Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

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2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

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Incidence of left ventricular dysfunction associated with chemotherapy drugs

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

Chemotherapy agents	Incidence (%)
Monoclonal antibodies	
Trastuzumab	1.7–20.1
Bevacizumab	1.6–4
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

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Factors associated with risk of cardiotoxicity following treatment with anthracyclines

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

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Factors associated with risk of cardiotoxicity following anti-HER2 compounds and VEGF inhibitors

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

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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) • 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

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Anthracycline equivalence dose considering doxorubicin in rapid infusion as a reference

Drug	Relative cardiotoxicity	Incidence of HF rises to >5% when cumulative dose exceeds (mg/m^2)
Doxorubicin rapid infusion	1	400
Epirubicin	0.7	900
Daunorubicin	~0.75	800
Idarubicin	0.53	150

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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 haemo-dynamics 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.

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Pathophysiological mechanisms of coronary artery disease in cancer treatment

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

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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.

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Cancer drug agents associated with QT prolongation and Torsade de Pointes

Cancer drug agents	Average QT Prolongation (ms)	Increase in QTc >60 ms (%)	QTc >500 ms (%)	Torsade de pointes (%)
Anthracyclines				
Doxorubicin	14	11-14	NA	NA
Histone deacetylase inhibitors				
Depsipeptide	14	20-23.8	NA	NA
Vorinostat	<10	2.7-6	<1	NA
Tyrosine kinase inhibitors				
Axitinib	<10	NA	NA	NA
Bosutinib	NA	0.34	0.2	NA
Cabozantinib	10-15	NA	NA	NA
Crizotinib	9-13	3.5	1.3	NA
Dasatinib	3-13	0.6-3	<1.4	NA
Lapatinib	6-13	11	6.1	NA
Nilotinib	5-15	1.9-4.7	<1.2	NA
Pazopanib	NA	NA	2	<0.3
Ponatinib	<10	NA	NA	NA
Sorafenib	8-13	NA	NA	NA
Sunitinib	9.6-15.4	1-4	0.5	<0.1
Vandetanib	36	12-15	4.3-8	Described, % NA
Vemurafenib	13-15	1.6	1.6	Described, % NA
Others				
Arsenic trioxide	35.4	35	25-60	2.5

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Risk factors for QT prolongation in cancer patients

Risk factors	
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

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Clinical factors associated with increased risk of cancer-associated venous thromboembolism

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

Modified from Khorana et al.

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Strategies for surveillance and management of drug-induced pulmonary hypertension

Baseline assessment	• Consider risk factors and associated conditions for PAH • Assess NYHA/WHO functional class • Consider 6-minute walk test • Consider NT-proBNP • Assess echocardiographic level of probability of PH
Surveillance strategy	**Asymptomatic** • Assess NYHA/WHO functional class every 3 months • Assess echocardiographic level of PAP every 3 months • Consider presence of other indications for right heart catheterization • Consider further evaluation for suspected PH **Symptomatic** • Assess NYHA/WHO functional class • Perform 6-minute walk test • Sample blood for NT-proBNP • Assess echocardiographic level of probability of PH • Consider indications for right heart catheterization in PH referral centre • Consider interruption of cancer therapy

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Strategies to reduce chemotherapy-induced cardiotoxicity

Chemotherapy drug	Potential cardioprotective measure
All chemotherapy drugs	Identify and treat cardiovascular risk factors
	Treat comorbidities (CAD, HF, PAD, HTN)
	QTc prolongation and torsade de pointes: - Avoid QT prolonging drugs - Manage electrolyte abnormalities
	Minimize cardiac irradiation
Anthracyclines and analogues	Limit cumulative dose (mg/m^2): - Daunorubicin <800 - Doxorubicin <360 - Epirubicin <720 - Mitoxantrone <160 - Idarubicin <150
	Altered delivery systems (liposomal doxorubicin) or continuous infusions
	Dexrazoxane as an alternative
	ACE-Is or ARBs
	β-blockers
	Statins
	Aerobic exercise
Trastuzumab	ACE-Is
	β-blockers

