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Cardio-oncology (MG Fradley, Section Editor)

# Cancer and Coronary Artery Disease: Common Associations, Diagnosis and Management Challenges

*Debashish Das, MBBS, MD, MRCP (UK)*[1]
*Alex Asher, MBBS, MRCP (UK)*[2]
*Arjun K. Ghosh, MBBS MRCP (UK) MRCP (Card) MSc PhD FHEA*[1,3,*]

**Address**
[*,1]Cardio-Oncology Service, Department of Cardiology, Barts Heart Centre, Barts Health NHS Trust, St Bartholomew's Hospital, West Smithfield, London, EC1A 7BE, UK
Email: arjun.ghosh2@bartshealth.nhs.uk
[2]Department of Cardiology, Barts NHS Health Trust, Royal London Hospital, Whitechapel Road, London, E1 1BB, UK
[3]Cardio-Oncology Service, Department of Cardiology, University College London Hospital, 235 Euston Road, London, NW1 2BU, UK

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## Opinion statement

Coronary artery disease (CAD) and cancer often occur in the same patients via common biological pathways and shared risk factors. A variety of chemotherapeutic agents and radiotherapy can influence the development and progression of CAD. The diagnosis of ischaemic heart disease may be challenging in certain cases such as premature CAD secondary to radiotherapy. The management of CAD in cancer patients in the stable, acute and chronic settings can often be complicated by issues related to ongoing or previous cancer treatment or the cancer itself. A multidisciplinary approach in the setting of a cardio-oncology service is often best-served to optimally treat such patients.

## Introduction

The steady decline in cancer mortality due to advances in medical therapies has been a true success in modern medicine over the last two decades [1•]. The consequences of this have led to some new challenges in cardiovascular medicine. Heart disease and cancer still remain the two leading causes of death worldwide and are closely linked with shared risk factors; this may indicate a shared biology [2]. In addition, with an ageing population, patients presenting with oncological disease increasingly have coexisting heart disease [3]. Moreover, the cardio-toxic effects of contemporary cancer treatments, despite improving survival chances, have increased the number of cancer survivors with cardiac problems [2, 4, 5•, 6]. Considerations about heart disease in oncological patients must be made before, during and after oncological therapeutic interventions and has led to the growth of "cardio-oncology" [1•]. In this review, we describe the current challenges faced by cardio-oncology patients in particular reference to coronary artery disease.

# Shared biology

There is frequent coexisting coronary artery disease (CAD) with cancer [7, 8]. This is largely driven by the shared risk factor of age and the increasing use of cancer therapies in elderly patients. Biologically related pathways exist resulting in smoking-related coronary disease and lung cancer. Patients who may have mild CAD prior to their oncological diagnosis may have disease progression due to the pro-inflammatory and hypercoagulable states that result as a consequence of the cancer itself, let alone the effects of certain cancer treatments. This hypercoagulable state also increases the risk of stent thrombosis in patients previously treated or planned for treatment by percutaneous coronary intervention [9]. Additionally, clonal haematopoiesis of indeterminate potential (CHIP; the presence of an expanded somatic blood-cell clone in persons without other haematologic abnormalities) commonly seen in older people increases the risk of blood cancers and doubles the risk of coronary artery disease [10].

## Coronary artery disease and chemotherapy

Patients who are actively being treated with oncological therapies together with those who have survived their cancer may also be at increased risk of developing CAD due to the cardio-toxic effects of the treatment itself. These catalogues of effects can result in the acceleration of atherosclerotic plaque formation, acute thrombosis and coronary vasospasm culminating in future acute coronary syndromes [11].

The most common anti-cancer drug treatments involved in the development of CAD are the antimetabolites, anti-microtubule agents, monoclonal antibody-based tyrosine kinase inhibitors, small molecule tyrosine kinase inhibitors and platinum-containing anti-cancer drugs [12–14] (Table 1).

