

PREVENTION AND MANAGEMENT OF CARDIOVASCULAR COMPLICATIONS DURING CANCER THERAPY

General Principles

Chemotherapy-induced cardiomyopathy, in general, can occur acutely soon after treatment, within a few months of treatment, or many years later, and may be prevented with an ARB or ACE inhibitor, and most probably beta blockers such as carvedilol (a beta blocker with antioxidant properties).¹⁻⁴ Most cardiotoxicity after anthracycline therapy occurs within the first year and is associated with anthracycline dose and LVEF status at the end of treatment. Early detection and prompt drug therapy are important for substantial recovery of cardiac function.⁵

Recommendations in general are provided in Figure 1 and Tables 1 and 2.

Specific Chemotherapy Agents

Anthracyclines can cause dilated cardiomyopathy or endomyocardial fibrosis. Diastolic dysfunction may persist even years after therapy with anthracyclines. The risk is greatly increased when there is a history of irradiation that causes myocardial and endocardial fibrosis, particularly in the right ventricle. Specific recommendations for anthracycline chemotherapy are presented in Tables 3-5, and Figure 2 and 3. Sacubitril-valsartan may provide protection in patients with cancer undergoing chemotherapy with increased cardiac troponin I levels attributable to anthracycline treatment.⁶

Specific recommendations for **HER2-targeted** therapies are presented in Tables 6 and 7, and Figures 4 and 5.

Specific recommendations for **fluopyrimidine** therapy are presented in Table 8.

Specific recommendations for **vascular endothelial growth factor inhibitors** are presented in Table 9, and Figures 6 and 7.

Specific recommendations for **BCR-ABL TKI** are presented in Table 10, and Figures 8 and 9. Dasanitib, in particular, may cause pulmonary hypertension mainly detected by increased TR.⁷

Specific recommendations for **BTKI** are presented in Table 11.

Recommendations for **multiple myeloma** therapies are presented in Table 12, and Figures 10-12.

Recommendations for **rapidly accelerated fibrosarcoma (RAF) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor** treatment are presented in Table 13, and Figure 13.

Recommendations for **immunotherapy** are presented in Tables 14 and 15, and Figures 14 and 15. The main cardiac complication is myocarditis due direct or indirect toxicity.⁷

Recommendations for **androgen-deprivation therapy** are presented in Table 16, and Figure 16.

Recommendations **for endocrine therapy for breast cancer** are presented in Table 17.

Recommendations for **cyclin-dependent kinase 4/6 inhibitor** therapy are presented in Table 18.

Recommendations for **anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR) inhibitors** are presented in Table 19, and Figure 17.

Recommendations for **chimeric antigen receptor T cell and tumour-infiltrating lymphocytes** therapies are presented in Tables 20 and 21, and Figure 18. Cancer-related Takotsubo syndrome is the main cardiac complication.⁷

Recommendations for **radiotherapy** to a volume including the heart are presented in Table 22, and Figure 19.

Recommendations for **haematopoietic stem cell transplantation** are presented in Table 23, and Figure 20.

General recommendations for specific cardiac disease entities and presented in relevant Chapters.

References

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Primary and secondary cancer-therapy related CV toxicity prevention strategies

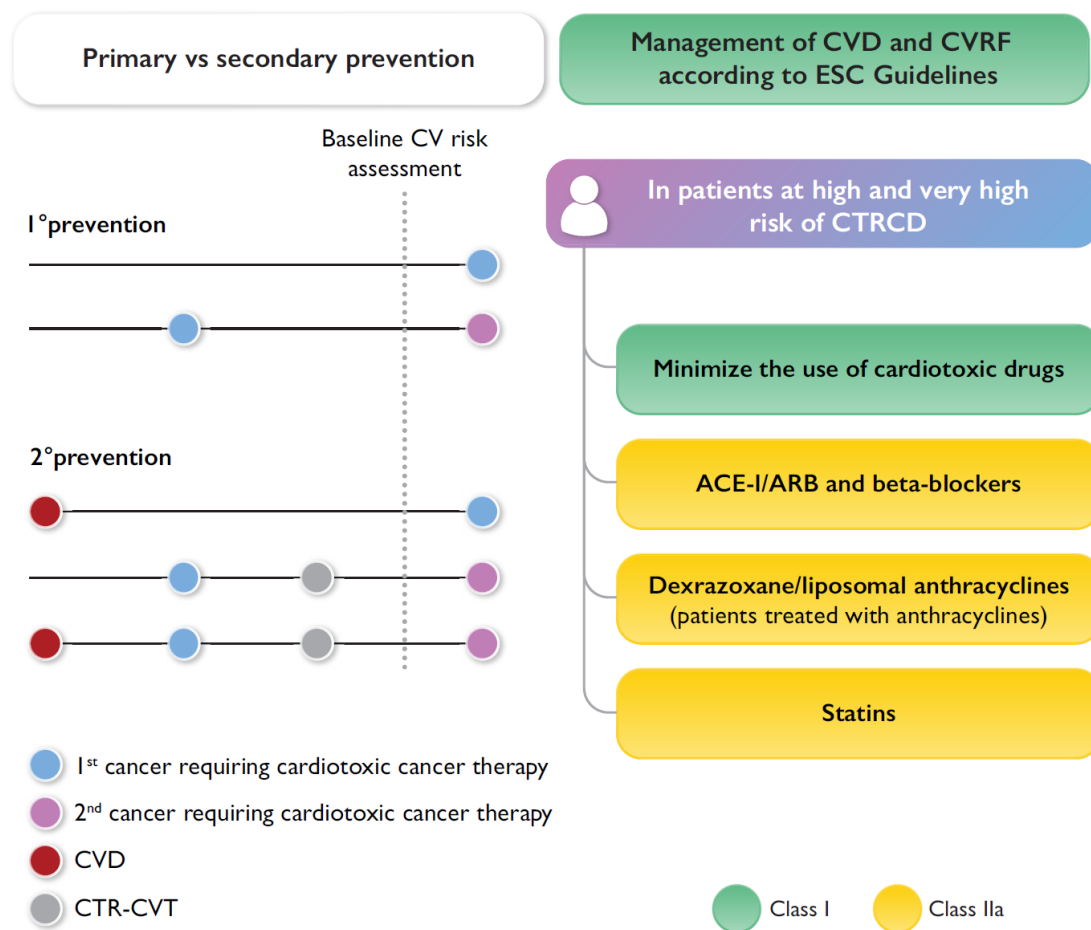


Figure 1. ESC 2022 GL on cardio-oncology. Primary and secondary cancer therapy-related cardiovascular toxicity prevention.

Left panel represents examples of five different primary or secondary prevention strategies definition based on the history of pre-existing CVD and/or prior CTR-CVT. **Right panel** describes general strategies to mitigate CTR-CVT risk in patients at high and very high risk of CTRCD

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; CTR-CVT, cancer therapy-related cardiovascular toxicity; CTRCD, cancer therapy-related cardiac dysfunction; ESC, European Society of Cardiology.

Table 1. ESC 2022 GL on cardio-oncology Prevention of cancer therapy-related cardiovascular toxicity

Primary prevention

Management of CVRF according to the 2021 ESC Guidelines on CVD prevention in clinical practice before, ^a during, and after cancer therapy.	I C
Dexrazoxane in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated. ^b	IIa B
Liposomal anthracyclines in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated.	IIa B
ACE-I or ARB and beta-blockers recommended for HF, ^c for primary prevention in high- and very high-risk patients receiving anthracyclines and/or anti-HER2 therapies.	IIa B
ACE-I or ARB and beta-blockers recommended for HF ^f for primary prevention in high- and very high-risk patients receiving targeted cancer therapies that may cause HF. ^d	IIa C
Statins for primary prevention in adult patients with cancer at high and very high CV toxicity risk. ^e	IIa B

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CV, cardiovascular; CVD, CV disease; CVRF, CV risk factors; ESC, European Society of Cardiology; HER2, human epidermal receptor 2; HF, heart failure; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; MEK, mitogen-activated extracellular signal-regulated kinase; PI, proteasome inhibitors; RAF, rapidly accelerated fibrosarcoma; VEGFi, vascular endothelial growth factor inhibitors.

a Without delaying cancer treatments.

b As per the European Medicine Agency: ≥ 350 mg/m² doxorubicin or equivalent; as per the United States Food and Drug Administration: ≥ 300 mg/m² doxorubicin or equivalent.

c Carvedilol (preferred beta-blocker for CV protection if there is no contraindication), bisoprolol, controlled/extended-release metoprolol succinate and nebivolol.

d VEGFi and bevacizumab, RAF inhibitor, MEK inhibitor, PI, dasatinib, ponatinib, and osimertinib.

e According to HFA-ICOS risk assessment tools

Secondary prevention

Management of CVD according to applicable ESC Guidelines is recommended before ^a during, and after cancer therapy.	I C
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a Without delaying cancer treatments

Table 2. ESC 2022 GL on cardio-oncology. Recommendation for the management of cardiovascular disease and cancer therapy-related cardiovascular toxicity in patients receiving anticancer treatment

A specialist CV assessment^a is recommended for optimal diagnostic workup and management of patients with cancer who present with new CV toxicity during and after cancer treatment. I C

a Cardio-oncology referral is recommended when available; alternatively, patients should be referred to a specialized cardiologist with expertise in managing CVD in patients with cancer.

Table 3. ESC 2022 GL on cardio-oncology. Anthracycline equivalence dose

	Doxorubicin	Epirubicin	Daunorubicin	Mitoxantrone	Idarubicin ^a
CV toxicity dose ratio	1	0.8	0.6	10.5	5
Isoequivalent dose	100 mg/m ²	125 mg/m ²	167 mg/m ²	9.5 mg/m ²	20 mg/m ²

This table refers to anthracycline equivalence dose using doxorubicin as a reference. Note that these isoequivalent doses are derived from paediatric CS.

CS, cancer survivors; CV, cardiovascular.

^aData for idarubicin are based upon an estimated anticancer efficacy ratio, not derived from cardiotoxicity data. The CV toxicity dose ratio provides the value that should be used to multiply the dose of the anthracycline of interest to convert to isoequivalent doses of doxorubicin; e.g. to convert 125 mg/m² of epirubicin to doxorubicin isoequivalent, multiply the dose by 0.8 (125 mg/m² × 0.8 = 100 mg/m² of doxorubicin).

Table 4. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during anthracycline chemotherapy and in the first 12 months after therapy

TTE

Baseline echocardiography^a in all patients with cancer before anthracycline Chemotherapy. I B

In all adults receiving anthracycline chemotherapy, echocardiogram within 12 months after completing treatment. I B

In high- and very high-risk patients, echocardiography every two cycles and within 3 months after completing treatment. I C

In moderate-risk patients, additional echocardiography after a cumulative dose of ≥250 mg/m² of doxorubicin or equivalent. IIa C

In low-risk patients, additional echocardiography after a cumulative dose of ≥250 mg/m² of doxorubicin or equivalent. IIb C

Cardiac serum biomarkers

Baseline measurement of NP and cTn in high- and very high-risk patients prior to anthracycline chemotherapy. I B

Baseline measurement of NP and cTn in low- and moderate-risk patients IIa C

prior to anthracycline chemotherapy.

cTn and NP monitoring before every cycle during anthracycline chemotherapy and 3 and 12 months after therapy completion in high and very high-risk patients.	I B
cTn and NP monitoring every two cycles during anthracycline chemotherapy and within 3 months after therapy completion in moderate-risk patients and in low-risk patients receiving a cumulative dose of ≥ 250 mg/m ² of doxorubicin or equivalent.	IIa C
cTn and NP monitoring every two cycles during anthracycline chemotherapy and within 3 months after therapy completion in low-risk patients.	IIb C
cTn, cardiac troponin; NP, natriuretic peptides; TTE, transthoracic echocardiography.	
a If echocardiography is unavailable or non-diagnostic, follow general cardiac imaging modalities recommendations.	