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Summarizes the potential benefits of exercise during and/or after cancer treatment

Improvement of:

- Cardiorespiratory and cardiovascular function
- Body composition (preservation or increase in muscle mass, loss of fat mass)
- Immune function
- Chemotherapy completion rates
- Muscle strength and flexibility
- Body image, self-esteem and mood

Reduction in:

- Number and severity of side effects including nausea, fatigue and pain
- Reduction of hospitalization duration
- Reduction of stress, depression and anxiety

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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 3-4HTN, %
Bevacizumab	20	6754	23.6	7.9
Sunitinib	13	4999	21.6	6.8
Sorafenib	13	2492	15.3	4.4
Axitinib	10	1908	40.1	13.1
Vandetanib	11	3154	24.2	6.8
Regorafenib	5	750	44.4	12.5

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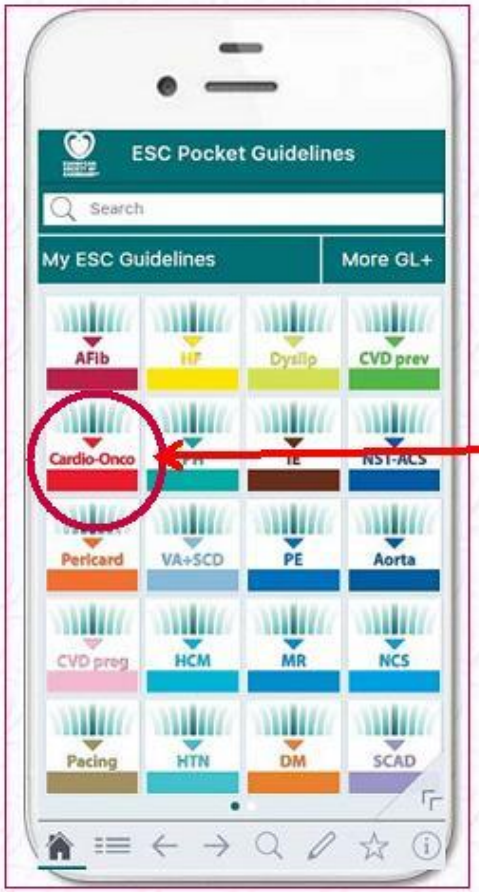

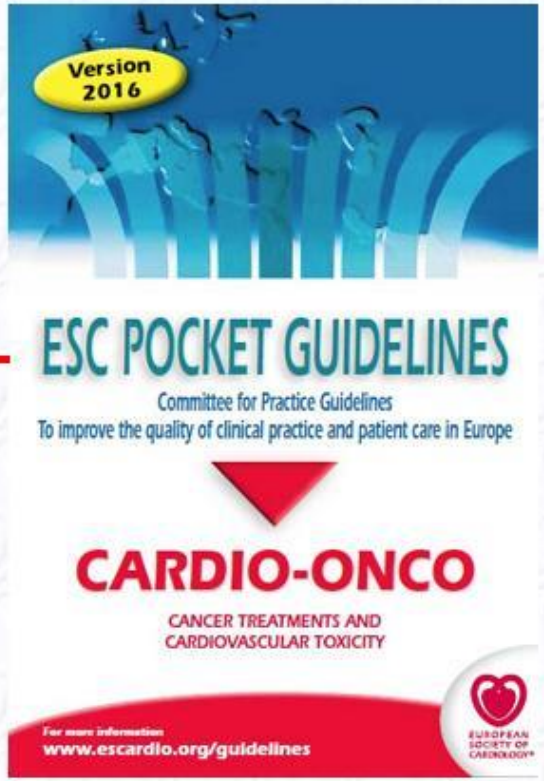

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