A number of anti-cancer drugs [5-flourouracil (5FU), capecitabine, docetaxel, paclitaxel and sorafenib] have shown a particular preponderance for coronary vasospasm [15•, 16, 17], while others have shown a preponderance for acute coronary thrombosis, such as bevacizumab [18, 19]. The development of atherosclerotic CAD has been noted in those using a combination of these

**Table 1. Chemotherapeutic agents associated with ischemic cardio-toxicity**

| Drug class | Agent | Cancer-treated | Mechanism of cardiac insult |
|---|---|---|---|
| Monoclonal antibody | Rituximab<br>Bevacizumab | Lung<br>Renal<br>Colon | Hypertension<br>Thromboembolism<br>Platelet hyperactivity |
| Anti-metabolite | 5-Fluorouracil<br>Capecitabine | Gastrointestinal<br>Breast | Vasospasm |
| Platinum-based | Cisplatin | Testicular<br>Breast<br>Head and neck | Vasospasm<br>Hypertension<br>Platelet hyperactivity |
| Anti-tubular | Paclitaxel<br>Vinblastine | Ovarian<br>Breast<br>Lung | Vasospasm<br>Hypertension |
| Tyrosine kinase inhibitor | Nilotinib<br>Ponatinib<br>Sunitinib<br>Sorafenib | Leukaemia<br>Sarcoma<br>Renal<br>Liver | Arterial thromboembolism |
| Novel antibiotic | Bleomycin | Lymphoma<br>Testicular<br>Ovarian | Vascular endothelial dysfunction |

treatments, in fact the combination of bevacizumab, bleomycin and vinblastine increases the long-term risk of CAD and myocardial infarction by 1.5 to 7-fold [20].

Tyrosine–kinase inhibitors like nilotinib and ponatinib have also been associated with cardiac ischaemia leading to myocardial infarction [21, 22]. The mechanisms may include aggravation of a preexisting atherosclerotic condition or arterial thromboembolism [23, 24].

The association between aromatase inhibitors like anastrazole, letrozole and exemestane and general cardiovascular disease, and CAD is however more controversial [25, 26]. Aromatase inhibitors (AIs) reduce oestrogen concentrations through the inhibition of androgen conversion. Estrogens regulate fibrinolytic systems, antioxidant systems, serum lipid concentrations and the production of vasoactive molecules. Through this, they are thought to confer cardio-protection and are postulated to be a cause of the higher incidence of cardiovascular disease in men when compared to women. The age of incidence of CAD tends to be higher in women when compared to men. Additionally, the incidence of CAD increases post-menopause. It is therefore thought that the reduction of circulating oestrogens induced by AIs leads to a reduction of oestrogen-mediated cardio-protective effects, which in turn translate to an increased risk of cardiovascular disease (CVD) [27].

A large systematic review and meta-analysis of aromatase inhibitors and tamoxifen in post-menopausal women with breast cancer however indicated that the increased risk of cardiovascular events with AIs relative to tamoxifen was likely the result of cardio-protective effects of tamoxifen (rather than detrimental effects of AIs themselves) [26].

Androgen–deprivation therapy in prostate cancer has also been shown in a number of observational studies to increase the risk of CVD although the biological mechanisms are yet to be fully elucidated [28, 29].

Clinical manifestations of CAD from anti-cancer drug treatments can also vary in timings and presentation, from early onset coronary spasm to later atherosclerosis causing angina and subsequent ischaemia cardio-myopathy [2]. Though not fully elucidated, the pathology behind some of the cardio-toxic side effects of current chemotherapy cancer treatments in relation to CAD include increased low-density lipoprotein levels, platelet activation, endothelial damage and vasospasm [14, 30, 31]. Endothelial damage, and in turn increased risk of thromboembolism, is thought to be as a result of increased release of pro-inflammatory cytokines (IL1, TNF-α). The degree of endothelial damage and its subsequent clinical manifestations can vary and are dependent on a number of factors. The extent of endothelial damage can depend on the type, dose and regimen of anti-neoplastic treatment [32].

