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Cardiovascular health of patients with cancer: challenges abound

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Cardiovascular health of patients with cancer: challenges abound

Short title: Opportunities and challenges in cardio-oncology

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Abstract

Patients with cancer have elevated cardiovascular risks compared to those without cancer. As cancer incidence increases and cancer-related mortality decreases, cardiovascular diseases in patients with a history of cancer will become increasingly important. This in turn is reflected by the exponentially increasing amount of cardio-oncology research in recent years. This narrative review aims to summarize the key existing literature in several main areas of cardio-oncology, including the epidemiology, natural history, prevention, management, and determinants of the cardiovascular health of patients with cancer, and identify relevant gaps in evidence for further research.

Keywords: cardio-oncology; cancer; cardiology; social determinants of health; risk factors; epidemiology; cancer therapy

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Introduction

Cardio-oncology, an emerging subspecialty at the intersection between cardiology and oncology, has received increasing attention in recent years. Since 2010, the number of cardio-oncology publications in peer-reviewed journals has grown exponentially, exceeding 260 publications in 2021, and accruing over 5000 relevant citations.(1) The significance of cardio-oncology as both a clinical and research field of interest was further consolidated by the cardio-oncology guidelines published in 2022 by the European Society of Cardiology (ESC),(2) which represented the first cardio-oncology guideline published by a major cardiovascular society. Given the above, this narrative review aimed to summarize the key existing evidence in several main areas of cardio-oncology, including epidemiology, risk factors, cancer therapy-related cardiotoxicity, and social determinants of health. We additionally sought to discuss the 2022 ESC guidelines and identified gaps in knowledge. We further sought to highlight gaps in evidence and areas for further research.

Epidemiology of cardiovascular conditions in patients with cancer

Cancer has been one of the most common causes of mortality and morbidity globally. In 2019, an estimated 10 million deaths and 250 million disability-adjusted life years were attributable to cancer.(3) The same year saw an estimated 23.6 million new cases of cancer, constituting a 26.3% increase compared to 2010, and is expected to continue rising in the future.(3) Concurrently, improving cancer therapeutics, amongst other factors, have led to consistently declining mortality rates amongst patients with cancer, with an estimated 33% reduction in 2019 compared to 1991.(4)

This combination of increasing cancer incidence and declining cancer-related mortality rates will result in a ever growing number of cancer survivors, who will have increased risks of

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incident cardiovascular diseases and cardiovascular mortality when compared to the general population. This was demonstrated by a Canadian study of 4,519,243 adults, which found that patients with cancer had a 33% increase in the risk of cardiovascular mortality, a 44% increase in the risk of incident stroke, a 62% increase in the risk of incident heart failure, and a 243% increase in the risk of incident pulmonary embolism.(5) These findings were mostly replicated by a contemporary study of 12,414 individuals from the Atherosclerosis Risk In Communities (ARIC) study,(6) as well as another study of 1.1 million Taiwanese patients.(7) Similarly, large-scale studies using data from the Surveillance, Epidemiology, and End Results (SEER) program of the United States demonstrated that patients with cancer had significantly increased risks of fatal heart disease and cardiovascular mortality.(8,9) Importantly, there is evidence that cardiovascular diseases and cardiovascular risk factors are undertreated in patients with cancer,(10,11) and a study by Agarwal and colleagues found that cardiovascular burden increased in American patients with cancer between 2003 and 2014.(12) Overall, these findings and the temporal trends in cancer epidemiology suggest that cardiovascular diseases in patients with cancer will become an ever-more important clinical issue.