Table 5. ESC 2022 GL on cardio-oncology. Recommendations for the management of cancer treatment-related cardiac dysfunction during anthracycline chemotherapy

Anthracycline chemotherapy-induced symptomatic CTRCD

HF during anthracycline chemotherapy. ^a	I B
Discontinuation of anthracycline chemotherapy symptomatic severe CTRCD. ^a	I C
Temporary interruption of anthracycline chemotherapy, and a multidisciplinary approach regarding the decision.	I C
A multidisciplinary approach regarding interruption vs. continuation of anthracycline Chemotherapy.	I C

Anthracycline chemotherapy-induced asymptomatic CTRCD

Temporary interruption of anthracycline chemotherapy and initiation of HF therapy	I C
A multidisciplinary approach regarding the decision when to restart	I C
Continuation of anthracycline chemotherapy in asymptomatic patients who have LVEF $\geq 50\%$ and who have developed a significant fall in GLS ^a or a troponin or a NP elevation >ULN.	I C
ACE-I/ARB and/or beta-blockers. ^b for asymptomatic patients who have LVEF $\geq 50\%$ and who have developed a significant fall in GLS ^a	IIa B
ACE-I/ARB and/or beta-blockers. ^b for asymptomatic patients who have LVEF $\geq 50\%$ and who have developed a troponin elevation >ULN	IIa B
ACE-I/ARB and/or beta-blockers. ^b for asymptomatic patients who have LVEF $\geq 50\%$	IIB C

and who have developed NP >ULN

Strategies for restarting anthracycline chemotherapy in patients with CTRCD

Liposomal anthracycline^c in patients with moderate or severe symptomatic or asymptomatic CTRCD^a who require further anthracycline chemotherapy to reduce the risk of further CV toxicity. IIb C

Dexrazoxane^d in patients with moderate or severe symptomatic or asymptomatic CTRCD^c who require further anthracycline chemotherapy to reduce the risk of further CV toxicity. IIb C

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction; NP, natriuretic peptides; ULN, upper limit of normal.

a Significant fall in GLS=relative reduction .15%.

b Avoid hypotension.

c See text for specific liposomal doxorubicin type and malignancies.

d As per the European Medicines Agency: ≥ 350 mg/m² doxorubicin or equivalent; as per the United States Food and Drug Administration: ≥ 300 mg/m² doxorubicin or equivalent.

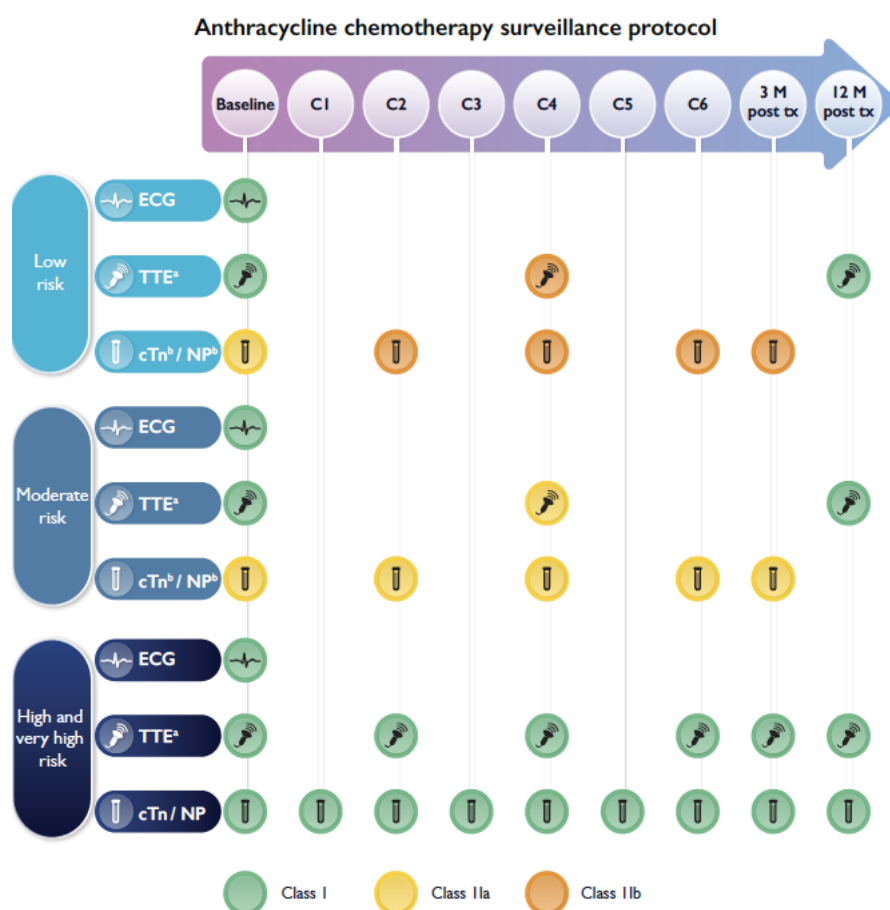


Figure 2. ESC 2022 GL on cardio-oncology. Cardiovascular toxicity monitoring in patients receiving anthracycline chemotherapy.

cTn, cardiac troponin; C, chemotherapy cycle; ECG, electrocardiogram; M, months; NP, natriuretic peptides; TTE, transthoracic echocardiography; tx, treatment. Biomarker and TTE assessment should ideally be performed before the corresponding anthracycline cycle (C1–C6).

a Cardiac magnetic resonance should be considered for the assessment of cardiac function when TTE is unavailable or not diagnostic. In moderate-risk patients, TTE should be considered after a cumulative dose of ≥ 250 mg/m² of doxorubicin or equivalent. In low-risk patients, TTE may be considered after a cumulative dose of ≥ 250 mg/m² of doxorubicin or equivalent.

b Measurement of NP and/or cTn is recommended in all patients with cancer if these biomarkers are going to be used during treatment monitoring.

c Tn and NP monitoring every two cycles during anthracycline chemotherapy and within 3 months after therapy completion may be considered in low-risk patients (Class IIb, Level C). cTn and NP monitoring every two cycles during anthracycline chemotherapy and within 3 months after therapy completion should be considered in moderate-risk patients and in low-risk patients receiving a cumulative dose of ≥ 250 mg/m² of doxorubicin or equivalent (Class IIa, Level C).

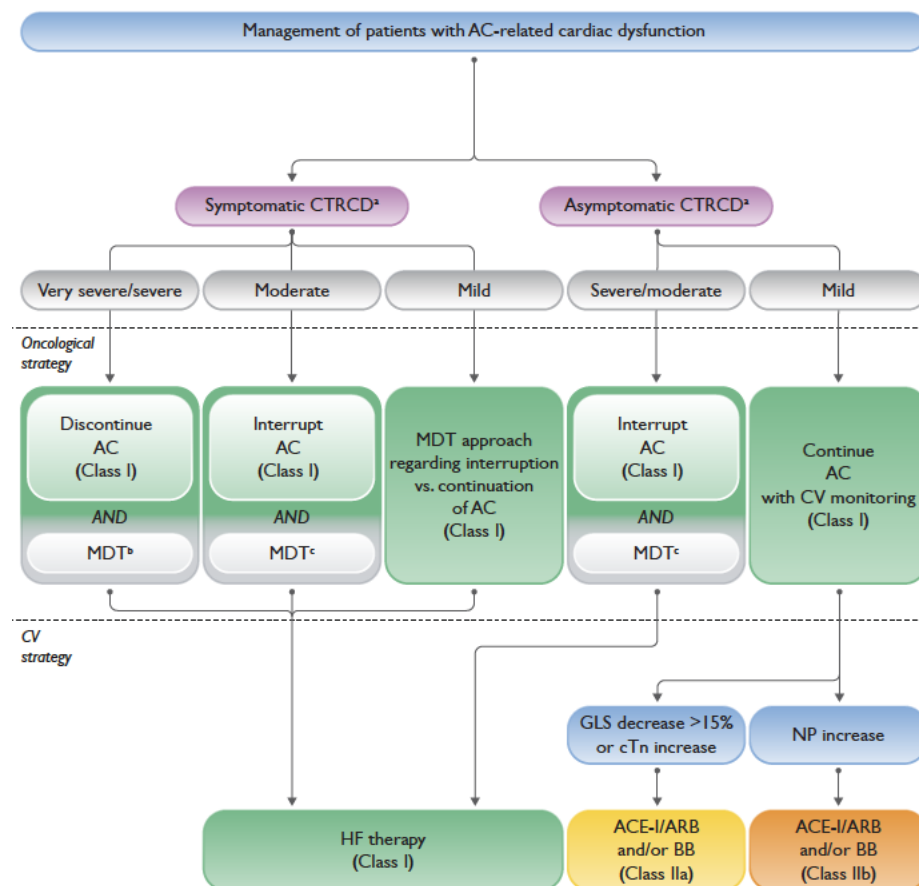


Figure 3. ESC 2022 GL on cardio-oncology. Management of anthracycline chemotherapy-related cardiac dysfunction.

AC, anthracycline chemotherapy; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MDT, multidisciplinary team; NP, natriuretic peptides.

a See Chapter 92 for complete definition (symptomatic CTRCD: symptomatic confirmed HF syndrome; asymptomatic severe CTRCD: LVEF,40%; asymptomatic moderate CTRCD: LVEF 40–49%; asymptomatic mild CTRCD: LVEF.50%).

b In rare exceptions, anthracycline chemotherapy may be restarted after recovery of LV function with optimal HF therapy.

c A MDT discussion is recommended before restarting anthracycline chemotherapy after recovery of LV function.

Table 6. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during human epidermal receptor 2-targeted therapies and in the first 12 months after therapy

TTE

Baseline echocardiography ^a before HER2-targeted therapies in all patients	I B
In patients receiving neoadjuvant or adjuvant HER2-targeted therapies, echocardiography every 3 months and within 12 months after completing treatment	I B
In low-risk HER2+ EBC patients ^b who are asymptomatic and with a normal assessment after 3 months, reduce monitoring to every 4 months.	IIb C
In high- and very high-risk HER2+ EBC patients, ^b more frequent echocardiography monitoring ^c during treatment.	IIa C
In metastatic HER2+ disease, echocardiography every 3 months during the first year; if the patient remains asymptomatic without CV toxicity, then surveillance can be reduced to every 6 months during future treatment. ^d	I C
In metastatic HER2+ disease patients at high- and very high-risk, more frequent Echocardiography monitoring. ^d	IIb C

Cardiac biomarkers

Baseline NP and cTn measurement in high- and very high-risk patients prior to anti-HER2-targeted therapies.	I C
NP and cTn monitoring every 2–3 cycles during therapy and 3 and 12 months after the end of therapy should be considered in high- and very high-risk HER2+ EBC patients. ^b	IIa C
Baseline cTn measurement in low- and moderate-risk patients post-anthracycline chemotherapy but prior to starting anti-HER2-targeted therapies.	IIa A
NP and cTn monitoring at baseline, every 3 months, and 12 months after therapy considered in low- and moderate-risk HER2+ EBC patients. ^b	IIb C

HER2, human epidermal receptor 2; NP, natriuretic peptides; TTE, transthoracic echocardiography.

a If echocardiography is unavailable or non-diagnostic, follow general cardiac imaging modalities recommendations.

b These recommendations are also applicable for HER2+ non-BC patients.

c Every 2–3 cycles depending on the absolute risk and local availability.

d Patients at low and moderate risk.