## Coronary artery disease secondary to radiotherapy

Chemotherapy agents are not alone in their cardio-toxic effects. Radiotherapy too has been shown to increase the risk of CAD and has been linked to significant mortality and morbidity due to its cardiac adverse effects [33]. The degree of CAD secondary to radiation therapy depends on a number of factors. These include radiation dosage, anterior exposure without shielding and preexisting heart disease. Studies have shown a linear relationship with the risk of coronary events with radiation dose with an increased risk of 7.4% per grey (Gy) [34]. The cardio-toxic effects of radiation can present from weeks to many years post-treatment [35, 36]. Interestingly, vascular wall changes have been shown to take effect days post-radiation exposure [37]. However, a common presentation is that of survivors in the "late-effects" setting, patients who had been exposed to more intense and less shielded radiation decades prior (e.g. mantle radiotherapy for Hodgkin lymphoma) as seen in the Childhood Cancer Survivor Study [38]. These patients often develop complex and challenging coronary artery lesions. Radiation-induced CAD often manifests in ostial lesions or proximal segments of the main epicardial vessels [39]. Those who have received radiotherapy for breast cancer (especially left breast) often manifest with lesions in the left anterior descending artery as well the distal diagonal branches [40]. Despite "heart-sparing" or "heart-dose minimising" modern radiotherapy techniques, CAD remains still a significant cardio-toxic side effect.

## Diagnosis of myocardial ischaemia/infarction in patients with cancer

The diagnosis of and treatment of CAD in cancer patients can be unique and challenging for a number of different reasons both disease and patient-specific. To further complicate matters, there remains a lack of consensus on the management of such patients. The Society for Cardiovascular Angiography and Interventions (SCAI) has attempted to address this by releasing an expert consensus statement to provide cardiologist and oncologist guidance for treating patients facing concomitant CAD and cancer [41••]. There does however remain a lack of consensus on how best to define ischaemic cardio-toxicities [42•]. Like all cardiac patients, the diagnosis and evaluation of CAD in cancer patients can be via non-invasive stress testing, diagnostic imaging

and or coronary angiography. A number of patient-related factors influence the clinical decision-making with respect to investigating and treating potential CAD. These include patient frailty and associated comorbidities such as thrombocytopaenia or pancytopaenia. Often, there are specific challenges regarding timings of investigations and the subsequent CAD treatment if needed. Patients can often have time constraints imposed by their oncologist for urgent or scheduled cancer therapy, medical or surgical. There are clear national guidelines for treatment timelines for cancer in the UK [43]. The current targets are:

- no more than 2 months (62 days) wait between the date the hospital receives an urgent referral for suspected cancer and the start of treatment
- no more than 31 days wait between the meeting at which you and your doctor agree the treatment plan and the start of treatment

The presence of CAD or other cardiac disease can lead to delay in the initiation of cancer treatment by the oncological team for fear of making the patient's cardiac status worse or increasing surgical risk. There are no clear guidelines of timings of potential cardiac investigations and treatment for cancer patients in this context.

The timings for and urgency for cardiac investigations and potential subsequent treatments often rely on the impetus of the cardiologist receiving the referral and the time it takes for this referral to be received. This underpins the need for a dedicated cardio-oncology team with an expertise in the unique challenges the oncological patient brings [2, 3, 44]. The cardio-oncology team can facilitate rapid assessment and management and in turn preventing detrimental delays in oncological treatment. A dedicated cardio-oncology service not only provides rapid assessment but also facilitates direct communication between oncologists and cardiologists about shared patients through multidisciplinary meetings. The cardio-oncology team should comprise of cardiologists from traditional cardiology subspecialties providing a comprehensive cardiac opinion. A dedicated cardiac interventionist within the group can aid the nuanced management of these patients in the context of CAD in oncological patients, both in terms of medical management and the technical feasibility aspects of revascularisation. A common example of the complexity of these patients includes coronary stenting in a patient on chemotherapy and with a low platelet count. Together with the lack of clinical consensus and the differing patient-related challenges, it is important for the cardio-oncology team to tailor their management plans to the individual needs of the patients. Interventional cardiologists will often be asked to review cancer patients with known or expected CAD with a view to cardiac optimization in the context of initiating or continuing anti-cancer therapy or prior to potential cancer-related surgery. With reference to pre-surgical cardiac optimisation, the European Society of Cardiology (ESC) provides clear guidelines in pre-operative cardiac risk assessment [45]. While not specific for cancer patients, they can be extrapolated for reference in deciding the need for cardiac investigations and potential management of cancer patients awaiting surgical treatment. Currently, the ESC suggests that cardiac patients should be divided into two groups—those with stable and those with unstable cardiac conditions (the latter including unstable angina, acute heart failure, significant cardiac arrhythmias, symptomatic valvular