Despite the established association between cancer and cardiovascular risk, quantification of cardiovascular disease burden in patients with different types of cancer is still incomplete. The risk factors and therapies differ for different cancers, the associated cardiovascular burden may be different, and an accurate and personalized approach to prognostication is important when communicating with patients. Additionally, there are substantial ethnic differences in cardiovascular burden.(13–15) Some large-scale studies of Caucasian-predominant cohorts have quantified the cardiovascular burden in patients with cancer in general,(5,9,16,17) and some have stratified for the type/site of cancer.(5,18–23) However, findings from Caucasian-predominant cohorts may not be translatable to other ethnicities. Recent years have also seen

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more such studies using data from non-Caucasian cohorts,(19,20,22,23) although they remain relatively uncommon – a common phenomenon in cardio-oncology research.(1,24) Further to such ethnic underrepresentation, there is substantial heterogeneity in the definition of cardiovascular outcomes between studies. Notably, many made use of time-fixed point estimates (e.g. incidence rates) as summary statistics. For the lay person, these may be more difficult to understand than time-specific estimates (e.g. five-year risk(20)). These also assume a constant incidence rate, which has been shown to be untrue.(5) Overall, ethnically diverse studies quantifying the cardiovascular burden in patients with various cancer types/sites, using more clinically relevant estimates, and a uniform definition of cardiovascular outcomes remains warranted (**Table 1**).

Shared biological risk factors between cancer and cardiovascular diseases

The reasons underlying such elevated cardiovascular risks in patients with cancer are complex and incompletely understood. Aside from the adverse cardiovascular effects of cancer therapies,(25,26) the main underlying factors likely include shared risk factors, and heightened inflammation and oxidative stress in cancer.(27) In particular, obesity, physical inactivity, diabetes mellitus, smoking, alcoholism, and poor diet, all of which are well-established cardiovascular risk factors, have been associated with elevated risks of cancer. A meta-analysis of 98 studies demonstrated strong associations between obesity and cancer in both male and female patients,(28) while a study of 1.46 million white adults demonstrated significant associations between obesity and cancer-related mortality.(29) Similarly, a meta-analysis of 71 prospective cohort studies demonstrated a strong, inverse, non-linear dose-response relationship between the amount of physical activity and cancer mortality.(30) A meta-analysis of 151 cohorts including over 32 million individuals found strong associations between type 2 diabetes mellitus and multiple cancer types, although the association for some cancers may

have been attributable to confounders.(31) Additionally, smoking has long been recognized as a strong risk factor for multiple cancers, particularly respiratory cancers,(32) and has been identified as the risk factor to which the highest number of cancer deaths were attributable in 2019.(33) High alcohol intake has been similarly demonstrated to associate with elevated risks of multiple cancer types, as seen in a meta-analysis of 572 studies including 486,538 cancer cases.(34) Finally, poor diet has been shown to account for 80,110 new cases of cancer in the United States in 2015, with colorectal cancer having the highest number and proportion of diet-related cases, and with low consumption of whole grain / dairy products, and high consumption of processed meats being the most important dietary factors.(35) The mechanisms underlying these associations are complex and incompletely understood, with inflammation, oxidative stress and insulin resistance being some of the key mechanistic drivers.(27) Nonetheless, a detailed discussion of these mechanisms is beyond the scope of this review – we refer interested readers to specific reviews.(27,36,37)

These risk factors are interlinked, and the effects of each risk factor are difficult to isolate. Although it is obvious that optimization of cardiovascular risk factors can lower cardiovascular risk, the multifactorial nature of cardiovascular diseases in patients with cancer means that the efficacy and optimal strategy of controlling these risk factors and managing cardiovascular conditions may not be the same in these patients. Although the 2022 ESC cardio-oncology guidelines detailed the long-term follow-up of cancer survivors, the majority of recommendations were only based on expert consensus or low-quality observational studies.(2) Further high-quality research of the long-term cardiovascular care of patients with cancer is required (**Table 1**).