Table 7. ESC 2022 GL on cardio-oncology. Recommendations for the management of cancer treatment-related cardiac dysfunction during human epidermal receptor 2-targeted therapies

HER2-targeted therapy-induced symptomatic CTRCD

HF therapy in symptomatic moderate-to-severe CTRCD with LVEF <50%^a during HER2-targeted treatment. I B

Temporary interruption of HER2-targeted treatment in moderate or severe symptomatic CTRCD^a and the decision to restart should be based on a multidisciplinary approach after improvement of LV function and symptoms resolved.^b I C

In mild symptomatic CTRCD,^a HF therapy and a multidisciplinary approach regarding the decision to continue vs. interrupt HER2-targeted therapy I C

HER2-targeted therapy-induced asymptomatic CTRCD

Temporary interruption of HER2-targeted therapy and initiation of HF therapy in asymptomatic severe CTRCD.^a I C

A multidisciplinary approach regarding the decision to restart HER2-targeted treatment in patients with severe asymptomatic CTRCD.^a I C

Continuation of HER2-targeted therapy in asymptomatic moderate (LVEF 40–49%) CTRCD^a with more frequent cardiac monitoring. IIa B

Continuation of HER2-targeted therapy in asymptomatic mild (LVEF ≥50%) CTRCD^a with more frequent cardiac monitoring. I C

ACE-I/ARB and beta-blockers in asymptomatic moderate (LVEF 40–49%) CTRCD^c during HER2-targeted treatment. I C

ACE-I/ARB and/or beta-blockers in asymptomatic patients receiving HER2-targeted therapies who have LVEF ≥50% but develop a significant fall in GLS^a while continuing HER2-targeted therapy.^c IIa B

ACE-I/ARB and/or beta-blockers in asymptomatic patients receiving HER2-targeted therapies who have LVEF ≥50% but develop a new troponin or NP rise while continuing HER2-targeted therapy.^e IIa B

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; HER2, human epidermal receptor 2; HF, heart failure; LV, left ventricular; LVEF, LV ejection fraction; NP, natriuretic peptides.

a See Chapter 92

b For patients where HER2-targeted therapy has been interrupted and who have recovered LVEF ≥40% and are now asymptomatic, resumption of HER2-targeted therapy should be considered supported by HF therapy and echocardiography and cardiac biomarkers assessment every two cycles for the first four cycles after restarting and then frequency can be reduced.

c Avoid hypotension

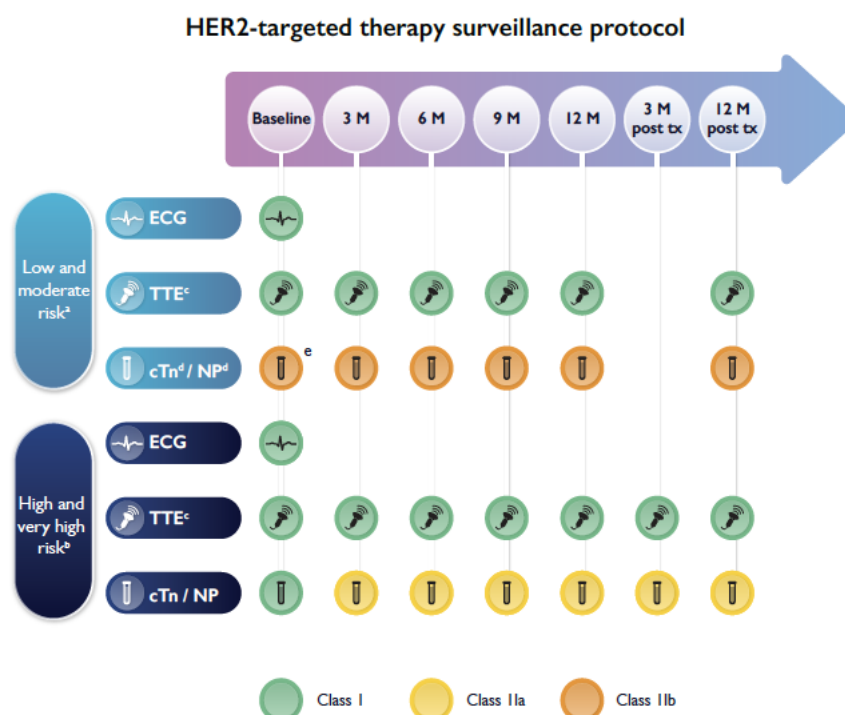


Figure 4. ESC 2022 GL on cardio-oncology. Cardiovascular toxicity monitoring in patients receiving human epidermal receptor 2-targeted therapies.

cTn, cardiac troponin; CV, cardiovascular; EBC, early breast cancer; ECG, electrocardiogram; HER2, human epidermal receptor 2; M, months; NP, natriuretic peptides; TTE, transthoracic echocardiography; tx, treatment. This protocol refers to CV toxicity monitoring in patients receiving neoadjuvant or adjuvant anti-HER2 targeted therapies for non-metastatic disease or first year in metastatic disease. Biomarker assessment should ideally be performed before the corresponding trastuzumab cycle. TTE should be performed in week 2 or 3 of a 3-weekly trastuzumab cycle.

a In low-risk HER2+ EBC patients who are asymptomatic and with a normal assessment after 3 months, reducing TTE monitoring to every 4 months may be considered (Class IIb, Level C).

In low- and moderate-risk metastatic HER2+ disease, TTE surveillance can be reduced to every 6 months after the first year in asymptomatic patients with normal TTE assessment (Class I, Level C).

b In high- and very high-risk metastatic HER2+ disease, TTE monitoring every 2–3 cycles may be considered depending on the absolute risk and local availability.

c Cardiac magnetic resonance should be considered for the assessment of cardiac function when TTE is unavailable or not diagnostic.

d Measurement of NP and/or cTn is recommended in all patients with cancer if these biomarkers are going to be used during treatment monitoring.

e Baseline cTn measurement should be considered in low- and moderate-risk patients after anthracycline chemotherapy but prior to starting anti-HER2 targeted therapies for CV toxicity risk prediction.

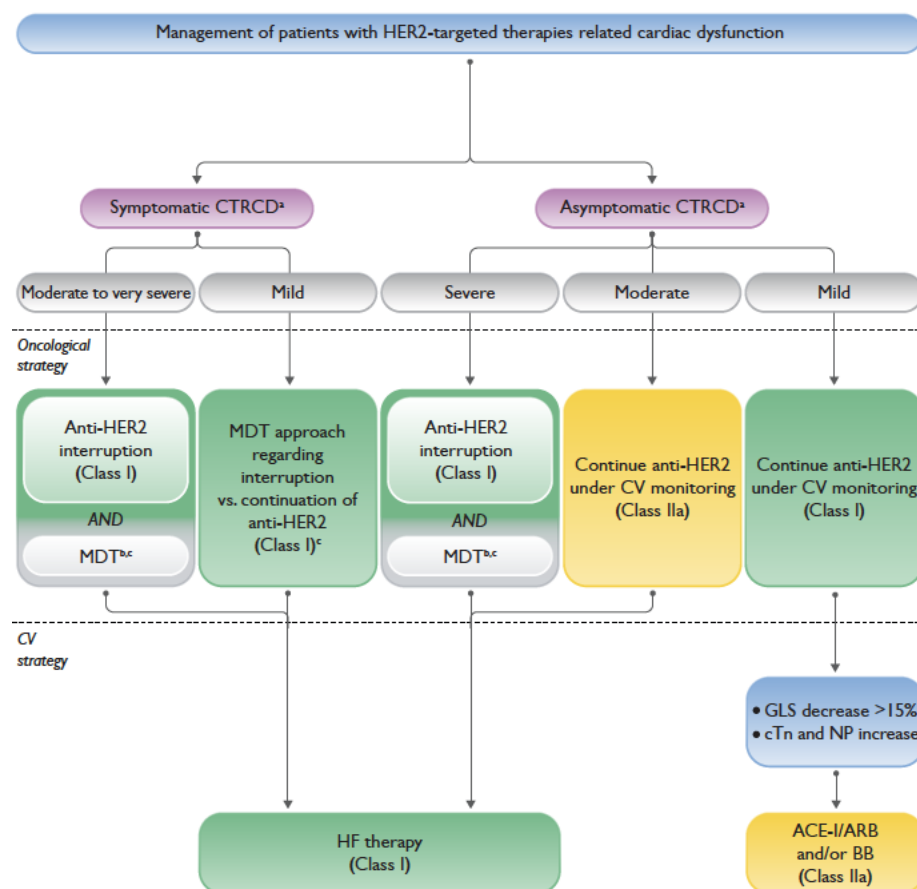


Figure 5. ESC 2022 GL on cardio-oncology. Management of human epidermal receptor 2-targeted therapy-related cardiac dysfunction.

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; GLS, global longitudinal strain; HER2, human epidermal receptor 2; HF, heart failure; LVEF, left ventricular ejection fraction; MDT, multidisciplinary team; NP, natriuretic peptides.

a Symptomatic CTRCD: symptomatic confirmed HF syndrome; asymptomatic severe CTRCD: LVEF, 40%; asymptomatic moderate CTRCD: LVEF 40–49%; asymptomatic mild CTRCD: LVEF 50%.

b For patients in whom HER2-targeted therapy has been interrupted, whose signs and symptoms of HF do not resolve and/or LVEF remains 40%, resumption of HER2-targeted therapy may be considered if no alternative therapeutic option exists. In advanced cancer that only responds well to trastuzumab, the risk/benefit ratio may warrant continued therapy if other options remain limited.

c For patients where HER2-targeted therapy has been interrupted and who have recovered LVEF $\geq 40\%$ and are now asymptomatic, resumption of HER2-targeted therapy should be considered, supported by HF therapy, and echocardiography and cardiac biomarker assessment every two cycles for the first four cycles after restarting and then the frequency can be reduced.

Table 8. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during fluoropyrimidine therapy

Baseline CV risk assessment and evaluation including BP measurement, ECG, lipid profile, HbA1c measurement, and SCORE2/ SCORE2-OP ^a or equivalent before starting fluoropyrimidines.	I C
A baseline echocardiogram in patients with a history of symptomatic CVD before starting fluoropyrimidines.	I C
Screening for CAD ^b may be considered in patients at high and very high risk of CAD ^a before fluoropyrimidines.	IIb C

BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; HbA1c, glycated haemoglobin; SCORE2, Systematic Coronary Risk Estimation 2; SCORE2-OP, Systematic Coronary Risk Estimation 2—Older Persons.

a SCORE2 (<70 years) or SCORE2-OP (≥70 years) CV risk stratification: <50 years: low risk <2.5%, moderate risk 2.5% to <7.5%, high risk ≥7.5%; 50–69 years: low risk <5%; moderate risk 5% to <10%; high risk ≥10%; ≥70 years: low risk <7.5%, moderate risk 7.5% to <15%, high risk ≥15%.

b According to pre-existing CVD and local protocols

Table 9. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during vascular endothelial growth factor inhibitors

BP monitoring

BP measurement for patients treated with VEGFi, bevacizumab, or ramucirumab at every clinical visit. I C

Daily home monitoring of BP for patients treated with VEGFi during the first cycle, after each increase of VEGFi dose, and every 2–3 weeks thereafter I C

ECG monitoring

In patients treated with VEGFi at moderate or high risk of QTc prolongation, QTc^a monitoring monthly during the first 3 months and every 3–6 months thereafter.^b I C

Echocardiography

Baseline echocardiography in high- and very high-risk patients treated with VEGFi or bevacizumab. I C

Baseline echocardiography in low- and moderate-risk patients treated with a I Ia C

Echocardiography every 4 months during the first year in moderate-risk patients receiving VEGFi or bevacizumab. IIb C

Echocardiography every 3 months during the first year in high- and very high-risk patients receiving a VEGFi or bevacizumab.^c IIa C

Echocardiography every 6–12 months in moderate- and high-risk patients with cancer who require long-term treatment with a VEGFi. IIa C

Cardiac biomarker

NP at baseline and then every 4 months during the first year in moderate-risk patients receiving a VEGFi. IIb C

NP at baseline, 4 weeks after starting treatment, and then every 3 months during the first year in high- and very high-risk patients receiving a VEGFi. IIa C

BP, blood pressure; ECG, electrocardiogram; NP, natriuretic peptides; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction; VEGFi, vascular endothelial growth factor inhibitors.

^a QTc interval using Fridericia correction ($QTcF = QT / \sqrt[3]{RR}$) is the preferred method.

^b Consider an ECG 2 weeks after starting treatment in high-risk patients and new monitoring in the case of any dose increase.

^c An additional echocardiography 4 weeks after starting treatment should be considered in selected high- and very high-risk patients according to local availability, especially if cardiac biomarker surveillance is not available.

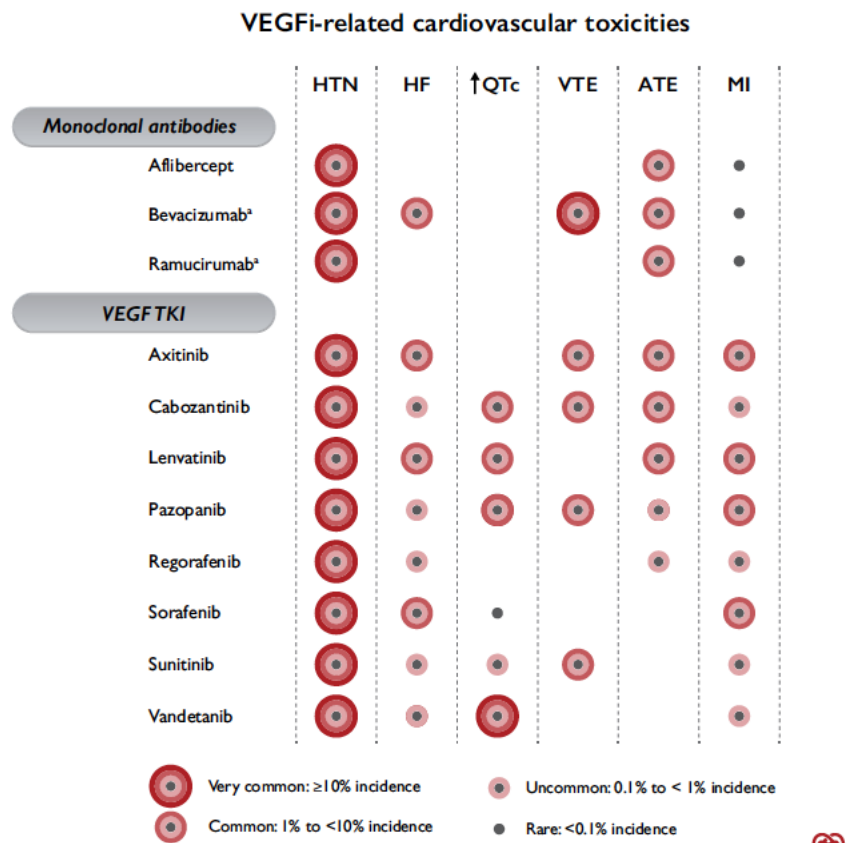


Figure 6. ESC 2022 GL on cardio-oncology. Vascular endothelial growth factor inhibitors-related cardiovascular toxicities.

