

# 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)

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**SD** See the *European Heart Journal* online for supplementary data that includes background information and detailed discussion of the data that have provided the basis of the guidelines.

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## Table of contents

|   |           |
|---|-----------|
| <b>1. Preamble</b> .....  | <b>8</b>  |
| <b>2. Introduction</b> .....  | <b>10</b> |
| 2.1. Cancer and cardiovascular needs of patients with cancer ...  | 10        |
| 2.2. Role of cardio-oncology services .....   | 10        |
| 2.3. General principles of cardio-oncology .....  | 11        |
| <b>3. Cancer therapy-related cardiovascular toxicity definitions</b> .....  | <b>14</b> |
| <b>4. Cardiovascular toxicity risk stratification before anticancer therapy</b> .....   | <b>16</b> |
| 4.1. General approach to cardiovascular toxicity risk in patients with cancer .....   | 16        |
| 4.2. History and clinical examination .....   | 21        |
| 4.3. Electrocardiogram .....  | 21        |
| 4.4. Cardiac serum biomarkers .....   | 23        |
| 4.5. Cardiovascular imaging .....   | 24        |
| 4.6. Cardiopulmonary fitness assessment .....   | 25        |
| 4.7. Cardiovascular risk evaluation before cancer surgery .....   | 26        |
| 4.8. Genetic testing .....  | 26        |
| <b>5. Prevention and monitoring of cardiovascular complications during cancer therapy</b> .....                                 | <b>26</b> |
| 5.1. General principles .....   | 26        |
| 5.2. Primary prevention strategies .....  | 28        |
| 5.2.1. Primary prevention of cancer therapy-related cardiovascular toxicity during anthracycline chemotherapy .....             | 28        |
| 5.2.2. Primary prevention of radiation-induced cardiovascular toxicity .....  | 28        |
| 5.3. Secondary prevention strategies .....  | 29        |
| 5.4. Cardiovascular surveillance during cancer therapies .....  | 29        |
| 5.4.1. Cardiac serum biomarkers .....   | 29        |
| 5.4.2. Cardiac imaging .....  | 29        |
| 5.5. Cancer therapy-related cardiovascular toxicity monitoring protocols .....  | 31        |
| 5.5.1. Anthracycline chemotherapy .....   | 31        |
| 5.5.2. HER2-targeted therapies .....  | 31        |
| 5.5.3. Fluoropyrimidines .....  | 33        |
| 5.5.4. Vascular endothelial growth factor inhibitors .....  | 33        |
| 5.5.5. Multitargeted kinase inhibitors targeting BCR-ABL ...  | 36        |
| 5.5.6. Bruton tyrosine kinase inhibitors .....  | 39        |
| 5.5.7. Multiple myeloma therapies .....   | 40        |
| 5.5.8. Rapidly accelerated fibrosarcoma and mitogen-activated extracellular signal-regulated kinase inhibitor treatment .....   | 43        |
| 5.5.9. Immune checkpoint inhibitors .....   | 45        |
| 5.5.10. Androgen deprivation therapies for prostate cancer .....  | 46        |
| 5.5.11. Endocrine therapies for breast cancer .....   | 48        |
| 5.5.12. Cyclin-dependent kinase 4/6 inhibitors .....  | 48        |
| 5.5.13. Anaplastic lymphoma kinase inhibitors .....   | 49        |
| 5.5.14. Epidermal growth factor receptor inhibitors .....   | 49        |
| 5.5.15. Chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies .....                                    | 50        |
| 5.5.16. Radiotherapy .....  | 51        |
| 5.5.17. Haematopoietic stem cell transplantation .....  | 51        |
| 5.5.18. Other cancer treatments .....   | 54        |
| <b>6. Diagnosis and management of acute and subacute cardiovascular toxicity in patients receiving anticancer treatment</b> ... | <b>54</b> |
| 6.1. Cancer therapy-related cardiac dysfunction .....   | 54        |
| 6.1.1. Anthracycline chemotherapy-related cardiac dysfunction .....   | 54        |
| 6.1.2. Human epidermal receptor 2-targeted therapy-related cardiac dysfunction .....  | 56        |
| 6.1.3. Immune checkpoint inhibitor-associated myocarditis and non-inflammatory heart failure .....                              | 58        |
| 6.1.4. Chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies and heart dysfunction ...                 | 62        |
| 6.1.5. Heart failure during haematopoietic stem cell transplantation .....  | 63        |
| 6.1.6. Takotsubo syndrome and cancer .....  | 63        |
| 6.2. Coronary artery disease .....  | 63        |
| 6.2.1. Acute coronary syndromes .....   | 63        |
| 6.2.2. Chronic coronary syndromes .....   | 65        |
| 6.3. Valvular heart disease .....   | 65        |
| 6.4. Cardiac arrhythmias .....  | 66        |
| 6.4.1. Atrial fibrillation .....  | 66        |
| 6.4.2. Long corrected QT interval and ventricular arrhythmias .....   | 70        |
| 6.4.3. Bradyarrhythmias .....   | 72        |
| 6.5. Arterial hypertension .....  | 72        |
| 6.6. Thrombosis and thromboembolic events .....   | 75        |
| 6.6.1. Venous thromboembolism .....   | 75        |
| 6.6.2. Arterial thromboembolism .....   | 76        |
| 6.6.3. Intracardiac thrombosis .....  | 76        |
| 6.6.4. Anticoagulation therapy .....  | 77        |
| 6.7. Bleeding complications .....   | 78        |
| 6.7.1. High-risk patients .....   | 78        |
| 6.7.2. Antiplatelet therapy .....   | 78        |
| 6.7.3. Management of bleeding .....   | 78        |
| 6.8. Peripheral artery disease .....  | 79        |
| 6.9. Pulmonary hypertension .....   | 79        |
| 6.10. Pericardial diseases .....  | 80        |
| 6.10.1. Pericarditis .....  | 80        |
| 6.10.2. Pericardial effusion .....  | 80        |
| <b>7. End-of-cancer therapy cardiovascular risk assessment</b> .....  | <b>81</b> |
| 7.1. Cardiovascular evaluation during the first year after cardiotoxic anticancer therapy .....                                 | 81        |
| 7.2. Which cancer survivors require cardiovascular surveillance in the first year after cancer treatment? .....                 | 81        |
| 7.3. Management of cancer therapy-related cardiac dysfunction at the end-of-therapy assessment .....                            | 82        |
| 7.4. Cardiopulmonary exercise testing and fitness during the end-of-therapy assessment .....                                    | 82        |
| 7.5. The role of cardiac rehabilitation .....   | 82        |
| <b>8. Long-term follow-up and chronic cardiovascular complications in cancer survivors</b> .....                                | <b>84</b> |
| 8.1. Cancer survivors .....   | 84        |
| 8.1.1. Adult survivors of childhood and adolescent cancer .....   | 84        |
| 8.1.2. Adult cancer survivors .....   | 85        |
| 8.2. Myocardial dysfunction and heart failure .....   | 87        |
| 8.3. Coronary artery disease .....  | 88        |
| 8.4. Valvular heart disease .....   | 89        |
| 8.5. Peripheral artery disease and stroke .....   | 89        |
| 8.6. Pericardial complications .....  | 89        |
| 8.7. Arrhythmias and autonomic disease .....  | 90        |

|  |            |
|--|------------|
| 8.8. Metabolic syndrome, lipid abnormalities, diabetes mellitus, and hypertension .....                                  | 90         |
| 8.9. Pregnancy in cancer survivors .....   | 90         |
| 8.10. Pulmonary hypertension .....   | 91         |
| <b>9. Special populations .....</b>  | <b>91</b>  |
| 9.1. Cardiac tumours .....   | 91         |
| 9.2. Pregnant patients with cancer .....   | 91         |
| 9.2.1. Left ventricular dysfunction and heart failure .....  | 92         |
| 9.2.2. Venous thromboembolism and pulmonary embolism .....   | 92         |
| 9.3. Carcinoid valvular heart disease .....  | 95         |
| 9.4. Amyloid light-chain cardiac amyloidosis .....   | 96         |
| 9.5. Cardiac implantable electronic devices .....  | 98         |
| <b>10. Patient information, communication, and self-management ...</b>   | <b>102</b> |
| <b>11. The role of scientific societies in the promotion and development of cardio-oncology in modern medicine .....</b> | <b>103</b> |
| <b>12. Key messages .....</b>  | <b>103</b> |
| <b>13. Future needs .....</b>  | <b>104</b> |
| <b>14. Gaps in evidence .....</b>  | <b>105</b> |
| <b>15. 'What to do' and 'what not to do' messages from the Guidelines .....</b>  | <b>105</b> |
| <b>16. Quality indicators for cardio-oncology .....</b>  | <b>114</b> |
| <b>17. Supplementary data .....</b>  | <b>114</b> |
| <b>18. Data availability statement .....</b>   | <b>114</b> |
| <b>19. Author information .....</b>  | <b>114</b> |
| <b>20. Appendix .....</b>  | <b>114</b> |
| <b>21. References .....</b>  | <b>115</b> |

## Tables of Recommendations

|   |    |
|---|----|
| Recommendation Table 1 — Recommendations for a general approach to cardiovascular toxicity risk categorization .....  | 21 |
| Recommendation Table 2 — Recommendations for electrocardiogram baseline assessment .....  | 23 |
| Recommendation Table 3 — Recommendation for cardiac biomarker assessment prior to potentially cardiotoxic therapies .....   | 24 |
| Recommendation Table 4 — Recommendations for cardiac imaging modalities in patients with cancer .....   | 25 |
| Recommendation Table 5 — Recommendations for primary prevention of cancer therapy-related cardiovascular toxicity .....   | 28 |
| Recommendation Table 6 — Recommendation for secondary prevention of cancer therapy-related cardiovascular toxicity .....  | 29 |
| Recommendation Table 7 — Recommendations for baseline risk assessment and monitoring during anthracycline chemotherapy and in the first 12 months after therapy .....                                       | 31 |
| Recommendation Table 8 — Recommendations for baseline risk assessment and monitoring during human epidermal receptor 2-targeted therapies and in the first 12 months after therapy .....                    | 32 |
| Recommendation Table 9 — Recommendations for baseline risk assessment and monitoring during fluoropyrimidine therapy .....  | 33 |
| Recommendation Table 10 — Recommendations for baseline risk assessment and monitoring during vascular endothelial growth factor inhibitors .....  | 36 |
| Recommendation Table 11 — Recommendations for baseline risk assessment and monitoring during second- and third-generation breakpoint cluster region–Abelson oncogene locus tyrosine kinase inhibitors ..... | 39 |

|  |    |
|--|----|
| Recommendation Table 12 — Recommendations for baseline risk assessment and monitoring during Bruton tyrosine kinase inhibitor therapy .....  | 39 |
| Recommendation Table 13 — Recommendations for baseline risk assessment and monitoring during multiple myeloma therapies .....  | 43 |
| Recommendation Table 14 — Recommendations for baseline risk assessment and monitoring during combined rapidly accelerated fibrosarcoma and mitogen-activated extracellular signal-regulated kinase inhibitor therapy ..... | 44 |
| Recommendation Table 15 — Recommendations for baseline risk assessment and monitoring during immunotherapy .....   | 46 |
| Recommendation Table 16 — Recommendations for baseline risk assessment and monitoring during androgen deprivation therapy for prostate cancer .....  | 48 |
| Recommendation Table 17 — Recommendations for baseline risk assessment and monitoring during endocrine therapy for breast cancer .....   | 48 |
| Recommendation Table 18 — Recommendations for baseline risk assessment and monitoring during cyclin-dependent kinase 4/6 inhibitor therapy .....   | 49 |
| Recommendation Table 19 — Recommendations for baseline risk assessment and monitoring during anaplastic lymphoma kinase and epidermal growth factor receptor inhibitors .....  | 49 |
| Recommendation Table 20 — Recommendations for baseline risk assessment and monitoring in patients receiving chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies .....                           | 51 |
| Recommendation Table 21 — Recommendations for baseline risk assessment of patients before radiotherapy to a volume including the heart .....   | 51 |
| Recommendation Table 22 — Recommendations for baseline risk assessment in haematopoietic stem cell transplantation patients .....  | 53 |
| Recommendation Table 23 — Recommendation for the management of cardiovascular disease and cancer therapy-related cardiovascular toxicity in patients receiving anticancer treatment .....                                  | 54 |
| Recommendation Table 24 — Recommendations for the management of cancer treatment-related cardiac dysfunction during anthracycline chemotherapy .....   | 56 |
| Recommendation Table 25 — Recommendations for the management of cancer treatment-related cardiac dysfunction during human epidermal receptor 2-targeted therapies .....  | 58 |
| Recommendation Table 26 — Recommendations for the diagnosis and management of immune checkpoint inhibitor-associated myocarditis .....   | 61 |
| Recommendation Table 27 — Recommendations for the diagnosis and management of Takotsubo syndrome in patients with cancer .....   | 63 |
| Recommendation Table 28 — Recommendations for the management of acute coronary syndromes in patients receiving anticancer treatment .....  | 64 |
| Recommendation Table 29 — Recommendation for the management of chronic coronary syndromes in patients receiving anticancer treatment .....   | 65 |
| Recommendation Table 30 — Recommendations for the management of valvular heart disease in patients receiving anticancer treatment .....  | 65 |



Recommendation Table 31 — Recommendations for the management of atrial fibrillation in patients receiving anticancer treatment ..... 69

Recommendation Table 32 — Recommendations for the management of long corrected QT interval and ventricular arrhythmias in patients receiving anticancer treatment ..... 72

Recommendation Table 33 — Recommendations for the management of arterial hypertension in patients receiving anticancer treatment ..... 74

Recommendation Table 34 — Recommendations for the management of venous thromboembolism in patients receiving anticancer treatment ..... 77

Recommendation Table 35 — Recommendations for venous thromboembolism prophylaxis during anticancer treatment ..... 78

Recommendation Table 36 — Recommendation for management of peripheral artery disease during anticancer treatment ..... 79

Recommendation Table 37 — Recommendations for the management of pulmonary hypertension during anticancer treatment ..... 80

Recommendation Table 38 — Recommendations for the management of pericardial diseases in patients receiving anticancer treatment ..... 81

Recommendation Table 39 — Recommendations for end-of-cancer therapy cardiovascular risk assessment ..... 84

Recommendation Table 40 — Recommendations for cardiovascular surveillance in asymptomatic adults who are childhood and adolescent cancer survivors ..... 85

Recommendation Table 41 — Recommendations for cardiovascular surveillance in asymptomatic adult cancer survivors ... 86

Recommendation Table 42 — Recommendations for adult cancer survivors who develop cancer therapy-related cardiac dysfunction late after cardiotoxic cancer therapy ..... 88

Recommendation Table 43 — Recommendations for adult cancer survivors with coronary artery disease ..... 88

Recommendation Table 44 — Recommendations for adult cancer survivors with valvular heart disease ..... 89

Recommendation Table 45 — Recommendation for adult cancer survivors with pericardial complications ..... 90

Recommendation Table 46 — Recommendations for cardiovascular monitoring in cancer survivors during pregnancy ... 91

Recommendation Table 47 — Recommendations for cardiovascular assessment and monitoring of pregnant women with cancer ..... 95

Recommendation Table 48 — Recommendations for carcinoid valvular heart diseases ..... 95

Recommendation Table 49 — Recommendations for amyloid light-chain cardiac amyloidosis diagnosis and monitoring ..... 98

Recommendation Table 50 — Recommendations for risk stratification and monitoring for patients with cardiac implantable electronic devices undergoing radiotherapy ..... 102

**List of tables**

Table 1 Classes of recommendations ..... 9

Table 2 Levels of evidence ..... 9

Table 3 Cancer therapy-related cardiovascular toxicity definitions ... 15

Table 4 Heart Failure Association–International Cardio-Oncology Society baseline cardiovascular toxicity risk stratification ..... 18

Table 5 Anthracycline equivalence dose ..... 19

Table 6 Factors that could influence peri-operative risk during cancer surgery and preventive strategies ..... 26

Table 7 Cancer treatments that predispose to acute coronary syndromes ..... 63

Table 8 Risk factors for drug-induced QT prolongation and torsade de pointes ..... 70

Table 9 Classification of corrected QT interval prolongation induced by cancer drug therapy ..... 70

Table 10 Risk factors for future cardiovascular disease at the end-of-cancer therapy cardiovascular risk assessment ..... 82

Table 11 Risk categories for asymptomatic adults who are childhood and adolescent cancer survivors ..... 85

Table 12 Risk categories for asymptomatic adult cancer survivors ... 86

Table 13 Management strategies and surgery indications for symptomatic and asymptomatic patients with benign and malignant cardiac tumours ..... 93

**List of figures**

Figure 1 Video 1 Central Illustration: Dynamics of cardiovascular toxicity risk of patients with cancer over their therapy continuum ..... 11

Figure 2 Cardio-oncology care pathways ..... 12

Figure 3 Baseline cardiovascular toxicity risk assessment checklist ... 13

Figure 4 Dimensions of cancer therapy-related cardiovascular toxicity risk and disease severity ..... 14

Figure 5 Baseline cardiovascular toxicity risk assessment before anticancer therapy ..... 17

Figure 6 General cardio-oncology approach after Heart Failure Association–International Cardio-Oncology Society cardiovascular toxicity risk assessment ..... 20

Figure 7 Baseline screening recommendations for patients with cancer treated with potentially cardiotoxic drugs ..... 22

Figure 8 Recommended transthoracic echocardiography and cardiac magnetic resonance imaging parameters in the evaluation of patients with cancer ..... 24

Figure 9 Primary and secondary cancer therapy-related cardiovascular toxicity prevention ..... 27

Figure 10 Cardiovascular toxicity monitoring in patients receiving anthracycline chemotherapy ..... 30

Figure 11 Cardiovascular toxicity monitoring in patients receiving human epidermal receptor 2-targeted therapies ..... 32

Figure 12 Vascular endothelial growth factor inhibitors-related cardiovascular toxicities ..... 34

Figure 13 Cardiovascular toxicity monitoring in patients receiving vascular endothelial growth factor inhibitors ..... 35

Figure 14 Breakpoint cluster region–Abelson oncogene locus tyrosine kinase inhibitor-related cardiovascular toxicities ..... 37

Figure 15 Second- and third-generation breakpoint cluster region–Abelson oncogene locus tyrosine kinase inhibitors surveillance protocol ..... 38

Figure 16 Multiple myeloma drug-related cardiovascular toxicities ... 40

Figure 17 Cardiovascular monitoring in patients with multiple myeloma receiving proteasome inhibitors ..... 41

Figure 18 Risk factors for venous thromboembolic events in patients with multiple myeloma ..... 42

Figure 19 Rapidly accelerated fibrosarcoma and mitogen-activated extracellular signal-regulated kinase inhibitor-related cardiovascular toxicities ..... 44

|   |     |
|---|-----|
| Figure 20 Cardiovascular surveillance in patients treated with immune checkpoint inhibitors .....                                     | 45  |
| Figure 21 Androgen deprivation therapy-related cardiovascular toxicities .....  | 47  |
| Figure 22 Anaplastic lymphoma kinase and epidermal growth factor receptor inhibitor-related cardiovascular toxicities .....           | 50  |
| Figure 23 Radiotherapy mean heart dose and associated cardiovascular toxicity risk .....  | 52  |
| Figure 24 Risk factors and cardiovascular surveillance in patients referred for haematopoietic stem cell transplantation .....        | 53  |
| Figure 25 Management of anthracycline chemotherapy-related cardiac dysfunction .....  | 55  |
| Figure 26 Management of human epidermal receptor 2-targeted therapy-related cardiac dysfunction .....                                 | 57  |
| Figure 27 Direct and indirect immune checkpoint inhibitor-related cardiovascular toxicity .....                                       | 59  |
| Figure 28 Diagnosis and management of immune checkpoint inhibitor-related myocarditis .....   | 60  |
| Figure 29 Diagnosis and management workup in cancer-related Takotsubo syndrome .....  | 62  |
| Figure 30 Pathophysiology of atrial fibrillation associated with cancer .....   | 67  |
| Figure 31 Structured approach to anticoagulation for atrial fibrillation in patients with cancer .....                                | 68  |
| Figure 32 Corrected QT interval monitoring before and during treatment with corrected QT interval-prolonging anticancer drugs ...     | 71  |
| Figure 33 Recommended threshold for asymptomatic hypertension treatment in different clinical scenarios .....                         | 73  |
| Figure 34 Treatment of arterial hypertension in patients with cancer .....  | 74  |
| Figure 35 Risk factors for venous thromboembolism in patients with cancer .....   | 75  |
| Figure 36 Structured approach to anticoagulation for venous thromboembolism in patients with active cancer .....                      | 76  |
| Figure 37 Management of cancer therapy-related cardiac dysfunction after cancer therapy .....   | 83  |
| Figure 38 Long-term follow-up in cancer survivors .....   | 87  |
| Figure 39 Location of primary and secondary cardiac tumours .....   | 92  |
| Figure 40 Diagnostic algorithm for cardiac masses .....   | 93  |
| Figure 41 Cardiac monitoring protocol for pregnant women receiving anthracycline-based chemotherapy .....                             | 94  |
| Figure 42 Carcinoid heart disease: clinical features and diagnostic tests .....   | 96  |
| Figure 43 Non-invasive diagnosis of amyloid light-chain cardiac amyloidosis .....   | 97  |
| Figure 44 Risk stratification in patients with a cardiac implantable electronic device undergoing radiotherapy .....                  | 99  |
| Figure 45 Management of patients with a cardiac implantable electronic device located in the radiotherapy treatment beam ....         | 100 |
| Figure 46 Management of patients with a cardiac implantable electronic device located outside the radiotherapy treatment volume ..... | 101 |
| Figure 47 Patient information, communication, and self-management .....   | 102 |
| Figure 48 The role of scientific societies in the promotion and development of cardio-oncology .....                                  | 103 |

## Abbreviations and acronyms

|           |  |
|-----------|--|
| 2D        | Two-dimensional  |
| 3D        | Three-dimensional  |
| 5-FU      | 5-fluorouracil   |
| 5HIAA     | 5-hydroxyindoleacetic acid   |
| a'        | Late diastolic velocity of mitral annulus obtained by tissue Doppler imaging   |
| ABC       | Atrial fibrillation Better Care  |
| ABI       | Ankle-brachial index   |
| AC        | Anthracycline chemotherapy   |
| ACE-I     | Angiotensin-converting enzyme inhibitors   |
| ACS       | Acute coronary syndromes   |
| ADT       | Androgen deprivation therapy   |
| ADVANCE   | Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation   |
| AF        | Atrial fibrillation  |
| AI        | Aromatase inhibitors   |
| AL-CA     | Amyloid light-chain cardiac amyloidosis  |
| ALK       | Anaplastic lymphoma kinase   |
| ANS       | Autonomic nervous system   |
| ARB       | Angiotensin receptor blockers  |
| ARISTOTLE | Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation  |
| ASCVD     | AtheroSclerotic Cardiovascular Disease   |
| ASPIRE    | Carfilzomib, Lenalidomide, and Dexamethasone vs. Lenalidomide and Dexamethasone for the Treatment of Patients with Relapsed Multiple Myeloma |
| ASTCT     | American Society for Transplantation and Cellular Therapy  |
| ATAC      | 'Arimidex' and Tamoxifen Alone or in Combination   |
| ATE       | Arterial thromboembolism   |
| AV        | Atrioventricular   |
| BB        | Beta-blockers  |
| BC        | Breast cancer  |
| BCR-ABL   | Breakpoint cluster region–Abelson oncogene locus   |
| BIG       | Breast International Group   |
| BLEED     | Increased bleeding risk  |
| BMI       | Body mass index  |
| BNP       | B-type natriuretic peptide   |
| BP        | Blood pressure   |
| BTK       | Bruton tyrosine kinase   |
| C         | Chemotherapy cycle   |
| CABG      | Coronary artery bypass graft   |
| CAD       | Coronary artery disease  |
| CARDIOTOX | CARDIOvascular TOXicity induced by cancer-related therapies  |
| CAR-T     | Chimeric antigen receptor T cell   |
| CCB       | Calcium channel blockers   |
| CCS       | Chronic coronary syndromes   |
| CCTA      | Coronary computed tomography angiography   |

|  |  |           |  |
|--|--|-----------|--|
| CCU                                    | Coronary care unit   | ESC-CCO   | European Society of Cardiology Council of Cardio-Oncology  |
| CDK                                    | Cyclin-dependent kinase  | ESH       | European Society of Hypertension   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc | Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke (2 points)—Vascular disease, Age 65–74 years, Sex category (female) | EuroSCORE | European System for Cardiac Operative Risk Evaluation  |
| CIED                                   | Cardiac implantable electronic device  | FAC       | Fractional area change   |
| CML                                    | Chronic myeloid leukaemia  | FDA       | Food and Drug Administration   |
| CMR                                    | Cardiac magnetic resonance   | FLT3      | FMS-like tyrosine kinase 3   |
| COMPASS-CAT                            | Prospective COmparison of Methods for thromboembolic risk assessment with clinical Perceptions and AwareneSS in real-life patients—Cancer Associated Thrombosis  | FWLS      | Free wall longitudinal strain  |
| CPET                                   | Cardiopulmonary exercise testing   | GI        | Gastrointestinal   |
| CrCl                                   | Creatinine clearance   | GLS       | Global longitudinal strain   |
| CRF                                    | Cardiorespiratory fitness  | GnRH      | Gonadotropin-releasing hormone   |
| CRS                                    | Cytokine release syndrome  | GU        | Genitourinary  |
| CS                                     | Cancer survivors   | GVHD      | Graft vs. host disease   |
| CT                                     | Computed tomography  | Gy        | Gray   |
| CTLA-4                                 | Cytotoxic T lymphocyte-associated antigen-4  | HAS-BLED  | Hypertension, Abnormal renal and liver function, Stroke, Bleeding Labile international normalized ratio, Elderly, Drugs or alcohol |
| cTn                                    | Cardiac troponin   | HbA1c     | Glycated haemoglobin   |
| CTRCD                                  | Cancer therapy-related cardiac dysfunction   | HDU       | High-dependency unit   |
| CTR-CVT                                | Cancer therapy-related cardiovascular toxicity   | HER2      | Human epidermal receptor 2   |
| CV                                     | Cardiovascular   | HF        | Heart failure  |
| CVD                                    | Cardiovascular disease   | HFA       | Heart Failure Association  |
| CVRF                                   | Cardiovascular risk factors  | HFmrEF    | Heart failure with mildly reduced ejection fraction  |
| DAPT                                   | Dual antiplatelet therapy  | HFpEF     | Heart failure with preserved ejection fraction   |
| DASISION                               | DASatinib vs. Imatinib Study In treatment-Naïve chronic myeloid leukaemia patients   | HFrEF     | Heart failure with reduced ejection fraction   |
| DL                                     | Dyslipidaemia  | HG        | Hyperglycaemia   |
| DM                                     | Diabetes mellitus  | HIIT      | High-intensity interval training   |
| DNR                                    | Do not resuscitate   | HSCT      | Haematopoietic stem cell transplantation   |
| DVT                                    | Deep vein thrombosis   | hs-cTn    | High-sensitivity cardiac troponin  |
| E                                      | Mitral inflow early diastolic velocity obtained by pulsed wave   | HTN       | Hypertension   |
| e′                                     | Early diastolic velocity of the mitral annulus obtained by tissue Doppler imaging  | ICD       | Implantable cardioverter defibrillator   |
| EACTS                                  | European Association for Cardio-Thoracic Surgery   | ICI       | Immune checkpoint inhibitors   |
| EBC                                    | Early breast cancer  | ICOS      | International Cardio-Oncology Society  |
| ECG                                    | Electrocardiogram  | ICU       | Intensive care unit  |
| Echo                                   | Echocardiography   | IHD       | Ischaemic heart disease  |
| ECV                                    | Extracellular volume fraction  | IMiD      | Immunomodulatory drugs   |
| eGFR                                   | Estimated glomerular filtration rate   | i.v.      | Intravenous  |
| EGFR                                   | Epidermal growth factor receptor   | IVC       | Inferior vena cava   |
| EMA                                    | European Medicines Agency  | IVS       | Intraventricular septum  |
| EMB                                    | Endomyocardial biopsy  | LA        | Left atrial  |
| ENGAGE AF-TIMI 48                      | Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48   | LAA       | Left atrial appendage  |
| ENOXACAN                               | Enoxaparin and Cancer  | LGE       | Late gadolinium enhancement  |
| EoL                                    | End of life  | LIMA      | Left internal mammary artery   |
| ERS                                    | European Respiratory Society   | LMWH      | Low-molecular-weight heparins  |
| ESC                                    | European Society of Cardiology   | LQTS      | Long QT syndrome   |
|  |  | LS        | Longitudinal strain  |
|  |  | LV        | Left ventricular   |
|  |  | LVD       | Left ventricular dysfunction   |
|  |  | LVEDD     | Left ventricular end diastolic diameter  |
|  |  | LVEF      | Left ventricular ejection fraction   |
|  |  | LVV       | Left ventricular volume  |
|  |  | M         | Months   |
|  |  | MACE      | Major adverse cardiovascular events  |
|  |  | MCS       | Mechanical circulatory support   |
|  |  | MDT       | Multidisciplinary team   |

|              |   |          |   |
|--------------|---|----------|---|
| MedDRA       | Medical dictionary for regulatory activities  | SMART    | Second manifestations of arterial disease   |
| MEK          | Mitogen-activated extracellular signal-regulated kinase   | sPAP     | Systolic pulmonary artery pressure  |
| MHD          | Mean heart dose   | SPEP     | Serum protein electrophoresis   |
| MI           | Myocardial infarction   | STEMI    | ST-segment elevation myocardial infarction  |
| MM           | Multiple myeloma  | STIR     | Short tau inversion recovery  |
| MUGA         | Multigated acquisition nuclear imaging  | STS PROM | Society of Thoracic Surgeons – Predicted Risk of Mortality                        |
| N            | No  | SVT      | Supraventricular tachycardia  |
| NOAC         | Non-vitamin K antagonist oral anticoagulants  | SYNTAX   | SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery |
| NP           | Natriuretic peptides  | TAPSE    | Tricuspid annular plane systolic excursion  |
| NSTE-ACS     | Non-ST-segment elevation acute coronary syndromes   | TAVI     | Transcatheter aortic valve implantation   |
| NT-proBNP    | N-terminal pro-B-type natriuretic peptide   | TBIP     | Thromboembolic risk, Bleeding risk, drug–drug Interactions, Patient preferences   |
| PAD          | Peripheral artery disease   | TdP      | Torsade de pointes  |
| PAH          | Pulmonary arterial hypertension   | TIL      | Tumour-infiltrating lymphocytes   |
| PAP          | Pulmonary arterial pressure   | TKI      | Tyrosine kinase inhibitors  |
| PCI          | Percutaneous coronary intervention  | TRV      | Tricuspid regurgitation velocity  |
| PD-1         | Programmed death-1  | TTE      | Transthoracic echocardiography  |
| PD-L1        | Programmed death-ligand 1   | TTS      | Takotsubo syndrome  |
| PE           | Pulmonary embolism  | tx       | Treatment   |
| Peric-E      | Pericardial effusion  | ULN      | Upper limit of normal   |
| PET          | Positron emission tomography  | UPEP     | Urine protein electrophoresis   |
| PH           | Pulmonary hypertension  | VA       | Ventricular arrhythmias   |
| PI           | Proteasome inhibitors   | VascTox  | Vascular toxicity   |
| Pleu-E       | Pleural effusion  | VEGF     | Vascular endothelial growth factor  |
| PRECISE-DAPT | PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy   | VEGFi    | Vascular endothelial growth factor inhibitors                                     |
| PRONOUNCE    | A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease                   | VH       | Very high risk  |
| PW           | Left ventricular posterior wall   | VHD      | Valvular heart disease  |
| QI           | Quality indicator   | VKA      | Vitamin K antagonists   |
| ↑QTc         | Corrected QT interval prolongation  | VTE      | Venous thromboembolism  |
| QTc          | Corrected QT interval   | Y        | Yes   |
| QTcF         | Corrected QT interval using Fridericia correction   |          |   |
| RA           | Right atrial  |          |   |
| RAF          | Rapidly accelerated fibrosarcoma  |          |   |
| RCT          | Randomized controlled trial   |          |   |
| RIMA         | Right internal mammary artery   |          |   |
| ROCKET AF    | Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation |          |   |
| RT           | Radiotherapy  |          |   |
| RV           | Right ventricular   |          |   |
| RVEF         | Right ventricular ejection fraction   |          |   |
| RVV          | Right ventricular volume  |          |   |
| s'           | Systolic velocity of tricuspid annulus obtained by doppler tissue imaging   |          |   |
| SBr          | Sinus bradycardia   |          |   |
| SCORE2       | Systematic Coronary Risk Estimation 2   |          |   |
| SCORE2-OP    | Systematic Coronary Risk Estimation 2—Older Persons   |          |   |
| SEER         | Surveillance, Epidemiology, and End Results   |          |   |

## 1. Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, guidelines are not a substitute for the patient's relationship with their practitioner. The final decisions concerning an individual patient must be made by the responsible health professional(s), based on what they consider to be the most appropriate in the circumstances. These decisions are made in consultation with the patient and caregiver as appropriate.

Guidelines are intended for use by health professionals. To ensure that all users have access to the most recent recommendations, the ESC makes its Guidelines freely available. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

A great number of guidelines have been issued in recent years by the ESC. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (<https://www.escardio.org/Guidelines>). The ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

**Table 1** Classes of recommendations

|                            | Definition       | Wording to use   |                                |
|----------------------------|------------------|--|--------------------------------|
| Classes of recommendations | <b>Class I</b>   | Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.                        | Is recommended or is indicated |
|                            | <b>Class II</b>  | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.         |                                |
|                            | Class IIa        | Weight of evidence/opinion is in favour of usefulness/efficacy.  | Should be considered           |
|                            | Class IIb        | Usefulness/efficacy is less well established by evidence/opinion.  | May be considered              |
|                            | <b>Class III</b> | Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. | Is not recommended             |

**Table 2** Levels of evidence

|                     |  |
|---------------------|--|
| Level of evidence A | Data derived from multiple randomized clinical trials or meta-analyses.                      |
| Level of evidence B | Data derived from a single randomized clinical trial or large non-randomized studies.        |
| Level of evidence C | Consensus of opinion of the experts and/or small studies, retrospective studies, registries. |

In addition to the publication of Clinical Practice Guidelines, the ESC carries out the EURObservational Research Programme of international registries of cardiovascular diseases and interventions, which are essential to assess diagnostic/therapeutic processes, use of resources and adherence to guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on high-quality data collected during routine clinical practice.

Furthermore, the ESC develops sets of quality indicators (QIs), which are tools to evaluate the level of implementation of the guidelines and may be used by the ESC, hospitals, healthcare providers and professionals to measure clinical practice, and in educational programmes, alongside the key messages from the guidelines, to improve quality of care and clinical outcomes.

The Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. The selection procedure aimed to ensure that there is a representative mix of members predominantly from across the whole of the ESC region and from relevant ESC Subspecialty Communities.

Consideration was given to diversity and inclusion, notably with respect to gender and country of origin. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and scored according to predefined scales, as outlined below. The Task Force followed the ESC voting procedures. All recommendations subject to a vote achieved at least 75% among voting members.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (<http://www.escardio.org/Guidelines>) and have been compiled in a report and published in a supplementary document simultaneously to the guidelines.

This process ensures transparency and prevents potential biases in the development and review processes. Any changes in declarations of interest that arise during the writing period were notified to the



ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new guidelines. The Committee is also responsible for the approval process of these guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts, including a mix of members from across the whole of the ESC region and from relevant ESC Subspecialty Communities and National Cardiac Societies. After appropriate revisions, the guidelines are signed off by all the experts involved in the Task Force. The finalized document is signed off by the CPG for publication in the *European Heart Journal*. The guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their writing.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations, including condensed pocket guideline versions, summary slides, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access the full-text version of the guidelines, which is freely available via the ESC website and the *European Heart Journal*. The National Cardiac Societies of the ESC are encouraged to endorse, adopt, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgement, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription and to respect the ethical rules of their profession.

Off-label use of medication may be presented in this guideline if sufficient level of evidence shows that it can be considered medically appropriate to a given condition and if patients could benefit from the recommended therapy. However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- (1) the specific situation of the patient. In this respect, it is specified that, unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest to do so, with regard to the quality, safety and efficacy of care, and only after the patient has been informed and has provided consent;
- (2) country-specific health regulations, indications by governmental drug regulatory agencies and the ethical rules to which health professionals are subject, where applicable.

## 2. Introduction

This is the first European Society of Cardiology (ESC) guideline on cardio-oncology. The aim of this guideline is to help all the healthcare professionals providing care to oncology patients before, during, and

after their cancer treatments with respect to their cardiovascular (CV) health and wellness. This guideline provides guidance on the definitions, diagnosis, treatment, and prevention of cancer therapy-related CV toxicity (CTR-CVT), and the management of CV disease (CVD) caused directly or indirectly by cancer. This area of medicine has limited trials and evidence on which to base decision-making and, where evidence is limited, this guideline provides the consensus of expert opinion to guide healthcare professionals.

This guideline includes the definitions of CTR-CVT ([Section 3](#)),<sup>1</sup> and provides a personalized approach to care based upon the baseline CV toxicity risk assessment ([Section 4](#)) and new protocols for CV surveillance during cancer treatment ([Section 5](#)). The management of acute CTR-CVT is addressed in [Section 6](#), where patients with active cancer are those receiving anticancer treatment. Throughout these sections, decision-making depends upon the risk/benefit balance of oncology treatment efficacy and the severity and impact of CTR-CVT. Guidance is provided for the first 12 months after completion of cardiotoxic treatments ([Section 7](#)), when subacute CVD can emerge, and when patients who developed CTR-CVT during cancer treatment are reviewed. Diagnosis and management of the long-term CV complications of previous oncology treatments, beyond 12 months after completing the cardiotoxic treatments, and integration into the overall survivorship strategy for cancer survivors (CS) is presented in [Section 8](#) with new long-term surveillance recommendations for high-risk patients.

In [Section 9](#), we address special populations where CVDs are directly caused by the cancer, or where special considerations are required. [Section 10](#) provides information for patients' involvement in their own care. The final section highlights the role of the ESC and the ESC Council of Cardio-Oncology (ESC-CCO).

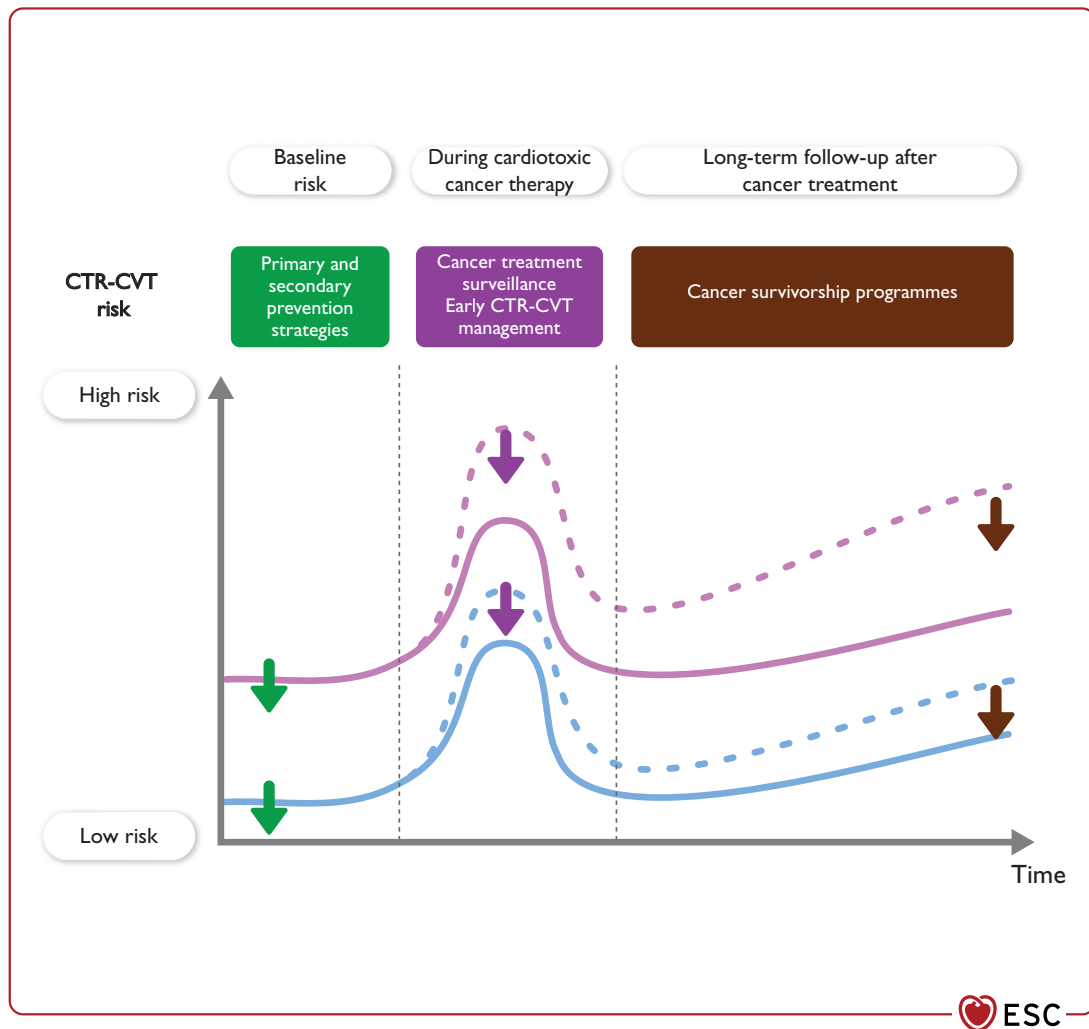
CTR-CVT risk is a dynamic variable, and the risk changes throughout the pathway of care ([Figure 1](#), [Video 1](#)). Absolute risk of CTR-CVT is important to understand and balance against the absolute benefit of the cancer treatment before and during treatment. However, CTR-CVT risk can be influenced by several variables, including implementation of primary prevention treatments, optimization of pre-existing CVD, dose, frequency, and duration of oncology treatment, emergence of CV complications during treatment and their severity, and in CS, the overall cumulative treatment received, the time since treatment, and the interaction with other CVDs.

### 2.1. Cancer and cardiovascular needs of patients with cancer

Since the 1990s, there has been a steady decline in cancer-related mortality mirrored by a steady increase in CS.<sup>2,3</sup> In this context, treatment-related side effects have gained more significance. Management of CTR-CVT has a tremendous impact on the type of anticancer therapies that patients can receive as well as the long-term morbidity and mortality outcomes of patients with cancer. Effective management of patients with both cancer and CVD requires the unique interest and expertise of healthcare providers, which has led to the formation of a new discipline: cardio-oncology.<sup>4,5</sup> A recently published ESC-CCO document describes appropriate criteria for the organization and implementation of cardio-oncology services.<sup>5</sup>

### 2.2. Role of cardio-oncology services

The overarching goal of the cardio-oncology discipline is to allow patients with cancer to receive the best possible cancer treatments safely,



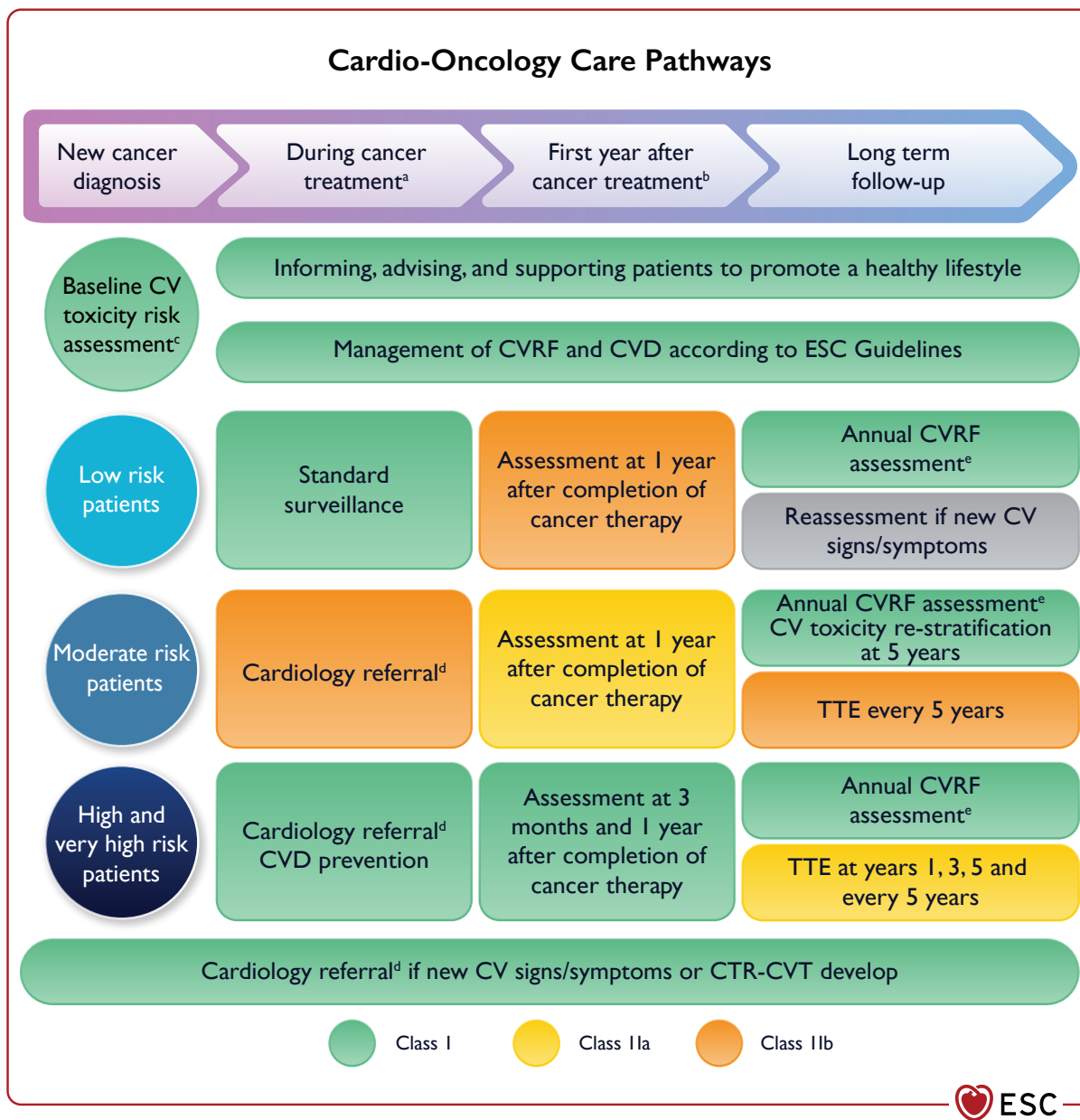
**Figure 1** Video 1 Central Illustration: Dynamics of cardiovascular toxicity risk of patients with cancer over their therapy continuum. CS, cancer survivors; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; CTR-CVT risk is a dynamic variable that changes through the pathway of care, and is influenced by several conditions including age, cancer history, pre-existing CVRF or CVD, and previous cardiotoxic cancer therapy. The CTR-CVT risk changes during and after treatment according to type, dose, frequency, and duration of oncology treatment (blue solid line). Pre-existing CVRF, CVD, or previous cancer treatments may increase the magnitude of acute and long-term CV toxicity risk (purple solid line). CTR-CVT risk remains variable in extent during anticancer treatment and may or may not gradually increase over time (dotted lines). Cardio-oncology strategy may reduce the magnitude of CTR-CVT by: (1) optimizing CVD and CVRF management (green arrows); (2) considering cardioprotective strategies in high-risk patients (green arrows); (3) organizing cancer treatment surveillance; and (4) introducing early cardioprotection after the detection of subclinical CTR-CVT (purple arrows). CV risk assessment within the first year after completion of cardiotoxic cancer therapy identifies CS who require long-term follow-up. Cancer survivorship programmes that include annual CV risk assessment and CVRF/CVD management are recommended to minimize long-term CV adverse events (brown arrows).

minimizing CTR-CVT across the entire continuum of cancer care.<sup>5</sup> Before initiation of cancer therapies with a known CV toxicity profile, the cardio-oncology team should identify and treat CV risk factors (CVRF) and pre-existing CVDs and define an appropriate prevention and surveillance plan for early identification and appropriate management of potential CV complications (Figure 2). Another important aspect is the participation in interdisciplinary discussions regarding the benefits and risks of certain cancer treatments and their continuation or interruption should side effects become apparent. After cancer treatment has been completed, the focus shifts to co-ordination of long-term follow-up and treatment. For patients on long-term cancer

therapies with CV toxicity risk, surveillance should continue until the treatment is finished.<sup>6-8</sup> There is also the need for re-assessment of CV risks in patients requiring treatment for secondary malignancies.

### 2.3. General principles of cardio-oncology

A guiding principle of cardio-oncology is the integration of clinical disciplines. Cardio-oncology providers must have knowledge of the broad scope of cardiology, oncology, and haematology management.<sup>5</sup> Recommendations are formed regarding the most permissible (from a

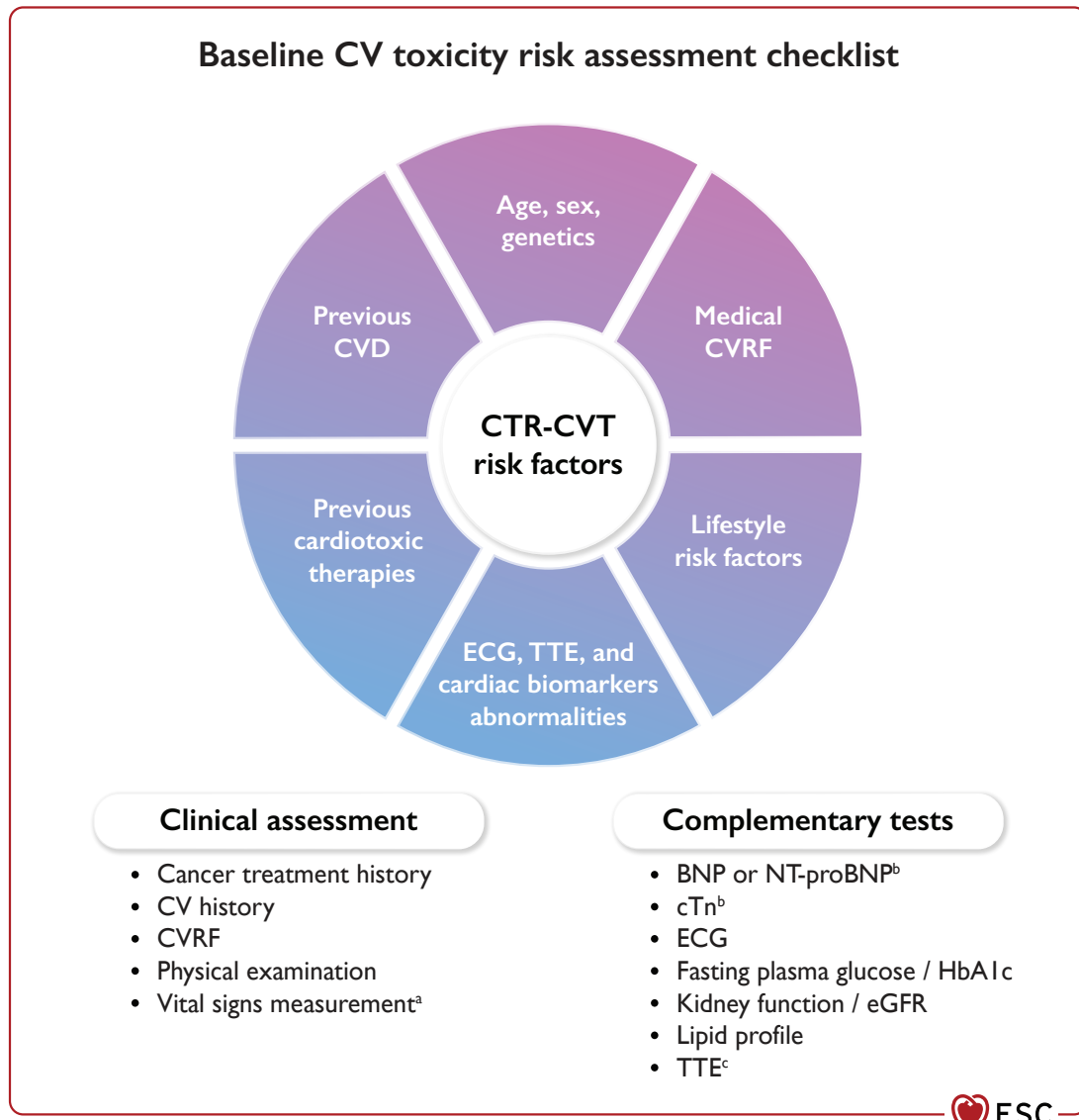


**Figure 2** Cardio-oncology care pathways. BP, blood pressure; CS, cancer survivors; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; ECG, electrocardiogram; ESC, European Society of Cardiology; HbA1c, glycated haemoglobin; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; NP, natriuretic peptides; RT, radiotherapy; TTE, transthoracic echocardiography. <sup>a</sup>CV surveillance according to baseline CV toxicity risk, type of cancer, cancer stage, and cancer therapy. <sup>b</sup>CTR-CVT risk assessment is recommended during the first year after cardiotoxic cancer treatment to establish a long-term follow-up care plan. <sup>c</sup>The use of HFA-ICOS risk assessment tools should be considered to assess CTR-CVT risk in patients with cancer scheduled to receive cardiotoxic anticancer therapy. Clinical assessment and ECG are recommended at baseline in all patients with cancer and echocardiography, cardiac biomarkers, or other cardiac imaging tests in selected patients according to baseline CV toxicity risk and cancer treatment type (see [Figure 7](#)). <sup>d</sup>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. <sup>e</sup>Annual CV risk assessment (including clinical review, BP, lipid profile, HbA1c, ECG, and NP) and CVRF management is recommended in CS who were treated with a potentially cardiotoxic cancer drug or RT to a volume exposing the heart.

CVD perspective) and the most effective (from an oncological perspective) cancer treatment. Adjudication of CV events occurring in patients on active therapy is another important aspect of cardio-oncology practice.<sup>1,3</sup> This is in addition to recommendations on best treatment and management practices. This includes the full

scope of CV therapies, including healthy lifestyle promotion and pharmacological, device, and surgical treatments.<sup>4,9,10</sup>

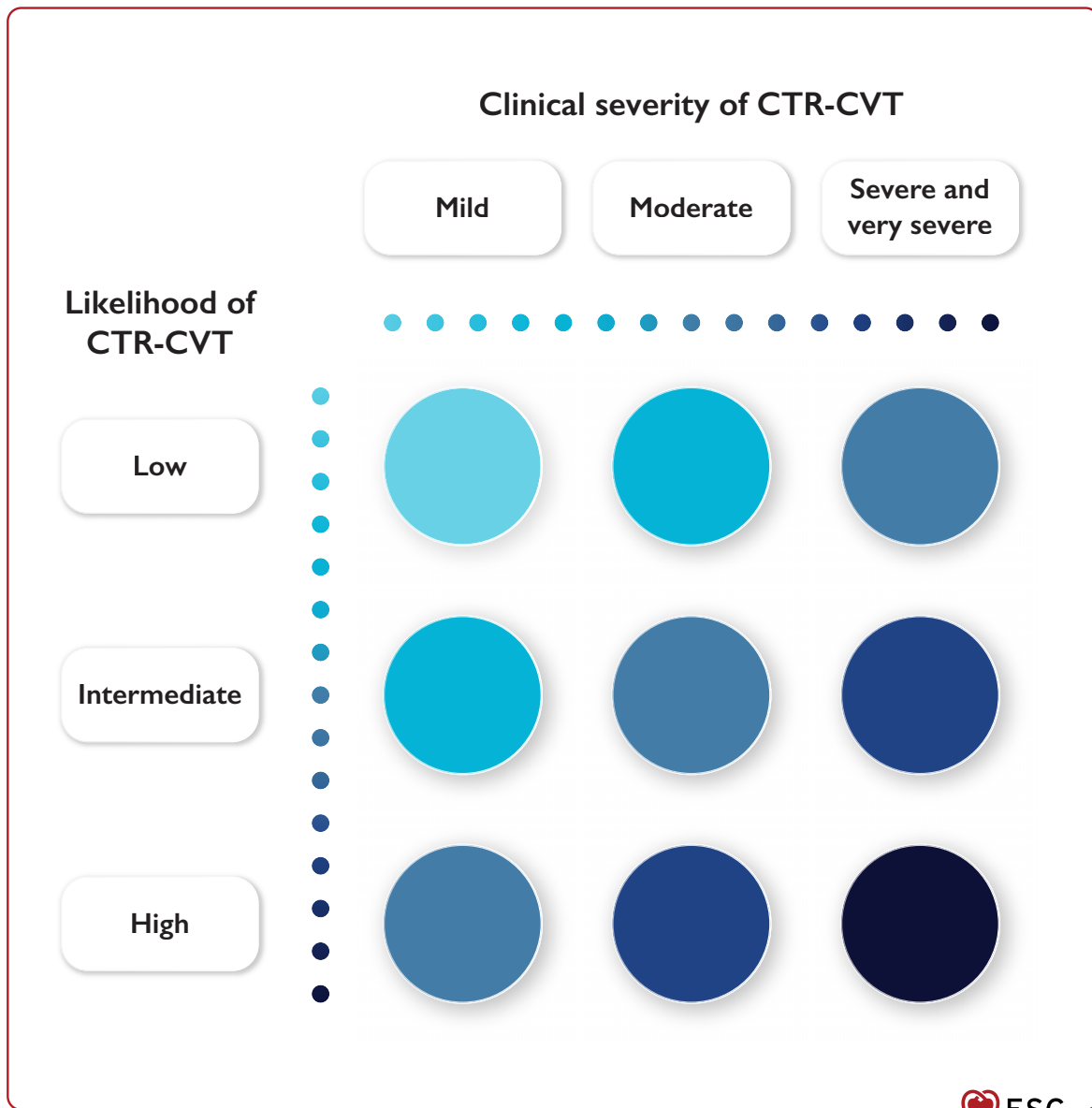
The principle underlying the dynamic course of CTR-CVT development in patients with cancer is that the absolute risk depends on their baseline risk and changes with exposure to cardiotoxic therapies over



**Figure 3** Baseline cardiovascular toxicity risk assessment checklist. BNP, B-type natriuretic peptide; cTn, cardiac troponin; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, CV disease; CVRF, cardiovascular risk factors; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; NT-proBNP, N-terminal pro-BNP; TTE, transthoracic echocardiography. <sup>a</sup>Including blood pressure, heart rate, height, weight, and body mass index. <sup>b</sup>Cardiac biomarkers (troponin and NP) should be measured in patients at risk of CTRCD where available and results should be interpreted according to the patient clinical status, type of cancer treatment, and kidney function. <sup>c</sup>Consider other CV complementary tests in selected patients: cardiac magnetic resonance, coronary computed tomography angiography, CPET (in selected patients for pre-operative [lung, colon, and rectal cancers] risk stratification). See [Section 4.6](#).

time ([Figure 3](#)).<sup>11</sup> This has been recognized in conceptual models, with risk stratification tools designed to grade patients with cancer into low, moderate, high, and very high risk of CV complications prior to starting treatment. These have been published by the Heart Failure Association (HFA) of the ESC in collaboration with the International Cardio-Oncology Society (ICOS) (see [Section 4](#)).<sup>12,13</sup> Severity, duration, and type of manifestation of CTR-CVT vary by type of malignancy and cancer treatment. The risk itself can be understood in two ways: (1) the likelihood of its occurrence and (2) the severity of the complication ([Figure 4](#)). For example, a patient could be very likely to experience a CTR-CVT, but if this event is mild, oncology treatment should continue. Conversely, a patient at low likelihood could

still be at high risk according to the severity of the event, which would lead to interruption of cancer treatment, e.g. a significant decline in left ventricular (LV) ejection fraction (LVEF) to < 40% with anthracycline chemotherapy. The timeline of these developments may also be rather different. After the cardiotoxic cancer treatment has been completed, a new risk assessment is recommended to establish different long-term trajectories of CV health. These trajectories are impacted by the permanent CV toxic effects and cardiac or vascular injury of some cancer therapies, patient-related CVRF, environmental factors, and stressors (e.g. acute viral infections). The aim should be to personalize approaches to minimize CTR-CVT and improve both cancer and CV outcomes.



**Figure 4** Dimensions of cancer therapy-related cardiovascular toxicity risk and disease severity. CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular. The ultimate risk is the combination of the likelihood (based on reported incidence) and degree (severity or grade) of the adverse event. The most vulnerable patient groups are those at high likelihood of experiencing a severe adverse event. The level of attention that needs to be devoted to these patients varies accordingly. The risk and type of CTR-CVT, as well as the potential for reversibility, depends on different factors, listed in [Figure 3](#), that should be considered to define global CV and oncological prognosis and to individualize CTR-CVT surveillance. Additional factors that add to the complexity of CTR-CVT risk assessment are the cancer type and prognosis, and type, duration, and intensity of cancer treatment.

### 3. Cancer therapy-related cardiovascular toxicity definitions

Several terminologies and definitions have previously been proposed to describe the spectrum of CTR-CVT, leading to inconsistencies in diagnosis and management. The need to harmonize these definitions has frequently been stated and recognized, and resulted in the recent international definitions of CTR-CVT<sup>1</sup> supported by this guideline ([Table 3](#); [Supplementary data, Table S1](#)). This document will focus on consensus definitions for cardiomyopathy and heart failure

(HF), myocarditis, vascular toxicities, hypertension, cardiac arrhythmias, and corrected QT interval (QTc) prolongation. The definitions of other CTR-CVT, including pericardial and valvular heart diseases (VHDs), are the same as those used for the general cardiology population. For cardiac injury, cardiomyopathy, and HF, the descriptive term cancer therapy-related cardiac dysfunction (CTRCD) is recommended as it captures the broad spectrum of possible presentations and the aetiological link with the broad scope of various cancer therapies, including chemotherapy, targeted agents, immune therapies, and radiation therapy.



**Table 3** Cancer therapy-related cardiovascular toxicity definitions

| CTRCD   |  |  |                                   |
|---|--|--|-----------------------------------|
| <b>Symptomatic CTRCD (HF)<sup>a,b</sup></b>   | Very severe  | HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation  |                                   |
|   | Severe   | HF hospitalization   |                                   |
|   | Moderate   | Need for outpatient intensification of diuretic and HF therapy   |                                   |
|   | Mild   | Mild HF symptoms, no intensification of therapy required   |                                   |
| <b>Asymptomatic CTRCD</b>   | Severe   | New LVEF reduction to <40%   |                                   |
|   | Moderate   | New LVEF reduction by ≥10 percentage points to an LVEF of 40–49%<br>OR<br>New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers <sup>c</sup> |                                   |
|   | Mild   | LVEF ≥ <b>50%</b><br>AND new relative decline in GLS by >15% from baseline<br>AND/OR new rise in cardiac biomarkers <sup>c</sup>   |                                   |
| ICI myocarditis (either pathohistological diagnosis or clinical diagnosis)                                |  |  |                                   |
| <b>Pathohistological diagnosis (EMB)</b>  | Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy   |  |                                   |
| <b>Clinical diagnosis<sup>d</sup></b>   | <b>cTn elevation</b> (new or significant change from baseline) <sup>e</sup> <b>with 1 major criterion or 2 minor criteria</b> , after exclusion of ACS and acute infectious myocarditis based on clinical suspicion <sup>f</sup>   |  |                                   |
|   | <p><b>Major criterion:</b></p> <ul style="list-style-type: none"> <li>• CMR diagnostic for acute myocarditis (modified Lake Louise criteria)<sup>g</sup></li> </ul> <p><b>Minor criteria:</b></p> <ul style="list-style-type: none"> <li>• Clinical syndrome (including any one of the following: fatigue, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnoea, lower-extremity oedema, palpitations, light-headedness/dizziness, syncope, muscle weakness, cardiogenic shock)</li> <li>• Ventricular arrhythmia (including cardiac arrest) and/or new conduction system disease</li> <li>• Decline in LV systolic function, with or without regional wall motion abnormalities in a non-Takotsubo pattern</li> <li>• Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis</li> <li>• Suggestive CMR<sup>h</sup></li> </ul> |  |                                   |
| <b>Severity of myocarditis</b>  | <ul style="list-style-type: none"> <li>• <b>Fulminant:</b> Haemodynamic instability, HF requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia</li> <li>• <b>Non-fulminant:</b> 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</li> <li>• <b>Steroid refractory:</b> non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other aetiologies) despite high-dose methylprednisolone</li> </ul>  |  |                                   |
| <b>Recovery from myocarditis</b>  | <ul style="list-style-type: none"> <li>• <b>Complete recovery:</b> 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</li> <li>• <b>Recovering:</b> Ongoing improvement in patient clinical symptoms, signs, biomarkers, and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression</li> </ul>  |  |                                   |
| Vascular toxicity (for general cardiology definitions, see <a href="#">Supplementary data, Table S1</a> ) |  |  |                                   |
| <b>Asymptomatic vascular toxicity</b>   | <b>CAD</b>   | <b>Symptomatic vascular toxicity</b>   | <b>Stroke</b>                     |
|   | <b>PAD</b>   |  | <b>Transient ischaemic attack</b> |
|   | <b>Carotid artery disease</b>  |  | <b>MI</b>                         |
|   | <b>Venous thrombosis</b>   |  | <b>ACS</b>                        |
|   | <b>Arterial thrombosis</b>   |  | <b>CCS</b>                        |
|   | <b>Peripheral vasoreactivity</b>   |  | <b>PAD</b>                        |

Continued

|   | Coronary epicardial vasoreactivity  |  | Vasospastic angina   |
|---|---|--|----------------------|
|   | Coronary microvascular vasoreactivity   |  | Microvascular angina |
|   |   |  | Raynaud's phenomenon |
| <b>Arterial hypertension</b>  |   |  |                      |
| <b>Treatment threshold for hypertension before, during, and after therapy</b> | <b>In patients with high CV risk<sup>1</sup>:</b> ≥130 mmHg systolic and/or ≥80 mmHg diastolic  |  |                      |
|   | <b>Otherwise:</b> ≥140 mmHg systolic and/or ≥90 mmHg diastolic  |  |                      |
| <b>Cancer therapy holding threshold</b>                                       | ≥180 mmHg systolic and/or ≥110 mmHg diastolic   |  |                      |
| <b>Hypertensive emergency</b>   | (Very high) BP elevation associated with acute hypertension-mediated organ damage (heart, retina, brain, kidneys, and large arteries), requiring immediate BP reduction to limit extension or promote regression of target organ damage |  |                      |
| <b>Cardiac arrhythmias</b>  |   |  |                      |
| <b>QT prolongation</b>  | <b>Prolonged: QTcF &gt; 500 ms<sup>1</sup></b>  |  |                      |
| <b>Bradycardia</b>  | <b>For general cardiology definitions, see <a href="#">Supplementary data, Table S1</a></b>   |  |                      |
| <b>Supraventricular tachycardia</b>   |   |  |                      |
| <b>Ventricular arrhythmias</b>  |   |  |                      |
| <b>AF</b>   |   |  |                      |

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ACS, acute coronary syndromes; AF, atrial fibrillation; BNP, B-type natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CCS, chronic coronary syndromes; CMR, cardiac magnetic resonance; cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; ECV, extracellular volume fraction; EMB, endomyocardial biopsy; ESC, European Society of Cardiology; GLS, global longitudinal strain; HF, heart failure; HFmrEF, HF with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICI, immune checkpoint inhibitors; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAD, peripheral artery disease; QTcF, corrected QT interval using Fridericia correction; SCORE2, Systematic Coronary Risk Estimation 2; SCORE2-OP, Systematic Coronary Risk Estimation 2—Older Persons. See [Supplementary data, Table S1](#) for expanded definitions.

