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Title page

European Society of Cardiology quality indicators for the prevention and management of cancer therapy-related cardiovascular toxicity in cancer treatment

Developed in collaboration with the Heart Failure Association of the European Society of Cardiology.

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Abstract and keywords

Abstract

Aims: To develop quality indicators (QIs) for the evaluation of the prevention and management of cancer therapy-related cardiovascular toxicity.

Methods and results: We followed the European Society of Cardiology (ESC) methodology for QI development which comprises (i) identifying the key domains of care for the prevention and management of cancer therapy-related cardiovascular toxicity in patients on cancer treatment, (ii) performing a systematic review of the literature to develop candidate QIs, and (iii) selecting of the final set of QIs using a modified Delphi process. Work was undertaken in parallel with the writing of the 2022 ESC Guidelines on Cardio-Oncology and in collaboration with the European Haematology Association, the European Society for Therapeutic Radiology and Oncology and the International Cardio-Oncology Society. In total, 5 main and 9 secondary QIs were selected across five domains of care: (i) Structural framework, (ii) Baseline cardiovascular risk assessment, (iii) Cancer therapy related cardiovascular toxicity, (iv) Predictors of outcomes, and (v) Monitoring of cardiovascular complications during cancer therapy.

Conclusion: We present the ESC Cardio-Oncology QIs with their development process and provide an overview of the scientific rationale for their selection. These indicators are aimed at quantifying and improving the adherence to guideline-recommended clinical practice and improving patient outcomes.

Keywords: Quality indicators, cardio-oncology, assessment, treatment, cancer therapy-related cardiovascular toxicity, outcomes

European Society of Cardiology quality indicators for the prevention and management of cancer therapy-related cardiovascular toxicity in patients with cancer.

Developed in collaboration with the Heart Failure Association of the European Society of Cardiology.

Introduction

Cardio-oncology has emerged in recent years as a distinct entity that requires specialist expertise different to that provided by cardiology and/or oncology services. The complexity of the acute cardiovascular presentations from cytotoxic, targeted and immunotherapies necessitates co-operation between various specialists to ensure holistic delivery of care that aims to identify and mitigate the risks of cardiovascular complications during and after cancer therapy.[1-3] The greater numbers of cancers that are treated with cardiotoxic therapies, alongside the better screening for cancer therapy-related cardiovascular toxicity (CTR-CVT), create a need to develop tools to measure the quality of cardio-oncology care and capture outcomes.

The European Society of Cardiology (ESC) strives to develop suites of quality indicators (QIs) for its Clinical Practice Guidelines to facilitate the implementation of these evidenced-based guidelines and enable the quantification of the quality-of-care delivery. [4] Thus, in parallel with the writing of the 2022 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): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC),[5] and in collaboration with the European Haematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS), a group of domain experts in cardio-oncology was formed to construct QIs that span the breadth of cardio-oncology care and capture the key aspects of its care delivery and outcomes that are relevant to patients.

Methods

We used the ESC methodology for the development of QIs which comprises the following steps: (i) identifying key domains of care for the prevention and management of CTR-CVT in patients on cancer treatment, (ii) undertaking a systematic literature review to develop candidate QIs, and (iii) selecting of the final set of QIs using a modified Delphi process.[4] Structural QIs are the measures that evaluate care quality at institutional level, while process QIs are the measures that evaluate care quality at the patient level. Furthermore, QIs allow the capture of relevant outcomes that have an association with the quality-of-care delivery.

Members of the development group

The development group comprised Task Force members of the 2022 Guidelines on Cardio-Oncology, members of the ESC QI Committee, nominees from the Council of Cardio-Oncology (CO-Council) and the ESC Patient Forum, as well as international experts in Cardio-oncology field including representatives from IC-OS, EHA and ESTRO.