ATE, arterial thromboembolism; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HTN, hypertension; MedDRA, medical dictionary for regulatory activities; MI, myocardial infarction; ↑QTc, corrected QT interval prolongation; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; VEGFi, vascular endothelial growth factor inhibitors; VTE, venous thromboembolism. Adverse reactions reported in multiple clinical trials or during post-marketing use are listed by system organ class (in MedDRA) and frequency. If the frequency is unknown or cannot be estimated from the available data, a blank space has been left.

a Bevacizumab: hypertension frequency 5–42% (EMA); 60–77% of the patients who received bevacizumab in combination with erlotinib. Pre-existing hypertension should be adequately controlled before starting treatment. Ramucirumab: hypertension frequency 16–26% (EMA/FDA); in combination with erlotinib, the incidence of hypertension was 24–45%. Patients with uncontrolled hypertension were excluded from the trials. Figure developed from EMA prescribing information, FDA prescribing information.

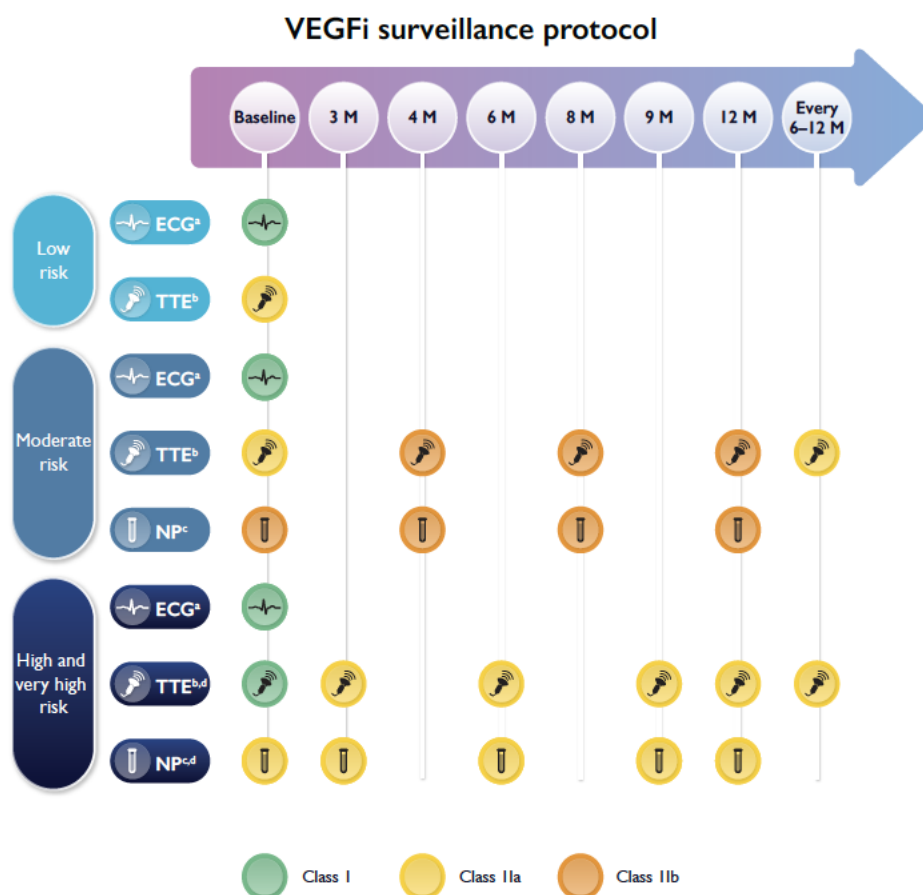


Figure 7. ESC 2022 GL on cardio-oncology. Cardiovascular toxicity monitoring in patients receiving vascular endothelial growth factor inhibitors.

ECG, electrocardiogram; M, months; NP, natriuretic peptides; QTc, corrected QT interval; TTE, transthoracic echocardiography; VEGFi, vascular endothelial growth factor inhibitors.

a In patients treated with VEGFi at moderate or high risk of QTc prolongation, ECG is recommended (Class I, Level C) monthly during the first 3 months and every 3–6 months thereafter. Consider an ECG 2 weeks after starting treatment in high-risk patients and new monitoring in the case of any dose increase.

b Cardiac magnetic resonance should be considered for the assessment of cardiac function when TTE is unavailable or not diagnostic.

c Measurement of NP is recommended in all patients with cancer if these biomarkers are going to be used during treatment monitoring.

d TTE and NP should be considered at 4 weeks after starting treatment in very high-risk patients.

Table 10. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during second- and third-generation breakpoint cluster region– Abelson oncogene locus tyrosine kinase inhibitors

Baseline CV risk assessment ^a in patients who require second- or third-generation BCR-ABL TKI.	I C
In patients treated with nilotinib or ponatinib, CV risk assessment ^a every 3 month during the first year and every 6–12 months thereafter.	I C
QTc ^b measurement at baseline, at 2 and 4 weeks after starting nilotinib, and 2 weeks after any dose increase	IIa C
Baseline echocardiography in all patients before starting second- and third-generation BCR-ABL TKI.	IIa C
Baseline echocardiography in patients scheduled to receive dasatinib.	I C
Echocardiography every 3 months during the first year in high- and very high-risk patients receiving dasatinib or ponatinib.	IIa C
Echocardiography every 6–12 months in patients who require long-term (>12 months) ponatinib or dasatinib.	IIb C
Serial assessment of ankle brachial index to detect subclinical peripheral vascular disease.	IIb C

BCR-ABL, breakpoint cluster region–Abelson oncogene locus; BP, blood pressure; CV, cardiovascular; ECG, electrocardiogram; HbA1c, glycated haemoglobin; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction; TKI, tyrosine kinase inhibitors.

^a Physical examination, BP measurement, ECG, lipid profile, and HbA1c measurement. Coronary artery calcium scoring can reclassify CV disease risk upwards and downwards in addition to conventional risk factors, and may be considered at baseline in low- and moderate-risk patients as per HFA-ICOS risk assessment tools.

^b QTc interval using Fridericia correction ($QTcF = QT/3\sqrt{RR}$) is the preferred method.

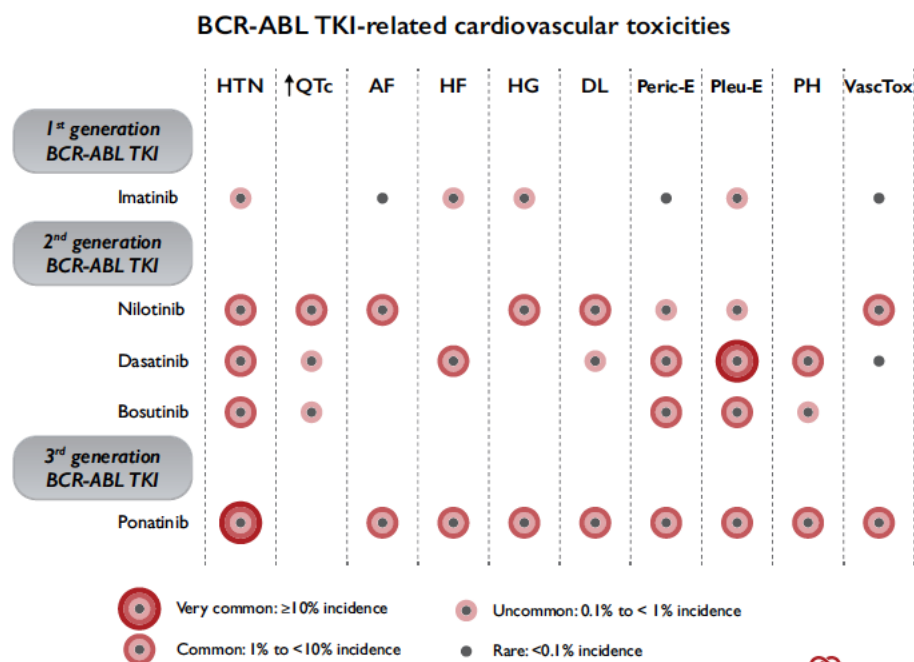


Figure 8. ESC 2022 GL on cardio-oncology. Breakpoint cluster region–Abelson oncogene locus tyrosine kinase inhibitor-related cardiovascular toxicities.

AF, atrial fibrillation; BCR-ABL, breakpoint cluster region–Abelson oncogene locus; DL, dyslipidaemia; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HG, hyperglycaemia; HTN, hypertension; MedDRA, medical dictionary for regulatory activities; MI, myocardial infarction; PAD, peripheral artery disease; Peric-E, pericardial effusion; PH, pulmonary hypertension; Pleu-E, pleural effusion; ↑QTc, corrected QT interval prolongation; TKI, tyrosine kinase inhibitors; VascTox, vascular toxicity (stroke, MI, PAD). Adverse reactions reported in multiple clinical trials or during post-marketing use are listed by system organ class (in MedDRA) and frequency. If the frequency is unknown or cannot be estimated from the available data, a blank space has been left. Figure developed from EMA prescribing information, FDA prescribing information.

Second and third generation BCR-ABL TKI surveillance protocol

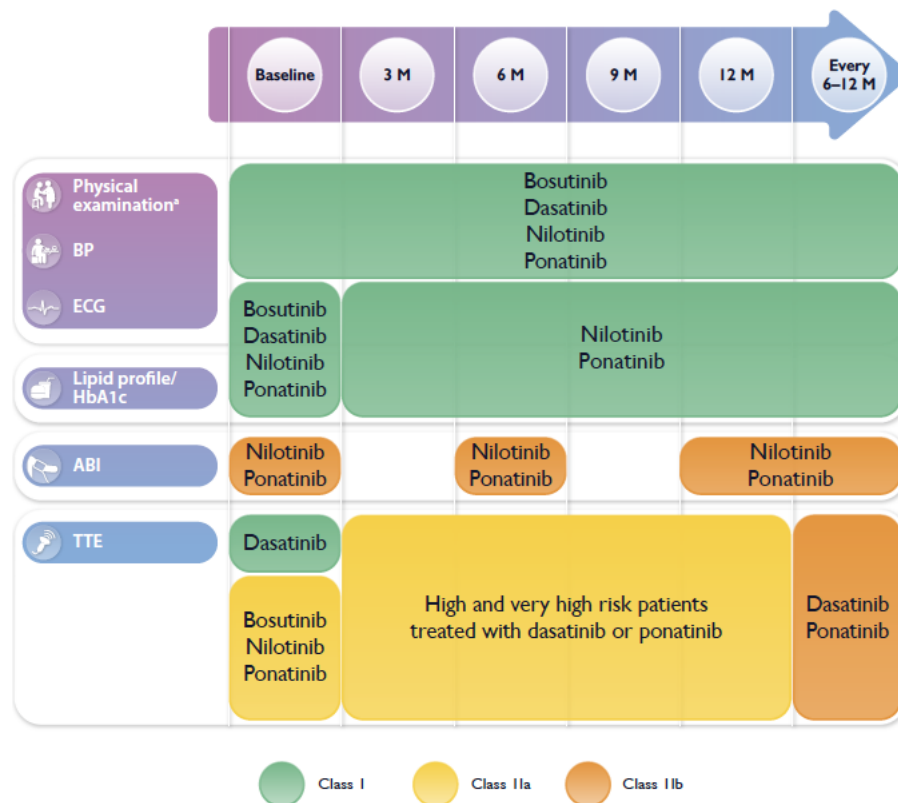


Figure 9. ESC 2022 GL on cardio-oncology. Second- and third-generation breakpoint cluster region–Abelson oncogene locus tyrosine kinase inhibitors surveillance protocol.

ABI, ankle–brachial index; BCR-ABL, breakpoint cluster region–Abelson oncogene locus; BP, blood pressure; CV, cardiovascular; ECG, electrocardiogram; HbA1c, glycated haemoglobin; M, months; TKI, tyrosine kinase inhibitors; TTE, transthoracic echocardiography.

a Coronary artery calcium scoring can reclassify CV risk upwards and downwards in addition to conventional risk factors, and may be considered in men and women with calculated CV risk around decision thresholds.