<sup>a</sup>With LVEF and supportive diagnostic biomarkers based on the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF.<sup>14</sup>  
<sup>b</sup>*Symptomatic CTRCD* represents HF, which is a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) and has traditionally been divided into distinct phenotypes based on the measurement of LVEF: ≤40% = HFrEF; 41–49% = HFmrEF; ≥50% = HFpEF.  
<sup>c</sup>cTnI/cTnT > 99th percentile, BNP ≥ 35 pg/mL, NT-proBNP ≥ 125 pg/mL or new significant rise from baseline beyond the biological and analytical variation of the assay used.  
<sup>d</sup>Clinical diagnoses should be confirmed with magnetic resonance imaging or EMB if possible and without causing treatment delays. Treatment with immunosuppression should be promptly initiated while awaiting further confirmatory testing in symptomatic patients.  
<sup>e</sup>Both troponin I and troponin T can be used; however, clinical observations suggest that troponin T may be falsely elevated in patients with concomitant myositis and without myocarditis.<sup>15–17</sup>  
<sup>f</sup>According to local protocols.  
<sup>g</sup>Diagnostic CMR: Based on updated Lake Louise criteria<sup>18</sup>; T2-based criterion + T1-based criterion ± supportive criteria (T2-based criteria: regional or global increase of native T2, or T2 signal intensity; T1-based criteria: regional or global increase of native T1, or regional or global increase in the ECV, or presence of LGE; supportive criteria: pericarditis and/or regional or global LV systolic dysfunction).  
<sup>h</sup>Suggestive CMR: meeting some but not all of the modified Lake Louise criteria. The presence of T2- or T1-based criteria may support a diagnosis of acute myocardial inflammation in the appropriate clinical scenario.  
<sup>i</sup>SCORE2 (<70 years), SCORE2-OP (≥70 years) or equivalent.<sup>19</sup> 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%.  
<sup>j</sup>QTcF 480–500 ms: correct reversible causes, minimize other QT prolonging medications, close QTcF monitoring. Fridericia correction is recommended (QTcF = QT/√RR).<sup>20</sup>

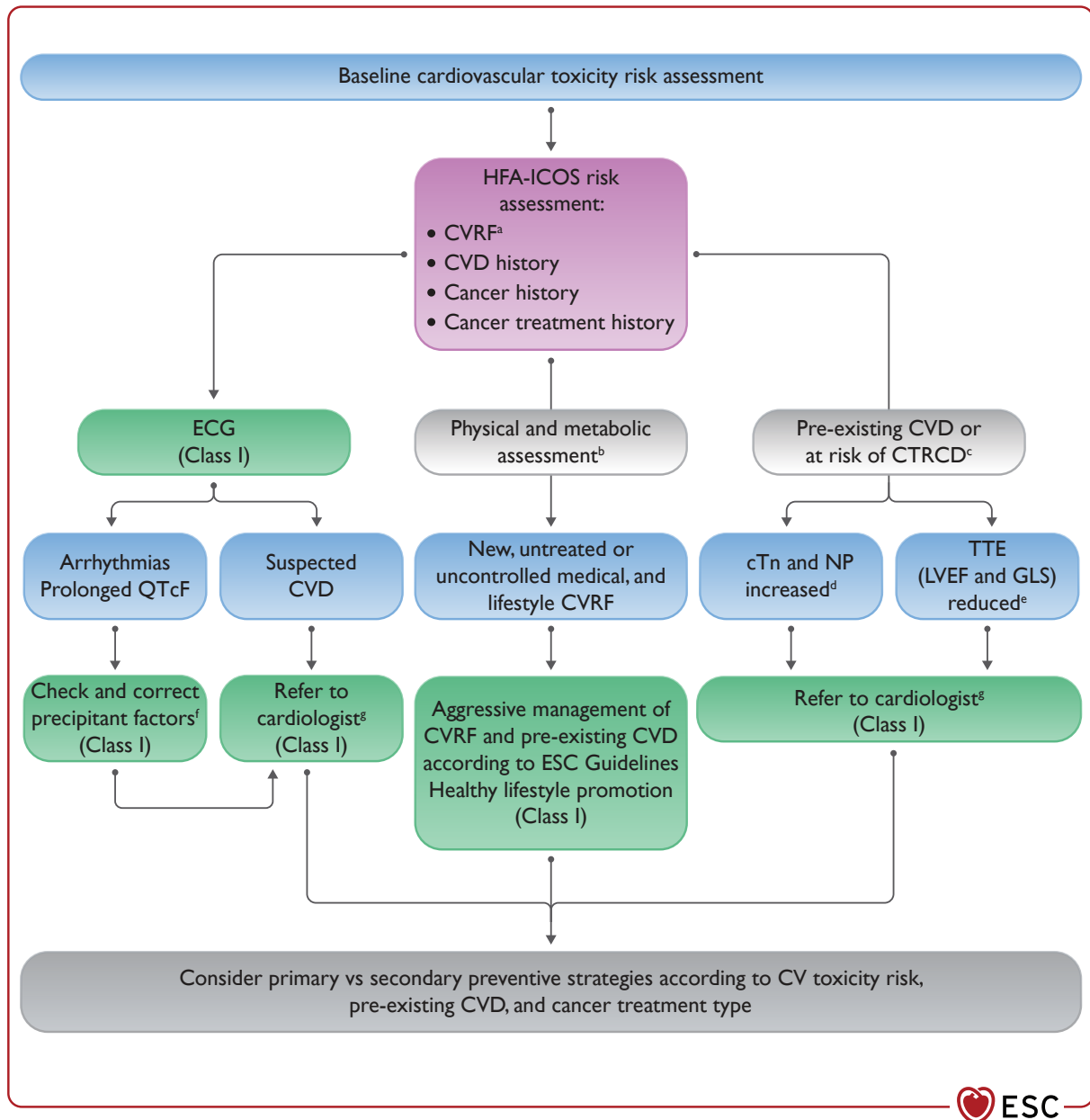
## 4. Cardiovascular toxicity risk stratification before anticancer therapy

The optimal time to consider CVD prevention strategies in patients with cancer is at the time of cancer diagnosis and prior to the initiation of cancer treatment.<sup>4,5</sup> This enables the oncology team to consider CV risk while making cancer treatment choices, educating patients regarding their CV risk, personalizing CV surveillance and follow-up strategies, and making appropriate referrals of high-risk patients to cardio-oncology services. These strategies are needed to mitigate CVD risk, and improve the adherence to effective cancer treatments and the overall survival.

CVD prevention strategies require a personalized approach. Risk assessment is a challenging task and it is vital that clinicians adopt a systematic approach without delaying oncological treatment.<sup>12,21,22</sup> [Figure 5](#) provides a comprehensive approach to risk assessment. The choice of the cardiac tests (electrocardiogram [ECG], biomarkers, and imaging) should be individualized based on CV risk and the planned cancer treatments.

### 4.1. General approach to cardiovascular toxicity risk in patients with cancer

Pre-treatment CTR-CVT risk assessment should ideally be performed using a recognized risk stratification method where multiple risk factors are incorporated to determine patient-specific risk.<sup>23</sup>



**Figure 5** Baseline cardiovascular toxicity risk assessment before anticancer therapy. BNP, B-type natriuretic peptide; cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; CVD, CV disease; CVRF, CV risk factors; ECG, electrocardiogram; ESC, European Society of Cardiology; GLS, global longitudinal strain; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; LVEF, left ventricular ejection fraction; NP, natriuretic peptides (including BNP and NT-proBNP); NT-proBNP, N-terminal pro-BNP peptide; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction; TTE, transthoracic echocardiography. <sup>a</sup>When assessing CVRF, include information about unhealthy lifestyle including sedentary behaviour, smoking, and alcohol intake. <sup>b</sup>See [Figure 3](#). <sup>c</sup>According to cancer treatment and HFA-ICOS risk assessment. <sup>d</sup>cTnI/T > 99th percentile, BNP ≥ 35 pg/mL, NT-proBNP ≥ 125 pg/mL. <sup>e</sup>Patients with baseline LVEF < 50% or in the low normal range (LVEF 50–54%) should be referred to a specialized cardiologist or cardio-oncologist. When TTE is used, ideally three-dimensional-LVEF and GLS should be measured. If GLS assessment is not available, other markers of longitudinal function (e.g. annular Doppler velocity) should be considered. Cardiac magnetic resonance should be considered if echocardiography is of non-diagnostic quality. <sup>f</sup>Anaemia, infections, electrolyte abnormalities, metabolic problems, other QTc-prolonging drugs. <sup>g</sup>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.

Only a limited number of retrospective risk scores have been published in patients with cancer. Most of these scores have been developed for specific cancer-patient groups and cannot be readily applied or extrapolated to other type of malignancies.<sup>24–29</sup> While further

validation is needed, HFA-ICOS risk assessment tools should be considered to determine pre-treatment risk of CTR-CVT as they are easy to use and implement in oncology and haematology services ([Table 4](#); [Supplementary data, Tables S2–S7](#)).<sup>12,13</sup> Other CV risk

**Table 4** Heart Failure Association–International Cardio-Oncology Society baseline cardiovascular toxicity risk stratification

| Baseline CV toxicity risk factors                       | Anthracycline chemotherapy | HER2-targeted therapies | VEGF inhibitors | BCR-ABL inhibitors | Multiple myeloma therapies | RAF and MEK inhibitors |
|---|----------------------------|-------------------------|-----------------|--------------------|----------------------------|------------------------|
| <b>Previous CVD</b>                                     |                            |                         |                 |                    |                            |                        |
| HF/cardiomyopathy/CTRCD                                 | VH                         | VH                      | VH              | H                  | VH                         | VH                     |
| Severe VHD  | H                          | H                       | –               | –                  | –                          | H                      |
| MI or PCI or CABG                                       | H                          | H                       | VH              | –                  | –                          | H                      |
| Stable angina   | H                          | H                       | VH              | –                  | –                          | H                      |
| Arterial vascular disease                               | –                          | –                       | VH              | VH                 | VH                         | –                      |
| Abnormal ankle-brachial pressure index                  | –                          | –                       | –               | H                  | –                          | –                      |
| PH  | –                          | –                       | –               | H                  | –                          | –                      |
| Arterial thrombosis with TKI                            | –                          | –                       | –               | VH                 | –                          | –                      |
| Venous thrombosis (DVT/PE)                              | –                          | –                       | H               | M2                 | VH                         | –                      |
| Arrhythmia <sup>a</sup>                                 | –                          | M2                      | M2              | M2                 | M2                         | M1                     |
| QTc ≥ 480 ms  | –                          | –                       | H               | H                  | –                          | –                      |
| 450 ≤ QTc < 480 ms (men);<br>460 ≤ QTc < 480 ms (women) | –                          | –                       | M2              | M2                 | –                          | –                      |
| Prior PI CV toxicity                                    | –                          | –                       | –               | –                  | VH                         | –                      |
| Prior IMiD CV toxicity                                  | –                          | –                       | –               | –                  | H                          | –                      |
| <b>Cardiac imaging</b>                                  |                            |                         |                 |                    |                            |                        |
| LVEF < 50%  | H                          | H                       | H               | H                  | H                          | H                      |
| LVEF 50–54%   | M2                         | M2                      | M2              | –                  | M2                         | M2                     |
| LV hypertrophy  | –                          | –                       | –               | –                  | M1                         | –                      |
| Cardiac amyloidosis                                     | –                          | –                       | –               | –                  | VH                         | –                      |
| <b>Cardiac biomarkers</b>                               |                            |                         |                 |                    |                            |                        |
| Elevated baseline cTn <sup>b</sup>                      | M1                         | M2                      | M1              | –                  | M2                         | M2                     |
| Elevated baseline NP <sup>b</sup>                       | M1                         | M2                      | M1              | –                  | H                          | M2                     |
| <b>Age and CVRF</b>                                     |                            |                         |                 |                    |                            |                        |
| Age ≥ 80 years  | H                          | H                       | –               | –                  | –                          | M1                     |
| Age 65–79 years   | M2                         | M2                      | –               | –                  | –                          | M1                     |
| Age ≥ 75 years  | –                          | –                       | H               | H                  | H                          | M1                     |
| Age 65–74 years   | –                          | –                       | M1              | M2                 | M1                         | M1                     |
| Age ≥ 60 years  | –                          | –                       | –               | M1                 | –                          | –                      |
| CVD 10-year risk score > 20%                            | –                          | –                       | –               | H                  | –                          | –                      |
| Hypertension <sup>c</sup>                               | M1                         | M1                      | H               | M2                 | M1                         | M2                     |
| Chronic kidney disease <sup>d</sup>                     | M1                         | M1                      | M1              | M1                 | M1                         | M1                     |
| Proteinuria   | –                          | –                       | M1              | –                  | –                          | –                      |
| DM <sup>e</sup>   | M1                         | M1                      | M1              | M1                 | M1                         | M1                     |
| Hyperlipidaemia <sup>f</sup>                            | –                          | –                       | M1              | M1                 | M1                         | –                      |
| Family history of thrombophilia                         | –                          | –                       | –               | M1                 | M1                         | –                      |

Continued

| Current cancer treatment                            |    |                 |    |    |   |    |    |
|---|----|-----------------|----|----|---|----|----|
| Dexamethasone > 160 mg/month                        | –  | –               | –  | –  | – | M1 | –  |
| Includes anthracycline before HER2-targeted therapy | –  | M1 <sup>g</sup> | –  | –  | – | –  | –  |
| Previous exposure to                                |    |                 |    |    |   |    |    |
| Anthracycline                                       | H  | M2 <sup>h</sup> | H  | –  | – | H  | H  |
| Trastuzumab   | –  | VH              | –  | –  | – | –  | –  |
| RT to left chest or mediastinum                     | H  | M2              | M1 | –  | – | M1 | M2 |
| Non-anthracycline chemotherapy                      | M1 | –               | –  | –  | – | –  | –  |
| Lifestyle risk factors                              |    |                 |    |    |   |    |    |
| Current smoker or significant smoking history       | M1 | M1              | M1 | H  | – | M1 | M1 |
| Obesity (BMI > 30 kg/m <sup>2</sup> )               | M1 | M1              | M1 | M1 | – | M1 | M1 |

AF, atrial fibrillation; BCR-ABL, breakpoint cluster region–Abelson oncogene locus; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DM, diabetes mellitus; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; H, high risk; HbA1c, glycated haemoglobin; HER2, human epidermal receptor 2; HF, heart failure; IMiD, immunomodulatory drugs; LV, left ventricular; LVEF, left ventricular ejection fraction; M, moderate risk; MEK, mitogen-activated extracellular signal-regulated kinase; MI, myocardial infarction; MM, multiple myeloma; NP, natriuretic peptides (including BNP and NT-proBNP); NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PH, pulmonary hypertension; PI, proteasome inhibitors; QTc, corrected QT interval; RAF, rapidly accelerated fibrosarcoma; RT, radiotherapy; TKI, tyrosine kinase inhibitors; ULN, upper limit of normal; VEGFi, vascular endothelial growth factor inhibitors; VH, very high risk; VHD, valvular heart disease.

An expanded version of this table is provided in [Supplementary data, Tables S2–S7](#).

**Risk level: Low risk** = no risk factors OR one moderate risk factor; **moderate risk (M)** = moderate risk factors with a total of 2–4 points (Moderate 1 [M1] = 1 point; Moderate 2 [M2] = 2 points); **high risk (H)** = moderate risk factors with a total of ≥5 points OR any high-risk factor; **very-high risk (VH)** = any very-high risk factor.

<sup>a</sup>AF, atrial flutter, ventricular tachycardia, or ventricular fibrillation.

<sup>b</sup>Elevated above the ULN of the local laboratory reference range.

<sup>c</sup>Systolic BP > 140 mmHg or diastolic BP > 90 mmHg, or on treatment.

<sup>d</sup>eGFR < 60 mL/min/1.73 m<sup>2</sup>.

<sup>e</sup>HbA1c > 7.0% or > 53 mmol/mol, or on treatment.

<sup>f</sup>Non-high density lipoprotein cholesterol > 3.8 mmol/L (> 145 mg/dL) or on treatment.

<sup>g</sup>High risk if anthracycline chemotherapy and trastuzumab delivered concurrently.

<sup>h</sup>Previous malignancy (not current treatment protocol).

**Table 5 Anthracycline equivalence dose**

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

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.

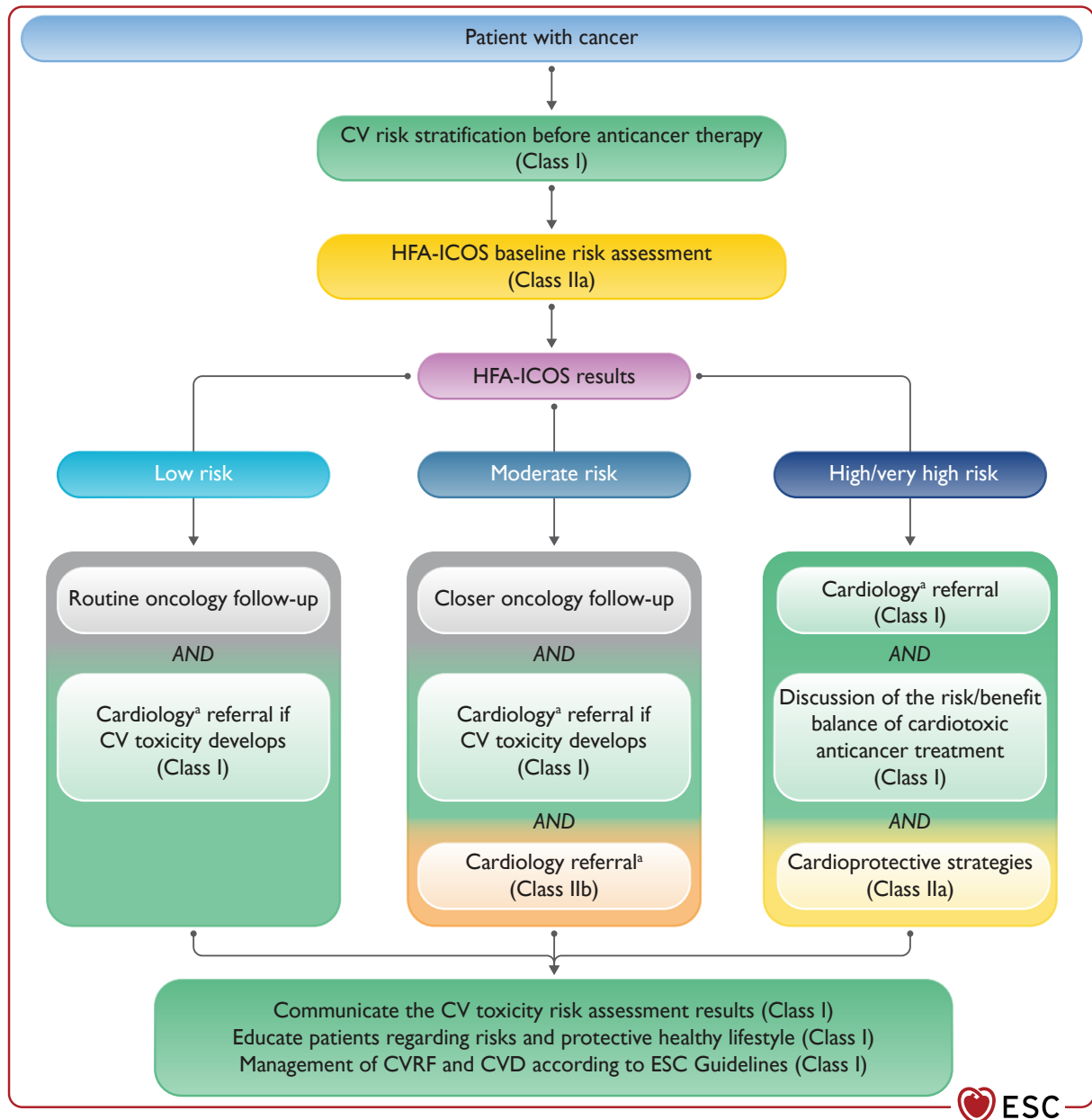
<sup>a</sup>Data for idarubicin are based upon an estimated anticancer efficacy ratio, not derived from cardiotoxicity data. The CV toxicity dose ratio provides the value that should be used to multiply the dose of the anthracycline of interest to convert to isoequivalent doses of doxorubicin; e.g. to convert 125 mg/m<sup>2</sup> of epirubicin to doxorubicin isoequivalent, multiply the dose by 0.8 (125 mg/m<sup>2</sup> × 0.8 = 100 mg/m<sup>2</sup> of doxorubicin).

calculators (e.g. SMART [Second manifestations of arterial disease] risk score, ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation] risk score, SCORE2 [Systematic Coronary Risk Estimation 2], SCORE2-OP [Systematic Coronary Risk Estimation 2—Older Persons], ASCVD [Atherosclerotic Cardiovascular Disease] risk score, U-Prevent, and lifetime risk calculators) may be considered at baseline for the

assessment of CV risk, considering that cancer itself may increase the likelihood of CVD.<sup>19,23,30,31</sup>

Baseline risk assessment should be considered by the treating oncology or haematology team for all patients diagnosed with cancer who are scheduled to receive a cancer treatment identified to have a clinically significant level of CRT-CVT, or by a cardiologist if appropriate. In the case of patients scheduled to receive





**Figure 6** General cardio-oncology approach after Heart Failure Association–International Cardio-Oncology Society cardiovascular toxicity risk assessment. CV, cardiovascular; CVD, CV disease; CVRF, CV risk factors; ESC, European Society of Cardiology; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society. <sup>a</sup>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.

anthracycline chemotherapy, the total planned cumulative anthracycline dose is also relevant, and  $\geq 250$  mg/m<sup>2</sup> of doxorubicin or equivalent should be considered higher risk (Table 5).<sup>32</sup>

CV risk stratification results should be discussed with the patient and documented in clinical notes. This process will also enable future validation of these tools.

Cardiology referral (cardio-oncology programme or cardiologist with expertise in managing CVD in patients with cancer) is

recommended for patients identified to be at high or very high risk for CTR-CVT at baseline (Table 4) to institute strategies to mitigate risk.<sup>33</sup> Patients at moderate risk can benefit from closer cardiac monitoring, strict management of traditional CVRF, and selected moderate-risk patients may also benefit from a cardio-oncology referral (Figure 6). Low-risk patients can be followed within the oncology programme with appropriate referral to cardio-oncology if a CTR-CVT emerges or new or uncontrolled CVRF appear.

**Recommendation Table 1 — Recommendations for a general approach to cardiovascular toxicity risk categorization**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| CV toxicity risk stratification <sup>c</sup> before starting potentially cardiotoxic anticancer therapy is recommended in all patients with cancer. <sup>12,14,19,21,25,28,31</sup>   | I                  | B                  |
| Communicating the results of the CV toxicity risk assessment to the patient and other appropriate healthcare professionals is recommended.  | I                  | C                  |
| The use of HFA-ICOS risk assessment should be considered to stratify CV toxicity risk in patients with cancer scheduled to receive cardiotoxic anticancer therapy. <sup>12</sup>  | IIa                | C                  |
| It is recommended that patients categorized to be at low CV toxicity risk should proceed to anticancer therapy without delay.   | I                  | C                  |
| In patients categorized at moderate CV toxicity risk, cardiology referral <sup>d</sup> may be considered. <sup>e</sup>  | IIb                | C                  |
| Cardiology referral <sup>d</sup> is recommended in high-risk and very high-risk patients before anticancer therapy. <sup>f</sup>  | I                  | C                  |
| Discussion of the risk/benefit balance of cardiotoxic anticancer treatment in high- and very high-risk patients in a multidisciplinary approach prior to starting treatment is recommended.                                     | I                  | C                  |
| Cardiology referral <sup>d</sup> is recommended for patients with cancer and pre-existing CVD or abnormal findings at baseline CV toxicity risk assessment <sup>g</sup> who require potentially cardiotoxic anticancer therapy. | I                  | C                  |

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CV, cardiovascular; CVD, CV disease; ECG, electrocardiogram; GLS, global longitudinal strain; HbA1c, glycated haemoglobin; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiography; ULN, upper limit of normal; VHD, valvular heart disease.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Including clinical history and physical examination, ECG, general blood test, HbA1c, lipid profile, and cardiac serum biomarkers and/or TTE (according to cancer drug type and CV toxicity risk).

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

<sup>e</sup>Without delaying cancer treatments.

<sup>f</sup>Unless there is an oncology emergency requiring immediate cancer treatment.

<sup>g</sup>Moderate-to-severe pre-existing CVDs or new abnormal findings (baseline cardiac serum biomarkers > ULN, LVEF ≤ 50%, GLS under normal local values, previously undiagnosed moderate-to-severe myocardial, pericardial, or VHDs, abnormal baseline ECG).

## 4.2. History and clinical examination

A careful clinical history and physical examination is recommended as part of the baseline risk assessment. Oncology patients can be divided into two cohorts with respect to the presence or absence of pre-existing CVD. A primary prevention strategy can be considered in patients without previous CVD or CTR-CVT while secondary

prevention includes interventions in patients with prior or active CVD or previous CTR-CVT.<sup>12</sup>

Reviewing traditional risk factors for CVD is recommended. Where present, the efficacy of treatment and control of these modifiable risk factors should be determined to ensure optimal control during cancer therapy.<sup>4,34</sup> Although recent SCORE2 and SCORE2-OP<sup>19</sup> tables are not focused on patients with cancer, risk calculation is recommended for patients with cancer >40 years of age (unless they are automatically categorized as being at high risk or very high risk based on documented CVD, diabetes mellitus [DM], kidney disease, or a highly elevated single risk factor) as a reference to optimize CVRF treatment goals.<sup>19,31,35</sup> A family history of premature CVD should be considered because genetic abnormalities associated with CVD may predispose patients with cancer to a higher risk of CTR-CVT.<sup>36–38</sup> Lifestyle factors such as smoking, alcohol consumption, sedentary lifestyle, exposure to pollution, and frailty are important shared risk factors for both cancer and CVD. Information on prior history of cancer, cardiotoxic cancer therapies, and their respective doses should be collected. Patients should be asked about typical cardiac symptoms (e.g. chest pain with activity, dyspnoea on exertion, orthopnoea, palpitations, and peripheral oedema), which can guide clinical examination and investigations. Physical examination should document vital signs and look for potential indicators of undiagnosed CVD such as HF, pericardial disease, VHD, and arrhythmias.<sup>39–42</sup>

The second scenario is secondary prevention in patients with a prior history of CVD. These patients with cancer are potentially at high or very high risk of future CV events,<sup>12</sup> and require a more comprehensive clinical evaluation of their CVD, its severity, and prior and current treatments. Depending on the type and severity of CVD, additional investigations—including resting or stress echocardiography, cardiac magnetic resonance (CMR), nuclear perfusion imaging, and coronary computed tomography angiography (CCTA)—may be indicated to determine risk status. Identifying prior CVD should not automatically be a reason to withhold cancer therapy but considered an opportunity to optimize CV risk prior to and during treatment. Risk/benefit discussions should include the patient, oncologist or haematologist, and—where available—a specialized cardio-oncology service.

Additional factors that add to the complexity of baseline CV risk assessment are the cancer type and prognosis, and type, duration, and intensity of cancer treatment (Figure 1).<sup>4,12,43</sup> Clinical history, physical examination features, and treatment-related risk factors that contribute to CTR-CVT for various cancer therapies are summarized in Supplementary data, Table S8. These risk factors should be collected and considered along with baseline ECG, cardiac serum biomarkers, and cardiac imaging tests (summarized in Figure 7) to complete baseline CTR-CVT evaluation.


## 4.3. Electrocardiogram

A baseline 12-lead ECG is a readily available test that can provide important clues to underlying CVD. ECG evidence of chamber enlargement, conduction abnormalities, arrhythmias, ischaemia, or prior myocardial infarction (MI), and low voltages should be interpreted in the clinical context. A baseline ECG is recommended prior to starting a cancer treatment known to cause QTc prolongation.<sup>44–49</sup> Measurement of QTc using the Fridericia correction (QTcF) is

Baseline clinical CV assessment, physical exam and ECG are recommended in all cancer patients scheduled for cardiotoxic therapies<sup>a</sup>

|   | Patient risk level                                    | TTE <sup>b</sup>              | NP                   | cTn                |
|---|---|-------------------------------|----------------------|--------------------|
| Anthracyclines  | Very high risk, Moderate risk, Low risk               | Class I, Class IIa, Class IIb | Class I, Class IIa   | Class I, Class IIa |
| HER2-targeted therapies <sup>c</sup>                  | Very high risk, Moderate risk, Low risk               | Class I, Class IIa, Class IIb | Class I, Class IIa   | Class I, Class IIa |
| Fluoropyrimidines                                     | Other conditions (Previous CVD)                       | Class I                       |                      |                    |
| VEGFi   | Very high risk, Moderate risk, Low risk               | Class I, Class IIa, Class IIb | Class IIa, Class IIb |                    |
| Second- and third-generation BCR-ABL TKI <sup>d</sup> | Other conditions (All patients)                       | Class IIa                     |                      |                    |
| BTK inhibitors  | Very high risk  | Class I                       |                      |                    |
| PI <sup>e</sup>                                       | Very high risk, Moderate risk, Low risk               | Class I, Class IIa            | Class I, Class IIa   |                    |
| RAF and MEK inhibitors                                | Very high risk, Moderate risk, Low risk               | Class I, Class IIa            |                      |                    |
| ICI   | Very high risk, Other conditions (All other patients) | Class I, Class IIa            | Class I, Class IIa   | Class I, Class IIa |
| Osimertinib   | Other conditions (All patients)                       | Class I                       |                      |                    |
| CAR-T and TIL   | Other conditions (Previous CVD, All other patients)   | Class I, Class IIa            | Class I, Class IIa   | Class I, Class IIa |
| RT to a volume including the heart                    | Other conditions (Previous CVD)                       | Class IIa                     |                      |                    |
| HSCT  | Other conditions (All patients)                       | Class I, Class IIa            | Class IIa            |                    |

Very high risk  
  Moderate risk  
  Low risk  
  Other conditions  
  Class I  
  Class IIa  
  Class IIb

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**Figure 7** Baseline screening recommendations for patients with cancer treated with potentially cardiotoxic drugs. 3D, three-dimensional; ADT, androgen deprivation therapy; AL-CA, amyloid light-chain cardiac amyloidosis; BC, breast cancer; BCR-ABL, breakpoint cluster region-Abelson oncogene locus; BNP, B-type natriuretic peptide; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T cell; CDK, cyclin-dependent kinase; CMR, cardiac magnetic resonance; cTn, cardiac troponin; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; GLS, global longitudinal strain; HER2, human epidermal receptor 2; HSCT, haematopoietic stem cell transplantation; ICI, immune checkpoint inhibitors; LVEF, left ventricular ejection fraction; MEK, mitogen-activated extracellular signal-regulated kinase; NP, natriuretic peptides (including BNP and NT-proBNP); NT-proBNP, N-terminal pro-B-type natriuretic peptide; PI, proteasome inhibitors; RAF, rapidly accelerated fibrosarcoma; RT, radiotherapy; TIL, tumour-infiltrating lymphocytes; TKI, tyrosine kinase inhibitors; TTE, transthoracic echocardiography; VEGFi, vascular endothelial growth factor inhibitors. <sup>a</sup>Including patients scheduled to receive ADT for prostate cancer, CDK 4/6 inhibitors, endocrine hormone therapy for BC and anaplastic lymphoma kinase inhibitors. <sup>b</sup>TTE is recommended as the first-line modality for the assessment of cardiac function. 3D echocardiography is recommended to measure LVEF. GLS is recommended in all patients with cancer having echocardiography, if available. CMR should be considered when echocardiography is unavailable or not diagnostic. <sup>c</sup>Baseline cTn measurement should be considered (Class IIa, Level A) in low- and moderate-risk patients post-anthracycline chemotherapy but prior to starting HER2-targeted therapies. Baseline NP and cTn measurement may be considered (Class IIb, Level C) in low- and moderate-risk patients. <sup>d</sup>Baseline echocardiography is recommended in patients scheduled to receive dasatinib (Class I, Level C). <sup>e</sup>NP and cTn measurements are recommended at baseline in patients with AL-CA (Class I, Level B).

recommended.<sup>44–48</sup> When baseline QTcF prolongation is recognized, the correction of reversible causes and the identification of genetic conditions that prolong QT is recommended (see Section 6.4.2).<sup>45</sup>

Left atrial enlargement on baseline ECG before ibrutinib has been shown to be a predictor for the development of atrial fibrillation (AF) during chemotherapy.<sup>50,51</sup> The presence of atrioventricular (AV) conduction delays and premature atrial complexes are associated with the development of atrial arrhythmias in patients undergoing autologous haematopoietic stem cell transplantation (HSCT).<sup>52</sup>

**Recommendation Table 2 — Recommendations for electrocardiogram baseline assessment**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| An ECG is recommended in all patients starting cancer therapy as part of their baseline CV risk assessment.     | I                  | C                  |
| In patients with an abnormal baseline ECG, <sup>c</sup> referral to a cardiologist <sup>d</sup> is recommended. | I                  | C                  |

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AF, atrial fibrillation; CV, cardiovascular; ECG, electrocardiogram; LV, left ventricular; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Advanced conduction disease (left bundle branch block, right bundle branch block, second degree heart block, severe first degree heart block with a PR interval >300 ms); Q waves in two or more contiguous leads; LV hypertrophy; AF/atrial flutter if previously undiagnosed; QTc prolongation using Fridericia correction formula ( $QTcF = QT^3 / \sqrt{RR}$ ) >450 ms for men and >460 ms for women or other ECG abnormality raising concern.

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

#### 4.4. Cardiac serum biomarkers

The literature on the use of biomarkers for CTR-CVT risk stratification before cancer therapy is limited, and recommendations are mostly based on expert opinion.<sup>12,43,53–55</sup> Four recent position papers based on collaboration among the Cardio-Oncology Study Group of the HFA of the ESC, the ESC-CCO, and ICOS have suggested that measurement of cardiac serum biomarkers—cardiac troponin (cTn) I or T and natriuretic peptides (NP) (e.g. B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP])—help in baseline CV risk stratification of patients scheduled for cancer therapies including anthracyclines, human epidermal receptor 2 (HER2)-targeted therapies, vascular endothelial growth factor (VEGF) inhibitors (VEGFi), proteasome inhibitors (PI), immune checkpoint inhibitors (ICI), chimeric antigen receptor T cell (CAR-T) and tumour-infiltrating lymphocytes (TIL) therapies, allowing identification of those who may benefit from cardioprotective therapy.<sup>12,43,53,54</sup> Baseline cardiac serum biomarker measurements are required if the degree of change in the biomarkers is to be used to identify subclinical cardiac injury during cancer treatment.

A few studies of paediatric and adult patients requiring anthracycline chemotherapy have reported that patients with cancer with an increased cTn before treatment were more likely to develop CTRCD.<sup>56–58</sup> However, most published studies have not reported on the prognostic value of baseline cTn measurements, possibly due to the low prevalence of patients with previous CVD or CVRF in these studies.<sup>55,59,60</sup> A study of 251 women receiving trastuzumab for early HER2-positive breast cancer (BC) reported that 19% of the patients who developed cardiac dysfunction during trastuzumab therapy had positive ultrasensitive troponin I at baseline (>80 ng/L).<sup>61</sup> Furthermore, baseline high cTnI level was a predictor of lack of recovery despite optimal HF therapy.<sup>61</sup> These findings have been confirmed in a subsequent study of 533 patients with BC who had serial high-sensitivity cTn (hs-cTn) I and T measurements during trastuzumab therapy.<sup>62</sup> Increased baseline cTn (>40 ng/L and >14 ng/L for hs-cTnI and hs-cTnT, respectively) was associated with a four-fold risk of developing LV dysfunction (LVD).<sup>62</sup> However, given the high proportion of patients with previous anthracycline exposure in both studies, these elevated cTn levels are not a true baseline as they reflect pre-trastuzumab but post-anthracycline chemotherapy. It is unclear whether pre-treatment cTn levels will be predictive of LVD in patients before any treatment, or for those BC patients treated with trastuzumab without prior anthracyclines.

NP are another potential biomarker for CV risk stratification. Several studies have shown the role of NP measurement at baseline or NP changes to predict future CTR-CVT.<sup>63–65</sup> In patients with multiple myeloma (MM), pre-treatment NP may be a predictive marker for subsequent CV adverse events. In 109 patients with relapsed MM, BNP > 100 pg/mL or NT-proBNP > 125 pg/mL levels before initiation of carfilzomib were associated with an odds ratio of 10.8 for subsequent CV adverse events.<sup>66</sup> Therefore, baseline NP measurement is recommended in high- and very high-risk patients and should be considered in low- and moderate-risk patients before PI treatment.

Baseline elevated values of CV functional peptides (including NT-proBNP) and hs-cTnT were strongly related to all-cause mortality in 555 patients with different types of tumours, suggesting that the presence of a subclinical myocardial injury might be directly linked to disease progression.<sup>67</sup> However, in the CARDIOTOX (CARDIOvascular TOXicity induced by cancer-related therapies) registry, in 855 patients treated with a range of oncological treatments, including radiotherapy (RT), both NT-proBNP and cTn elevation at baseline were not associated with the development of severe CTRCD (LVEF < 40% or clinical HF).<sup>68</sup>

There has also been interest in other novel biomarkers for CTR-CVT risk stratification before cancer treatment; however, the literature is limited. Candidates include myeloperoxidase, C-reactive protein, galectin-3, arginine–nitric oxide metabolites, growth differentiation factor-15, placental growth factor, fms-like tyrosine kinase-1, micro-ribonucleic acids, and immunoglobulin E.<sup>60,69–71</sup> Currently, there is no evidence to support routine measurement of these novel biomarkers and more research is required.

### Recommendation Table 3 — Recommendation for cardiac biomarker assessment prior to potentially cardiotoxic therapies

| Recommendation  | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Baseline measurement of NP <sup>c</sup> and/or cTn <sup>d</sup> is recommended in all patients with cancer at risk of CTRCD if these biomarkers are going to be measured during treatment to detect CTRCD. <sup>e,53,55</sup> | I                  | C                  |

cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; NP, natriuretic peptides.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>NPs including B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide.

<sup>d</sup>cTn includes any of troponin I, troponin T, or hs-cTnT.

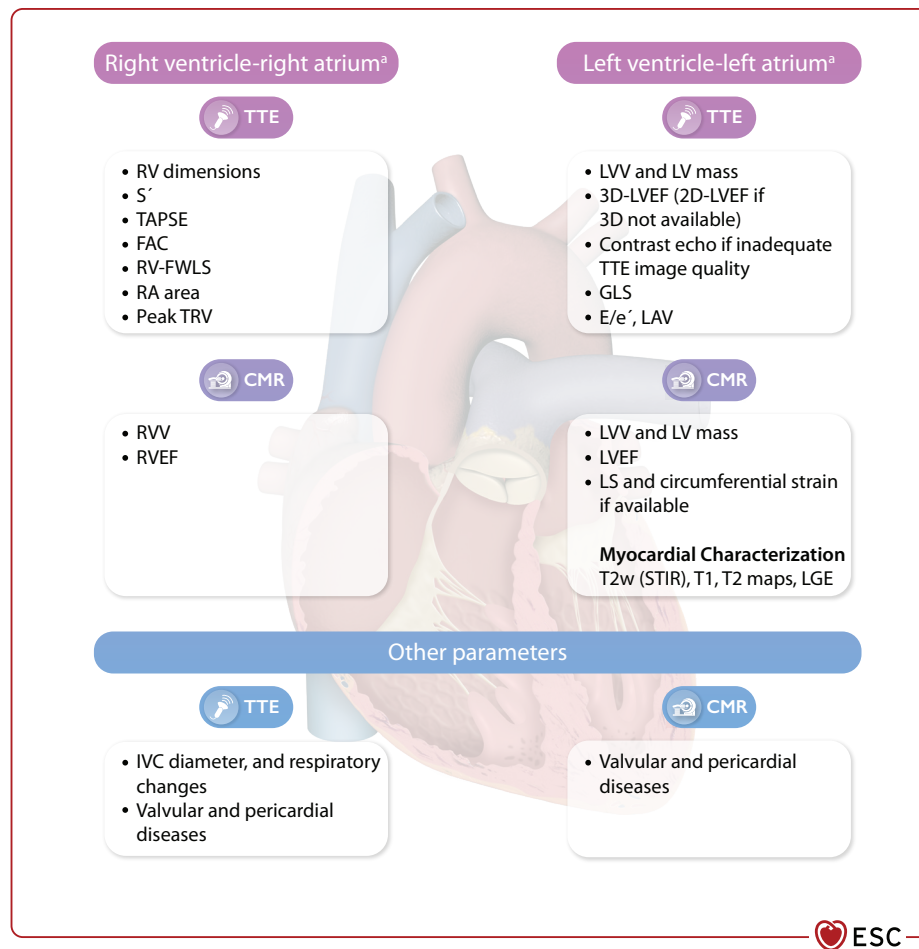
<sup>e</sup>Specific recommendations for baseline cardiac biomarkers in patients with cancer at low, moderate, high, and very high risk of cancer therapy-related cardiovascular toxicity are included in Section 5.

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## 4.5. Cardiovascular imaging

CV imaging has an important role in identifying patients with subclinical CVD, determining the degree of pre-existing cardiac comorbidity prior to decisions regarding cancer therapy, and serves as a reference for identification of changes during treatment and long-term follow-up.<sup>12,54,72–74</sup> Transthoracic echocardiography (TTE) is the preferred imaging technique for baseline risk stratification as it provides quantitative assessment of LV and right ventricular (RV) function, chamber dilation, LV hypertrophy, regional wall motion abnormalities, diastolic function, VHD, pulmonary arterial pressure (PAP), and pericardial disease, which may influence the therapeutic decision.<sup>22,72</sup> Suggestions for the components of a baseline echocardiography study are provided in Figure 8.

Current definitions of CTRCD are based on a reduction of LVEF and/or relative changes in global longitudinal strain (GLS) (Table 3). Three-dimensional (3D) echocardiography is the preferred echocardiography modality for the assessment of LVEF and cardiac



**Figure 8** Recommended transthoracic echocardiography and cardiac magnetic resonance imaging parameters in the evaluation of patients with cancer. 2D, two-dimensional; 3D, three-dimensional; BP, blood pressure; CMR, cardiac magnetic resonance; E, mitral inflow early diastolic velocity obtained by pulsed wave; e', early diastolic velocity of the mitral annulus obtained by tissue doppler imaging; echo, echocardiography; FAC, fractional area change; FWLS, free wall longitudinal strain; GLS, global longitudinal strain; IVC, inferior vena cava; LAV, left atrial volume; LGE, late gadolinium enhancement; LS, longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; LVV, left ventricular volume; RA, right atrial; RV, right ventricular; RVEF, right ventricular ejection fraction; RVV, right ventricular volume; s', systolic velocity of tricuspid annulus obtained by doppler tissue imaging; STIR, short tau inversion recovery; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography; TRV, tricuspid regurgitation velocity. <sup>a</sup>Changes in systemic arterial BP and loading conditions may influence cardiac function measurements.



volumes.<sup>54,75–79</sup> If 3D echocardiography is not feasible (e.g. unavailable or poor tracking), the modified two-dimensional (2D) Simpson's biplane method is recommended.<sup>80,81</sup> In patients with inadequate TTE image quality, ultrasound-enhancing contrast agents should be added to improve evaluation of LV function and volumes if two or more LV segments are not well visualized.<sup>82</sup> Alternatively, in subjects with poor-quality echocardiography windows, when available, CMR should be considered (Figure 8).<sup>14,72,83,84</sup> If TTE and CMR are both unavailable for the assessment of LVEF, multigated acquisition nuclear imaging (MUGA) can be considered as a third-line modality. MUGA scans should be avoided whenever possible due to radiation exposure and the inability to obtain other important information (e.g. VHD, PAP, or GLS).

Baseline LVEF and GLS are recommended in all patients evaluated with TTE before cardiotoxic cancer treatment initiation to stratify CTR-CVT risk and to identify significant changes during treatment.<sup>8,64</sup> Changes in loading conditions occur frequently during chemotherapy (e.g. volume increase due to intravenous [i.v.] fluids, volume loss due to vomiting or diarrhoea, blood pressure [BP] and heart rate changes with pain or stress) and may affect cardiac volumes, LVEF, and GLS quantification. Systemic arterial BP measurement is recommended with all resting TTE as it can influence cardiac function measurements and should be recorded on the TTE report. A baseline borderline (50–54%) or reduced (<50%) LVEF is a risk factor for future CTR-CVT from most cardiotoxic cancer therapies, in particular with anthracyclines or trastuzumab.<sup>12,24,74</sup> Increased baseline indexed LV end-diastolic volume can be a predictor of major CV events (symptomatic HF or cardiac death) during anthracycline chemotherapy in patients with preserved LVEF.<sup>85</sup>

A normal LVEF does not exclude CTRCD and deformation parameters can detect early systolic impairment with sufficient test reliability.<sup>86–89</sup> Determination of GLS using speckle tracking is recommended at baseline, using three apical views,<sup>90</sup> particularly in moderate- and high-risk patients. Baseline GLS can predict LVD<sup>89–94</sup> in patients receiving anthracyclines and/or trastuzumab. Strain measurements may be subject to inter-vendor variability<sup>95</sup> and serial GLS measurement for each patient is recommended to be performed using the same machine/software. A median GLS change of 13.6% predicted a future fall in LVEF with a 95% upper limit of GLS reduction of 15%.<sup>93</sup> Using the 15% cut-off improves specificity and is therefore the threshold recommended when monitoring GLS during cancer therapy. Global circumferential strain<sup>96</sup> has been reported to identify patients at risk of CTRCD, but data are currently insufficient to recommend its use routinely. Baseline LV diastolic function may be associated with a small risk of subsequent systolic dysfunction, especially with anthracyclines and trastuzumab, although the evidence is not consistent.<sup>97,98</sup> Chest computed tomography (CT) or CMR may be helpful for identifying subclinical CVD such as coronary calcium or intracardiac masses on readily available routine imaging performed for cancer staging.<sup>99</sup>

In the secondary prevention setting or patients with symptoms or signs of pre-existing CVD, a careful evaluation should begin with a comprehensive TTE.<sup>73</sup> This is both to obtain baseline assessment as in the primary prevention setting and to determine the severity of the underlying CVD. In case of poor-quality or uninterpretable TTE images, or if a specific CVD is identified (e.g. hypertrophic

cardiomyopathy), CMR should be considered for further risk assessment.

Functional imaging tests for myocardial ischaemia—including stress echocardiography, perfusion CMR, or nuclear myocardial perfusion imaging—should be performed to assess for ischaemia in symptomatic patients (stable angina, limiting dyspnoea) if clinical suspicion of coronary artery disease (CAD) exists, especially prior to use of cancer therapies associated with vascular toxicity (e.g. fluoropyrimidines, VEGFi, breakpoint cluster region–Abelson oncogene locus [BCR-ABL], tyrosine kinase inhibitors [TKI]). Alternatively, in patients with low to intermediate pre-test probability of CAD, CCTA is a robust alternate modality with high sensitivity to rule out obstructive CAD.<sup>100,101</sup>

**Recommendation Table 4 — Recommendations for cardiac imaging modalities in patients with cancer**

| General  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Echocardiography is recommended as the first-line modality for the assessment of cardiac function in patients with cancer. <sup>4,12,54,94</sup>                         | I                  | C                  |
| 3D echocardiography is recommended as the preferred echocardiographic modality to measure LVEF. <sup>77–79,89</sup>  | I                  | B                  |
| GLS is recommended in all patients with cancer having echocardiography, if available. <sup>75,80,81,89,90,92,93,102,103</sup>  | I                  | C                  |
| CMR should be considered for the assessment of cardiac function when echocardiography is unavailable or non-diagnostic. <sup>83,104,105</sup>                            | IIa                | C                  |
| MUGA may be considered when TTE is not diagnostic and CMR is not available. <sup>106–108</sup>   | IIb                | C                  |
| <b>Baseline cardiac imaging prior to potentially cardiotoxic therapies<sup>c</sup></b>   |                    |                    |
| Baseline comprehensive TTE is recommended in all patients with cancer at high risk and very high risk of CV toxicity before starting anticancer therapy. <sup>d,54</sup> | I                  | C                  |

3D, three-dimensional; CMR, cardiac magnetic resonance; CTR-CVT, cancer therapy-related CV toxicity; CV, cardiovascular; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition nuclear imaging; TTE, transthoracic echocardiography.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Specific recommendations for baseline CV imaging in patients with cancer at low or moderate risk of CTR-CVT are included in Section 5.

<sup>d</sup>Except asymptomatic patients referred to breakpoint cluster region–Abelson oncogene locus therapy (BCR-ABL) where baseline TTE should be considered (see Figure 7 and Section 5.5.5).

## 4.6. Cardiopulmonary fitness assessment

Maximal cardiopulmonary exercise testing (CPET) assesses the integrative capacity of the CV system to transport oxygen and energy substrate to skeletal muscle during exercise,<sup>109</sup> described as cardiorespiratory fitness (CRF). CPET can therefore provide a more global assessment of CV health than organ-specific tools. CPET-derived

CRF—typically measured as the peak rate of oxygen consumption<sup>110,111</sup> or metabolic equivalents<sup>111,112</sup> during exercise—is one of the most robust predictors of CV health and longevity,<sup>113,114</sup> and improves risk classification.<sup>115–121</sup> Evidence for CPET pre-treatment is limited to pre-operative risk stratification particularly for patients with lung,<sup>122</sup> colon,<sup>123</sup> and rectal<sup>124</sup> cancers. Whether CPET performed prior to cardiotoxic cancer therapies is prognostic of future CV events is unknown.

#### 4.7. Cardiovascular risk evaluation before cancer surgery

Cancer surgery remains the primary treatment modality for many cancers. Cardio-oncology teams should be involved in pre-operative CV risk stratification to identify and provide appropriate management and surveillance of the potential risk factors.<sup>5</sup>

In patients undergoing oncological surgery, peri-operative cardiac complications are determined by patient-related risk factors, the tumour type, concomitant cancer therapies, and the expected surgical risk. To ensure safe cancer surgery, consultations should be directed at: (1) patients with previous significant or symptomatic CVD; (2) patients at high and very high CV toxicity risk, according to baseline HFA-ICOS risk assessment tools,<sup>12</sup> when adjuvant (post-surgery) cancer treatment is planned; and (3) patients who have received neoadjuvant (prior to surgery) cancer therapy that is potentially cardiotoxic. Pre-operative clinical evaluation should not delay surgery. Complementary tests required for the patients included in groups 1 and 2 should be guided by general ESC Guidelines.<sup>125</sup> However, in group 3 patients, the pre-operative evaluation should be aimed at confirming that no relevant events have occurred during CV monitoring (Section 5). Table 6 summarizes factors that could influence peri-operative risk during cancer surgery.

#### 4.8. Genetic testing


Candidate gene and genome-wide association studies have resulted in the identification of 40 candidate genes and single nucleotide polymorphisms associated with anthracycline-related cardiac

dysfunction.<sup>37,126–128</sup> It should be noted that with the advent of immunotherapies, germline genes may not be the only genetic predispositions to CTR-CVT. A study of patients with ICI-associated myocarditis identified that the selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumours and skeletal muscle, with ribonucleic acid sequencing studies revealing expression of cardiac-specific genes in the tumour,<sup>129</sup> raising the intriguing possibility that somatic mutations in the tumour itself could contribute to CTR-CVT. A list of genetic variants associated with CVD during cancer therapy is provided (Supplementary data, Table S9) and has recently been reviewed.<sup>38</sup>

Routine use of genetic testing for the assessment of CTR-CVT risk prior to initiation of cancer therapy is not currently recommended. In the future, a personalized genetic approach may help define individual susceptibility to CVD in patients with cancer and more research is required.

### 5. Prevention and monitoring of cardiovascular complications during cancer therapy

#### 5.1. General principles

CTR-CVT risk may vary according to cancer type and stage, anticancer drugs, doses, and underlying comorbidities. Certain therapy combinations (drug–drug or drug–radiation) may have a synergistically toxic effect on the heart, possibly depending on the timing of these therapies (sequential or concomitant) and previous comorbidities. The pathophysiology of CTR-CVT is out of the scope of this guideline and is extensively reviewed in the  ESC CardioMed textbook.<sup>130</sup>

CVD and cancer share common modifiable and non-modifiable risk factors (Figure 3).<sup>4,131,132</sup> The first step is to optimize lifestyle CVRF, smoking cessation, restricting alcohol consumption to a maximum of 100 g per week, and maintaining adequate physical activity.<sup>30</sup> Exercise prescription seems to be a promising treatment to

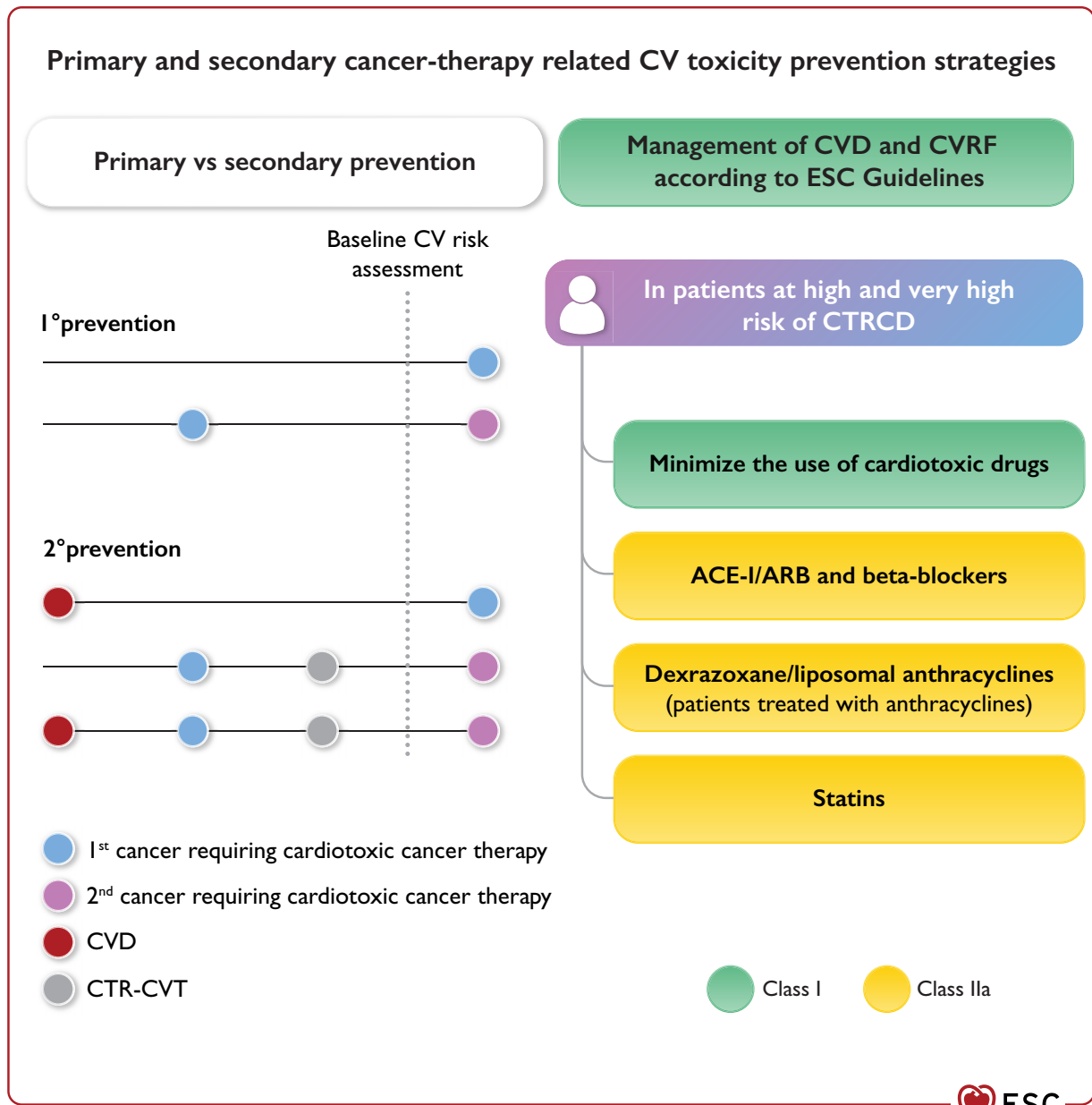
**Table 6** Factors that could influence peri-operative risk during cancer surgery and preventive strategies

|                                   | Factors that could influence peri-operative risk during cancer surgery  | Preventive strategies   |
|-----------------------------------|---|---|
| <b>Patient-related factors</b>    | <ul style="list-style-type: none"> <li>• Lifestyle risk factors: smoking, obesity, sedentary lifestyle</li> <li>• Poorly controlled CVRF: hypertension, DM</li> <li>• Pre-existing CVD including CTR-CVT</li> <li>• Cardiac medications that increase peri-operative bleeding risk (e.g. antiplatelets and anticoagulants)</li> <li>• Historical primary malignancy</li> <li>• Current cancer type, stage and location</li> </ul> | <ul style="list-style-type: none"> <li>• Optimal management of CVRF and CVD (Section 5)</li> <li>• Optimize VTE and ATE preventive strategies (Section 6)</li> </ul>                  |
| <b>Neoadjuvant cancer therapy</b> | <ul style="list-style-type: none"> <li>• Neoadjuvant cardiotoxic cancer treatments (see Section 5; especially anthracycline chemotherapy and/or trastuzumab, ICI, VEGFi, fluoropyrimidine, and thoracic RT)</li> <li>• Cancer treatments that increase peri-operative bleeding risk (e.g. VEGFi, BTK inhibitors)</li> <li>• Thrombocytopaenia caused by cancer treatment</li> </ul>   | <ul style="list-style-type: none"> <li>• Ensure optimal CV monitoring of neoadjuvant therapy (Section 5)</li> <li>• Optimize VTE and ATE preventive strategies (Section 6)</li> </ul> |

ATE, arterial thromboembolism; BTK, Bruton tyrosine kinase; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DM, diabetes mellitus; ICI, immune checkpoint inhibitors; RT, radiotherapy; VEGFi, vascular endothelial growth factor inhibitors; VTE, venous thromboembolism.

counteract anticancer treatment side effects and different types of training can be prescribed during cancer therapy according to a patient's individual characteristics.<sup>133</sup> A healthy lifestyle decreases the risks of cancer, CVD, and transition from diagnosed cancer to subsequent CVD.<sup>134,135</sup>

Poor CRF is associated with a higher prevalence of acute and chronic CTR-CVT and exercise positively impacts CRF during chemotherapy, although in a recent meta-analysis, the ability of exercise to prevent CTRCD is unclear.<sup>136,137</sup> CVRF must be corrected with intensive treatment of arterial hypertension,<sup>138</sup> DM,<sup>139</sup> and



**Figure 9** Primary and secondary cancer therapy-related cardiovascular toxicity prevention. 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.<sup>12</sup> **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.

dyslipidaemia,<sup>140</sup> and underlying CVD and modifiable comorbidities should be managed according to appropriate 2021 ESC Guidelines on CVD prevention in clinical practice (Figure 9).<sup>19</sup>

Special attention should also be paid to the polypharmacy frequently seen in patients with cancer, reducing the use of drugs that may interfere with cancer therapies to the essential and actively monitoring their CV side effects and drug–drug interactions.<sup>141</sup> Electrolyte imbalances such as hypokalaemia and hypomagnesaemia should be corrected. The CV risk management plan should be shared with the cancer specialist team, the primary care physician, and the patient to coordinate treatment strategies.

## 5.2. Primary prevention strategies

Primary prevention of CTR-CVT aims to avoid or minimize the development of CV damage due to therapy in patients without CVD<sup>12,142</sup> and requires a multidisciplinary team (MDT) discussion between oncologists and cardiologists for complex patients with cancer with multiple comorbidities.<sup>4,21,22,43,143,144</sup>

### 5.2.1. Primary prevention of cancer therapy-related cardiovascular toxicity during anthracycline chemotherapy

Neurohormonal therapies during anthracycline chemotherapy (with or without subsequent trastuzumab treatment) reduced the risk of significant LVEF decline during follow-up in several small randomized controlled trials (RCTs) (Supplementary data, Table S10).<sup>145–154</sup> Recent meta-analyses including patients with cancer treated with anthracycline chemotherapy and HER2-targeted therapies reported that renin–angiotensin–aldosterone system blockers, beta-blockers, and mineralocorticoid receptor antagonists have a significant benefit in preventing LVEF reduction, but no statistical differences in the incidence of overt HF or other clinical outcomes were demonstrated (Supplementary data, Table S11).<sup>155–160</sup> This may be due, in part, to the fact that most trials included patients with a low baseline CTRCD risk and therefore larger RCTs are needed in high-risk populations.

From the oncological perspective, some strategies that have been investigated include managing anthracycline-related toxicity by adjusting the infusion time and dose intensity.<sup>161</sup> Dexrazoxane and liposomal anthracyclines are currently approved in patients with high and very high CTRCD risk or who have already received high cumulative anthracyclines doses.<sup>158,162–167</sup> Dexrazoxane is protective against anthracycline-induced CTRCD. Currently, dexrazoxane is formally approved in adult patients with advanced or metastatic BC who have already received a minimum cumulative anthracycline dose of 300 mg/m<sup>2</sup> of doxorubicin or equivalent (Table 5; Supplementary data, Table S12).<sup>163</sup> In clinical practice, dexrazoxane infusion (dosage ratio dexrazoxane/doxorubicin is 10/1; e.g. 500 mg/m<sup>2</sup> dexrazoxane per 50 mg/m<sup>2</sup> doxorubicin) should be considered (at least 30 min prior to each anthracycline cycle) in adult patients with cancer scheduled to receive a high total cumulative anthracycline dose for curative treatment, and in patients with high and very high CTRCD risk (including those with pre-existing HF or low-normal or reduced LVEF) where anthracycline chemotherapy is deemed essential.<sup>163</sup>

Pegylated and non-pegylated liposomal doxorubicin<sup>164,165,168</sup> modify pharmacokinetics and tissue distribution without compromising antitumour efficacy. Pegylated and non-pegylated liposomal doxorubicin are approved for metastatic BC and pegylated liposomal doxorubicin is also approved for advanced ovarian cancer, acquired immune deficiency syndrome-related Kaposi sarcoma, and MM. In a recent meta-analysis of 19 trials, in both the adjuvant and metastatic context, liposomal doxorubicin was reported to be less cardiotoxic than conventional doxorubicin.<sup>165</sup> Liposomal daunorubicin is also available for acute leukaemia patients in place of daunorubicin when pre-existing LVD is present.<sup>164,165</sup>

### 5.2.2. Primary prevention of radiation-induced cardiovascular toxicity

Primary prevention of RT-induced damage to the CV system depends on technological advances that allow improved targeting of RT delivery, thereby maintaining or increasing oncological efficacy while reducing CTR-CVT.<sup>169,170</sup> Modern techniques strive to minimize the mean heart dose (MHD), either by shaping the dose distribution (intensity-modulated RT) or by using respiratory management (gating or breath-hold).<sup>171,172</sup> Proton therapy offers the potential to further decrease exposure to surrounding healthy organs.<sup>173</sup> However, complete cardiac avoidance is not always possible due to the proximity of the tumour (e.g. central lung tumours, mediastinal lymphomas, irradiation of the internal mammary chain in BC). In patients where RT only has a consolidating role and the risk of RT-induced CV injury is very high (e.g. due to baseline risk factors), a MDT is needed to consider the risk/benefit of RT.<sup>171,174</sup>

There are no proven medical therapies to prevent RT-induced CV toxicity. One component of RT-induced CV toxicity is accelerating pre-existing CAD, and therefore tight control of CVRFs is recommended.

### Recommendation Table 5 — Recommendations for primary prevention of cancer therapy-related cardiovascular toxicity

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Management of CVRF according to the 2021 ESC Guidelines on CVD prevention in clinical practice is recommended before, <sup>c</sup> during, and after cancer therapy. <sup>19</sup>        | I                  | C                  |
| Dexrazoxane should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated. <sup>d,158</sup>                      | IIa                | B                  |
| Liposomal anthracyclines should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated. <sup>e,164,165,168</sup> | IIa                | B                  |

Continued

|   |     |   |
|---|-----|---|
| ACE-I or ARB and beta-blockers recommended for HF <sup>f</sup> should be considered for primary prevention in high- and very high-risk patients receiving anthracyclines and/or anti-HER2 therapies. <sup>145,150,155–157,159,160,175</sup> | IIa | B |
| ACE-I or ARB and beta-blockers recommended for HF <sup>f</sup> should be considered for primary prevention in high- and very high-risk patients receiving targeted cancer therapies that may cause HF. <sup>g</sup>                         | IIa | C |
| Statins should be considered for primary prevention in adult patients with cancer at high and very high CV toxicity risk. <sup>h,149,176–185</sup>  | IIa | B |

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Without delaying cancer treatments.

<sup>d</sup>As per the European Medicine Agency:  $\geq 350$  mg/m<sup>2</sup> doxorubicin or equivalent; as per the United States Food and Drug Administration:  $\geq 300$  mg/m<sup>2</sup> doxorubicin or equivalent.

<sup>e</sup>See Section 5.2.1 for specific liposomal doxorubicin type and malignancies.

<sup>f</sup>Carvedilol (preferred beta-blocker for CV protection if there is no contraindication),<sup>186</sup> bisoprolol, controlled/extended-release metoprolol succinate and nebivolol.

<sup>g</sup>VEGFi and bevacizumab, RAF inhibitor, MEK inhibitor, PI, dasatinib, ponatinib, and osimertinib.

<sup>h</sup>According to HFA-ICOS risk assessment tools (Section 4.1; Table 4).

### 5.3. Secondary prevention strategies

Secondary prevention refers to interventions in patients with pre-existing CVD, including prior CTR-CVT, and new emerging CTR-CVT during cancer therapy. CVD and comorbidities should receive the optimal therapy before and during cancer therapy as discussed in previous sections. Regular clinical assessments, physical examinations, and CV investigations (including 12-lead ECG, TTE, and cardiac biomarkers) are recommended in patients receiving specific cardiotoxic cancer therapies, with the frequency of surveillance guided by baseline risk and the emergence of new CTR-CVT.<sup>5,12,33,53,54,187–190</sup>

#### Recommendation Table 6 — Recommendation for secondary prevention of cancer therapy-related cardiovascular toxicity

| Recommendation   | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Management of CVD according to applicable ESC Guidelines is recommended before, <sup>c</sup> during, and after cancer therapy. | I                  | C                  |

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CVD, cardiovascular disease; ESC, European Society of Cardiology.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Without delaying cancer treatments.

### 5.4. Cardiovascular surveillance during cancer therapies

A careful clinical evaluation and physical examination is recommended during cancer treatment to detect early signs and symptoms of CTR-CVT. ECG monitoring is required in patients at risk of cardiac arrhythmias according to specific drug protocols.

#### 5.4.1. Cardiac serum biomarkers

During therapy, NP and cTn should be used for CTRCD screening and diagnosis and they may also serve to guide therapy.<sup>55,63,191–194</sup>

The release of cTn and NP differ for different cancer treatments. Therefore, an increase in biomarker level should be interpreted in the patient clinical context (cancer treatment timing and comorbidities).

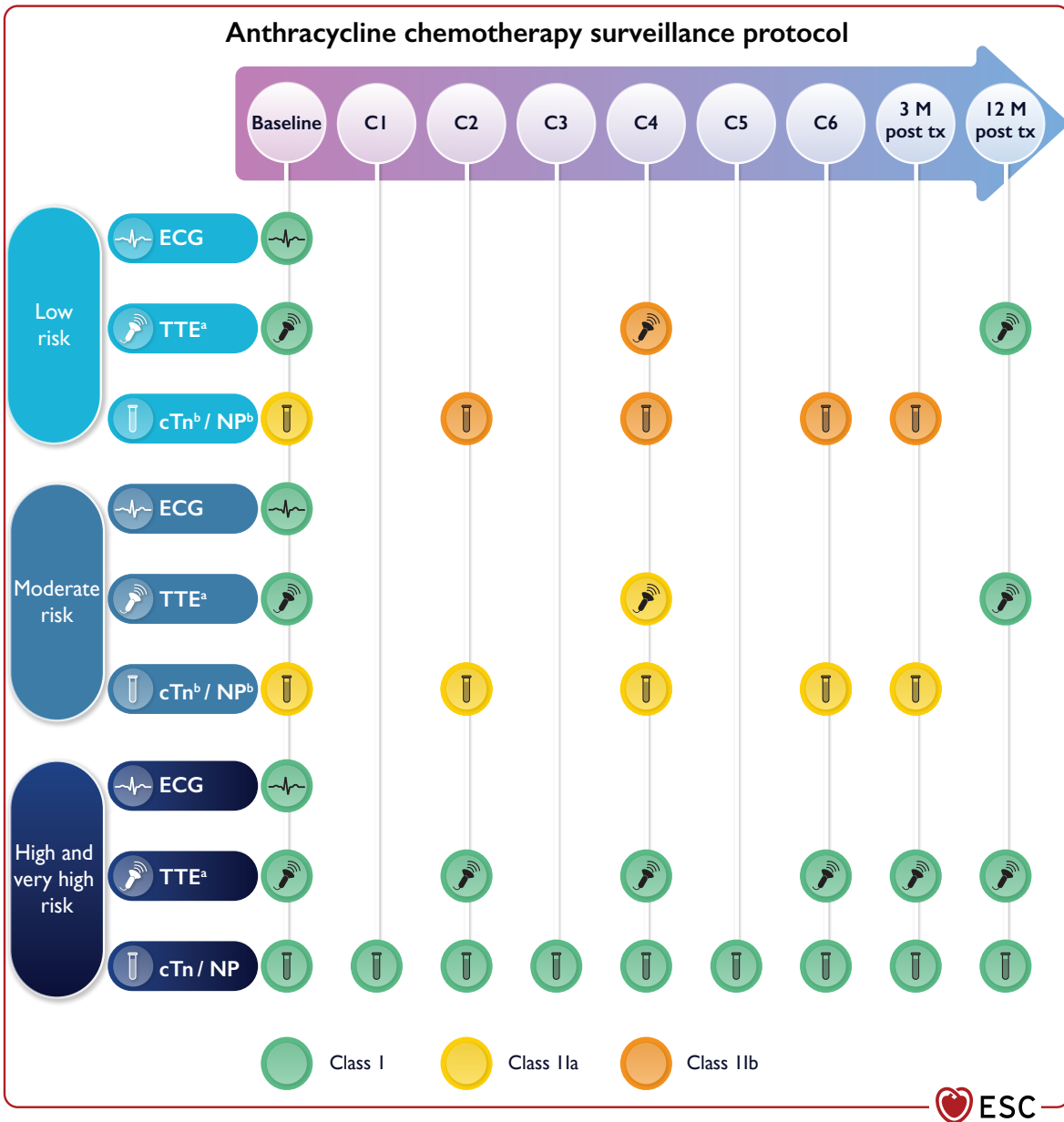
It is important to consider that generally accepted cut-offs and reference values of CV biomarkers have not been established for patients with cancer or for those who receive cancer therapies. In addition, levels of NP and cTn may differ according to local laboratories and may be altered by many factors, including age, sex, renal function, obesity, infections, and comorbidities such as AF and pulmonary embolism (PE).<sup>53,63,195–197</sup>

#### 5.4.2. Cardiac imaging

Cardiac imaging plays a critical role in clinical decision-making during the cancer process.<sup>72,198</sup> Imaging techniques—particularly advanced echocardiography and CMR—facilitate early diagnosis and management of CTR-CVT.<sup>22,54,94</sup> The frequency of cardiac imaging monitoring during therapy should be adapted according to the estimated baseline risk<sup>12</sup> and the expected CTR-CVT manifestation.<sup>54</sup> The cardiac imaging technique used should be based on local expertise and availability, and the same imaging modality (i.e. 3D-TTE, 2D-TTE, CMR) is recommended throughout the entire treatment to decrease inter-technique variability.<sup>94,199,200</sup> Cardiac imaging should be performed at any time if patients receiving cardiotoxic therapies present with new cardiac symptoms.