disease, recent myocardial infarction or residual myocardial ischaemia). If stable, surgery can proceed without further investigations. If deemed unstable, the type of surgery awaited can be classified by risk (low, intermediate or high) (Table 2). If low-risk surgery, it can proceed without further cardiac investigations. For those patients with intermediate or high risk, functional capacity of the patients should be assessed. If the patient can achieve > 4 metabolic equivalents (METS) on exercise testing, medical management of CAD with statin and beta-blocker therapy should be initiated/continued and the patient can progress with surgery (Fig. 1). If the patient cannot achieve at least four METS and they have three or more of the following risk factors: angina pectoris, prior myocardial infarction, acute heart failure, stroke/transient ischaemic attack renal dysfunction and/or diabetes mellitus requiring insulin therapy. Non-invasive ischaemia testing is the first investigation of choice.

The American Society of Echocardiography has also produced an expert consensus statement stating all cancer patients treated with radiotherapy should be considered as being at high-risk for CAD [32, 46]. They state that these patients should have stress testing 5–10 years after exposure, even if asymptomatic. Secondly, reassessment should occur every 5 years even if asymptomatic. The use of computed tomography coronary angiography (CTCA) for monitoring these patients is attractive due its non-invasive nature although it is associated with radiation exposure. Its use will likely increase in the future in this scenario with a potential role of CT-guided FFR (fractional flow reserve) testing as an alternative to non-invasive functional testing. Currently, invasive coronary angiography remains the gold standard for identifying anatomical lesions.

## Treatment of myocardial ischaemia/infarction in patients with cancer

### *Stable coronary artery disease*

Treatment pathways for CAD in cancer patients will follow the same three possibilities as the general population: medical management, percutaneous intervention or coronary artery bypass surgery. The need for personalised care is of high importance. Therapies in cancer patients will often be dictated by the stage and prognosis of malignancy, severity of cardiac disease, comorbidities and lastly pre-morbid function of the cancer patient.

**Table 2. Relative 30-day cardiovascular morbidity and mortality risk for non-cardiac surgery**

| Low-risk surgery | Intermediate risk surgery | High risk surgery |
|---|---|---|
| Dental | Head and neck | Aortic |
| Minor gynaecological | Peripheral angioplasty | Major vascular |
| Minor urological | Neurological | Major gastrointestinal |
| Ophthalmic | Major orthopaedic | Organ transplant |
| Superficial plastic | Major gynaecological | |
| | Major urological | |
| | Splenectomy | |
| | Cholecystectomy | |

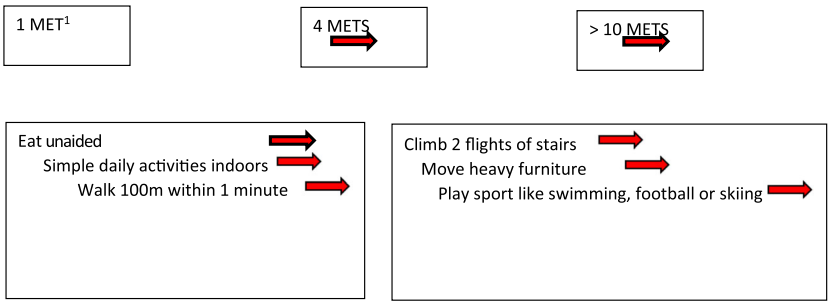


**Fig. 1.** Graded intensities of physical activity and the corresponding metabolic equivalents. MET metabolic equivalent.