Cancer therapy-related cardiotoxicity

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Adverse cardiovascular effects of cancer therapies are an important contributor to cardiovascular diseases in patients with cancer.(38) A large number of studies have demonstrated clear evidence for cardiotoxicities due to anthracyclines,(39) ErB2/HER2 inhibitors,(40) androgen deprivation therapy,(41,42) immune checkpoint inhibitors,(43–45) epidermal growth factor receptor inhibitors,(46) vascular endothelial growth factor (VEGF) signaling pathway inhibitors,(47) and radiotherapy.(48) Specifically, whilst heart failure and ischaemic heart disease are well-recognized cardiotoxic effects of cancer therapies, studies have suggested that arrhythmias, such as atrial fibrillation and ventricular tachyarrhythmias, may be important consequences and even prognosticators of cancer therapy-related cardiotoxicity.(38,49,50) Furthermore, pulmonary hypertension may be another overlooked cardiotoxic effect of cancer therapies, with diagnosis being difficult due to its non-specific clinical presentation.(51,52) Nevertheless, a detailed review of the evidence underlying associations between different cancer therapies and cardiotoxicities is outside the scope of this review, and interested readers may refer to the appropriate references above.(39–48) The pathophysiological mechanisms of such cardiotoxicities are complex and incompletely understood, but mostly relate to inhibition of DNA transcription and protein synthesis (e.g. alkylating agents, HER2 inhibitors, anthracyclines), oxidative stress and reactive oxygen species (e.g. anthracyclines), microtubular disassembly disruption (e.g. taxanes), immune activation causing autoimmune responses (e.g. immune checkpoint inhibitors), blockade of sex hormone pathways (e.g. androgen deprivation therapy), and/or fibrosis of the myocardium or other cardiac structure (e.g. radiotherapy).(25,41,48,53) Moreover, some studies have shown that premorbid cardiometabolic conditions, including hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation / flutter, and high body-mass index, are risk factors for adverse cardiovascular events related to cancer therapies, such as anthracyclines,(54) VEGF inhibitors,(55) and HER2 inhibitors.(56) It is also noteworthy that there may be significant differences in cardiovascular risks associated with different cancer therapeutic agents in the

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same class, such as enzalutamide and abiraterone which are both androgen receptor signaling inhibitors used in androgen deprivation therapy.(57)

Epidemiology and risk stratification

Cancer therapies sensibly prioritize cancer-specific efficacy. The issue of cardiotoxicity was thus often explored and studied only after these therapies have been widely adopted. There are many gaps in the understanding of cancer therapy-related cardiotoxicity, which will likely remain the case due to rapid and continual advances in cancer therapy. For instance, the predisposing and prognostic factors of cancer therapy-related cardiotoxicity are incompletely understood. These gaps in evidence are present not only due to the novelty of some cancer treatments, but also because certain life-threatening cardiotoxic effects, such as myocarditis related to immune checkpoint inhibitors, are extremely uncommon.(58) Cancer therapy-related cardiotoxicity burden, especially long-term burden, in non-Caucasian patients is also only increasingly studied in recent years,(20,59–64) These gaps in understanding meant that developing cardiovascular risk tools specific for patients with cancer is difficult. Additionally, the inherently different treatment and natural history of different cancers may necessitate separate risk models for different cancers or even cancer therapies, which may require frequent updating and recalibration owing to the rapid advancement of cancer therapeutics.

The complexity of these challenges and the paucity of specific cardiovascular risk stratification tools were evident from the 2022 ESC cardio-oncology guidelines, which recommended the HFA-ICOS risk assessment tool for patients on a limited range of cancer therapies (e.g. anthracyclines), and a cautious use of the SCORE2 / SCORE2-OP cardiovascular risk scores in others (e.g. androgen deprivation therapy).(2,65) However, the evidence underlying the

HFA-ICOS risk assessment tool was weak, with most being low-quality observational studies or expert consensus.(65) Furthermore, this tool only offered qualitative cardiovascular risk assessment for some cancer therapies, which is not ideal for clinicians who are obliged to clearly communicate the risks of cancer therapies to patients. The qualitative nature also meant that the tool could not take into account interactions between different comorbidities, which have been shown to be prognostically important.(64) Meanwhile, the SCORE2 and SCORE2-OP risk scores were originally developed for use in the general population, has not been thoroughly validated in patients with cancer, particularly non-Caucasian ones. Similar issues exist for most other common cardiovascular risk scores such as QRISK3 and JBS3. Whilst recent years have seen attempts to develop cardiovascular risk scores for patients with breast cancer,(66) acute myeloid leukaemia,(67) prostate cancer,(68) or diffuse large B-cell lymphoma treated with anthracyclines,(69) these scores generally lacked thorough external validation and have not seen widespread clinical use, with the 2022 ESC guidelines opting for the more general HFA-ICOS risk assessment tool instead. Similar studies have remained scarce, and much more effort is urgently required to address the unmet need of risk stratification tools in patients with cancer (**Table 1**).