New definitions of CTRCD are presented in Section 3.<sup>1</sup> Early recognition of asymptomatic CTRCD allows clinicians to incorporate cardioprotective therapy before there is a significant decline in LVEF, which may or may not be reversible, and also decreases the risk of interruptions in cancer therapy, which could otherwise affect patients' survival.<sup>22,43,72,94</sup> For the diagnosis and management of asymptomatic CTRCD during cancer treatment, TTE—including 3D-LVEF and GLS assessment—is the preferred technique to detect and confirm cardiac dysfunction.<sup>72,83,93,102</sup> GLS evaluation is particularly important in patients with low-normal LVEF to confirm or not asymptomatic myocardial damage.<sup>201</sup> It is recommended to use the same vendor to analyse GLS during cancer treatment to accurately compare values over time.<sup>73</sup> Therefore, a relative change in GLS has been suggested as the ideal tool to identify asymptomatic mild CTRCD.<sup>1,4,94</sup> Different thresholds have been considered in the literature in recent years.<sup>93,202,203</sup> Currently, a relative GLS decrease of >15% compared with baseline is the recommended threshold as it reflects the 95% upper





**Figure 10** 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). <sup>a</sup>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  $\geq 250$  mg/m<sup>2</sup> of doxorubicin or equivalent. In low-risk patients, TTE may be considered after a cumulative dose of  $\geq 250$  mg/m<sup>2</sup> of doxorubicin or equivalent. <sup>b</sup>Measurement of NP and/or cTn is recommended in all patients with cancer if these biomarkers are going to be used during treatment monitoring. cTn 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  $\geq 250$  mg/m<sup>2</sup> of doxorubicin or equivalent (Class IIa, Level C).

limit in the meta-analysis of GLS to predict future significant LVEF reduction.<sup>93</sup> Using the 15% threshold will maximize specificity and minimize overdiagnosis of CTRCD and guide cardioprotective therapy.<sup>1,4,93</sup>

In patients with poor TTE image quality or when TTE is not diagnostic, CMR should be considered, including fast strain-encoded CMR when available.<sup>105,204–206</sup> MUGA can be considered as a third-line modality.



## 5.5. Cancer therapy-related cardiovascular toxicity monitoring protocols

### 5.5.1. Anthracycline chemotherapy

Anthracycline-induced CTRCD is a dose-dependent and cumulative process of variable onset that may present with symptomatic or asymptomatic CTRCD.<sup>4</sup>

Figure 10 summarizes the recommended monitoring protocol during anthracycline therapy according to baseline CTRCD risk (Table 4). Clinical assessment combined with cardiac biomarkers (cTn and NP) and TTE (including 3D-LVEF and GLS when available) can identify both symptomatic and asymptomatic CTRCD with a reasonably high negative predictive value. This topic has been extensively reviewed in two recent HFA position statements.<sup>53,54</sup> Classifying patients based on their risk of anthracycline-induced CV toxicity has allowed the early implementation of personalized preventive strategies (Section 5.2.1).<sup>14</sup> Patients with pre-existing CVD should be treated with guideline-based medical therapy.<sup>14,19,207</sup>

#### Recommendation Table 7 — Recommendations for baseline risk assessment and monitoring during anthracycline chemotherapy and in the first 12 months after therapy

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| <b>TTE</b>   |                    |                    |
| Baseline echocardiography <sup>c</sup> is recommended in all patients with cancer before anthracycline chemotherapy. <sup>12,24,208–210</sup>                                  | I                  | B                  |
| In all adults receiving anthracycline chemotherapy, an echocardiogram is recommended within 12 months after completing treatment. <sup>208</sup>                               | I                  | B                  |
| In high- and very high-risk patients, echocardiography is recommended every two cycles and within 3 months after completing treatment. <sup>24,208–210</sup>                   | I                  | C                  |
| In moderate-risk patients, additional echocardiography should be considered after a cumulative dose of $\geq 250$ mg/m <sup>2</sup> of doxorubicin or equivalent. <sup>7</sup> | IIa                | C                  |
| In low-risk patients, additional echocardiography may be considered after a cumulative dose of $\geq 250$ mg/m <sup>2</sup> of doxorubicin or equivalent. <sup>7</sup>         | IIb                | C                  |
| <b>Cardiac serum biomarkers</b>  |                    |                    |
| Baseline measurement of NP and cTn is recommended in high- and very high-risk patients prior to anthracycline chemotherapy. <sup>55,65,211</sup>                               | I                  | B                  |

Continued

|  |     |   |
|--|-----|---|
| Baseline measurement of NP and cTn should be considered in low- and moderate-risk patients prior to anthracycline chemotherapy. <sup>211</sup>   | IIa | C |
| cTn and NP monitoring before every cycle during anthracycline chemotherapy and 3 and 12 months after therapy completion is recommended in high- and very high-risk patients. <sup>55,175,211</sup>   | I   | B |
| 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 $\geq 250$ mg/m <sup>2</sup> of doxorubicin or equivalent. <sup>55,59,212,213</sup> | IIa | C |
| cTn and NP monitoring every two cycles during anthracycline chemotherapy and within 3 months after therapy completion may be considered in low-risk patients. <sup>55,59,212,213</sup>   | IIb | C |

cTn, cardiac troponin; NP, natriuretic peptides; TTE, transthoracic echocardiography.  
<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

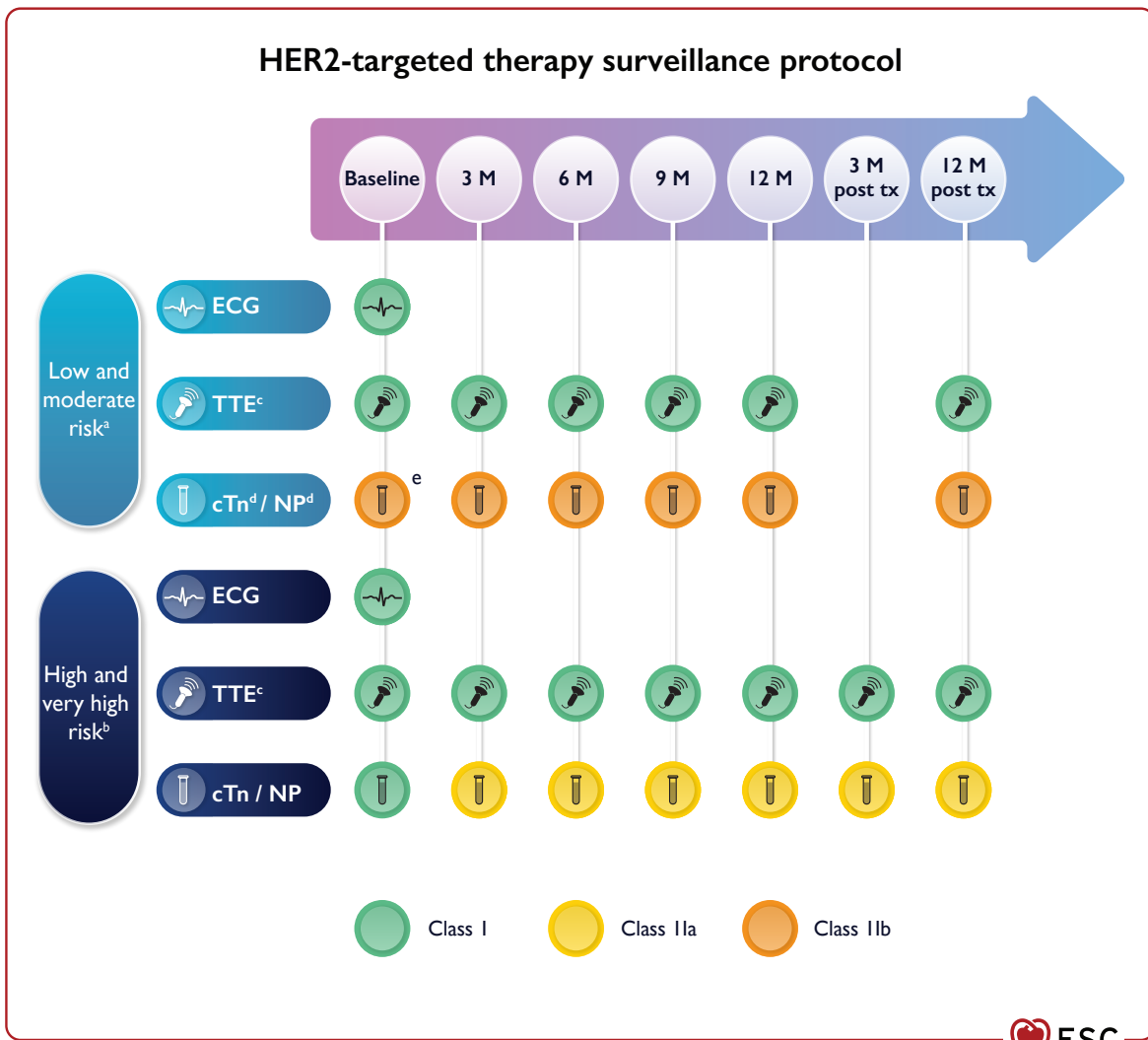
<sup>c</sup>If echocardiography is unavailable or non-diagnostic, follow general cardiac imaging modalities recommendations (see Section 4.5).

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### 5.5.2. HER2-targeted therapies

HER2-targeted therapies are a crucial part of the treatment of patients with HER2-positive invasive BC in both early and metastatic settings. In the neoadjuvant and/or adjuvant settings, drugs currently approved are trastuzumab, pertuzumab, trastuzumab emtansine, and neratinib. In the metastatic setting, trastuzumab, pertuzumab, trastuzumab emtansine, tucatinib, and trastuzumab deruxtecan are currently approved.<sup>214–216</sup> Trastuzumab can also be used in patients with HER2-overexpressing metastatic gastric adenocarcinomas in combination with platinum-based chemotherapy and either capecitabine or 5-fluorouracil (5-FU). It is recognized that anti-HER2 therapies may lead to LVD in up to 15–20% of patients and to overt HF if surveillance is missed, or in high- and very high-risk patients.<sup>217–220</sup> LV function surveillance based on LVEF and GLS is recommended prior to and every 3 months during HER2-targeted therapies treatment surveillance (Figure 11).<sup>22</sup> However, this single algorithm has not been tested in low- or high-risk patients and increased frequency of assessment (according to local availability) is recommended in high-risk patients.

The use of cardiac serum biomarkers to identify CTRCD is less well-defined during anti-HER2 treatments.<sup>217</sup> Measurement of cTn in BC patients after anthracycline-based chemotherapy but prior to trastuzumab should be considered, as an elevated cTn identifies patients at higher risk of trastuzumab-induced CTRCD. Serial NP measurement was more sensitive than cTn at predicting subsequent declines in LVEF during trastuzumab treatment.<sup>74</sup>



**Figure 11** 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. <sup>a</sup>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). <sup>b</sup>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. <sup>c</sup>Cardiac magnetic resonance should be considered for the assessment of cardiac function when TTE is unavailable or not diagnostic. <sup>d</sup>Measurement of NP and/or cTn is recommended in all patients with cancer if these biomarkers are going to be used during treatment monitoring. <sup>e</sup>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.

For patients requiring adjuvant chemotherapy and anti-HER2-targeted therapy, the use of non-anthracycline chemotherapy should be considered by the MDT according to risk of relapse, cardiac risks, and in discussion with the treating oncologist.<sup>217</sup> When anthracycline chemotherapy in the (neo)-adjuvant setting is necessary, sequential use (anthracyclines followed by taxanes and anti-HER2 agents) has been shown to significantly decrease the incidence of CTRCD in several adjuvant trials, compared with concomitant use in earlier trials.<sup>220–224</sup>

**Recommendation Table 8 — Recommendations for baseline risk assessment and monitoring during human epidermal receptor 2-targeted therapies and in the first 12 months after therapy**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| <b>TTE</b>   |                    |                    |
| Baseline echocardiography <sup>c</sup> is recommended before HER2-targeted therapies in all patients. <sup>225</sup> | I                  | B                  |

Continued

|  |            |          |
|--|------------|----------|
| In patients receiving neoadjuvant or adjuvant HER2-targeted therapies, echocardiography is recommended every 3 months and within 12 months after completing treatment. <sup>225,226</sup>  | <b>I</b>   | <b>B</b> |
| In low-risk HER2+ EBC patients <sup>d</sup> who are asymptomatic and with a normal assessment after 3 months, reducing monitoring to every 4 months may be considered.   | <b>IIb</b> | <b>C</b> |
| In high- and very high-risk HER2+ EBC patients, <sup>d</sup> more frequent echocardiography monitoring <sup>e</sup> should be considered during treatment.   | <b>IIa</b> | <b>C</b> |
| In metastatic HER2+ disease, echocardiography is recommended 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. <sup>f</sup> | <b>I</b>   | <b>C</b> |
| In metastatic HER2+ disease patients at high- and very high-risk, more frequent echocardiography monitoring <sup>e</sup> may be considered.  | <b>IIb</b> | <b>C</b> |
| <b>Cardiac biomarkers</b>  |            |          |
| Baseline NP and cTn measurement are recommended in high- and very high-risk patients prior to anti-HER2-targeted therapies. <sup>227,228</sup>   | <b>I</b>   | <b>C</b> |
| 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. <sup>d,55</sup>  | <b>IIa</b> | <b>C</b> |
| Baseline cTn measurement should be considered in low- and moderate-risk patients post-anthracycline chemotherapy but prior to starting anti-HER2-targeted therapies. <sup>55,62</sup>  | <b>IIa</b> | <b>A</b> |
| NP and cTn monitoring at baseline, every 3 months, and 12 months after therapy may be considered in low- and moderate-risk HER2+ EBC patients. <sup>d,55</sup>   | <b>IIb</b> | <b>C</b> |

BC, breast cancer; cTn, cardiac troponin; CV, cardiovascular; EBC, early breast cancer; HER2, human epidermal receptor 2; NP, natriuretic peptides; TTE, transthoracic echocardiography.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>If echocardiography is unavailable or non-diagnostic, follow general cardiac imaging modalities recommendations (see Section 4.5).

<sup>d</sup>These recommendations are also applicable for HER2+ non-BC patients.

<sup>e</sup>Every 2–3 cycles depending on the absolute risk and local availability.

<sup>f</sup>Patients at low and moderate risk.

### 5.5.3. Fluoropyrimidines

Fluoropyrimidines such as 5-FU and its oral prodrug capecitabine are mainly used for gastrointestinal (GI) malignancies and advanced BC. The most common CTR-CVTs are angina pectoris, ischaemia-related ECG abnormalities, hypertension, Takotsubo syndrome (TTS), and MI (even in patients with normal coronary arteries),<sup>1,4,10,43,229,230</sup> with rarer CTR-CVT including myocarditis, arrhythmias, and peripheral arterial toxicity (Raynaud’s phenomenon and ischaemic stroke).<sup>231</sup> The incidence of myocardial ischaemia varies according to the dose, scheduling, and route of administration and

is up to 10%.<sup>232</sup> Among the several mechanisms responsible for 5-FU-induced myocardial ischaemia are coronary vasospasm and endothelial injury.<sup>233</sup> Chest pain and ischaemic ECG changes usually occur at rest (less typically during exercise) within days of drug administration and sometimes persist even after treatment cessation. CTR-CVT risk markedly increases in patients with cancer with pre-existing CAD. Aggressive control of modifiable CVRFs, according to the 2021 ESC Guidelines on CVD prevention in clinical practice,<sup>19</sup> is recommended during and after treatment. A baseline TTE is recommended in patients with a history of symptomatic CV to confirm the presence of pre-existing regional wall motion abnormalities or LVD. Screening for CAD may be considered in selected high- and very high-risk patients before the administration of these drugs and according to local protocols and current recommendations.<sup>12,234,235</sup>

### Recommendation Table 9 — Recommendations for baseline risk assessment and monitoring during fluoropyrimidine therapy

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Baseline CV risk assessment and evaluation including BP measurement, ECG, lipid profile, HbA1c measurement, and SCORE2/SCORE2-OP <sup>c</sup> or equivalent is recommended <sup>19</sup> before starting fluoropyrimidines. | <b>I</b>           | <b>C</b>           |
| A baseline echocardiogram is recommended in patients with a history of symptomatic CVD before starting fluoropyrimidines.   | <b>I</b>           | <b>C</b>           |
| Screening for CAD <sup>d</sup> may be considered in patients at high and very high risk of CAD <sup>c</sup> before fluoropyrimidines.   | <b>IIb</b>         | <b>C</b>           |

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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

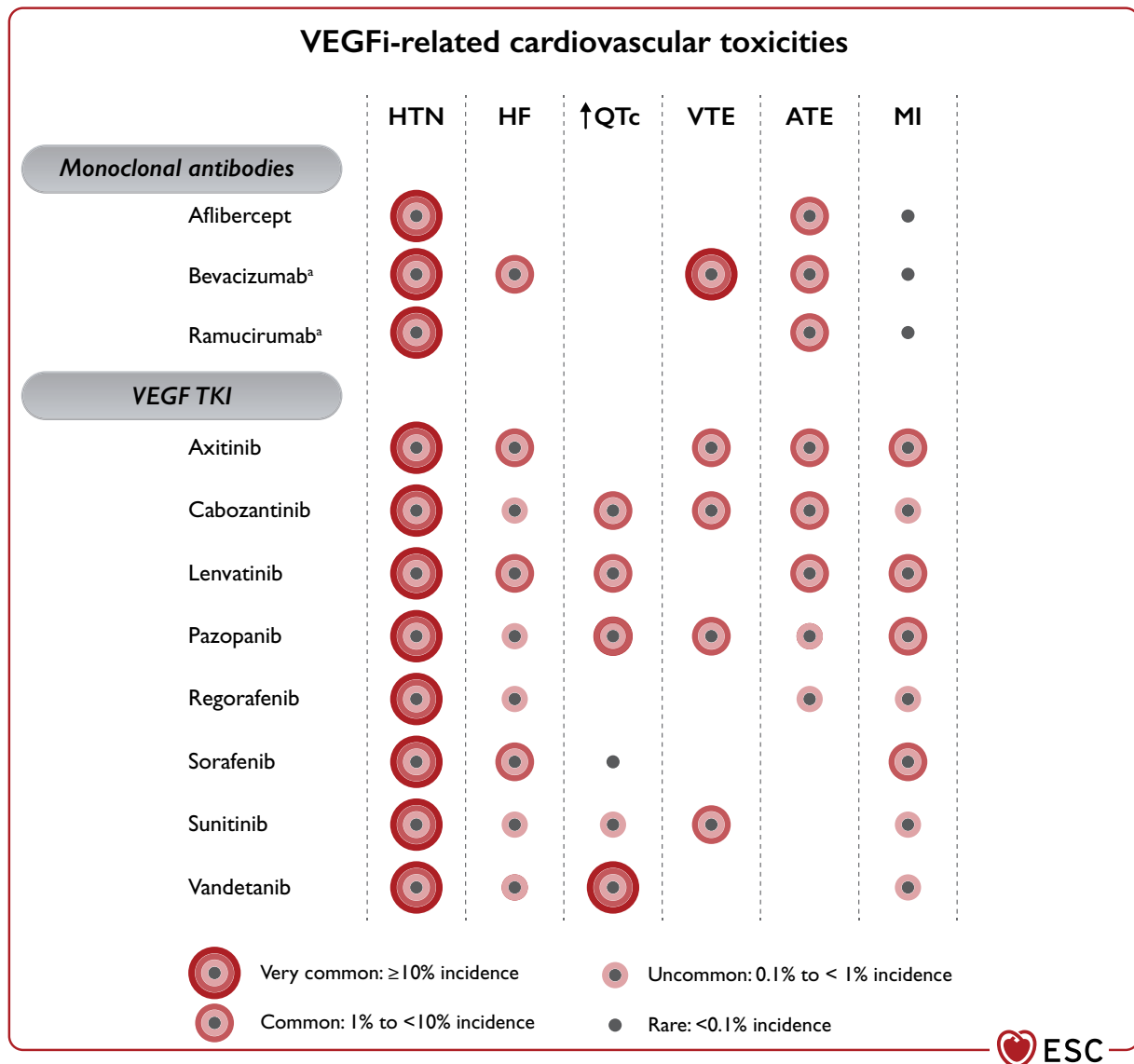
<sup>c</sup>SCORE2 (<70 years) or SCORE2-OP (≥70 years) CV risk stratification: <50 years: low risk <2.5%, moderate risk 2.5% to <7.5%, high risk ≥7.5%; 50–69 years: low risk <5%; moderate risk 5% to <10%; high risk ≥10%; ≥70 years: low risk <7.5%, moderate risk 7.5% to <15%, high risk ≥15%.

<sup>d</sup>According to pre-existing CVD and local protocols.<sup>234</sup>

### 5.5.4. Vascular endothelial growth factor inhibitors

Aberrant activation of kinases plays a critical role in both the development of numerous cancer types and in CV and metabolic homeostasis. Inhibition of the VEGF signalling pathway is achieved with either monoclonal antibodies (administered i.v.) against circulating VEGF or with small-molecule TKI (taken orally) targeting VEGF receptors.<sup>236</sup> VEGFi are used for the treatment of numerous cancer types, including renal, thyroid, and hepatocellular carcinomas. However, their use is associated with a wide array of CV complications including hypertension, HF, QTc prolongation, and acute vascular events (Figure 12).<sup>131,237–240</sup> It can be challenging to assess the prognosis of patients experiencing severe CV side effects because

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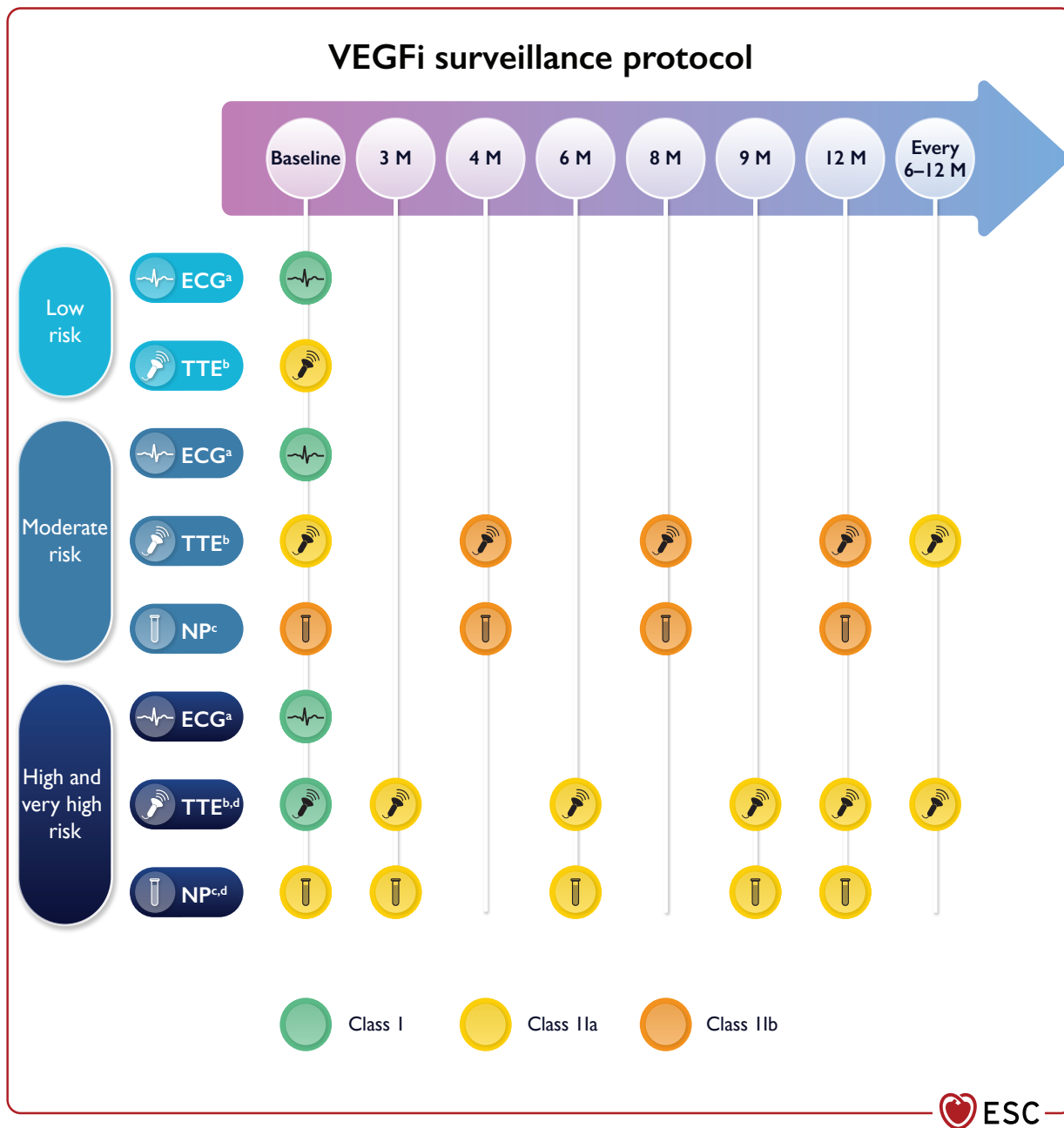
**Figure 12** Vascular endothelial growth factor inhibitors-related cardiovascular toxicities. ATE, arterial thromboembolism; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HTN, hypertension; MedDRA, medical dictionary for regulatory activities; MI, myocardial infarction; ↑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. <sup>a</sup>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,<sup>252</sup> FDA prescribing information.<sup>253</sup>

these drugs are often used in patients with advanced cancer. The goal must be to continue VEGFi treatment for as long as possible with initiation or optimization of CV treatment if indicated.

Hypertension is a class effect and is the most reported adverse event under VEGFi treatment. It occurs within hours or days, is dose-dependent, and is usually reversed by VEGFi discontinuation.<sup>131,239,241–243</sup> The risk is higher in patients with pre-existing hypertension or CVD, previous anthracycline treatment, advanced age, history of smoking, hyperlipidaemia, and/or obesity (Table 4).<sup>4,244</sup>

LVD and HF occur in a minority of patients in RCTs,<sup>245</sup> but are reported more frequently in routine practice<sup>246</sup> and are often reversible.<sup>247</sup> Acute arterial events (aortic dissection, stroke, arterial thrombosis, acute coronary events, vasospasm) and venous thromboembolism (VTE) can also complicate treatment with VEGFi.<sup>248</sup> QTc prolongation has been described with sunitinib, sorafenib, and vandetanib,<sup>249</sup> but it is rarely related to severe arrhythmic events, except with vandetanib.<sup>250</sup> Some small-molecule TKI (e.g. sorafenib and sunitinib) can cause AF<sup>251</sup> and HF.<sup>43,129,247</sup>

A baseline CV risk assessment includes clinical examination, BP measurement, and an ECG with baseline QTcF measurement (see Section 4).<sup>20</sup> Especially in patients with known hypertension, BP should be controlled before VEGFi therapy. A baseline TTE is recommended for high- and very high-risk patients.<sup>14</sup> Patients with impaired LV function and/or patients at high or very high risk of developing HF should be referred to the cardiologist before starting VEGFi therapy.<sup>14</sup>



**Figure 13** 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. <sup>a</sup>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 (Section 6.4). Consider an ECG 2 weeks after starting treatment in high-risk patients and new monitoring in the case of any dose increase (see Section 6.4.2). <sup>b</sup>Cardiac magnetic resonance should be considered for the assessment of cardiac function when TTE is unavailable or not diagnostic. <sup>c</sup>Measurement of NP is recommended in all patients with cancer if these biomarkers are going to be used during treatment monitoring. <sup>d</sup>TTE and NP should be considered at 4 weeks after starting treatment in very high-risk patients.

Monitoring during and after treatment is indicated for all patients treated with a VEGFi and is based on close clinical follow-up using serial ECGs, biomarkers, and echocardiography. Early recognition and treatment of hypertension are essential to prevent other CV complications, especially HF. Home BP monitoring is recommended daily during the first cycle, after each increase of anticancer therapy dose, and every 2–3 weeks thereafter.<sup>138,254,255</sup> When treatment with a VEGFi is stopped, a drop in BP must be anticipated and BP-lowering therapy must be reduced and/or interrupted accordingly (Section 6).

In patients at risk of QTc prolongation, regular monitoring of the QTc interval is recommended after a dose increase, whenever other QT-prolonging agents are added, or if electrolyte imbalances occur (Section 6).

Patients treated with a VEGFi must also be screened regularly for symptoms and clinical signs of HF. Regular NP measurement and echocardiography can be useful for the detection of CTRCD, although evidence is weak (Figure 13).<sup>138,254,255</sup>

**Recommendation Table 10 — Recommendations for baseline risk assessment and monitoring during vascular endothelial growth factor inhibitors**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| <b>BP monitoring</b>  |                    |                    |
| BP measurement is recommended 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 is recommended.                                   | I                  | C                  |
| <b>ECG monitoring</b>   |                    |                    |
| In patients treated with VEGFi at moderate or high risk of QTc prolongation, QTc <sup>c</sup> monitoring is recommended monthly during the first 3 months and every 3–6 months thereafter. <sup>d</sup> | I                  | C                  |
| <b>Echocardiography</b>   |                    |                    |
| Baseline echocardiography is recommended in high- and very high-risk patients treated with VEGFi or bevacizumab.  | I                  | C                  |
| Baseline echocardiography should be considered in low- and moderate-risk patients treated with a VEGFi or bevacizumab.  | IIa                | C                  |

Continued

|  |     |   |
|--|-----|---|
| Echocardiography may be considered every 4 months during the first year in moderate-risk patients receiving VEGFi or bevacizumab.  | IIb | C |
| Echocardiography should be considered every 3 months during the first year in high- and very high-risk patients receiving a VEGFi or bevacizumab. <sup>e</sup>               | IIa | C |
| Echocardiography every 6–12 months should be considered in moderate- and high-risk patients with cancer who require long-term treatment with a VEGFi.                        | IIa | C |
| <b>Cardiac biomarker</b>   |     |   |
| NP may be considered at baseline and then every 4 months during the first year in moderate-risk patients receiving a VEGFi.  | IIb | C |
| NP should be considered 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 |

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

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

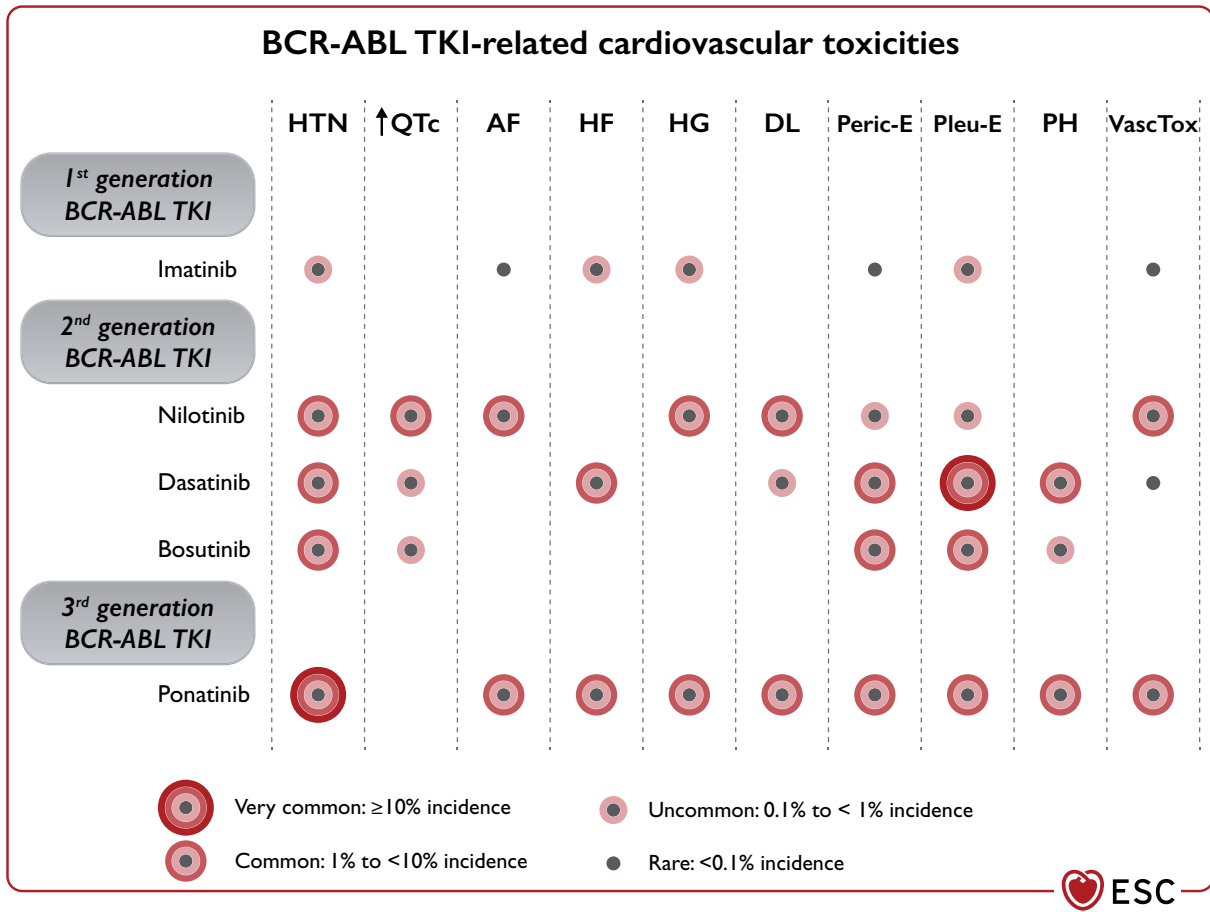
<sup>d</sup>Consider an ECG 2 weeks after starting treatment in high-risk patients and new monitoring in the case of any dose increase (see Section 6.4.2).

<sup>e</sup>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.

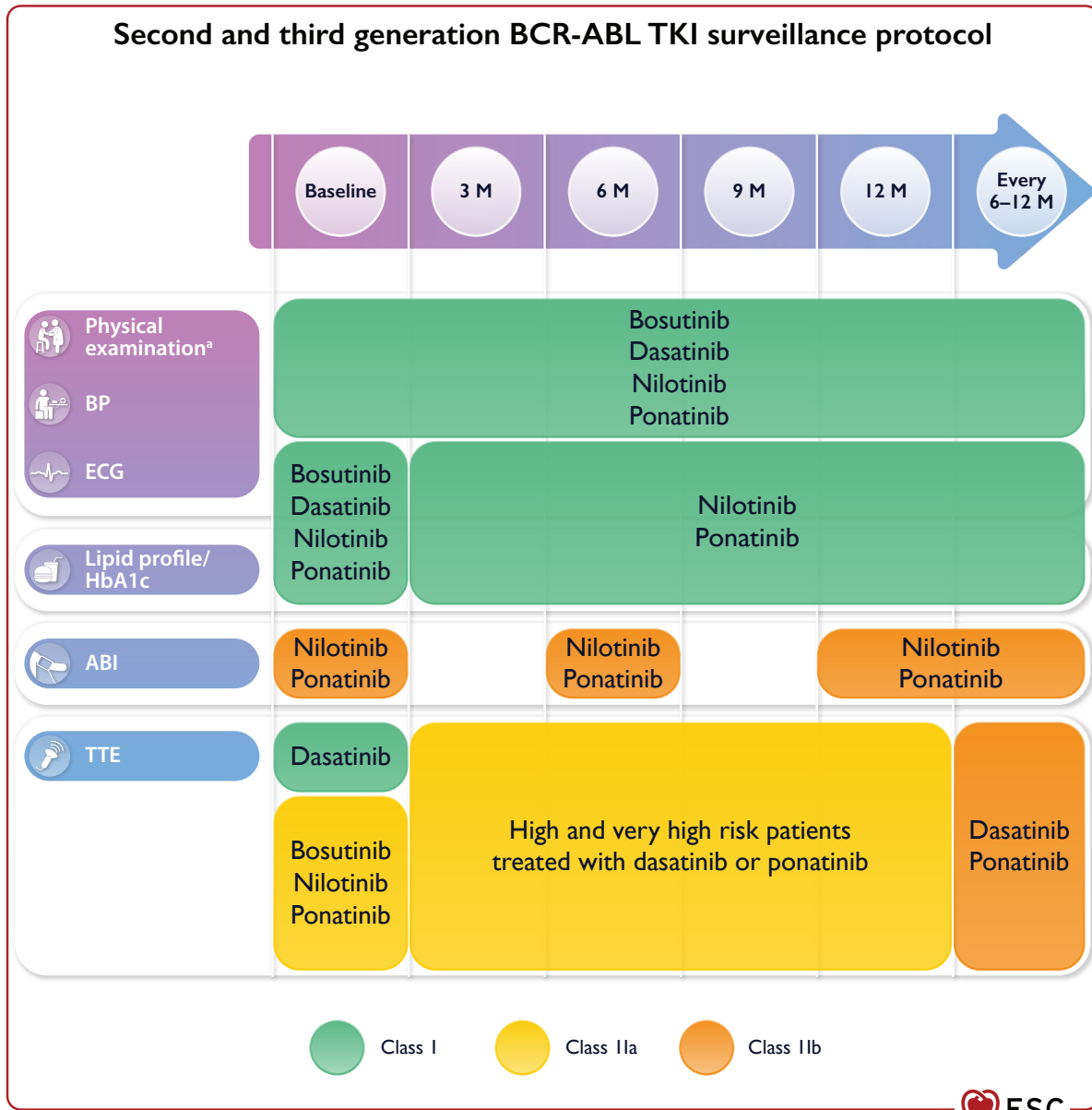
### 5.5.5. Multitargeted kinase inhibitors targeting BCR-ABL

Chronic myeloid leukaemia (CML) results from aberrant activation of ABL1 kinase due to a chromosomal translocation. Small-molecule TKIs targeting BCR-ABL—including imatinib, bosutinib, dasatinib, nilotinib, and ponatinib—have proven effective in the treatment of CML. The toxicities associated with these TKIs are unique and due to ‘off-target’ effects of each drug. Dasatinib is associated with group 1 pulmonary hypertension (PH), HF, and pleural and pericardial effusion, whereas nilotinib and ponatinib are generally associated with vascular events (Figure 14).<sup>131,256–259</sup> Second-generation BCR-ABL TKI may induce a QTc prolongation (see Section 6.4.2). CV toxicity risk is higher in patients aged >65 years (relative risk 1.8) and in those with underlying DM (relative risk 2.5), hypertension (relative risk 3.2) or pre-existing CAD (relative risk 2.6).<sup>256–258,260</sup> Before BCR-ABL TKI therapy, it is critical to define baseline CV toxicity risk with special attention to BP, glucose, and lipids.





**Figure 14** 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.<sup>261</sup> Figure developed from EMA prescribing information,<sup>252</sup> FDA prescribing information.<sup>253</sup>



**Figure 15** 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. <sup>a</sup>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.<sup>19</sup>

Baseline ECG is recommended in all patients and QTc monitoring in patients treated with second-generation BCR-ABL TKI. Depending on the type of therapy used, specific CV assessments should be performed after drug initiation (Figure 15).<sup>256</sup>

**Recommendation Table 11 — Recommendations for baseline risk assessment and monitoring during second- and third-generation breakpoint cluster region–Abelson oncogene locus tyrosine kinase inhibitors**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Baseline CV risk assessment <sup>c</sup> is recommended in patients who require second- or third-generation BCR-ABL TKI. <sup>256,261</sup>   | I                  | C                  |
| In patients treated with nilotinib or ponatinib, CV risk assessment <sup>c</sup> is recommended every 3 months during the first year and every 6–12 months thereafter. <sup>256,261</sup> | I                  | C                  |
| QTc <sup>d</sup> measurement should be considered at baseline, at 2 and 4 weeks after starting nilotinib, and 2 weeks after any dose increase. <sup>259</sup>                             | IIa                | C                  |
| Baseline echocardiography should be considered in all patients before starting second- and third-generation BCR-ABL TKI.  | IIa                | C                  |
| Baseline echocardiography is recommended in patients scheduled to receive dasatinib.  | I                  | C                  |
| Echocardiography should be considered every 3 months during the first year in high- and very high-risk patients receiving dasatinib or ponatinib.   | IIa                | C                  |
| Echocardiography may be considered every 6–12 months in patients who require long-term (>12 months) ponatinib or dasatinib.   | IIb                | C                  |
| Serial assessment of ankle brachial index may be considered to detect subclinical peripheral vascular disease.  | IIb                | C                  |

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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.<sup>19</sup>

<sup>d</sup>QTc interval using Fridericia correction (QTcF = QT/√RR) is the preferred method.

**5.5.6. Bruton tyrosine kinase inhibitors**

Bruton tyrosine kinase (BTK) inhibitors are increasingly used to treat lymphoid malignancies. Ibrutinib, a first-in-class irreversible

oral inhibitor of BTK, has proven highly effective in chronic lymphocytic leukaemia and related B-cell malignancies including mantle cell lymphoma, Waldenström macroglobulinemia, and marginal zone lymphomas.<sup>262</sup> These disorders are usually diagnosed in elderly patients in whom frequent comorbidities coexist at diagnosis that increase the risk of CTR-CVT.<sup>263,264</sup> Ibrutinib has been associated with bleeding diathesis, infections, and an increased risk of hypertension, AF, and HF.<sup>265–267</sup> Ibrutinib may also cause ventricular arrhythmias without prolonging QT.<sup>267,268</sup> Acalabrutinib is a second-generation BTK inhibitor with greater BTK selectivity. In a recent phase III, randomized, multicentre, open-label, non-inferiority study, acalabrutinib demonstrated a non-inferior progression-free survival compared to ibrutinib in patients with previously treated chronic lymphocytic leukaemia with a lower incidence of symptomatic CV events.<sup>269</sup> However, grade ≥3 AF (symptomatic AF where urgent intervention is indicated)<sup>270</sup> and AF in patients ≥75 years old or with previous AF history were comparable between groups, as was the risk of CV events in patients with pre-existing CVRFs or CVD.<sup>271</sup> Therefore, we currently do not have enough data to establish different monitoring strategies in patients treated with these drugs.

Due to the lack of evidence-based recommendations, the management of these CV events is challenging.<sup>264</sup> Antihypertensive initiation has been associated with a lower risk of a major adverse CV events (MACE).<sup>264</sup> Opportunistic screening for AF by pulse-taking or ECG rhythm strip is recommended at every clinical visit during BTK inhibitor therapy.<sup>272</sup>

Due to a higher bleeding risk, ibrutinib should be temporarily interrupted in patients requiring dual antiplatelet therapy (DAPT) and 3–7 days before invasive procedures. In case of emergency interventions, platelet transfusion should be considered to minimize bleeding risks.<sup>262</sup>

**Recommendation Table 12 — Recommendations for baseline risk assessment and monitoring during Bruton tyrosine kinase inhibitor therapy**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| <b>BP monitoring and management</b>  |                    |                    |
| BP measurement is recommended for patients treated with BTK inhibitors at every clinical visit. <sup>264</sup>                                   | I                  | B                  |
| Weekly home monitoring of BP during the first 3 months and every month thereafter should be considered for patients treated with BTK inhibitors. | IIa                | C                  |
| <b>Echocardiography</b>  |                    |                    |
| Baseline echocardiography is recommended in high-risk patients <sup>c</sup> scheduled to receive BTK inhibitors. <sup>267,268</sup>              | I                  | C                  |
| TTE is recommended in all patients who develop AF during BTK inhibitor therapy.  | I                  | C                  |

Continued

| AF   |     |
|--|-----|
| Opportunistic screening for AF by pulse-taking or ECG rhythm strip is recommended at every clinical visit during BTK inhibitor therapy. <sup>273</sup> | I C |

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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.

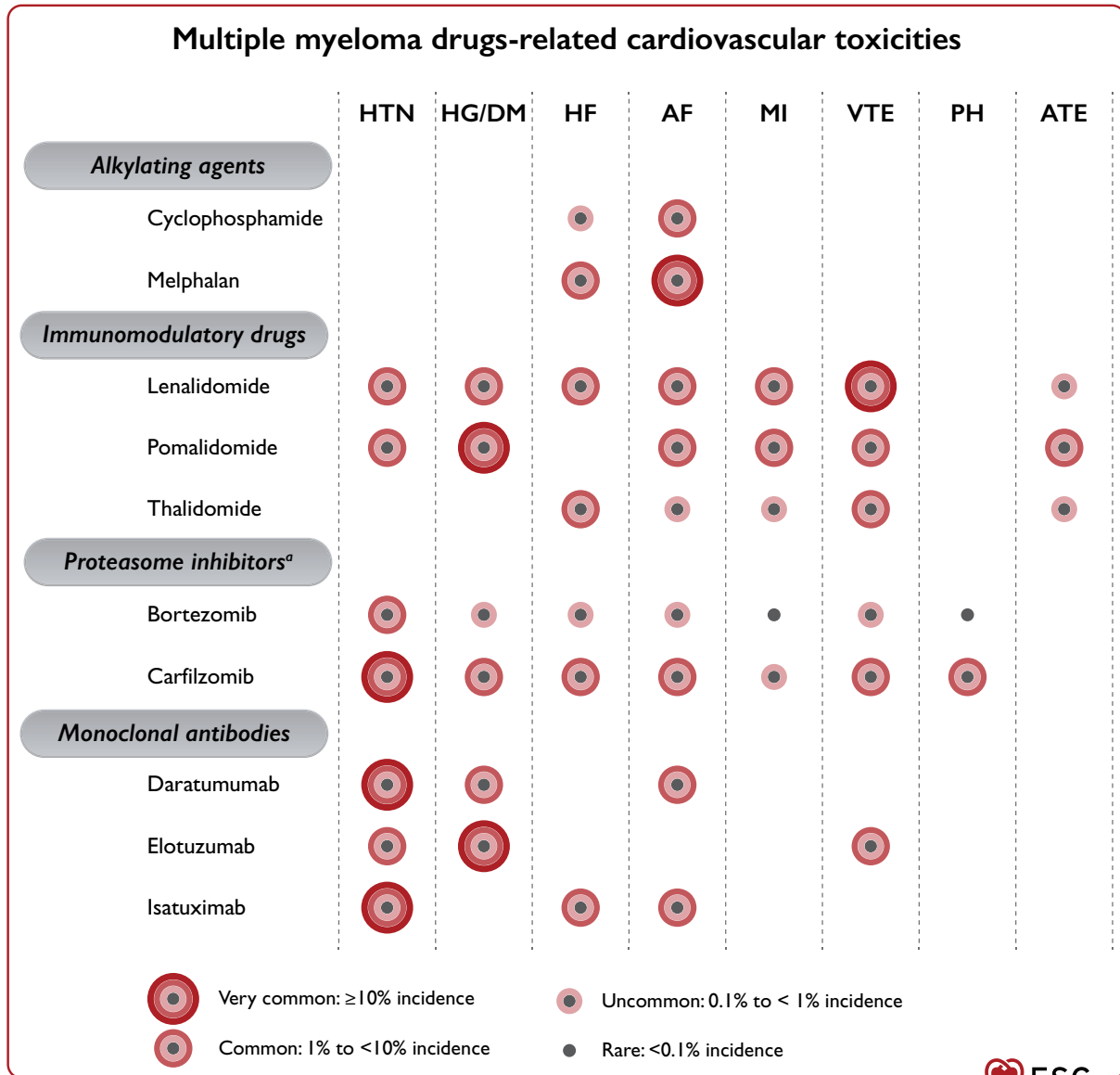
<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

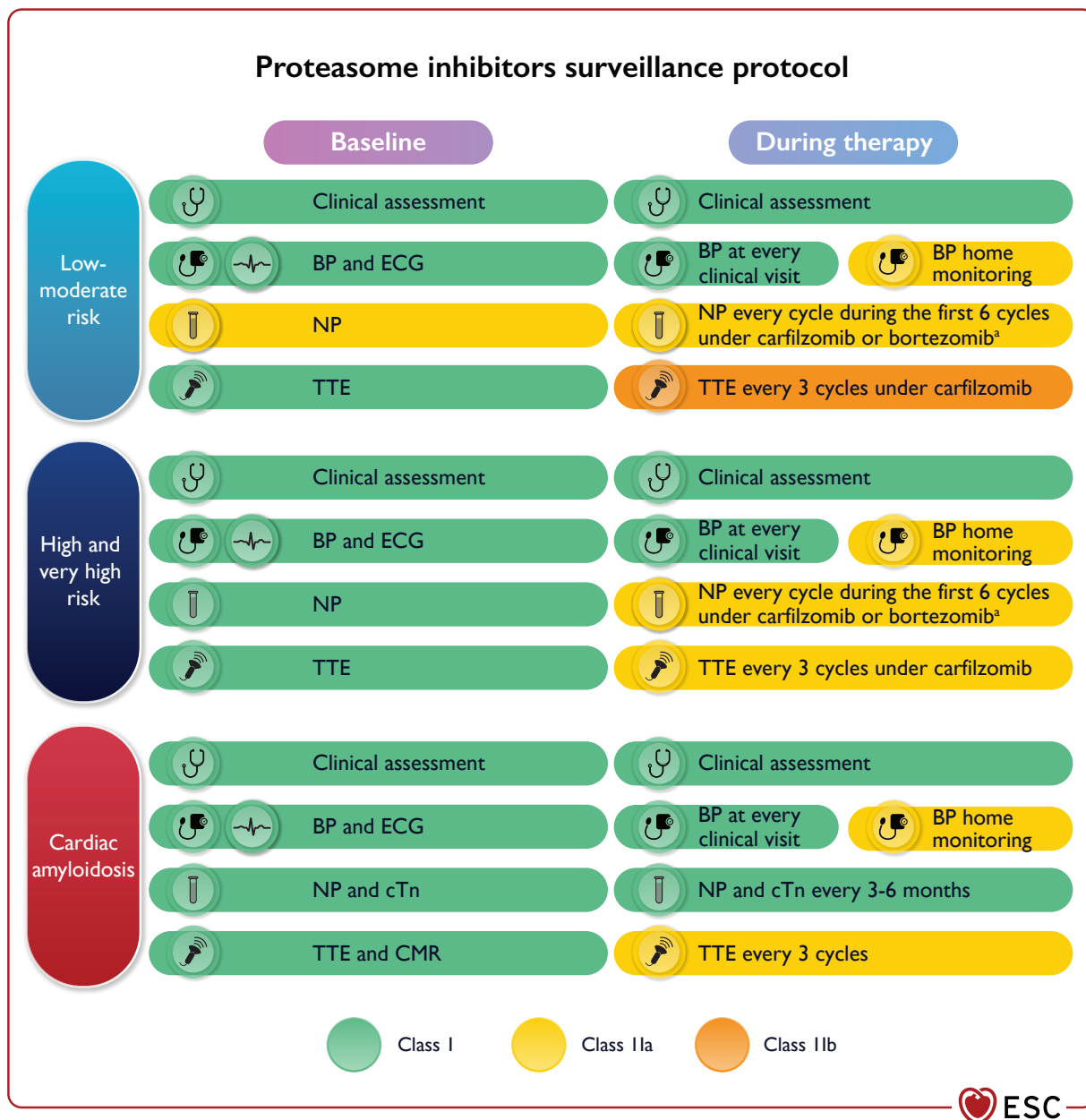
<sup>c</sup>Male, age ≥ 65 years, previous history of hypertension, DM, QTc ≥ 480 ms, AF, HF, cardiomyopathy, or severe VHD.<sup>263,274,275</sup>

### 5.5.7. Multiple myeloma therapies

There are many classes of pharmacotherapy that are approved for the treatment of MM using a range of combinations. These include immunomodulatory drugs (IMiD), dexamethasone, PI, and monoclonal antibodies (e.g. daratumumab). PI—including bortezomib, carfilzomib, and ixazomib—have become a mainstay of therapy for newly diagnosed MM as well as relapsed disease.<sup>276,277</sup> Several large studies using combination therapy for MM have demonstrated an increased risk of serious CV adverse events.<sup>278–281</sup> MM patients being treated with PI have a high incidence of coexistent CV comorbidities



**Figure 16** 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. <sup>a</sup>Ixazomib 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,<sup>252</sup> FDA prescribing information.<sup>253</sup>



**Figure 17** 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. <sup>a</sup>Every 2 months for patients treated with ixazomib.

and increased baseline CV risk.<sup>282,283</sup> PI have been associated with a variety of CV toxicities including hypertension, HF,<sup>284</sup> acute coronary syndromes (ACS),<sup>66</sup> arrhythmias,<sup>285</sup> PH,<sup>286</sup> and VTE (Figure 16).<sup>287,288</sup> During therapy, cardiac biomarkers and TTE are important diagnostic and prognostic tools that can inform clinical decision-making (Figure 17).<sup>66</sup>

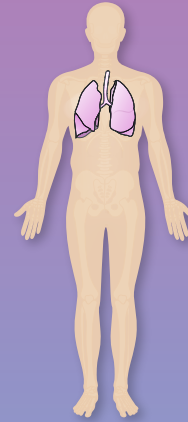
HF—especially HF with preserved ejection fraction (HFpEF)—is a frequent manifestation of cardiac amyloidosis, but it is also an important adverse effect of PI therapy, especially under carfilzomib.

In a safety analysis of patients with MM being treated with carfilzomib, 7.2% of patients were found to have new HF.<sup>284</sup> In another study, 23% of patients with MM treated with carfilzomib developed clinical HF and/or LVD.<sup>289</sup> The mechanism is not well understood but is possibly related to PI-induced oxidative stress within myocytes, inhibition of the proteasome, or transient endothelial dysfunction.<sup>281,283</sup> Although no studies have yet addressed the optimal follow-up scheme in patients with MM treated with PI, a common scheme consists of 3–6-monthly visits with ECG, complete blood

## Risk factors for venous thromboembolic events in patients with multiple myeloma

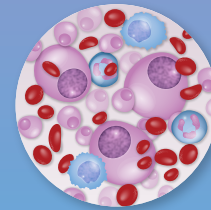
### Patient-related risk factors

- Previous VTE
- Acute infections
- Autoimmune disease
- Central venous catheter
- Chronic renal disease
- Cigarette smoking
- CVD
- DM
- General surgery
- History of inherited thrombophilia
- Immobilization, surgery, trauma
- Obesity (BMI >30 kg/m<sup>2</sup>)



### Myeloma-related risk factors

- Advanced disease status
- Erythropoietin-stimulating agents
- High dexamethasone doses
- Hyper-viscosity state
- Thalidomide/lenalidomide/ponalidomide



**Figure 18** Risk factors for venous thromboembolic events in patients with multiple myeloma. BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; VTE, venous thromboembolism.

tests (including NP and cTn) and echocardiography surveillance during PI therapy.<sup>290</sup> A recent prospective study of patients with relapsed MM confirmed the utility of NP to assist in risk stratification as well as management of CV morbidity during treatment.<sup>66</sup> Hypertension, another adverse effect of PI, may also contribute to the development of HFpEF.

Patients with MM are at elevated risk of thrombosis due to both patient- and myeloma-related factors, particularly the combination of PI and IMiD (Figure 18).<sup>279,287,291–297</sup> In the ASPIRE (Carfilzomib, Lenalidomide, and Dexamethasone vs. Lenalidomide and Dexamethasone for the Treatment of Patients with Relapsed Multiple Myeloma) study, patients treated

with a combination of carfilzomib, lenalidomide, and dexamethasone had higher rates of VTE compared with those treated with lenalidomide and dexamethasone (6.6% vs. 3.9%).<sup>279</sup> Oncological guidelines recommend the use of aspirin or prophylactic doses of low-molecular-weight heparins (LMWH) in low-risk patients receiving thalidomide- or lenalidomide-based regimens.<sup>298</sup> In patients at high risk of VTE, therapeutic doses of LMWH are recommended.<sup>299</sup> The role of non-vitamin K antagonist oral anticoagulants (NOAC) in MM patients needs further validation in larger trials, but recent small studies have confirmed the efficacy and safety of low doses of apixaban and rivaroxaban for VTE prevention.<sup>300–302</sup>



**Recommendation Table 13 — Recommendations for baseline risk assessment and monitoring during multiple myeloma therapies**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| <b>BP monitoring</b>   |                    |                    |
| BP measurement is recommended for patients treated with PI at every clinical visit.  | I                  | C                  |
| Home monitoring of BP weekly during the first 3 months and monthly thereafter should be considered for patients treated with PI.   | IIa                | C                  |
| <b>Cardiac serum biomarkers</b>  |                    |                    |
| Measurement of NP is recommended prior to PI in high- and very high-risk patients. <sup>66,303</sup>   | I                  | C                  |
| Measurement of NP should be considered prior to PI in low- and moderate-risk patients. <sup>66</sup>   | IIa                | C                  |
| In patients receiving carfilzomib or bortezomib, measurement of NP should be considered at baseline and every cycle during the first 6 cycles. <sup>c,66</sup>   | IIa                | B                  |
| NP and cTn measurements are recommended at baseline and every 3–6 months in patients with AL-CA. <sup>d,290</sup>  | I                  | B                  |
| <b>TTE</b>   |                    |                    |
| Baseline echocardiography, including assessment for AL-CA, is recommended in all patients with MM scheduled to receive PI.   | I                  | C                  |
| Echocardiography surveillance every 3 cycles should be considered in high- and very high-risk patients receiving carfilzomib. <sup>280</sup>   | IIa                | B                  |
| Echocardiography surveillance every 3 cycles may be considered in low- and moderate-risk patients receiving carfilzomib.   | IIb                | C                  |
| Echocardiography surveillance should be considered every 3–6 months in patients with AL-CA treated with PI. <sup>d,290</sup>   | IIa                | C                  |
| <b>VTE prophylaxis</b>   |                    |                    |
| Therapeutic doses of LMWH are recommended in patients with MM with previous VTE. <sup>296,298,302,304,305</sup>  | I                  | B                  |
| Prophylactic doses of LMWH are recommended in patients with MM with VTE-related risk factors <sup>e</sup> (excluding previous VTE) at least during the first 6 months of therapy. <sup>296,304,305</sup>                                   | I                  | A                  |
| Aspirin should be considered as an alternative to LMWH in patients with MM with no risk factors or one VTE-related risk factor <sup>e</sup> (excluding previous VTE) at least during the first 6 months of therapy. <sup>296,304–307</sup> | IIa                | B                  |

Continued

|  |            |          |
|--|------------|----------|
| Low doses of apixaban or rivaroxaban <sup>f</sup> may be considered as an alternative to LMWH or aspirin in patients with MM with VTE-related risk factors <sup>e</sup> (excluding previous VTE) at least during the first 6 months of therapy. <sup>300–302</sup> | <b>IIb</b> | <b>C</b> |
|--|------------|----------|

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Every 2 months for patients treated with oral ixazomib.

<sup>d</sup>Depending on HF severity and treatment.

<sup>e</sup>See Figure 18.<sup>295,296,299</sup>

<sup>f</sup>Low doses of apixaban (2.5 mg twice a day) or rivaroxaban (10 mg once a day).

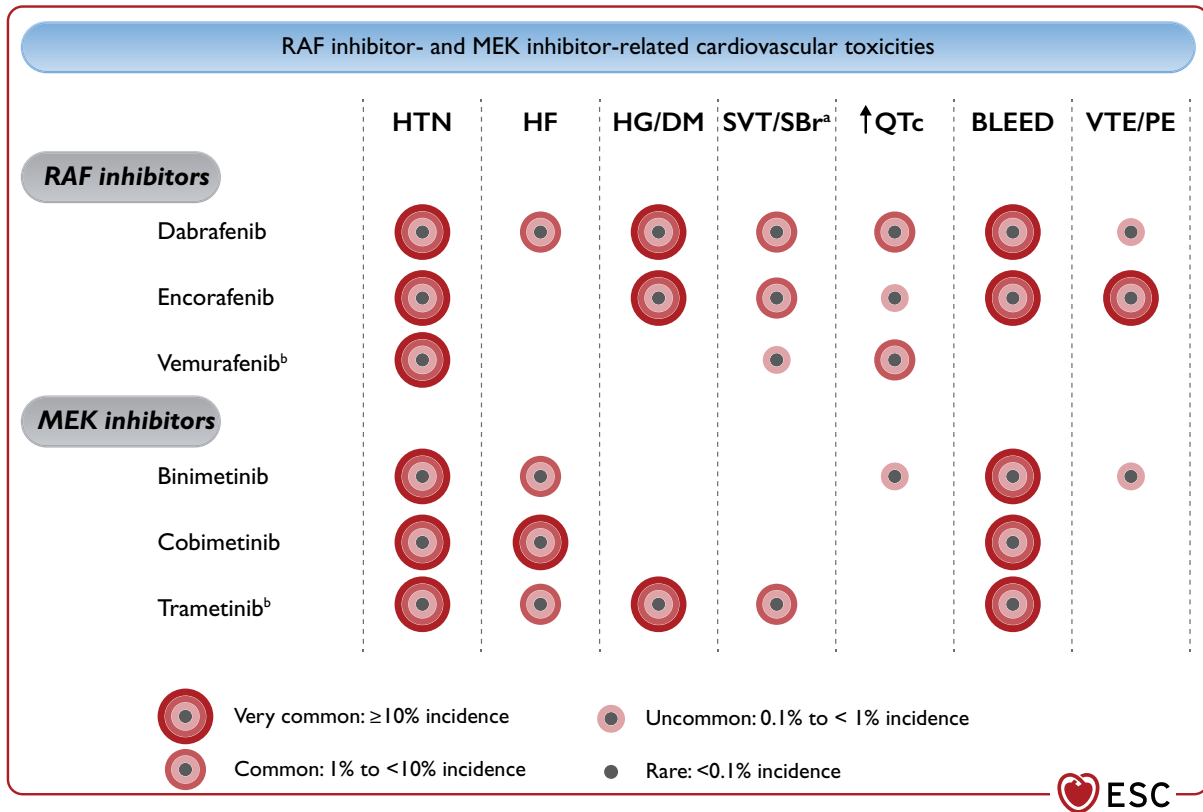
### 5.5.8. Rapidly accelerated fibrosarcoma and mitogen-activated extracellular signal-regulated kinase inhibitor treatment

The rapidly accelerated fibrosarcoma (RAF) inhibitors—vemurafenib, dabrafenib, and encorafenib—are approved for the treatment of metastatic melanoma with a *BRAF* V600 mutation. The mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors—trametinib, cobimetinib, binimetinib, and selumetinib—have also shown significant clinical activity in melanoma patients whose tumour contains a *BRAF* V600 mutation, and are now largely used in combination with RAF inhibitors. The main CV effects to be considered are hypertension, PE, and CTRCD, which are associated with all combinations of RAF and MEK inhibitors, and QTc prolongation, associated solely with the coadministration of cobimetinib and vemurafenib (Figure 19).<sup>12,308,309</sup> RAF inhibitor treatment alone or in combination with a MEK inhibitor is associated with an increased risk of MI and AF.<sup>308</sup>

Patients with cancer with pre-existing CVD have an increased frequency of CV adverse events during treatment with MEK and RAF inhibitors, and therefore baseline risk stratification is recommended.<sup>12</sup> Most cardiac complications induced by administration of MEK and RAF inhibitors seem to be attributable to the MEK inhibitor, with the RAF inhibitor enhancing the toxic effects of the MEK inhibitor.<sup>310–313</sup> Hypertension and LVD were twice as frequent when MEK and RAF inhibitors were coadministered compared with single therapy with RAF inhibitor alone.<sup>314</sup>

CTRCD can manifest any time from the first month of therapy to 2 years after the end of the oncological treatment.<sup>315</sup> Baseline TTE is recommended in patients at moderate to high risk of CTR-CVT. During treatment, it is necessary to monitor BP at each visit and promote weekly outpatient monitoring during the first 3 months and monthly thereafter. In patients treated with cobimetinib/vemurafenib, an ECG is recommended at 2 and 4 weeks after initiation of treatment and every 3 months thereafter. In high-risk patients, periodic monitoring of ventricular function with echocardiography should be considered every 6–12 months.

CV protective medications (such as angiotensin-converting enzyme inhibitors [ACE-I], angiotensin receptor blockers [ARB],



**Figure 19** 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 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. <sup>a</sup>Dabrafenib is related with SBr. Encorafenib is related with SVT. Vemurafenib rarely causes AF. Trametinib is related with bradycardia in some post-marketing reports. <sup>b</sup>Peripheral oedema is very common. Figure developed from EMA prescribing information,<sup>252</sup> FDA prescribing information.<sup>253</sup>

and beta-blockers) have not been evaluated in patients treated with MEK and RAF inhibitors but, from a mechanistic perspective, beta-blockers might prevent CTRCD induced by MEK inhibitors. The MEK/ERK pathway has a cardiac protective effect, regulated by beta-adrenergic signalling, which also controls the p38 mitogen-activated protein kinases pathway, associated with cardiotoxic effects. Beta-blockers might exert their cardioprotective effects by reducing p38 signalling.<sup>315</sup>

**Recommendation Table 14 — Recommendations for baseline risk assessment and monitoring during combined rapidly accelerated fibrosarcoma and mitogen-activated extracellular signal-regulated kinase inhibitor therapy**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| BP monitoring at each clinical visit and weekly outpatient monitoring during the first 3 months of treatment and monthly thereafter is recommended.                | I                  | C                  |
| In patients treated with cobimetinib/vemurafenib, an ECG is recommended at 2 and 4 weeks after initiation of treatment and every 3 months thereafter. <sup>c</sup> | I                  | C                  |
| Baseline echocardiography is recommended in all high- and very high-risk patients scheduled to receive combined RAF and MEK inhibitors.                            | I                  | C                  |
| Baseline echocardiography may be considered in low- and moderate-risk patients scheduled to receive combined RAF and MEK inhibitors.                               | IIb                | C                  |
| Echocardiography should be considered 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.

<sup>a</sup>Class of recommendation.

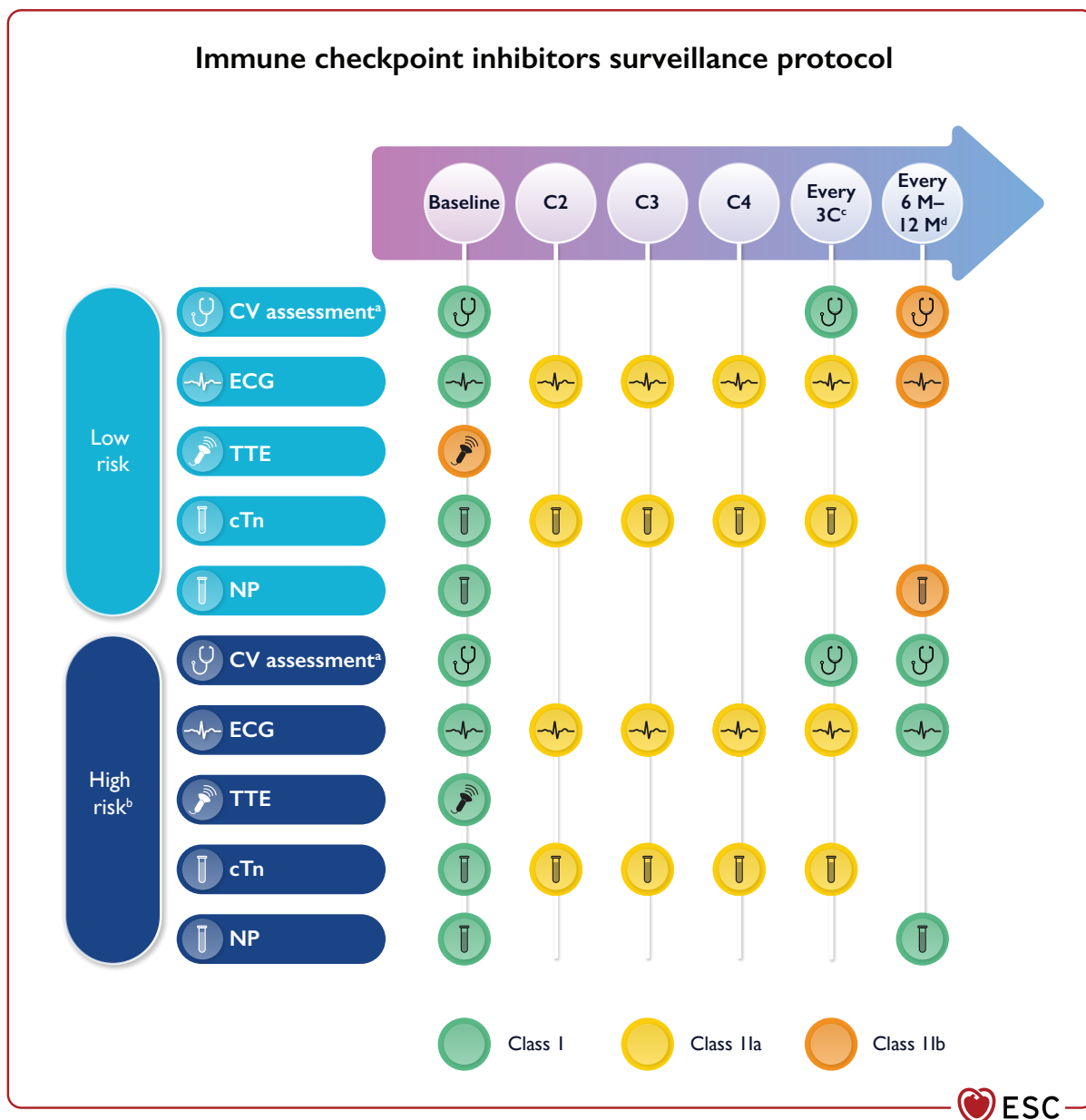
<sup>b</sup>Level of evidence.

<sup>c</sup>Consider an ECG and new monitoring in the case of any dose increase (see Section 6.4.2).