For cancer patients with a known history of ischaemic heart disease, who are asymptomatic, the prevention of acute coronary syndromes and progression of CAD should be the main goals. Close monitoring and conventional risk factor modification are the mainstays in this approach. The mechanism of action of the chemotherapeutic agent is important. Agents such as 5-FU are known to precipitate chest pain due to coronary vasospasm rather than progression of atherosclerotic plaque [47]. As such, concomitant treatment with vasodilators such as oral nitrates may alleviate symptoms allowing optimal cancer treatment to continue unimpeded [48]. At present, there is no evidence that suggests percutaneous intervention in stable angina provides any prognostic benefit over medical therapy, where possible medical management for stable angina is thus preferable. However, in cancer patients, is it fair to use similar prognostic benchmarks as the general population? Medical management can often be a process of trial and reassessment. This clearly is a process that takes up a degree of time, which is a precious commodity for cancer patients. Coronary angioplasty is a day-case procedure with limited recovery time and could provide instant symptomatic relief to the patient. Where the cancer prognosis is more favourable, coronary revascularisation, be it percutaneous coronary intervention (PCI) or CABG, prior to and during cancer treatment may be a better approach. Of course, this has to be balanced by the increased bleeding risk associated for the duration of dual anti-platelet therapy (DAPT) post-percutaneous intervention. More research is required in this field to provide an answer as to optimal timing of such an intervention.

### *Acute coronary syndromes in the cancer patient*

Studies have shown that circa 5% of acute coronary syndrome (ACS) presentations are in patients with concurrent cancer [49]. Cancer patients with ACS present their own unique challenges. PCI is the gold standard therapy for ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI)/unstable angina, and lastly, stable angina refractory to optimal medical therapy [50, 51]. This medical practice has been established from large randomised trials in which the presence of cancer has typically been an exclusion criterion. Moreover, a history of cancer is also not collected in the large PCI registries. There is therefore a scarcity of evidence on how best to treat the cancer population in an ACS setting. It is not surprising that retrospective studies looking at cancer

patients presenting with ACS have been found them to be less likely treated with PCI in both STEMI and NSTEMI clinical presentations when compared to the general population [49]. Patients with cancer, additionally, can have varying presentations and often can present with atypical symptoms. Frequently, acute chest pain while on chemotherapy responds well to the termination of the agent, especially if 5FU is the agent in question. 5FU causes vasospasm and responds well to vasodilators.

*Treatment considerations for ACS in the cancer patient*

Due to expansion of heart attack networks within the UK thrombolysis for STEMI has now become far less frequent. However, it is to be noted that thrombocytopaenia, which is not uncommon in cancer patients, and cerebral cancer are absolute contraindications for thrombolysis. Moreover, once the decision to proceed to PCI has been made in the cancer patient, there are still some important considerations to be made. This largely focussed on bleeding risks (de novo and in the context of potential cancer surgery) and duration of DAPT needed post-stent insertion. As described previously, thrombocytopaenia and clotting abnormalities are not uncommon in the cancer patient. PCI itself involves the administration of a number of blood thinning medications before, during and after the procedure. Antiplatelets are given to patients before and after PCI and during the procedure itself while heparin is given to prevent clot formation on the cardiac catheters. GP2b3a inhibitors are often given in the ACS setting. A platelet count of above 50,000/mL is advisable for most interventional procedures in the absence of coagulopathy. When platelet counts drop below 30,000/mL, revascularization and duration of DAPT should be decided after a risk/benefit analysis best carried out in the setting of a cardio-oncology multidisciplinary team meeting [2, 44]. Careful liaison with haematologists is important to minimise bleeding risks where the patient is thromobocytopaenic. Indeed, in some cases, platelet transfusions may be warranted pre-procedurally.