Table 11. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during Bruton tyrosine kinase inhibitor therapy

BP monitoring and management

BP measurement for patients treated with BTK inhibitors at every clinical visit. I B

Weekly home monitoring of BP during the first 3 months and every month thereafter for patients treated with BTK inhibitors. IIa C

Echocardiography

Baseline echocardiography in high-risk patients^a scheduled to receive BTK inhibitors. I C

TTE in all patients who develop AF during BTK inhibitor therapy. I C

AF

Opportunistic screening for AF by pulse-taking or ECG rhythm strip at every clinical visit during BTK inhibitor therapy. I C

AF, atrial fibrillation; BP, blood pressure; BTK, Bruton tyrosine kinase; DM, diabetes mellitus; ECG, electrocardiogram; HF, heart failure; QTc, corrected QT interval; TTE, transthoracic echocardiography; VHD, valvular heart disease.

a Male, age ≥ 65 years, previous history of hypertension, DM, QTc ≥ 480 ms, AF, HF, cardiomyopathy, or severe VHD.

Table 12. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during multiple myeloma therapies

BP monitoring

BP measurement for patients treated with PI at every clinical visit. I C

Home monitoring of BP weekly during the first 3 months and monthly thereafter for patients treated with PI. IIa C

Cardiac serum biomarkers

Measurement of NP prior to PI in high- and very high-risk patients. I C

Measurement of NP prior to PI in low- and moderate-risk patients. IIa C

In patients receiving carfilzomib or bortezomib, measurement of NP at baseline and every cycle during the first 6 cycles.^a IIa B

NP and cTn measurements at baseline and every 3–6 months in patients with AL-CA.^b I B

TTE

Baseline echocardiography, including assessment for AL-CA, in all patients with MM scheduled to receive PI. I C

Echocardiography surveillance every 3 cycles in high- and very high-risk patients receiving carfilzomib. IIa B

Echocardiography surveillance every 3 cycles in low- and moderate-risk patients receiving carfilzomib.	I Ib C
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Echocardiography surveillance every 3–6 months in patients with AL-CA treated with PI. ^b	I Ia C
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VTE prophylaxis

Therapeutic doses of LMWH in patients with MM with previous VTE	I B
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Prophylactic doses of LMWH in patients with MM with VTE-related risk factors ^c (excluding previous VTE) at least during the first 6 months of therapy.	I A
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Aspirin as an alternative to LMWH in patients with MM with no risk factors or one VTE-related risk factor ^c (excluding previous VTE) at least during the first 6 months of therapy.	I Ia B
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Low doses of apixaban or rivaroxaban ^d as an alternative to LMWH or aspirin in patients with MM with VTE-related risk factors ^c (excluding previous VTE) at least during the first 6 months of therapy.	I Ib C
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AL-CA, amyloid light-chain cardiac amyloidosis; BP, blood pressure; cTn, cardiac troponin; HF, heart failure; LMWH, low-molecular-weight heparins; MM, multiple myeloma; NP, natriuretic peptides; PI, proteasome inhibitors; TTE, transthoracic echocardiography; VTE, venous thromboembolism.

a Every 2 months for patients treated with oral ixazomib.

b Depending on HF severity and treatment.

c See Figure 15.

d Low doses of apixaban (2.5 mg twice a day) or rivaroxaban (10 mg once a day).

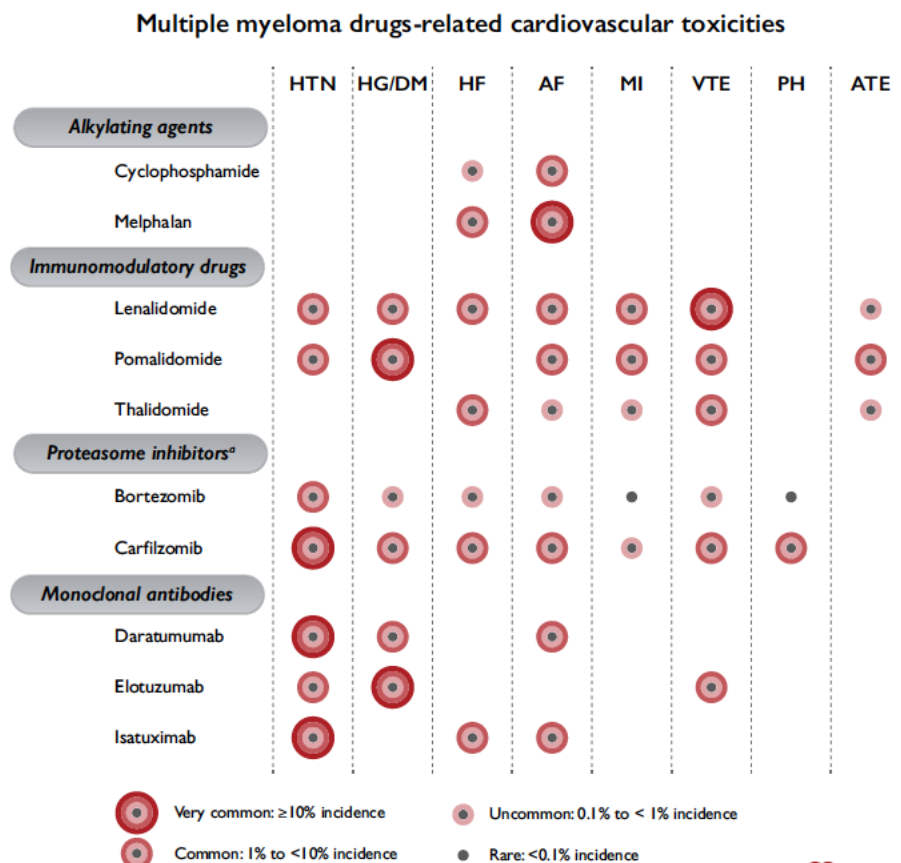


Figure 10. ESC 2022 GL on cardio-oncology. Multiple myeloma drug-related cardiovascular toxicities.

AF, atrial fibrillation; ATE, arterial thromboembolism; DM, diabetes mellitus; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HG, hyperglycaemia; HTN, hypertension; MedDRA, medical dictionary for regulatory activities; MI, myocardial infarction; PH, pulmonary hypertension; VTE, venous thromboembolism.

Adverse reactions reported in multiple clinical trials or during post-marketing use are listed by system organ class (in MedDRA) and frequency. If the frequency is unknown or cannot be estimated from the available data, a blank space has been left. aIxazomib produces peripheral oedema in up to 18% of patients and hyperglycaemia in combination with lenalidomide or pomalidomide and dexamethasone. Figure developed from EMA prescribing information, FDA prescribing information

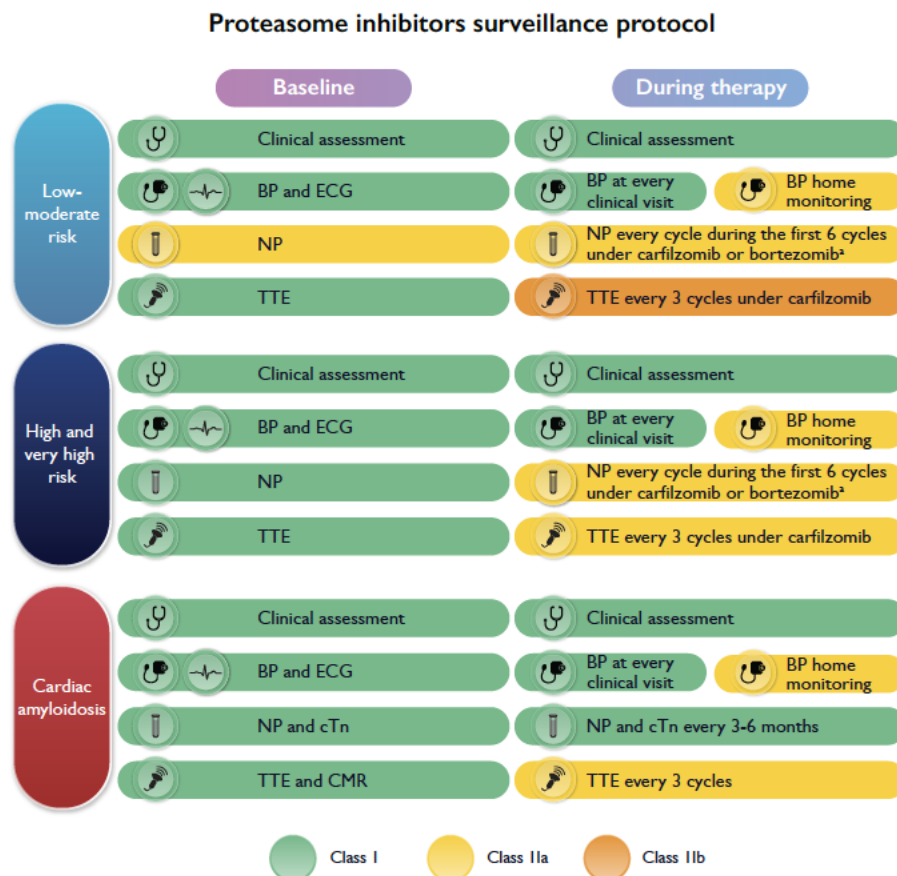


Figure 11. ESC 2022 GL on cardio-oncology. Cardiovascular monitoring in patients with multiple myeloma receiving proteasome inhibitors.

BP, blood pressure; CMR, cardiac magnetic resonance; cTn, cardiac troponin; ECG, electrocardiogram; NP, natriuretic peptides; TTE, transthoracic echocardiography.

^aEvery 2 months for patients treated with ixazomib.

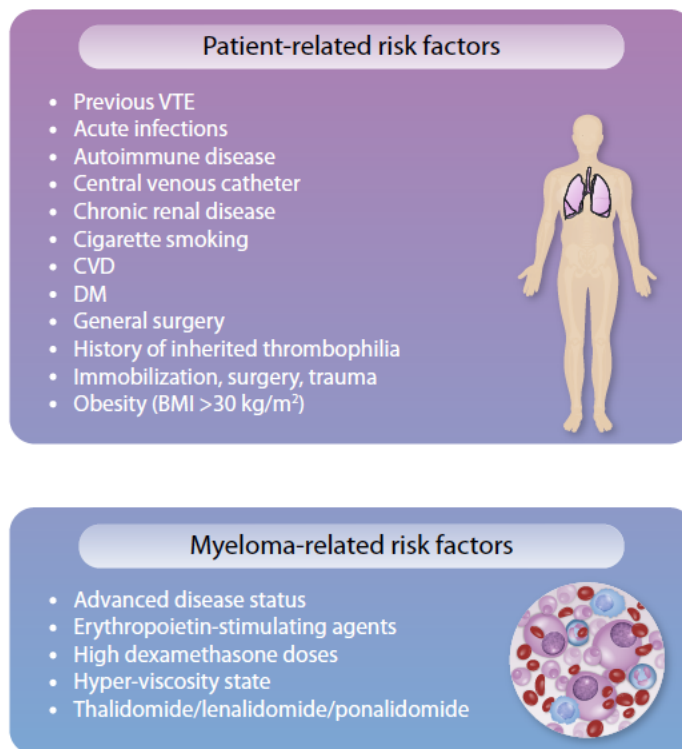
Risk factors for venous thromboembolic events in patients with multiple myeloma

Figure 12. ESC 2022 GL on cardio-oncology. Risk factors for venous thromboembolic events in patients with multiple myeloma.

BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; VTE, venous thromboembolism.

Table 13. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during combined rapidly accelerated fibrosarcoma and mitogen-activated extracellular signal-regulated kinase inhibitor therapy

BP monitoring at each clinical visit and weekly outpatient monitoring during the first 3 months of treatment and monthly thereafter	I C
In patients treated with cobimetinib/vemurafenib, ECG at 2 and 4 weeks after initiation of treatment and every 3 months thereafter. ^a	I C
Baseline echocardiography in all high- and very high-risk patients scheduled to receive combined RAF and MEK inhibitors.	I C
Baseline echocardiography in low- and moderate-risk patients scheduled to receive combined RAF and MEK inhibitors.	IIb C
Echocardiography every 4 months during the first year in high- and very high-risk patients receiving combined RAF and MEK inhibitors.	IIa C

BP, blood pressure; ECG, electrocardiogram; MEK, mitogen-activated extracellular signal-regulated kinase; RAF, rapidly accelerated fibrosarcoma.