### 5.5.9. Immune checkpoint inhibitors

Immunotherapies, which harness the immune system to destroy cancer cells, come in different forms but the most widely used are ICI.<sup>316</sup> The immune checkpoints are proteins expressed in the T cells that inhibit their activation when they contact a body cell. ICI include monoclonal antibodies that block the immune brakes or regulators, cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) (ipilimumab,

tremelimumab), programmed death-1 (PD-1) (nivolumab, cemiplimab, pembrolizumab), and programmed death-ligand 1 (PD-L1) (atezolizumab, avelumab, durvalumab) expressed in the cancer cells, with the consequent cytotoxic immune response. By blocking these checkpoints from binding with their partner proteins, ICI inhibit the 'off' signal, activating T cells and promoting killing of cancer cells. Although their pathophysiology is not clearly defined, ICI may also trigger an



**Figure 20** 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. <sup>a</sup>Including physical examination, BP, lipid profile, and HbA1c. <sup>b</sup>Dual ICI, combination ICI-cardiotoxic therapy, ICI-related non-CV events, prior CTRCD or CVD. <sup>c</sup>Every three cycles until completion of therapy to detect subclinical ICI-related CV toxicity. <sup>d</sup>In patients who require long-term (>12 months) ICI treatment.

overactivation of T cells against non-cancerous tissues, leading to immune-related adverse events.<sup>317</sup> Immune-related CV side effects may lead to life-threatening CV complications such as fulminant myocarditis, myopericarditis, cardiac dysfunction, arrhythmias, or MI, which often results in the discontinuation of ICI.<sup>318,319</sup>

The largest case series of 122 patients with ICI-associated myocarditis had early onset of symptoms (median of 30 days after initial exposure to ICI), and up to 50% died.<sup>320</sup> Late CV events (>90 days) are less well characterized but generally exhibit a higher risk of non-inflammatory HF, progressive atherosclerosis, hypertension, and mortality rates.<sup>321</sup> Other CV toxicities described during ICI therapy are MI, AV block, supra-ventricular and ventricular arrhythmias, sudden death, Takotsubo-like syndrome, non-inflammatory HF, hypercholesterolaemia, pericarditis, pericardial effusion, ischaemic stroke, and VTE.<sup>322</sup> A meta-analysis including 32 518 patients receiving ICI treatment reported an increased risk of myocarditis, pericardial diseases, HF, dyslipidaemia, MI, and cerebral arterial ischaemia.<sup>323</sup> Conditions related with high baseline ICI-related CV toxicity risk include dual ICI therapy (e.g. ipilimumab and nivolumab), combination ICI therapy with other cardiotoxic therapies, and patients with ICI-related non-CV events or prior CTRCD or CVD (Figure 20).<sup>324,325</sup> All patients on ICI treatment should have an ECG and troponin assay at baseline (Figure 20).<sup>326–329</sup> High-risk patients should additionally have a TTE evaluation at baseline. Due to the lack of evidence-based recommendations, the monitoring of ICI therapy is challenging. Once started on therapy, ECG, cTn, and NP should be checked.<sup>330–332</sup> In the JAVELIN trial, which assessed avelumab plus axitinib vs. sunitinib, no clinical value was observed for on-treatment routine TTE monitoring in asymptomatic patients.<sup>333</sup> However, in high-risk patients, and in those with high baseline cTn levels, TTE monitoring may be considered. In patients who develop ECG abnormalities, new biomarker changes, or new cardiac symptoms at any time, prompt cardio-oncology evaluation is strongly recommended, including TTE for the evaluation of LVEF and GLS, and CMR when myocarditis is suspected (Table 3).<sup>334</sup>

### Recommendation Table 15 — Recommendations for baseline risk assessment and monitoring during immunotherapy

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| ECG, NP, and cTn measurements are recommended in all patients before starting ICI therapy. <sup>333</sup>               | I                  | B                  |
| Baseline echocardiography is recommended in high-risk patients <sup>c</sup> before starting ICI therapy. <sup>333</sup> | I                  | B                  |
| Baseline echocardiography may be considered in all patients before starting ICI therapy.                                | Iib                | C                  |

Continued

|   |     |   |
|---|-----|---|
| Serial ECG and cTn measurements should be considered 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. <sup>333</sup> | Ila | B |
| CV assessment <sup>d</sup> is recommended every 6–12 months in high-risk patients <sup>c</sup> who require long-term (>12 months) ICI treatment. <sup>321–323,335,336</sup>   | I   | C |
| CV assessment <sup>d</sup> may be considered every 6–12 months in all patients who require long-term (>12 months) ICI treatment.  | Iib | C |

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Dual ICI, combination ICI-cardiotoxic therapy; ICI-related non-CV events, prior CTRCD, or CVD.

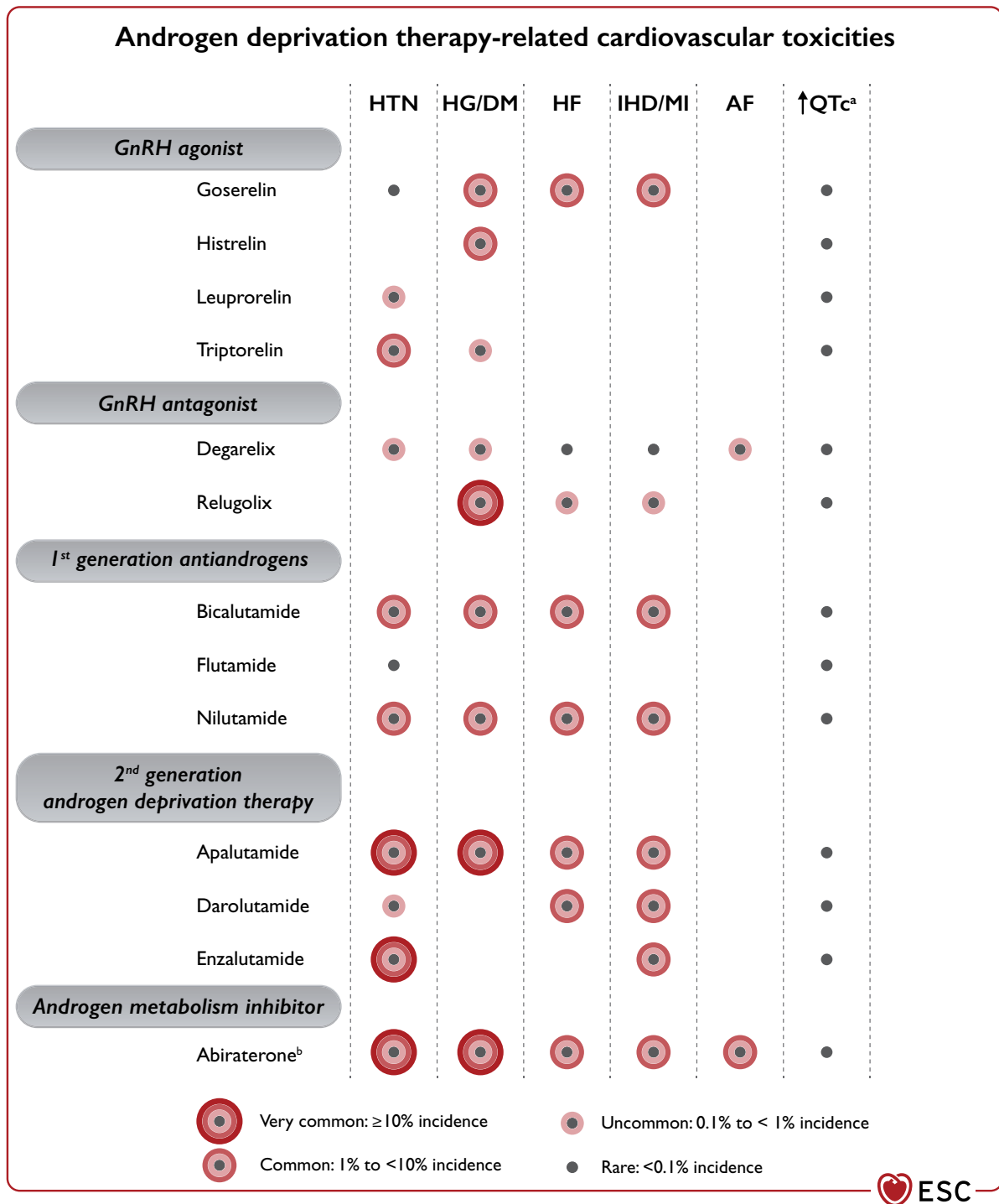
<sup>d</sup>Physical examination, BP, NP (BNP or NT-proBNP), lipid profile, HbA1c, and ECG.

### 5.5.10. Androgen deprivation therapies for prostate cancer

Androgen deprivation therapy (ADT) is prescribed in 40% of men with prostate cancer as neoadjuvant and/or adjuvant therapy to RT or for biochemical relapse following prostate cancer surgery. Gonadotropin-releasing hormone (GnRH) agonists are the most frequently prescribed ADT. However, GnRH agonists are associated with an increased CV risk and mortality, particularly in patients with prostate cancer aged >60 years.<sup>337,338</sup> Baseline risk stratification in patients requiring GnRH agonists depends on vascular disease risk (Figure 21).<sup>339,340</sup> No dedicated CV toxicity risk calculators have been developed for patients receiving ADT. It was the consensus of the authors to recommend SCORE2 or SCORE2-OP to stratify CV risk in patients receiving ADT without previous CVD.<sup>19</sup>

The use of GnRH antagonists represents an alternative in the treatment of prostate cancer, and preclinical and clinical (HERO trial)<sup>341</sup> data suggest that GnRH antagonist use is associated with significantly lower overall mortality and CV events compared with agonists.<sup>342</sup> However, more research is needed in this field. In the PRONOUNCE trial, no difference in MACE at 1 year was observed between degarelix (a GnRH antagonist) and leuprolide (a GnRH agonist), although the trial was stopped early.<sup>343</sup> Lower CV event rates were detected compared with previous studies and all patients were reviewed by a cardiologist at enrolment (leading to optimal CVRF management).<sup>343</sup>

The main CV effects to be considered are hypertension, DM, ischaemic heart disease (IHD) and CTRCD.<sup>339,344</sup> ADT is uncommonly associated with QTc prolongation and rarely causes torsade de pointes (TdP) through blockade of testosterone effects on ventricular repolarization.<sup>345,346</sup> ECG monitoring and correction of QT prolongation precipitant factors (see Section 6.4.2; Table 9; Supplementary data, Table S13) is recommended<sup>340,347,348</sup> during prostate cancer treatment if the baseline QTc interval is prolonged.<sup>49,339,340,347,349,350</sup>



**Figure 21** 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. <sup>a</sup>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. <sup>b</sup>Increased risk of QTc prolongation in combination with ADT. <sup>49,339,340,349,350</sup> Figure developed from EMA prescribing information, <sup>252</sup> FDA prescribing information. <sup>253</sup>

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### Recommendation Table 16 — Recommendations for baseline risk assessment and monitoring during androgen deprivation therapy for prostate cancer

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Baseline CV risk assessment <sup>c</sup> and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP <sup>d</sup> is recommended in patients treated with ADT without pre-existing CVD. <sup>19,341,342</sup> | I                  | B                  |
| Baseline and serial ECGs are recommended in patients at risk of QTc prolongation during ADT therapy. <sup>e,339–342</sup>   | I                  | B                  |
| A GnRH antagonist should be considered in patients with pre-existing symptomatic CAD <sup>f</sup> who require ADT. <sup>341,342</sup>   | IIa                | B                  |
| Annual CV risk assessment <sup>c</sup> is recommended during ADT. <sup>19,339,341,342</sup>   | I                  | B                  |

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>BP, lipids, fasting glucose, HbA1c, ECG, and patient education on healthy lifestyle and lifestyle risk factor control is recommended.

<sup>d</sup>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%.

<sup>e</sup>See Table 9.

<sup>f</sup>CCS and ACS.

#### 5.5.11. Endocrine therapies for breast cancer

Endocrine therapy is a common treatment as 65–70% of all early and metastatic BC patients develop hormone receptor-positive disease.<sup>22</sup> Selective oestrogen receptor modulators (tamoxifen, toremifene) or aromatase inhibitors (AI) (letrozole, anastrozole, or exemestane) are recommended in early BC (EBC) according to menopausal status, comorbidities, and the risk of disease relapse. The use of AI in combination with cyclin-dependent kinase (CDK) 4/6 inhibitors is recommended as first- or second-line therapy in patient with hormone receptor-positive/HER2-negative metastatic BC.

The use of AI increases the risk of dyslipidaemia, metabolic syndrome, hypertension, HF, and MI.<sup>339</sup> In the ATAC ('Arimidex' and Tamoxifen Alone or in Combination) trial, anastrozole-treated patients with pre-existing CAD experienced more CV events (17% vs. 10%) and cholesterol level elevation (9% vs. 5%) than those treated with tamoxifen.<sup>351,352</sup> Similarly, HF was significantly more common with letrozole compared with tamoxifen in the BIG (Breast International Group) 1–98 trial.<sup>353</sup> Longer AI treatment duration was associated with increased odds of developing CVD in two large meta-analyses.<sup>354,355</sup> Significantly increased VTE risk has been consistently demonstrated with tamoxifen<sup>351,353</sup> and it is not recommended in patients with thrombotic risks. Toremifene and

high-dose tamoxifen were found to prolong QTc interval<sup>339,340</sup>; however, no risk data have been published in patients treated with the standard tamoxifen dose used in BC (20 mg/day).

The risks of VTE, hypercholesterolaemia, and CVD should be discussed with patients, while recognizing that the absolute benefits of preventing BC recurrence usually outweigh the CV risks.<sup>339</sup> In patients <70 years old without clinical manifestations of atherosclerotic disease, estimation of 10-year fatal and non-fatal CVD risk with SCORE2 (if ≥70 years, SCORE2-OP) is recommended.<sup>19</sup> Cholesterol levels and BP should be monitored regularly in patients receiving AI.<sup>356</sup> Physical activity and healthy diet are also advised to reduce weight and cholesterol levels. Smoking cessation is strongly recommended to reduce CV risk (e.g. CAD during AI therapy and VTE during tamoxifen therapy).

### Recommendation Table 17 — Recommendations for baseline risk assessment and monitoring during endocrine therapy for breast cancer

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Baseline CV risk assessment <sup>c</sup> and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP <sup>d,e</sup> is recommended in BC patients receiving endocrine therapies without pre-existing CVD. <sup>19</sup> | I                  | C                  |
| Annual CV risk assessment <sup>c</sup> is recommended during endocrine therapy in BC patients with high 10-year risk of (fatal and non-fatal) CV events according to SCORE2/SCORE2-OP. <sup>d,e</sup>                                       | I                  | C                  |
| CV risk assessment <sup>c</sup> should be considered 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. <sup>d,e</sup>  | IIa                | C                  |

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>BP, lipids, fasting glucose, HbA1c, ECG and patient education on healthy lifestyle and lifestyle risk factor control.

<sup>d</sup>Or other validated CV risk scores.

<sup>e</sup>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%.<sup>19</sup>

#### 5.5.12. Cyclin-dependent kinase 4/6 inhibitors

The use of CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) in combination with endocrine therapy is approved for the treatment of patients with hormone receptor-positive/HER2-negative metastatic BC. This combination has resulted in improvements in progression-free survival and, in some trials, overall survival.<sup>357–359</sup> CDK 4/6 inhibitors have demonstrated a potential for QT prolongation,<sup>339,360</sup> particularly with ribociclib. The phase III trials of ribociclib incorporated routine ECG monitoring.<sup>361–368</sup>



Baseline ECG is recommended and ECGs should be repeated at day 14 of the first cycle, before the second cycle, with any dose increase and as clinically indicated.<sup>357</sup>

In patients who already have, or are at significant risk of developing, QT prolongation (Section 6.4.2), the risks/benefits for ribociclib should be discussed by a MDT. Importantly, the use of ribociclib should be avoided in combination with drugs known to prolong QT interval and/or strong CYP3A inhibitors.<sup>357</sup>

The prescribing information does not recommend ribociclib in combination with tamoxifen due to a higher risk of QTc prolongation.<sup>252,367</sup>

**Recommendation Table 18 — Recommendations for baseline risk assessment and monitoring during cyclin-dependent kinase 4/6 inhibitor therapy**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| QTc <sup>c,d</sup> monitoring is recommended at baseline and 14 and 28 days in all patients with cancer receiving ribociclib. <sup>361,365,367,368</sup>   | I                  | A                  |
| QTc <sup>c,d</sup> monitoring is recommended in patients treated with ribociclib with any dose increase. <sup>361,365,367,368</sup>  | I                  | B                  |
| QTc <sup>c</sup> monitoring should be considered in patients treated with palbociclib or abemaciclib who have a baseline QTc above the normal range <sup>c</sup> or other conditions that may prolong the QTc interval. <sup>e</sup> | IIa                | C                  |

QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction.  
<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

<sup>c</sup>QT interval using Fridericia correction ( $QTcF = QT / \sqrt{RR}$ ) 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.<sup>369</sup>

<sup>d</sup>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.

<sup>e</sup>See Section 6.4.2 and Table 8.

**5.5.13. Anaplastic lymphoma kinase inhibitors**

Patients with cancer treated with anaplastic lymphoma kinase (ALK) inhibitors may develop adverse CV events including sinus bradycardia, AV block, QTc prolongation, hypertension, hyperglycaemia, and dyslipidaemia.<sup>370,371</sup> ACS and HF have rarely been described under crizotinib.<sup>372</sup> A baseline ECG is recommended in patients prior to starting an ALK inhibitor, especially crizotinib, and patients may have an ECG 4 weeks after the start of treatment and every 3–6 months thereafter, particularly if the baseline ECG is abnormal. Home BP monitoring should be considered in patients treated with brigatinib or lorlatinib. Patients receiving lorlatinib or

crizotinib treatment should have cholesterol levels checked every 3–6 months and treated if elevated.

**5.5.14. Epidermal growth factor receptor inhibitors**

Osimertinib is an oral irreversible, epidermal growth factor receptor (EGFR)-TKI approved for patients with non-small cell lung cancer expressing EGFR mutations. Recent data have shown that osimertinib is associated with an increased risk of QTc prolongation, AF, VTE, LVD, and HF (Figure 22).<sup>373,374</sup> A study of 123 patients with EGFR-mutant non-small cell lung cancer treated with osimertinib reported a 4.9% incidence of HF or MI and a significant decrease in LVEF <53% in 11% of patients with TTE surveillance.<sup>375</sup> Pre-existing hypertension and older age are risk factors for LVD and HF (3.9% and 2.6% incidence, respectively).<sup>376</sup> LVD and HF were more common during the first year of therapy.<sup>376</sup>

Baseline CV risk stratification, ECG and TTE prior to starting osimertinib is recommended. Three-monthly echocardiographic surveillance for new LVD during osimertinib treatment should be considered. Close monitoring of magnesium levels is also recommended to minimize the risk of osimertinib-induced hypomagnesaemia and QTc prolongation.

**Recommendation Table 19 — Recommendations for baseline risk assessment and monitoring during anaplastic lymphoma kinase and epidermal growth factor receptor inhibitors**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Baseline CV risk assessment <sup>c</sup> is recommended in patients before ALK inhibitors and EGFR inhibitors.         | I                  | C                  |
| Baseline echocardiography is recommended in all patients with cancer before starting osimertinib. <sup>376</sup>       | I                  | B                  |
| Home BP monitoring should be considered for patients treated with brigatinib, crizotinib, or lorlatinib.               | IIa                | C                  |
| Cholesterol profile assessment every 3–6 months should be considered for patients on crizotinib and lorlatinib.        | IIa                | C                  |
| Echocardiography should be considered every 3 months in patients during osimertinib therapy. <sup>376</sup>            | IIa                | B                  |
| ECG should be considered 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.

<sup>a</sup>Class of recommendation.

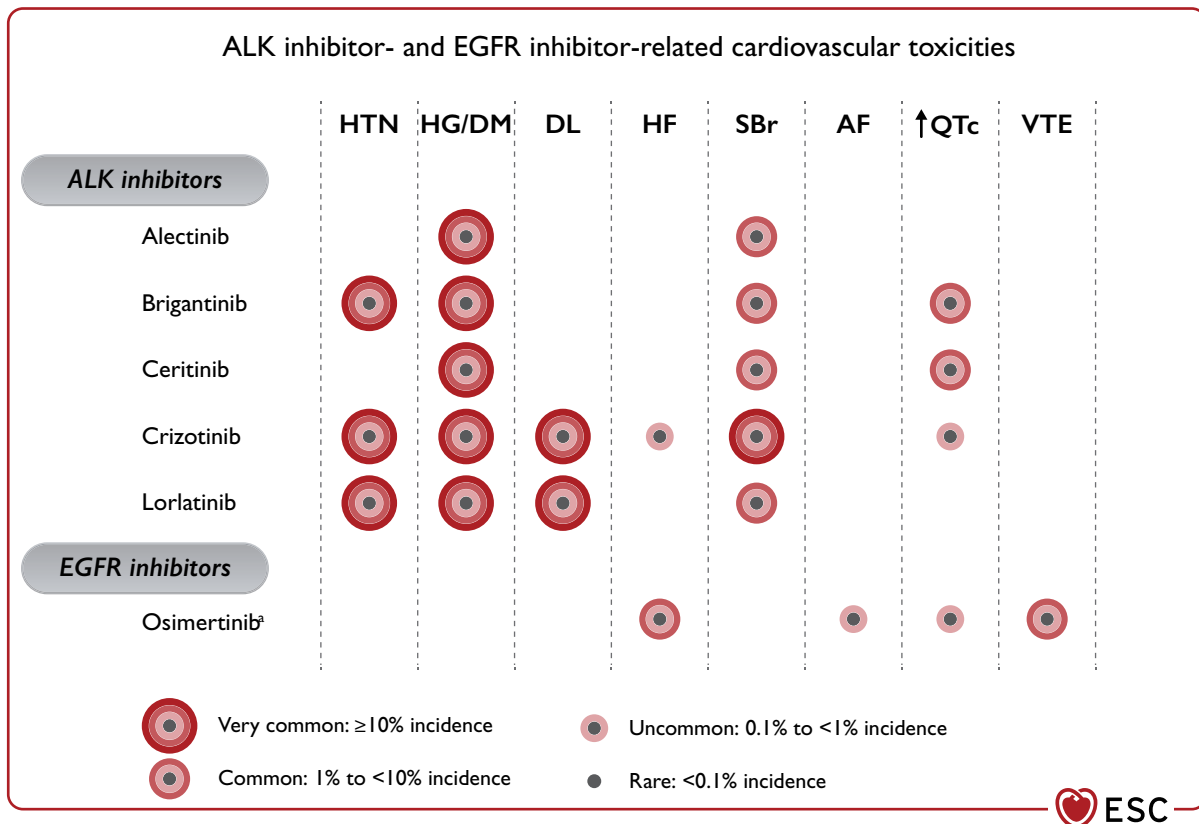
<sup>b</sup>Level of evidence.

<sup>c</sup>Physical examination, BP measurement, ECG, lipid profile, and HbA1c measurement.

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**Figure 22** 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. <sup>a</sup>Osimertinib increases the risk of hypomagnesaemia. Figure developed from EMA prescribing information, <sup>252</sup> FDA prescribing information. <sup>253</sup>

### 5.5.15. Chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies

CAR-T therapy is used for the treatment of acute lymphocytic leukaemia and aggressive B-cell lymphomas. <sup>377</sup> Although the reported incidence is variable, there is a growing recognition of the association between CAR-T therapy and CTR-CVT, including LVD, HF, cardiac arrhythmias, pericardial effusion, TTS, and cardiac arrest. <sup>378–383</sup> The majority of the described CV toxicities have been shown to be associated with the occurrence of cytokine release syndrome (CRS). <sup>377,384</sup> Baseline CV evaluation including ECG, NP, and cTn is recommended in all patients. Baseline TTE should also be considered, especially in patients with pre-existing CVRF and CVD. After receiving CAR-T therapy, patients may develop systemic inflammatory syndromes. <sup>385</sup> CRS should be suspected when a patient develops fever, with or without tachypnoea, tachycardia, hypotension, hypoxia, and/or other end-organ dysfunction hours to days after treatment. <sup>385</sup> A high index of suspicion is necessary to diagnose

CRS and to distinguish it from other conditions that occur in these settings (infections, HF, drug reactions, and PE). <sup>378,386</sup> Among adults, there was a relationship between CRS and CV events. An elevation in cTn is commonly seen in patients with CRS and is associated with an increased risk for subsequent CV events. <sup>378</sup> In a recent retrospective pharmacovigilance study, CAR-T was associated with tachyarrhythmias (AF the most common, followed by ventricular arrhythmias), cardiomyopathy, and pleural and pericardial diseases. <sup>379</sup> Globally, the fatality rate of CV and pulmonary adverse events was 30.9%. <sup>378,379,387</sup> Early cardiac evaluation in patients with cTn increase should include NP, ECG, and echocardiography (see [Section 6.1.4](#) for management). <sup>388</sup>

Adoptive cellular therapy with TIL has emerged as an effective treatment option for unresectable stage III/IV metastatic melanoma. With TILs, the CV toxicity appears to be related to direct myocardial and vascular toxicity. <sup>380</sup> Baseline assessment and CV surveillance in patients before TIL therapies is the same pathway recommended for CAR-T therapies.

**Recommendation Table 20 — Recommendations for baseline risk assessment and monitoring in patients receiving chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Baseline ECG, NP, and cTn are recommended in all patients with cancer before starting CAR-T and TIL therapies. <sup>388</sup>        | I                  | C                  |
| A baseline echocardiography is recommended in patients with pre-existing CVD before starting CAR-T and TIL therapies. <sup>388</sup> | I                  | C                  |
| A baseline echocardiography should be considered before starting CAR-T and TIL therapies. <sup>388</sup>                             | IIa                | C                  |
| Measurement of NP, cTn, and echocardiography are recommended in patients who develop CRS of ASTCT $\geq 2$ . <sup>c,378,388</sup>    | I                  | C                  |

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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  $\pm$  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.

**5.5.16. Radiotherapy**

RT increases the risk of developing subsequent CVD and peripheral artery disease (PAD).<sup>173,389–394</sup> There is ongoing debate regarding the safest radiation dose, which cardiac substructures are most sensitive to RT-induced injury, and the most appropriate strategies to minimize RT-related CVD.<sup>395,396</sup> The heart is considered a radiosensitive ‘organ at risk’ during RT and radiation exposure to the heart should be kept as low as reasonably achievable because there is no ‘safe’ dose (Figure 23).<sup>389,390</sup> RT-induced CV toxicity risk categorization based on MHD<sup>389,397</sup> is recommended over categorization based on prescribed dose, which may not accurately reflect cardiac radiation exposure (e.g. 35 Gray [Gy] prescribed dose to approximately 70% of the heart is equivalent to approximately 25 Gy MHD, whereas 35 Gy prescribed dose to approximately 40% of the heart is equivalent to approximately 15 Gy MHD). However, MHD is not a perfect metric, and in some patients, a very small portion of the heart might be irradiated to a very high dose, still conveying a substantial risk despite a low MHD.<sup>398</sup> Therefore, depending on dose distribution and exposure of specific cardiac substructures and CVRFs, the cancer treatment team may judge the patient to belong to a higher-risk category.<sup>397,399–401</sup>

Strategies to prevent and attenuate CV complications of RT have focused on reducing radiation exposure of the heart and CV substructures during cancer treatment and include the following.

- (1) Modification of cancer management to omit RT. This emphasizes the importance of integrating a personalized cardio-oncology evaluation.<sup>402–404</sup>
- (2) Modification of the dose and volume of RT treatments where possible. RT protocols should target the minimum volume required to the minimum dose needed to obtain the desired clinical benefit.
- (3) Modification of delivery techniques to reduce cardiac radiation exposure should lead to a considerable reduction in risk. Modern heart-sparing RT strategies include: the optimal use of modern intensity-modulated photon RT technologies; the use of deep inspiration breath-hold or respiratory-gated techniques in BC,<sup>405</sup> lymphoma,<sup>406</sup> and lung cancer;<sup>407</sup> or the use of image-guided RT to ensure accuracy of delivery and proton beam therapy.<sup>408</sup>

The incidence of cardiac events following RT may vary according to patient risk factors and synergistic effects of radiation with other cardiotoxic cancer treatments.<sup>12,173</sup>

There are no known RT-specific secondary preventative measures (e.g. drug treatments) to reduce the risk of CV events following RT. However, given the known importance of conventional CVRF on the incidence of RT-related events, optimization of modifiable CVRF is recommended in all patients before and after RT.

**Recommendation Table 21 — Recommendations for baseline risk assessment of patients before radiotherapy to a volume including the heart**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Baseline CV risk assessment <sup>c</sup> and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP <sup>d</sup> is recommended. <sup>19,389</sup> | I                  | B                  |
| Baseline echocardiography should be considered in patients with previous CVD before RT to a volume including the heart.   | IIa                | C                  |

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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.

<sup>a</sup>Class of recommendation.

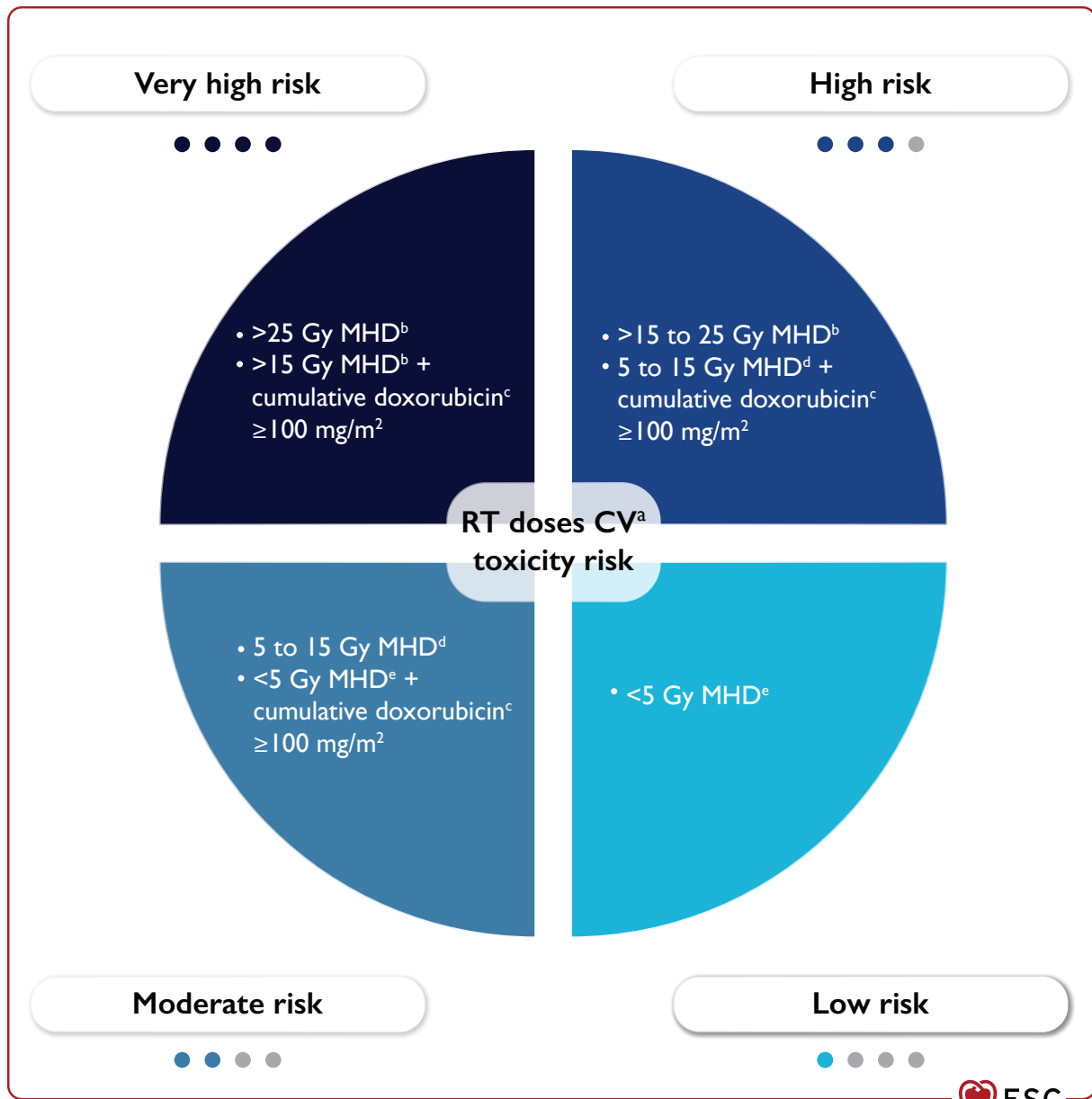
<sup>b</sup>Level of evidence.

<sup>c</sup>BP, lipids, fasting glucose, HbA1c, ECG and patient education on healthy lifestyle and lifestyle risk factor control.

<sup>d</sup>SCORE2 (<70 years) or SCORE2-OP ( $\geq 70$  years) CV risk stratification: <50 years: low risk <2.5%, moderate risk 2.5% to <7.5%, high risk  $\geq 7.5\%$ ; 50–69 years: low risk <5%; moderate risk 5% to <10%; high risk  $\geq 10\%$ ;  $\geq 70$  years: low risk <7.5%, moderate risk 7.5% to <15%, high risk  $\geq 15\%$ .<sup>19</sup>

**5.5.17. Haematopoietic stem cell transplantation**

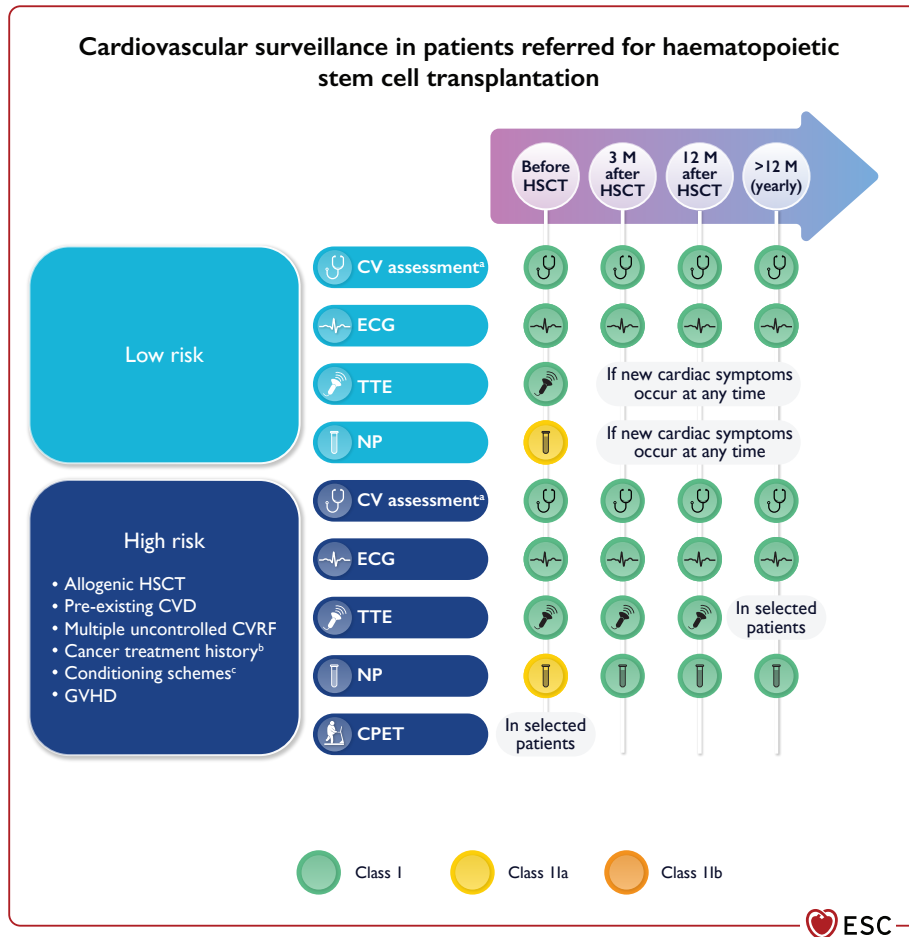
HSCT constitutes a potentially curative therapeutic option for many haematological malignancies. Improvements in HSCT techniques and supportive strategies have markedly decreased treatment-related mortality (Supplementary data, Table S14).<sup>409,410</sup> There is a growing recognition of HSCT-related CV toxicities and HSCT survivors constitute a population at high future CV risk. Several factors contribute to define the risk of HSCT-related CV toxicities, including the HSCT



**Figure 23** Radiotherapy mean heart dose and associated cardiovascular toxicity risk. CV, cardiovascular; Gy, Gray; MHD, mean heart dose; RT, radiotherapy. <sup>a</sup>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.<sup>397,399–401</sup> <sup>b</sup>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. <sup>c</sup>Or equivalent. <sup>d</sup>Or prescribed RT 15–34 Gy to a volume exposing the heart if MHD is not available. <sup>e</sup>Or prescribed RT < 15 Gy to a volume exposing the heart if MHD is not available.

type (higher risk after allogeneic HSCT), multiple uncontrolled CVRF, pre-existing CV conditions (AF or atrial flutter, sick sinus syndrome, ventricular arrhythmias, CAD, MI, moderate-to-severe VHD, and HF or LVEF <50%),<sup>411</sup> direct cardiotoxic effects of anticancer therapies received prior to and during HSCT (anthracycline-combined induction regimen, mediastinal RT, total body irradiation, or cyclophosphamide-based conditioning regimen) (Supplementary

data, Table S14) and the development of graft vs. host disease (GVHD), thrombotic microangiopathy, or sepsis.<sup>410,412</sup> In the early phase following HSCT (<100 days), the most frequent CV event is AF, although some patients may experience HF, hypertension, hypotension, pericardial effusion, or VTE.<sup>413,414</sup> Late toxicities include DM, dyslipidaemia, metabolic syndrome, hypertension, HF, CAD, conduction disorders, and pericardial effusion.<sup>410</sup> Acute



**Figure 24** 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. <sup>a</sup>Including physical examination, BP, lipid profile, and HbA1c. <sup>b</sup>Mediastinal or mantle field radiation, alkylating agents, >250 mg/m<sup>2</sup> doxorubicin or equivalent. <sup>c</sup>Total body irradiation, alkylating agents.

GVHD is associated with thrombosis and inflammatory myocardial damage (myocarditis, HF, conduction abnormalities, arrhythmias, and pericardial effusions), and chronic GVHD has been linked with increasing risk of hypertension, DM, and dyslipidaemia.<sup>415,416</sup>

A comprehensive CV evaluation, including NP assessment, ECG, and TTE, has become a core component of the pre-HSCT assessment<sup>409,410</sup> to detect undiagnosed CVD, stratify CTR-CVT risk, and optimize pre-existing CV conditions.<sup>411,417–420</sup> In early surveillance, TTE monitoring is recommended in high-risk HSCT recipients at 3 and 12 months as LVEF and GLS can decrease after transplant (see Section 7). Independent factors associated with long-term CVD in HSCT survivors are allogenic HSCT, pre-existing CVD or multiple uncontrolled CVRF, cancer treatment history (mediastinal or mantle field radiation, alkylating agents, >250 mg/m<sup>2</sup> doxorubicin or equivalent), high-risk conditioning schemes (total body irradiation, alkylating agents), and GVHD.<sup>410</sup> Figure 24 summarizes strategies for the prevention and attenuation of CV complications in patients undergoing HSCT.

**Recommendation Table 22 — Recommendations for baseline risk assessment in haematopoietic stem cell transplantation patients**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Baseline and serial CV risk assessment (3 and 12 months, then yearly) including BP measurement, ECG, lipid measurement, and HbA1c is recommended in HSCT patients. | I                  | C                  |
| Echocardiography is recommended in all patients before HSCT.   | I                  | C                  |
| Baseline NP measurement should be considered before HSCT. <sup>417,418</sup>   | IIa                | C                  |

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

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.



### 5.5.18. Other cancer treatments

Several other cancer therapies may also induce clinically relevant CV events. Cyclophosphamide, cisplatin, ifosfamide, and taxanes (paclitaxel and docetaxel) can induce myocardial dysfunction and HF.<sup>4</sup> Cyclophosphamide CV toxicity is primarily seen in patients receiving high doses (>140 mg/kg) before HSCT and typically occurs within days of drug administration.<sup>410</sup>

Platinum-containing chemotherapy (cisplatin, carboplatin, oxaliplatin) may cause vascular disease (vasospasm, MI, and venous and arterial thrombosis). These may occur during treatment and also contribute to increased long-term risk of CAD in survivors. Patients with testicular cancer treated with cisplatin have a higher risk for vascular disease at long-term follow-up.<sup>421</sup> The risk of the individual patient is still hard to predict, but lifestyle interventions, a high degree of clinical suspicion in patients who experience chest pain, and close CVRF monitoring is recommended during and after therapy.<sup>422</sup> Cisplatin<sup>422</sup> infrequently causes HF; however, because it requires the administration of a high i.v. volume to avoid renal toxicity, patients with pre-existing CVD may develop symptomatic HF.

Arsenic trioxide is used to treat some leukaemias and myelomas. Arsenic trioxide frequently prolongs the QT interval (26–93% of patients), and life-threatening ventricular tachyarrhythmias have been reported.<sup>45,259</sup> QTc prolongation was observed 1–5 weeks after arsenic trioxide infusion and then returned towards baseline by the end of 8 weeks. Patients receiving treatment with arsenic trioxide should be monitored weekly with ECG during the first 8 weeks of therapy. Electrolyte monitoring is also required as arsenic trioxide may induce hypokalaemia, hypomagnesaemia, and renal dysfunction. Risk factors for QT prolongation should be controlled before, during, and after cancer treatment (Section 6.4.2).

Several FMS-like tyrosine kinase 3 (FLT3) inhibitors (first-generation: midostaurin; second-generation: gilteritinib) have been tested for the treatment of acute myeloid leukaemias. Gilteritinib-induced differentiation syndrome (fever, dyspnoea, pleuropericardial effusion, pulmonary oedema, peripheral oedema, hypotension, renal dysfunction, and rash) requires early corticosteroid therapy and haemodynamic monitoring until resolution of symptoms. Midostaurin and gilteritinib may prolong QTc interval and close electrolyte surveillance and minimizing drug–drug interactions are required (see Section 6.4.2; Table 9; Supplementary data, Tables S15 and S16).<sup>423</sup>

## 6. Diagnosis and management of acute and subacute cardiovascular toxicity in patients receiving anticancer treatment

A coordinated MDT is recommended to discuss patients with cancer who develop acute CV complications of their cancer treatment.<sup>5</sup> Referral to a specialized cardio-oncology service is recommended for patients with cancer who present with new CTR-CVT during and after cancer treatment.<sup>12</sup> The prevention and management of CVD in patients with cancer should generally follow published ESC Guidelines for specific CVD. This chapter provides guidance on the management of CTR-CVT that occur during cancer treatment, and highlights where management differs for patients with cancer compared with those without. The decision to initiate CV treatment

(medication, devices) needs to include consideration of a range of factors including both cancer and CV symptom burden, cancer prognosis, ongoing cancer treatment requirements including alternative options, possible adverse drug reactions, drug–drug interactions, and patient preferences. An extensive list of drug–drug interactions is provided in Supplementary data, Tables S15–S17.

### Recommendation Table 23 — Recommendation for the management of cardiovascular disease and cancer therapy-related cardiovascular toxicity in patients receiving anticancer treatment

| Recommendation   | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| A specialist CV assessment <sup>c</sup> is recommended for optimal diagnostic workup and management of patients with cancer who present with new CV toxicity during and after cancer treatment. <sup>5</sup> | I                  | C                  |

CV, cardiovascular; CVD, cardiovascular disease.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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.

## 6.1. Cancer therapy-related cardiac dysfunction

### 6.1.1. Anthracycline chemotherapy-related cardiac dysfunction

CTRCD during anthracycline chemotherapy may present clinically or be detected in asymptomatic patients during surveillance (Figure 10; Table 3).<sup>4</sup> The diagnosis of anthracycline chemotherapy-related cardiac dysfunction includes new CV symptoms, new abnormalities in cardiac function on CV imaging, and/or new increases in cardiac biomarkers (Table 3). A MDT discussion is recommended to consider the risk/benefit ratio of continuing anthracycline chemotherapy in patients who develop new CTRCD.

Discontinuation of anthracycline chemotherapy is recommended in patients with cancer who develop severe symptomatic CTRCD.<sup>22</sup> There are rare exceptions where rechallenge with further anthracycline chemotherapy may be considered after a MDT discussion, using prevention strategies described below and under close monitoring with each cycle of anthracycline chemotherapy. Temporary interruption of anthracycline chemotherapy is recommended in patients who develop moderate symptomatic CTRCD, and in patients who develop moderate or severe asymptomatic CTRCD. A MDT approach regarding interruption vs. continuation of anthracycline chemotherapy is recommended in patients who develop mild symptomatic CTRCD.

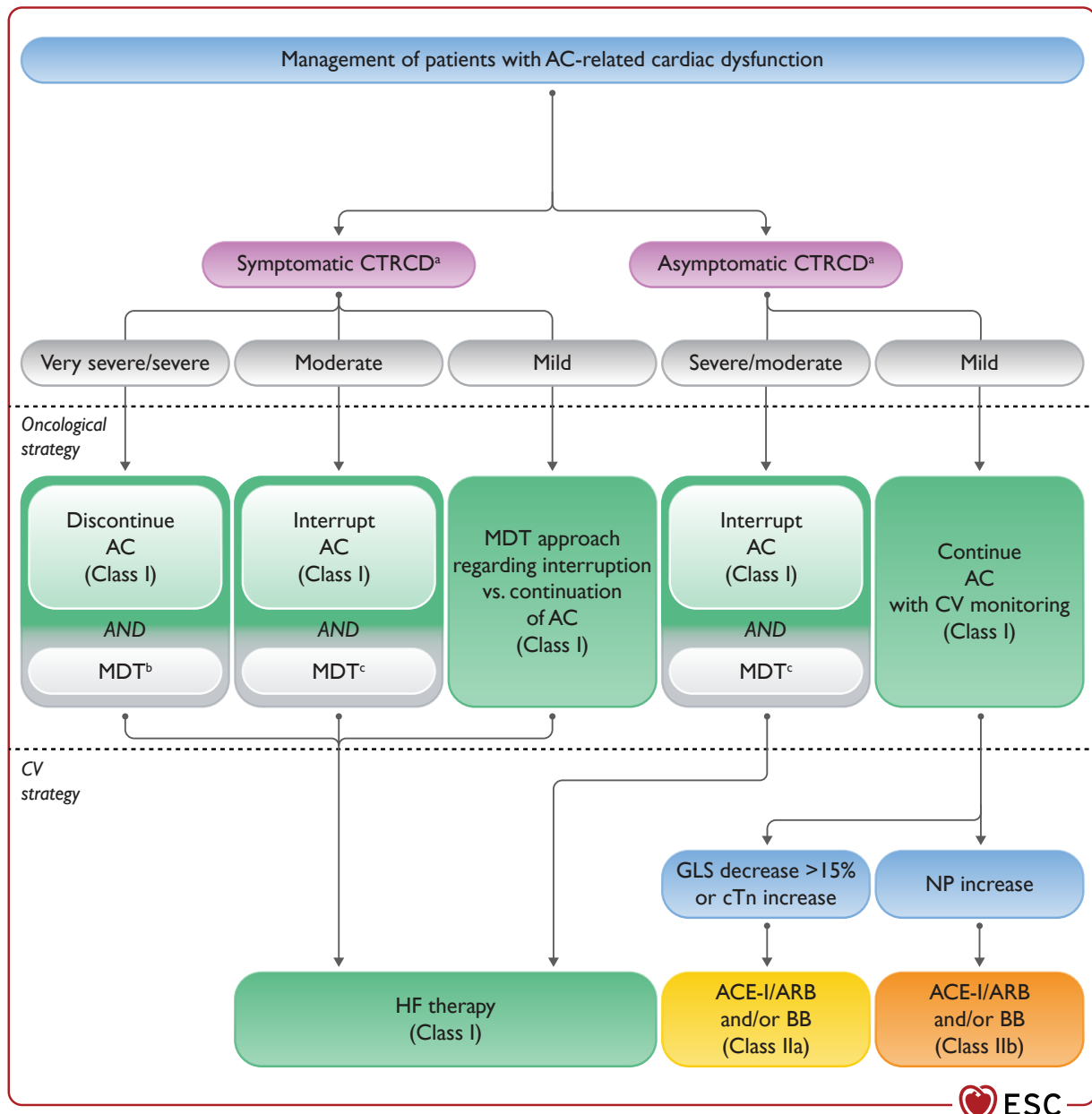
Guideline-based HF therapy is recommended in patients who develop symptomatic CTRCD or asymptomatic moderate or severe CTRCD during anthracycline chemotherapy. The use of an ACE-I/ARB or angiotensin receptor–neprilysin inhibitor, a beta-blocker, a sodium–glucose co-transporter 2 inhibitor, and a mineralocorticoid receptor antagonist is recommended unless the drugs are contraindicated or not tolerated. Up-titration to target doses as described in the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF is recommended.<sup>14</sup> ACE-I, ARB, and/or beta-blockers



should be considered in mild asymptomatic CTRCD while anthracycline chemotherapy continues uninterrupted (Figure 25).<sup>1,14,102,424</sup> The beneficial effects of aerobic exercise before and during anthracycline chemotherapy have been demonstrated and is recommended for patients with cancer who develop CTRCD.<sup>11</sup>

A MDT is recommended to discuss restarting anthracycline chemotherapy in patients who developed mild or moderate

symptomatic CTRCD, or moderate or severe asymptomatic CTRCD, after recovery of LV function under HF treatment. If there is a compelling reason to continue anthracycline chemotherapy, three other strategies exist in addition to continuing ACE-I/ARB and beta-blockers at target doses for HF.<sup>14</sup> First, minimizing the dose of anthracycline chemotherapy administered. Second, switching to liposomal anthracycline preparations. Third, pre-treatment



**Figure 25** 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. <sup>a</sup>See Table 3 (Section 3) 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%). <sup>b</sup>In rare exceptions, anthracycline chemotherapy may be restarted after recovery of LV function with optimal HF therapy. <sup>c</sup>A MDT discussion is recommended before restarting anthracycline chemotherapy after recovery of LV function.

with dexrazoxane before each further cycle of anthracycline chemotherapy (Section 5.2.1).

Close cardiac monitoring every 1–2 cycles is recommended in patients who restart anthracycline chemotherapy following an episode of CTRCD and in patients with mild asymptomatic CTRCD while they continue anthracycline chemotherapy.

### Recommendation Table 24 — Recommendations for the management of cancer treatment-related cardiac dysfunction during anthracycline chemotherapy

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| <b>Anthracycline chemotherapy-induced symptomatic CTRCD</b>  |                    |                    |
| HF therapy is recommended for patients who develop symptomatic CTRCD during anthracycline chemotherapy. <sup>c,208,425</sup>   | I                  | B                  |
| Discontinuation of anthracycline chemotherapy is recommended in patients who develop symptomatic severe CTRCD. <sup>c</sup>  | I                  | C                  |
| Temporary interruption of anthracycline chemotherapy is recommended in patients who develop symptomatic moderate CTRCD <sup>c</sup> and a multidisciplinary approach regarding the decision to restart is recommended. | I                  | C                  |
| A multidisciplinary approach regarding interruption vs. continuation of anthracycline chemotherapy is recommended in patients who develop mild symptomatic CTRCD. <sup>c</sup>   | I                  | C                  |
| <b>Anthracycline chemotherapy-induced asymptomatic CTRCD</b>   |                    |                    |
| Temporary interruption of anthracycline chemotherapy and initiation of HF therapy is recommended in patients who develop asymptomatic moderate or severe CTRCD. <sup>c,22</sup>  | I                  | C                  |
| A multidisciplinary approach regarding the decision when to restart is recommended in all patients with moderate or severe asymptomatic CTRCD. <sup>c,22</sup>   | I                  | C                  |
| Continuation of anthracycline chemotherapy is recommended in asymptomatic patients who have LVEF $\geq$ 50% and who have developed a significant fall in GLS <sup>c</sup> or a troponin or a NP elevation $>$ ULN.     | I                  | C                  |
| Asymptomatic patients who have LVEF $\geq$ 50% and who have developed a significant fall in GLS <sup>c</sup> should be considered for ACE-I/ARB and/or beta-blockers. <sup>d,75,93,102</sup>                           | IIa                | B                  |
| Asymptomatic patients who have LVEF $\geq$ 50% and who have developed a troponin elevation $>$ ULN should be considered for ACE-I/ARB and/or beta-blockers. <sup>d,147,211</sup>                                       | IIa                | B                  |

Continued

|   |     |   |
|---|-----|---|
| Asymptomatic patients who have LVEF $\geq$ 50% and who have developed NP $>$ ULN may be considered for ACE-I/ARB and/or beta-blockers. <sup>d,211</sup>   | IIb | C |
| <b>Strategies for restarting anthracycline chemotherapy in patients with CTRCD</b>  |     |   |
| Liposomal anthracycline <sup>e</sup> may be considered in patients with moderate or severe symptomatic or asymptomatic CTRCD <sup>c</sup> who require further anthracycline chemotherapy to reduce the risk of further CV toxicity. | IIb | C |
| Dexrazoxane <sup>f</sup> may be considered in patients with moderate or severe symptomatic or asymptomatic CTRCD <sup>c</sup> who require further anthracycline chemotherapy to reduce the risk of further CV toxicity.             | IIb | C |

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>See Table 3. Significant fall in GLS = relative reduction  $>$ 15%.

<sup>d</sup>Avoid hypotension.

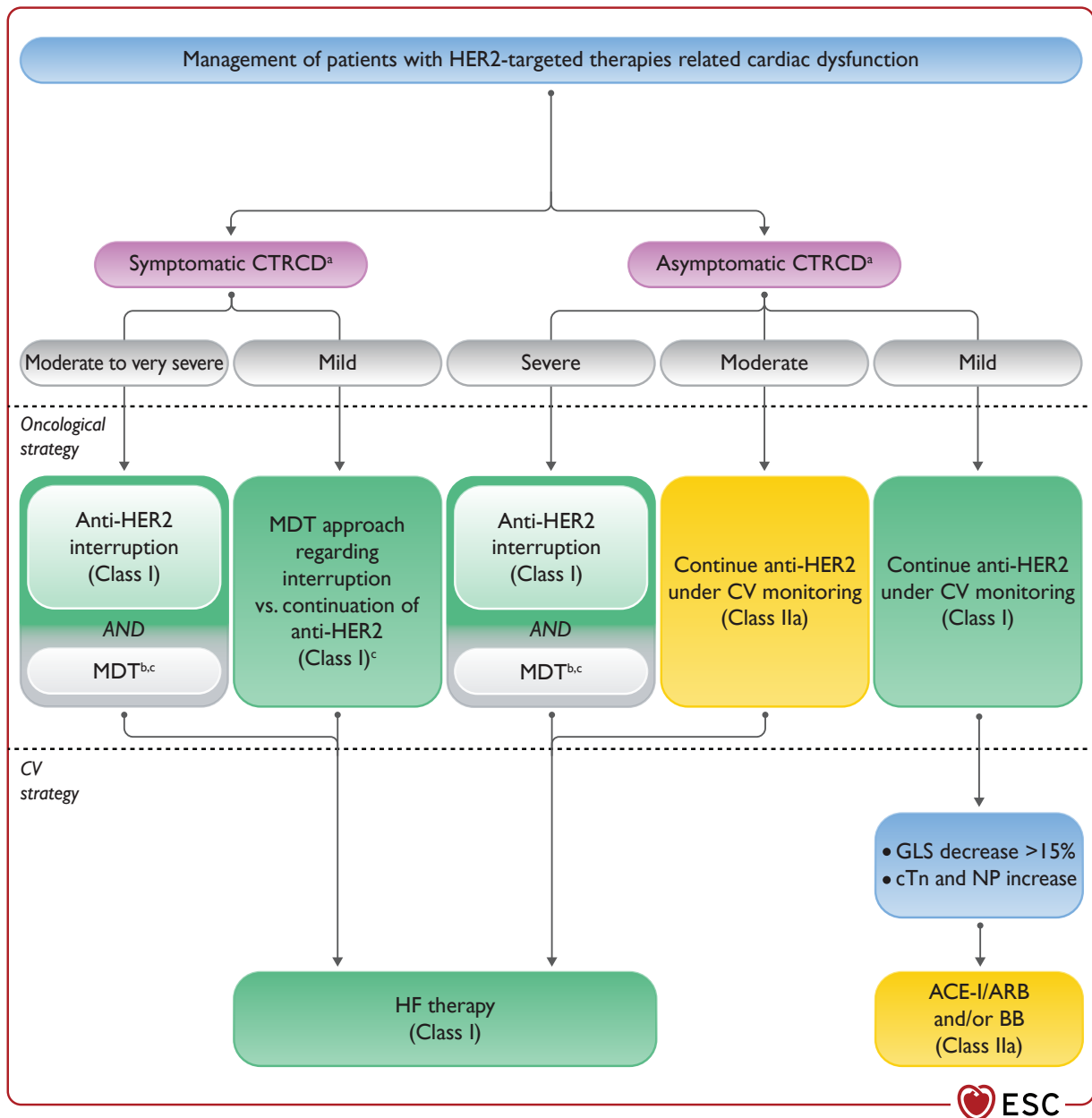
<sup>e</sup>See text for specific liposomal doxorubicin type and malignancies (Section 5.2).

<sup>f</sup>As per the European Medicines Agency:  $\geq$  350 mg/m<sup>2</sup> doxorubicin or equivalent; as per the United States Food and Drug Administration:  $\geq$  300 mg/m<sup>2</sup> doxorubicin or equivalent.

### 6.1.2. Human epidermal receptor 2-targeted therapy-related cardiac dysfunction

The diagnosis of HER2-targeted therapy-related CTRCD can be made using the combination of new CV symptoms, imaging, and biomarkers. Patients may present with symptomatic CTRCD or may be asymptomatic.<sup>426</sup> Early treatment of symptomatic and asymptomatic severe CTRCD (LVEF  $<$  40%), according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF,<sup>14</sup> is recommended to prevent worsening HF,<sup>425</sup> particularly when targeted cancer therapy is continued.<sup>427</sup> In patients who develop CTRCD, a MDT is recommended to guide clinical decisions. Temporary interruption is recommended in patients who develop moderate or severe symptomatic CTRCD or severe asymptomatic CTRCD (LVEF  $<$  40%) during HER2-targeted therapy. In patients with mild symptomatic CTRCD, a MDT approach is recommended to continue vs. interrupt HER2-targeted therapy. In patients with asymptomatic moderate CTRCD (LVEF 40–49%), HER2-targeted treatment should be continued, and cardioprotective therapy (ACE-I/ARB and beta-blockers) is recommended with frequent cardiac monitoring.<sup>22,33,189</sup> In patients with asymptomatic mild CTRCD (LVEF  $\geq$  50% with a significant new GLS reduction and/or cardiac biomarker increase), continuing HER2-targeted treatment is recommended and cardioprotective therapy (ACE-I/ARB and/or beta-blockers) should be considered.<sup>22,211,428,429</sup>

Frequent cardiac surveillance with cardiac imaging and cardiac serum biomarkers is recommended in all patients with CTRCD



**Figure 26** 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. <sup>a</sup>See [Table 3 \(Section 3\)](#) (symptomatic CTRCD: symptomatic confirmed HF syndrome; asymptomatic severe CTRCD: LVEF < 40%; asymptomatic moderate CTRCD: LVEF 40–49%; asymptomatic mild CTRCD: LVEF > 50%). <sup>b</sup>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.<sup>22</sup> <sup>c</sup>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 biomarker assessment every two cycles for the first four cycles after restarting and then the frequency can be reduced.<sup>22</sup>

who continue HER2-targeted cancer therapies and in those who restart after an interruption following resolution of HF signs and symptoms and recovery of LVEF ≥ 40% (and ideally recovery to LVEF ≥ 50%) ([Figure 26](#)).<sup>22,33,189</sup> Echocardiography and cardiac

serum biomarker measurement every two cycles for the first four cycles after restarting HER2-targeted therapy is recommended, and then the frequency can be reduced if cardiac function and biomarker levels remain stable.

**Recommendation Table 25 — Recommendations for the management of cancer treatment-related cardiac dysfunction during human epidermal receptor 2-targeted therapies**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| <b>HER2-targeted therapy-induced symptomatic CTRCD</b>  |                    |                    |
| HF therapy is recommended for patients who develop symptomatic moderate-to-severe CTRCD with LVEF < 50% <sup>c</sup> during HER2-targeted treatment. <sup>14,61,430,431</sup>   | I                  | B                  |
| Temporary interruption of HER2-targeted treatment is recommended in patients who develop moderate or severe symptomatic CTRCD <sup>c</sup> and the decision to restart should be based on a multidisciplinary approach after improvement of LV function and symptoms resolved. <sup>d</sup> | I                  | C                  |
| In patients who develop mild symptomatic CTRCD, <sup>c</sup> HF therapy and a multidisciplinary approach regarding the decision to continue vs. interrupt HER2-targeted therapy are recommended. <sup>d,431,432</sup>   | I                  | C                  |
| <b>HER2-targeted therapy-induced asymptomatic CTRCD</b>   |                    |                    |
| Temporary interruption of HER2-targeted therapy and initiation of HF therapy is recommended in patients who develop asymptomatic severe CTRCD. <sup>c</sup>   | I                  | C                  |
| A multidisciplinary approach regarding the decision to restart HER2-targeted treatment is recommended in patients with severe asymptomatic CTRCD. <sup>c</sup>  | I                  | C                  |
| Continuation of HER2-targeted therapy should be considered in patients who develop asymptomatic moderate (LVEF 40–49%) CTRCD <sup>c</sup> with more frequent cardiac monitoring. <sup>33,189,428,433</sup>  | IIa                | B                  |
| Continuation of HER2-targeted therapy is recommended in patients who develop asymptomatic mild (LVEF ≥ 50%) CTRCD <sup>c</sup> with more frequent cardiac monitoring. <sup>428</sup>  | I                  | C                  |
| ACE-I/ARB and beta-blockers are recommended in patients who develop asymptomatic moderate (LVEF 40–49%) CTRCD <sup>c</sup> during HER2-targeted treatment. <sup>e,189</sup>   | I                  | C                  |
| ACE-I/ARB and/or beta-blockers should be considered in asymptomatic patients receiving HER2-targeted therapies who have LVEF ≥ 50% but develop a significant fall in GLS <sup>c</sup> while continuing HER2-targeted therapy. <sup>e,22,428</sup>   | IIa                | B                  |

Continued

ACE-I/ARB and/or beta-blockers should be considered in asymptomatic patients receiving HER2-targeted therapies who have LVEF ≥ 50% but develop a new troponin or NP rise while continuing HER2-targeted therapy.<sup>e,22,211,428</sup>

IIa

B

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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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>See Table 3.

<sup>d</sup>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.

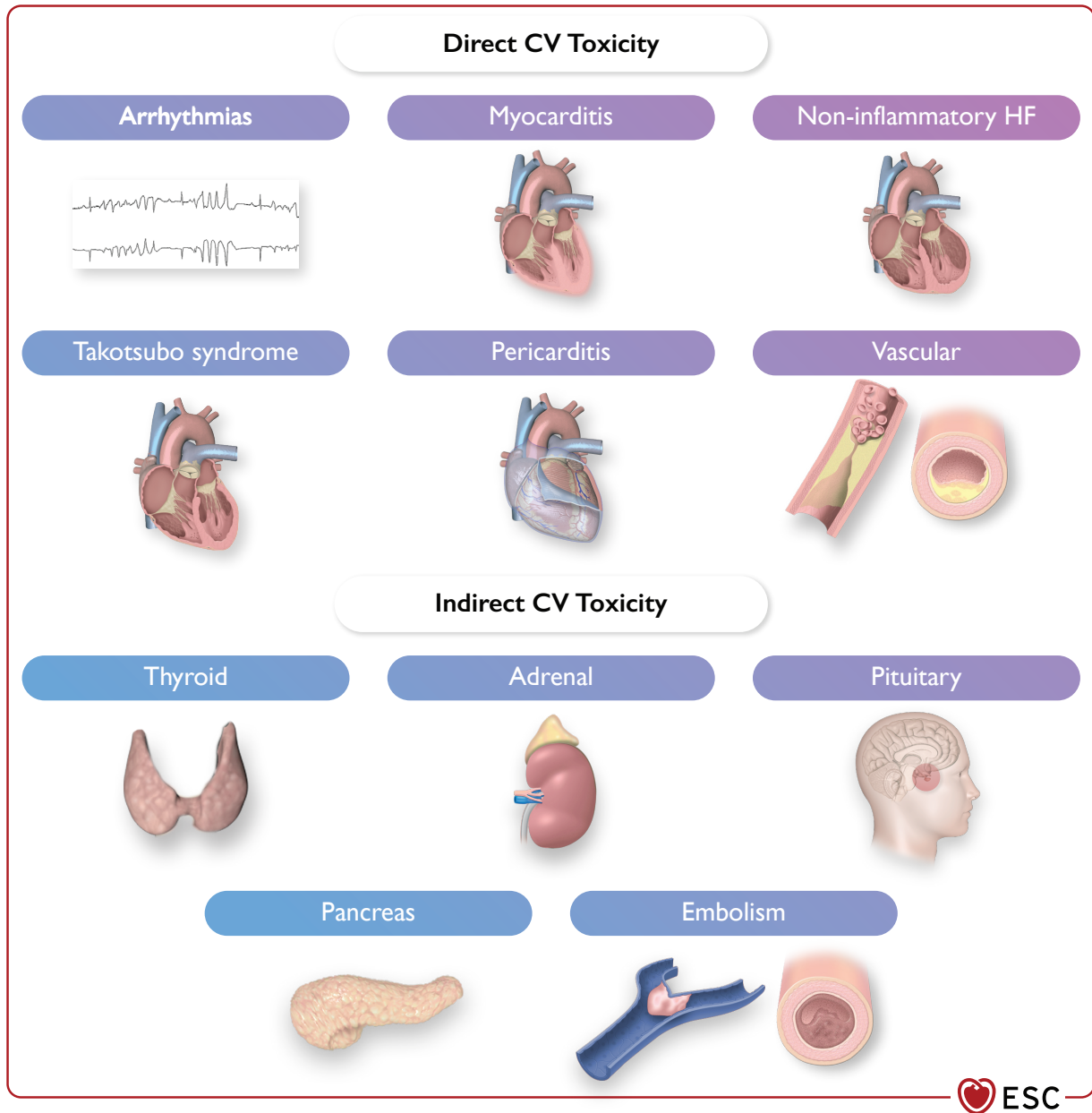
<sup>e</sup>Avoid hypotension.