Considerations for vascular access are also important. Radial vascular access where feasible would be the preferred mode of access as this minimises the risk of any major bleeding complications, especially for those at increased risk such as patients with active cancer. However, this may not be always possible especially within the cancer population who may have had a number of vascular access insertions for cancer therapy and their general ill health making radial access more challenging. In addition, in patients with previous chest wall radiotherapy, there may be stenosis of vessels such as the subclavian making arterial access by the radial route challenging.
The cancer population can often have complex coronary artery disease, largely due to age and smoking as shared risk factors. Triple vessel disease is still conventionally treated through coronary artery bypass grafting (CABG) in the general population. The decision for CABG in the cancer patient will largely be driven by the prognosis of the cancer. Those patients who have poor prognosis would not be suitable for an open-heart operation given the risks of surgery and recovery time needed. Medical therapy again would be the first line with an aim for symptom control. However, if this

is not achieved, the concept of palliative stenting may become more common. PCI technology has improved such that traditionally difficult to treat lesions such as chronic total occlusions are now more treatable. Wire escalation technologies now allow for dissection re-entry and retrograde techniques allowing for more complex revascularisation percutaneously.

### *Post-PCI management*

Post-PCI it is still conventional therapy to treat with 12 months DAPT when a drug-eluting stent (DES) is placed. Bleeding risks of the cancer patient, such as thrombocytopaenia, or the need for future cancer-related surgery might make this recommended duration of DAPT unattractive. Bare metal stents while requiring only 1 month of DAPT are felt to be inferior to their drug-eluting counterparts. There are emerging data to suggest that newer 3rd generation DES require a much smaller duration of DAPT possibly only 1–3 months while the recent ACC/AHA guidelines state that 6 months of DAPT may be sufficient in many cases [52, 53]. As such, interventionists where possible should refrain from inserting bare metal stents.

Patients requiring anticoagulation provide added complexity. Though not specific to the cancer patient, guidance is provided by the ESC to aid decision-making for duration of potential triple therapy [DAPT and an oral anticoagulant (OAC)]. For those patients with increased risk of bleeding, the ESC suggests a one-month regimen of triple therapy followed by 11 months of either clopidogrel and OAC or aspirin and OAC (class II level A evidence) [50]. Alternatively, if bleeding risk is extremely high, one could consider one antiplatelet, aspirin or clopidogrel alone with an OAC for 12 months then OAC alone thereafter.

While the evidence for secondary prevention and prognostic medications such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors and statin therapy is largely derived from studies excluding cancer patients, their use however is still recommended in the cancer patients as per use in the general population.

## Conclusion

It is clear that cancer and coronary heart disease are in many patients intertwined. As cancer therapies evolve and improve today's cancer, patient will become tomorrow's cardiac patient. As cancer survival rates improve, there will have to be a culture shift in the way cardiologists treat these patients. Moreover, cardiovascular disease is now one of the most common key determinants in long-term survival rates of cancer patients. These patients present with their own unique challenges, and it is therefore not unsurprising to see the rise as cardio-oncology as a speciality. While cardio-oncology services have been established in the USA and in parts of Europe, it is still a relatively new concept in the UK and many other countries. Nonetheless, a perceived clinical need is

driving a number of hospitals to develop focussed cardio-oncology services such as the Barts Heart Centre, St Bartholomew's Hospital and University College Hospital London providing coordinated and specialised care for the cardiac needs of cancer patients [44].

## Author Contributions

AKG conceived the paper and supervised the drafting of the manuscript which was performed by DD with assistance from AA.

## Compliance with Ethical Standards

**Conflict of Interest**
Debashish Das, Alex Asher, and Arjun K. Ghosh declare they have no conflict of interest.

**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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