^a Consider an ECG and new monitoring in the case of any dose increase

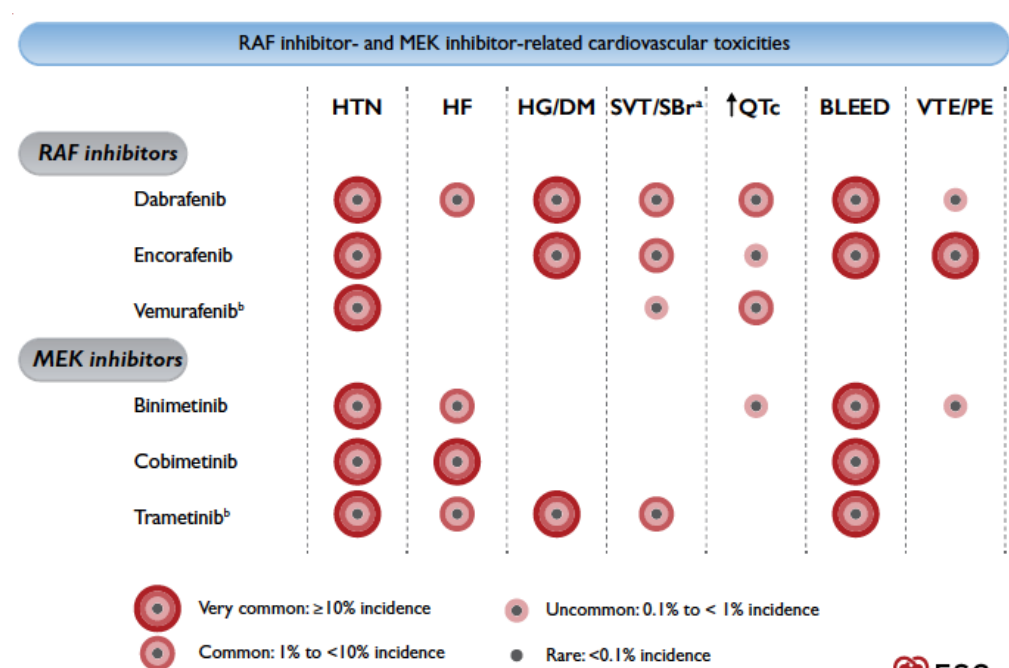


Figure 13. ESC 2022 GL on cardio-oncology. Rapidly accelerated fibrosarcoma and mitogen-activated extracellular signal-regulated kinase inhibitor-related cardiovascular toxicities.

AF, atrial fibrillation; BLEED, increased bleeding risk; DM, diabetes mellitus; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HG, hyperglycaemia; HTN, hypertension; MedDRA, medical dictionary for regulatory activities; MEK, mitogen-activated extracellular signal-regulated kinase; PE, pulmonary embolism; ↑QTc, corrected QT interval prolongation; RAF, rapidly accelerated fibrosarcoma; SBr, sinus bradycardia; SVT, supraventricular tachycardia; VTE, venous thromboembolism. Adverse reactions reported in multiple clinical trials or during post-marketing use are listed by systemorgan class (in MedDRA) and frequency. If the frequency is unknown or cannot be estimated from the available data, a blank space has been left.

a Dabrafenib is related with SBr. Encorafenib is related with SVT. Vemurafenib rarely causes AF. Trametinib is related with bradycardia in some post-marketing reports.

b Peripheral oedema is very common.

Figure developed from EMA prescribing information, FDA prescribing information.

Table 14. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during immunotherapy

ECG, NP, and cTn measurements in all patients before starting ICI therapy.	I B
Baseline echocardiography in high-risk patients ^a before starting ICI therapy.	I B
Baseline echocardiography in all patients before starting ICI therapy.	IIb C
Serial ECG and cTn measurements before ICI doses 2, 3, and 4, and if normal, reduce to every three doses until completion of therapy to detect subclinical ICI-related CV toxicity.	IIa B
CV assessment ^b every 6–12 months in high-risk patients ^a who require long-term (>12 months) ICI treatment.	I c
CV assessment ^b may be considered every 6–12 months in all patients who require long-term (>12 months) ICI treatment.	IIb C

BNP, B-type natriuretic peptide; BP, blood pressure; cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; HbA1c, glycated haemoglobin; ICI, immune checkpoint inhibitors; NP, natriuretic peptides; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

a Dual ICI, combination ICI-cardiotoxic therapy; ICI-related non-CV events, prior CTRCD, or CVD.

b Physical examination, BP, NP (BNP or NT-proBNP), lipid profile, HbA1c, and ECG.

Table 15. ESC 2022 GL on cardio-oncology. Recommendations for the diagnosis and management of immune checkpoint inhibitor-associated myocarditis

cTn, ECG, and CV imaging (echocardiography and CMR) to diagnose ICI-associated myocarditis..	I C
In patients with suspected ICI-associated myocarditis, temporary interruption of ICI treatment until the diagnosis is confirmed or refuted.	I C
EMB to confirm the diagnosis of ICI-associated myocarditis if the diagnosis is suspected but not confirmed after cardiac imaging and biomarkers. ^a	IIa C
Interruption of ICI treatment in confirmed ICI-associated myocarditis.	I C
Continuous ECG monitoring to assess for new AV block and tachyarrhythmias during the acute phase for all patients with symptomatic ICI-associated myocarditis.	I C
Early high-dose corticosteroids ^b in confirmed ICI-associated myocarditis.	I C
Continuation of high-dose corticosteroids for the treatment of ICI-associated myocarditis until resolution of symptoms, LV systolic dysfunction, conduction	I C

abnormalities, and significant cTn reduction.^c

Switching from i.v. to oral prednisolone after clinical improvement (resolution of symptoms, LV systolic dysfunction, conduction abnormalities, and significant cTn reduction). ^d	IIa C
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Second-line immunosuppression treatment in steroid-refractory ICI-associated myocarditis. ^e	IIa C
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Admission to ICU (level 3), treatment with i.v. methylprednisolone, and optimal CV treatment including mechanical support (when indicated) for patients with ICI-associated fulminant myocarditis.	I C
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A single dose of i.v. methylprednisolone ^b should in unstable ^f patients with cancer where ICI-induced myocarditis is suspected.	IIa C
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A multidisciplinary discussion before restarting ICI treatment in selected patients with previous uncomplicated ICI-associated myocarditis.	I C
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AV, atrioventricular; CMR, cardiac magnetic resonance; cTn, cardiac troponin; CV, cardiovascular; ECG, electrocardiogram; EMB, endomyocardial biopsy; HF, heart failure; ICI, immune checkpoint inhibitors; ICU, intensive care unit; i.v., intravenous; LGE, late gadolinium enhancement; LV, left ventricular; LVD, LV dysfunction; LVEF, LV ejection fraction.

a See Chapter 92 for ICI-related myocarditis definition. EMB should be considered in unstable patients or when CMR is contraindicated.

b Early: ≤24 h; high-dose corticosteroids (methylprednisolone 500–1000 mg/day).

c Reduction of cTn by .50% from peak level.

d Complete recovery: Patients with complete resolution of acute symptoms, normalization of biomarkers, or reduction of cTn by .50% from peak level and recovery of LVEF after discontinuation of immunosuppression are considered to have achieved complete recovery. CMR may still show LGE or elevated T1 due to fibrosis but any suggestion of acute oedema should be absent. Incomplete recovery: (1) an increase in symptoms or biomarkers of myocarditis or an inability to taper immunosuppression without a clinical or biomarker flare; (2) patients with persistent LVD despite resolution of acute symptoms with immunosuppression.

e Steroid refractory: non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other aetiologies) despite high-dose methylprednisolone.

f Unstable: patients with symptomatic HF, ventricular arrhythmias, new complete heart block.

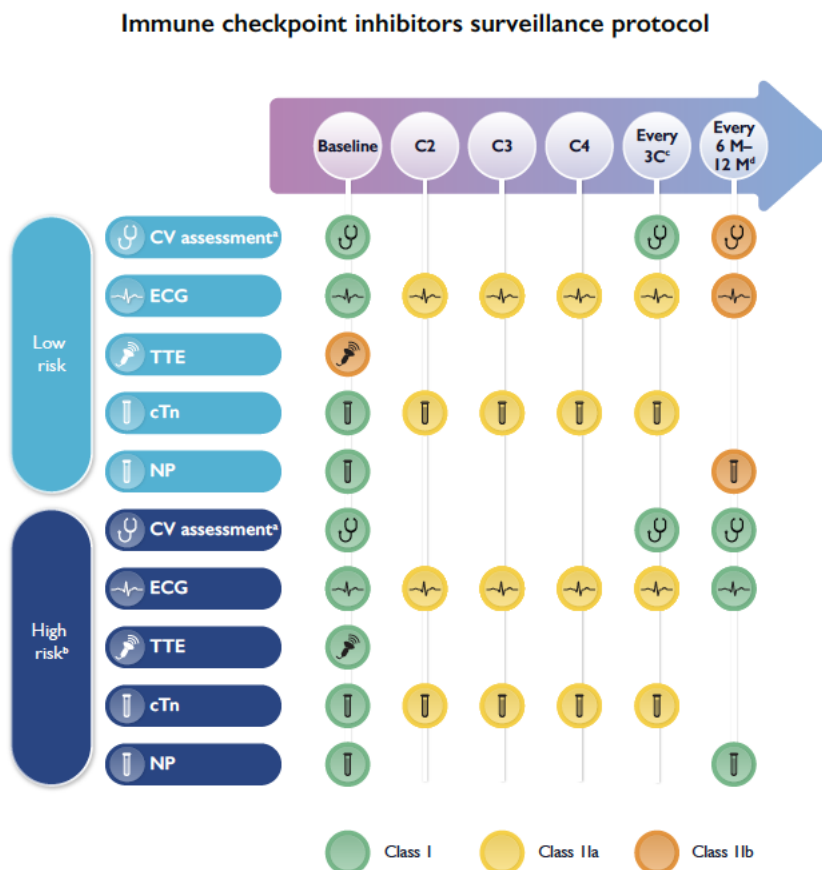


Figure 14. ESC 2022 GL on cardio-oncology. Cardiovascular surveillance in patients treated with immune checkpoint inhibitors.

BNP, B-type natriuretic peptide; BP, blood pressure; C, chemotherapy cycle; cTn, cardiac troponin; CV, cardiovascular; CVD, cardiovascular disease; CTRCD, cancer therapy-related cardiac dysfunction; ECG, electrocardiogram; HbA1c, glycated haemoglobin; ICI, immune checkpoint inhibitors; M, months; NP, natriuretic peptides (including BNP and NT-proBNP); NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTE, transthoracic echocardiography.

a Including physical examination, BP, lipid profile, and HbA1c.

b Dual ICI, combination ICI-cardiotoxic therapy, ICI-related non-CV events, prior CTRCD or CVD.

c Every three cycles until completion of therapy to detect subclinical ICI-related CV toxicity. d In patients who require long-term (>12 months) ICI treatment.

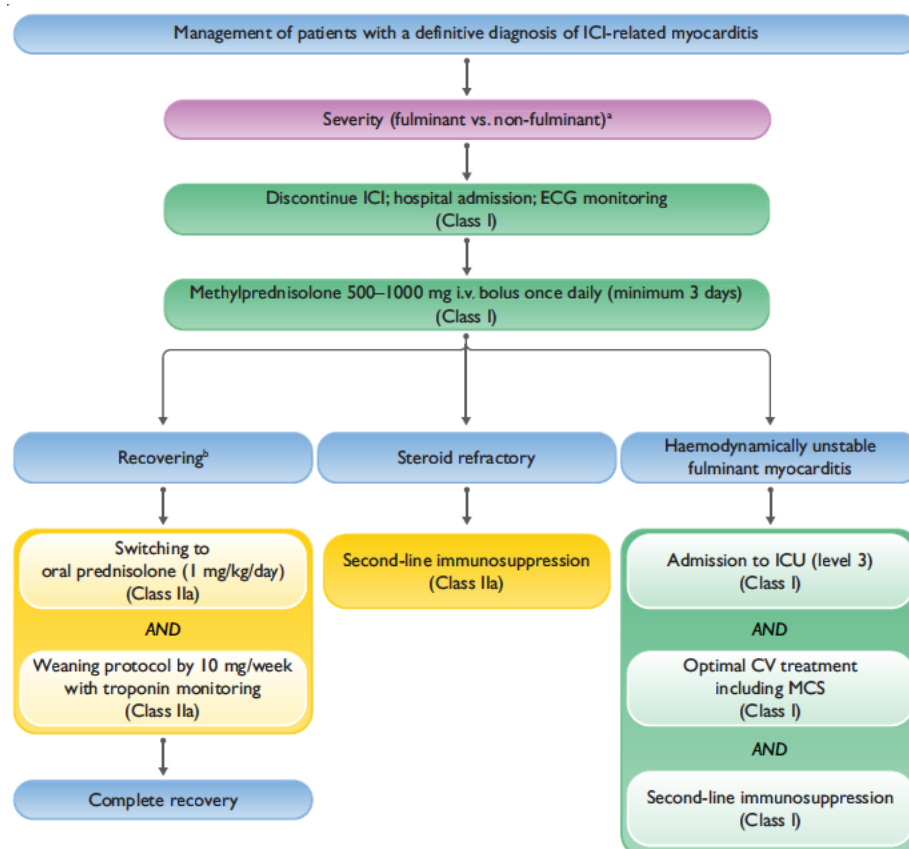


Figure 15. ESC 2022 GL on cardio-oncology. Diagnosis and management of immune checkpoint inhibitor-related myocarditis.