Prevention and management

Compared to cardiovascular risk stratification, there has been somewhat more interest in the prevention and management of cancer therapy-related cardiotoxicity. One of the best examples of such is dexrazoxane, which has long been demonstrated to be efficacious for preventing anthracycline-related cardiotoxicity.(70,71) As such, dexrazoxane was recommended by the 2022 ESC cardio-oncology guidelines for use in patients with high cardiac risks, as were liposomal anthracyclines which have been shown to be associated with significantly lower incidences of cardiotoxicity.(2,72) More recently, statins have been explored for the same

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purpose. Although PREVENT, the first randomized controlled trial testing statin's efficacy in patients receiving anthracyclines, showed no significant effect on absolute change in left ventricular ejection fraction,(73) the subsequent STOP-CA trial demonstrated statin's efficacy in reducing significant reductions in left ventricular ejection fraction.(74) Subsequent meta-analyses confirmed that statin significantly reduced the incidence of cardiotoxicity, whilst high levels of heterogeneity, likely due to inter-study differences in follow-up durations and baseline cardiovascular risk, precluded meaningful conclusions to be drawn for changes in left ventricular ejection fraction.(75,76) Besides statins, a meta-analysis of 11 randomized controlled trials has demonstrated that beta-blockers reduced the incidence of symptomatic heart failure, and improved cardiac function.(77) Observational studies have suggested that other agents may have similar effects, such as sodium-glucose cotransporter-2 inhibitors and metformin.(78,79) Meanwhile, a pairwise meta-analysis and a network meta-analysis failed to find heart failure therapies to be efficacious in preventing HER2 inhibitor-related cardiotoxicity.(80,81)

On the other hand, the 2022 ESC cardio-oncology guidelines provided relatively detailed guidance on the cardiovascular surveillance for patients with cancer while receiving cancer therapies, as well as the management of cancer therapy-related cardiotoxicity.(2) For the latter, there was a recurring theme of multidisciplinary team care, initiation of workup and treatments according to the presenting clinical syndrome (e.g. heart failure, or acute coronary syndrome) similar to those in patients without cancer, and interrupting cancer therapy with the potential for re-initiation in non-severe cases after resolution of the acute cardiotoxicity.(2) These recommendations were centered around the critical cardio-oncology concept of 'permissive cardiotoxicity', where cardiotoxicity is to be proactively minimized with minimal impact on the overall cancer treatment.(82)

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Nonetheless, as was the case for many other areas, the recommendations made by 2022 ESC cardio-oncology guidelines, in terms of the prevention and management of cancer therapy-related cardiotoxicity, were heavily reliant on low-quality observational studies and/or expert consensus. Further to the abovementioned PREVENT and STOP-CA trials, there have been an increasing number of cardiovascular-focused trials either comparing cancer therapeutic agents or testing cardioprotective strategies. For instance, the PRONOUNCE trial compared degarelix (a gonadotropin-releasing hormone antagonist) against leuprolide (a gonadotropin-releasing hormone agonist), both commonly used for the treatment of prostate cancer, in terms of the risk of major adverse cardiovascular events,(83) a question which several observational studies had attempted to answer but arrived at contradicting conclusions.(84,85) Unfortunately, patient recruitment for PRONOUNCE was impacted by the COVID-19 pandemic, and the trial was ended prematurely resulting in underpowered analyses, which found no significant differences between the two agents.(83) There are also a number of ongoing randomized controlled trials being conducted in diverse populations. For instance, the ongoing Norwegian PRADAII trial will assess the efficacy of sacubitril/valsartan, which had shown promising results in pre-clinical and observational studies,(86) in preventing cardiotoxicity in patients with breast cancer receiving adjuvant epirubicin with/without trastuzumab/pertuzumab (NCT03760588).(87) Another example is an Egyptian trial which will assess the efficacy of rosuvastatin in preventing cardiotoxicity in patients with breast cancer receiving both doxorubicin and trastuzumab (NCT05338723). Also ongoing is another Taiwanese trial which will assess the efficacy of initiating sacubitril/valsartan as preventive therapy versus rescue therapy in patients with breast cancer receiving trastuzumab (NCT05892146). The multinational, European RESILIENCE trial will assess the efficacy of remote ischaemic conditioning, which had not shown significant benefits in smaller trials of low-risk patients,(88,89) in patients with lymphoma and high cardiovascular risks receiving