Target population and domains of care

The group initially defined the target population for whom the QIs will apply and the key domains of cardio-oncology care which encompass the developed indicators. The target population was defined as patients with an established cardiovascular disease prior to commencing cancer treatment and those who were at high risk of cardiovascular complications during or after receiving cancer treatment.

For each domain, the measurement period was specified to clarify the timepoint at which each QI is measured. These timepoints extended from the period before starting cancer treatment (for the assessment of the cardiovascular toxicity risks) to the long-term follow up after the completion of cancer therapy (for the identification of potential cardiovascular consequences of cancer treatment).

Further specifications were provided for individual QIs including a numerator, which is the criteria by which the QI is accomplished and a denominator, which is the eligibility criteria for the QIs. Given that structural QIs are binary measurements of the availability of certain services, only numerators are defined for the structural QIs. Both main and secondary QIs were developed based on the voting scores on the validity and the feasibility of the candidate QIs.

Systematic Review methods

Search Strategy

We conducted a systematic review of published literature using the Preferred Reporting for Systematic Review and Meta-Analyses (PRISMA) statement.[6] A search strategy was developed using keywords and medical subject headings that included Cardio-toxicity, Cardio-oncology, Oncology, Haemato-oncology, Quality indicators and Outcome measures and medical subject headings such as 'Cancer', 'oncological treatment', 'risk factor' and 'quality indicator' (**Supplementary Material online- Table 1**).

We developed separate search strategies for MEDLINE and Embase via OVID® using an iterative process incorporating result of hand searching from reference lists and grey literature.

Eligibility criteria

Studies included were those that evaluated the cardiovascular consequences of cancer therapy in adult patients (>18 years old) who have been treated with at least one cardiotoxic treatment at any point including chemotherapy, radiotherapy and immunotherapy. We included randomised

controlled trials and observational studies as well as consensus documents that are published in English between 01 January 2015 and 10 September 2021. We excluded systematic reviews, meta-analysis, conference abstracts and case reports. Studies with no defined intervention or outcome measures were also excluded.

Study selection

Endnote X9 (Clarivate Analytics, London, UK) was used to manage references and remove duplicates. Two authors (EB and GL) independently examined the abstracts of the retrieved studies which were assessed against the eligibility criteria. Disagreements were resolved through a third reviewer (SA) and full text article review.

Data extraction

For each included study, the systematic review team extracted the definitions of the target population, intervention(s), comparison(s) and outcome measure(s). Data were collated using an Excel spreadsheet.

Data synthesis

Modified Delphi process

The modified Delphi approach was used to evaluate the candidate QIs derived from the literature review.[4] The members of the group were made aware of the ESC criteria for QI development to standardize the voting process, and each candidate QI was ranked by each panellist on a 9-point

ordinal scale for both validity and feasibility using an online questionnaire (See supplement for criteria table). Two rounds of voting were conducted using the Delphi process with a series of virtual meetings between April 2021 until July 2022 to discuss the voting results and address concerns and queries.

Analysis of voting results

The 9-point ordinal scale used for voting implied that ratings of 1–3 meant that the QI is not valid/feasible; ratings of 4–6 meant that the QI is of an uncertain validity/feasible; and ratings of 7–9 meant that the QI is valid/feasible. For each candidate QI, the median and the mean deviation from the median were calculated to evaluate the central tendency and the dispersion of the votes. Indicators, with median scores ≥7 for validity, ≥4 for feasibility, and with minimal dispersion, were included in the final set of QIs. The development group was asked to modify the phrasing of the candidate QIs to reach consensus on the inclusion of the indicator in the final set.

Results

Systematic review results

The domains of care identified were: (i) Structural framework, (ii) Baseline cardiovascular risk assessment, (iii) CTR-CVT, (iv) Predictors of outcomes and (v) Monitoring of cardiovascular complications during cancer therapy. The literature search retrieved 1081 articles, of which 64 met the inclusion

criteria (see **Figure 1**). These studies were used to extract 33 candidate QIs which were included in the first voting round. In total 5 (15%) of the candidate QIs were included as main QIs. Of the remaining indicators, 19 (58%) were excluded and 9 (27%) were considered in a second Delphi round and included as secondary QIs (see **Table 1**).