CMR, cardiac magnetic resonance; CV, cardiovascular; ECG, electrocardiogram; HF, heart failure; ICI, immune checkpoint inhibitor; ICU, intensive care unit; i.v., intravenous; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support.

a Fulminant: haemodynamic instability, HF requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia. Non-fulminant: including symptomatic but haemodynamically and electrically stable patients and incidental cases diagnosed at the same time as other immuno-related adverse events. Patients may have reduced LVEF but no features of severe disease.

b Recovering: ongoing improvement in patient clinical symptoms, signs, biomarkers, and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression. Complete recovery: patients with complete resolution of acute symptoms, normalization of biomarkers, and recovery of LVEF after discontinuation of immunosuppression. CMR may still show LGE or elevated T1 due to fibrosis, but any suggestion of acute oedema should be absent.

Table 16. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during androgen deprivation therapy for prostate cancer

Baseline CV risk assessment ^a and estimation of 10-year fatal and non-fatal CVD risk With SCORE2 or SCORE2-OP ^b in patients treated with ADT without pre-existing CVD	I B
Baseline and serial ECGs in patients at risk of QTc prolongation during ADT therapy. ^c	I B
A GnRH antagonist in patients with pre-existing symptomatic CAD ^d who require ADT	IIa B
Annual CV risk assessment ^c during ADT	I B

ACS, acute coronary syndromes; ADT, androgen deprivation therapy; BP, blood pressure; CAD, coronary artery disease; CCS, chronic coronary syndromes; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; GnRH, gonadotropin-releasing hormone; HbA1c, glycated haemoglobin; QTc, corrected QT interval; SCORE2, Systematic Coronary Risk Estimation 2; SCORE2-OP, Systematic Coronary Risk Estimation 2—Older Persons.

a BP, lipids, fasting glucose, HbA1c, ECG, and patient education on healthy lifestyle and lifestyle risk factor control is recommended.

b SCORE2 (<70 years) or SCORE2-OP (≥70 years) CV risk stratification: <50 years: low risk <2.5%, moderate risk 2.5% to 7.5%, high risk ≥7.5%; 50–69 years: low risk <5%; moderate risk 5% to <10%; high risk ≥10%; ≥70 years: low risk <7.5%, moderate risk 7.5% to <15%, high risk ≥15%.

c See Chapter 94.

d CCS and ACS.

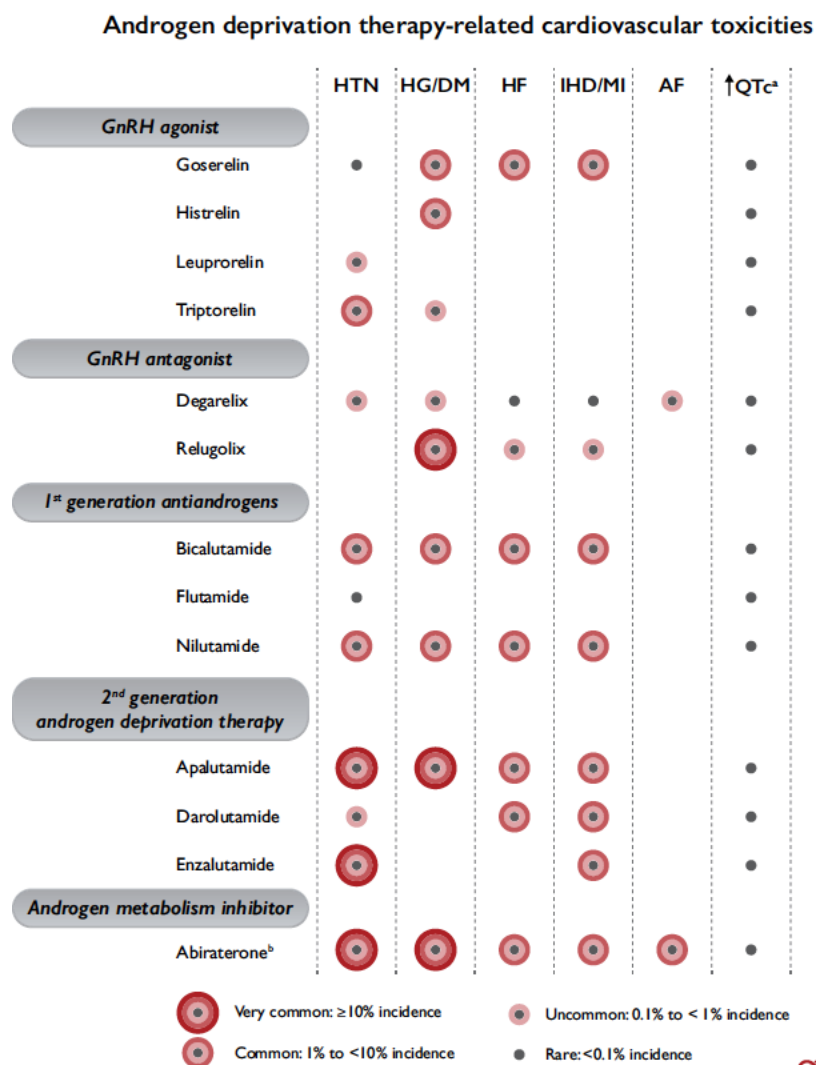


Figure 16. ESC 2022 GL on cardio-oncology. Androgen deprivation therapy-related cardiovascular toxicities.

ADT, androgen deprivation therapy; AF, atrial fibrillation; DM, diabetes mellitus; EMA, European Medicines Agency; FDA, Food and Drug Administration; GnRH, gonadotropin-releasing hormone; HF, heart failure; HG, hyperglycaemia; HTN, hypertension; IHD, ischaemic heart disease; MedDRA, medical dictionary for regulatory activities; MI, myocardial infarction; ↑QTc, corrected QT interval prolongation; TdP, torsade de pointes. Adverse reactions reported in multiple clinical trials or during post-marketing use are listed by system organ class (in MedDRA) and frequency. If the frequency is unknown or cannot be estimated from the available data, a blank space has been left.

a ADT may prolong the QTc interval. In patients with a history of risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess the benefit/risk ratio including the potential for TdP prior to initiating the treatment.

b Increased risk of QTc prolongation in combination with ADT.

Figure developed from EMA prescribing information, FDA prescribing information.

Table 17. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during endocrine therapy for breast cancer

Baseline CV risk assessment ^a and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP ^{b,c} in BC patients receiving endocrine therapies without pre-existing CVD.	I C
Annual CV risk assessment ^a during endocrine therapy in BC patients with high 10-year risk of (fatal and non-fatal) CV events according to SCORE2/SCORE2-OP. ^{b,c}	I C
CV risk assessment ^a every 5 years in BC patients with low or moderate 10-year risk of (fatal and non-fatal) CV events according to SCORE2/SCORE2-OP. ^{b,c}	IIa C

BC, breast cancer; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; HbA1c, glycated haemoglobin; SCORE2, Systematic Coronary Risk Estimation 2; SCORE2-OP, Systematic Coronary Risk Estimation 2—Older persons.

a BP, lipids, fasting glucose, HbA1c, ECG and patient education on healthy lifestyle and lifestyle risk factor control.

b Or other validated CV risk scores.

c SCORE2 (<70 years) or SCORE2-OP (≥70 years) CV risk stratification: <50 years: low risk <2.5%, moderate risk 2.5% to <7.5%, high risk ≥7.5%; 50–69 years: low risk <5%; moderate risk 5% to <10%; high risk ≥10%; ≥70 years: low risk <7.5%, moderate risk 7.5% to <15%, high risk ≥15%.

Table 18. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during cyclin-dependent kinase 4/6 inhibitor therapy

QTc ^{a,b} monitoring at baseline and 14 and 28 days in all patients with cancer receiving ribociclib.	I A
QTc ^{a,b} monitoring in patients treated with ribociclib with any dose increase	I B
QTc ^a monitoring in patients treated with palbociclib or abemaciclib who have a baseline QTc above the normal range or other conditions that may prolong the QTc interval.	IIa C

QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction.

a QT interval using Fridericia correction ($QTcF = QT/3\sqrt{RR}$) is the preferred method in patients with cancer. Upper 99% limit of normal for QTc values in the general population are 450 ms for men and 460 ms for women.

b According to the European Medicines Agency: (1) ribociclib should be interrupted when QTcF.480 ms; (2) if QTcF prolongation resolves to ,481 ms, resume treatment at the same dose level; (3) if QTcF≥481 ms recurs, interrupt dose until QTcF resolves to <481 ms and then resume ribociclib at next lower dose level.

Table 19. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring during anaplastic lymphoma kinase and epidermal growth factor receptor inhibitors

Baseline CV risk assessment ^a in patients before ALK inhibitors and EGFR inhibitors.	I C
Baseline echocardiography in all patients with cancer before starting Osimertinib.	I B
Home BP monitoring for patients treated with brigatinib, crizotinib, or lorlatinib.	IIa C
Cholesterol profile assessment every 3–6 months for patients on crizotinib and lorlatinib.	IIa C
Echocardiography every 3 months in patients during osimertinib therapy.	IIa B
ECG 4 weeks after starting therapy and every 3–6 months in patients during ALK inhibitor therapy.	IIa C

ALK, anaplastic lymphoma kinase; BP, blood pressure; CV, cardiovascular; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; HbA1c, glycated haemoglobin.

^a Physical examination, BP measurement, ECG, lipid profile, and HbA1c measurement.

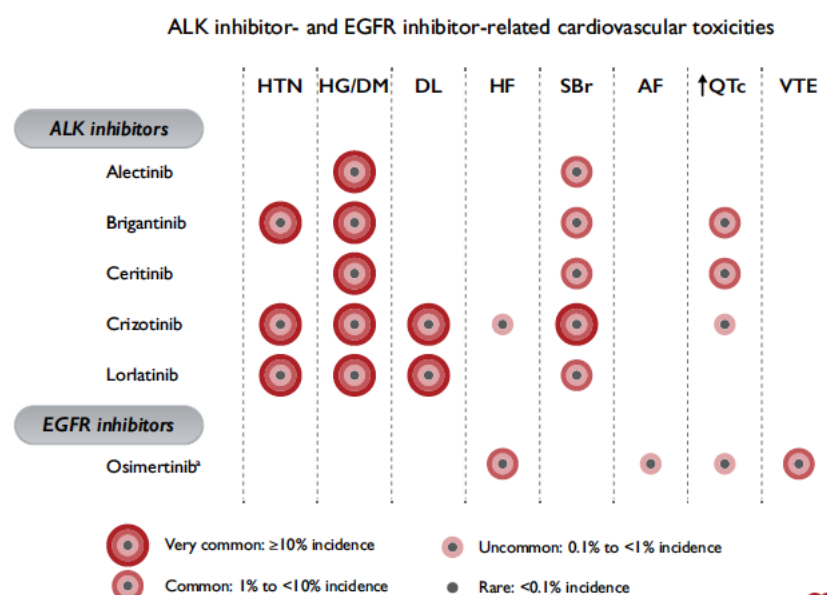


Figure 17. ESC 2022 GL on cardio-oncology. Anaplastic lymphoma kinase and epidermal growth factor receptor inhibitor-related cardiovascular toxicities.

AF, atrial fibrillation; ALK, anaplastic lymphoma kinase; DL, dyslipidaemia; DM, diabetes mellitus; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HG, hyperglycaemia; HTN, hypertension; MedDRA, medical dictionary for regulatory activities; ↑QTc, corrected QT interval prolongation; SBr, sinus bradycardia; VTE, venous thromboembolism.