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anthracyclines (NCT05223413). These trials and other emerging epidemiological and observational studies will hopefully give much-needed insights into the prevention and treatment of cancer therapy-related cardiotoxicity, not only pertaining to the efficacy of individual agents, but also the optimal regimen and timing of such agents (**Table 1**).

Social determinants of health

Social determinants of health (SDOH), broadly referring to socioeconomic factors that may affect health, have been increasingly recognized as a determinant of cardiovascular health. A large-scale prospective cohort study of 182,375 participants from 20 countries demonstrated significant associations between low education levels and higher risk of major adverse cardiovascular events,(90) with similar findings in another large cohort study of 303,036 participants from Asia or Australasia.(91) A cohort study of participants from United States and Finland also demonstrated associations between low income and increased risks of sudden cardiac death, non-sudden cardiac death, and non-fatal myocardial infarction,(92) the significance of which may increase with age.(93) Similar associations have been demonstrated in patients with cancer. A study of 81,418 Canadian patients with cancer showed that a rural residence, low education level, and low income were all associated with elevated risk of incident cardiovascular diseases.(94) Similarly, another study of 1,139,767 American women with breast or gynaecological cancers found associations between rural residence and higher risk of cardiovascular mortality, which was likely driven by behavioural risk factors (e.g. smoking) and poorer access to healthcare.(95) Unlike in the general population where the association between income and cardiovascular risk appeared to be mostly applicable to older persons,(93) such associations were observed in adolescent and young adult cancer survivors too, as evident from an analysis of data from the United States' nationally representative National Health Interview Survey (NHIS).(96)

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Notwithstanding the above, most studies have only explored selected aspects of SDOH, and few have explored links between SDOH and cardiovascular health in patients with cancer comprehensively. This is difficult due to the inter-correlated nature of multiple domains of SDOH, the lack of a universal and objective definition of SDOH, and the broadness of SDOH, which means very few studies collected sufficient data to explore SDOH comprehensively.(97) Recently, Satti, Chan and colleagues made the first such venture, constructing a poly-social risk score from NHIS data and demonstrating strong relationships between worse social deprivation and worse cardiovascular health in American cancer survivors.(98) This is an important first step, but the observational and cross-sectional nature of the NHIS data used precluded delineation of temporal and causal relationships, and the additive, non-weighted nature of the constructed poly-social risk score likely neglected the varying importance of individual domains. Also notably, due to limitations inherent to NHIS, cardiovascular health was defined using an abbreviated version of the American Heart Association's Life's Essential Eight, which is likely different from other prior studies' endpoints, e.g. cardiovascular mortality(95) or incident cardiovascular disease,(94) in significance.

The drivers of SDOH's association with cardiovascular health in patients with cancer are unclear. Some studies in the general population have found access to healthcare as a driver,(95) which was also demonstrated in the above study by Satti, Chan and colleagues in cancer survivors.(98) The above study also identified differences in economic stability, neighbourhood / environmental / social cohesion, community and social support, and food security as potential drivers,(98) but the inter-correlated nature of these factors meant that these findings may best be seen as exploratory, and the lower-level, more mechanistic drivers are yet to be elucidated. A related study by Chan and colleagues also suggested that psychological distress may drive

the above association for SDOH,(99) consistent with observations in non-cancer cohorts.(100) Overall, further research into the definition, quantification, modelling, and drivers of SDOH's association with cardiovascular health in patients with cancer is warranted, as is systematizing the definition of cardiovascular health in relevant studies, and translating these findings into policies that effectively address deprivation-related inequalities in cardio-oncology (**Table 1**).