Insert Figure 1 here

Quality indicators

Insert Table 1 here

Domain 1: Structural Framework

Two QIs have been selected in this domain. The first is a main QIs that captures the need for dedicated healthcare professionals for cardio-oncology patients (**Main 1**). The second defines the appropriate composition of a multidisciplinary team in this setting (**Secondary 1**), which should consist of at least an oncologist, cardiologist and a specialist nurse. The team should ideally have access to other services such as a radiologist, surgeon, haematologist, palliative care expert, physiotherapist, pharmacist, psychologist, general practitioner, and dietitian. Given the implementation of this QI may be challenging in some healthcare centres, it was included as a secondary one.

Domain 2: Baseline cardiovascular risk assessment

The QIs under this domain relate to the importance of a comprehensive cardiovascular assessment prior to commencing cancer treatment. That is, the documentation of previous cardiovascular

history (for instance, history or clinical evidence of venous thrombo-embolism) (**Main 2.1**), as well as the identification of modifiable risk factors associated with cardiovascular complications such as diabetes and hypertension (**Main 2.2**). The other QI in this domain relates to the need to ensure that shared decision-making is discussed with the patient when determining the treatment strategy (**Main 2.3**). In addition, the assessment of cardiovascular risk by performing a comprehensive clinical assessment may identify patients at higher risk and highlight strategies to mitigate this risk (**Secondary 2.1**).

Domain 3: Cancer therapy related cardiovascular toxicity (CTR-CVT)

Given CTR-CVT is associated with cardiovascular mortality during and after cancer treatment,[7,8] capturing the annual rate of hospitalisation due to CTR-CVT has been selected as a main QIs (**Main 3**). After starting cancer treatment, it is important to perform a comprehensive cardiovascular assessment for patients developing signs and/or symptoms of CTR-CVT (**Secondary 3.2**). However, CTR-CVT can sometimes be asymptomatic and at various time points. As such, two QIs have been selected to ensure appropriate follow up for high-risk individuals (**Secondary 3.3**) and within 3 months from the completion of cancer treatment (**Secondary 3.3**). [5,9]

Domain 4: Predictors of outcomes

Heart failure and in particular heart failure with reduced Ejection Fraction (HFrEF) is a well-documented complication of cancer treatment and patients should be closely monitored in the first year following completion of treatment.[7,10] Early diagnosis is an important measure along with appropriate management with guideline-directed medical therapy including beta-blockers, renin-

angiotensin-aldosterone inhibitors, and sodium glucose co-transporter2 inhibitors (**Secondary 4.1**). [11] This QI has been aligned with the ESC guidelines for HF and the respective QI for HFrEF. [12,13] The second QI in this domain is a more specific indicator that pertains to reducing the risk of anthracycline and HER2 therapies by commencing prognostic treatment for moderate or severe asymptomatic CTRCD (**Secondary 4.2**).

Domain 5: Monitoring of cardiovascular complications during cancer therapy

Whilst different types of cancer treatment may have an impact on the cardiovascular system, certain treatments are known to be more toxic than others.[14] As such, close monitoring for patients on HER2 therapies with a structured assessment to their side-effect profile may help identify and address these adverse events early (**Secondary 5.1**). For those on tyrosine kinase inhibitors, the assessment of blood pressure at every visit (**Secondary 5.2**) may have a role in recognising the potential implications of this therapy. [15]

Discussion

This document presents the ESC QIs for cardio-oncology and highlights the breadth of this field which span across various clinical settings. These indicators have been developed in parallel with the writing of the 2022 ESC guidelines on cardio-oncology and using the ESC methodology. [4,5] We have identified 5 domains of care for cardio-oncology and selected 5 main and 9 secondary QIs across these domains. They include structural indicators of care quality such as the availability of a multi-disciplinary team, the benefits of which have been previously highlighted [16], as well as process and outcome QIs, with particular focus on shared decision-making as a key factor for successful treatment. [17]

