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Guideline Driven Care in Cardio-Oncology: ESC Position Paper

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Presenter Disclosure Information

Advancing Cardiovascular Care of the Oncology Patient

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- I will not discuss off label use or investigational use in my presentation.
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[1] Representing the International CardiOncology Society (ICOS)

Pocket Guidelines and smartphone app also available!

The ESC document attempts to summarize a large and diverse spectrum of clinical experience, limited clinical research, and historical reports on the topic.

The document is organized according to these 9 conditions and generally describes CV complications of cancer therapy, strategies for prevention and attenuation of CV complications, long-term surveillance for cancer survivors, and suggests future directions.

- myocardial dysfunction and heart failure (HF);
- coronary artery disease (CAD);
- valvular disease;
- arrhythmias, especially those induced by QT-prolonging drugs;
- arterial hypertension;
- thromboembolic disease;
- peripheral vascular disease and stroke;
- pulmonary hypertension and
- pericardial complications.

Key Phrases/Words:

Complexity
Optimal CV care
Interactions between disciplines
Define a curriculum
Engagement in the development of new therapies
Survivorship
Appropriate evaluation of CV events

Table 1 Incidence of left ventricular dysfunction associated with chemotherapy drugs[10–21]

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m² 12.5–16 g/m²	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20.1[20a]
Bevacizumab	1.6–4[14b]
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellanous	
Everolimus	<1
Temsirolimus	<1

Table 2 Factors associated with risk of cardiotoxicity following treatment with anthracyclines[a]

Risk factors

• Cumulative dose
• Female sex
• Age
  - >65 years old
  - Paediatric population (<18 years)
• Renal failure
• Concomitant or previous radiation therapy involving the heart
• Concomitant chemotherapy
  - alkylating or antimicrotubule agents
  - immuno- and targeted therapies
• Pre-existing conditions
  - Cardiac diseases associating increased wall stress
  - Arterial hypertension
  - Genetic factors

[a]Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) or anthracenedione (mitoxantrone).

Table 3 Factors associated with risk of cardiotoxicity following anti-HER2 compounds and VEGF inhibitors[70–72]

Agent	Risk factors
Anti-HER2 compounds	
- Antibodies - Trastuzumab - Pertuzumab - T-DM1 - Tyrosine kinase inhibitor - Lapatinib	• Previous or concomitant anthracycline treatment *(short time between anthracycline and anti-HER2 treatment)* • Age (>65 years) • High BMI >30 kg/mg^2 • Previous LV dysfunction • Arterial hypertension • Previous radiation therapy
VEGF inhibitors	
- Antibodies - Bevacizumab - Ramucirumab	Pre-existing HF, significant CAD or left side VHD (e.g. mitral regurgitation), chronic ischaemic cardiomyopathy • Previous anthracycline
- Tyrosine kinase inhibitors - Sunitinib - Pazopanib - Axitinib - Neratinib - Afatinib - Sorafenib - Dasatinib	• Arterial hypertension • Pre-existing cardiac disease

BMI = body mass index; CAD = coronary artery disease; HER2 = human epidermal growth factor receptor 2; HF = heart failure; MI = myocardial infarction; VEGF = vascular endothelial growth factor; VHD = valvular heart disease.

Table 4 Baseline risk factors for cardiotoxicity

Current myocardial disease	*Demographic and other CV risk factors*
• Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide[a]) • Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) • Moderate and severe VHD with LVH or LV impairment • Hypertensive heart disease with LV hypertrophy • Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Restrictive cardiomyopathy • Cardiac sarcoidosis with myocardial involvement • Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	• Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) • Arterial hypertension • Diabetes mellitus • Hypercholesterolaemia
Previous cardiotoxic cancer treatment	***Lifestyle risk factors***
• Prior anthracycline use • Prior radiotherapy to chest or mediastinum	• Smoking • High alcohol intake • Obesity • Sedentary habit

AF = atrial fibrillation; CABG = coronary artery bypass graft; CAD = coronary artery disease; CV = cardiovascular; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; VHD = valvular heart disease.

[a]B-type natriuretic peptide >100pg/ml or N-terminal pro-B-type natriuretic peptide >400pg/ml with no alternative cause.

Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: **- 3D-based LVEF** **- 2D Simpson's LVEF** **- GLS**	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: **- Troponin I** **- High-sensitivity Troponin I** **- BNP** **- NT-proBNP**	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

ACE-Is = angiotensin converting enzyme inhibitors; BNP = B-type natriuretic peptide; ECVF = extacellular volume fraction; GLS = global longitudinal strain; LV = left ventricular; LLN = lower limit of normality; LVEF = left ventricular ejection fraction; MUGA = multigated radionuclide angiography; NT-proBNP = N-terminal fragment B-type natriuretic peptide.

2.1.3 Key points

- Cancer patients treated with potentially cardiotoxic therapy are at high risk of developing HF and should therefore receive medical care aimed at obtaining strict control of cardiovascular risk factors.
- LVEF should be determined before and periodically during treatment for early detection of cardiac dysfunction in patients receiving potentially cardiotoxic chemotherapy, with a method that provides sufficient image quality and, preferably, using the same method during follow-up.
- This group has decided to consider the lower limit of normal of LVEF in echocardiography as 50%, in line with the definition of cardiotoxicity commonly used in registries and trials in patients with cancer.
- A patient with a significant decrease in LVEF (e.g. a decrease >10%), to a value that does not drop below the lower limit of normal, should undergo repeated assessment of LVEF shortly after and during the duration of cancer treatment.
- If LVEF decreases >10% to a value below the lower limit of normal (considered as an LVEF <50%), ACE inhibitors (or ARBs) in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated, as these patients are at high risk of developing HF.
- ACE inhibitors (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated.