Monitoring progress

Whilst progress is continually being made in cardio-oncology, it is important to stay critical and assess whether such progress has translated into differences in practice and patient outcomes. Unfortunately, these studies of temporal trends are exceedingly rare. A nationwide, American study demonstrated evolving cardiovascular needs amongst patients with cancer.(101) Another study using the same database showed reducing rates of cardiovascular mortality, particularly in males and patients living in rural areas.(102) Meanwhile, a population-based Hong Kong study of patients with prostate cancer receiving androgen deprivation therapy observed reducing mortality but increasing cardiovascular risk, even after accounting for competing risks, suggesting that improvements in these patients' cardiovascular care lagged behind those in their cancer therapies.(19) Another population-based Hong Kong study of patients with cancer receiving immune checkpoint inhibitors demonstrated persistently poor completeness of cardio-metabolic work-up prior to initiating these agents.(103) More studies like these are needed to monitor the progress that we, as a field, are making (**Table 1**). To this end, the ESC has developed standardized quality indicators for use in monitoring the quality of care in the prevention and management of cancer therapy-related cardiotoxicity.(104) Studies making use of such tools will be instrumental in guiding further research.

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Call for action

Whilst a number of societal statements or summaries have been published outlining gaps in evidence and roadmaps for research in specific areas of basic / translational, clinical or social research,(105–108) few have provided a broad overview of the gaps in evidence in cardio-oncology. To this end, we summarized the afore-identified gaps in evidence in **Table 1** and **Figure 1**. Contrasting some statements which were centred around research pipelines or methods,(107,108) we opted for a more general approach by highlighting areas of particular interest in each of the key areas reviewed above, such that our summary complemented other more specific, method-based statements. We hope that this provides a holistic guidance to cardio-oncology for both novices and experts in cardio-oncology research.

Conclusion

Cardiovascular diseases in patients with cancer are an increasingly important healthcare problem. Whilst much progress has been made in the understanding of these conditions, further research into the epidemiology, natural history, prevention, management, and determinants of cardiovascular health in these patients remains urgently required to address this growing clinical issue and improve clinical care.

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Table 1. Critical gaps in the cardio-oncology literature.

Domain	Key areas for research
Epidemiology	• Cardiovascular burden in non-Caucasian patients with cancer • Long-term cardiovascular burden in patients with cancer • Cardiovascular burden in patients with different types/sites of cancers • Standardizing the definition of cardiovascular outcome in cardio-oncology studies • Use of estimates that are clinically easy to interpret and communicate
Cardiovascular risk factors	• Interplay between cardiovascular risk factors • Long-term management of cardiovascular risk factors in patients with cancer • Mechanisms underlying the increased cardiovascular risk in patients with cancer
Cancer therapy-related cardiotoxicity	
Epidemiology	• Burden in non-Caucasian patients with cancer receiving specific cancer therapies • Long-term burden specific to different cancer therapies
Mechanisms	• Mechanisms underlying cancer therapy-related cardiotoxicity • Potential targets for preventing / ameliorating cancer therapy-related cardiotoxicity
Risk stratification	• Development and validation of cardiovascular risk stratification tools specific to cancer therapies • Development and validation of more sensitive and/or specific biomarkers for cancer therapy-related cardiotoxicity • Assessment of the performance of cardiovascular risk stratification tools developed for the general population when used on patients with cancer
Prevention and management	• The efficacy of different chemoprevention or treatment for cardiotoxicities related to different cancer therapies • Optimal regimen of cardiovascular medications as chemoprevention or treatment • Optimal timing of cardiovascular medications as chemoprevention or treatment
Social determinants of health	• Standardizing the definition and quantification of social determinants of health, with special attention paid to the interplay and overlap between different potential domains • Delineating the drivers underlying the associations between social determinants of health and cardiovascular health in patients with cancer