Cardio-oncology is expanding with increasing patient population and complexity, creating a need to standardize the methods by which care delivery is measured and outcomes captured given the existing variation and the room for improvement. [18] Calls have been made to establish designated cardio-oncology centres across Europe in line with the growing number of patients in need for specialists' input and multidisciplinary management plans. [19] Patients on cancer treatment are at a higher risk for developing cardiovascular complications, and a number of strategies may help mitigate these risks. As such, we combined existing evidence with expert consensus to develop a suite of QIs for patients considered for or receiving cancer treatment.

We are not aware of any previous initiative that aimed to develop internationally endorsed set of QIs for cardio-oncology patients. The widespread implementation of these indicators enables the conduction of meaningful comparative analyses across different centres and regions to highlight disparities and standardise patient care. Besides, the integration of these QIs into a system of data collection may facilitate the establishment of a unified registry for cardio-oncology that may help generate evidence and monitor patterns of care delivery over time.

Although there are obvious strengths to the study, there are some limitations that need to be acknowledged. The final QIs were determined by expert opinion via the Delphi process and therefore reflects the views of the Working Group members. However, this was preceded by a systematic literature review and the Delphi method used to independently record experts' votes to select the QIs and also we applied the ESC criteria to standardise the voting process. The feasibility of the QIs is an issue and relates to organisational barriers and limited resources in clincial practice across Europe. We acknowledge that there is a variance of resources and the QIs may not be feasible currently but can be used to standardise care and improve patient services in the future.

Conclusion

We present the ESC Cardio-Oncology QIs along with the development process and provide an overview of the scientific rationale for their selection. These indicators are aimed at quantifying and

improving adherence to guideline-recommended clinical practice and improving patient outcomes with particular focus on the cardio-toxic effects of cancer regimens and their effect on the cardiovascular system.

Conflict of Interest:

G Lee: Grants: Horizon 2020.

S Aktaa- Educational events (Wondr medical), European Society of Cardiology.

E. Baker- Health Education England Post Doctoral Research Fellowship

C Gale: BHF, NIHR, Horizon 2020, Daichii Sankyo NHS Joint Working Party, Abbott Diabetes, BMS/Pfizer. Honoraria: Astra Zeneca, Boston Scientific, Menarini, Raisio Group, Wondr Medical, Zydus. Boards: Amgen, Bayer, BMS, Boehringer Ingelheim, Chiesi Ltd, Daichii Sankyo, Menarini Diagnostics UK, iRhythm. Leadership: NICE indicator advisory committee, Deputy Editor: EHJ Quality of Care and Clinical Outcomes, Oxford University Press, Chair ESC Quality Indicator Committee.

G Gulati: Honoraria: AstraZeneca, BMS, Roche, Orion Pharma, Novartis. Leadership: Board member Norwegian Cardiology Society

R. Asteggiano- Royalties from Springer.

S Szmit: Amgen, Angelini, Astra Zeneca, BMS, Bayer, Gilead, Pfizer

A Cohen Solal: Vifor, Novartis, MSD, Bayer, Sanofi, Boehringer Ingelheim, Amgen, Servier

P Garrdio: Honoraria: Advisory Role: Abbvie, Amgen, Astra Zeneca, Bayer, BMS, Daichi, GSK, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Sanofi. Speaker: Janssen, MSD, Novartis, Medscape, Takeda, TouchTime. Support attending meetings: Astra Zeneca, BMS. Leadership: ESMO Council member

A Sverdlov: Future Leader Fellowships (Awards IDs 101918 & 106025). Medical Research Future Fund (Australia). NSW Department of Health, RACE Oncology. Honoraroa: Celgene Pty Ltd, BMS, Novarits, BMS, AstraZeneca, Boehringer Ingelheim.Leadership: ESC, Joint Cardiac Society of Australia and New Zealand and Clinical Oncology Society of Australia Cardio-Oncology Working Group, Global Cardio-Oncology Registry.