Adverse reactions reported in multiple clinical trials or during post-marketing use are listed by system organ class (in MedDRA) and frequency. If the frequency is unknown or cannot be estimated from the available data, a blank space has been left.

^a Osimertinib increases the risk of hypomagnesaemia.

Figure developed from EMA prescribing information, FDA prescribing information

Table 20. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment and monitoring in patients receiving chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies

Baseline ECG, NP, and cTn in all patients with cancer before starting CAR-T and TIL therapies.	I C
A baseline echocardiography in patients with pre-existing CVD before starting CAR-T and TIL therapies.	I C
A baseline echocardiography before starting CAR-T and TIL therapies.	IIa C
Measurement of NP, cTn, and echocardiography in patients who develop CRS of ASTCT $\geq$ 2. ^a	I C

ASTCT, American Society for Transplantation and Cellular Therapy; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; cTn, cardiac troponin; CVD, cardiovascular disease; ECG, electrocardiogram; NP, natriuretic peptides; TIL, tumour-infiltrating lymphocytes.

a Determine CRS grade according to ASTCT grading: Grade 1: fever; Grade 2: fever AND hypotension not requiring vasopressors AND/OR hypoxia requiring low-flow nasal oxygen; Grade 3: fever AND hypotension requiring one vasopressor + vasopressin AND/OR hypoxia requiring high-flow nasal cannula or facemask or non-rebreather mask or Venturi mask; Grade 4: fever AND hypotension requiring multiple vasopressors, not including vasopressin AND/OR hypoxia requiring positive airway pressure.

Table 21. ESC 2022 GL on cardio-oncology. Recommendations for the diagnosis and management of Takotsubo syndrome in patients with cancer

Coronary angiography (invasive or CCTA) to exclude ACS.	I C
CMR to exclude myocarditis and MI.	I B
QT-prolonging drugs are not recommended during the acute TTS phase. ^a	

ACS, acute coronary syndromes; CMR, cardiac magnetic resonance; CCTA, coronary computed tomography angiography; LV, left ventricular; MI, myocardial infarction; QTc, corrected QT interval; TTS, Takotsubo syndrome.

a Until full recovery and normalization of LV function and QTc.

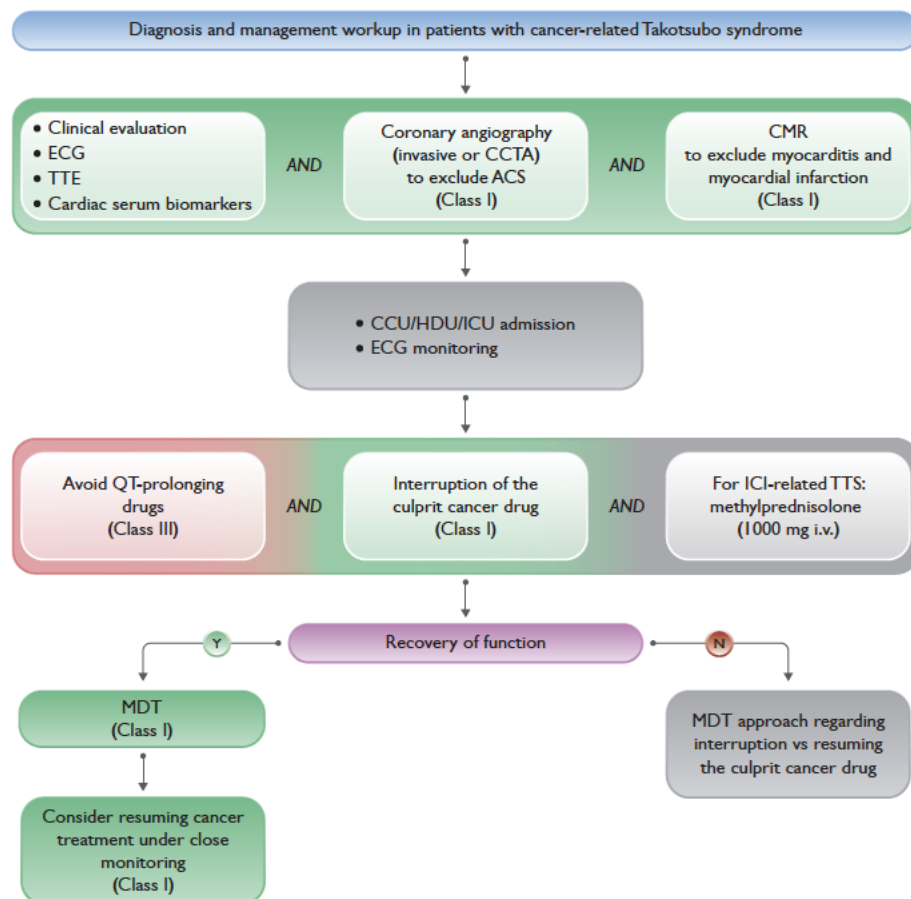


Figure 18. ESC 2022 GL on cardio-oncology. Diagnosis and management workup in cancer-related Takotsubo syndrome.

ACS, acute coronary syndromes; CCTA, coronary computed tomography angiography; CCU, coronary care unit; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HDU, high-dependency unit; ICI, immune checkpoint inhibitor; ICU, intensive care unit; i.v., intravenous; MDT, multidisciplinary team; N, no; TTE, transthoracic echocardiography; TTS, Takotsubo syndrome; Y, yes.

Table 22. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment of patients before radiotherapy to a volume including the heart

Baseline CV risk assessment ^a and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP ^b	I B
Baseline echocardiography in patients with previous CVD before RT to a volume including the heart.	IIa C

BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; HbA1c, glycated haemoglobin; RT, radiotherapy; SCORE2, Systematic Coronary Risk Estimation 2; SCORE2-OP, Systematic Coronary Risk Estimation 2—Older Persons.

a BP, lipids, fasting glucose, HbA1c, ECG and patient education on healthy lifestyle and lifestyle risk factor control.

b SCORE2 (<70 years) or SCORE2-OP (≥70 years) CV risk stratification: <50 years: low risk <2.5%, moderate risk 2.5% to <7.5%, high risk ≥7.5%; 50–69 years: low risk <5%; moderate risk 5% to <10%; high risk ≥10%; ≥70 years: low risk <7.5%, moderate risk 7.5% to <15%, high risk ≥15%.

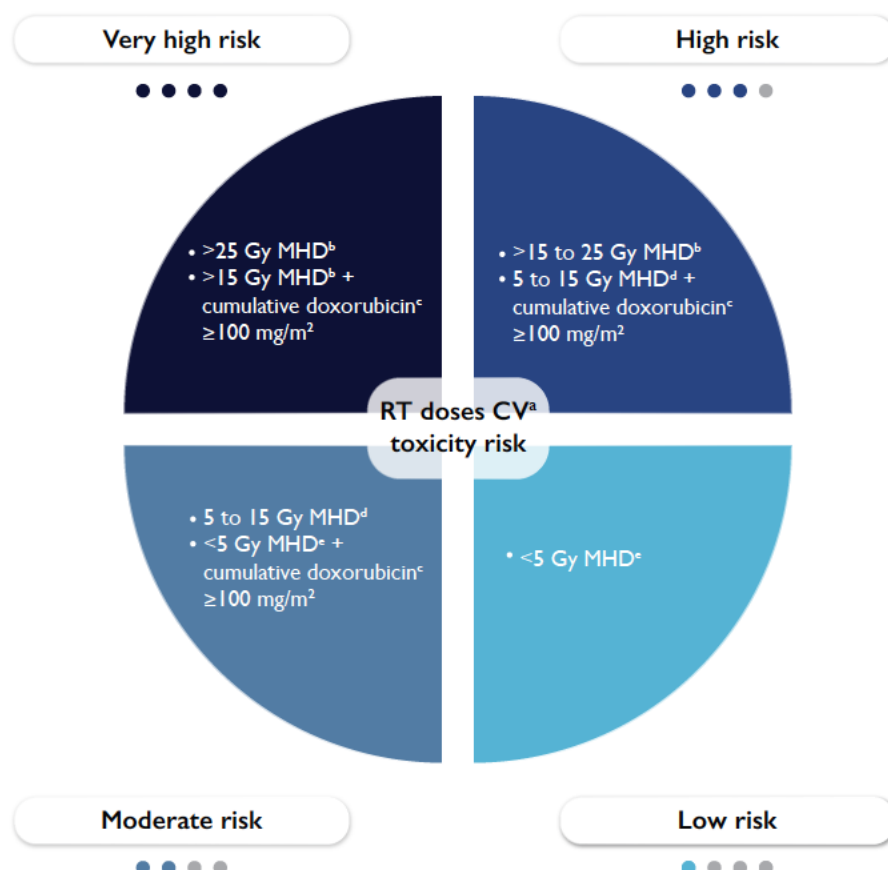


Figure 19. ESC 2022 GL on cardio-oncology. Radiotherapy mean heart dose and associated cardiovascular toxicity risk.

CV, cardiovascular; Gy, Gray; MHD, mean heart dose; RT, radiotherapy.

a RT risk categorization based on MHD is recommended over categorization based on prescribed dose, which may not accurately reflect cardiac radiation exposure. Depending on dose distribution and exposure of specific cardiac substructures (as well as clinical risk factors) the treatment team may judge the patient to belong to a higher risk category. In addition, a patient may be judged to belong to a lower risk category if only a small part of the heart was exposed to a relatively low prescribed dose.

b Or prescribed RT ≥35 Gy to a volume exposing the heart if MHD is not available. Note that in this case, the limited information about cardiac exposure does not allow one to distinguish between high- and very high-risk categories.

c Or equivalent.

d Or prescribed RT 15–34 Gy to a volume exposing the heart if MHD is not available. eOr prescribed RT, 15 Gy to a volume exposing the heart if MHD is not available.

Table 23. ESC 2022 GL on cardio-oncology. Recommendations for baseline risk assessment in haematopoietic stem cell transplantation patients

Baseline and serial CV risk assessment (3 and 12 months, then yearly) including BP measurement, ECG, lipid measurement, and HbA1c in HSCT patients.	I C
Echocardiography in all patients before HSCT.	I C
Baseline NP measurement should be considered before HSCT.	IIa C

BP, blood pressure; CV, cardiovascular; ECG, electrocardiogram; HbA1c, glycated haemoglobin; HSCT, haematopoietic stem cell transplantation; NP, natriuretic peptides.

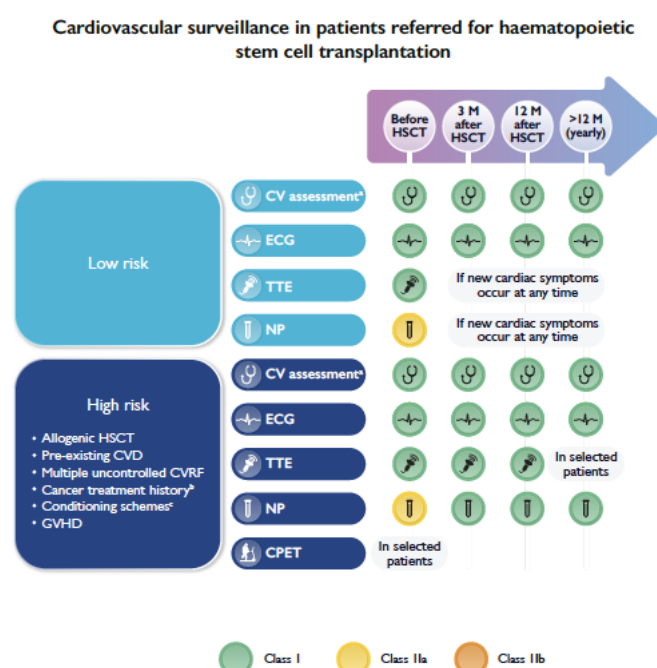


Figure 20. ESC 2022 GL on cardio-oncology. Risk factors and cardiovascular surveillance in patients referred for haematopoietic stem cell transplantation.

BNP, B-type natriuretic peptide; BP, blood pressure; CPET, cardiopulmonary exercise testing; CV, cardiovascular; CVD, CV disease; CVRF, cardiovascular risk factors; ECG, electrocardiogram; GVHD, graft vs. host disease; HbA1c, glycated haemoglobin; HSCT, haematopoietic stem cell transplantation; M, months; NP, natriuretic peptides (including BNP or NT-proBNP); NT-proBNP, N-terminal pro-BNP; TTE, transthoracic echocardiography.

a Including physical examination,

BP, lipid profile, and HbA1c.

b Mediastinal or mantle field radiation, alkylating agents, .250 mg/m² doxorubicin or equivalent.

c Total body irradiation, alkylating agents.