/10.1126/scitranslmed.3005066; PMID: 23720580.
59. Shen M, Liu C, Zhao SR, et al. Stepwise generation of human induced pluripotent stem cell-derived cardiac pericytes to model coronary microvascular dysfunction. *Circulation* 2023;147:515–8. https://doi.org/10.1161/circulationaha.122.061770; PMID: 36745700.
60. Nickel AC, Patel A, Saba NF, et al. Incidence of cancer treatment-induced arrhythmia associated with novel targeted chemotherapeutic agents. *J Am Heart Assoc* 2018;7:e010101. https://doi.org/10.1161/jaha.118.010101; PMID: 30371288.
61. Curtis AB, Karki R, Hattoum A, Sharma UC. Arrhythmias in patients ≥80 years of age. *J Am Coll Cardiol* 2018;71:2041–57. https://doi.org/10.1016/j.jacc.2018.03.019; PMID: 29724357.
62. Anker SD, Butler J, Khan MS, et al. Conducting clinical trials in heart failure during (and after) the COVID-19 pandemic: an expert consensus position paper from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2020;41:2109–17. https://doi.org/10.1093/eurheartj/ehaa461; PMID: 32498081.
63. Enriquez A, Biagi J, Redfearn D, et al. Increased incidence of ventricular arrhythmias in patients with advanced cancer and implantable cardioverter-defibrillators. *JACC Clin Electrophysiol* 2017;3:50–6. https://doi.org/10.1016/j.jacep.2016.03.001; PMID: 29759695.
64. Albert CM, Ma J, Rifai N, et al. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* 2002;105:2595–9. https://doi.org/10.1161/01.cir.0000017493.03108.1c; PMID: 12045163.
65. Guha A, Fradley MG, Dent SF, et al. Incidence, risk factors, and mortality of atrial fibrillation in breast cancer: a SEER-Medicare analysis. *Eur Heart J* 2022;43:300–12. https://doi.org/10.1093/eurheartj/ehab745; PMID: 34791123.
66. Jakobsen CB, Lamberts M, Carlson N, et al. Incidence of atrial fibrillation in different major cancer subtypes: a nationwide population-based 12 year follow up study. *BMC Cancer* 2019;19:1105. https://doi.org/10.1186/s12885-019-6314-9; PMID: 31726997.
67. Van Der Sluijs BM, Renier WO, Kappelle AC. Brain tumour as a rare cause of cardiac syncope. *J Neurooncol* 2004;67:241–4. https://doi.org/10.1023/B:NEON.0000021899.69560.e6; PMID: 15072474.
68. Lyon AR, López-Fernández T, Couch LS, et al. ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J Cardiovasc Imaging* 2022;23:e333–465. https://doi.org/10.1093/ehjci/jeac106; PMID: 36017575.
69. Romano LR, Spaccarotella CAM, Indolfi C, Curcio A. Revascularization and left ventricular dysfunction for ICD eligibility. *Life (Basel)* 2023;13:1940. https://doi.org/10.3390/life13091940; PMID: 37763344.
70. Itzhaki Ben Zadok O, Nardi Agmon I, Neiman V, et al. Implantable cardioverter defibrillator for the primary prevention of sudden cardiac death among patients with cancer. *Am J Cardiol* 2023;191:32–8. https://doi.org/10.1016/j.amjcard.2022.12.013; PMID: 36634547.
71. Lee C, Maan A, Singh JP, Fradley MG. Arrhythmias and device therapies in patients with cancer therapy-induced cardiomyopathy. *Heart Rhythm* 2021;18:1223–9. https://doi.org/10.1016/j.hrthm.2021.02.017; PMID: 33640446.
72. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;42:3427–520. https://doi.org/10.1093/eurheartj/ehab364; PMID: 34455430.
73. Suter TM, Ewer MS. Cancer drugs and the heart: importance and management. *Eur Heart J* 2013;34:1102–11. https://doi.org/10.1093/eurheartj/ehs181; PMID: 22789916.
74. Lund LH, Svennblad B, Dahlström U, Ståhlberg M. Effect of expanding evidence and evolving clinical guidelines on the prevalence of indication for cardiac resynchronization therapy in patients with heart failure. *Eur J Heart Fail* 2018;20:769–77. https://doi.org/10.1002/ejhf.929; PMID: 28949083.
75. Ajijola OA, Nandigam KV, Chabner BA, et al. Usefulness of cardiac resynchronization therapy in the management of doxorubicin-induced cardiomyopathy. *Am J Cardiol* 2008;101:1371–2. https://doi.org/10.1016/j.

amjcard.2007.12.037; PMID: 18435975.
76. Mohamed MO, Barac A, Contractor T, et al. Prevalence and in-hospital outcomes of patients with malignancies undergoing de novo cardiac electronic device implantation in the USA. *Europace* 2020;22:1083–96. https://doi.org/10.1093/europace/euaa087; PMID: 32361739.
77. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. *J Am Coll Cardiol* 2006;48:590–1. https://doi.org/10.1016/j.jacc.2006.05.016; PMID: 16875991.
78. Viola GM, Awan LL, Ostrosky-Zeichner L, et al. Infections of cardiac implantable electronic devices: a retrospective multicenter observational study. *Medicine* 2012;91:123–30. https://doi.org/10.1097/MD.0b013e31825592a7; PMID: 22543626.
79. Sridhar ARM, Lavu M, Yarlagadda V, et al. Cardiac implantable electronic device-related infection and extraction trends in the U.S. *Pacing Clin Electrophysiol* 2017;40:286–93. https://doi.org/10.1111/pace.13009; PMID: 28084622.
80. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace* 2015;17:767–77. https://doi.org/10.1093/europace/euv053; PMID: 25926473.
81. Blomström-Lundqvist C, Traykov V, Erba PA, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections: endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Europace* 2020;22:515–49. https://doi.org/10.1093/europace/euz246; PMID: 31702000.
82. Khalil M, Karimzad K, Durand JB, et al. Prevention of cardiac implantable electronic device-related infection in patients with cancer: the role of a comprehensive prophylactic bundle approach that includes the antimicrobial mesh. *Open Forum Infect Dis* 2020;7:ofaa433. https://doi.org/10.1093/ofid/ofaa433; PMID: 33204750.
83. Ali H, Foresti S, De Ambroggi G, et al. Practical considerations for cardiac electronic devices reimplantation following transvenous lead extraction due to related endocarditis. *J Clin Med* 2023;12:6908. https://doi.org/10.3390/jcm12216908; PMID: 37959373.