CG Tocchetti: Italian Ministero della Salute RF 2016, VivaLyfe, Univers Formazione, Menarini, Amgen. Patients: P75NTR.

P Zamorano: Honoraria: Novo Nordisk, Novaris, Philips, Bayer, Medtronic, Amgen.

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A Kirby: President of European Society of Radiation Therapy and Oncology

D Farmakis: Consulting fees: Abbott, Bayer, Boehringer-Ingelheim, Leo

G Curigliano- Grants: Merck, Astra Zeneca. Consulting fees: Roche, BMS, Novartis, Lily, Pfizer, Seagen, Ellipsis, Gilead, Merck, Celcuity, Daichii Sankyo. Leadership: ESMO Council
R Stephens. Honoraria: for being a cancer patient advocate working as a volunteer in cancer research

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T Lopez-Fernandes: Philips, Janssem, Incyte

Data Availability: The data underlying this article are available and in the online supplementary material.

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Table 1: ESC Cardio-oncology quality indicators for the management of patients with cancer or cancer survivors

DOMAIN 1: Structural framework
Main 1: Healthcare centres providing cancer treatment with available resources for patient education including dedicated health care professionals to optimise patient ability to manage self-care during and after treatment.
Numerator: centres providing cancer treatment with available resources for patient education including dedicated health care professionals to optimise patient ability to manage self-care during and after treatment.
Secondary 1: Healthcare centres providing cancer treatment with an available MDT for cardio-oncology. MDT should comprise as a minimum an oncologist**, a cardiologist and a specialist nurse*.
Numerator: centres providing cancer treatment with an available MDT for cardio-oncology.
DOMAIN 2: Baseline cardiovascular risk assessment
Main 2.1: Proportion of patients considered for cancer treatment[$] who are evaluated for prior history/clinical evidence of cardiovascular condition (including heart failure, coronary artery disease, arrhythmias, history of pulmonary embolism or deep vein thrombosis) prior to treatment
Numerator: patients considered for cancer treatment who are evaluated for a prior history of cardiovascular condition (including heart failure, coronary artery disease, arrhythmias, pulmonary embolism or deep vein thrombosis)) prior to treatment
Denominator: patients considered for cancer treatment
Measurement period: prior to treatment
Main 2.2: Proportion of patients considered for cancer treatment who have their modifiable cardiovascular risk factors (Diabetes Mellitus, Hypertension etc) identified prior to treatment
Numerator: patients considered for cancer treatment who have their modifiable cardiovascular risk factors (Diabetes Mellitus, Hypertension, etc) identified
Denominator: patients considered for cancer treatment
Measurement period: prior to treatment
Main 2.3: Proportion of patients considered for cancer treatment who have been engaged in shared decision-making when deciding treatment strategy
Numerator: patients considered for cancer treatment who have been engaged in shared decision-making when deciding treatment strategy
Denominator: patients considered for cancer treatment
Measurement period: prior to treatment
Secondary 2.1: Proportion of patients considered for cardiotoxic cancer treatment[#] who have an assessment of their cardiovascular risk using diagnostic tools

Numerator: patients considered for cardiotoxic cancer treatment who have an assessment of their cardiovascular risk assessment using diagnostic tools
Denominator: patients considered for cancer treatment
Measurement period: prior to treatment