### 6.1.3. Immune checkpoint inhibitor-associated myocarditis and non-inflammatory heart failure

Myocarditis is a severe complication of ICI with a high fatality rate that most frequently develops during the first 12 weeks of treatment, although late cases (after week 20) may occur.<sup>386</sup>

Other ICI-related CV toxicities include dyslipidaemia, ACS, vasculitis, AV block, supraventricular and ventricular arrhythmias, sudden death, TTS, non-inflammatory LVD, pericarditis, pericardial effusion, and ischaemic stroke, with higher risks for myocarditis (odds ratio 4.42) and dyslipidaemia (odds ratio 3.68) (Figure 27).<sup>323,325</sup>

The diagnosis of ICI-associated myocarditis is initially based on the presence of symptoms, a new increase in troponin (associated with either CV symptoms or non-CV immuno-related adverse events), and new ECG abnormalities (AV or intraventricular conduction disorders, bradycardia, tachyarrhythmias) (see Section 3; Table 3).<sup>17,434,435</sup> Any abnormal finding should prompt urgent CV imaging and other causes of myocardial injury (e.g. ACS, acute infectious myocarditis) should be excluded. Treatment with high-dose methylprednisolone should be promptly initiated in haemodynamically unstable patients (including those with ventricular arrhythmias [VA] or complete AV block) while awaiting further confirmatory testing.<sup>436</sup> TTE and CMR are recommended in all patients with suspected ICI-associated myocarditis. Currently, specific CMR features for ICI-induced myocarditis are not well described and modified Lake Louise criteria are recommended (Table 3).<sup>18</sup> Cardiac fluorodeoxyglucose positron emission tomography (PET) may be considered<sup>437,438</sup> if CMR is not available or contraindicated, although PET sensitivity is low and requires a strict 18-h carbohydrate-free fast.<sup>439</sup> Endomyocardial biopsy (EMB) should be considered in cases where the diagnosis is suspected but not confirmed non-invasively (e.g. conflicting results of cardiac imaging and biomarkers or clinically unstable patients).<sup>440</sup> All cases of ICI-associated myocarditis should be classified according to the severity of the myocarditis (fulminant



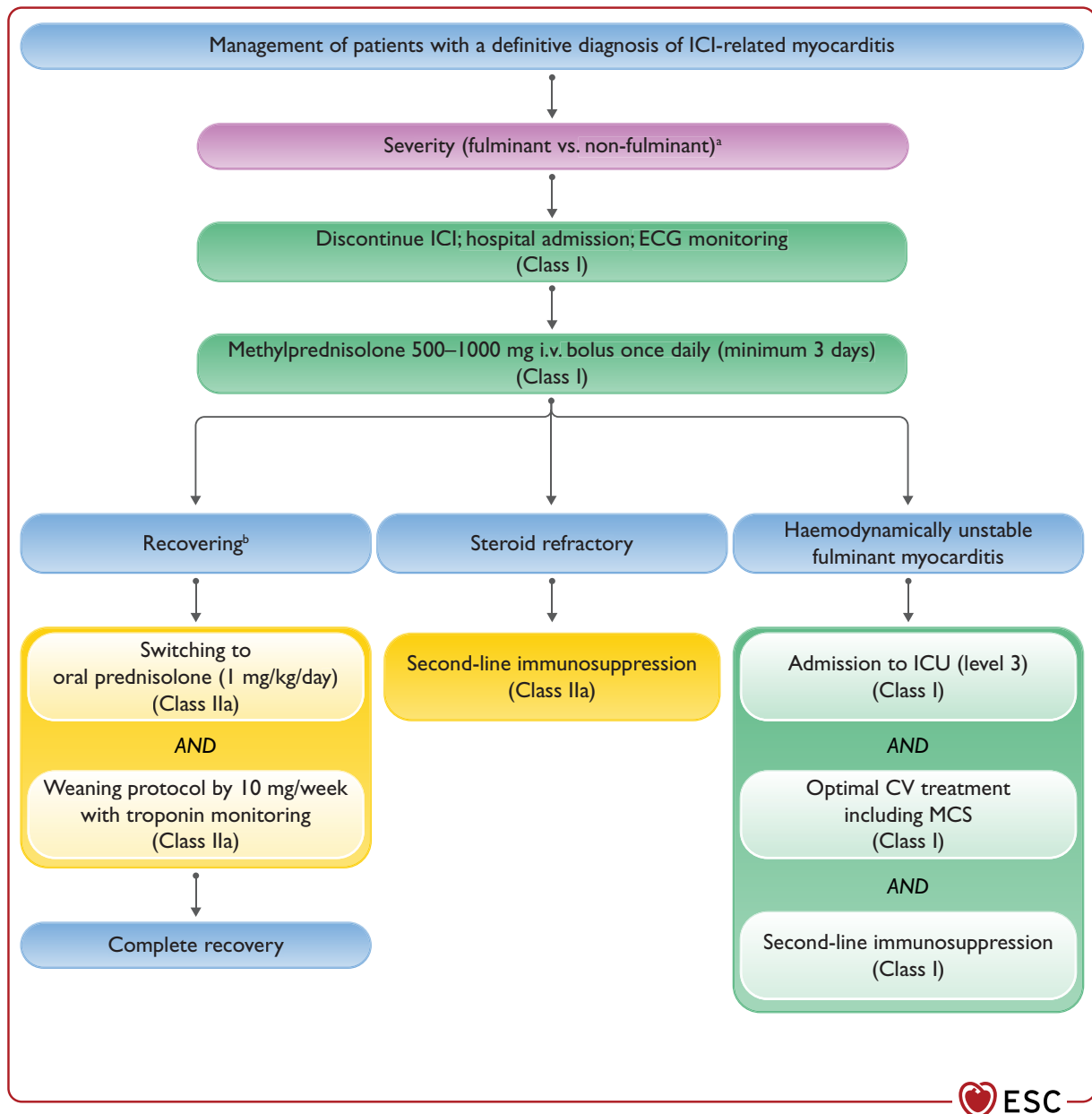
**Figure 27** Direct and indirect immune checkpoint inhibitor-related cardiovascular toxicity. CV, cardiovascular; HF, heart failure.

or non-fulminant, including symptomatic but haemodynamically and electrically stable patients and incidental cases diagnosed at the same time as other immune-related adverse events) to guide the management pathway (Figure 28).<sup>331</sup>

Interruption of ICI treatment is recommended in all cases of suspected ICI-associated myocarditis (any patient developing new cardiac symptoms, new cardiac arrhythmias, new heart blocks, or new troponin increase who has received an ICI therapy in the past 12 weeks) while investigations are performed. Once the abnormal findings have resolved, a MDT discussion is recommended to determine the risk/benefit to permanent stopping vs. resuming ICI treatment in patients with suspected but not confirmed myocarditis.

Cessation of ICI treatment is recommended in patients with cancer with fulminant or non-fulminant ICI-associated myocarditis and the patient should be admitted to hospital and a level 2 or 3 bed with continuous ECG monitoring is required. CV complications should be treated as per specific ESC Guidelines (HF,<sup>14</sup> tachyarrhythmias,<sup>441,442</sup> AV block,<sup>443</sup> or pericardial effusion<sup>444</sup>).

Treatment of both non-fulminant and fulminant ICI-associated myocarditis with methylprednisolone 500–1000 mg i.v. bolus once daily for the first 3–5 days should be started as soon as possible, once the diagnosis is considered likely, to reduce MACE including mortality.<sup>386,436</sup> If clinical improvement is observed (cTn reduced by >50% from peak level within 24–72 h and any LVD, AV block, and arrhythmias resolved), switching to oral prednisolone is



**Figure 28** 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. <sup>a</sup>**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. <sup>b</sup>**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.

recommended starting at 1 mg/kg up to 80 mg/day. Although the most appropriate weaning off protocol is not confirmed, a weekly reduction of oral prednisolone (most commonly by 10 mg per week) under clinical, ECG, and cTn surveillance should be considered (Figure 28). A reassessment of LV function and cTn should be considered when the prednisolone dose is reduced to 20 mg/day and then continue weaning the prednisolone by 5 mg per week to

5 mg/day, and a final reduction from 5 mg/day in 1-mg per week steps.

If the troponin does not reduce significantly (>50% reduction from peak) and/or AV block, ventricular arrhythmias, or LVD persist despite 3 days of i.v. methylprednisolone plus cardiac treatments, then steroid-resistant ICI-associated myocarditis is confirmed and second-line immunosuppression should be considered.<sup>22,445,446</sup>



There is a lack of data to recommend a specific second-line immunosuppression regimen and MDT discussion is recommended. Several agents are currently being investigated with promising results from case series including i.v. mycophenolate mofetil, anti-thymocyte globulin (anti-CD3 antibody), i.v. immunoglobulin, plasma exchange, tocilizumab, abatacept (CTLA-4 agonist), alemtuzumab (anti-CD52 antibody), and tofacitinib. Caution is advised against the use of infliximab for steroid-refractory myocarditis and HF.<sup>447,448</sup> Patients with fulminant ICI-associated myocarditis, complicated by haemodynamic and/or electrical instability, require admission to the intensive care unit (ICU) and cardiogenic shock should be managed according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF.<sup>14</sup> A single dose of i.v. methylprednisolone should be considered in clinically unstable patients with cancer where ICI-induced myocarditis is suspected at presentation but before definitive diagnosis can be confirmed.

Following recovery from ICI-associated myocarditis and weaning of oral steroid therapy, MDT discussion is recommended to review the decision on whether to restart ICI treatment. This depends on various factors including the severity of the ICI-associated myocarditis (fulminant vs. non-fulminant vs. asymptomatic), alternative oncology treatment options, metastatic vs. adjuvant/neoadjuvant indication, and reducing from dual ICI to single ICI treatment if triggered by combination ICI treatment.<sup>449</sup>

Non-inflammatory HF syndromes have also been observed in patients treated with ICI. These include TTS, non-inflammatory HF or LVD,<sup>450</sup> and post-MI HF.<sup>451,452</sup> Non-inflammatory HF is generally a late event and the diagnostic workflow should be based on defining the HF phenotype and excluding myocarditis, TTS, and ACS.<sup>14</sup> There is also evidence that vasculitis and CAD can occur after ICI treatment.<sup>335</sup> HF treatment as per the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF is indicated,<sup>14</sup> but there is no indication for immunosuppression if myocarditis has been excluded. Interruption vs. continuing ICI therapy depends on the severity of the HF syndrome and each case should be reviewed by a MDT. Arrhythmias, such as AF, can be seen in patients with ICI therapy without myocarditis (e.g. ICI-associated thyroiditis with thyrotoxicosis, ICI-associated pericarditis, or ICI-associated severe systemic inflammatory syndromes). ICI treatment can be continued after excluding myocarditis.

**Recommendation Table 26 — Recommendations for the diagnosis and management of immune checkpoint inhibitor-associated myocarditis**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| cTn, ECG, and CV imaging (echocardiography and CMR) are recommended to diagnose ICI-associated myocarditis. <sup>320,434,435,453</sup>                     | I                  | B                  |
| In patients with suspected ICI-associated myocarditis, temporary interruption of ICI treatment is recommended until the diagnosis is confirmed or refuted. | I                  | C                  |

Continued

|   |     |   |
|---|-----|---|
| EMB should be considered to confirm the diagnosis of ICI-associated myocarditis if the diagnosis is suspected but not confirmed after cardiac imaging and biomarkers. <sup>c</sup>  | IIa | C |
| Interruption of ICI treatment is recommended in patients with confirmed ICI-associated myocarditis.   | I   | C |
| Continuous ECG monitoring to assess for new AV block and tachyarrhythmias during the acute phase is recommended for all patients with symptomatic ICI-associated myocarditis.   | I   | C |
| Early high-dose corticosteroids <sup>d</sup> are recommended in patients with cancer and confirmed ICI-associated myocarditis. <sup>22,436,454</sup>  | I   | C |
| Continuation of high-dose corticosteroids is recommended for the treatment of ICI-associated myocarditis until resolution of symptoms, LV systolic dysfunction, conduction abnormalities, and significant cTn reduction. <sup>e</sup> | I   | C |
| Switching from i.v. to oral prednisolone should be considered after clinical improvement (resolution of: symptoms, LV systolic dysfunction, conduction abnormalities, and significant cTn reduction <sup>e</sup> ). <sup>f</sup>      | IIa | C |
| Second-line immunosuppression treatment should be considered in patients with steroid-refractory ICI-associated myocarditis. <sup>g</sup>   | IIa | C |
| Admission to ICU (level 3), treatment with i.v. methylprednisolone, and optimal CV treatment including mechanical support (when indicated) is recommended for patients with ICI-associated fulminant myocarditis. <sup>14</sup>       | I   | C |
| A single dose of i.v. methylprednisolone <sup>d</sup> should be considered in unstable <sup>h</sup> patients with cancer where ICI-induced myocarditis is suspected.  | IIa | C |
| A multidisciplinary discussion is recommended 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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>See Table 3 for ICI-related myocarditis definition. EMB should be considered in unstable patients or when CMR is contraindicated.

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

<sup>e</sup>Reduction of cTn by >50% from peak level.

<sup>f</sup>**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.

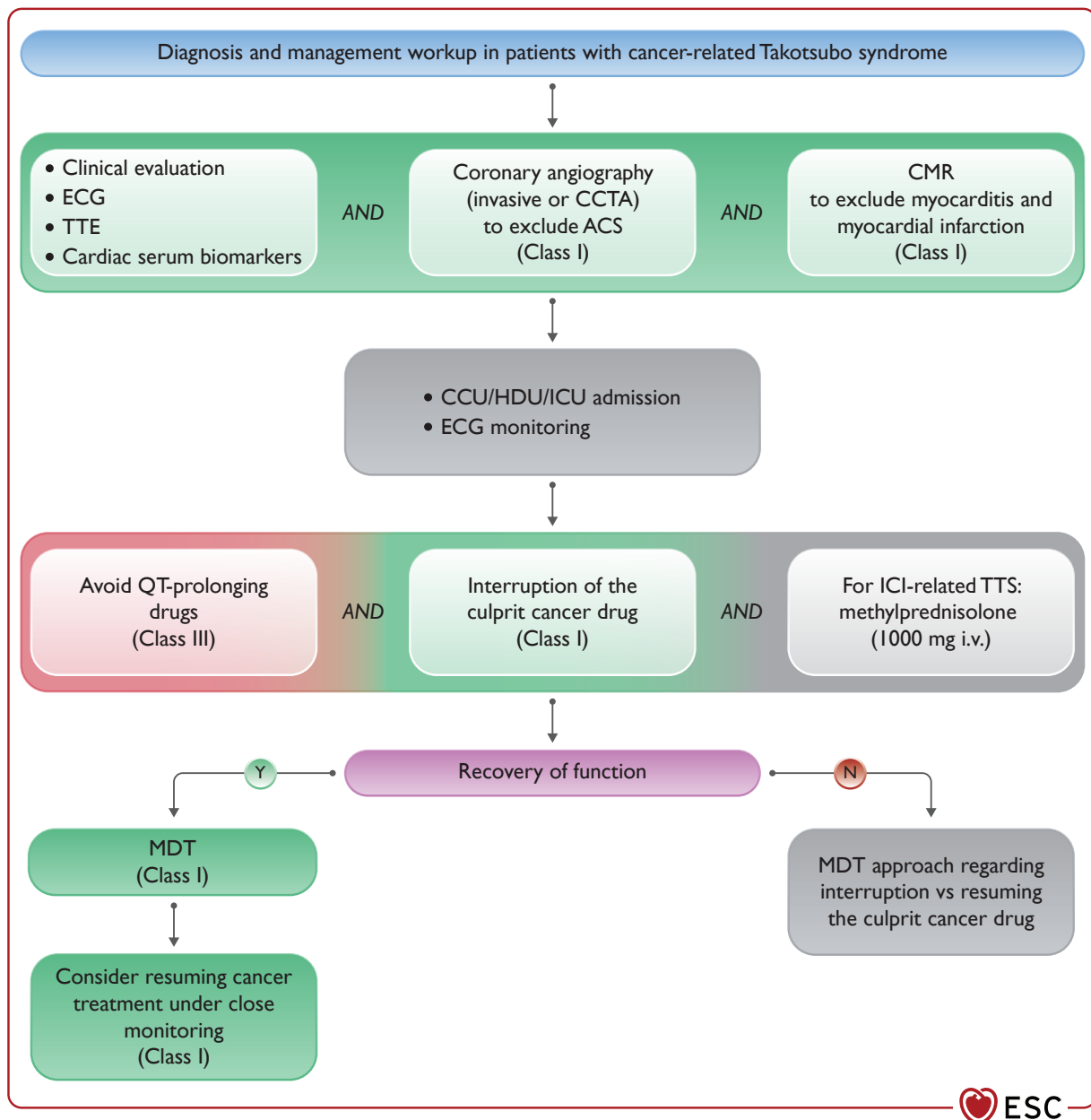
<sup>g</sup>**Steroid refractory:** non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other aetiologies) despite high-dose methylprednisolone (Table 3; Supplementary data, Table S1).

<sup>h</sup>**Unstable:** patients with symptomatic HF, ventricular arrhythmias, new complete heart block.

#### 6.1.4. Chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies and heart dysfunction

Although no large-scale studies on the multiple CV complications among adults treated with CAR-T therapies exist, small studies and case reports have shown that CV complications represent around 20% of adverse events.<sup>378</sup> CV complications are associated with high mortality rates, and are secondary to CRS and immune effector cell-associated neurotoxicity syndrome. The most common CV complications in patients receiving CAR-T therapies are arrhythmias (77.6%), including QTc prolongation, ventricular arrhythmias, and AF; HF (14.3%); and MI and VTE (0.5%).<sup>455</sup> When suspected, a

resting 12-lead ECG, continuous ECG monitoring, TTE, and cTn and NP are recommended. Admission to ICU (level 3) is recommended in severe cases due to the risk of malignant cardiac arrhythmias, circulatory collapse, and multiorgan system failure. In general, the degree of elevation of cytokines correlates with the severity of CRS. C-reactive protein is not specific for CRS and changes in C-reactive protein may lag behind clinical changes by  $\geq 12$  h. A dramatic elevation of interleukin-6 is a supportive finding for the diagnosis of CRS. Management of the specific CV complication should follow ESC Guidelines, with additional management of the CRS (e.g. the anti-interleukin-6 receptor antibody, tocilizumab, and dexamethasone).<sup>381</sup>



**Figure 29** 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.

Although CV complications are common with TIL therapies, survival does not appear to be significantly affected. The most frequent CV events are hypotension that may require treatment with i.v. fluids and pressors, AF, and to a lesser extent, cTn elevation suggestive of myocardial damage.<sup>380</sup> Further research is needed to define mechanisms and potential prevention strategies to help clinicians with the management of these CV events.

### 6.1.5. Heart failure during haematopoietic stem cell transplantation

CV complications during HSCT, including congestive HF,<sup>456</sup> arterial events, tamponade, and rhythm disturbances (AF, atrial flutter, and supraventricular tachycardia),<sup>457</sup> are uncommon but clinically relevant, and should be treated as per specific ESC Guidelines (HF,<sup>14</sup> tachyarrhythmias,<sup>273,441</sup> pericardial effusion,<sup>444</sup> or acute coronary syndrome<sup>458</sup>). Studies of treatments during HSCT to prevent both acute and late CV toxicity are limited.<sup>145</sup> ACE-I and beta-blockers may be effective, but this requires further confirmation. Outpatient and home-based exercise and education programmes instituted after HSCT can improve exercise capacity and quality of life,<sup>459</sup> and the role of exercise pre-habilitation prior to HSCT is being investigated.<sup>460,461</sup>

### 6.1.6. Takotsubo syndrome and cancer

The prevalence of malignant diseases is high in patients with TTS and is a risk factor for worse outcomes. Malignancy itself, some cancer treatments (5-FU, ICI, VEGFi), and the stress associated with the diagnosis, investigations, and treatment are recognized triggers or predisposing factors for TTS.<sup>462–466</sup> Diagnosis using general TTS criteria is recommended.<sup>467,468</sup> Investigations in a patient with cancer with suspected TTS should include clinical examination, ECG, TTE, cardiac biomarkers (cTn and NP), and CMR (Figure 29).<sup>468,469</sup> Most patients require invasive coronary angiography to exclude acute MI. In patients with advanced malignancy or significant thrombocytopenia where invasive coronary angiography is contraindicated, a CCTA is recommended. Cardiac imaging studies should be performed as early as possible when the diagnosis is suspected as LVD can be transient, and if significant LVD is detected then repeat imaging to confirm recovery is recommended.

Interruption of the culprit cancer drug in patients with TTS is recommended. QT-prolonging drugs should be avoided.<sup>467</sup> In cases of ICI-associated TTS, the role of immunosuppression is unknown and if myocardial inflammation is present in a TTS pattern on CMR then i.v. methylprednisolone is recommended given the overlap between ICI-induced TTS and ICI-induced myocarditis. Limited information exists regarding the feasibility of ICI rechallenge following TTS and after recovery of LV function.

A MDT discussion is recommended after recovery from the acute phase of TTS and, if restarting the culprit cancer drug is required from an oncology perspective, regular cardiac biomarker monitoring is recommended (e.g. cTn and NP measured before every ICI cycle, and TTE if a new rise in cardiac biomarkers occurs) (Figure 29).

### Recommendation Table 27 — Recommendations for the diagnosis and management of Takotsubo syndrome in patients with cancer

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Coronary angiography (invasive or CCTA) is recommended to exclude ACS.           | I                  | C                  |
| CMR is recommended to exclude myocarditis and MI. <sup>458</sup>                 | I                  | B                  |
| QT-prolonging drugs are not recommended during the acute TTS phase. <sup>c</sup> | III                | C                  |

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.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Until full recovery and normalization of LV function and QTc.

## 6.2. Coronary artery disease

### 6.2.1. Acute coronary syndromes

Patients with cancer are at increased risk of CAD because of shared CVRFs<sup>34</sup> and CV toxicity of cancer therapy<sup>12</sup> compounded by a cancer-induced pro-inflammatory and prothrombotic state (Table 7).<sup>467,468,470–473</sup>

Current knowledge on ACS in patients with cancer is based on observational data and registries demonstrating that, especially when diagnosed within 1 year, they are at increased risk for major CV events, bleeding, and cardiac and non-cardiac mortality.<sup>474–480</sup>

The proportion of ACS patients with a diagnosis of cancer is rising and constitutes about 3% of large series.<sup>475</sup>

Diagnosis of ACS is based on the same principles as in patients without cancer, including symptoms, an early 12-lead ECG, and serial measurements of hs-cTn for patients presenting with possible non-ST-segment elevation ACS (NSTEMI-ACS).<sup>458</sup> Clinical presentation can be atypical<sup>481</sup> or masked by cancer or therapy-related side effects; therefore, diagnostic suspicion should be increased in patients at high CV risk or treated with vascular cardiotoxic therapies

### Table 7 Cancer treatments that predispose to acute coronary syndromes

|  |  |
|--|--|
| Accelerated atherosclerosis and plaque rupture | ADT (GnRH agonists), ICI, nilotinib, ponatinib, radiation therapy, VEGFi   |
| Vasospasm                                      | Bleomycin, fluoropyrimidines, taxanes, VEGFi, vinca alkaloids  |
| Coronary thrombosis                            | Alkylating agents (cisplatin, cyclophosphamide), erlotinib, ICI, IMiD (lenalidomide, thalidomide), monoclonal antibodies (VEGFi, anti-CD20), nilotinib, platinum chemotherapy, PI, ponatinib, VEGFi. |

ADT, androgen deprivation therapy; GnRH, gonadotropin-releasing hormone; ICI, immune checkpoint inhibitors; IMiD, immunomodulatory drugs; PI, proteasome inhibitors; VEGFi, vascular endothelial growth factor inhibitors.

(Table 7). Echocardiography improves the diagnostic precision in patients with atypical symptoms and assesses for other cardiac causes of chest pain.

Management of ACS in patients with cancer can be challenging because of frailty, increased bleeding risk, thrombocytopenia, increased thrombotic risk, and the possible need for future surgery/interventions.<sup>482</sup> Cancer treatment should be temporarily interrupted, and an urgent multidisciplinary approach<sup>5</sup> is indicated to plan an individualized guideline-based management, taking into account cancer status, prognosis, and the patient's preferences regarding invasive management. As in patients without cancer, admission to a monitored unit and initiation of appropriate anti-ischaemic and antithrombotic treatment are indicated, in the absence of contraindications.

A large retrospective propensity score-matching analysis found that percutaneous coronary intervention (PCI), despite its lower use, was strongly associated with lower adjusted MACE and all-cause mortality in patients with cancer (Hodgkin and non-Hodgkin lymphomas and breast, lung, colon, and prostate cancers).<sup>483</sup> Therefore, immediate coronary angiography and PCI are recommended in patients with cancer and ACS if cancer prognosis is  $\geq 6$  months or if they have acute complications of ACS (cardiogenic shock, pulmonary oedema, ventricular tachyarrhythmias), where PCI offers palliation of symptoms.<sup>483</sup> When stenting is indicated, third-generation drug-eluting stents are preferred because of the lower risk of in-stent thrombosis. Balloon angioplasty is associated with worse outcome<sup>474</sup> and should only be used in case of severe thrombocytopenia or need for urgent surgery. Fractional flow reserve or instantaneous free wave ratio are advised by experts<sup>484</sup> to avoid unnecessary interventions while intravascular ultrasound and optical coherence tomography can be used to ensure optimal stent apposition and expansion, to avoid thrombotic complications.<sup>485</sup>

Retrospective data have demonstrated a lower use of invasive management in patients with cancer with ST-segment elevation MI (STEMI), with a better outcome for invasively treated patients.<sup>475,480,483</sup> PCI has not demonstrated a mortality benefit in patients with advanced cancer and NSTEMI-ACS compared with optimal medical therapy.<sup>479</sup> Therefore, a non-invasive approach can be attempted in low-risk (without signs or symptoms of ongoing ischaemia or haemodynamic instability) NSTEMI-ACS patients with poor cancer prognosis ( $< 6$  months).

Due to a potentially higher bleeding risk (especially in patients with active GI cancer),<sup>477</sup> the preferred antithrombotic strategy after drug-eluting stent consists of DAPT with aspirin and clopidogrel instead of newer P2Y12 antagonists. The duration of DAPT should be kept as short as possible (1–3 months).<sup>458</sup> In patients with need for therapeutic anticoagulation and antiplatelet therapy, a NOAC and single oral antiplatelet (preferably clopidogrel) is the default strategy after a short period of triple antithrombotic therapy (up to 1 week in hospital).<sup>458</sup> Coronary artery bypass graft (CABG) surgery can be considered in patients with extensive CAD who are not amenable with PCI, after MDT discussion and where cancer prognosis is  $> 12$  months.

Thrombocytopenia (platelet count  $< 100\,000/\mu\text{L}$ ) is present in about 10% of patients with cancer and may complicate ACS management. Based on a small series, coronary angiography can be safely performed in these patients when preventative measures to avoid bleeding are taken: platelet transfusion before catheterization (for platelets  $< 20\,000/\mu\text{L}$ ), radial access, careful haemostasis, and the use of a lower heparin dose (30–50 U/kg).<sup>486</sup> Antiplatelets should not be withheld unless platelet count is  $< 10\,000/\mu\text{L}$  for aspirin or  $< 30\,000/\mu\text{L}$  for clopidogrel. For PCI and CABG, experts advise minimum platelet counts of  $30\,000/\mu\text{L}$  and  $50\,000/\mu\text{L}$ , respectively.<sup>484</sup>

In case of MI with non-obstructive coronary arteries, CMR may be considered to detect other causes of myocardial injury, especially myocarditis and TTS.

When acute ischaemia is provoked by cancer therapy, alternative cancer therapies should be considered after a MDT discussion. In the case of coronary vasospasm secondary to fluoropyrimidines, and in the absence of an alternative therapy, a rechallenge, although controversial, can be considered in a monitored unit after exclusion of severe CAD (CT or coronary angiography) and after initiation of prophylactic therapy with long-acting nitrates and calcium channel blockers (CCB).<sup>487–489</sup>

Following ACS, a review of the cancer medications is recommended, and any cancer drug associated with thrombosis and MI should be stopped. Restarting cancer drugs associated with acute thrombosis and MI after ACS (Table 7) should occur only after a MDT to explore other cancer therapies, with appropriate patient education and consent. Cancer therapies not associated with MI can be restarted once revascularization, where indicated, has been completed and the patient is stabilized on ACS medical therapy without complications.

### Recommendation Table 28 — Recommendations for the management of acute coronary syndromes in patients receiving anticancer treatment

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| An invasive strategy is recommended in patients with cancer presenting with STEMI or high-risk NSTEMI-ACS with life expectancy $\geq 6$ months. <sup>475,479,483</sup>   | I                  | B                  |
| A conservative non-invasive strategy should be considered in patients with poor cancer prognosis <sup>c</sup> (with life expectancy $< 6$ months) and/or very high bleeding risk presenting with STEMI or NSTEMI-ACS. <sup>479</sup> | IIa                | C                  |
| A temporary interruption of cancer therapy is recommended in patients where the cancer therapy is suspected as a contributing cause. <sup>d,10,490</sup>   | I                  | C                  |
| A short DAPT strategy should be considered in patients with cancer with very high bleeding risk treated with PCI for an ACS. <sup>e</sup>  | IIa                | C                  |

Continued

|   |     |   |
|---|-----|---|
| In patients with cancer, thrombocytopenia, and ACS, aspirin is not recommended if platelets <10 000/ $\mu$ L.   | III | C |
| In patients with cancer, thrombocytopenia, and ACS, clopidogrel is not recommended if platelets <30 000/ $\mu$ L and prasugrel or ticagrelor are not recommended if platelets <50 000/ $\mu$ L. | III | C |
| Ticagrelor or prasugrel may be considered in patients with cancer with low bleeding risk and excessive thrombotic risk who are treated with PCI for ACS.  | IIb | C |

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ACS, acute coronary syndromes; CrCl, creatinine clearance; CV, cardiovascular; DAPT, dual antiplatelet therapy; GI, gastrointestinal; GU, genitourinary; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; ULN, upper limit of normal.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Related to advanced cancer stage and/or severe irreversible non-CV comorbidities.

<sup>d</sup>Anticancer therapies associated with high risk of ACS (very common [ $>10\%$ ]): capecitabine, paclitaxel, cisplatin, carfilzomib, bevacizumab, ramucirumab, aflibercept, axitinib, sorafenib, pazopanib, cabozantinib, lenvatinib, ponatinib, erlotinib.

<sup>e</sup>High risk of GI or GU bleeding, significant drug–drug interactions, severe renal dysfunction (CrCl <30 mL/min), significant liver disease (alanine aminotransferase/aspartate aminotransferase  $>2 \times$  ULN), or significant thrombocytopenia (platelet count <50 000/ $\mu$ L).

### 6.2.2. Chronic coronary syndromes

Several cancer treatments are associated with an increased risk of stable angina and chronic coronary syndromes (CCS).<sup>491</sup> 5-FU and capecitabine can precipitate effort angina in some cases.<sup>4,482,492</sup> Platinum-containing chemotherapy-induced ischaemia usually occurs after one of the first three cycles and in patients with underlying CAD.<sup>493</sup> The incidence of cardiac ischaemia is 1–5% with antimicrotubule agents, 2–3% with small-molecule VEGF-TKI, and 0.6–1.5% with VEGFi monoclonal antibody therapies.<sup>492</sup> Nilotinib, ponatinib,<sup>494</sup> and ICI<sup>335</sup> also accelerate atherosclerosis, which can lead to stable angina.

Patients receiving cancer therapy who present with new stable angina should have careful clinical evaluation, with aggressive CVRF modification and an initial medical management of their symptoms.<sup>484</sup> The diagnosis and management of CAD should follow the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.<sup>100</sup>

The management of CCS is similar in patients with and without cancer, in accordance with guideline recommendations.<sup>100</sup> However, in the setting of CCS, decisions regarding coronary revascularization should be undertaken by a MDT that includes cardio-oncology, intervention, and oncology specialists.<sup>5</sup> PCI in patients with cancer is associated with an increased risk of bleeding, 90-day readmissions for acute MI, in-hospital and long-term mortality, and the need for repeat revascularization, with the magnitude of risk depending on both cancer type and stage.<sup>495,496</sup> The excess bleeding risk should be mitigated by keeping the duration of DAPT as short as possible.<sup>497,498</sup> The risk is higher in patients with a cancer diagnosis within the preceding year.<sup>477</sup>

### Recommendation Table 29 — Recommendation for the management of chronic coronary syndromes in patients receiving anticancer treatment

| Recommendation   | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Individualized duration of DAPT is recommended in patients with cancer with CCS, following revascularization, based upon thrombotic/ ischaemic and bleeding risk, type and stage of cancer, and current cancer treatment. <sup>100,498</sup> | I                  | C                  |

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CCS, chronic coronary syndromes; DAPT, dual antiplatelet therapy.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

### 6.3. Valvular heart disease

New or worsening VHD in patients with cancer may be related to coexisting conditions, including CTRCD, ACS, PH, endocarditis, cardiac tumours, and mechanical prosthetic valve thrombosis.<sup>499,500</sup>

Pre-existing severe VHD is associated with an increased risk of CTRCD,<sup>12,501–503</sup> and may also pose a risk for cancer surgery outcomes. In patients with mechanical prosthetic valves, the risk of thrombosis vs. bleeding should be carefully balanced during chemotherapy treatment. In patients with severe VHD diagnosed at baseline assessment, a MDT is required before cancer therapy to decide the best treatment option. Cardiac surgery is frequently challenging in patients with cancer because of comorbidities, frailty, mediastinal fibrosis due to prior RT, impaired wound healing, and the need for urgent oncology treatment (surgery, chemotherapy, targeted cancer therapies that effect wound healing). Transcatheter aortic valve implantation (TAVI) may be a viable option for patients with cancer with severe aortic stenosis to limit recovery time and delays in starting cancer treatment.<sup>504–506</sup>

Patients with cancer suspected of new or worsening VHD, such as dyspnoea or a new cardiac murmur, or those with fever and positive blood cultures, should be screened for endocarditis and managed according to the recommendations from the 2021 ESC/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for the management of VHD,<sup>507</sup> while considering the cancer-related prognosis. If valve surgery or percutaneous valve treatment is indicated in a patient receiving cancer treatment, then a MDT is recommended regarding type of valve treatment and periprocedural management of cancer treatments.

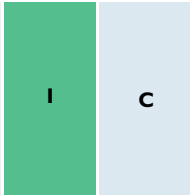
### Recommendation Table 30 — Recommendations for the management of valvular heart disease in patients receiving anticancer treatment

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| In patients with cancer and pre-existing severe VHD, management according to the 2021 ESC/ EACTS Guidelines for the management of VHD is recommended, taking into consideration cancer prognosis and patient preferences. <sup>507</sup> | I                  | C                  |

Continued



In patients with cancer developing new VHD during cancer therapy, management according to the 2021 ESC/EACTS Guidelines for the management of VHD<sup>507</sup> is recommended, taking into consideration cancer prognosis and patient comorbidities.



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EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; VHD, valvular heart disease.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 6.4. Cardiac arrhythmias

### 6.4.1. Atrial fibrillation

AF may occur in patients with cancer in different settings: it may be a marker of cancer type or occult cancer, or it may develop in patients undergoing surgery, chemotherapy, or RT.<sup>508,509</sup> All types of cancer show an increased risk of AF compared with the control group, but the risk of AF depends on the cancer type and stage.<sup>510,511</sup> AF during a cancer treatment may be caused by a specific therapy or interaction with a pre-existing substrate in older patients with cancer.

During cancer therapy AF may occur with a frequency ranging from 2% to 16%, according to a variety of factors,<sup>4,490,508,512–514</sup> and may present either as first-diagnosed AF or as recurrence of paroxysmal AF. The risk of developing AF is greater in patients older than 65 years and/or with pre-existing CVD.<sup>4,509,512,515</sup> Cancer surgery is associated with a variable rate of AF occurrence, with the highest incidence reported for lung surgery, ranging from 6% to 32%, but with occurrence also in cases of non-thoracic surgery (e.g. 4–5% after colectomy).<sup>509</sup>

Many anticancer drugs have been associated with an increased risk of AF both in terms of incident and recurrent AF (Supplementary data, Table S18).<sup>251</sup> AF may occur shortly after treatment<sup>516</sup> or weeks or months after starting treatment.<sup>517,518</sup> The pathophysiology of AF associated with cancer is complex and has been extensively reviewed elsewhere (Figure 30).<sup>509</sup>

In patients with cancer, the occurrence of AF is associated with a two-fold higher risk of systemic thromboembolism/stroke and a six-fold increase in the risk of HF.<sup>4,509,512</sup> The coexistence of cancer increases the risk of all-cause mortality, major bleeding, and intracranial haemorrhage in patients with AF. The association between cancer and ischaemic stroke differs between cancer types, and in some types, the risk of bleeding seems to exceed the thromboembolic risk.<sup>519</sup> The management of AF in patients with cancer should follow the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation<sup>273</sup> and the 'ABC pathway' (Atrial fibrillation Better Care) approach should be applied (A: Anticoagulation to avoid stroke/systemic embolism, B: Better symptom control with rate- and/or rhythm-control drugs and interventions, and C: Comorbidities and CVRF management, including lifestyle changes).<sup>273,520</sup>

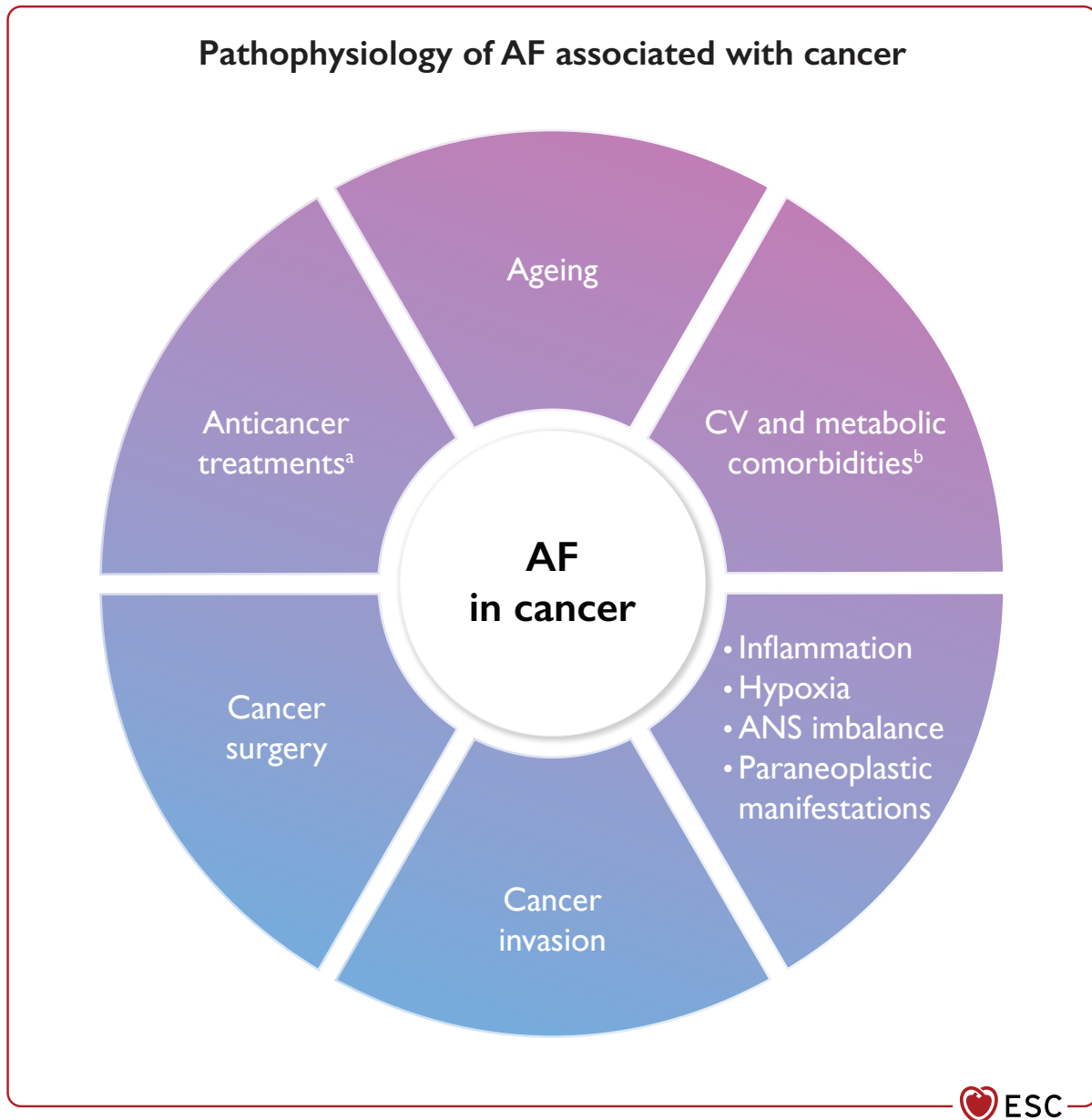
The acute management of AF in patients with cancer should consider electrical cardioversion in cases of haemodynamic instability,<sup>521</sup> while in others, the alternative between rate and rhythm control has several important considerations specific to patients with cancer. Drugs for rhythm control may lead to QT-interval prolongation,<sup>369</sup> frequently have drug–drug interactions with cancer therapies, or

may have a limited efficacy if a cancer therapy is the specific cause of the AF.<sup>508</sup> Among rate-control drugs, beta-blockers are preferred, especially if the cancer therapies have potential CTRCD risk, whereas diltiazem and verapamil should be avoided where possible due to their drug–drug interactions and negative inotropic effects.<sup>508</sup> The possibility of AF ablation should be discussed in selected patients with HF/LVD and/or uncontrolled symptoms, taking into consideration cancer status and prognosis in the context of a MDT approach.<sup>522</sup>

A complex issue in patients with cancer with new AF is risk stratification for stroke/systemic embolism, which according to guidelines, should be based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Congestive heart failure, Hypertension, Age  $\geq$  75 years [2 points], Diabetes mellitus, Stroke [2 points]—Vascular disease, Age 65–74 years, Sex category [female]).<sup>273,523,524</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc score has not been extensively validated in patients with cancer.<sup>525</sup> In a large cohort of patients with AF, the predictive value of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was lower in patients with cancer than in those without, but a progressive increase in the risk of ischaemic stroke according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was also found in AF patients with cancer (from 0.9% per year to 8.9% per year).<sup>519</sup> However, the scope of this score is not to identify high-risk patients, but rather to identify low-risk individuals in whom anticoagulation can be avoided. A study based on the Danish healthcare system data set found that CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of 0 and 1 in patients with recent cancer were linked with higher risk of stroke/thromboembolism at 2 years than in patients without recent cancer.<sup>526</sup> This concept should be considered in defining the risk/benefit ratio of anticoagulation in individual patients with cancer. Therefore, the decision for anticoagulation in patients with an active malignancy should take into account the enhanced thrombotic and/or bleeding risk and other risk prediction scores used for general AF populations.<sup>509</sup> For bleeding risk assessment, the HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding Labile international normalized ratio, Elderly, Drugs or alcohol) score may be considered. A proposed approach to anticoagulation therapy in cancer, based on the acronym T (thrombotic risk), B (bleeding risk), I (interactions among drugs), P (patient access and preferences), is outlined in Figure 31.<sup>519,527</sup>

Long-term anticoagulation is recommended in adult patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq$  2 in men or  $\geq$  3 in women and must be considered also when the score is 1 in men and 2 in women.<sup>273</sup> The clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent, post-operative) should not influence the indication of thromboprophylaxis.<sup>273</sup> The same approach can be proposed for patients with cancer and AF, also considering that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score likely underestimates their thromboembolic risk.<sup>530</sup> In the specific setting of cancer, decision-making on long-term oral anticoagulation should also consider the cancer-related type, stage, prognosis and the potentially changing thromboembolic or bleeding risk.<sup>508,509</sup> The use of vitamin K antagonists (VKA) in cancer is limited by their drawbacks in this setting; however, they remain the only indicated anticoagulants in patients with moderate to severe mitral stenosis or a mechanical prosthetic valve. LMWH constitute a viable short-term anticoagulation option, particularly in hospitalized patients with a recent cancer diagnosis, advanced cancer disease, or during some cancer treatments (e.g.



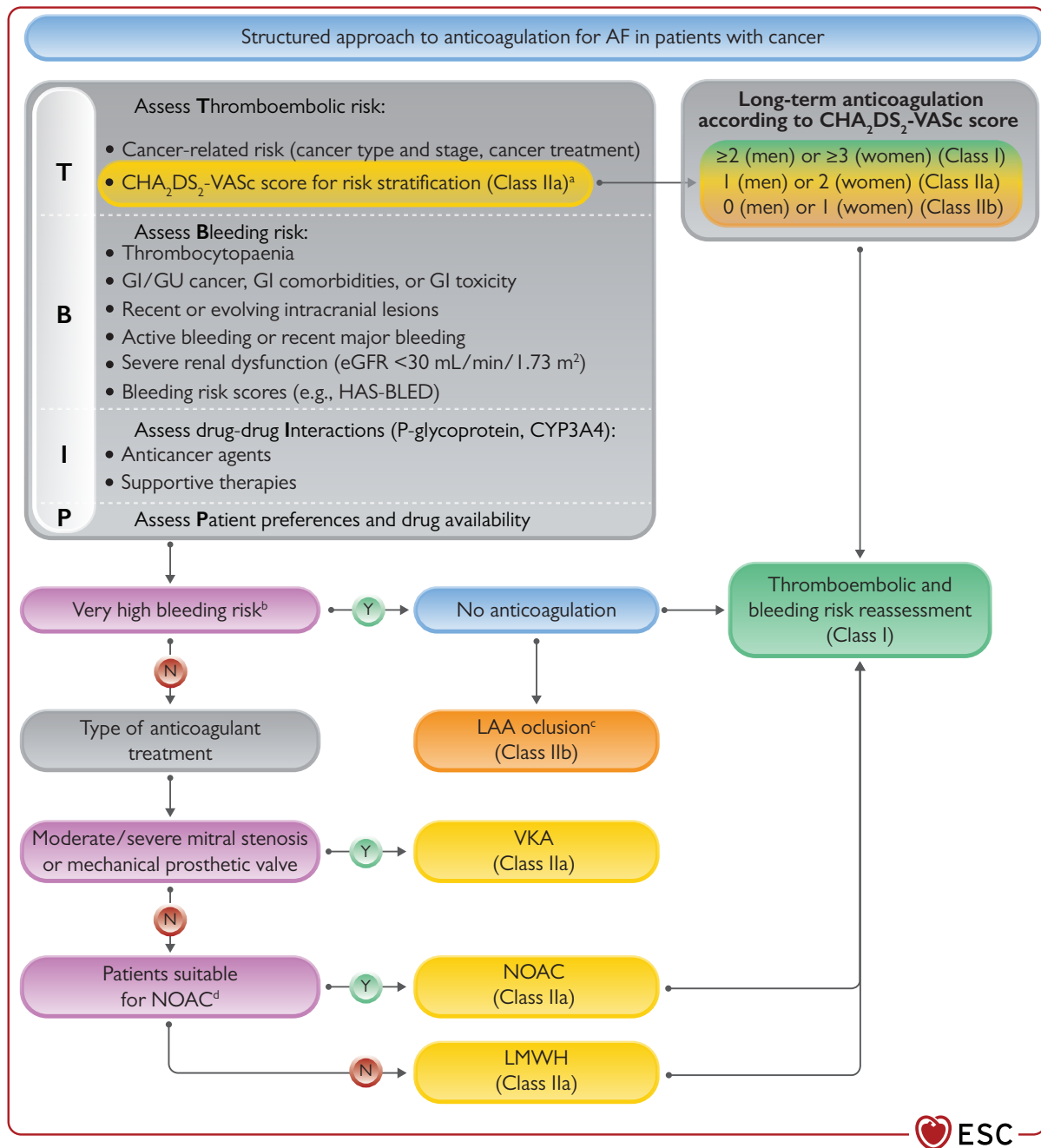


**Figure 30** Pathophysiology of atrial fibrillation associated with cancer. AF, atrial fibrillation; ANS, autonomic nervous system; CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; IHD, ischaemic heart disease; VHD, valvular heart disease. <sup>a</sup>Supplementary data, Table S18. <sup>b</sup>Obesity, hypertension, DM, CVDs (HF, VHD, IHD, cardiomyopathies, cardiac amyloidosis), thyroid diseases, obstructive sleep apnoea, chronic obstructive pulmonary disease, chronic kidney disease, autonomic dysfunction, alcohol consumption, genetic predisposition.

patients receiving myelosuppressive chemotherapy or with recent active bleeding). However, LMWH efficacy for stroke or systemic embolism prevention in AF has not been established and their use is only based on their proven efficacy and safety in VTE. The use of a NOAC for AF has not been evaluated in a dedicated RCT in patients with cancer. However, secondary analyses of seminal NOAC trials using direct factor Xa inhibitors (ROCKET AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation], ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic

Events in Atrial Fibrillation], ENGAGE AF-TIMI 48 [Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48]) and observational data suggest better safety and at least similar effectiveness of the NOAC when compared with VKA in patients with AF and active cancer.<sup>531–538</sup> NOAC use in cancer is limited by drug–drug interactions,<sup>508</sup> severe renal dysfunction, increased risk of bleeding in patients with unoperated or residual GI or genitourinary (GU) malignancies, or impaired GI absorption.

Left atrial appendage (LAA) occluder devices are used in very selected patients with cancer in clinical practice. The potential



**Figure 31** Structured approach to anticoagulation for atrial fibrillation in patients with cancer. AF, atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke (2 points)—Vascular disease, Age 65–74 years, Sex category (female); CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GU, genitourinary; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding Labile international normalized ratio, Elderly, Drugs or alcohol; LA, left atrial; LAA, left atrial appendage; LMWH, low-molecular-weight heparins; N, no; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonists; Y, yes. <sup>a</sup>In selected patients, cardiac imaging parameters related to increased thromboembolic risk should be considered (LAA thrombus, severely dilated left atrium, severely impaired LA strain<sup>528</sup>). <sup>b</sup>**Very high bleeding risk**: active or recent major bleeding (<1 month previously); recent/evolving intracranial lesions; platelet count <25 000/μL. According to the International Society on Thrombosis and Haemostasis,<sup>529</sup> major bleeding is defined as a fall in haemoglobin level ≥2 g/dL and/or transfusion of ≥2 units of red blood cells and/or fatal bleeding and/or bleeding in a critical area (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal). <sup>c</sup>**Percutaneous left atrial appendage closure** may be considered in patients with a life expectancy of >1 year who are at high thromboembolic and bleeding risk and in whom anticoagulation is contraindicated. <sup>d</sup>**Conditions favouring LMWH**: unoperated GI/GU cancer; GI comorbidities or toxicity; severe renal dysfunction (CrCl <15 mL/min); NOAC major drug–drug interactions, platelet count <50 000/μL.

complications related to the implant—including device-related thrombosis—and the lack of prospective data in the setting of patients with cancer have to be taken into consideration for this option. In a recent retrospective analysis of patients referred to LAA occlusion the risk of in-hospital ischaemic stroke/transient ischaemic attack was higher in patients with active cancer than in those with no cancer or prior history of cancer. The rate of in-hospital composite outcome (in-hospital death, ischaemic stroke/transient ischaemic attack, systemic embolism, bleeding requiring blood transfusion, pericardial effusion/cardiac tamponade treated with pericardiocentesis or surgically, and removal of embolized device) and 30-day/180-day readmission outcomes were not significantly different between the groups.<sup>539</sup>

The onset of AF may be related to transient factors, such as the peri-operative period or the effect of drugs known to facilitate AF onset. The traditional assumption that in these cases, AF may occur as an isolated event without recurrence may not be valid as the occurrence of AF may often be related to a pre-existing atrial substrate with vulnerability to AF.<sup>540</sup> Post-operative AF has been associated with a four- to five-fold risk of AF recurrence in the following 5 years, along with a comparable long-term thromboembolic risk with AF not related to surgery.<sup>273,540,541</sup> Anticoagulation therapy yielded a similarly lower risk of thromboembolic events and all-cause death in both groups.<sup>541</sup> In the absence of direct evidence, anticoagulation to prevent thromboembolic events should be considered in patients at risk for stroke with AF after cancer surgery considering the anticipated net clinical benefit and informed patient preferences.<sup>273</sup> Similarly, in patients with AF apparently related to transient factors—such as chemotherapy, other drugs, or electrolyte disturbances—a careful clinical assessment of the propensity to further develop AF is recommended, with need to revisit the risk/benefit ratio of long-term prescription of anticoagulation after a period of 3 months.

In patients with cancer and newly detected or recurrence of AF, decision making on anticancer treatment requires a cardio-oncology MDT management,<sup>5</sup> taking into account that neither the presence nor the risk of AF constitutes contraindications to anticancer treatment.<sup>508,517</sup>

**Recommendation Table 31 — Recommendations for the management of atrial fibrillation in patients receiving anticancer treatment**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| CHA <sub>2</sub> DS <sub>2</sub> -VASc score should be considered for risk stratification for stroke/systemic thromboembolism taking into account that it may underestimate the actual thromboembolic risk. <sup>519,526</sup>   | IIa                | C                  |
| Long-term anticoagulation is recommended for stroke/systemic thromboembolism prevention in patients with cancer with AF and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2 (men) or ≥3 (women) as per the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. <sup>273</sup> | I                  | C                  |

Continued

|  |     |   |
|--|-----|---|
| Long-term anticoagulation should be considered for stroke/systemic thromboembolism prevention in patients with cancer with AF and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score = 1 (men) or = 2 (women) as per the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. <sup>273</sup> | IIa | C |
| Patients with cancer, <sup>c</sup> AF, and CHA <sub>2</sub> DS <sub>2</sub> -VASc score 0 (men) or 1 (women) may have a higher thrombotic risk than patients without cancer and may be considered for therapeutic anticoagulation after consideration of the bleeding risk. <sup>526</sup>                       | IIb | C |
| Thromboembolic and bleeding risk reassessment is recommended during follow-up in patients with cancer with AF. <sup>9,273</sup>  | I   | C |
| NOAC should be considered for stroke prevention in preference to LMWH and VKA (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis) in patients without a high bleeding risk, significant drug–drug interactions, or severe renal dysfunction. <sup>531–537</sup>              | IIa | B |
| LMWH should be considered in patients with active cancer <sup>e</sup> and AF who are not suitable for NOAC. <sup>f,525</sup>   | IIa | C |
| LAA occlusion may be considered for stroke prevention in patients with cancer with AF and contraindications for long-term anticoagulation with a life expectancy >12 months. <sup>273,539</sup>  | IIb | C |
| Antiplatelet therapy or prophylactic LMWH are not recommended for stroke or systemic thromboembolism prevention in AF with cancer. <sup>273</sup>  | III | C |
| Heart rate control strategy, preferably with beta-blockers, should be considered in patients who develop well-tolerated AF while they are receiving active cancer treatment <sup>g</sup> .   | IIa | C |

5-FU, 5-fluorouracil; AF, atrial fibrillation; BMI, body mass index; CHA<sub>2</sub>DS<sub>2</sub>-VASc, Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes mellitus, Stroke (2 points)—Vascular disease, Age 65–74 years, Sex category (female); CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; EGFR, epidermal growth factor receptor; ESC, European Society of Cardiology; HF, heart failure; LAA, left atrial appendage; LMWH, low-molecular-weight heparins; LV, left ventricular; MM, multiple myeloma; NOAC, non-vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonists.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Factors that may increase thromboembolic risk in patients with cancer including comorbidities (proteinuria > 150 mg/24 h, eGFR < 45 mL/min/1.73 m<sup>2</sup>, BMI ≥ 30 kg/m<sup>2</sup>, thrombophilia), cancer type (pancreatic, gastric, ovarian, brain, lung, MM), cancer stage (metastatic disease) anticancer therapies: alkylating agents, aflibercept, bevacizumab, anthracyclines, capecitabine, 5-FU, gemcitabine, methotrexate, EGFR inhibitors, bleomycin, axitinib, lenvatinib, pazopanib, sorafenib, sunitinib, carfilzomib, irinotecan, taxanes, tasonermin, tretinoin.

<sup>d</sup>Stroke and bleeding risk may change during both cancer treatment and the course of the underlying disease; reassessment is important to inform treatment decisions and address potentially modifiable bleeding risk factors.

<sup>e</sup>Patients receiving cancer treatment, patients diagnosed with cancer in the past 6 months, and patients with progressive or advanced disease.

<sup>f</sup>High bleeding risk, severe renal dysfunction (CrCl < 15 mL/min); NOAC major drug–drug interactions.

<sup>g</sup>Asymptomatic or mild symptomatic patients without HF signs or symptoms or deterioration of LV function. The optimal heart rate target in AF patients is unclear. A resting heart rate <110 bpm (i.e. lenient rate control) should be considered as the initial heart rate target for rate control therapy. A review of rate vs. rhythm strategy should be made at the end of cancer treatment.<sup>273</sup>

### 6.4.2. Long corrected QT interval and ventricular arrhythmias

VA are not common during cancer, although their incidence increases in patients with advanced cancer and CV comorbidities.<sup>49,259,516,542</sup> Mechanisms proposed to explain cancer therapy-induced VA include: (1) direct effects of cancer drugs on the activity/expression of ionic channels that regulate the ventricular action potential,<sup>4,369,442,516,542,543</sup> and (2) a permanent arrhythmogenic substrate created by cancer and systemic inflammation caused by cancer, pre-existing CV comorbidities, and/or a new CTR-CVT.<sup>4,9,259,369,442,516,542,543</sup>

Treatment of cancer therapy-induced VA should follow general clinical guidelines.<sup>22,442,544</sup> In patients with asymptomatic self-terminating VA, drug discontinuation is not required unless they have additional CVRF or persistent ECG abnormalities.<sup>270</sup> Symptomatic VA require cancer drug dose reduction or discontinuation and patients should be referred to the cardiologist for evaluation and treatment.<sup>4,442</sup>

Recurrent symptomatic life-threatening VA require urgent intervention.<sup>4,270,442,544</sup> The administration of class IA, IC, and III antiarrhythmic drugs is limited by the risk of drug–drug interactions and QTc prolongation. Beta-blockers and class IB drugs are less likely to cause drug interactions or QTc prolongation. Beta-blockers are the preferred choice if the cancer drug is also associated with CTRCD. Amiodarone is the antiarrhythmic drug of choice in patients with structural heart disease and haemodynamic instability.

**Table 8 Risk factors for drug-induced QT prolongation and torsade de pointes**

| Correctable  | Non-correctable  |
|--|--|
| QT-prolonging drugs <sup>a</sup> <ul style="list-style-type: none"> <li>• Antiarrhythmics</li> <li>• Antibiotics</li> <li>• Antidepressants</li> <li>• Antifungals</li> <li>• Antiemetics</li> <li>• Antihistamines</li> <li>• Antipsychotics</li> <li>• Loop diuretics</li> <li>• Opioids (methadone)</li> </ul> Bradyarrhythmia<br>Electrolyte imbalance/abnormalities <ul style="list-style-type: none"> <li>• Hypokalaemia (<math>\leq 3.5</math> mEq/L)</li> <li>• Hypomagnesaemia (<math>\leq 1.6</math> mEq/L)</li> <li>• Hypocalcaemia (<math>\leq 8.5</math> mEq/L)</li> </ul> Inadequate dose adjustment of renal or hepatic cleared QT-prolonging drugs | Acute myocardial ischaemia<br>Age > 65 years<br>Baseline QTc interval prolongation <sup>b</sup><br>Family history of sudden death (congenital LQTS or genetic polymorphism)<br>Female sex<br>Impaired renal function (for renally excreted drugs)<br>Liver disease (for hepatically excreted drugs)<br>Personal history of syncope or drug-induced TdP<br>Pre-existing CVD (CAD, HF, LV hypertrophy) |

CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure; LQTS, long QT syndrome; LV, left ventricular; QTc, corrected QT interval; TdP, torsade de pointes.

<sup>a</sup>See <https://www.crediblemeds.org>.

<sup>b</sup>QTc using Fridericia correction ( $QTcF = QT/3\sqrt{RR}$ ) is recommended in patients with cancer.

**Table 9 Classification of corrected QT interval prolongation induced by cancer drug therapy**

| Classification  | Drugs  |
|---|--|
| <b>High risk:</b> QTcF prolongation $\geq 10$ ms and risk of TdP                              | <ul style="list-style-type: none"> <li>• Aclarubicin</li> <li>• Arsenic trioxide</li> <li>• Glasdegib</li> <li>• Nilotinib</li> <li>• Oxaliplatin</li> <li>• Pazopanib</li> <li>• Ribociclib</li> <li>• Sunitinib</li> <li>• Toremfene</li> <li>• Vandetanib</li> </ul>  |
| <b>Moderate risk:</b> QTcF prolongation $\geq 10$ ms and low or no risk of TdP (or uncertain) | <ul style="list-style-type: none"> <li>• Abarelix</li> <li>• Belinostat</li> <li>• Brigantini</li> <li>• Carbozantinib</li> <li>• Ceritinib</li> <li>• Crizotinib</li> <li>• Dovitinib</li> <li>• Entrectinib</li> <li>• Eribulin</li> <li>• Gilteritinib</li> <li>• Ivosidenib</li> <li>• Lapatinib</li> <li>• Lenvatinib</li> <li>• Osimertinib</li> <li>• Panobinostat</li> <li>• Rucaparib</li> <li>• Selpercatinib</li> <li>• Sorafenib</li> <li>• Tipiracil/trifluridine</li> <li>• Vemurafenib</li> </ul> |
| <b>Low risk:</b> QTcF prolongation $< 10$ ms <sup>a</sup>                                     | <ul style="list-style-type: none"> <li>• ADT</li> <li>• Afatinib</li> <li>• Axitinib</li> <li>• Binimetinib</li> <li>• Bortezomib</li> <li>• Bosutinib</li> <li>• Carfilzomib</li> <li>• Dabrafenib</li> <li>• Dasatinib</li> <li>• Encorafenib</li> <li>• Midostaurin</li> <li>• Pertuzumab</li> <li>• Ponatinib</li> <li>• Romidepsin</li> <li>• Quizartinib</li> <li>• Tamoxifen</li> <li>• Vorinostat</li> </ul>   |

ADT, androgen deprivation therapy; QTcF, corrected QT interval using Fridericia correction; TdP, torsade de pointes.

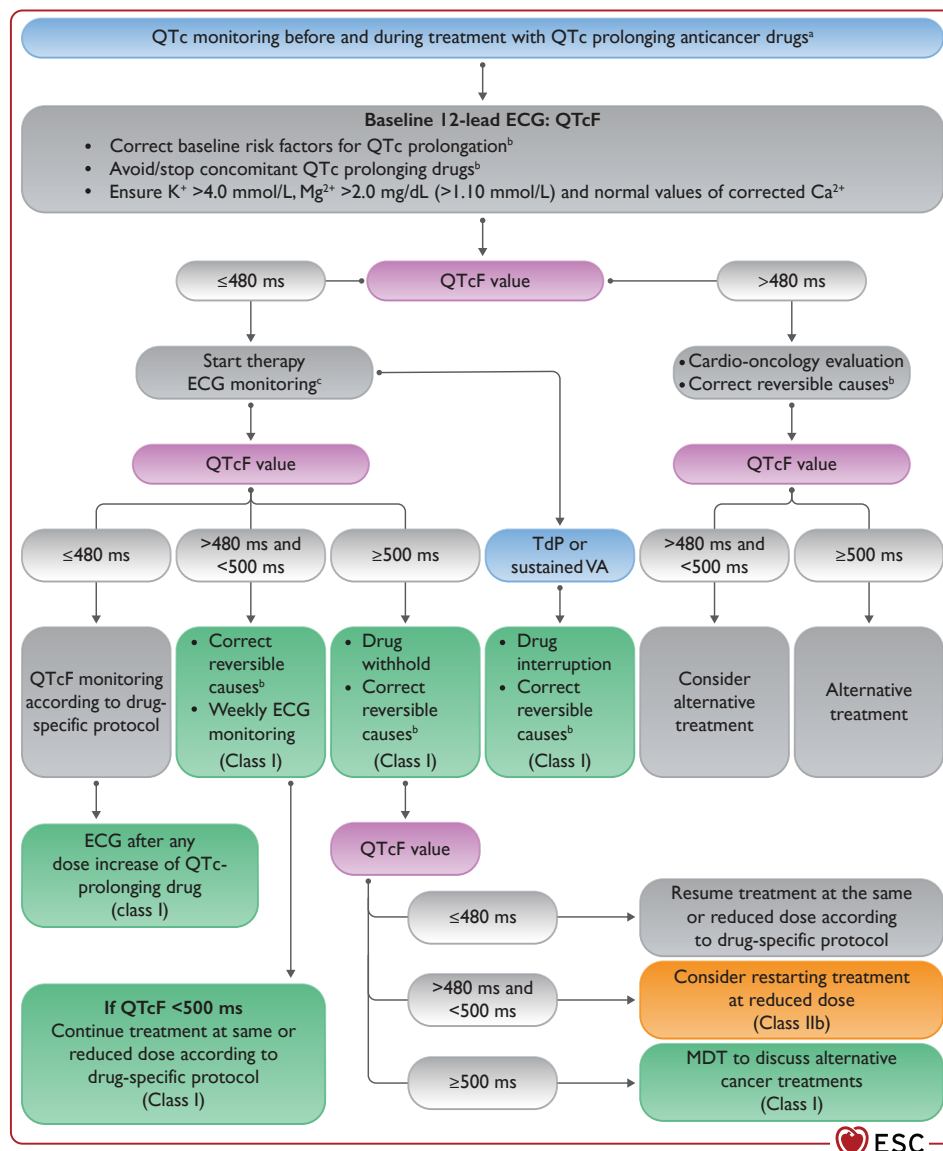
<sup>a</sup>ADT may prolong the QTc interval (GnRH agonist, GnRH antagonist, bicalutamide, flutamide, apalutamide, darolutamide, enzalutamide, and abiraterone) (see Figure 21). Developed from EMA prescribing information,<sup>252</sup> FDA prescribing information,<sup>253</sup> and AZCERT.<sup>547</sup>

Decisions on the use of antiarrhythmic drugs or device therapy (cardioverter defibrillators, catheter ablation) should consider life expectancy, quality of life, and complication risks.<sup>349</sup>

Most cancer therapy-induced VA are related to a prolongation of QTc leading to the development of TdP.<sup>259,516,542</sup> Risk factors for QTc prolongation and TdP are summarized in [Table 8](#).<sup>4,22,45,48,516,543</sup>

The upper 99% limits of normal for QTc values in the general population are 450 ms for men and 460 ms for women.<sup>545</sup> Although there is no threshold of QTc prolongation at which TdP can occur, a QTc ≥ 500 ms is associated with a two- to three-fold higher risk for TdP, while TdP rarely occurs when QTc is

<500 ms.<sup>442</sup> Although the incidence of QTc prolongation ≥500 ms and TdP is low during cancer therapy, QTc prolongation to levels that require closer monitoring (QTc ≥ 480 ms) is more common ([Table 9](#)).<sup>4,9,22,45,48,49,259,369,516,543,546</sup> Changes in the QT interval of >60 ms from baseline should not routinely affect treatment decisions if the QTc remains <500 ms.<sup>1</sup> Cardiology consultation is advised in patients with an abnormal baseline QTc interval, patients treated with drugs that prolong the QT interval, those who develop new cardiac symptoms (syncope or pre-syncope, rapid palpitations or QTc prolongation with new-onset bradycardia, high degree of heart block), and/or those with known inherited arrhythmia



**Figure 32** Corrected QT interval monitoring before and during treatment with corrected QT interval-prolonging anticancer drugs. Ca<sup>2+</sup>, calcium; ECG, electrocardiogram; K<sup>+</sup>, potassium; MDT, multidisciplinary team; Mg<sup>2+</sup>, magnesium; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction; TdP, Torsade de pointes; VA, ventricular arrhythmias. QT interval using Fridericia correction (QTcF = QT/√RR) is recommended in patients with cancer. Upper 99% limits of normal for QTc values in the general population are 450 ms for men and 460 ms for women.<sup>369</sup> [Table 9](#), [Table 8](#) and <https://www.crediblemeds.org>. <sup>c</sup>ECG monitoring at baseline, once steady-state anticancer drug levels have been achieved, after each dose modification, or any treatment interruption >2 weeks; monthly for the first 3 months, and then periodically during treatment depending on patient-specific risk factors and cancer treatment.

disorders.<sup>4,45,48,442,544</sup> The challenges for the cardio-oncology teams are to identify patients more susceptible to developing VA, determine whether a VA is directly due to CTR-CVT, individualize the treatment strategy, and optimize clinical monitoring during treatment.

Figure 32 shows the algorithm for the management of QTc prolongation during cancer therapy. In patients with cancer, the Fridericia formula is recommended and has demonstrated less error than other correction methods such as Bazett at both high and low heart rates.<sup>44</sup> In patients treated with QTc-prolonging drugs, serum electrolytes and other risk factors should be closely monitored and corrected, and concomitant QT-prolonging drugs avoided if possible.<sup>4,22,45,369,543</sup> For selected cancer drugs, there are specific manufacturer recommendations for ECG monitoring during treatment, dosage adjustments, or discontinuation of therapy in case of QTc prolongation.<sup>548</sup>

Although there are no recommendations, patients with cancer with QTc prolongation associated with severe bradycardia or sinus pauses may benefit from isoprenaline infusion or temporary pacing. Despite present restrictions, the improved prognosis for many malignancies is increasing the number of patients with cancer who are candidates for an implantable cardioverter defibrillator (ICD), particularly when life expectancy is >1 year (including patients who experienced resuscitated sudden cardiac death or severe VA from a QTc-prolonging drug with no alternative treatment available).

### Recommendation Table 32 — Recommendations for the management of long corrected QT interval and ventricular arrhythmias in patients receiving anticancer treatment

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| <b>How to manage QTc prolongation in patients with cancer</b>  |                    |                    |
| Discontinuation of QTc-prolonging cancer therapy is recommended in patients who develop TdP or sustained ventricular tachyarrhythmias during treatment. <sup>549</sup>   | I                  | C                  |
| Temporary interruption of QTc-prolonging cancer therapy is recommended in patients who develop asymptomatic QTcF ≥ 500 ms and an ECG should be repeated every 24 h until resolution of the QTcF prolongation. <sup>549</sup> | I                  | C                  |
| Immediate withdrawal of any offending drug and correction of electrolyte abnormalities and other risk factors <sup>c</sup> is recommended in patients with cancer who develop QTcF ≥ 500 ms. <sup>349,442,546</sup>          | I                  | C                  |
| Weekly ECG monitoring is recommended in asymptomatic patients with cancer with QTcF 480–500 ms who are treated with a QTc-prolonging cancer therapy. <sup>349,442,546</sup>  | I                  | C                  |
| A 12-lead ECG is recommended after any dose increase of QTc-prolonging cancer therapy. <sup>270,442,544</sup>  | I                  | C                  |

Continued

### Restarting QTc-prolonging cancer therapy

A multidisciplinary discussion is recommended before restarting QTc-prolonging drugs in patients who have developed significant QTcF prolongation, to discuss alternative cancer treatments.<sup>4,22,259,349,442,546</sup>

In patients who experienced significant QTcF prolongation, restarting the culprit QTc-prolonging cancer treatment may be considered, ideally at a reduced dose according to each drug recommendation.<sup>45,259,349,442,546,549</sup>

Weekly ECG monitoring during the first 4–6 weeks and then monthly thereafter is recommended in patients with cancer after restarting QTc-prolonging cancer therapy.<sup>549</sup>

ECG, electrocardiogram; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction; TdP, torsade de pointes.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>See <https://www.crediblemeds.org> and Table 8.

### 6.4.3. Bradyarrhythmias

AV conduction disease can be caused by ICI in the presence or absence of myocarditis. If the PR interval increases (new first-degree heart block) in patients treated with ICI, serial ECG monitoring is recommended, and if PR prolongation to >300 ms develops, the patient should be hospitalized under close ECG monitoring and i.v. methylprednisolone is recommended.<sup>550</sup>

IMiD (thalidomide, pomalidomide)<sup>285</sup> and ALK inhibitors (crizotinib, alectinib, brigatinib, or ceritinib)<sup>551</sup> are associated with sinus bradycardia. Holter ECG monitoring is recommended to exclude significant sinus pauses in symptomatic patients. In asymptomatic patients with normal LV function, sinus bradycardia is usually well tolerated and treatment can continue. If patients are symptomatic (syncope, pre-syncope of reduced exercise tolerance from chronotropic incompetence) then a trial of cancer drug withdrawal to confirm causation with the symptoms is recommended. A MDT discussion is needed to analyse risks/benefits of alternative cancer therapies vs. restarting the culprit cancer therapy at a lower dose with heart rate monitoring. In selected cases, when no cancer treatment alternative is available, pacing is indicated.