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	• Devising policies to translate research findings into patient care
Monitoring progress	• Temporal trends in clinical practice and adherence with guidelines • Whether changes in guidelines and/or clinical practice influenced patient outcomes • Using standardised quality indicators

Figure legend

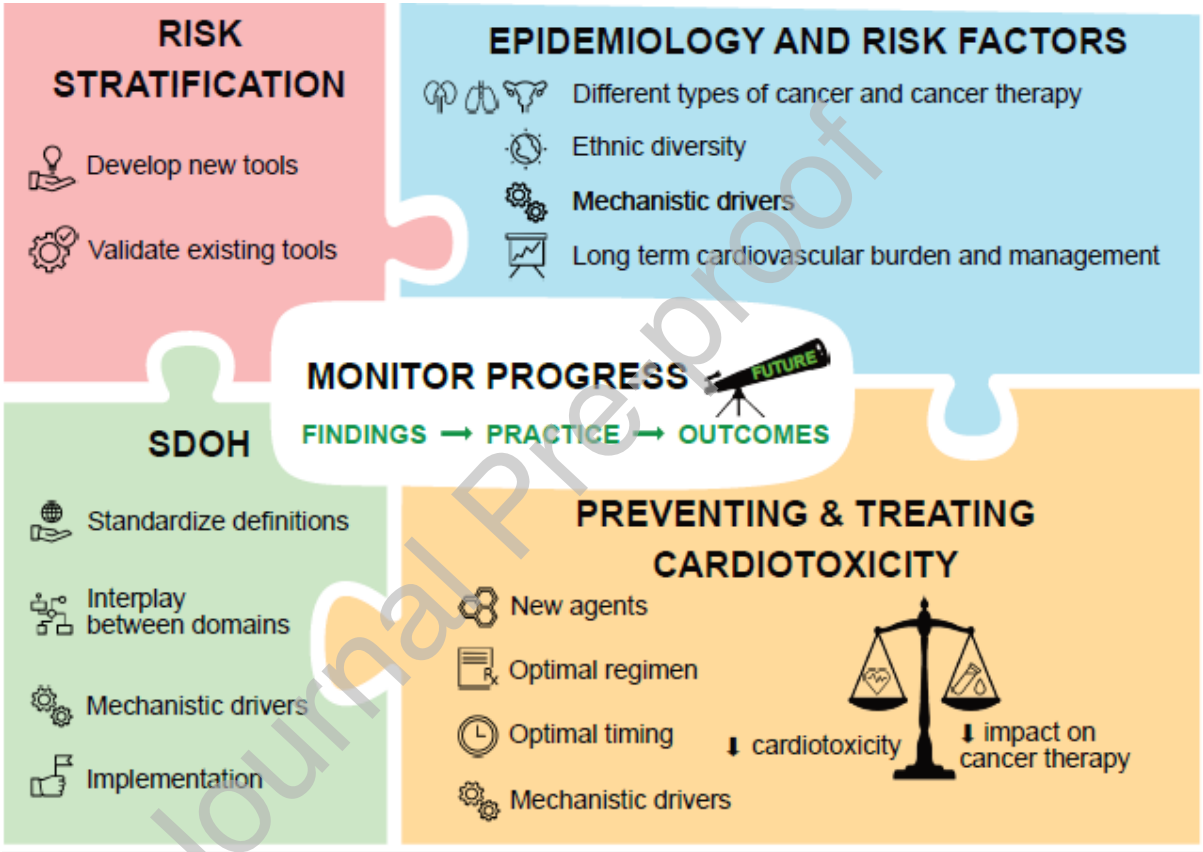

Figure 1. Graphical summary of the gaps in evidence for the main areas of research in cardio-oncology. SDOH, social determinants of health.

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Ethical Statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that all authors are responsible for the content and have read and approved the manuscript; and that the manuscript conforms to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published in *Annals in Internal Medicine*

We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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Conflicts of interest

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