DOMAIN 3: Cancer Therapy Related Cardiovascular Toxicity

Main 3: Annual rate of hospitalisation due to cancer therapy related cardiovascular toxicity
Numerator: patients on or have recently been on cancer treatment who are hospitalised due to cancer therapy related cardiovascular toxicity
Denominator: patients on or have recently been on cancer treatment
Measurement period: during or after treatment
Secondary 3.1: Proportion of patients with symptoms and/or signs of cancer therapy related cardiovascular toxicity during/after cardiotoxic cancer treatment who have a cardiovascular assessment
Numerator: patients with symptoms and/or signs of cancer therapy related cardiovascular toxicity during/after cardiotoxic cancer treatment who have a cardiovascular assessment
Denominator: patients with symptoms of cancer treatment-related toxicity during/after cardiotoxic cancer treatment
Measurement period: during and after treatment
Secondary 3.2: Proportion of patients at high risk[&] for cancer therapy related cardiovascular toxicity who are followed up after the completion of cardiotoxic cancer treatment to evaluate for adverse cardiac events
Numerator: patients at high risk[&] for cancer therapy related cardiovascular toxicity who are followed up after the completion of cardiotoxic cancer treatment to evaluate for adverse cardiac events
Denominator: patients after the completion of cardiotoxic cancer treatment
Measurement period: 1 and 5 years after treatment
Secondary 3.3: Proportion of patients who have a cardiovascular risk assessment 1 year after the completion of cardiotoxic cancer treatment[#]
Numerator: patients who have a cardiovascular risk assessment 1 year after the completion of cardiotoxic cancer treatment^
Denominator: patients within 1 year of the completion of cardiotoxic cancer treatment
Measurement period: 1 year after treatment

DOMAIN 4: Predictors of outcomes

Secondary 4.1: Proportion of patients who develop symptomatic HFrEF during cancer treatment and are prescribed medications such as beta blockers, ACEI/ARB/ARNI, MRA and SGLT2 inhibitors
Numerator: patients who develop HF during cancer treatment and are prescribed beta blockers, ACEI/ARB/ARNI, MRA and SGLT2 inhibitors
Denominator: patients who develop HF during cancer treatment
Measurement period: during and after treatment
Secondary 4.2: Proportion of patients treated with anthracyclines or HER2 targeted therapies and develop asymptomatic moderate or severe CTRCD during cancer treatment who are prescribed beta blockers and/or ACEI/ARB

Numerator: patients treated with anthracyclines or HER2 targeted therapies and develop asymptomatic moderate or severe CTRCD during cancer treatment who are prescribed beta blockers and/or ACEI/ARB
Denominator: patients treated with anthracyclines or HER2 targeted therapies and develop asymptomatic moderate or severe CTRCD during cancer treatment
Measurement period: during treatment

DOMAIN 5 : Monitoring of cardiovascular complications during cancer therapy

Secondary 5.1: Proportion of patients on HER2-targeted therapies who have their cardiovascular assessment^ every 3 months during the first year of treatment
Numerator: patients on HER2-targeted therapies who have their cardiovascular assessment every 3 months during the first year of treatment
Denominator: patients on HER2-targeted therapies
Measurement period: during & after treatment
Secondary 5.2: Proportion of patients on TKI, including BTKi, who have their blood pressure assessed at every clinical visit.
Numerator: Proportion of patients on TKI (including BTKi) who have their blood pressure assessed at every clinical visit.
Denominator: patients on TKI (including BTKi)
Measurement period: during and after treatment

ABBREVIATIONS: ACEI = angiotensin converting enzymes inhibitors, ARBs = angiotensin receptors blockers, ARNI = angiotensin receptor neprilysin inhibitor, BTKi = bruton tyrosine kinase inhibitors, CTR-CVT = Cancer therapy related cardiovascular toxicity DM = diabetes mellitus, DVT = deep venous thrombosis, HCPs = healthcare professionals, HF = heart failure, HFrEF = heart failure with reduced ejection fraction, HTN = hypertension, LVSD = left ventricular systolic dysfunction, MDT = multidisciplinary team, MRA = mineralocorticoid receptor antagonists, PE = pulmonary embolism, SGLT2 = sodium–glucose cotransporter 2 (SGLT2), TKI = tyrosine kinase inhibitors.