### 6.5. Arterial hypertension

Arterial hypertension in patients with cancer may be caused by their cancer treatments (e.g. VEGFi, second- and third-generation BCR-ABL TKI, brigatinib, ibrutinib, fluoropyrimidines, cisplatin, abiraterone, bicalutamide, enzalutamide), non-cancer drugs (e.g. corticosteroids, non-steroidal anti-inflammatory drugs), and other factors including stress, pain, excessive alcohol consumption, renal impairment, untreated sleep apnoea, obesity, and reduced exercise.<sup>552</sup> In all patients with cancer with new hypertension assessment, correction of these other factors is important before considering interruption of a cancer treatment.

Untreated hypertension<sup>344</sup> is a confirmed risk factor of HF during treatment with anthracyclines,<sup>553</sup> ibrutinib,<sup>264</sup> and VEGFi.<sup>554</sup> Given that many of the cancer therapies that cause hypertension also cause

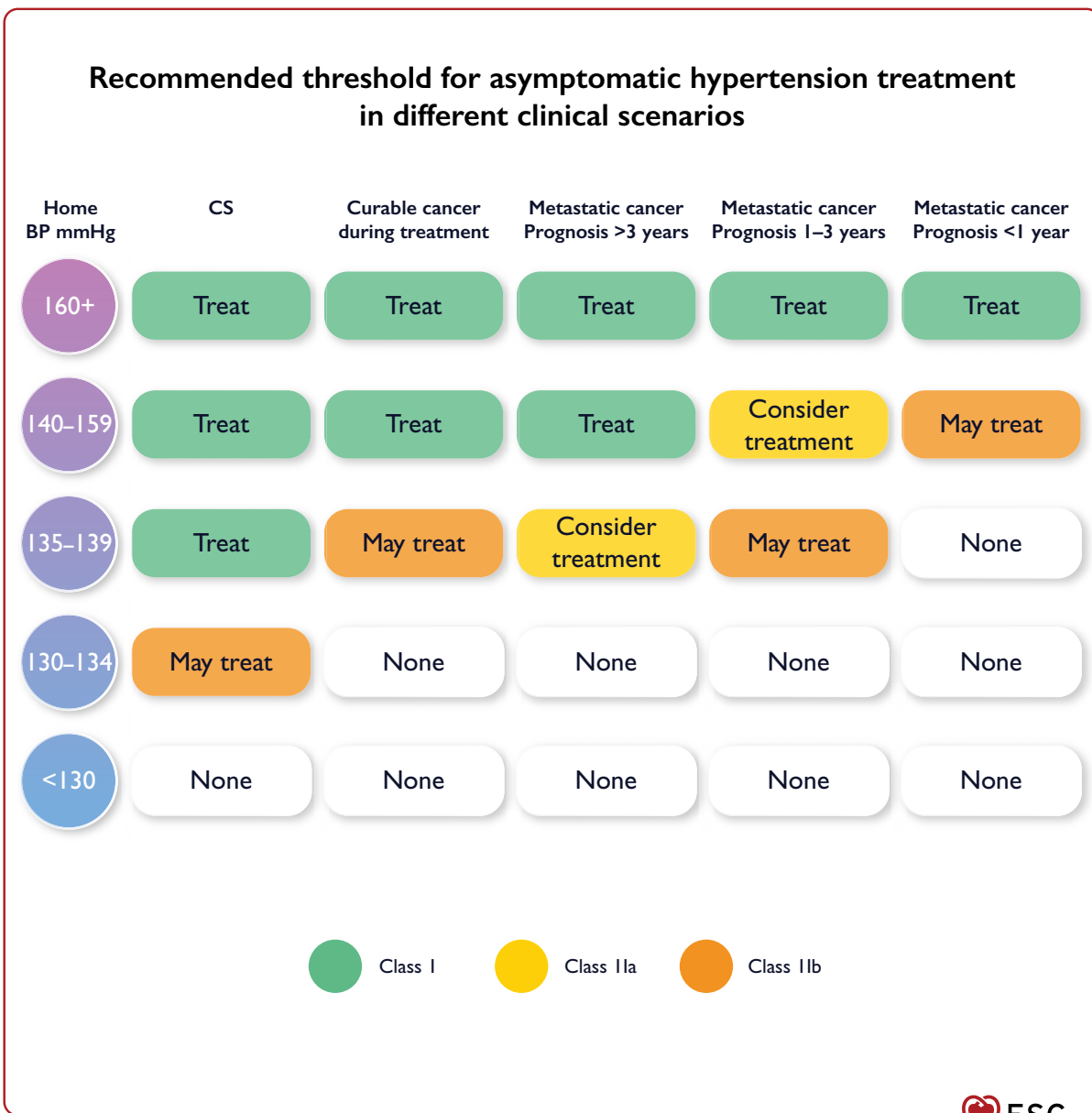


CTRCD, treatment of hypertension with ACE-I or ARB as first-line therapy is recommended to reduce the risk of CTRCD. Combination therapy with an ACE-I or ARB and a dihydropyridine CCB is recommended in patients with cancer with systolic BP  $\geq$  160 mmHg and diastolic BP  $\geq$  100 mmHg due to the more rapid onset of BP control with the combination compared with ACE-I/ARB monotherapy (Figures 33 and 34).

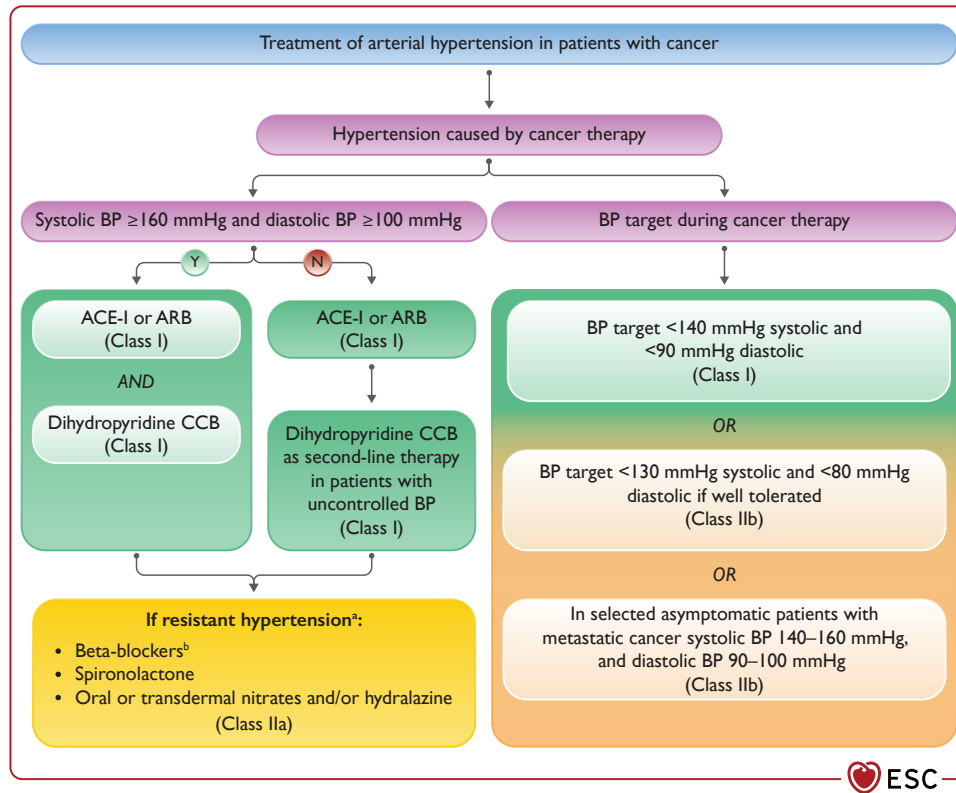
If severe hypertension is diagnosed (systolic BP  $\geq$  180 mmHg or diastolic BP  $\geq$  110 mmHg), the competing cancer and CV risks should be evaluated by a MDT, and any cancer therapy associated with hypertension should be deferred or temporarily withheld until the BP is controlled to values  $<$ 160 mmHg (systolic BP) and  $<$ 100 mmHg (diastolic BP). Culprit cancer therapy can be restarted once BP is controlled, with consideration for dose reduction.

In patients with resistant cancer therapy-related hypertension, spironolactone, oral or transdermal nitrates, and/or hydralazine should be considered. In patients with cancer with evidence of high sympathetic tone, stress, and/or pain, beta-blockers including carvedilol or nebivolol should be considered. Diuretics, preferably spironolactone, may be considered in patients with cancer with hypertension and evidence of increased fluid retention, with monitoring of BP, electrolytes, and renal function.

The decisions to initiate BP treatment and BP targets during the management of cancer-drug induced hypertension depend upon the context of the cancer and prognosis (Figure 34). CS should be treated according to the 2018 ESC/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension.<sup>138</sup>



**Figure 33** Recommended threshold for asymptomatic hypertension treatment in different clinical scenarios. BP, blood pressure; CS, cancer survivors.



**Figure 34** Treatment of arterial hypertension in patients with cancer. AF, atrial fibrillation; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; CCB, calcium channel blockers; HF, heart failure; MI, myocardial infarction; N, no; VEGFi, vascular endothelial growth factor inhibitors; Y, yes. <sup>a</sup>Resistant hypertension is defined as BP being uncontrolled despite treatment with optimal or best-tolerated doses of three or more drugs including a diuretic, and confirmed by ambulatory and home BP monitoring. <sup>b</sup>Consider beta-blockers (nebivolol or carvedilol are preferred in patients on VEGFi) at any treatment step, when there is a specific indication for their use, e.g. HF, angina, post-MI, or AF.

**Recommendation Table 33 — Recommendations for the management of arterial hypertension in patients receiving anticancer treatment**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| <b>General</b>  |                    |                    |
| Effective treatment of cancer therapy-induced arterial hypertension to prevent cancer treatment interruption and CV complications is recommended.   | I                  | C                  |
| A BP target <140 mmHg systolic and <90 mmHg diastolic is recommended during cancer therapy.   | I                  | C                  |
| A BP target <130 mmHg systolic and <80 mmHg diastolic may be considered during cancer therapy provided that the treatment is well tolerated.  | IIb                | C                  |
| In selected asymptomatic patients with metastatic cancer, a systolic BP 140–160 mmHg and diastolic BP 90–100 mmHg treatment threshold may be considered provided there is ongoing BP monitoring.  | IIb                | C                  |
| The competing cancer and CV risk evaluation is recommended if the systolic BP is ≥180 mmHg or diastolic BP ≥110 mmHg, and any cancer therapy associated with hypertension should be deferred or temporarily withheld until the BP is controlled to values <160 mmHg (systolic) and <100 mmHg (diastolic). | I                  | C                  |

Continued

| Cancer therapy-induced arterial hypertension treatment  |     |   |
|---|-----|---|
| ACE-I or ARB are the first-line antihypertensive drugs <sup>c</sup> recommended for BP management in patients with cancer. <sup>555–557</sup>                 | I   | B |
| Dihydropyridine CCB are recommended as second-line antihypertensive drugs for patients with cancer with uncontrolled BP.                                      | I   | C |
| Combination therapy with ACE-I or ARB and dihydropyridine CCB is recommended in patients with cancer with systolic BP ≥ 160 mmHg and diastolic BP ≥ 100 mmHg. | I   | C |
| Diltiazem and verapamil are not recommended to treat arterial hypertension in patients with cancer due to their drug–drug interactions. <sup>d</sup>          | III | C |

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; CCB, calcium channel blockers; CV, cardiovascular.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Unless contraindicated.

<sup>d</sup>In selected patients with cancer, who are intolerant to multiple other antihypertensive drugs, diltiazem and verapamil may be considered with close monitoring of drug–drug interactions.

## 6.6. Thrombosis and thromboembolic events

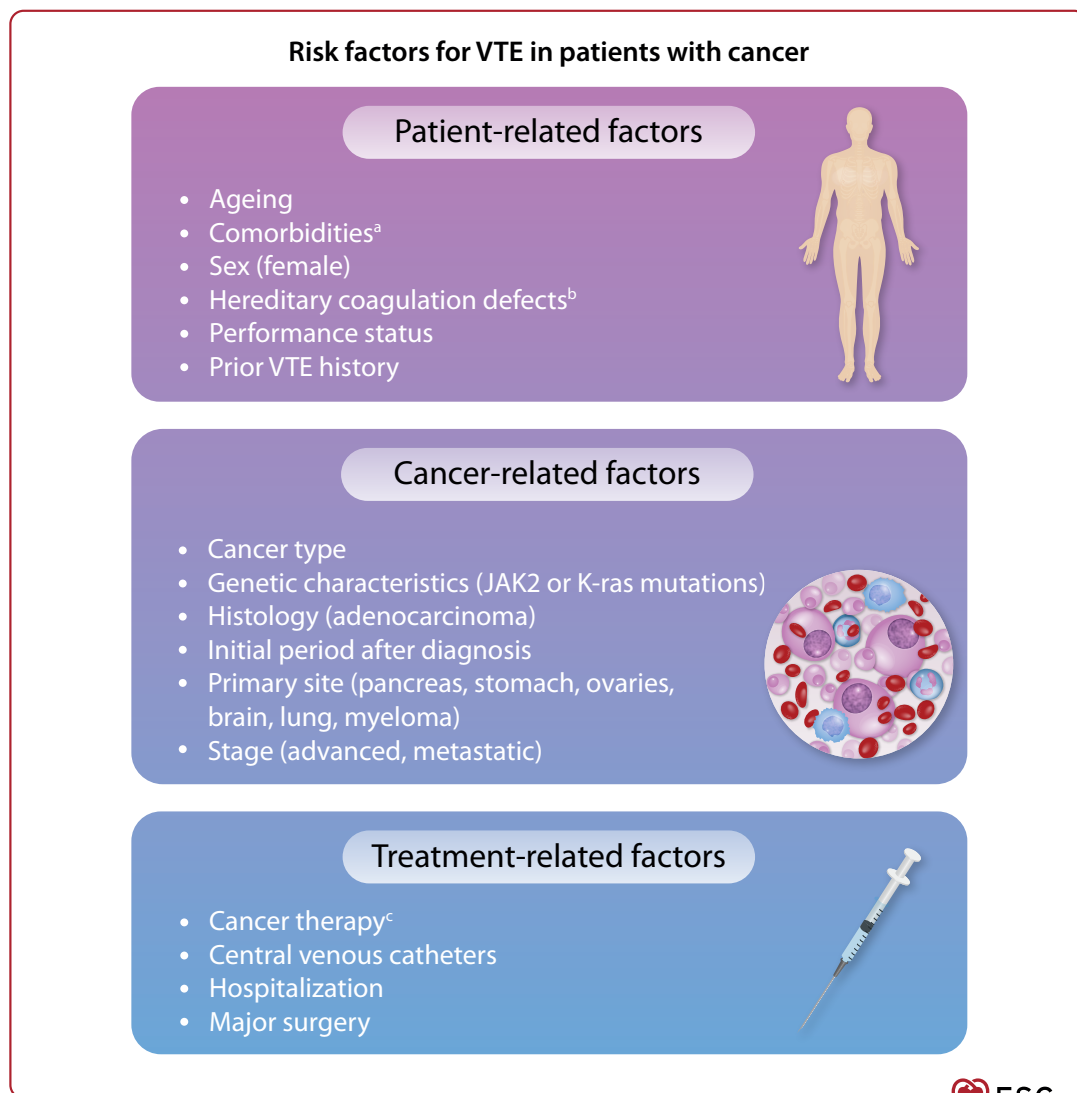
Thromboembolic events that develop during cancer and its treatment encompass both VTE and arterial thromboembolism (ATE) and are collectively referred to as cancer-associated thrombosis. Cancer-associated thrombosis is determined by the prothrombotic milieu induced by cancer, the prothrombotic properties of certain anticancer and adjunctive therapies, and patient-related risk factors, including demographics, genetic predisposition, and comorbidities.<sup>513</sup>

### 6.6.1. Venous thromboembolism

VTE, including deep vein thrombosis (DVT) and PE, is the second-leading cause of death in patients with malignancies.<sup>558</sup>

Cancer confers a five-fold higher risk of VTE and cancer-associated VTE represents 30% of all VTE cases.<sup>559,560</sup> The risk of VTE varies in the course of cancer, with the highest risk occurring in the period following cancer diagnosis, during hospitalization and chemotherapy, and upon development of metastatic disease.<sup>561,562</sup> Unprovoked VTE may be the first clinical sign of a malignancy, followed by a 5% incidence of cancer diagnosis during the subsequent 12 months.<sup>563</sup>

The risk factors for VTE in cancer are summarized in [Figure 35](#).<sup>564,565</sup> Patients with symptoms or signs suggestive of VTE, such as unilateral lower limb oedema or unexplained dyspnoea, should be screened with lower-extremity venous ultrasonography or contrast-enhanced CT for DVT and CT pulmonary angiography for PE, according to the 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism recommendations.<sup>566</sup>



**Figure 35** Risk factors for venous thromboembolism in patients with cancer. ATE, arterial thromboembolism; BMI, body mass index; CrCl, creatinine clearance; IMiD, immunomodulatory drugs; PI, proteasome inhibitors; VTE, venous thromboembolism. <sup>a</sup>Acute infection, chronic kidney disease (CrCl < 45 mL/min), pulmonary disease, obesity (BMI ≥ 30 kg/m<sup>2</sup>), ATE. <sup>b</sup>Factor V Leiden, prothrombin gene mutation. <sup>c</sup>Chemotherapy (carboplatin, cyclophosphamide, anthracyclines, antimetabolites, irinotecan, taxanes, tasonermin), anti-angiogenic agents (bevacizumab, axitinib, lenvatinib, pazopanib, sorafenib, sunitinib), IMiD (thalidomide, lenalidomide), PI (carfilzomib), hormonal therapy, erythropoiesis-stimulating agents.

and the second consensus document on diagnosis and management of acute deep vein thrombosis.<sup>567</sup>

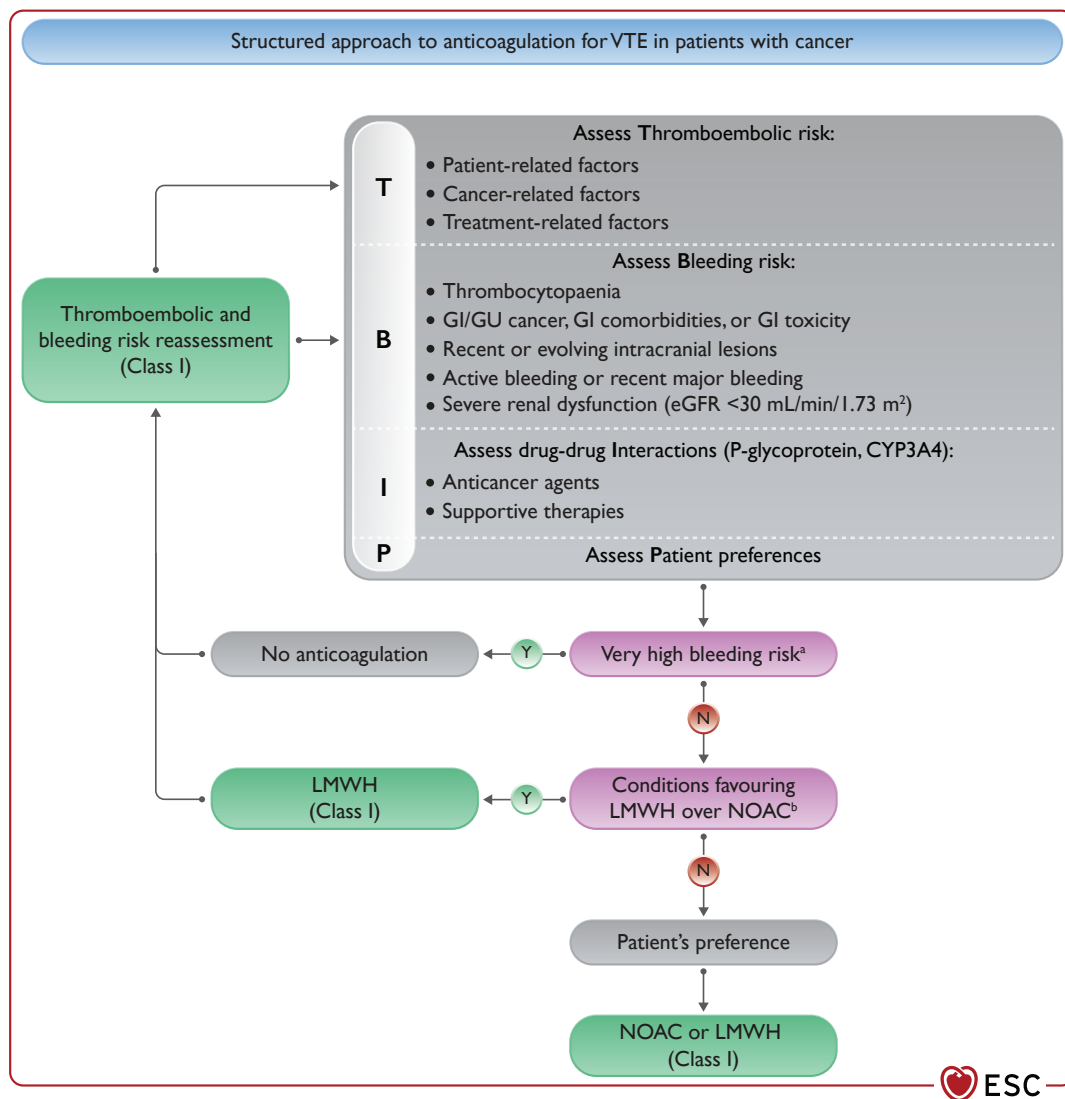
### 6.6.2. Arterial thromboembolism

Cancer carries a two-fold higher risk of ATE, including MI and ischaemic stroke.<sup>568</sup> ATE risk is higher in men, with advanced age, and in patients with lung or kidney cancer. Pathologies related to ATE in cancer include ischaemic stroke induced by AF or RT-induced carotid artery disease, embolization by tumour cells or non-bacterial thrombotic endocarditis, disseminated intravascular coagulation-related peripheral microcirculatory thromboembolism, paradoxical cerebral embolism in the course of VTE, and cerebral sinus thrombosis.<sup>569</sup>

### 6.6.3. Intracardiac thrombosis

Intracardiac thrombus in patients with malignancies may result from the prothrombotic properties of cancer and its treatment and the use of central venous catheters. Thrombus is the most common intracardiac mass and it can occur within any cardiac chamber. Right atrial thrombi are often related to a venous catheter where the line has inappropriately advanced into the right atrium. Intraventricular thrombi usually occur in the setting of CTRCD. LAA thrombi are most commonly associated with AF, which may also be related to cancer or its therapy.

Patients with systemic embolization should be screened for cardiac origin of thrombus initially with TTE and/or transoesophageal echocardiography.<sup>528</sup> CMR is more sensitive and specific than TTE



**Figure 36** Structured approach to anticoagulation for venous thromboembolism in patients with active cancer. CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GU, genitourinary; LMWH, low-molecular-weight heparins; N, no; NOAC, non-vitamin K antagonist oral anticoagulants; VTE, venous thromboembolism; Y, yes. <sup>a</sup>**Very high bleeding risk:** active or recent major bleeding (<1 month); recent/evolving intracranial lesions; platelet count <25 000/ $\mu$ L. According to the International Society on Thrombosis and Haemostasis,<sup>529</sup> major bleeding is defined as: fall in haemoglobin level  $\geq 2$  g/dL, transfusion of  $\geq 2$  units of red blood cells, fatal bleeding, or bleeding in a critical area (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal). <sup>b</sup>**Conditions favouring LMWH:** unoperated GI/GU cancer; GI comorbidities or toxicity; severe renal dysfunction (CrCl <15 mL/min); NOAC major drug–drug interactions, platelet count < 50 000/ $\mu$ L.

for detecting intracardiac thrombi and late gadolinium enhancement (LGE) CMR with the long inversion time technique is currently considered the gold standard.<sup>570,571</sup>

**6.6.4. Anticoagulation therapy**

Patients with cancer frequently have both an increased thrombotic risk and an increased bleeding risk associated with certain cancer locations (e.g. GI, intracranial), thrombocytopenia, and other coagulation defects (secondary to bone marrow invasion, cancer therapies, or cancer itself) and associated comorbidities (e.g. renal or hepatic dysfunction, GI toxicities). Several anticancer agents are further characterized by drug–drug interactions with anticoagulants. All these factors may render anticoagulation in cancer quite challenging. A proposed approach to anticoagulation therapy in cancer-associated venous thrombosis, based on the TBIP acronym (Thromboembolic risk, Bleeding risk, drug–drug Interactions, Patient preferences), is outlined in Figure 36.<sup>527</sup>

**6.6.4.1. Treatment and secondary prevention of venous thromboembolism**

Several large RCTs and meta-analyses have shown that LMWH decrease the risk of recurrent VTE by 40% compared to VKA, with a similar risk of major bleeding.<sup>572–576</sup> However, VKA are characterized by an unpredictable anticoagulation effect and low time in therapeutic range in patients with malignancies due to multiple drug–drug interactions, GI toxicity, malnutrition, and liver dysfunction.<sup>577</sup>

NOAC have been assessed as potential alternatives to LMWH for cancer-associated VTE, based on RCTs that compared edoxaban, rivaroxaban or apixaban to dalteparin.<sup>578–583</sup> The totality of evidence derived by these trials and subsequent meta-analyses<sup>584–586</sup> shows that NOAC are non-inferior to dalteparin in reducing the risk of VTE recurrence. The risk of major bleeding was similar, although NOAC were associated with an increased risk of clinically relevant non-major bleeding, particularly in patients with luminal GI and GU malignancies.<sup>586</sup> As a result, edoxaban, rivaroxaban, and apixaban are recommended for the treatment of VTE (DVT and PE) in patients with cancer without any of the following bleeding risk factors: unoperated GI or GU malignancies, history of recent bleeding or within 7 days of major surgery, significant thrombocytopenia (platelet count < 50 000/μL), severe renal dysfunction (creatinine clearance (CrCl < 15 mL/min), or GI comorbidities.<sup>582,586</sup> In addition, drug–drug interactions between NOAC, cancer therapies, and other concomitant treatments should be checked.<sup>587</sup> There are also concerns about NOAC in patients with GI toxicity such as vomiting or those having undergone gastrectomy or extensive intestine resection, as well as those with severely impaired renal function. Shared decision-making considering informed patient preferences should guide the choice of anticoagulation.

Incidentally encountered proximal DVT or PE should be treated in the same manner as symptomatic VTE as they bear similar rates of recurrence and mortality.<sup>588</sup>

The minimal duration of anticoagulation is 6 months and extended anticoagulation is suggested in the presence of active malignancy, metastatic disease, or chemotherapy use. Cohort studies have shown that extended LMWH therapy beyond 6 and up to 12 months is safe in cancer-associated VTE.<sup>589,590</sup> However, patients with cancer are also at high risk of bleeding during anticoagulant treatment and a periodic assessment of the risk/benefit ratio should be performed.

In VTE relapse under anticoagulation, the patient should be investigated for treatment adherence, cancer progression or relapse, while a different anticoagulation strategy should be endorsed (e.g. replacement of NOAC with LMWH). The management of patients with VTE and a platelet count <25 000/μL should be individualized by a MDT.<sup>299</sup>

The duration of anticoagulation in patients with catheter-associated thrombosis depends upon whether the catheter is removed or remains *in situ*. If removed, then anticoagulation should continue for a minimum of 3 months and until follow-up cardiac imaging confirms resolution of the thrombus. If the catheter remains *in situ*, then long-term therapeutic anticoagulation should continue.

**Recommendation Table 34 — Recommendations for the management of venous thromboembolism in patients receiving anticancer treatment**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Apixaban, edoxaban, or rivaroxaban <sup>c</sup> are recommended for the treatment of symptomatic or incidental VTE in patients with cancer without contraindications. <sup>d,578–581,584,585</sup> | I                  | A                  |
| LMWH are recommended for the treatment of symptomatic or incidental VTE in patients with cancer with platelet count >50 000/μL. <sup>298,299,578–581,584,585</sup>                                 | I                  | A                  |
| In patients with cancer with platelet counts of 25 000–50 000/μL, anticoagulation with half-dose LMWH may be considered after a multidisciplinary discussion. <sup>591</sup>                       | IIb                | C                  |
| Prolongation of anticoagulation therapy beyond 6 months should be considered in selected patients with active cancer <sup>e</sup> including metastatic disease. <sup>589,590</sup>                 | IIa                | A                  |
| <b>Catheter-associated VTE</b>   |                    |                    |
| Duration of anticoagulation in patients with cancer with a catheter-associated VTE is recommended for a minimum of 3 months and continuing longer if the catheter remains <i>in situ</i> .         | I                  | C                  |

CrCl, creatinine clearance; GI, gastrointestinal; GU, genitourinary; LMWH, low-molecular-weight heparins; ULN, upper limit of normal; VTE, venous thromboembolism.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Drugs are listed in alphabetical order

<sup>d</sup>High risk of GI or GU bleeding, GI absorption concerns, significant drug–drug interactions, severe renal dysfunction (CrCl < 15 mL/min), significant liver disease (alanine aminotransferase/aspartate aminotransferase > 2 × ULN), or significant thrombocytopenia (platelet count < 50 000/μL). In addition, patients with primary brain tumours or brain metastases and acute leukaemia were excluded from the seminal apixaban trial.<sup>580</sup>

<sup>e</sup>Patients receiving cancer treatment, patients diagnosed with cancer in the past 6 months, and patients with progressive or advanced disease.

**6.6.4.2. Primary prevention of venous thromboembolism**

Patients undergoing surgery and those who are hospitalized or in prolonged bed rest require thromboprophylaxis with low-dose anticoagulation.<sup>298,299,592–594</sup> The ENOXACAN (Enoxaparin and

Cancer) II study showed favourable outcomes with LMWH as primary thromboprophylaxis for 4 weeks after major abdominal or pelvic cancer surgery.<sup>595</sup> For ambulatory patients, VTE risk should be individually determined and proposed scores such as the Khorana or the COMPASS-CAT (prospective COmparison of Methods for thromboembolic risk assessment with clinical Perceptions and AwareneSS in real-life patients—Cancer Associated Thrombosis) score may be useful.<sup>596,597</sup> Further trials and a meta-analysis have shown that LMWH significantly reduced the incidence of symptomatic VTE in ambulatory patients with cancer receiving chemotherapy with acceptable safety.<sup>598–600</sup> Two randomized, placebo-controlled, double-blind clinical trials have assessed the role of NOAC in primary prevention of VTE in high-risk ambulatory patients receiving systemic cancer therapy (Khorana score  $\geq 2$ ).<sup>601,602</sup> Over a follow-up period of 180 days, apixaban (2.5 mg twice a day)<sup>601</sup> therapy resulted in a significantly lower rate of VTE, although the rate of major bleeding episodes was higher than with placebo. Rivaroxaban (10 mg once a day)<sup>602</sup> treatment resulted in a non-significantly lower incidence of VTE or death due to VTE with low bleeding risk (no significant differences with placebo). Further data on the use of NOAC in this setting are warranted. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, cancer prognosis, drug cost, and duration of prophylaxis.

**Recommendation Table 35 — Recommendations for venous thromboembolism prophylaxis during anticancer treatment**

| Recommendation  | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Extended prophylaxis with LMWH for 4 weeks post-operatively is recommended for patients with cancer undergoing major open or laparoscopic abdominal or pelvic surgery with low bleeding risk and high VTE risk. <sup>c,298,299,595</sup>  | I                  | B                  |
| Prophylactic LMWH for the primary prevention of VTE is indicated in hospitalized patients with cancer or those with prolonged bedrest or reduced mobility in the absence of bleeding or other contraindications. <sup>298,299,592,594</sup>   | I                  | B                  |
| For ambulatory patients with cancer at high risk of thrombosis receiving systemic therapy, <sup>d</sup> primary thromboprophylaxis with a NOAC (apixaban or rivaroxaban) or LMWH may be considered, provided there are no significant contraindications. <sup>e,298,593,594,601,602</sup> | IIb                | B                  |
| A discussion with the patient about the relative benefits and harms, cancer prognosis, drug cost, and duration of treatment is recommended prior to prophylactic anticoagulation for the primary prevention of VTE.   | I                  | C                  |

LMWH, low-molecular-weight heparins; NOAC, non-vitamin K antagonist oral anticoagulants; VTE, venous thromboembolism.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Reduced mobility, obesity, VTE history.

<sup>d</sup>Locally advanced or metastatic pancreas or lung cancer or Khorana score  $\geq 2$ .

<sup>e</sup>Risk factors for bleeding, significant drug–drug interactions, or severe renal dysfunction.

## 6.7. Bleeding complications

Bleeding complications are more common in patients with cancer than in patients without cancer. This may be directly related to the tumour itself, or indirectly related to chemotherapy- or RT-induced weakening of mucosal barriers.<sup>530</sup>

### 6.7.1. High-risk patients

GI and GU cancers are associated with a significant excess bleeding risk compared with other solid tumours.<sup>603</sup> Thrombocytopenia and platelet dysfunction due to haematological malignancies or bone marrow suppression can exacerbate bleeding. Other bleeding risk factors include advancing age, renal or hepatic impairment, metastatic disease, low body mass index, and treatment with ibrutinib, VEGFi, cetuximab, or bevacizumab.<sup>578,603–605</sup> Gastric protection with routine proton pump inhibitor use should be considered in all patients with cancer on DAPT<sup>606,607</sup> or anticoagulation.<sup>530</sup>

### 6.7.2. Antiplatelet therapy

Antiplatelet therapy, in particular DAPT, increases the risk of bleeding in patients with cancer.<sup>477</sup> Following ACS and/or PCI, the risk of bleeding is approximately 1.6-fold greater in patients with cancer than in those without.<sup>477,605</sup> The risk is greatest in those diagnosed with cancer in the preceding year, whereas more remote cancers carry lower excess risk.<sup>477</sup> The PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subSequent Dual Anti Platelet Therapy) score appears not to perform well for predicting bleeding in patients with cancer.<sup>477</sup> In order to reduce bleeding risk, the duration and intensity of DAPT should be minimized<sup>477,607</sup> and triple therapy avoided whenever possible. At the same time, DAPT—if indicated—should not be withheld without good reason. A recent expert consensus statement suggests reduced platelet count thresholds for CV therapies, recommending aspirin initiation for platelet counts  $>10\,000/\mu\text{L}$  and DAPT initiation (with aspirin and clopidogrel) for platelet counts  $>30\,000/\mu\text{L}$ .<sup>608</sup> In patients with platelet counts  $<50\,000/\mu\text{L}$ , clopidogrel is preferred over prasugrel or ticagrelor, and glycoprotein IIb/IIIa inhibitors should be avoided.<sup>608</sup> To reduce peri-procedural bleeding, PCI should preferably be undertaken via the radial approach<sup>484</sup> and prophylactic platelet transfusion may be considered for patients with platelet count  $<20\,000/\mu\text{L}$ .<sup>609</sup>

### 6.7.3. Management of bleeding

Basic principles of bleeding management should be followed with control of the bleeding source whenever possible. Platelet transfusions for significant thrombocytopenia and withholding and reversal of anticoagulation for life-threatening bleeding may be needed as in the general population.<sup>530,610</sup> Antifibrinolytic agents, such as tranexamic acid or e-aminocaproic acid, can be considered. Non-specific support of haemostasis using coagulation factor concentrates and specific reversal agents may be needed for patients on a NOAC with life-threatening bleeding.<sup>530</sup> Recombinant activated factor VII or activated prothrombin complex concentrates should be avoided in patients with recent thrombosis.



### 6.8. Peripheral artery disease

There is growing evidence that cancer therapy affects the vasculature. A recent meta-analysis showed a significantly increased arterial stiffness after anthracycline and non-anthracycline treatment.<sup>611</sup> Paraneoplastic acral vascular syndrome was described after initiation of nivolumab, with first symptoms 3 weeks after initiation of therapy.<sup>612</sup> Raynaud phenomenon has been associated with the use of bleomycin, cyclophosphamide, platinum compounds, vinca alkaloids, and fluoropyrimidines.<sup>491</sup> Usual treatment of Raynaud’s includes non-pharmacological measures to help prevent an episode (avoidance of provoking factors such as cold temperature, vasoconstricting drugs) and a long-acting dihydropyridine CCB (amlodipine, modified-release nifedipine).

Treatment with nilotinib or ponatinib may be associated with an increased risk of vascular adverse events, including arterial stiffness and PAD development.<sup>494</sup> In a subgroup of patients, these events are severe or even life-threatening.<sup>613</sup> Although the exact mechanisms remain unknown, we recommend screening for pre-existing PAD and for vascular risk factors such as DM in all patients before and during nilotinib or ponatinib therapy. Pooled data from three clinical trials showed arterial occlusive disease to be related to dose intensity in ponatinib-treated patients,<sup>614</sup> but PAD was not addressed separately. If rapidly progressive PAD occurs with second-generation TKI, it may be advisable to switch to an alternative lower-risk TKI (e.g. imatinib). Platelet aggregation inhibitors or anticoagulation and statins should be considered. Despite lack of evidence, all risk factors should be corrected.<sup>615</sup>

**Recommendation Table 36 — Recommendation for management of peripheral artery disease during anticancer treatment**

| Recommendation   | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| In patients who develop new symptomatic PAD, a multidisciplinary approach regarding the decision to continue vs. interrupt culprit cancer therapy <sup>c</sup> is recommended. | I                  | C                  |

PAD, peripheral artery disease; VEGFi, vascular endothelial growth factor inhibitors.  
<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>VEGFi, nilotinib, ponatinib, platin, etc.

### 6.9. Pulmonary hypertension

All five groups of the PH classification can be observed in patients with cancer. Several cancer drugs can cause group 1 PH (pulmonary arterial hypertension [PAH]), including carfilzomib, bosutinib, dasatinib,<sup>616</sup> ponatinib, interferon alpha, and alkylating agents (e.g. mitomycin C and cyclophosphamide, which mostly cause pulmonary veno-occlusive disease).<sup>617</sup> PH associated with left heart disease (group 2) is related to drugs causing HF (e.g. anthracyclines). PH associated with lung disease (group 3) is related to drugs and therapies causing pulmonary fibrosis (e.g. bleomycin, thoracic radiation). The most common pulmonary vascular disease complicating cancer is VTE, which can cause chronic thromboembolic PH (group 4). Of note, central venous catheters are important causes of group 4 PH

complicating cancer management. Other group 4 PH due to pulmonary artery obstructions includes angiosarcoma and other malignant tumours (e.g. renal carcinoma, uterine carcinoma, germ cell tumours of the testis).<sup>618</sup>

PH with unclear and/or multifactorial mechanisms (group 5) includes several conditions that may be complicated by complex and sometimes overlapping pulmonary vascular involvement. Tumoral PH includes pulmonary tumour micro-embolism and pulmonary tumour thrombotic microangiopathy.<sup>619</sup> Multiple causes of PH have been described in patients with chronic myeloproliferative disorders. In chronic myelogenous leukaemia, spleen enlargement and anaemia can give rise to hyperkinetic syndrome. In polycythaemia vera and essential thrombocythemia, there is an increased risk of VTE and chronic thromboembolic PH. Moreover, formation of a blood clot within the hepatic veins can lead to Budd–Chiari syndrome and subsequent porto-PH. Pulmonary extramedullary haematopoiesis complicating idiopathic or secondary myelofibrosis may also contribute to dyspnoea and PH.<sup>620</sup>

Symptoms of PH are non-specific, such as shortness of breath and fatigue. In later stages, symptoms of right-sided HF may develop. An ECG should be performed and examined for RV hypertrophy, but a normal ECG does not exclude PH. Echocardiography is the first choice for assessing PH probability in patients who develop symptoms and/or signs suggestive of PH during cancer treatment. When peak tricuspid regurgitation velocity (TRV) is  $\leq 2.8$  m/s (equating to an estimated systolic PAP [sPAP] of  $\leq 35$  mmHg) and no other signs of PH are present, then the probability of PH is low. In the absence of a tricuspid regurgitant jet, other echocardiography signs may increase suspicion of PH (e.g. RV/LV basal diameter ratio  $> 1$ , RV outflow tract acceleration time  $< 105$  ms, inferior vena cava diameter  $> 21$  mm with decreased inspiratory collapse).<sup>620</sup> Baseline TTE should be considered in patients receiving cancer drugs that can cause PH; however, a right-heart catheterization is required for definitive diagnosis of PH and to support PAH treatment decisions. In the DASISION (DASatinib vs. Imatinib Study In treatment-Naïve chronic myeloid leukemia patients) trial, 5% of patients randomized to dasatinib were diagnosed with PH, compared with 0.4% of those randomized to imatinib.<sup>621</sup> In patients who develop PH, dasatinib treatment should be interrupted and an alternative TKI should be used.<sup>616</sup>

Overall management of PH in oncology patients should be based on the 2022 ESC/European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension.<sup>620</sup> Referral to a PH centre is recommended for multidisciplinary management with the oncology team. In patients with CML treated with drugs causing PH-induced PAH, discontinuation of the potential culprit therapy is recommended if there is a high probability of new PH (peak TRV  $> 3.4$  m/s, equating to an estimated sPAP of  $\geq 50$  mmHg) until the diagnosis is confirmed or ruled out by a right-heart catheterization. In CML patients on dasatinib, an alternative BCR-ABL TKI is recommended if they develop symptomatic PAH or an asymptomatic increase in peak TRV  $> 3.4$  m/s. Dasatinib dose reduction and close monitoring of peak TRV with TTE every 4 weeks should be considered in CML patients who develop new asymptomatic peak TRV ranging from 2.9 to 3.4 m/s.<sup>620</sup> If peak TRV remains normal or mildly elevated on serial monitoring, then dasatinib can continue, with reduced TTE monitoring to every 3

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months. If peak TRV continues to rise, then right-heart catheterization should be performed, dasatinib treatment should be stopped, and PAH drugs should be considered if PAH is confirmed.

**Recommendation Table 37 — Recommendations for the management of pulmonary hypertension during anticancer treatment**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Right-heart catheterization and discontinuation of dasatinib is recommended in patients who develop symptomatic or asymptomatic increase in peak TRV >3.4 m/s.                            | I                  | C                  |
| Dasatinib dose reduction and close monitoring of peak TRV with echocardiography should be considered in patients who develop new asymptomatic peak TRV ranging from 2.9 to 3.4 m/s.       | IIa                | C                  |
| In patients with confirmed dasatinib-induced PAH <sup>c</sup> or new asymptomatic peak TRV >3.4 m/s, an alternative BCR-ABL inhibitor is recommended after peak TRV recovery to <2.8 m/s. | I                  | C                  |

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BCL-ABL, breakpoint cluster region–Abelson oncogene locus; PAH, pulmonary arterial hypertension; TRV, tricuspid regurgitation velocity.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Definite diagnosis of PAH requires a right-heart catheterization.

## 6.10. Pericardial diseases

Pericarditis and pericardial effusion can be related to a wide range of cancer treatments including chest radiation, cytotoxic therapies (anthracyclines, bleomycin, cyclophosphamide, cytarabine), targeted therapies (all-*trans* retinoic acid, arsenic trioxide, dasatinib), and immune-based therapies (interleukin-2, interferon- $\alpha$ 1c). A combination of therapies may have a synergistic effect on the pericardium. These therapy-induced complications must be differentiated from progressive cancer (local invasion, metastatic involvement, or mediastinal lymphatic drainage obstruction) and non-cancer-related causes such as infection, especially in immune-compromised patients.<sup>622</sup> A careful history and clinical examination are of help to determine the cause. TTE plays a central role in diagnosis and management. CT and CMR can provide additional information on pericardial inflammation and constrictive physiology. The principles for the diagnosis and management should follow the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases,<sup>444</sup> but there are some specific issues to consider in patients with cancer.<sup>482</sup>

### 6.10.1. Pericarditis

The diagnosis of pericarditis in patients with cancer follows the same principles as in those without, but symptoms can be atypical.<sup>444</sup> Acute pericarditis caused by radiation has become rare due to lower doses and improved radiation techniques. It occurs within days to weeks after treatment and is usually self-limiting, but can evolve towards constrictive pericarditis many years later (Section 8.6). Pericarditis caused by conventional cancer therapies often resolves

with standard therapy or after discontinuation of the treatment.<sup>444</sup> Cancer treatment interruption should be discussed with the cardio-oncology team. Treatment with anti-inflammatory drugs (e.g. ibuprofen) and colchicine, in the absence of contraindications, is recommended as it reduces the rate of recurrence requiring repeat intervention.<sup>623</sup> Low-to-moderate doses of steroids are only indicated for resistant cases except ICI-related pericarditis.<sup>444</sup>

ICI-associated pericarditis has a median time of onset of 30 days in retrospective surveillance studies and is associated with a poor prognosis, especially in case of concomitant myocarditis.<sup>444,624</sup>

In patients with severe ICI-associated pericarditis with moderate or severe effusion, ICI discontinuation and high-dose steroids (methylprednisolone 1 mg/kg/day) with or without colchicine are recommended, as well as pericardiocentesis in case of cardiac tamponade.<sup>624,625</sup> In case of refractory pericarditis, immunosuppressive drugs should be considered. For uncomplicated ICI-related pericarditis, the ICI might be continued and colchicine or non-steroidal anti-inflammatory drugs could be considered.<sup>326,444</sup> For patients requiring ICI discontinuation, restarting ICI can be considered in a MDT discussion after resolution of pericardial disease and under close monitoring.

### 6.10.2. Pericardial effusion

Pericardial effusions are often observed as an incidental finding in patients with cancer. Cancer therapy is the cause of a pericardial effusion in <30% of cases, although this may increase with the expanding use of ICI in cancer. Malignancy-related pericardial effusions caused by direct (lung, oesophageal, breast) or metastatic invasion (haematological malignancies, ovarian, melanoma) or by lymph node obstruction are generally associated with poor prognosis.

Clinical presentation depends on the size of the effusion and the speed of its growth.<sup>444</sup> Malignancy-related pericardial effusions make up >30% of patients presenting with cardiac tamponade<sup>626</sup> and usually develop slowly, resulting in larger pericardial effusions at the time of diagnosis compared with non-malignant pericardial effusions. Management consists of determination of the cause and evaluation of the haemodynamic impact. Small-to-medium-sized effusions (>4 and <20 mm) can be monitored with a reassessment 7–14 days after initial diagnosis and at further 4–6-weekly intervals.<sup>444,627</sup> In unstable patients with signs of tamponade, immediate echocardiographic-guided percutaneous pericardiocentesis is preferred over surgical pericardiotomy to minimize potential complications.<sup>628</sup> In patients with cardiac tamponade due to malignant pericardial effusions, colchicine may be useful to improve clinical outcomes and reduce the rate of repeat intervention.<sup>623</sup> Drainage of a pericardial effusion related to ICI is rarely required<sup>629</sup> and corticosteroids should be considered.<sup>630</sup> Intrapericardial instillation of cytostatic/sclerosing agents, colchicine,<sup>623</sup> and radiation for radiation-sensitive tumours can reduce recurrence after drainage. The creation of a pleuropericardial or pleuroperitoneal window with balloon pericardiotomy or surgery should be considered in case of recurrent malignant pericardial effusions after emergency pericardiocentesis.<sup>444</sup>

A surgical pericardial window should be considered if the percutaneous approach is not feasible and in stable patients with large ( $\geq 20$  mm) or rapidly expanding malignant pericardial effusions prior to the development of cardiac tamponade.

### Recommendation Table 38 — Recommendations for the management of pericardial diseases in patients receiving anticancer treatment

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| <b>General</b>  |                    |                    |
| Diagnosis and management of acute pericarditis in patients with cancer based on the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases is recommended and a multidisciplinary discussion is needed before interrupting cancer therapy. <sup>444</sup> | I                  | C                  |
| A surgical pericardial window should be considered if the percutaneous approach is not feasible or in cases of recurrent malignant pericardial effusions.   | IIa                | C                  |
| Intrapericardial instillation of cytostatic or sclerosing agents may be considered for prevention of recurrence.  | IIb                | C                  |
| <b>Diagnosis and management of ICI-associated pericarditis</b>  |                    |                    |
| Multimodality CV imaging (echocardiography, CMR ± CT), ECG and measurement of cardiac biomarkers are recommended to confirm the diagnosis, assess the haemodynamic consequences of pericardial disease, and rule out associated myocarditis.                                    | I                  | C                  |
| Prednisolone and colchicine are recommended for patients with ICI-associated pericarditis. <sup>326,624,625,630</sup>   | I                  | C                  |
| Interruption of ICI treatment in patients with confirmed ICI-associated pericarditis with moderate-to-severe pericardial effusion is recommended.   | I                  | C                  |
| A multidisciplinary discussion is recommended before restarting ICI treatment.  | I                  | C                  |

CMR, cardiac magnetic resonance; CT, computed tomography; CV, cardiovascular; ECG, electrocardiogram; ESC, European Society of Cardiology; ICI, immune checkpoint inhibitors.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 7. End-of-cancer therapy cardiovascular risk assessment

### 7.1. Cardiovascular evaluation during the first year after cardiotoxic anticancer therapy

End-of-cancer therapy CV risk assessment covers the first 12 months after the last cardiotoxic cancer treatment. These recommendations are where cardiotoxic cancer therapy has been successfully completed with good long-term prognosis. These recommendations are not indicated when cancer therapies are discontinued due to cancer progression and prognosis is poor, or where end-of-life care is indicated. Selected patients with cancer

continue on long-term oncology therapies, e.g. women with oestrogen receptor-positive early invasive BC. In this example, the end-of-therapy risk assessment refers to the timepoint from the last anthracycline or trastuzumab dose.

High-risk patients can be identified at completion of their cardiotoxic cancer therapies by their clinical characteristics, history of CTR-CVT during treatment, and by elevated cardiac biomarkers and/or abnormal CV imaging at follow up.<sup>53,54,92</sup> Cardiac serum biomarkers (NP and cTn) are useful given their high negative predictive value for future CV events.<sup>197,631</sup> In a prospective study of 2625 adult patients with cancer that assessed LVEF after anthracycline-based chemotherapy, the overall incidence of CTRCD was 9%; 98% of cases could be detected within 12 months after chemotherapy and the median time from chemotherapy to CTRCD detection was 3.5 months (interquartile range 3–6 months).<sup>208</sup> The response to ACE-I treatment declined when the interval between the end of chemotherapy and CTRCD detection lengthened; complete LVEF recovery was not observed in patients where treatment was delayed by >6 months.<sup>425</sup>

Measurement of cTn after completion of anthracycline chemotherapy during the end-of-treatment assessment should be considered. Rises in cTnI after anthracycline chemotherapy identify patients at risk of future cardiac dysfunction who then benefit from CV protection.<sup>4</sup> Educating patients with cancer of their potential increased CVD risk and supporting them to make appropriate healthy lifestyle choices is recommended. CS should also be advised to promptly report early signs and symptoms of possible CVD and inform medical teams of their previous cardiotoxic cancer therapies. CVRF including hypertension, DM, and dyslipidaemia correlate with the probability of future CV events in CS and should be well controlled after completion of cancer therapy.<sup>31,632,633</sup>

### 7.2. Which cancer survivors require cardiovascular surveillance in the first year after cancer treatment?

The end-of-treatment risk assessment ideally identifies those high-risk CS, who require long-term CV surveillance, based on the following criteria (Table 10):

- (1) Baseline high or very high risk based on HFA-ICOS risk assessment tools<sup>12</sup> (Section 4).
- (2) Cardiotoxic cancer therapy with a high risk of long-term CV complications<sup>7,21</sup> (Section 8).
- (3) Moderate or severe CTR-CVT diagnosed during cancer treatment (Table 3).<sup>68</sup>
- (4) New abnormalities in cardiac function detected by echocardiography, new elevated cardiac serum biomarkers, or newly CV symptoms detected at the end-of-therapy assessment (3 or 12 months after treatment).<sup>68,208</sup>

The timing of the first CV assessment after cardiotoxic cancer treatment depends on the risk defined by baseline CV assessment, the type of cancer therapy, and whether CTR-CVT was diagnosed during treatment.

In asymptomatic high-risk patients (Table 10), echocardiography and cardiac serum biomarkers are recommended at 3 and 12 months after completion of cancer therapy.<sup>53,54,59,61,68,148,208,425</sup> In

**Table 10 Risk factors for future cardiovascular disease at the end-of-cancer therapy cardiovascular risk assessment**

| High-risk conditions  |
|---|
| High- and very-high baseline CV toxicity risk based on HFA-ICOS assessment  |
| Specific anticancer treatment proven to have a high risk of long-term CV complications <sup>a</sup> <ul style="list-style-type: none"> <li>Doxorubicin<sup>b</sup> <math>\geq 250</math> mg/m<sup>2</sup></li> <li>RT <math>&gt; 15</math> Gy MHD<sup>c</sup></li> <li>Both doxorubicin<sup>b</sup> <math>\geq 100</math> mg/m<sup>2</sup> and RT 5–15 Gy MHD<sup>d</sup></li> <li>High-risk HSCT patients<sup>e</sup></li> </ul> |
| Moderate or severe CTR-CVT during cancer treatment (especially CTRCD), ICI-related myocarditis, cardiac arrhythmias, or severe vascular toxicities (ACS, stroke, PVD)   |
| New CV symptoms or new asymptomatic abnormalities in echocardiography and/or cardiac serum biomarkers at the end of therapy assessment  |

ACS, acute coronary syndromes; CTRCD, cancer therapy-related cardiac dysfunction; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; GVHD, graft vs. host disease; Gy, Gray; HFA, Heart Failure Association; HSCT, haematopoietic stem cell transplantation; ICI, immune checkpoint inhibitors; ICOS, International Cardio-Oncology Society; MHD, mean heart dose; PVD, peripheral vascular disease; RT, radiotherapy.

<sup>a</sup>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 is exposed to a relatively high prescribed dose (i.e. RT to left breast or left chest wall only).

<sup>b</sup>Or doxorubicin equivalent.

<sup>c</sup>Or prescribed RT  $\geq 35$  Gy to a volume exposing the heart if MHD is not available.

<sup>d</sup>Or prescribed RT 15–34 Gy to a volume exposing the heart if MHD is not available.

<sup>e</sup>High-risk HSCT patients: allogeneic HSCT; pre-existing CVD or multiple uncontrolled CVRF; cancer treatment history (mediastinal or mantle field radiation, alkylating agents,  $>250$  mg/m<sup>2</sup> doxorubicin or equivalent); conditioning schemes (total body irradiation, alkylating agents); development of GVHD.

asymptomatic moderate-risk patients (according to CV toxicity baseline risk stratification), echocardiography and cardiac serum biomarkers should be considered within 12 months after completion of cancer therapy.<sup>53,54,59,61,68,148,208</sup> In asymptomatic low-risk patients (according to CV toxicity baseline risk stratification), echocardiography and cardiac serum biomarkers may be considered within 12 months after completion of cancer therapy.<sup>634</sup>

All patients started on CV therapies (ACE-I/ARB/angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, sodium-glucose co-transporter 2 inhibitors, anti-hypertensive medications, antiarrhythmic medications, antiplatelet therapies, statins) for any CTR-CVT (especially CTRCD) should have a clinical assessment, ECG, echocardiography, and cardiac serum biomarkers (if LV systolic dysfunction/HF is a potential risk) at 3, 6, and 12 months after completing cancer treatment. A MDT-based approach to palliative and end-of-life care for patients with cancer with HF or other CTR-CVT should be focused on symptom relief according to general ESC Guidelines.

### 7.3. Management of cancer therapy-related cardiac dysfunction at the end-of-therapy assessment

During this end-of-treatment assessment, a review of cardioprotective medications initiated during cancer therapy to treat CTRCD is recommended (Figure 37). In selected patients with asymptomatic mild or moderate CTRCD who have fully recovered with normal TTE and cardiac serum biomarkers, a trial of weaning off CV medication should be considered after MDT discussion. This is most common after asymptomatic mild or moderate CTRCD secondary to trastuzumab, particularly in younger otherwise healthy HER2+ BC survivors with no exposure to anthracycline chemotherapy. Further assessment of cardiac function with TTE and cardiac serum biomarkers is recommended following withdrawal of CV medication in patients with previous CTRCD to ensure cardiac function remains normal.

Continuing long-term CV medication is generally recommended in patients with moderate and severe symptomatic or severe asymptomatic CTRCD due to the high rate of recurrent HF. Long-term treatment is also recommended in CS with mild or moderate CTRCD who fail to recover normal LV function at their end-of-therapy assessment (Figure 37).

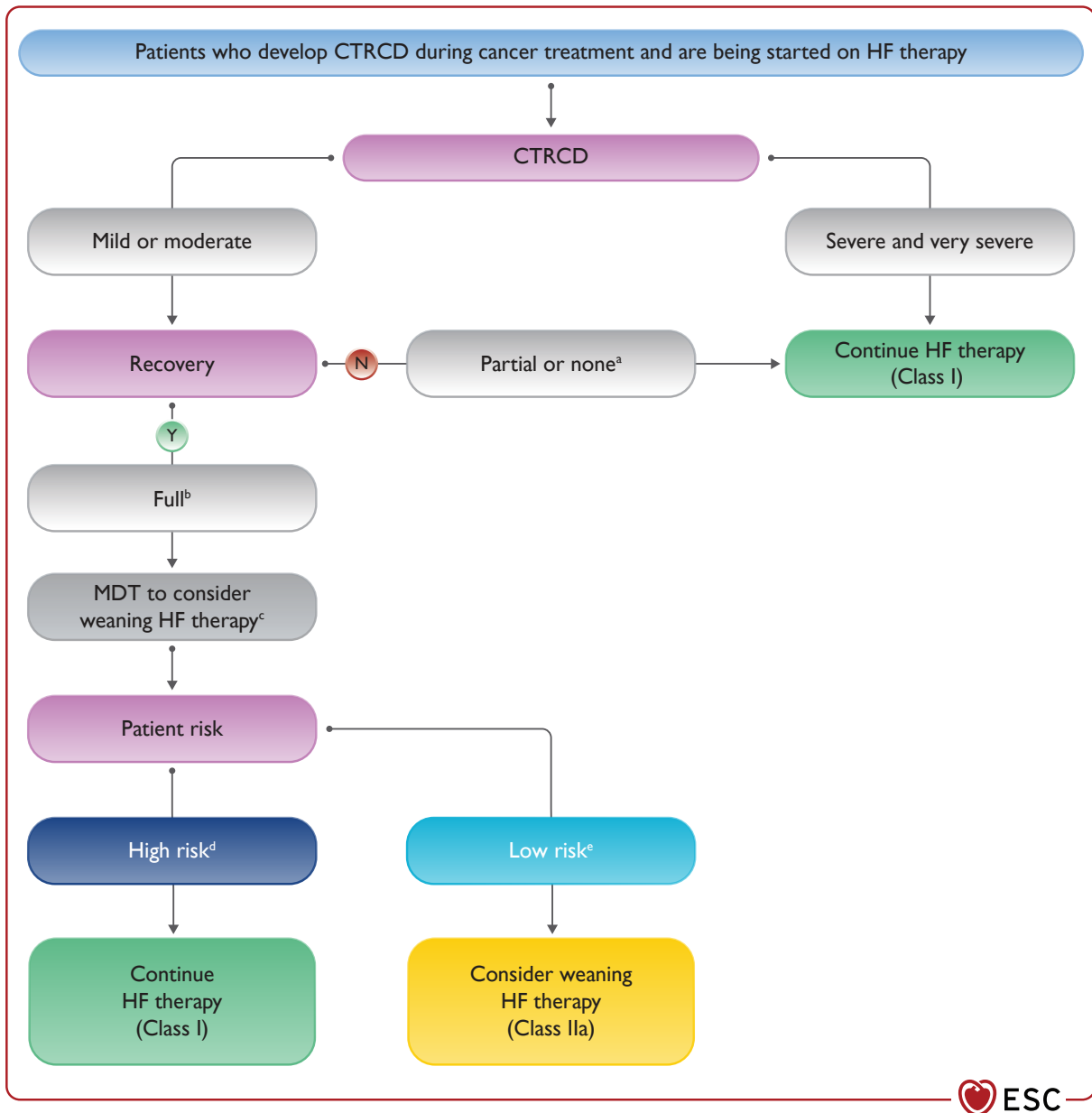
### 7.4. Cardiopulmonary exercise testing and fitness during the end-of-therapy assessment

CRF impairment is a strong predictor of patient outcome following cancer treatment and an intervention target in CS. Low CRF is associated with poor quality of life, increased morbidity, reduced exercise cardiac function and worse CVD risk profile, and is a robust independent predictor of all-cause, cancer-related, and CVD-related mortality in CS.<sup>119,120</sup> Recent evidence suggests the risk of CVD-related mortality in CS decreases by 14% per 1 metabolic equivalent (3.5 mL O<sub>2</sub>/kg/min) increase in CRF.<sup>120</sup>

CPET may be considered for CS with exertional limitation, who may have substantial benefit from cardiac rehabilitation. Eligible patients include those treated with higher doses of anthracycline chemotherapy and/or RT to a volume including the heart, high CV toxicity risk at baseline, patients who developed CTRCD during cancer therapy, and those identified with new abnormalities in LV function at their end-of-therapy assessment.<sup>11</sup> CPET can be an objective tool in the diagnosis of decreased physical capacity and identify CV vs. non-CV causes.<sup>635</sup>

### 7.5. The role of cardiac rehabilitation

Exercise is a potent multitargeted therapy that prevents and treats multiple competing mechanisms of CTR-CVT in CS, including CRF impairment,<sup>636</sup> CV injury, and pre-existing and new CVRF.<sup>137</sup> Prescribing exercise facilitates the delivery of therapeutic exercise that is individualized to a person's fitness level and systematically progressed to optimize physiological adaptation.<sup>637</sup> Current evidence demonstrates that supervised exercise therapy (including high-intensity interval training [HIIT]) is safe and well tolerated,<sup>638</sup> attenuates CTR-CVT risk, and improves CRF. Furthermore, HIIT reduces CVRF<sup>460</sup> and CV risk<sup>639</sup> in patients



**Figure 37** Management of cancer therapy-related cardiac dysfunction after cancer therapy. CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; LV, left ventricular; LVEF, left ventricular ejection fraction; MDT, multidisciplinary team; N, no; Y, yes. <sup>a</sup>**Partial or no recovery:** patients who do not meet all of the criteria for full recovery. <sup>b</sup>**Full recovery:** no signs or symptoms of HF + LVEF > 50% + GLS within normal range or similar to baseline measurements + cardiac serum biomarkers within the normal range or similar to baseline measurements <sup>c</sup>The **CTRCD trajectory** of each patient is unique and dynamic and withdrawal of HF therapy requires a MDT to consider several key points that help to stratify patients into low- or high-risk categories. **Key points to consider during a MDT discussion are:** HFA-ICOS baseline CV toxicity risk assessment, pre-existing indications for CV medication, class of cancer treatment causing CTRCD (generally reversible vs. generally irreversible), magnitude and duration of CTRCD before recovery, intensity of HF therapy needed to recover LV function, family history of cardiomyopathy or known cardiomyopathy gene carrier (see Section 4.8). <sup>d</sup>See Table 10. <sup>e</sup>**Low-risk patient characteristics:** low to moderate baseline CV toxicity risk (HFA-ICOS risk assessment), no pre-existing indications for CV medication, cancer treatment generally associated with reversible myocardial damage, asymptomatic mild CTRCD, early cardiac function recovery (3–6 months) under HF therapy, no family history of cardiomyopathy.

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with cancer in the pre-, active-, and post-treatment settings. HIIT-related benefits on CRF, physical activity behaviour, fatigue, and quality of life persist months post-intervention.<sup>640,641</sup> HIIT

may not be feasible in elderly and frail patients.<sup>642</sup> Dedicated cardio-oncology rehabilitation programmes are currently under development.<sup>11</sup>



**Recommendation Table 39 — Recommendations for end-of-cancer therapy cardiovascular risk assessment**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Educating and supporting patients with cancer to make appropriate healthy lifestyle choices is recommended. <sup>c</sup>  | I                  | C                  |
| Education is recommended for patients with cancer regarding recognition for early signs and symptoms of CVD.  | I                  | C                  |
| CVRF assessment is recommended during the first year after cancer therapy <sup>c,12,22,31,632,643</sup> and thereafter according to the 2021 ESC Guidelines on CVD prevention in clinical practice. <sup>19</sup>                       | I                  | B                  |
| In asymptomatic high-risk patients, <sup>d</sup> echocardiography and cardiac serum biomarkers are recommended at 3 and 12 months after completion of cancer therapy. <sup>53,54,59,61,68,148,208,425</sup>                             | I                  | B                  |
| In asymptomatic moderate-risk patients, <sup>e</sup> echocardiography and cardiac serum biomarkers should be considered within 12 months after completion of cancer therapy. <sup>53,54,59,61,68,148,208</sup>                          | IIa                | B                  |
| In asymptomatic low-risk patients, <sup>e</sup> echocardiography and cardiac serum biomarkers may be considered within 12 months after completion of cancer therapy. <sup>634</sup>   | IIb                | C                  |
| Cardiology referral <sup>f</sup> is recommended in patients with cancer with new cardiac symptoms or new asymptomatic abnormalities in echocardiography and/or cardiac serum biomarkers at the end of therapy assessment. <sup>11</sup> | I                  | C                  |
| In selected patients with exercise intolerance persisting at 12 months after cancer treatment and with normal resting echocardiogram and cardiac biomarkers, exercise stress echocardiography and/or CPET may be considered.            | IIb                | C                  |
| Targeted cardiac rehabilitation should be considered in CS with high CV risk. <sup>638–640</sup>  | IIa                | B                  |
| Long-term continuation of cardiac medication is recommended in patients who develop severe CTRCD during cancer therapy.   | I                  | C                  |
| CV follow-up and treatment optimization is recommended in patients who developed TKI-mediated hypertension during cancer therapy. <sup>644,645</sup>  | I                  | C                  |
| CV follow-up and treatment optimization is recommended in patients who developed vascular toxicities during cancer therapy. <sup>10,237</sup>   | I                  | C                  |

Continued

ECG follow-up is recommended in patients who developed QT lengthening or LQTS during cancer therapy.<sup>646</sup>

I

C

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CPET, cardiopulmonary exercise testing; CS, cancer survivors; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DM, diabetes mellitus; ECG, electrocardiogram; ESC, European Society of Cardiology; LQTS, long QT syndrome; TKI, tyrosine kinase inhibitors.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Including regulation of hypertension, DM, dyslipidaemia, smoking cessation, weight loss in case of obesity, and an adequate amount of exercise.

<sup>d</sup>High-risk patients: see Table 10.

<sup>e</sup>Moderate- or low-risk patients: according to CV toxicity baseline risk stratification.

<sup>f</sup>Cardio-oncology referral is recommended when available; alternatively, the patient should be referred to a cardiologist with expertise in managing CVD in patients with cancer.

## 8. Long-term follow-up and chronic cardiovascular complications in cancer survivors

### 8.1. Cancer survivors

#### 8.1.1. Adult survivors of childhood and adolescent cancer

The survival of children and adolescents with cancer has increased considerably in recent decades, with 5-year survival rates currently exceeding 80%.<sup>647</sup> However, the long-term health effects in the growing population of childhood and adolescent CS are a major concern.<sup>648</sup> CTR-CVT, as a consequence of treatment with anthracyclines, mitoxantrone, and/or chest-directed RT can manifest as CTRCD but also as VHD, CAD, arrhythmias, autonomic dysfunction, pericardial disease, and premature CV mortality, depending on the type of cardiotoxic treatment.<sup>643,649</sup>

CTRCD is one of the most frequent late effects in childhood CS who received cardiotoxic cancer treatment and contributes to significant morbidity and non-cancer-related mortality later in life.<sup>650</sup> The cumulative incidence of CTRCD varies depending on the diagnostic criteria applied and the population studied and ranges from 4.8% to 10.6% at 40–45 years of age.<sup>651</sup> RT to a field involving the heart increases the risk of CTRCD and valvular and vascular complications.<sup>652</sup>

Follow-up of paediatric CS according to the International Late Effects of Childhood Cancer Guideline Harmonization Group is recommended.<sup>653</sup> This includes risk stratification based upon the total cumulative dose of anthracycline chemotherapy and MHD delivered (Table 11). Annual review of CVRF and education to promote a healthy lifestyle is recommended. The frequency of CV review with TTE depends upon risk. A CV review should be considered every 5 years for moderate-risk childhood and adolescent adult CS and every 2 years for high-risk childhood and adolescent adult CS. A recent retrospective analysis has shown that quantification of LVEF >5 years after cancer diagnosis improves long-term childhood



**Table 11 Risk categories for asymptomatic adults who are childhood and adolescent cancer survivors**

| Risk category  | RT dose <sup>a</sup> (Gy MHD) | Total cumulative doxorubicin <sup>b</sup> dose (mg/m <sup>2</sup> ) | Combination therapy           |   |
|----------------|-------------------------------|---|-------------------------------|---|
|                |                               |   | RT dose <sup>a</sup> (Gy MHD) | Total cumulative doxorubicin <sup>b</sup> dose (mg/m <sup>2</sup> ) |
| Very high risk | >25 <sup>c</sup>              | ≥400  | >15 <sup>c</sup>              | ≥100  |
| High risk      | >15 to 25 <sup>c</sup>        | 250–399   | 5–15 <sup>d</sup>             | ≥100  |
| Moderate risk  | 5–15 <sup>d</sup>             | 100–249   | <5 <sup>e</sup>               | ≥100  |
| Low risk       | <5 <sup>e</sup>               | <100  | –                             | –   |

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

<sup>a</sup>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 is exposed to a relatively high prescribed dose.

<sup>b</sup>Or doxorubicin equivalent.

<sup>c</sup>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.

<sup>d</sup>Or prescribed RT 15–34 Gy to a volume exposing the heart if MHD is not available.

<sup>e</sup>Or prescribed RT < 15 Gy to a volume exposing the heart if MHD is not available.