Table 7 Pathophysiological mechanisms of coronary artery disease in cancer treatment[7,60,81,99,117–123]

Agent	Pathophysiological mechanism	Risk of coronary artery disease and acute coronary syndrome
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	• Endothelial injury • Vasospasm	• Up to 18% manifest myocardial ischaemia • Up to 7–10%: silent myocardial ischaemia
Platinum compounds (cisplatin)	• Procoagulant status • Arterial thrombosis	• 20-year absolute risk of up to 8% after testicular cancer • 2% risk of arterial thrombosis
VEGF inhibitors (bevacizumab, sorafenib, sunitinib)	• Procoagulant status • Arterial thrombosis • Endothelial injury	• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%
Radiotherapy	• Endothelial injury • Plaque rupture • Thrombosis	• 2–7-fold increased relative risk of myocardial infarction • Cumulative 30-year coronary events incidence of 10% in Hogdkin lymphoma survivors • Risk proportional to irradiation dose

5-FU = 5-fluorouracil; VEGF = vascular endothelial growth factor.

Table 8 Cancer drug agents associated with cardiac arrhythmias

Type of arrhythmia	Causative drug
Bradycardia	Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, doxorubicine, epirubicine, 5-FU, ifosfamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.
Sinus tachycardia	Anthracyclines, carmustine.
Atrioventricular block	Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.
Conduction disturbances	Anthracyclines, cisplatin, 5-FU, imatinib, taxanes.
Atrial fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), anthracyclines, antimetabolites (capecitabine, 5-FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerase II inhibitors (amsacrine, etoposide), taxanes, vinca alkaloids.
Supraventricular tachycardias	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, anthracyclines, antimetabolites (capecitabine, 5-FU, methotrexate), bortezomib, doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.
Ventricular tachycardia/fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5-FU, gemcitabine), arsenic trioxide, doxorubicin, interferons, IL-2, methothrexate, paclitaxel, proteasome inhibitors (bortezomib, carfilzomib), rituximab, romidepsin.
Sudden cardiac death	Anthracyclines (reported as very rare), arsenic trioxide (secondary to torsade de pointes), 5-FU (probably related to ischaemia and coronary spasm), interferons, nilotinib, romidepsin.

5-FU = 5-fluorouracil; IL-2 = interleukin 2; TKI = tyrosine kinase inhibitor.

Table 10 Risk factors for QT prolongation in cancer patients

Risk factors for QT prolongation	
Correctable	**Non-correctable**
Electrolyte imbalance • Nausea and emesis • Diarrhoea • Treatment with loop diuretics • Hypokalaemia (≤3.5 mEq/L) • Hypomagnesaemia (≤1.6 mg/dL) • Hypocalcaemia (≤8.5 mg/dL) **Hypothyroidism** **Concurrent use of QT-prolonging drugs** • Antiarrhythmic • Anti-infective • Antibiotic • Antifungal • Psychotropic • Antidepressant • Antipsychotic • Antiemetic • Antihistamine	• Family history of sudden death (occult congenital LQTS or genetic polymorphisms) • Personal history of syncope • Baseline QTc interval prolongation • Female gender • Advanced age • Heart disease • Myocardial infarction • Impaired renal function • Impaired hepatic drug metabolism

LQTS = long QT syndrome.

Table 11 Clinical factors associated with increased risk of cancer-associated venous thromboembolism (modified from Khorana et al.[182])

Cancer-related factors • Primary site of cancer (mostly pancreas, brain, stomach, kidney, lung, lymphoma, myeloma) • Histology (specially adenocarcinoma) • Advanced stage (metastatic) • Initial period after cancer diagnosis
Patient-related factors • Demographics: older age, female sex, African ethnicity • Comorbidities (infection, chronic kidney disease, pulmonary disease, atherothrombotic disease, obesity) • History of venous thromboembolism, inherited thrombophilia • Low performance status
Treatment-related factors • Major surgery • Hospitalization • Chemotherapy and anti-angiogenic agents • Hormonal therapy • Transfusions • Central venous catheters

Supplementary Table Most recent reviews and meta-analyses on the incidence of hypertension with major VEGF inhibitor treatment

Drug	Number of studies included	Number of patients	Incidence of all grades of HTN, %	Incidence of stage 3-4 HTN, %
Bevacizumab[165]	20	6754	23.6	7.9
Sunitinib[167]	13	4999	21.6	6.8
Sorafenib[168]	13	2492	15.3	4.4
Axitinib[169]	10	1908	40.1	13.1
Vandetanib[170]	11	3154	24.2	6.8
Regorafenib[171]	5	750	44.4	12.5

HTN = hypertension; VEGF = vascular endothelial growth factor.

ESC Position Paper on Cancer treatments and Cardiotoxicity

- A very ambitous task that was completed in a relatively short time
- The pocket guidelines and smart phone app are unique advantages
- The content was an excellent summary of a broad constellation of topics
- Complete guidelines will be done in 1-2 years
- A call for concerted research is a must!

Save the Date

Global Cardio-Oncology Summit 2017

September 20-21, 2017

London, UK

Additional details to follow.

British Cardio-Oncology Society
BC-OS.org

Canadian Cardiac Oncology Network

INTERNATIONAL CardiOncology SOCIETY

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- Personalised medicine & genetics
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- Anticoagulation and antithrombotic (AF, ACS)
- Radiation-induced cardiotoxicity
- Managing cardiac issues during BMSC transplants
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