[*]Ideally MDT should also involve a radiologist, surgeon, palliative care expert, physiotherapist, pharmacist, psychologist, general practitioner, and dietitian.

[&]High-risk patients are those with >10% risk of future cardiovascular toxicity according to HFA-ICOS risk assessment (Lyon AR et al. 2020)

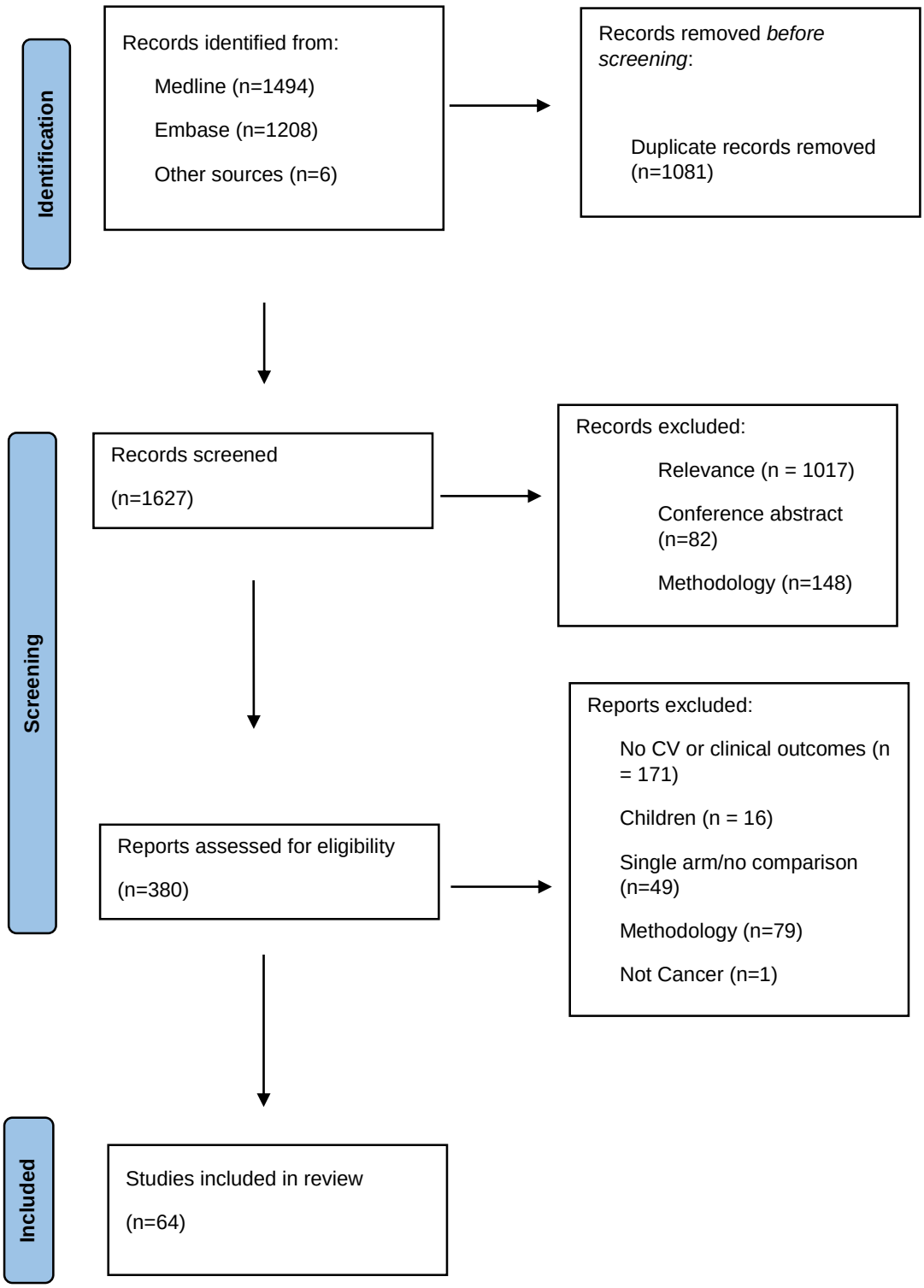
[#]Cardiotoxic cancer treatment is defined as any cancer treatment with potential cardiovascular side effects