CS risk stratification. A LVEF of 40–49% is associated with an almost eight-fold increased risk for LVEF <40% at 10-year follow-up compared with patients with a preserved LVEF (≥50%).<sup>654</sup> Lifelong surveillance for high-risk survivors is recommended.<sup>7</sup>

**Recommendation Table 40 — Recommendations for cardiovascular surveillance in asymptomatic adults who are childhood and adolescent cancer survivors**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Education of adults who are childhood and adolescent CS treated with anthracyclines, mitoxantrone, and/or RT to a volume including the heart and their healthcare providers regarding their increased CV risk is recommended. <sup>655–657</sup> | I                  | B                  |
| Annual screening for modifiable CVRF <sup>c</sup> is recommended in adults who are childhood and adolescent CS treated with anthracyclines, mitoxantrone, and/or RT to a volume including the heart.   | I                  | C                  |
| CV assessment <sup>d</sup> is recommended in female childhood and adolescent CS prior to pregnancy or in the first trimester.  | I                  | C                  |
| Echocardiography surveillance should be considered every 2 years in adults who are high-risk childhood and adolescent <sup>e</sup> CS. <sup>7</sup>  | IIa                | B                  |
| Echocardiography surveillance should be considered every 5 years in adults who are moderate-risk childhood and adolescent <sup>e</sup> CS. <sup>7,654</sup>  | IIa                | B                  |

BP, blood pressure; CS, cancer survivors; CV, cardiovascular; CVRF, cardiovascular risk factors; DM, diabetes mellitus; ECG, electrocardiogram; HbA1c, glycated haemoglobin; RT, radiotherapy; TTE, transthoracic echocardiography.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Obesity, sedentary lifestyle, cigarette smoking, alcohol intake, unhealthy diet, dyslipidaemia, hypertension, DM.

<sup>d</sup>BP, lipids, fasting glucose, HbA1c, ECG, and TTE.

<sup>e</sup>See Table 11.

**8.1.2. Adult cancer survivors**

Long-term cancer survivorship care is an advancing field of research. Many survivors will experience several cancer- and treatment-related late effects throughout their lives, including CTR-CVT. Besides affecting their physical and psychosocial health status, these might reduce life expectancy and quality of life. This is relevant in some cancer types, when CVD risk—especially CTRCD risk—exceeds cancer mortality.<sup>658,659</sup> The risk of fatal heart disease is increased more than two-fold in survivors of several solid cancers and lymphoma compared with the general population.<sup>660–662</sup>

CV risk assessment at the end of therapy (Section 7) identifies CS who require long-term cardiology follow-up beyond the first 12 months after completing their cancer treatment. Asymptomatic CS with new or persisting abnormalities at their end-of-therapy assessment will be identified as at high risk for future CV events and require long-term surveillance.

Specific cancer treatments carry the highest risk of long-term CV toxicity including anthracycline chemotherapy and RT where the heart is within the RT treatment volume. Progressive RT-related CV toxicity typically develops 5–10 years after the initial treatment, and may cause CAD and HF at an incidence up to six-fold higher than in the general population. An increased CV mortality compared with the general population has been attributed to radiation-associated heart disease in Hodgkin lymphoma, non-Hodgkin lymphoma, BC, and patients with lung cancer.<sup>663–665</sup> The incidence and progression of the radiation-related CV complications depends on the dose to the CV tissue and on concomitant cancer therapies and patient characteristics, such as pre-existing CVD, CVRF, and age.<sup>389,400</sup>

Late CV complications are also observed in CS who required HSCT. The incidence of HF increases up to 14.5% in women 15 years after HSCT. Risk factors for CVD following HSCT include age, anthracycline dose, chest radiation exposure, hypertension, DM, and smoking.<sup>666</sup>

Long-term follow-up surveillance, based on CV toxicity risks (Table 12), includes patient education and CVRF optimization. An annual clinical CV risk assessment is recommended for all adult CS to optimize CVRF control, promote a healthy lifestyle, and symptom review. This can be done in collaboration with primary care or a

**Table 12 Risk categories for asymptomatic adult cancer survivors**

| Risk category <sup>a</sup>                         | Patient characteristics   |
|--|---|
| <b>Very high risk</b>                              | <ul style="list-style-type: none"> <li>Very high baseline CV toxicity risk pre-treatment</li> <li>Doxorubicin<sup>b</sup> <math>\geq 400</math> mg/m<sup>2</sup></li> <li>RT &gt; 25 Gy MHD<sup>c</sup></li> <li>RT &gt; 15–25 Gy MHD<sup>c</sup> + doxorubicin<sup>b</sup> <math>\geq 100</math> mg/m<sup>2</sup></li> </ul> |
| <b>Early high risk (&lt;5 years after therapy)</b> | <ul style="list-style-type: none"> <li>High baseline CV toxicity risk</li> <li>Symptomatic or asymptomatic moderate-to-severe CTRCD during treatment</li> <li>Doxorubicin<sup>b</sup> 250–399 mg/m<sup>2</sup></li> <li>High-risk HSCT<sup>d</sup></li> </ul>   |
| <b>Late high risk</b>                              | <ul style="list-style-type: none"> <li>RT &gt; 15–25 Gy MHD<sup>c</sup></li> <li>RT 5–15 Gy MHD<sup>e</sup> + doxorubicin<sup>b</sup> <math>\geq 100</math> mg/m<sup>2</sup></li> <li>Poorly controlled CVRF</li> </ul>   |
| <b>Moderate risk</b>                               | <ul style="list-style-type: none"> <li>Moderate baseline CV toxicity risk</li> <li>Doxorubicin<sup>b</sup> 100–249 mg/m<sup>2</sup></li> <li>RT 5–15 Gy MHD<sup>e</sup></li> <li>RT &lt; 5 Gy MHD<sup>f</sup> + doxorubicin<sup>b</sup> <math>\geq 100</math> mg/m<sup>2</sup></li> </ul>                                     |
| <b>Low risk</b>                                    | <ul style="list-style-type: none"> <li>Low baseline CV toxicity risk and normal end-of-therapy cardiac assessment</li> <li>Mild CTRCD during therapy but recovered by the end of cancer therapy</li> <li>RT &lt; 5 Gy MHD<sup>f</sup></li> <li>Doxorubicin<sup>b</sup> &lt; 100 mg/m<sup>2</sup></li> </ul>                   |

CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; GVHD, graft vs. host disease; Gy, Gray; HSCT, haematopoietic stem cell transplantation; MHD, mean heart dose; RT, radiotherapy. References: 397,399,400,673,674

<sup>a</sup>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 in case only a small part of the heart is exposed to a relatively high prescribed dose.

<sup>b</sup>Or equivalent.

<sup>c</sup>Or prescribed RT  $\geq 35$  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.

<sup>d</sup>High-risk HSCT patients: allogenic HSCT; pre-existing CVD or multiple uncontrolled CVRF; cancer treatment history (mediastinal or mantle field radiation, alkylating agents, >250 mg/m<sup>2</sup> doxorubicin or equivalent); conditioning schemes (total body irradiation, alkylating agents); development of GVHD.

<sup>e</sup>Or prescribed RT 15–34 Gy to a volume exposing the heart if MHD is not available.

<sup>f</sup>Or prescribed RT < 15 Gy to a volume exposing the heart if MHD is not available.

specialist in CV medicine with expertise in CVRF management. CS at high or very high risk of future CVD can be divided into those at high early risk (within 5 years of completing cancer therapy) and those at high late risk (>30 years from completing treatment). The timing and frequency of other complementary tests depends upon the risk for CTR-CVT (Figure 38).

CS with a high or very high baseline risk and patients with abnormal LV function at the end-of-therapy assessment have a high or very high

early risk, particularly in the first 2 years.<sup>61,667,668</sup> Annual CV assessment with clinical examination, ECG, and NP measurement is recommended in CS. TTE should be considered at years 1, 3, and 5 after completion of cardiotoxic cancer therapy and every 5 years thereafter in asymptomatic very high- and early high-risk adult CS.

In adult CS with late high CTR-CVT risk (e.g. young adults with Hodgkin lymphoma or sarcomas who received a high total cumulative anthracycline dose or patients treated with high-dose radiation to a field involving the heart, e.g. Mantle RT) there is a progressive risk of CTRCD.<sup>661,669</sup> Annual CV assessment with clinical examination, ECG, and NP measurement is recommended, starting 5 years after the end of treatment, provided the end-of-therapy assessment at 12 months is normal. TTE should also be considered every 5 years, as well as non-invasive screening for CAD (Section 8.3) and carotid disease (Section 8.5) according to local protocols.<sup>670</sup>

The long-term effects of CTRCD caused by trastuzumab and other targeted cancer therapies (e.g. TKI) beyond 10 years are unknown. Currently, there is no recommendation for lifelong surveillance in these CS unless they have another indication.

CV assessment with clinical examination, ECG, echocardiography, and NP measurement every 5 years should be considered in asymptomatic adult CS at moderate risk of future CTR-CVT and a normal end-of-therapy CV assessment.

#### Recommendation Table 41 — Recommendations for cardiovascular surveillance in asymptomatic adult cancer survivors

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Annual CV risk assessment, <sup>c</sup> including ECG and NP, and CVRF management is recommended in CS who were treated with a potentially cardiotoxic cancer drug or RT. <sup>d,631–633,671,672</sup>       | <b>I</b>           | <b>B</b>           |
| CV toxicity risk restratification <sup>e</sup> is recommended 5 years after therapy to organize long-term follow-up.   | <b>I</b>           | <b>C</b>           |
| Echocardiography at years 1, 3, and 5 after completion of cardiotoxic cancer therapy and every 5 years thereafter should be considered in asymptomatic very high- and early high-risk adult CS. <sup>f</sup> | <b>IIa</b>         | <b>C</b>           |
| Echocardiography should be considered in asymptomatic late high-risk adult CS <sup>f</sup> starting at 5 years after radiation to a volume including the heart and then every 5 years.                       | <b>IIa</b>         | <b>C</b>           |
| Echocardiography may be considered every 5 years in asymptomatic moderate-risk adult CS. <sup>f</sup>  | <b>IIb</b>         | <b>C</b>           |
| Non-invasive screening for CAD <sup>g</sup> should be considered every 5–10 years in asymptomatic patients who received >15 Gy MHD, <sup>d</sup> starting at 5 years after radiation.                        | <b>IIa</b>         | <b>C</b>           |
| Carotid ultrasound imaging should be considered every 5 years in asymptomatic patients with a history of head/neck RT, starting at 5 years after radiation and every 5–10 years thereafter.                  | <b>IIa</b>         | <b>C</b>           |

Continued

Renal artery ultrasound should be considered in patients with a history of abdominal and pelvic radiation who present with worsening renal function and/or systemic hypertension.

|            |          |
|------------|----------|
| <b>IIa</b> | <b>C</b> |
|------------|----------|

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BP, blood pressure; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CS, cancer survivors; CT, computed tomography; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; ECG, electrocardiogram; HbA1c, glycated haemoglobin; MHD, mean heart dose; NP, natriuretic peptides; RT, radiotherapy.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Clinical review, BP, lipid profile, HbA1c.

<sup>d</sup>RT risk categorization based on MHD is recommended over categorization based on prescribed dose ( $\geq 35$  Gy to a volume exposing the heart if MHD is not available).

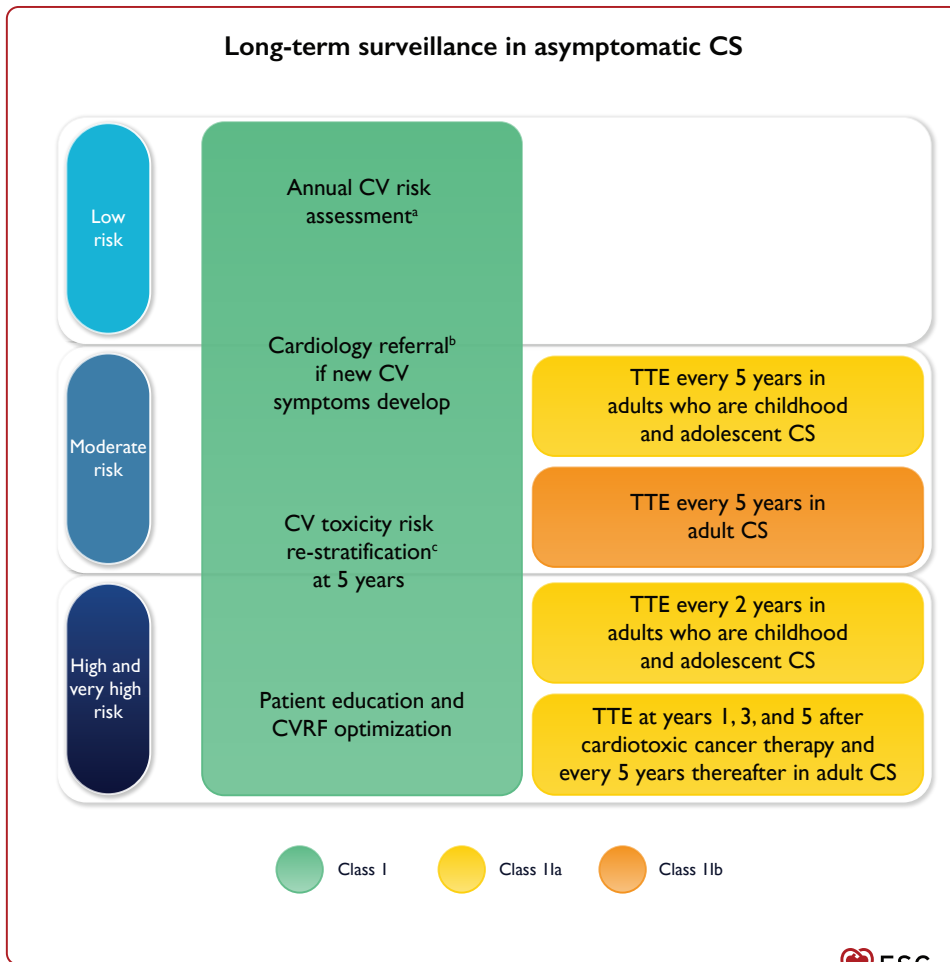
<sup>e</sup>Restratification includes evaluation of new or pre-existing CVRF and CVD (including CTR-CVT).

<sup>f</sup>See Table 12.

<sup>g</sup>Stress echocardiography, cardiac CT, stress CMR, single-photon emission CT stress test, according to local protocol.<sup>234</sup>

## 8.2. Myocardial dysfunction and heart failure

HF treatment in CS should follow the current 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF.<sup>14</sup> Treatment with ACE-I/ARB and/or beta-blockers is recommended for both symptomatic and asymptomatic CS who have LVEF < 50% detected on CV assessment.<sup>14,61,208,675</sup> In CS with mild asymptomatic CTRCD detected on CV assessment (LVEF > 50% but new fall in GLS and/or cardiac serum biomarker increase), treatment with ACE-I/ARB and/or beta-blockers may be considered.



**Figure 38** Long-term follow-up in cancer survivors. BP, blood pressure; CAD, coronary artery disease; CS, cancer survivors; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; ECG, electrocardiogram; HbA1c, glycated haemoglobin; NP, natriuretic peptides; TTE, transthoracic echocardiography. <sup>a</sup>Clinical review, BP, lipid profile, HbA1c, ECG, NP. In selected patients, non-invasive screening for CAD and carotid or renal diseases every 5–10 years, starting at 5 years after radiation may be considered. <sup>b</sup>Cardio-oncology referral is recommended when available; alternatively, the patient should be referred to a specialized cardiologist with expertise in managing CVD in patients with cancer. <sup>c</sup>Restratification includes evaluation of new or pre-existing CVRF and CVD (including CTR-CVT).

**Recommendation Table 42 — Recommendations for adult cancer survivors who develop cancer therapy-related cardiac dysfunction late after cardio-toxic cancer therapy**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| ACE-I/ARB and/or beta-blockers are recommended in adult CS with moderate asymptomatic CTRCD. <sup>c,208,425,675–678</sup> | I                  | C                  |
| ACE-I/ARB and/or beta-blockers may be considered in adult CS with mild asymptomatic CTRCD. <sup>d</sup>                   | IIb                | C                  |

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CS, cancer survivors; CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>New LVEF reduction by  $\geq 10$  percentage points to an LVEF of 40–49% OR new LVEF reduction by  $< 10$  percentage points to an LVEF of 40–49% AND either new relative decline in GLS by  $> 15\%$  from baseline OR new rise in cardiac biomarkers.

<sup>d</sup>LVEF  $\geq 50\%$  and new relative decline in GLS by  $> 15\%$  from baseline AND/OR new rise in cardiac biomarkers.

### 8.3. Coronary artery disease

Any vascular location within the RT treatment volume is at increased risk for both accelerated atherosclerosis and RT-related vasculopathy.<sup>173,392</sup> RT to the chest (e.g. treatment of Hodgkin lymphoma, early-stage BC, lung and oesophageal cancer, and for some patients receiving infradiaphragmatic irradiation if the apex of the heart is within the treatment volume) increases the risk of CAD. The latency between RT and the appearance of CAD varies from a few years to several decades, depending upon the presence or absence of pre-existing atherosclerosis and the age of the patient at the time of RT. This is a serious complication for young CS with a good prognosis and long-life expectancy (e.g. BC and Hodgkin lymphoma).<sup>389,390</sup> Patients treated for mediastinal Hodgkin lymphoma have shown an increased risk of CAD as a first cardiac event.<sup>400</sup> RT-induced CAD depends on the location of the RT treatment volume and most commonly affects either the proximal left anterior descending or the right coronary arteries. RT-related vasculopathy is progressive and typically manifests in severe, diffuse, long, smooth and concentric angiographic lesions.<sup>679,680</sup>

The risk and severity of CAD increases with radiation dose, larger volume exposed, younger age at time of treatment ( $< 25$  years),<sup>390</sup> time from treatment, smoking,<sup>400</sup> the presence of other typical CVRF, type of radiation source, and concurrent metabolic risk factors.<sup>493</sup> RT accelerates pre-existing atherosclerosis leading to increased ACS risk within 10 years of treatment.<sup>681</sup>

Patients with RT-induced CAD undergoing PCI with bare-metal stent or balloon angioplasty have an increased risk of all-cause and CV mortality.<sup>682</sup> Conversely, after PCI with a drug-eluting stent, there is no difference in target lesion revascularization or cardiac mortality between patients with and without prior chest RT.<sup>683</sup>

Surgical revascularization in patients with prior RT may be complicated by poor tissue healing (skin and sternum), RT-induced injury to the left and right internal mammary arteries (LIMA and RIMA, respectively), inadequate target coronary vessels, and increased sternotomy-related pain.<sup>684</sup> Pre-operative assessment of internal

mammary artery viability, venous access, and sternal wound healing is recommended in CS with RT-induced CAD where CABG is considered. PCI with drug-eluting stents may be considered over CABG in CS with RT-induced severe left main or three-vessel disease, with a high SYNTAX (SYNERgy between percutaneous coronary intervention with TAXus and cardiac surgery) score ( $> 22$ ), in whom the planned PCI is technically feasible given the increased complications associated with CABG after mediastinal RT.

Screening for CAD should be considered in high-risk patients who have received chest RT to a treatment volume including the heart. Screening should take the form of functional imaging and/or CCTA beginning at 5 years post-RT.<sup>234,484</sup> The natural history of RT-related vasculopathy is different to atherosclerosis and may accelerate rapidly.<sup>173</sup> Functional cardiac imaging should be considered in asymptomatic CS with pre-existing CAD or when new significant CAD is detected on anatomical imaging. In asymptomatic patients with inducible ischaemia secondary to RT-induced CAD, a MDT is recommended to discuss revascularization needs according to the location of the RT-induced CAD, the ischaemia burden, LV function, arrhythmia burden, time since treatment, time since previous normal review (if available), concomitant valvular disease, risks of surgical or percutaneous revascularization, medical options, and patient preference.<sup>173</sup>

Platinum-based chemotherapies are now recognized to cause CAD in CS. Cisplatin-based chemotherapy for testicular cancer is associated with a 1.5–7-fold increased risk of developing CAD.<sup>421,493,685</sup> Testicular CS who received platinum-based chemotherapy should have their CVRF tightly controlled and be educated to report any new chest pain or cardiac symptoms to their doctor promptly. The role of screening for CAD in patients who received platinum-based chemotherapy is unknown.

Aggressive risk-factor modification and CV diagnostic work-up strongly enhance survival.<sup>5,672</sup> Medical therapy with aspirin and statins for primary/secondary prevention, and beta-blockers and nitrates for symptom control, are recommended in CS.<sup>686,687</sup>

**Recommendation Table 43 — Recommendations for adult cancer survivors with coronary artery disease**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| <b>Asymptomatic radiation-induced CAD detected during surveillance</b>   |                    |                    |
| Non-invasive stress testing <sup>c</sup> is recommended in asymptomatic CS with new moderate or severe radiation-induced CAD detected on CCTA to guide ischaemia-directed management. <sup>635,688</sup> | I                  | C                  |
| A MDT discussion is recommended for clinical decision-making in patients with radiation-induced CAD and inducible ischaemia or severe left main CAD.   | I                  | C                  |
| <b>Symptomatic CAD</b>   |                    |                    |
| Pre-operative assessment of LIMA and RIMA viability, venous access, and sternal wound healing is recommended in CS with radiation-induced CAD where CABG is considered.                                  | I                  | C                  |

Continued

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PCI may be considered in CS with radiation-induced CAD with severe left main or three-vessel disease with a high SYNTAX score (>22) in whom the procedure is technically feasible.<sup>682,689,690</sup>

|     |   |
|-----|---|
| IIb | B |
|-----|---|

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TAVI should be considered for patients with symptomatic severe aortic stenosis caused by radiation at intermediate surgical risk.<sup>504,506,693,694,696,697</sup>

|     |   |
|-----|---|
| IIa | B |
|-----|---|

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CABG, coronary artery bypass graft; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CS, cancer survivors; LIMA, left internal mammary artery; MDT, multidisciplinary team; PCI, percutaneous coronary intervention; RIMA, right internal mammary artery; SYNTAX, SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery.

CS, cancer survivors; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MDT, multidisciplinary team; STS PROM, Society of Thoracic Surgeons–Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation; VHD, valvular heart disease.

<sup>a</sup>Class of recommendation.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>b</sup>Level of evidence.

<sup>c</sup>According to local protocols and Non-invasive imaging in coronary syndromes: recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography, in collaboration with the American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance recommendations.<sup>234</sup>

<sup>c</sup>Surgical risks include: vascular access, sternal and skin wound healing, concomitant cardiac disease, radiation-induced lung and thoracic vessels disease, aortic calcification, STS PROM/EuroSCORE II.

### 8.4. Valvular heart disease

VHD can appear in CS at any point in time but typically occurs 10 or more years after cancer treatment.<sup>691</sup> Chest RT is the main risk factor in CS, in particular at higher dose ranges, which can cause either stenosis or regurgitation, or both.<sup>391</sup> The reported incidences of valvular regurgitation are up to 40% of CS survivors who received high-dose chest RT to a volume involving the heart, with <10% presenting with clinically significant VHD.<sup>670</sup>

### 8.5. Peripheral artery disease and stroke

Peripheral arterial and cerebrovascular disease in CS can be due to the continuum of vascular disease pre-existing before, or developing during or after cancer therapy. Cancer therapies such as cisplatin, BCR-ABL inhibitors, and RT can have a direct long-lasting effect on the vasculature. Approximately 30% of CML patients on nilotinib may develop PAD, which is clinically recognized 2–4 years after the start of therapy.<sup>698</sup> The disease process may progress even after discontinuation of nilotinib. Long-term vascular effects, generally associated with vascular reactivity, can also be seen in patients treated with ponatinib, cisplatin, and bleomycin.<sup>699,700</sup> Accelerated vascular aging, inflammation, fibrosis, and atherosclerosis are characteristic consequences of RT.<sup>701</sup> Up to 30% of patients may develop significant carotid artery stenoses (>70%) after head/neck radiation.<sup>702,703</sup>

Prognosis and management depend on the extent and severity of VHD, as it does in patients without cancer.<sup>692</sup> TAVI should be considered for patients with symptomatic RT-induced severe aortic stenosis at intermediate surgical risk.<sup>504,506,693,694</sup> Similar strategies with percutaneous mitral valve repair or replacement can be considered.<sup>695</sup> Importantly, commonly used calculators such STS PROM (Society of Thoracic Surgeons–Predicted Risk of Mortality) or EuroSCORE (European System for Cardiac Operative Risk Evaluation) II<sup>507</sup> may underestimate the surgery-related risk in CS, and especially those who develop RT-induced VHD, due to additional RT-related risk factors such as pericardial calcification, aortic calcification, increased bleeding risk, impaired skin healing, and RT-related pulmonary fibrosis. A Heart Team with cardiac surgeons, interventional cardiologists, and cardio-oncology specialists should review each case to guide appropriate treatment. The Heart Team recommendation should be discussed with the patient, who can then make an informed treatment choice.

Vascular disease can also be an indirect consequence of cancer and its therapy, e.g. via reduction in physical activity, hyperlipidaemia, DM, obesity, hypothyroidism, and/or kidney disease. These CVRF-related effects are mostly additive to the direct treatment-related effects. Promoting vascular health and preventing vascular disease in CS is recommended.<sup>672</sup> This should be in line with the 2021 ESC Guidelines on CVD prevention in clinical practice.<sup>19</sup>

### 8.6. Pericardial complications

The risk of long-term pericardial complications after cancer drug-induced acute pericarditis, caused by anthracyclines, cyclophosphamide, cytarabine, and bleomycin, is unknown but generally considered low. Long-term dasatinib treatment may lead to pericardial effusion and pericarditis. The incidence of long-term ICI-associated pericardial complications is low.<sup>10</sup>

**Recommendation Table 44 — Recommendations for adult cancer survivors with valvular heart disease**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| A MDT approach is recommended to discuss and define the surgical risk <sup>c</sup> in CS with severe VHD. | I                  | C                  |

RT-induced chronic pericardial diseases can appear months to decades after the initial RT and constrictive pericarditis is the most serious.<sup>173,392</sup> Incidence is difficult to determine, and many cases are initially asymptomatic.<sup>704</sup> Five-yearly echocardiographic surveillance for pericardial constriction in CS following RT-induced acute pericarditis may be considered. The absolute risk is considerably reduced with modern radiation protocols,<sup>704</sup> but a high rate of pericardial effusion has still been reported in patients with lung (grade ≥ 2, >40%<sup>705</sup>) and oesophageal cancer (>25%<sup>706</sup>) treated with RT.

Pericardial disease has been less investigated than other RT-induced CVD, and clear protocols for post-therapy surveillance are lacking.<sup>707,708</sup> In CS with chronic pericardial effusions following RT, cardiac imaging can assess for evidence of inflammation,

Continued



constriction, or tamponade.<sup>709</sup> Percutaneous balloon pericardiectomy or pericardial window creation should be used in selected cases for large or growing chronic effusions if haemodynamic compromise develops. Management of these conditions should follow general guideline recommendations.<sup>14,444</sup>

#### Recommendation Table 45 — Recommendation for adult cancer survivors with pericardial complications

| Recommendation  | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Patients with acute pericarditis during RT to a volume including the heart are at higher risk of developing chronic constrictive pericarditis, hence echocardiography surveillance every 5 years may be considered. | IIb                | C                  |

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RT, radiotherapy.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 8.7. Arrhythmias and autonomic disease

Arrhythmias, conduction disease, and autonomic disease are common complications in CS. Conduction disease after thoracic RT is typically associated with other CTR-CVT.<sup>710</sup> It may include AV block, bundle branch block, and sick sinus syndrome that should be monitored and treated according to the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy.<sup>443</sup> Patients who require valve replacement after thoracic RT have a high risk of post-operative AV block requiring permanent pacemaker therapy.<sup>711</sup> Supraventricular and ventricular arrhythmias are more common in patients after thoracic RT,<sup>712</sup> possibly due to RT-induced myocardial fibrosis. A common long-term complication after HSCT is supraventricular arrhythmia including AF and atrial flutter,<sup>457</sup> particularly in CS treated with anthracyclines or with new CVRF or CV toxicity.

Autonomic dysfunction is an emerging but poorly understood complication observed in CS, and is most frequently observed as a late complication after thoracic RT. Orthostatic hypotension, postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia, and loss of circadian heart rate variability can occur.<sup>713,714</sup> Physicians caring for these patients should consider referral for autonomic evaluation. In addition, the perception of angina pain may be impaired,<sup>714</sup> making the diagnosis of post-radiation CAD challenging. Evidence-based pharmacological treatment strategies are based on studies of patients with other autonomic dysfunction aetiologies (e.g. DM or infiltrative diseases) and the reported effectiveness is generally poor.<sup>714</sup>

## 8.8. Metabolic syndrome, lipid abnormalities, diabetes mellitus, and hypertension

There is a growing understanding about shared CVRF that may be responsible for cancer development or progression and premature CV morbi-mortality.<sup>34</sup> Modifiable CVRF continue to be underdiagnosed and undertreated in CS, especially hypertension,<sup>715</sup> obesity, DM, metabolic syndrome,<sup>716</sup> and dyslipidaemia. Early diagnosis via

standardized risk-based screening and management of these conditions according to general ESC Guidelines is recommended<sup>19</sup> to improve long-term outcomes in CS.<sup>672</sup>

Increasing numbers of patients with cancer are already overweight or obese at cancer diagnosis,<sup>717</sup> and additional weight gain is a frequent complication of anticancer treatments.<sup>718</sup> Obesity is associated with metabolic syndrome, worsening CVRF, and cancer. Increasing evidence indicates that being overweight increases the risk of cancer recurrence and reduces the likelihood of disease-free survival and overall survival among those diagnosed with cancer.<sup>719–724</sup> There is also growing evidence to support intentional weight loss post-treatment in CS, which may result in improved prognosis and survival.<sup>719</sup> Dietary patterns characterized by a high intake of vegetables/fruits and whole grains has been shown to be associated with reduced mortality and cancer recurrence when compared with a high intake of refined grains, processed and red meats, and high-fat dairy products.<sup>725–727</sup>

The identification and treatment of hyperlipidaemia in CS is associated with a profound impact on outcomes.<sup>182,183</sup> There is a benefit for CS from an all-cause mortality perspective as well as for decreasing cancer recurrence.<sup>728–730</sup>

Several studies have demonstrated the therapeutic benefits of exercise during primary anticancer treatment,<sup>731,732</sup> and exercise is recommended during and after anticancer treatment.<sup>11,733</sup> For CS,<sup>734</sup> aerobic exercise results in improved survival.<sup>735</sup> Based on current guidelines, patients undergoing anticancer therapy and long-term CS should be encouraged to exercise for at least 150 min per week.<sup>736</sup>

## 8.9. Pregnancy in cancer survivors

Improvements in the treatment of cancer have led to an increasing number of female paediatric and adolescent CS who experience pregnancy many years after their oncological treatments. Approximately 60% of them will have been previously exposed to anthracycline chemotherapy or chest RT and they have a 15-fold increase in their lifetime risk of developing HF.<sup>737</sup> As young CS enter their reproductive years and contemplate pregnancy, it is important to understand the impact of cancer and its treatment on fertility, pregnancy outcomes, and CV health. There are limited data available regarding CV risk in pregnancy following cancer treatments. The overall incidence of LVD or HF associated with pregnancy in female adult CS varies according to the studied population. In a single institution report including 337 female CS treated with cardiotoxic therapies, 58 (17%) had a subsequent pregnancy.<sup>738</sup> Cardiac events, defined as LVEF < 50% on two TTE or new CAD, were identified in 17 patients.<sup>738</sup> Patients with cardiac events were likely to be younger at cancer diagnosis, received a higher cumulative dose of anthracycline, and had a longer delay (in years) from cancer treatment to first pregnancy compared with pregnant women with no cardiac event.<sup>738</sup> In a recent meta-analysis of six studies, the weighted risk of pregnancy-associated LVD or HF in CS treated with anthracyclines was 1.7% with no reported maternal cardiac deaths.<sup>739</sup> Major risk factors for CV events during pregnancy in CS include CTRCD (incidence 28%; 47.4-fold higher odds),<sup>739</sup> younger age at cancer diagnosis,<sup>738,740</sup> longer time from cancer treatment to first pregnancy, and cumulative anthracycline dose.<sup>738</sup>



Management by an expert MDT (the pregnancy heart team) is recommended for all CS with CTRCD who are considering pregnancy.<sup>739,741,742</sup> The risk of HF in CS without CTRCD is low, although vigilance remains important for potential maternal cardiac complications.

### Recommendation Table 46 — Recommendations for cardiovascular monitoring in cancer survivors during pregnancy

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| In high-risk female CS, pre-pregnancy counselling and management during pregnancy and around delivery by a multidisciplinary pregnancy heart team is recommended.  | I                  | C                  |
| A baseline CV evaluation including history, physical examination, ECG, NP, and echocardiography is recommended in female CS with a history of CTRCD who are considering pregnancy.   | I                  | C                  |
| A baseline CV evaluation including history, physical examination, ECG, and echocardiography should be considered in all female CS who received potentially cardiotoxic cancer therapy and are considering pregnancy.       | IIa                | C                  |
| A CV evaluation including echocardiography is recommended at 12 weeks of pregnancy in female CS who are either high-risk or who received potentially cardiotoxic cancer therapy and did not have a baseline CV assessment. | I                  | C                  |
| A second CV evaluation including echocardiography should be considered at 20 weeks of pregnancy in high-risk female CS <sup>c</sup> who received potentially cardiotoxic cancer therapy.                                   | IIa                | C                  |

CS, cancer survivors; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; ECG, electrocardiogram, NP, natriuretic peptides.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>See Tables 11 and 12.

## 8.10. Pulmonary hypertension

Long-term clinical evaluation may be considered in patients who develop PH during therapy (Section 6). In patients with new exertional dyspnoea, fatigue, or angina, a TTE is recommended to assess the probability of PH. As TTE alone is not enough to confirm the diagnosis of PH, CS diagnosed with high PH probability require a right-heart catheterization to confirm the diagnosis. PH should be treated according to general guidelines with referral to a specialist PH service.<sup>620</sup>

## 9. Special populations

### 9.1. Cardiac tumours

Cardiac tumours are classified as either benign or malignant.<sup>743</sup> Over 90% of primary cardiac tumours are benign (myxomas are

predominant in adults, rhabdomyomas in children).<sup>744</sup> Malignant primary tumours most commonly consist of sarcomas (approximately 65%) or lymphomas (approximately 25%).<sup>745</sup> Cardiac metastases (from melanoma, lymphoma, leukaemia, breast, lung, and oesophageal cancers) are much more common than primary cardiac tumours (Figure 39).<sup>746</sup> Presenting symptoms are paraneoplastic (fever, weakness, fatigue), thromboembolic, haemodynamic (due to compression or obstruction from the tumour) or arrhythmic.<sup>747,748</sup>

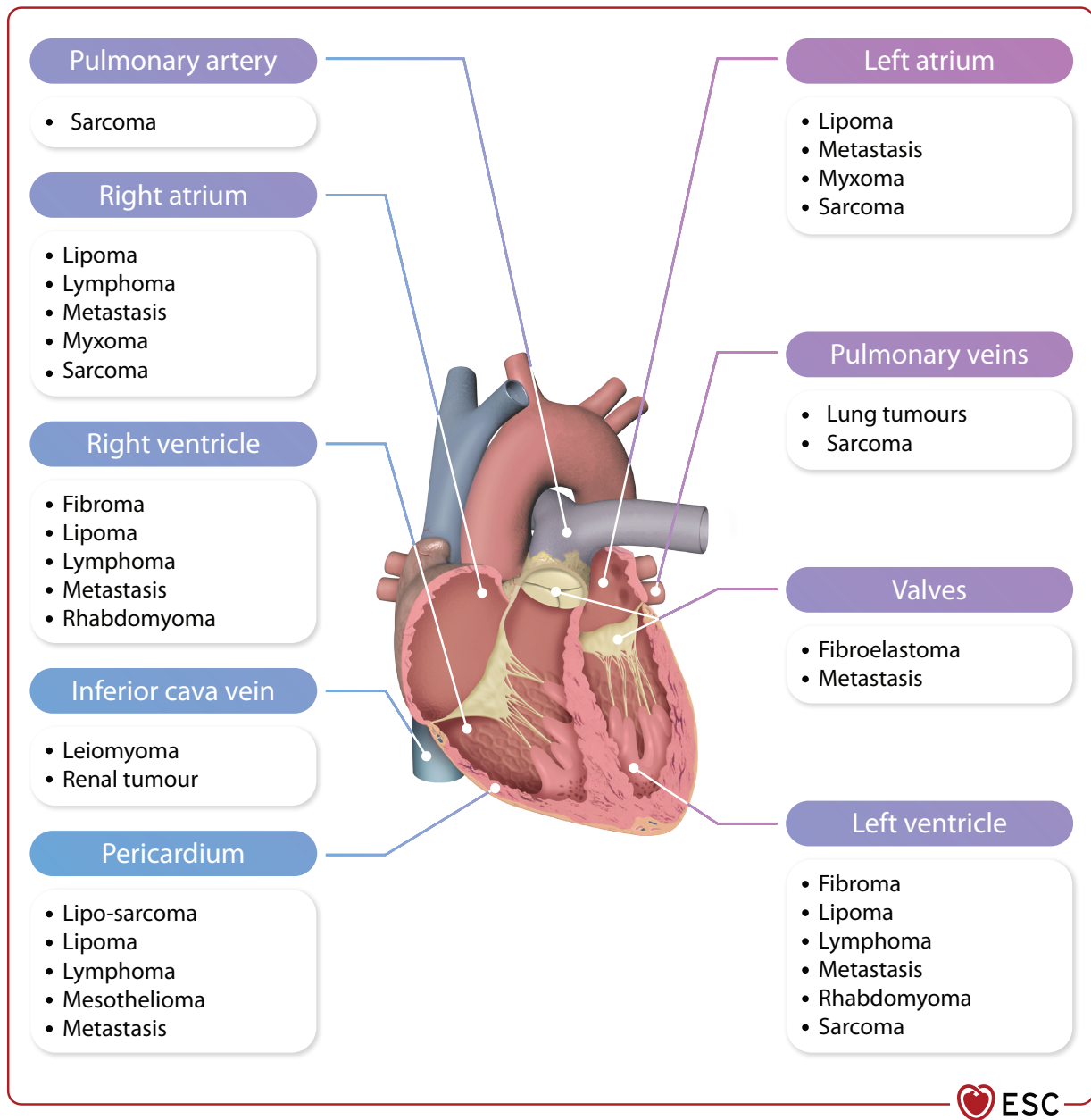
The diagnostic pathway should be based on knowledge about tumour type epidemiology, imaging features, and usually the requirement for a histopathological diagnosis. This topic has been extensively reviewed in ESC CardioMed,<sup>749</sup> and here we summarize the main recommendations for differential diagnosis and management. Differential diagnosis should exclude cardiac thrombi or the presence of chemotherapy catheters. Imaging must assess the possibilities of cardiac surgery, and may include: (1) echocardiography (initial approach using TTE or transoesophageal echocardiography)<sup>748,750</sup>; (2) CMR (for cardiac tumour tissue characterization)<sup>751,752</sup>; and (3) CT and PET (to distinguish malignant from benign lesions and assess for non-cardiac metastatic disease or primary cancers) (Figure 40).<sup>753,754</sup>

Myxomas are primarily treated with surgery with a good prognosis. Malignant tumours are associated with a poor prognosis and evidence of the best treatment is lacking. Complete surgical resection is often impossible and adjuvant RT, systemic chemotherapy, and/or debulking palliative surgery are needed.<sup>755</sup> Cardiac aggressive B-cell lymphomas require histopathological diagnosis (often obtained via analysis of pericardial effusion, EMB, or direct surgical biopsy) and are treated with chemotherapy, possibly followed by RT (Table 13).<sup>756</sup>

### 9.2. Pregnant patients with cancer

The diagnosis of cancer during pregnancy is uncommon (1 in every 1000 pregnant women is diagnosed with cancer), with BC, melanoma, and cervical cancer being the most frequent diagnoses.<sup>757</sup> Chemotherapy is generally not applied during the first trimester due to the high risk of foetal congenital abnormalities (up to 20%) and cytotoxic chemotherapies have different risk profiles during the second or third trimesters.<sup>758,759</sup> Furthermore, chemotherapy administration is usually not given beyond week 34 of gestation to provide a 3-week window between the last cycle and delivery.<sup>757</sup> Supplementary data, Table S19 summarizes the chemotherapies for pregnant patients with cancer.<sup>760,761</sup>

Cardiac assessment prior to chemotherapy in pregnant women with cancer should consist of clinical history, physical examination, ECG, cardiac biomarker assessment and TTE (Figure 41).<sup>741</sup> Baseline and follow-up TTE should be interpreted in the context of physiological haemodynamic alterations during pregnancy. In normal pregnancy, increase in stroke volume, heart rate, and pre-load blood volume, and decrease in systemic vascular resistance, lead to an increase in cardiac output from the first trimester to 80–85% above baseline by the third trimester.<sup>762–764</sup> An increase in LV mass and LV and RV volumes is observed in the third trimester. During normal pregnancy, LVEF is usually unchanged and can be used for CTRCD monitoring. Although NP and cTn may be slightly elevated during normal pregnancy (NT-proBNP < 300 ng/L, BNP < 100 pg/mL,<sup>14</sup> and hs-cTnT<sup>765,766</sup>), serial evaluation may be useful for



**Figure 39** Location of primary and secondary cardiac tumours.

close CTRCD monitoring during cancer treatment with the higher cut-off NP levels for pregnancy.

The topic of CVD during pregnancy has been extensively reviewed in the 2018 ESC Guidelines for the management of CVD during pregnancy.<sup>741</sup> Here we focus on specific recommendations in pregnant women with cancer receiving anthracycline chemotherapy.

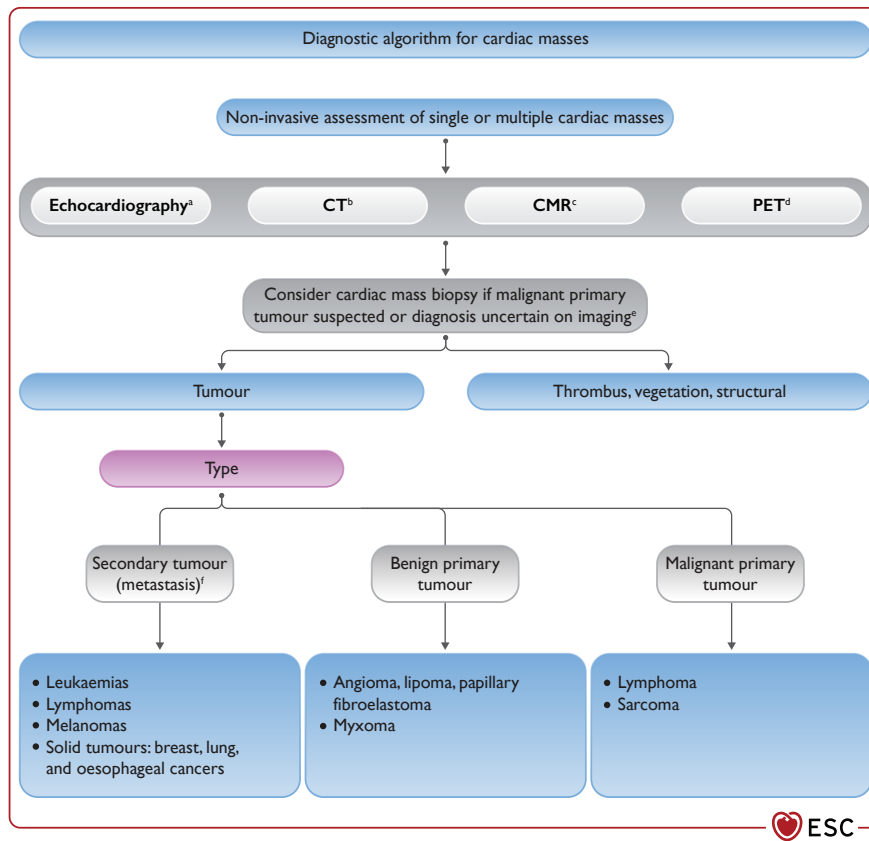
### 9.2.1. Left ventricular dysfunction and heart failure

Medical history evaluating signs and symptoms of HF should be performed at every clinical visit of pregnant women with cancer receiving anthracycline chemotherapy. More frequent CV evaluations with

TTE during treatments with potential CTRCD risk should be advised (e.g. every 4–8 weeks or every two cycles for a 3-weekly anthracycline chemotherapy cycle). The management of clinical HF or asymptomatic LVD during pregnancy is fully described in the 2018 ESC Guidelines for the management of CVD during pregnancy.<sup>741</sup>

### 9.2.2. Venous thromboembolism and pulmonary embolism

Pregnant patients with cancer have an increased risk of developing VTE, especially when hospitalized.<sup>767–769</sup> Identified risks for VTE in pregnant patients include having a history of BC or previous chemotherapy in the past 6 months.

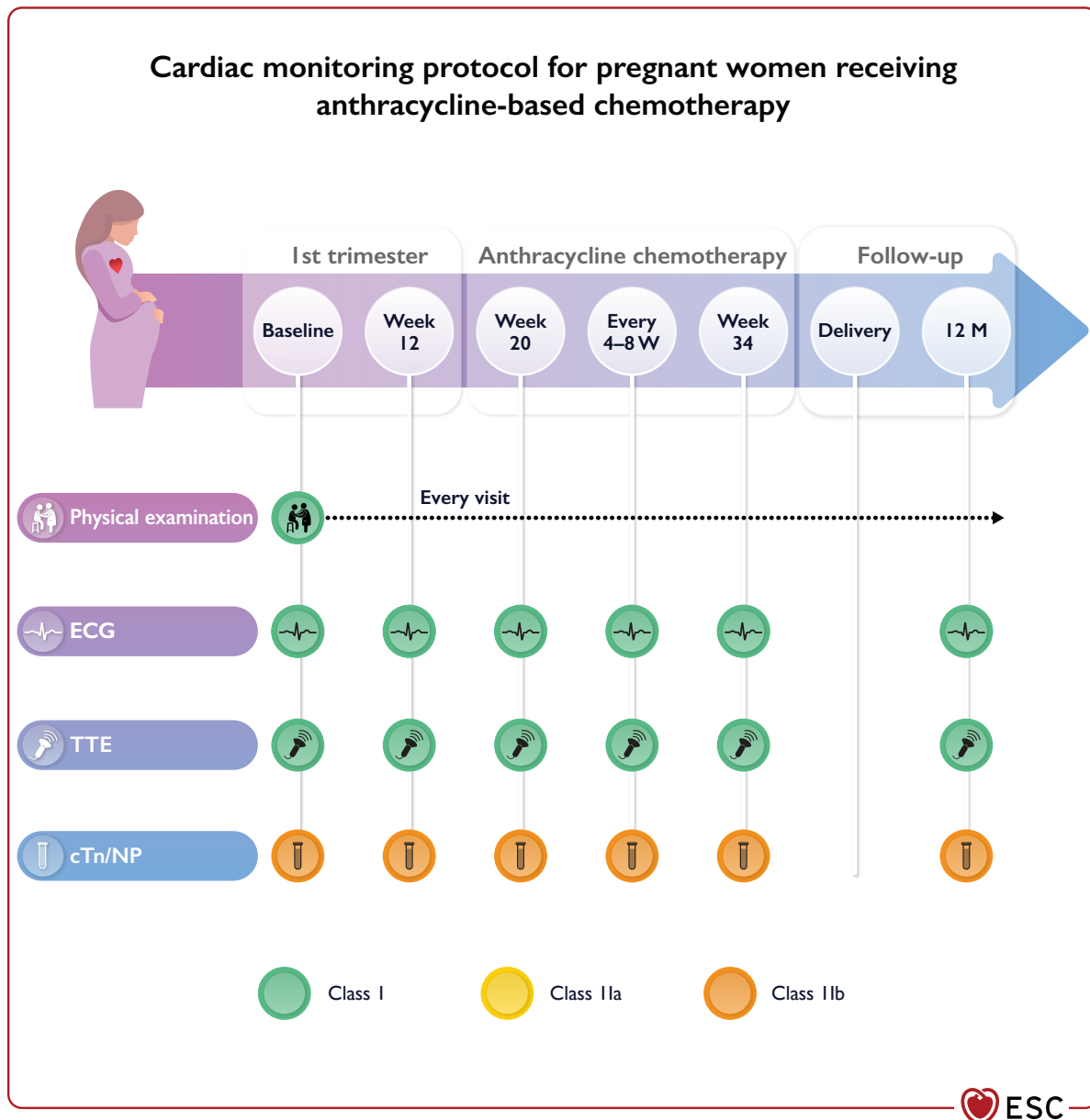


**Figure 40** Diagnostic algorithm for cardiac masses. CMR, cardiac magnetic resonance; CT, computed tomography; PET, positron emission tomography; TTE, transthoracic echocardiography. <sup>a</sup>TTE/transoesophageal echocardiography: location, size, and haemodynamic disturbances. Contrast echocardiography to assess vascularization. <sup>b</sup>Identify primary extra-cardiac malignancy. Reveal extra-cardiac changes. Staging of malignant lesions. <sup>c</sup>Tissue characterization (fat infiltration, necrosis, haemorrhage, calcification, and vascularization). Exclude thrombus. <sup>d</sup>Distinguish malignant vs. benign lesions. Staging of malignant lesions. <sup>e</sup>Mass biopsy of suspected primary malignant cardiac tumours and/or biopsy of extracardiac masses if detected and safer to biopsy. <sup>f</sup>20–30 times more likely than primary tumours.

**Table 13** Management strategies and surgery indications for symptomatic and asymptomatic patients with benign and malignant cardiac tumours

| Classification           |              | Management strategies   | Surgery indications   |
|--------------------------|--------------|---|---|
| <b>Benign tumours</b>    | Asymptomatic | MDT discussion is required considering: tumour type, location, size, growth rate, and likelihood of embolism. Anticoagulation should be considered for left-sided tumours or right-sided tumours associated with an intracardiac shunt, according to the individual's embolic and bleeding risk | If left-sided and endocardial: even if small and incidental, a MDT is needed to consider the indication for surgical removal due to the embolic risk  |
|                          | Symptomatic  | Non-surgical management for: <ul style="list-style-type: none"> <li>• Rhabdomyomas (possible spontaneous regression)</li> <li>• Intramural haemangioma (possible response to corticosteroids)</li> <li>• Unresectable cases: if antiarrhythmic therapy is sufficient</li> </ul>                 | Surgical resection is indicated in all other cases. For large, benign, unresectable, symptomatic cardiac tumours (obstruction, severe HF, or malignant arrhythmias), heart transplantation may be indicated in some cases |
| <b>Malignant tumours</b> | Asymptomatic | Histopathological diagnosis is required   | If primary cardiac sarcoma, a complete surgical resection may increase survival   |
|                          | Symptomatic  | Chemotherapy and/or RT are the only therapeutic options for secondary cardiac tumours. If primary cardiac lymphoma: chemotherapy  | Secondary cardiac tumours may also be treated with palliative cardiac surgery   |

HF, heart failure; MDT, multidisciplinary team; RT, radiotherapy.



**Figure 41** Cardiac monitoring protocol for pregnant women receiving anthracycline-based chemotherapy. cTn, cardiac troponin; ECG, electrocardiogram; M, months; NP, natriuretic peptides; TTE, transoesophageal echocardiography; W, week.

Recommendations for the diagnosis and treatment of PE during pregnancy are the same as in the general 2018 ESC Guidelines for the management of CVD during pregnancy<sup>741</sup> and 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism.<sup>566</sup>

Determination of VTE risk score and the use of thromboprophylaxis protocols may be useful to prevent maternal

morbidity and/or mortality due to VTE.<sup>770</sup> LMWH have become the drug of choice for the prophylaxis and treatment of VTE in pregnant patients.<sup>741</sup> The recommendation for thromboprophylaxis should be individualized, weighing the risks of bleeding vs. thromboembolism in pregnant patients with cancer.

**Recommendation Table 47 — Recommendations for cardiovascular assessment and monitoring of pregnant women with cancer**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Management by an expert MDT (the pregnancy heart team) in an expert centre is recommended for pregnant women with cancer who require cardiotoxic cancer therapy. <sup>741</sup>           | I                  | C                  |
| Cardiac assessment prior to cardiotoxic cancer therapy in pregnant women is recommended and consists of clinical history, physical examination, ECG, and echocardiography. <sup>741</sup> | I                  | C                  |
| Monthly or bimonthly CV evaluation, including TTE, should be considered during cardiotoxic cancer therapy <sup>c</sup> in pregnant women with cancer.                                     | IIa                | C                  |
| cTn may be considered at baseline and during anthracycline chemotherapy in pregnant women with cancer.  | IIb                | C                  |

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cTn, cardiac troponin; CV, cardiovascular; ECG, electrocardiogram; MDT, multidisciplinary team; TTE, transthoracic echocardiography.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>For patients receiving anthracycline-based chemotherapy.

**9.3. Carcinoid valvular heart disease**

Carcinoid tumours represent rare neuroendocrine malignancies originating from the enterochromaffin cells (Figure 42).<sup>771</sup> Carcinoid syndrome is a rare cause of acquired VHD including mainly right-sided valvular lesions, but also left-sided involvement, pericardial effusion, and myocardial metastases.<sup>772</sup> Coronary artery vasospasm and paroxysmal atrial or ventricular tachycardias may rarely occur due to sympathetic stimulation. Cardiac metastases are reported with an incidence of 3.8% on the ventricles, confirmed by PET-CT scans.<sup>773,774</sup> Data from the SEER (Surveillance, Epidemiology, and End Results) registry identified that approximately 20% of patients with neuroendocrine malignancies develop carcinoid syndrome (7.6–32.4%), which is associated with shorter survival (4.7 years compared with 7.1 years in patients without carcinoid syndrome) and poor quality of life.<sup>775</sup> It is estimated that 20–50% of these patients present cardiac involvement, especially of the right-sided cardiac valves.<sup>771</sup> In the presence of a patent foramen ovale, interatrial shunt, primary bronchial neuroendocrine tumour, or extensive liver metastases, humoral substances directly enter the systemic circulation, causing left-sided valvular involvement in up to one-third of cases.<sup>776</sup>

NP should be considered for screening and surveillance of patients at risk of carcinoid cardiac involvement and TTE is recommended in patients with NT-proBNP > 260 pg/mL or clinical signs or symptoms.<sup>777–780</sup> In asymptomatic patients with NT-proBNP < 260 pg/mL, repeat clinical and NP assessment should be considered every 6 months.

Survival has improved in carcinoid tumours, with the use of somatostatin analogues and surgical techniques in liver metastasis. However, right HF still represents a major cause of death.<sup>781,782</sup> Many patients with severe tricuspid regurgitation due to carcinoid

syndrome require both tricuspid and pulmonary valve surgery.<sup>783</sup> Administration of i.v. somatostatin analogues (e.g. octreotide) is recommended to avoid a peri-operative carcinoid crisis. The infusion should be started on the morning of the procedure (up to 12 h pre-operatively), continued throughout the procedure (surgery, pre-operative coronary angiography, pacemaker implantation), and post-operatively for at least 48 h following valve surgery or until stable if a carcinoid crisis is triggered post-operatively.<sup>772</sup>

The optimal choice of valve prosthesis is still a matter of debate due to the balance of risk of both accelerated bioprosthetic valve degeneration vs. bleeding risks in patients with extensive liver metastases requiring therapeutic anticoagulation for mechanical valves.<sup>784,785</sup> Complications include AV block, requiring pacemaker implantation in 25% of patients.<sup>786</sup> Frequently, the reduced RV function does not improve despite tricuspid valve replacement and HF persists.<sup>787</sup> Thrombus formation on the tricuspid bioprosthesis can occur, especially during the first 3 months post-operatively, and oral anticoagulation with VKA may be considered. Persistent serotonin elevation can cause recurrent bioprosthesis valve fibrosis. Valve-in-valve transcatheter intervention has been reported in bioprosthetic valve failure in metastatic carcinoid heart disease; however, future research is needed to define its role.<sup>783,788,789</sup>

In patients with left-sided carcinoid valvular involvement, closure of interatrial shunts should be considered, although only sparse data exist for this approach.

**Recommendation Table 48 — Recommendations for carcinoid valvular heart diseases**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Echocardiography <sup>c</sup> is recommended for the detection of carcinoid cardiac involvement in all patients with carcinoid syndrome and elevated NP levels and/or clinical signs of carcinoid heart disease, and for surveillance every 3 or 6 months depending on the severity of cardiac involvement and clinical status. <sup>772,790,791</sup> | I                  | B                  |
| NP should be considered for screening and surveillance of carcinoid heart disease every 6 months. <sup>777–780</sup>   | IIa                | B                  |
| A MDT discussion for optimal medial management to prevent carcinoid crisis is recommended before any invasive or surgical cardiac procedure.   | I                  | C                  |
| Valve replacement surgery is recommended in symptomatic patients with severe carcinoid tricuspid or pulmonary VHD and an expected survival ≥ 12 months. <sup>d,783,785</sup>   | I                  | C                  |
| Valve replacement surgery should be considered in patients with asymptomatic severe carcinoid tricuspid or pulmonary VHD, progressive RV dysfunction/dilatation, and an expected survival ≥ 12 months. <sup>d,772</sup>  | IIa                | C                  |

Continued

Valve replacement or repair surgery is recommended in symptomatic patients with severe carcinoid mitral or aortic VHD and an expected survival  $\geq 12$  months.<sup>783,785</sup>

|   |   |
|---|---|
| I | C |
|---|---|

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### 9.4. Amyloid light-chain cardiac amyloidosis

Amyloid light-chain amyloidosis is a plasma cell dyscrasia, which is typically treated with therapies very similar to those used in MM, including PI-based therapy.<sup>792</sup> It can occur in conjunction with myeloma or independently as a light-chain protein-producing disorder. Amyloid light-chain amyloidosis is a systemic disease<sup>793,794</sup> and it is critical to have a high degree of suspicion for the diagnosis of cardiac involvement (amyloid light-chain cardiac amyloidosis [AL-CA]) because a combination of specialized tests is needed to make an accurate diagnosis (Figure 43).<sup>290,793,795,796</sup>

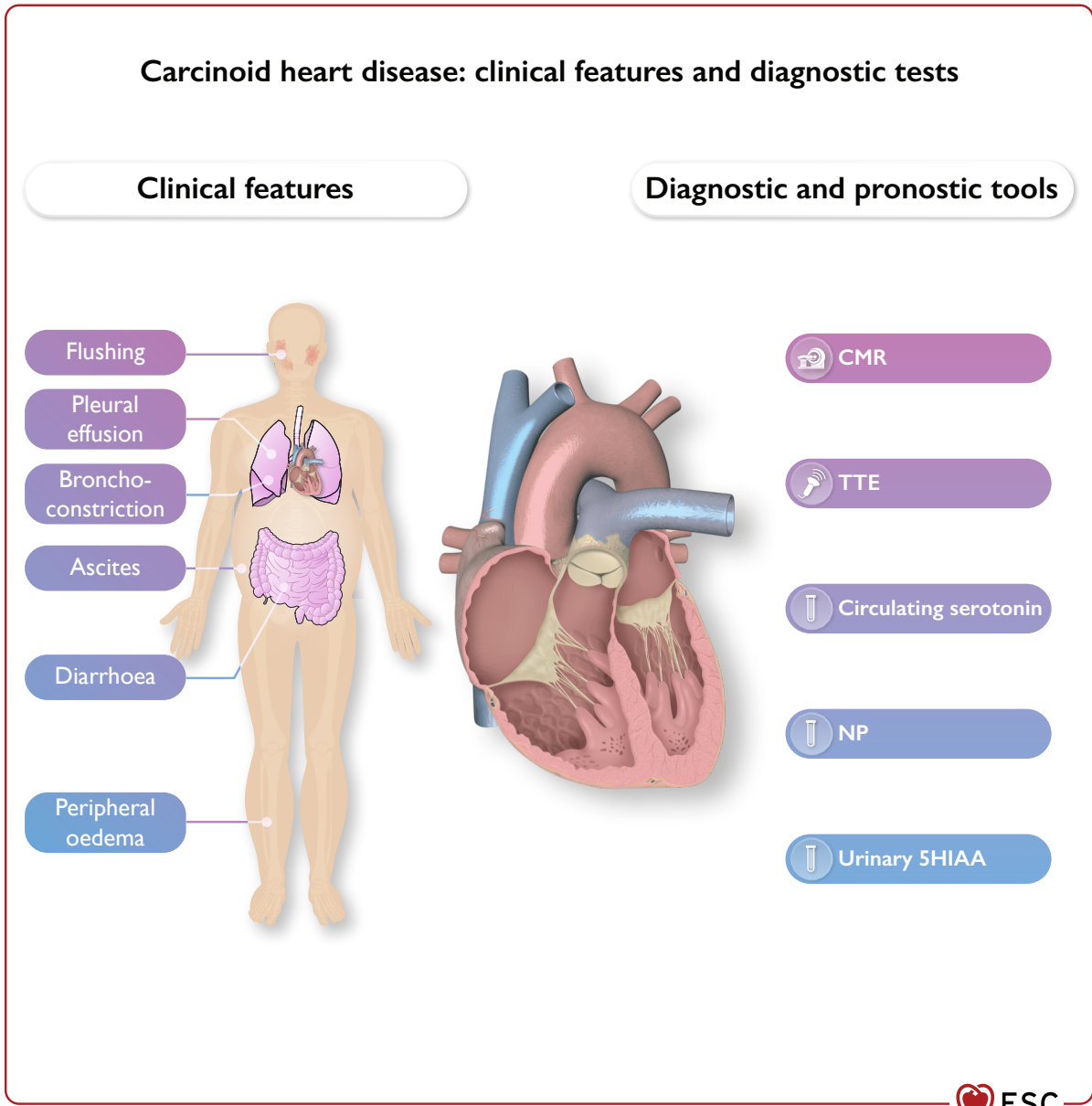
MDT, multidisciplinary team; NP, natriuretic peptides; RV, right ventricular; VHD, valvular heart disease.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Including saline contrast infusion at baseline to rule out patent foramen ovale.

<sup>d</sup>With controlled serotonin concentrations.

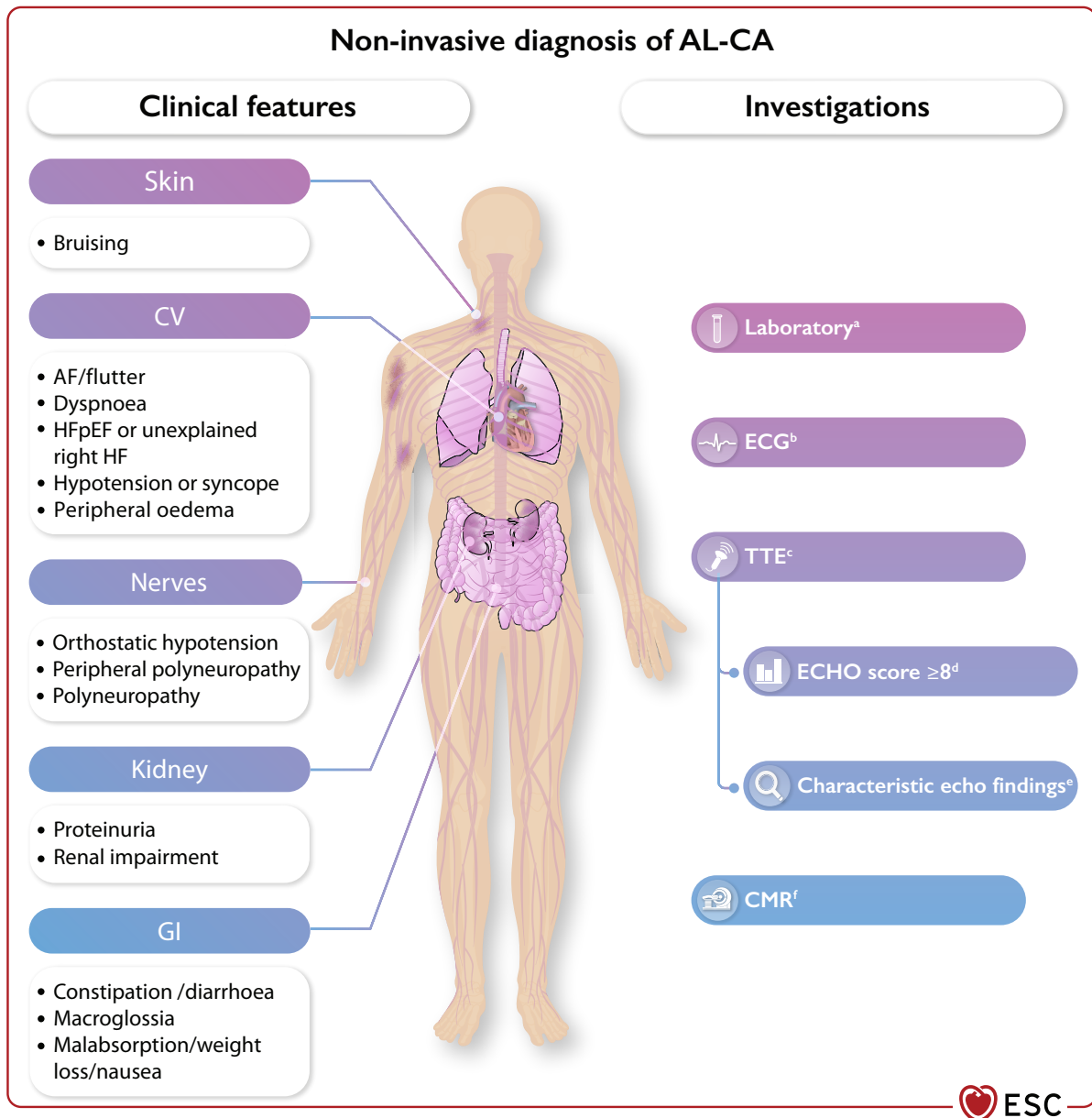


**Figure 42** Carcinoid heart disease: clinical features and diagnostic tests. 5HIAA, 5-hydroxyindoleacetic acid; CMR, cardiac magnetic resonance; NP, natriuretic peptides; TTE, transthoracic echocardiography.

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**Figure 43** Non-invasive diagnosis of amyloid light-chain cardiac amyloidosis. <sup>a</sup>, late diastolic velocity of mitral annulus obtained by tissue Doppler imaging; AF, atrial fibrillation; AL-CA, amyloid light-chain cardiac amyloidosis; CMR, cardiac magnetic resonance; CV, cardiovascular; E, mitral inflow early diastolic velocity obtained by pulsed wave; <sup>e</sup>, early diastolic velocity of mitral annulus obtained by tissue doppler imaging; ECG, electrocardiogram; echo, echocardiography; ECV, extracellular volume fraction; GI, gastrointestinal; GLS, global longitudinal strain; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IVS, interventricular septum; LGE, late gadolinium enhancement; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PW, left ventricular posterior wall; <sup>s</sup>, systolic velocity of tricuspid annulus obtained by Doppler tissue imaging; SPEP, serum protein electrophoresis; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography; UPEP, urine protein electrophoresis. Individually, the clinical manifestations and findings on cardiac testing for AL-CA are non-specific. Integration of all clinical and diagnostic findings is necessary when assessing the likelihood of the diagnosis. <sup>a</sup>Disproportionately high NT-proBNP; persisting elevated troponin levels; abnormal free light-chain levels (AL-CA); positive SPEP and/or UPEP (AL-CA). <sup>b</sup>Disproportionately low QRS voltage; early conduction system disease; pseudo-infarct pattern. <sup>c</sup>Unexplained LV thickness  $\geq 12$  mm + 1 or 2 characteristic echo findings or ECHO score  $\geq 8$ ; idiopathic pericardial effusion. <sup>d</sup>ECHO score: relative LV wall thickness (IVS + PW/LVEDD)  $> 0.6$  (3 points), Doppler  $E/e' > 11$  (1 point); TAPSE  $\leq 19$  mm (2 points); GLS  $\geq -13\%$  (1 point); systolic longitudinal strain apex to base ratio  $> 2.9$  (3 points). <sup>e</sup>Characteristic echocardiography findings: grade  $\geq 2$  diastolic dysfunction; reduced <sup>s</sup>, <sup>e</sup>, and <sup>a</sup> velocities ( $< 5$  cm/s); decreased GLS to  $\geq -15\%$ . <sup>f</sup>Diffuse subendocardial or transmural LGE; elevated native T1 values; abnormal gadolinium kinetics (myocardial nulling preceding or coinciding with the blood pool); ECV  $\geq 0.40\%$  (strongly supportive).

Cardiac serum biomarkers are an essential step in the diagnostic and prognostic assessments for these patients.<sup>797–799</sup> AL-CA has been extensively reviewed in a recent position paper from the Working Group on Myocardial and Pericardial Diseases.<sup>290</sup>

The classical non-invasive definition of AL-CA is based on clinical suspicion, biomarkers, TTE, CMR, and nuclear scintigraphy criteria (Figure 43). Persistent troponin elevation and disproportionately high NT-proBNP (generally >300 ng/L in the absence of renal failure or AF) to ventricular function parameters on TTE is a characteristic red flag for AL-CA.<sup>800</sup> A decrease in GLS with a distinctive apical sparing pattern (preserved GLS values in the LV apical region) is considered specific for cardiac amyloidosis, although it is not helpful to distinguish between amyloid light-chain and transthyretin amyloidosis.<sup>801</sup> Additionally, GLS  $\geq -15\%$  may serve as an independent prognostic factor of poor overall survival in patients with AL-CA.<sup>802</sup> CMR with LGE and parametric imaging has emerged as a new non-invasive gold-standard for diagnosis (Figure 43).<sup>803,804</sup> Nuclear scintigraphy can differentiate transthyretin amyloidosis from AL-CA supported by the presence of monoclonal protein.<sup>290</sup> EMB should be considered in patients with suspected AL-CA involvement if CMR is not diagnostic.<sup>290</sup> A rare condition that may coexist with AL-CA is light-chain deposition disease, which frequently associates extensive renal involvement and poor prognosis.<sup>799</sup>

Recently, a staging system for AL-CA has demonstrated the prognostic impact of cTnT and NT-proBNP levels.<sup>797</sup> Heart progression criteria are defined by NT-proBNP progression (>30% and >300 ng/L increase), cTnT progression ( $\geq 33\%$  increase) or ejection fraction decrease ( $\geq 10\%$  decrease).<sup>805–807</sup> However, evaluating a cardiac response to treatment using a decrease in NT-proBNP levels and New York Heart Association class improvement is still challenging.