[^]Assessment includes an echocardiography (at baseline and within 12 months after completing treatment and include a documentation of LVEF and GLS assessment), cardiac troponins and NPs in high and very high-risk patients (at baseline, before every anthracycline cycle and 3 and 12 months after therapy completion).

***Oncologist includes three specialists: medical oncologist, haematologist and radiation oncologist*

$ Cancer treatment includes chemotherapy, targeted agents, hormone therapies, immune therapies, and radiation therapy

Figure 1: PRISMA Flow Chart for selection of included studies



Supplementary Table 1: Summary of Systematic Search Strategy:

Overview:	
Interface	Ovid
Databases	Ovid MEDLINE (1946-09/2021)
	OVID Embase (1996 – 09/2021)
Date of Search	10/09/2021
Study Types	Randomised controlled trials
	Observational Studies
Limits	English language
	Publication date (01/2015 – 09/2021)
	Human participants

Multi-database search strategy			
Line	Syntaxes	Medline Count	Embase Count
1	Cancer.mp or exp Neoplasms/	4062443	5979401
2	Oncolog*.mp.	192715	433643
3	(Cardi* adj2 Oncolog*).mp.	2054	
4	Exp Hematologic Neoplasms/	22630	2683889
5	Exp Neoplasm Metastasis/	212519	726618
6	Tumo$r.mp.	1751026	3248675
7	1 OR 2 OR 3 OR 4 OR 5 OR 6	64536526	7958749
8	Chemotherapy.mp. or Drug Therapy/	1680342	3345858
9	Exp Radiotherapy/	195119	650486
10	Exp Immunotherapy/	295456	251265
11	Hormone Therapy.mp.	451409	321092

12	Exp Anthracyclines/	73107	24044
13	Anti-HER2.mp.	2783	5245
14	Interferon therapy.mp.	179072	324111
15	Exp Molecular Targeted Therapy/	32361	45045
16	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	2595775	4314485
17	Exp Risk Factors/ or Exp Myocardial Infarction/ or Exp Coronary Artery Disease/ or Cardiac Risk Factor.mp. or Exp Cardiovascular Disease	3148169	4747672
18	Exp Hypertension/	298582	
19	Hypercholesterolaemia.mp. or exp Hypercholesterolemia	29939	80112
20	Exp Diabetes Mellitus/	454034	1098310
21	Exp obesity/	231117	581631
22	Exp smoking/	153832	427178
23	Exp Sedentary Behaviour/	11444	16400
24	(Genetic adj4 cardi*).mp.	4339	6731
25	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24	372322	5977616
26	7 AND 16 AND 25	106343	443506
27	(Quality adj3 indicator*).mp.	28024	23010
28	Exp Quality indicators, Health Care/	23282	3557512
29	Exp Cardiotoxicity	2952	47561
30	Patient reported outcomes.mp. or exp patient reported outcome measures/	21756	46722
31	Risk adj2 (assessment or stratification).mp.	358906	711406
32	Exp Risk Assessment/	291461	631873
33	Risk stratification.mp.	35915	62686

34	(Palliative adj2 Care).mp.	71410	56306
35	Exp Patient Satisfaction/ or patient experience.mp.	94943	160638
36	Care pathway.mp.	3167	5919
37	Antithrombotic therapy.mp. or exp anticoagulants/	233281	741542
38	Exp mortality/	405758	1253302
39	Exp morbidity/	600267	401283
40	27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39	1662667	5789671
41	26 AND 40	28501	224365
42	Limit step 41 to English and published since 2015	1494	1208