AL-CA frequently results in HF, major cardiac arrhythmias, orthostatic hypotension, sudden cardiac death, and an increased risk of arterial and venous thrombosis.<sup>808–810</sup> Beta-blockers, ACE-I, ARB, or angiotensin receptor-neprilysin inhibitor may not be well tolerated because of hypotension.<sup>290</sup> The management of AF is very complex in this population. Amiodarone is the preferred antiarrhythmic treatment and digitalis should be used with caution. Anticoagulation is recommended in all AL-CA patients with AF independent of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score due to the high prothrombotic risk unless there is a contraindication.<sup>290</sup> Currently, the guidelines for implanted devices, including pacemakers and ICDs, do not provide specific recommendations for AL-CA and decisions should be individualized after a MDT discussion.<sup>811</sup>

Optimal systemic therapy for AL-CA is rapidly changing, and the efficacy of certain combination therapies continues to improve.<sup>812,813</sup> Autologous HSCT for AL-CA is not universally utilized but is a viable treatment option.<sup>814</sup> Therapies for AL-CA are evolving, and daratumumab and PI show promise for improved outcomes.<sup>792,815–817</sup> Clinical observations, but no RCT evidence, suggest the potential role of doxycycline to improve survival in patients with AL-CA.<sup>818,819</sup>

### Recommendation Table 49 — Recommendations for amyloid light-chain cardiac amyloidosis diagnosis and monitoring

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| Echocardiography, NP, and cTn are recommended for the diagnosis of AL-CA in patients with plasma cell dyscrasia. <sup>290,820–822</sup>                               | I                  | B                  |
| CMR is recommended in patients with suspected AL-CA. <sup>290,803,804</sup>   | I                  | A                  |
| EMB should be considered in patients with suspected AL-CA involvement if CMR is not diagnostic. <sup>290</sup>  | IIa                | C                  |
| Admission with inpatient ECG monitoring should be considered for high-risk patients with AL-CA requiring PI during their first cycle of therapy. <sup>c,808,811</sup> | IIa                | C                  |

AL-CA, amyloid light-chain cardiac amyloidosis; CMR, cardiac magnetic resonance; cTn, cardiac troponin; ECG, electrocardiogram; EMB, endomyocardial biopsy; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; NP, natriuretic peptides; PI, proteasome inhibitors.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>According to baseline evaluation using HFA-ICOS PI risk assessment tools (see Section 4).

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## 9.5. Cardiac implantable electronic devices

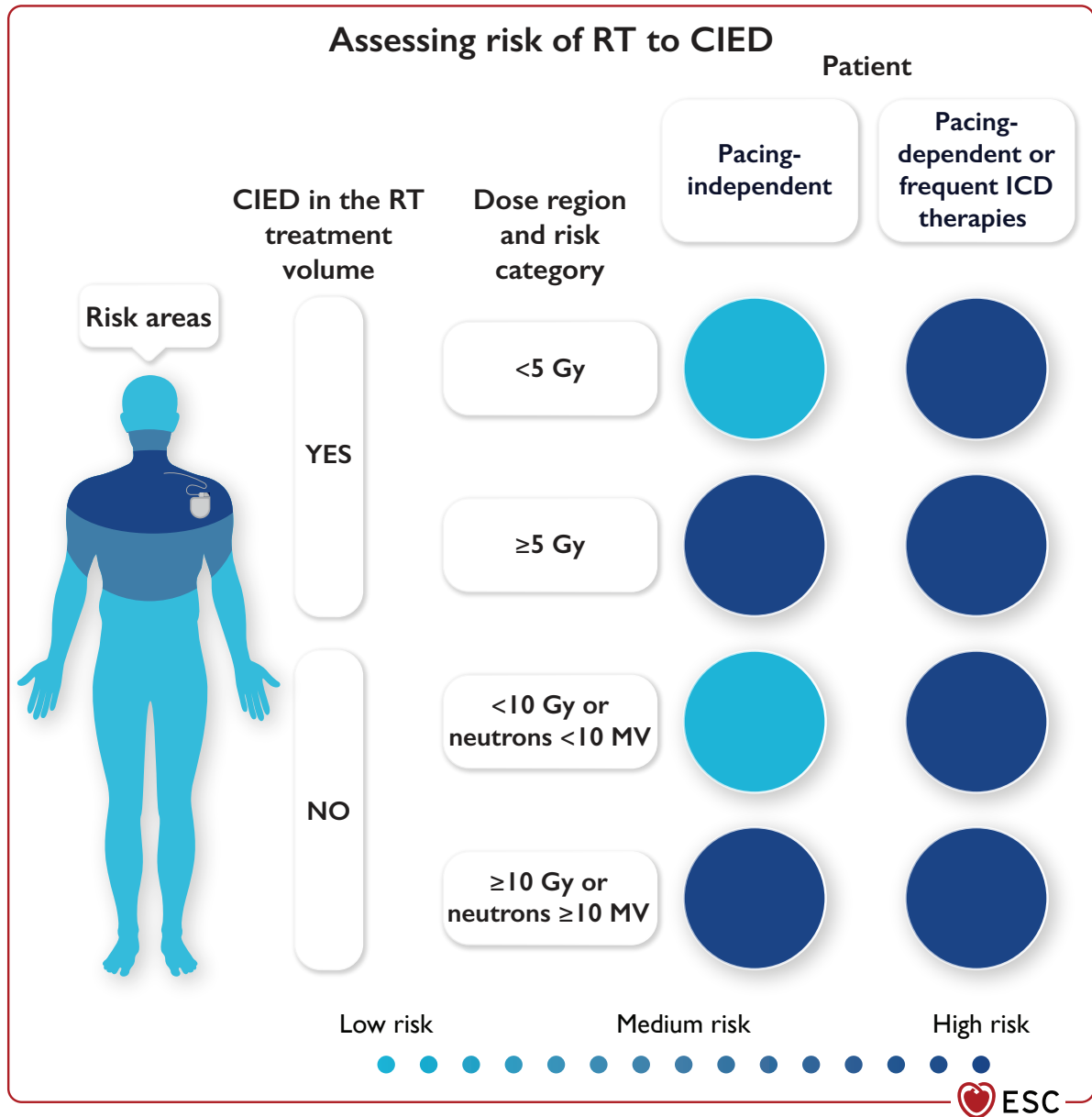
RT can cause malfunction of cardiac implantable electronic devices (CIEDs).<sup>443,823</sup> The risk of RT-induced CIED malfunction generally increases with the radiation dose,<sup>824,825</sup> although the strongest predictor of malfunction is the magnitude of exposure to neutron emission from high-energy photon RT, conventionally defined as a beam energy >10 megavolts (MV).<sup>824,826,827</sup> Non-neutron-producing treatment is therefore preferable in patients with a CIED.<sup>826</sup>

RT-induced CIED malfunction can manifest in: (1) transient interference, with inappropriate triggering during the irradiation only; (2) a reset, reverting to backup settings, recoverable with device reprogramming; and, rarely (3) permanent damage to the device due to direct CIED irradiation.<sup>826,827</sup>

The clinical consequences of a CIED malfunction include the inhibition of pacing and inappropriate pacing at maximum sensor rate.<sup>826</sup> The clinical effects of device malfunction are greatest when the patient is pacing-dependent. Theoretically, oversensing might lead to inappropriate ICD shocks, although this has not been reported in the literature.<sup>826</sup>

More recent registries have reported minimal or no adverse effects of RT on CIED malfunction.<sup>827,828</sup> Nevertheless, as it is not possible to predict the behaviour of a CIED within or close to an RT treatment volume, general recommendations should be followed to minimize patient risk (Figures 44–46).<sup>188,824,825</sup>

Patients with a CIED should be reviewed by their cardiologist/electrophysiologist to assess the risk of CIED malfunction and

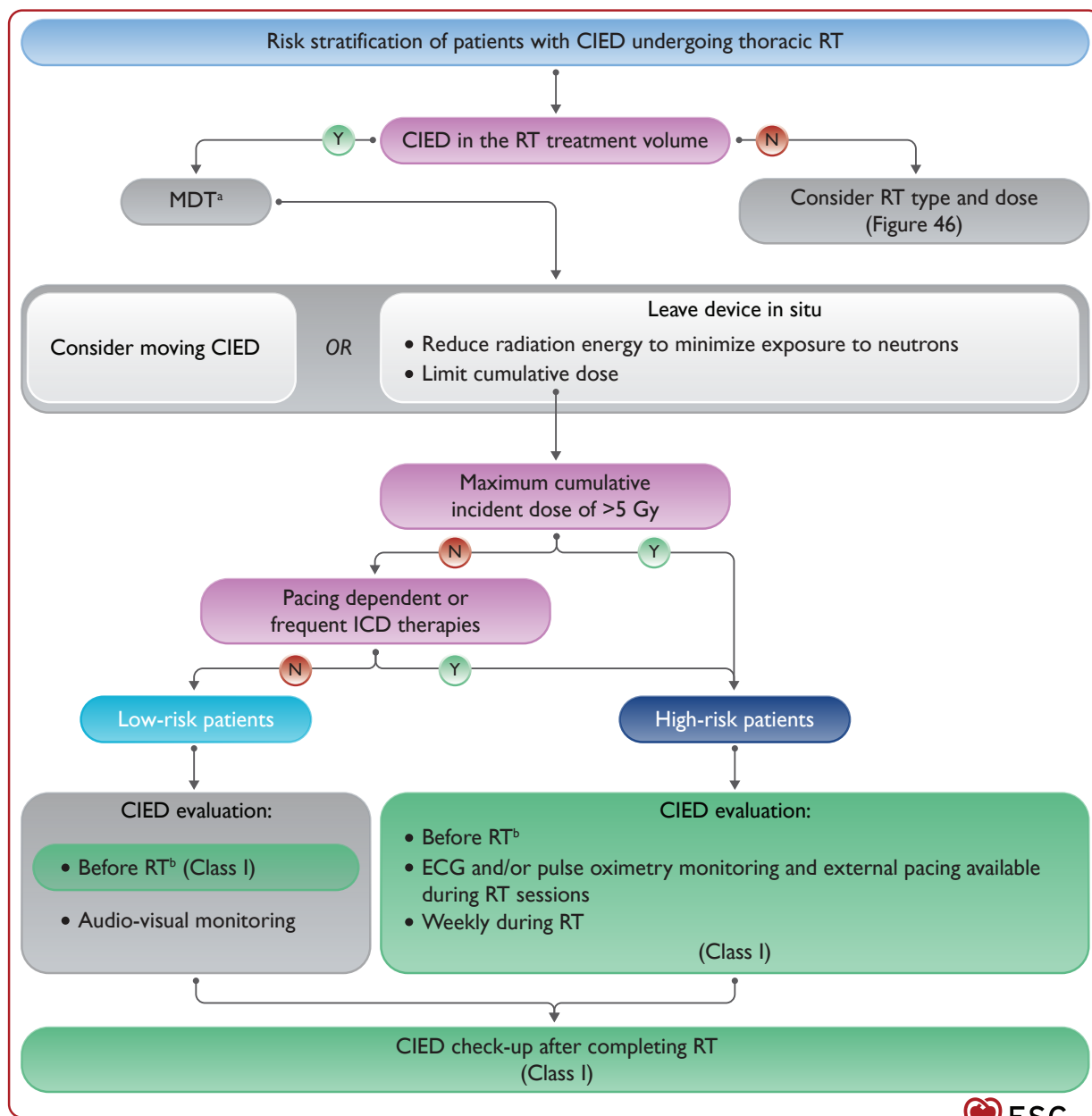


**Figure 44** Risk stratification in patients with a cardiac implantable electronic device undergoing radiotherapy. CIED, cardiac implantable electronic device; Gy, Gray; ICD, implantable cardioverter defibrillator; MV, megavolt; RT, radiotherapy.

patients should be informed of the potential risks of RT.<sup>443</sup> For patients with rate-adaptive pacemakers, consideration should be given to temporary deactivation of the sensor during RT. Although inactivation of antitachycardia therapies in patients with ICDs is recommended in several publications, by either reprogramming or application of a magnet to ICDs, it is infrequently performed in clinical practice.<sup>826</sup>

CIEDs should not be placed directly in the RT treatment volume and the cumulative dose should not exceed 2 Gy to a pacemaker or 1 Gy to an ICD.<sup>827</sup> If the CIED is situated in the path of the planned radiation beam, it could also interfere with

adequate tumour treatment. The photon beam energy should be kept <10 MV as the risk of device malfunction/damage increases above this threshold. If higher doses are needed or if the CIED cannot be kept out of the beam, consideration should be given to removing and relocating the CIED away from the beam, although this will only very rarely be necessary. The main reason for device relocation is to allow adequate RT treatment of the tumour, but consideration should also be given to possible RT-induced CIED malfunction/damage with consequent need for CIED replacement.<sup>826</sup> However, CIED explant and resiting carries significant risks, including the risk of infection, which may be of

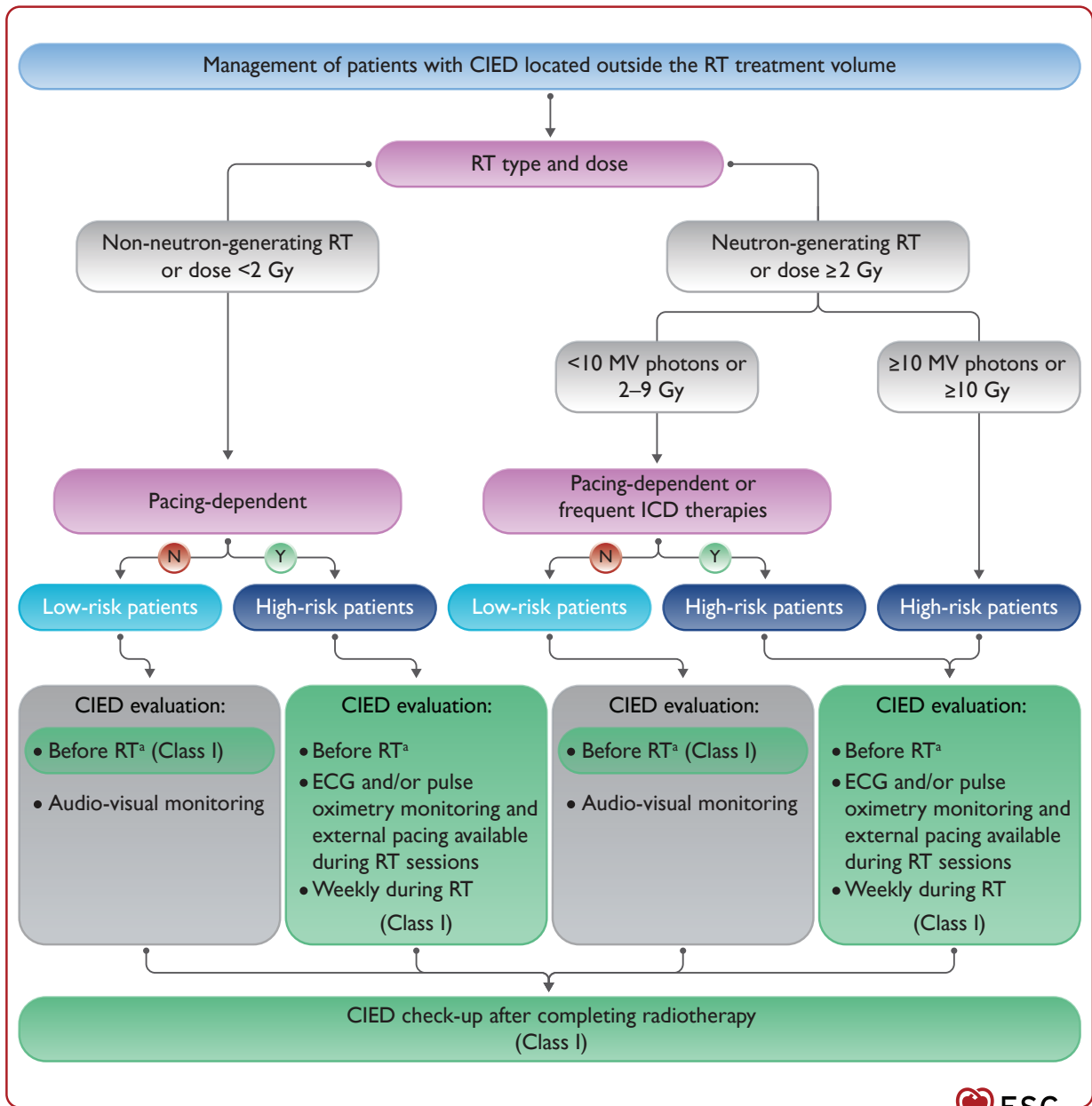


**Figure 45** Management of patients with a cardiac implantable electronic device located in the radiotherapy treatment beam. CIED, cardiac implantable electronic device; ECG, electrocardiogram; Gy, Gray; ICD, implantable cardioverter defibrillator; MDT, multidisciplinary team; N, no; RT, radiotherapy; Y, yes. <sup>a</sup>**Multidisciplinary discussion must consider:** (1) whether the CIED is interfering with the RT dose delivered to the tumour; (2) whether the RT is interfering with CIED function (aim to not exceed 2 Gy to permanent pacemaker and 1 Gy to ICD); (3) risks of moving the CIED: infection (especially in immunocompromised patients), procedural complications (e.g. bleeding with thrombocytopenia); for younger patients with good prognosis, consider long-term effects of losing an access site (lead extraction/RT-induced thrombosis). <sup>b</sup>If last CIED check >3 months earlier.

particular importance in patients receiving chemotherapy or those who are immunosuppressed. For most patients in whom definitive tumour treatment is planned, the risk/benefit ratio will usually favour device relocation, whereas for patients receiving palliative RT or with significant comorbidities, relocation could be avoided.<sup>826</sup> These decisions should be made by a MDT in

conjunction with the patient. Device relocation is not recommended for CIEDs receiving a maximum cumulative incident dose of <5 Gy, where the risk is considered negligible.<sup>826,828</sup>

There should be continuous visual and voice contact with the patient during each treatment fraction. CIEDs should be periodically checked in patients with ICDs, especially those receiving >10 MV



**Figure 46** Management of patients with a cardiac implantable electronic device located outside the radiotherapy treatment volume. CIED, cardiac implantable electronic device; ECG, electrocardiogram; Gy, Gray; ICD, implantable cardioverter defibrillator; MV, megavolt; N, no; RT, radiotherapy; Y, yes. <sup>a</sup>If last CIED check >3 months earlier.

photon beam energy.<sup>827,829</sup> For patients receiving electron or kV photon beam RT, CIED evaluation appears largely unnecessary.<sup>827</sup> For patients treated with proton beam RT, special consideration should be paid to the neutron component of the beam, as the risk

of CIED reset is potentially significant.<sup>824,830</sup> The CIED should be re-checked within 2 weeks of completion of RT treatment. Systematic remote CIED monitoring may be helpful to optimize the patient's surveillance.<sup>831</sup>

**Recommendation Table 50 — Recommendations for risk stratification and monitoring for patients with cardiac implantable electronic devices undergoing radiotherapy**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| Risk stratification including planned radiation type and energy, dose to CIED, the patient's device type, and pacing dependence is recommended prior to starting treatment. <sup>824,825,827,828</sup> | I                  | C                  |
| In patients undergoing RT, a CIED check is recommended in all patients before and after completing RT, and during RT according to individual risk. <sup>824,826</sup>                                  | I                  | C                  |
| In patients with a CIED undergoing RT at high risk of arrhythmia and/or device dysfunction, ECG monitoring and/or pulse oximetry are recommended during every RT session. <sup>827,829,831</sup>       | I                  | C                  |

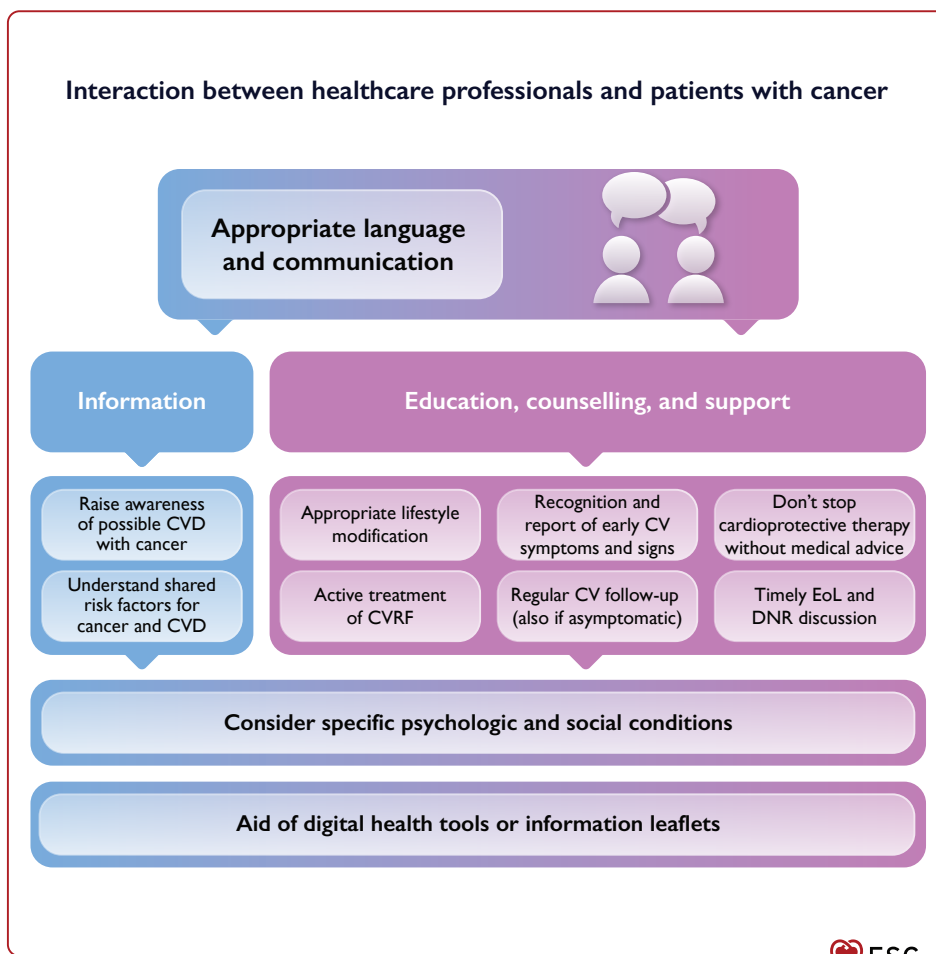
CIED, cardiac implantable electronic device; ECG, electrocardiogram; RT, radiotherapy.  
<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

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## 10. Patient information, communication, and self-management

Collaboration between different healthcare professionals and patients is of paramount importance for the most effective management of patients with cancer and CVD. Appropriate language and communication should be used to allow patients to receive clear and accurate information about their condition, and play an active role in managing their treatment.<sup>11</sup>

The first goal of this process is to raise the patient's awareness of the possible presence or development of a CVD, either during cancer or after having some oncological therapy. Patients should understand that cancer and CVD share many CVRF and reducing risk is vital for the prevention of cancer, cancer relapse, and the development or worsening of a CVD during or after treatment. Patients should be informed—at the end of chemotherapy—that a personalized follow-up plan and regular CV controls are needed to detect potential reversible stages of CV toxicities. Education, counselling, and support to promote healthy lifestyle and to treat modifiable



**Figure 47** Patient information, communication, and self-management. CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DNR, do not resuscitate; EoL, end of life.



CVRF should be offered to patients with cancer, in order to reduce the burden of complications during and after anticancer therapy. Patients should receive guidance to recognize and to report signs and symptoms of CVD, in order to receive prompt and effective treatment, ideally without interfering with their cancer treatment. Patients should also be advised not to stop cardioprotective therapies without medical guidance, even if they recover their cardiac function. To help in this complex task, leaflets specifically designed for this context may be used,<sup>832,833</sup> eventually with the aid of digital tools (Figure 47).

## 11. The role of scientific societies in the promotion and development of cardio-oncology in modern medicine

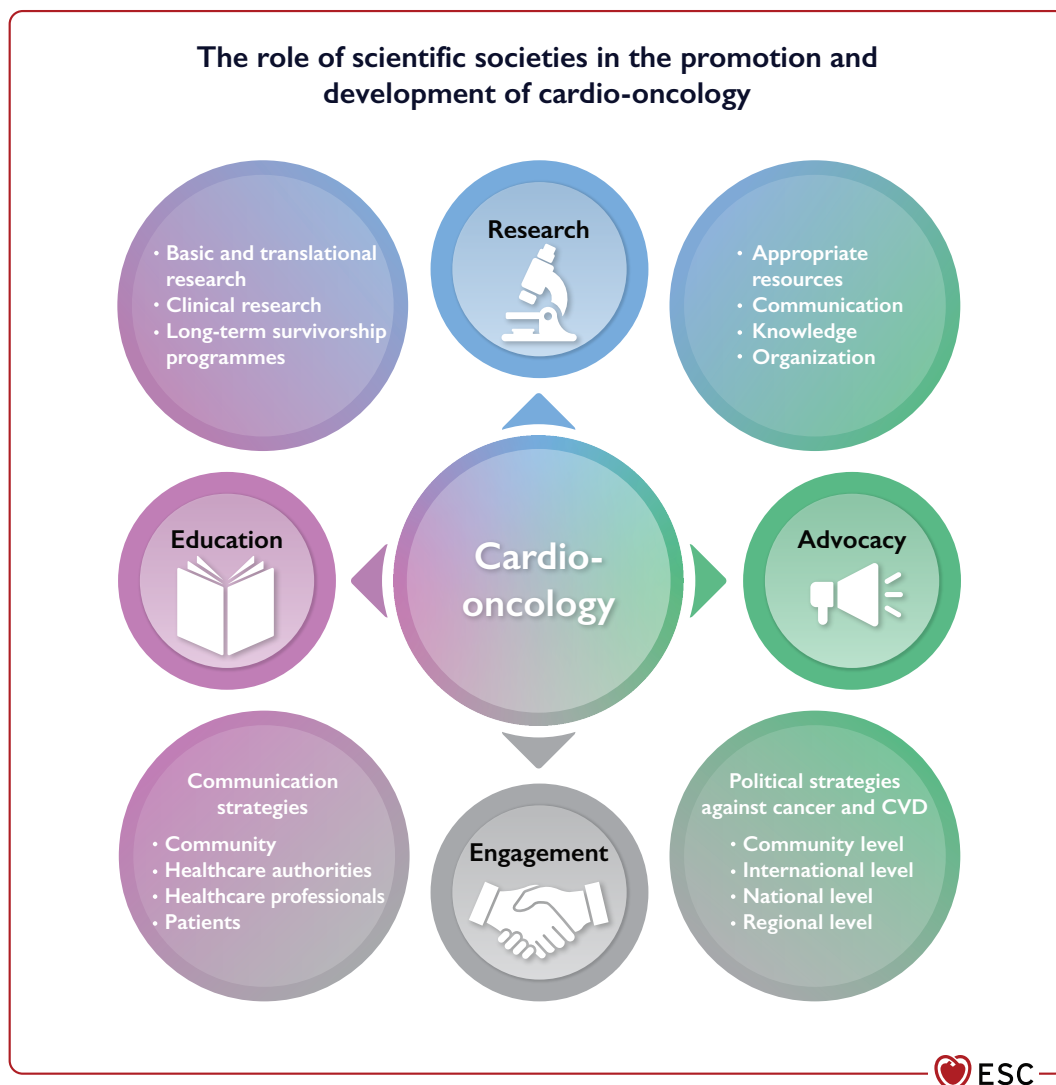
Cardio-oncology is a subspecialty that has seen huge development and growth in recent years with the formation—in almost all national and international societies—of cardio-oncology working groups.

Moreover, cancer and medical associations have also developed an increasing interest in cardio-oncology. Important roles of these scientific societies are clinical research, education, and advocacy. The ESC-CCO strategic plan and mission include improvement of prevention, diagnosis, treatment, and management of CTR-CVT and enhancement of the standard of care for patients with cancer (Figure 48).

## 12. Key messages

This is the first ESC cardio-oncology Guideline and contains 272 new recommendations. The key messages from this guideline are:

- A guiding principle of cardio-oncology is integration, and cardio-oncology providers must have knowledge of the broad scope of cardiology, oncology, and haematology. Communication between different healthcare professionals is critical to optimize the care of patients with cancer and CVD.
- Cardio-oncology programmes facilitate cancer treatment by minimizing unnecessary cancer therapy interruptions and CTR-CVT



**Figure 48** The role of scientific societies in the promotion and development of cardio-oncology. CVD, cardiovascular disease.

across the entire continuum of cancer care. In patients who develop CTR-CVT, a MDT discussion is required to balance the risk/benefit of cancer treatment discontinuation.

- There is a new international definition of CTR-CVT (Table 3).
- CV toxicity risk is a dynamic variable. This guideline is structured to provide a personalized approach to care based upon the baseline CV toxicity risk. A baseline CV risk assessment is recommended for all patients with cancer scheduled to receive a potentially cardiotoxic anticancer therapy. This enables the oncology team to consider CV risk while making cancer treatment choices, educating patients regarding their CV risk, and personalizing CV surveillance and follow-up strategy.
- Primary prevention of CV toxicity from cancer therapy aims to avoid or minimize the development of CTR-CVT in patients without CVD.
- Secondary prevention refers to interventions in patients with pre-existing CVD, including prior or new CTR-CVT. A MDT is recommended when patients with cancer have complex CVD that may impact on their cancer treatment.
- Defining and delivering an appropriate prevention and surveillance plan for potential CV complications is recommended. Optimal management of CVRF and pre-existing CVD is mandatory to facilitate cancer therapy and to improve patients' prognosis.
- Detailed monitoring pathways during cancer therapy—including 3D echocardiography, GLS, and cardiac biomarkers—are provided to detect CV toxicity based upon specific cancer therapies and baseline CV toxicity risk.
- Treatment recommendations for CTRCD during and after cancer therapy depend upon CTRCD severity and symptoms. New guidance on continuing trastuzumab in BC patients who develop asymptomatic moderate CTRCD (LVEF 40–49%) while starting cardioprotective medication is provided.
- Use of a structured algorithm to guide decisions regarding anticoagulation management in patients with cancer presenting with AF or VTE encompassing the TBIP assessment is encouraged.
- After cancer treatment is completed, the focus of the cardio-oncology team shifts to coordination of long-term follow-up. This starts with an 'end-of-treatment' assessment in the first year after treatment, reviewing patients with cancer who have received cardiotoxic anticancer therapies to reassess their CV toxicity risk and guide long-term surveillance planning.
- A new algorithm (Figure 37) is provided to guide weaning off of CV medication in CS.
- Patients with cancer, CS, and the patient's family/carers should receive guidance to promote healthy lifestyle and recognize and report signs and symptoms of CVD, to receive prompt and effective treatment, without interfering with their cancer treatment.
- Patients must receive psychological support when needed and clear and accurate information about their condition to play an active role in managing their treatment and increase adherence to cancer and CV treatments.

### 13. Future needs

There are a low number of dedicated cardio-oncology services and most patients are reviewed in general cardiology clinics in Europe

and worldwide. Strategic investments in cardio-oncology care networks and cardio-oncology services provision are needed to meet the projected increased clinical demand in the near future,<sup>834</sup> and to facilitate research, training, and educational activities. A dedicated training core curriculum for a minimum of 1-year medical training is urgently needed. It may include: (1) knowledge of the broad scope of cardiology, oncology, and haematology; (2) CV competencies for CTR-CVT prevention, surveillance, and management of patients with cancer in dedicated outpatients' cardio-oncology clinics; (3) inpatient consultative services; and (4) dedicated time to achieve competences in CV imaging, HF, and vascular cardiology.

Collaboration between healthcare providers, clinical and basic investigators, healthcare authorities, regulatory bodies, advocacy groups, and patients' associations is needed to address future needs (see Section 11).

As this Guideline was developed, it became clear that there is a significant lack of RCT to guide decision-making, with many recommendations supported by level of evidence C. This is complicated by the fast-moving pace of new oncology treatment developments against a background of dynamic CV toxicity likelihood. Therefore, large numbers of patients and longer follow-up are required to provide sufficient statistical power and definitive answers. In the future, the following strategies and areas of research are priorities:

- New trial designs focusing upon the 'at-risk' cancer patient populations.
- Validating current HFA-ICOS risk assessment tools and surveillance algorithms.
- Assessment of new technologies for the detection of early CTRCD, broadening the biomarker panel and recognizing the specific patterns in early myocardial damage.
- Refining CV risk scores (e.g. EuroSCORE II, SCORE2, SCORE2-OP, CHA<sub>2</sub>DS<sub>2</sub>-VASc, HAS-BLED, SYNTAX) for application in cancer populations.
- Optimal treatment of steroid-resistant ICI CV toxicity and long-term CV effects of ICI therapy.
- Selection criteria for modern percutaneous structural (TAVI, Mitraclip, LAA occluder devices) and electrophysiological (ablation) CV therapies in patients with active cancer.
- Patient-specific predictive algorithms for QTc prolongation with cancer drugs.
- Assessment of genetic profiles in more specific CTRCD risk prediction.
- Identification of the cancer patient populations with mild or moderate CTRCD during treatment who can safely wean off long-term CV medication.
- Optimal modalities for screening long-term survivor populations for the complications of anthracycline chemotherapy and mediastinal radiation.
- Creation of large cardio-oncology registries to collect 'big data' on large patient populations.
- Application of artificial intelligence and other new data analytics to identify new patients with cancer at risk and new parameters that can predict risk of CTR-CVT, response to specific cardioprotective interventions, and long-term risk and safety to wean off CV therapies initiated during cancer treatment.

## 14. Gaps in evidence

Cancer and CVD are the two major public health problems with great economic and social impact. In addition, CTR-CVT are associated with an excess of both CV and oncological mortality, especially when they limit patients' ability to complete effective treatments. However, the intersection of cancer and CVD has only recently gained wider interest and many areas with lack of evidence need to be addressed in future research.

### Role of cardio-oncology services and cardio-oncology care networks

- Robust evidence on the impact of dedicated cardio-oncology programmes and cardio-oncology rehabilitation on the prognosis of patients with cancer and survivors.
- Specification of roles of different healthcare professionals (including nurses and pharmacists) in cardio-oncology teams.
- Cardio-oncology care networks to improve the management of patients with cancer and to discuss difficult cases.
- Cardio-oncology team support and involvement in oncology trials design (including patients' representatives).
- Understand how to engage patients with cancer in their own CV care (inclusion of digital tools).

### Research, education, and training in cardio-oncology

- Consensus about CV toxicity definitions used in oncology trials.
- Define standards for CV toxicity monitoring in oncology trials to avoid unexpected CV toxicities when new drugs are approved for clinical use.
- Relevant model systems to allow high-throughput screening of new cancer treatments for CV toxicity.
- Improved knowledge on CV toxicity mechanisms of new targeted cancer therapies and ICI and optimal treatment of CV toxicities.
- Improved knowledge on the effects of radiation to specific cardiac substructures and the interactions between cardiotoxic systemic therapy and RT.
- Further research into the underlying mechanisms that connect CVD and cancer, such as a genetic predisposition to CV toxicity.

- Personalized medicine and use of big data and artificial intelligence tools.

### Cardiovascular toxicity risk stratification

- Development of CV toxicity risk prediction tools including both treatment- and patient-related risk factors.
- Validated prospective CV toxicity risk scores based on clinical outcomes.
- Further research on the role of genetics in CV toxicity risk stratification.
- Validation of CPET parameters for CV outcomes in patients with cancer.

### Prevention, diagnosis, and management of CTR-CVT

- Raise awareness of the benefits of minimizing CV risk in patients with cancer in order to reduce the risk of CTR-CVT.
- More data on new technologies (biomarkers, advanced echocardiography, CMR, etc.) and genetic profiles for the detection of early CV toxicity.
- Prospective studies showing the impact on outcomes and/or quality of life (and frailty) of early CTR-CVT diagnosis and treatment.
- Further evidence from prospective RCTs to define when cardio-protective medications improve patients' outcomes.
- Further research on the potential for aerobic exercise to reduce CTR-CVT.
- RCTs of (new) CV therapies in patients with different types of CTR-CVT.

### Long-term cancer survivorship programmes

- Development of optimal CV follow-up programmes after treatment for cancer (research on risk stratification, efficacy, and frequency of screening protocols).
- Best screening strategies for RT-induced CAD.
- Further research on CV preventive strategies for long-term CS.

## 15. 'What to do' and 'what not to do' messages from the Guidelines

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> |
|---|--------------------|--------------------|
| <b>Recommendation Table 1 for a general approach to cardiovascular toxicity risk categorization</b>   |                    |                    |
| CV toxicity risk stratification before starting potentially cardiotoxic anticancer therapy is recommended in all patients with cancer.  | I                  | B                  |
| Communicating the results of the CV toxicity risk assessment to the patient and other appropriate healthcare professionals is recommended.  | I                  | C                  |
| It is recommended that patients categorized as low CV toxicity risk should proceed with anticancer therapy without delay.   | I                  | C                  |
| Cardiology referral is recommended in high-risk and very high-risk patients before anticancer therapy.  | I                  | C                  |
| Discussion of the risk/benefit balance of cardiotoxic anticancer treatment in high- and very high-risk patients in a multidisciplinary approach prior to starting treatment is recommended.           | I                  | C                  |
| Cardiology referral is recommended for patients with cancer and pre-existing CVD or abnormal findings at baseline CV toxicity risk assessment who require potentially cardiotoxic anticancer therapy. | I                  | C                  |

Continued

| <b>Recommendation Table 2 for electrocardiogram baseline assessment</b>   |   |   |
|---|---|---|
| An ECG is recommended in all patients starting cancer therapy as part of their baseline CV risk assessment.   | I | C |
| In patients with an abnormal baseline ECG, referral to a cardiologist is recommended.   | I | C |
| <b>Recommendation Table 3 for cardiac biomarker assessment prior to potentially cardiotoxic therapies</b>   |   |   |
| Baseline measurement of NP and/or cTn is recommended in all patients with cancer at risk of CTRCD if these biomarkers are going to be measured during treatment to detect CTRCD.  | I | C |
| <b>Recommendation Table 4 for cardiac imaging modalities in patients with cancer</b>  |   |   |
| <b>General</b>  |   |   |
| Echocardiography is recommended as the first-line modality for the assessment of cardiac function in patients with cancer.  | I | C |
| 3D echocardiography is recommended as the preferred echocardiographic modality to measure LVEF.   | I | B |
| GLS is recommended in all patients with cancer having echocardiography, if available.   | I | C |
| <b>Baseline cardiac imaging prior to potentially cardiotoxic therapies</b>  |   |   |
| Baseline comprehensive TTE is recommended in all patients with cancer at high risk and very high risk of CV toxicity before starting anticancer therapy.  | I | C |
| <b>Recommendation Table 5 for primary prevention of cancer therapy-related cardiovascular toxicity</b>  |   |   |
| Management of CVRF according to the 2021 ESC Guidelines on CVD prevention in clinical practice is recommended before, during, and after cancer therapy.   | I | C |
| <b>Recommendation Table 6 for secondary prevention of cancer therapy-related cardiovascular toxicity</b>  |   |   |
| Management of CVD according to applicable ESC Guidelines is recommended before, during, and after cancer therapy.   | I | C |
| <b>Recommendation Table 7 for baseline risk assessment and monitoring during anthracycline chemotherapy and in the first 12 months after therapy</b>  |   |   |
| <b>TTE</b>  |   |   |
| Baseline echocardiography is recommended in all patients with cancer before anthracycline chemotherapy.   | I | B |
| In all adults receiving anthracycline chemotherapy, an echocardiogram is recommended within 12 months after completing treatment.   | I | B |
| In high- and very high-risk patients, echocardiography is recommended every two cycles and within 3 months after completing treatment.  | I | C |
| <b>Cardiac serum biomarkers</b>   |   |   |
| Baseline measurement of NP and cTn is recommended in high- and very high-risk patients prior to anthracycline chemotherapy.   | I | B |
| cTn and NP monitoring before every cycle during anthracycline chemotherapy and 3 and 12 months after therapy completion is recommended in high- and very high-risk patients.  | I | B |
| <b>Recommendation Table 8 for baseline risk assessment and monitoring during HER2-targeted therapies and in the first 12 months after therapy</b>   |   |   |
| <b>TTE</b>  |   |   |
| Baseline echocardiography is recommended before HER2-targeted therapies in all patients.  | I | B |
| In patients receiving neoadjuvant or adjuvant HER2-targeted therapies, echocardiography is recommended every 3 months and within 12 months after completing treatment.  | I | B |
| In metastatic HER2+ disease, echocardiography is recommended 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. | I | C |
| <b>Cardiac biomarkers</b>   |   |   |
| Baseline NP and cTn measurement are recommended in high- and very high-risk patients prior to anti-HER2-targeted therapies.   | I | C |

Continued

| <b>Recommendation Table 9 for baseline risk assessment and monitoring during fluoropyrimidine therapy</b>  |   |   |
|--|---|---|
| Baseline CV risk assessment and evaluation including BP measurement, ECG, lipid profile, HbA1c measurement, and SCORE2/SCORE2-OP or equivalent is recommended before starting fluoropyrimidines. | I | C |
| A baseline echocardiogram is recommended in patients with a history of symptomatic CVD before starting fluoropyrimidines.  | I | C |
| <b>Recommendation Table 10 for baseline risk assessment and monitoring during VEGFi</b>  |   |   |
| <b>BP monitoring</b>   |   |   |
| BP measurement is recommended 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 is recommended.                            | I | C |
| <b>ECG monitoring</b>  |   |   |
| In patients treated with VEGFi at moderate or high risk of QTc prolongation, QTc monitoring is recommended monthly during the first 3 months and every 3–6 months thereafter.                    | I | C |
| <b>Echocardiography</b>  |   |   |
| Baseline echocardiography is recommended in high- and very high-risk patients treated with VEGFi or bevacizumab.   | I | C |
| <b>Recommendation Table 11 for baseline risk assessment and monitoring during second- and third-generation BCR-ABL tyrosine kinase inhibitors</b>  |   |   |
| Baseline CV risk assessment is recommended in patients who require second- or third-generation BCR-ABL TKI.  | I | C |
| In patients treated with nilotinib or ponatinib, CV risk assessment is recommended every 3 months during the first year and every 6–12 months thereafter.  | I | C |
| Baseline echocardiography is recommended in patients scheduled to receive dasatinib.   | I | C |
| <b>Recommendation Table 12 for baseline risk assessment and monitoring Bruton tyrosine kinase inhibitor therapy</b>  |   |   |
| <b>BP monitoring and management</b>  |   |   |
| BP measurement is recommended for patients treated with BTK inhibitors at every clinical visit.  | I | B |
| <b>Echocardiography</b>  |   |   |
| Baseline echocardiography is recommended in high-risk patients scheduled to receive BTK inhibitors.  | I | C |
| TTE is recommended in all patients who develop AF during BTK inhibitor therapy.  | I | C |
| <b>AF</b>  |   |   |
| Opportunistic screening for AF by pulse-taking or ECG rhythm strip is recommended at every clinical visit during BTK inhibitor therapy.  | I | C |
| <b>Recommendation Table 13 for baseline risk assessment and monitoring during multiple myeloma therapies</b>   |   |   |
| <b>BP monitoring</b>   |   |   |
| BP measurement is recommended for patients treated with PI at every clinical visit.  | I | C |
| <b>Cardiac serum biomarkers</b>  |   |   |
| Measurement of NP is recommended prior to PI in high- and very high-risk patients.   | I | C |
| NP and cTn measurements are recommended at baseline and every 3–6 months in patients with AL-CA.   | I | B |
| <b>TTE</b>   |   |   |
| Baseline echocardiography, including assessment for AL-CA, is recommended in all patients with MM scheduled to receive PI.   | I | C |

Continued

|   |   |   |
|---|---|---|
| <b>VTE prophylaxis</b>  |   |   |
| Therapeutic doses of LMWH are recommended in patients with MM with previous VTE.  | I | B |
| Prophylactic doses of LMWH are recommended in patients with MM with VTE-related risk factors (excluding previous VTE) at least during the first 6 months of therapy.                              | I | A |
| <b>Recommendation Table 14 for baseline risk assessment and monitoring during combined RAF and MEK inhibitor therapy</b>  |   |   |
| BP monitoring at each clinical visit and weekly outpatient monitoring during the first 3 months of treatment and monthly thereafter is recommended.   | I | C |
| In patients treated with cobimetinib/vemurafenib, an ECG is recommended at 2 and 4 weeks after initiation of treatment and every 3 months thereafter.   | I | C |
| Baseline echocardiography is recommended in all high- and very high-risk patients scheduled to receive combined RAF and MEK inhibitors.   | I | C |
| <b>Recommendation Table 15 for baseline risk assessment and monitoring during immunotherapy</b>   |   |   |
| ECG, NP, and cTn measurements are recommended in all patients before starting ICI therapy.  | I | B |
| Baseline echocardiography is recommended in high-risk patients before starting ICI therapy.   | I | B |
| CV assessment is recommended every 6–12 months in high-risk patients who require long-term (>12 months) ICI treatment.  | I | C |
| <b>Recommendation Table 16 for baseline risk assessment and monitoring during androgen deprivation therapy for prostate cancer</b>  |   |   |
| Baseline CV risk assessment and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP is recommended in patients treated with ADT without pre-existing CVD.                 | I | B |
| Baseline and serial ECGs are recommended in patients at risk of QTc prolongation during ADT therapy.  | I | B |
| Annual CV risk assessment is recommended during ADT.  | I | B |
| <b>Recommendation Table 17 for baseline risk assessment and monitoring during endocrine therapy for breast cancer</b>   |   |   |
| Baseline CV risk assessment and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP is recommended in BC patients receiving endocrine therapies without pre-existing CVD. | I | C |
| Annual CV risk assessment is recommended during endocrine therapy in BC patients with high 10-year risk of (fatal and non-fatal) CV events according to SCORE2/SCORE2-OP.                         | I | C |
| <b>Recommendation Table 18 for baseline risk assessment and monitoring during cyclin-dependent kinase 4/6 inhibitor therapy</b>   |   |   |
| QTc monitoring is recommended at baseline and 14 and 28 days in all patients with cancer receiving ribociclib.  | I | A |
| QTc monitoring is recommended in patients treated with ribociclib with any dose increase.   | I | B |
| <b>Recommendation Table 19 for baseline risk assessment and monitoring during ALK and EGFR inhibitors</b>   |   |   |
| Baseline CV risk assessment is recommended in patients before ALK inhibitors and EGFR inhibitors.   | I | C |
| Baseline echocardiography is recommended in all patients with cancer before starting osimertinib.   | I | B |
| <b>Recommendation Table 20 for baseline risk assessment and monitoring in patients receiving chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies</b>                   |   |   |
| Baseline ECG, NP, and cTn are recommended in all patients with cancer before starting CAR-T and TIL therapies.  | I | C |
| A baseline echocardiography is recommended in patients with pre-existing CVD before starting CAR-T and TIL therapies.   | I | C |
| Measurement of NP, cTn, and echocardiography are recommended in patients who develop CRS of ASTCT $\geq$ 2.   | I | C |

Continued



| <b>Recommendation Table 21 for baseline risk assessment of patients before radiotherapy to a volume including the heart</b>   |   |   |
|---|---|---|
| Baseline CV risk assessment and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP is recommended.   | I | B |
| <b>Recommendation Table 22 for baseline risk assessment in haematopoietic stem cell transplantation patients</b>  |   |   |
| Baseline and serial CV risk assessment (3 and 12 months, then yearly) including BP measurement, ECG, lipid measurement, and HbA1c is recommended in HSCT patients.  | I | C |
| Echocardiography is recommended in all patients before HSCT.  | I | C |
| <b>Recommendation Table 23 for the management of cardiovascular disease and cancer therapy-related cardiovascular toxicity in patients receiving anticancer treatment</b>   |   |   |
| A specialist CV assessment 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 |
| <b>Recommendation Table 24 for the management of cancer treatment-related cardiac dysfunction during anthracycline chemotherapy</b>   |   |   |
| <b>Anthracycline chemotherapy-induced symptomatic CTRCD</b>   |   |   |
| HF therapy is recommended for patients who develop symptomatic CTRCD during anthracycline chemotherapy.   | I | B |
| Discontinuation of anthracycline chemotherapy is recommended in patients who develop symptomatic severe CTRCD.  | I | C |
| Temporary interruption of anthracycline chemotherapy is recommended in patients who develop symptomatic moderate CTRCD and a multidisciplinary approach regarding the decision to restart is recommended.   | I | C |
| A multidisciplinary approach regarding interruption vs. continuation of anthracycline chemotherapy is recommended in patients who develop mild symptomatic CTRCD.   | I | C |
| <b>Anthracycline chemotherapy-induced asymptomatic CTRCD</b>  |   |   |
| Temporary interruption of anthracycline chemotherapy and initiation of HF therapy is recommended in patients who develop asymptomatic moderate or severe CTRCD.   | I | C |
| A multidisciplinary approach regarding the decision when to restart is recommended in all patients with moderate or severe asymptomatic CTRCD.  | I | C |
| Continuation of anthracycline chemotherapy is recommended in asymptomatic patients who have LVEF $\geq$ 50% and who have developed a significant fall in GLS or a troponin or a NP elevation >ULN.  | I | C |
| <b>Recommendation Table 25 for the management of cancer treatment-related cardiac dysfunction during HER2-targeted therapies</b>  |   |   |
| <b>HER2-targeted therapy-induced symptomatic CTRCD</b>  |   |   |
| HF therapy is recommended for patients who develop symptomatic moderate-to-severe CTRCD with LVEF < 50% during HER2-targeted treatment.   | I | B |
| Temporary interruption of HER2-targeted treatment is recommended in patients who develop moderate or severe symptomatic CTRCD and the decision to restart should be based on a multidisciplinary approach after improvement of LV function and symptoms resolved. | I | C |
| In patients who develop mild symptomatic CTRCD, HF therapy and a multidisciplinary approach regarding the decision to continue vs. interrupt HER2-targeted therapy are recommended.   | I | C |
| <b>HER2-targeted therapy-induced asymptomatic CTRCD</b>   |   |   |
| Temporary interruption of HER2-targeted therapy and initiation of HF therapy is recommended in patients who develop asymptomatic severe CTRCD.  | I | C |
| A multidisciplinary approach regarding the decision to restart HER2-targeted treatment is recommended in patients with severe asymptomatic CTRCD.   | I | C |
| Continuation of HER2-targeted therapy is recommended in patients who develop asymptomatic mild (LVEF $\geq$ 50%) CTRCD <sup>c</sup> with more frequent cardiac monitoring.  | I | C |
| ACE-I/ARB and beta-blockers are recommended in patients who develop asymptomatic moderate (LVEF 40–49%) CTRCD <sup>c</sup> during HER2-targeted treatment.  | I | C |
| <b>Recommendation Table 26 for the diagnosis and management of immune checkpoint inhibitor-associated myocarditis</b>   |   |   |
| cTn, ECG, and CV imaging (echocardiography and CMR) are recommended to diagnose ICI-associated myocarditis.   | I | B |
| In patients with suspected ICI-associated myocarditis, temporary interruption of ICI treatment is recommended until the diagnosis is confirmed or refuted.  | I | C |

Continued

|   |     |   |
|---|-----|---|
| Interruption of ICI treatment is recommended in patients with confirmed ICI-associated myocarditis.   | I   | C |
| Continuous ECG monitoring to assess for new AV block and tachyarrhythmias during the acute phase is recommended for all patients with symptomatic ICI-associated myocarditis.   | I   | C |
| Early high-dose corticosteroids are recommended in patients with cancer and confirmed ICI-associated myocarditis.   | I   | C |
| Continuation of high-dose corticosteroids is recommended for the treatment of ICI-associated myocarditis until resolution of symptoms, LV systolic dysfunction, conduction abnormalities, and significant cTn reduction.  | I   | C |
| Admission to ICU (level 3), treatment with i.v. methylprednisolone, and optimal CV treatment including mechanical support (when indicated) is recommended for patients with ICI-associated fulminant myocarditis.   | I   | C |
| A multidisciplinary discussion is recommended before restarting ICI treatment in selected patients with previous uncomplicated ICI-associated myocarditis.  | I   | C |
| <b>Recommendation Table 27 for the diagnosis and management of Takotsubo syndrome in patients with cancer</b>   |     |   |
| Coronary angiography (invasive or CCTA) is recommended to exclude ACS.  | I   | C |
| CMR is recommended to exclude myocarditis and MI.   | I   | B |
| QT-prolonging drugs are not recommended during the acute TTS phase.   | III | C |
| <b>Recommendation Table 28 for the management of acute coronary syndromes in patients receiving anticancer treatment</b>  |     |   |
| An invasive strategy is recommended in patients with cancer presenting with STEMI or high-risk NSTEMI-ACS with life expectancy $\geq 6$ months.   | I   | B |
| A temporary interruption of cancer therapy is recommended in patients where the cancer therapy is suspected as a contributing cause.  | I   | C |
| In patients with cancer, thrombocytopenia and ACS, aspirin is not recommended if platelets $< 10\,000/\mu\text{L}$ .  | III | C |
| In patients with cancer, thrombocytopenia and ACS, clopidogrel is not recommended if platelets $< 30\,000/\mu\text{L}$ and prasugrel or ticagrelor are not recommended if platelets $< 50\,000/\mu\text{L}$ .   | III | C |
| <b>Recommendation Table 29 for the management of chronic coronary syndromes in patients receiving anticancer treatment</b>  |     |   |
| Individualized duration of DAPT is recommended in patients with cancer with CCS, following revascularization, based upon thrombotic/ischaemic and bleeding risk, type and stage of cancer, and current cancer treatment.  | I   | C |
| <b>Recommendation Table 30 for the management of valvular heart disease in patients receiving anticancer treatment</b>  |     |   |
| In patients with cancer and pre-existing severe VHD, management according to the 2021 ESC/EACTS Guidelines for the management of VHD is recommended, taking into consideration cancer prognosis and patient preferences.  | I   | C |
| In patients with cancer developing new VHD during cancer therapy, management according to the 2021 ESC/EACTS Guidelines for the management of VHD is recommended, taking into consideration cancer prognosis and patient comorbidities.   | I   | C |
| <b>Recommendation Table 31 for the management of atrial fibrillation in patients receiving anticancer treatment</b>   |     |   |
| Long-term anticoagulation is recommended for stroke/systemic thromboembolism prevention in patients with cancer with AF and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score $\geq 2$ (men) or $\geq 3$ (women) as per the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. | I   | C |
| Thromboembolic and bleeding risk reassessment is recommended during follow-up in patients with cancer with AF.  | I   | C |
| Antiplatelet therapy or prophylactic LMWH are not recommended for stroke or systemic thromboembolism prevention in AF with cancer.  | III | C |
| <b>Recommendation Table 32 for the management of long QTc and ventricular arrhythmias in patients receiving anticancer treatment</b>  |     |   |
| <b>How to manage QTc prolongation in patients with cancer</b>   |     |   |
| Discontinuation of QTc-prolonging cancer therapy is recommended in patients who develop TdP or sustained ventricular tachyarrhythmias during treatment.   | I   | C |
| Temporary interruption of QTc-prolonging cancer therapy is recommended in patients who develop asymptomatic QTcF $\geq 500$ ms and an ECG should be repeated every 24 h until resolution of the QTcF prolongation.  | I   | C |
| Immediate withdrawal of any offending drug and correction of electrolyte abnormalities and other risk factors is recommended in patients with cancer who develop QTcF $\geq 500$ ms.  | I   | C |
| Weekly ECG monitoring is recommended in asymptomatic patients with cancer with QTcF 480–500 ms who are treated with a QTc-prolonging cancer therapy.  | I   | C |

Continued

|   |     |   |
|---|-----|---|
| A 12-lead ECG is recommended after any dose increase of QTc-prolonging cancer therapy.  | I   | C |
| <b>Restarting QTc-prolonging cancer therapy</b>   |     |   |
| A multidisciplinary discussion is recommended before restarting QTc-prolonging drugs in patients who have developed significant QTcF prolongation, to discuss alternative cancer treatments.  | I   | C |
| Weekly ECG monitoring during the first 4–6 weeks and then monthly thereafter is recommended in patients with cancer after restarting QTc-prolonging cancer therapy.   | I   | C |
| <b>Recommendation Table 33 for the management of arterial hypertension in patients receiving anticancer treatment</b>   |     |   |
| <b>General</b>  |     |   |
| Effective treatment of cancer therapy-induced arterial hypertension to prevent cancer treatment interruption and CV complications is recommended.   | I   | C |
| A BP target <140 mmHg systolic and <90 mmHg diastolic is recommended during cancer therapy.   | I   | C |
| The competing cancer and CV risk evaluation is recommended if the systolic BP is $\geq 180$ mmHg or diastolic BP $\geq 110$ mmHg, and any cancer therapy associated with hypertension should be deferred or temporarily withheld until the BP is controlled to values <160 mmHg (systolic) and <100 mmHg (diastolic). | I   | C |
| <b>Cancer therapy-induced arterial hypertension treatment</b>   |     |   |
| ACE-I or ARB are the first-line antihypertensive drugs recommended for BP management in patients with cancer.   | I   | B |
| Dihydropyridine CCB are recommended as second-line antihypertensive drugs for patients with cancer with uncontrolled BP.  | I   | C |
| Combination therapy with ACE-I or ARB and dihydropyridine CCB is recommended in patients with cancer with systolic BP $\geq 160$ mmHg and diastolic BP $\geq 100$ mmHg.   | I   | C |
| Diltiazem and verapamil are not recommended to treat arterial hypertension in patients with cancer due to their drug–drug interactions.   | III | C |
| <b>Recommendation Table 34 for the management of venous thromboembolism in patients receiving anticancer treatment</b>  |     |   |
| Apixaban, edoxaban, or rivaroxaban are recommended for the treatment of symptomatic or incidental VTE in patients with cancer without contraindications.  | I   | A |
| LMWH are recommended for the treatment of symptomatic or incidental VTE in patients with cancer with platelet count $>50\,000/\mu\text{L}$ .  | I   | A |
| <b>Catheter-associated VTE</b>  |     |   |
| Duration of anticoagulation in patients with cancer with a catheter-associated VTE is recommended for a minimum of 3 months and continuing longer if the catheter remains <i>in situ</i> .  | I   | C |
| <b>Recommendation Table 35 for venous thromboembolism prophylaxis during anticancer treatment</b>   |     |   |
| Extended prophylaxis with LMWH for 4 weeks post-operatively is recommended for patients with cancer undergoing major open or laparoscopic abdominal or pelvic surgery with low bleeding risk and high VTE risk.   | I   | B |
| Prophylactic LMWH for the primary prevention of VTE is indicated in hospitalized patients with cancer or those with prolonged bed rest or reduced mobility in the absence of bleeding or other contraindications.   | I   | B |
| A discussion with the patient about the relative benefits and harms, cancer prognosis, drug cost, and duration of treatment is recommended prior to prophylactic anticoagulation for the primary prevention of VTE.   | I   | C |
| <b>Recommendation Table 36 for management of peripheral artery disease during anticancer treatment</b>  |     |   |
| In patients who develop new symptomatic PAD, a multidisciplinary approach regarding the decision to continue vs. interrupt culprit cancer therapy is recommended.   | I   | C |
| <b>Recommendation Table 37 for the management of pulmonary hypertension during anticancer treatment</b>   |     |   |
| Right-heart catheterization and discontinuation of dasatinib is recommended in patients who develop symptomatic or asymptomatic increase in peak TRV $> 3.4$ m/s.   | I   | C |
| In patients with confirmed dasatinib-induced PAH or new asymptomatic peak TRV $> 3.4$ m/s, an alternative BCR-ABL inhibitor is recommended after peak TRV recovery to $< 2.8$ m/s.  | I   | C |
| <b>Recommendation Table 38 for the management of pericardial diseases in patients receiving anticancer treatment</b>  |     |   |
| <b>General</b>  |     |   |
| Diagnosis and management of acute pericarditis in patients with cancer based on the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases is recommended and a multidisciplinary discussion is needed before interrupting cancer therapy.  | I   | C |

Continued

| <b>Diagnosis and management of ICI-associated pericarditis</b>   |   |   |
|--|---|---|
| Multimodality CV imaging (echocardiography, CMR ± CT), ECG and measurement of cardiac biomarkers are recommended to confirm the diagnosis, assess the haemodynamic consequences of pericardial disease, and rule out associated myocarditis. | I | C |
| Prednisolone and colchicine are recommended for patients with ICI-associated pericarditis.   | I | C |
| Interruption of ICI treatment in patients with confirmed ICI-associated pericarditis with moderate-to-severe pericardial effusion is recommended.  | I | C |
| A multidisciplinary discussion is recommended before restarting ICI treatment.   | I | C |
| <b>Recommendation Table 39 for end-of-cancer therapy cardiovascular risk assessment</b>  |   |   |
| Educating and supporting patients with cancer to make appropriate healthy lifestyle choices is recommended.  | I | C |
| Education is recommended for patients with cancer regarding recognition for early signs and symptoms of CVD.   | I | C |
| CVRF assessment is recommended during the first year after cancer therapy and thereafter according to the 2021 ESC Guidelines on CVD prevention in clinical practice.  | I | B |
| In asymptomatic high-risk patients, echocardiography and cardiac serum biomarkers are recommended at 3 and 12 months after completion of cancer therapy.   | I | B |
| Cardiology referral is recommended in patients with cancer with new cardiac symptoms or new asymptomatic abnormalities in echocardiography and/or cardiac serum biomarkers at the end of therapy assessment.                                 | I | C |
| Long-term continuation of cardiac medication is recommended in patients who develop severe CTRCD during cancer therapy.  | I | C |
| CV follow-up and treatment optimization is recommended in patients who developed TKI-mediated hypertension during cancer therapy.  | I | C |
| CV follow-up and treatment optimization is recommended in patients who developed vascular toxicities during cancer therapy.  | I | C |
| ECG follow-up is recommended in patients who developed QT lengthening or LQTS during cancer therapy.   | I | C |
| <b>Recommendation Table 40 for cardiovascular surveillance in asymptomatic adults who are childhood and adolescent cancer survivors</b>  |   |   |
| Education of adults who are childhood and adolescent CS treated with anthracyclines, mitoxantrone, and/or RT to a volume including the heart and their healthcare providers regarding their increased CV risk is recommended.                | I | B |
| Annual screening for modifiable CVRF is recommended in adults who are childhood and adolescent CS treated with anthracyclines, mitoxantrone, and/or RT to a volume including the heart.  | I | C |
| CV assessment is recommended in female childhood and adolescent CS prior to pregnancy or in the first trimester.   | I | C |
| <b>Recommendation Table 41 for cardiovascular surveillance in asymptomatic adult cancer survivors</b>  |   |   |
| Annual CV risk assessment, including ECG and NP, and CVRF management is recommended in CS who were treated with a potentially cardiotoxic cancer drug or RT.   | I | B |
| CV toxicity risk restratification is recommended 5 years after therapy to organize long-term follow-up.  | I | C |
| <b>Recommendation Table 42 for adult cancer survivors who develop cancer therapy-related cardiac dysfunction late after cardiotoxic cancer therapy</b>   |   |   |
| ACE-I/ARB and/or beta-blockers are recommended in adult CS with moderate asymptomatic CTRCD.   | I | C |
| <b>Recommendation Table 43 for adult cancer survivors with coronary artery disease</b>   |   |   |
| <b>Asymptomatic radiation-induced CAD detected during surveillance</b>   |   |   |
| Non-invasive stress testing is recommended in asymptomatic CS with new moderate or severe radiation-induced CAD detected on CCTA to guide ischaemia-directed management.   | I | C |
| A MDT discussion is recommended for clinical decision-making in patients with radiation-induced CAD and inducible ischaemia or severe left main CAD.   | I | C |

Continued

| <b>Symptomatic CAD</b>   |   |   |
|--|---|---|
| Pre-operative assessment of LIMA and RIMA viability, venous access, and sternal wound healing is recommended in CS with radiation-induced CAD where CABG is considered.  | I | C |
| <b>Recommendation Table 44 for adult cancer survivors with valvular heart disease</b>  |   |   |
| A MDT approach is recommended to discuss and define the surgical risk in CS with severe VHD.   | I | C |
| <b>Recommendation Table 46 for cardiovascular monitoring in cancer survivors during pregnancy</b>  |   |   |
| In high-risk female CS, pre-pregnancy counselling and management during pregnancy and around delivery by a multidisciplinary pregnancy heart team is recommended.  | I | C |
| A baseline CV evaluation including history, physical examination, ECG, NP, and echocardiography is recommended in female CS with a history of CTRCD who are considering pregnancy.   | I | C |
| A CV evaluation including echocardiography is recommended at 12 weeks of pregnancy in female CS who are either high-risk or who received potentially cardiotoxic cancer therapy and did not have a baseline CV assessment.   | I | C |
| <b>Recommendation Table 47 for cardiovascular assessment and monitoring of pregnant women with cancer</b>  |   |   |
| Management by an expert MDT (the pregnancy heart team) in an expert centre is recommended for pregnant women with cancer who require cardiotoxic cancer therapy.   | I | C |
| Cardiac assessment prior to cardiotoxic cancer therapy in pregnant women is recommended and consists of clinical history, physical examination, ECG, and echocardiography.   | I | C |
| <b>Recommendation Table 48 for carcinoid valvular heart diseases</b>   |   |   |
| Echocardiography is recommended for the detection of carcinoid cardiac involvement in all patients with carcinoid syndrome and elevated NP levels and/or clinical signs of carcinoid heart disease, and for surveillance every 3 or 6 months depending on the severity of cardiac involvement and clinical status. | I | B |
| A MDT discussion for optimal medial management to prevent carcinoid crisis is recommended before any invasive or surgical cardiac procedure.   | I | C |
| Valve replacement surgery is recommended in symptomatic patients with severe carcinoid tricuspid or pulmonary VHD and an expected survival $\geq 12$ months.   | I | C |
| Valve replacement or repair surgery is recommended in symptomatic patients with severe carcinoid mitral or aortic VHD and an expected survival $\geq 12$ months.   | I | C |
| <b>Recommendation Table 49 for amyloid light-chain cardiac amyloidosis diagnosis and monitoring</b>  |   |   |
| Echocardiography, NP, and cTn are recommended for the diagnosis of AL-CA in patients with plasma cell dyscrasia.   | I | B |
| CMR is recommended in patients with suspected AL-CA.   | I | A |
| <b>Recommendation Table 50 for risk stratification and monitoring for patients with cardiac implantable electronic devices undergoing radiotherapy</b>   |   |   |
| Risk stratification including planned radiation type and energy, dose to CIED, the patient's device type, and pacing dependence is recommended prior to starting treatment.  | I | C |
| In patients undergoing RT, a CIED check is recommended in all patients before and after completing RT, and during RT according to individual risk.   | I | C |
| In patients with a CIED undergoing RT at high risk of arrhythmia and/or device dysfunction, ECG monitoring and/or pulse oximetry are recommended during every RT session.  | I | C |

3D, three-dimensional; ACE-I, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndromes; ADT, androgen deprivation therapy; AF, atrial fibrillation; AL-CA, amyloid light-chain cardiac amyloidosis; ALK, anaplastic lymphoma kinase; ARB, angiotensin receptor blocker; ASTCT, American Society for Transplantation and Cellular; AV, atrioventricular; BC, breast cancer; BCR-ABL, breakpoint cluster region–Abelson oncogene locus; BP, blood pressure; BTK, Bruton tyrosine kinase; CABG, coronary artery bypass graft; CAD, coronary artery disease; CAR-T, chimeric antigen receptor T cell; CCB, calcium channel blockers; CCS, chronic coronary syndromes; CCTA, coronary computed tomography angiography; CHA<sub>2</sub>DS<sub>2</sub>-VASc, Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes mellitus, Stroke (2 points)—Vascular disease, Age 65–74 years, Sex category (female); CIED, cardiac implantable electronic device; CMR, cardiac magnetic resonance; CRS, cytokine release syndrome; CT, computed tomography; cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; CS, cancer survivors; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DAPT, dual antiplatelet therapy; EACTS, European Association for Cardio-Thoracic Surgery; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; ESC, European Society of Cardiology; GLS, global longitudinal strain; HbA1c, glycated haemoglobin; HER2, human epidermal receptor 2; HF, heart failure; HSCT, haematopoietic stem cell transplantation; ICI, immune checkpoint inhibitors; ICU, intensive care unit; i.v., intravenous; LIMA, left internal mammary artery; LMWH, low-molecular-weight heparins; LQTS, long QT syndrome; LV, left ventricular; LVEF, left ventricular ejection fraction; MDT, multidisciplinary team; MEK, mitogen-activated extracellular signal-regulated kinase; MI, myocardial infarction; MM, multiple myeloma; NP, natriuretic peptides; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; PAD, peripheral artery disease; PAH, pulmonary arterial hypertension; PI, proteasome inhibitors; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia correction; RAF, rapidly accelerated fibrosarcoma; RIMA, right internal mammary artery; RT, radiotherapy; SCORE2, Systematic Coronary Risk Estimation 2; SCORE2-OP, Systematic Coronary Risk Estimation 2—Older Persons; STEMI, ST-segment elevation myocardial infarction; TdP, torsade de pointes; TIL, tumour-infiltrating lymphocytes; TKI, tyrosine kinase inhibitors; TTE, transthoracic echocardiography; TTS, Takotsubo syndrome; TRV, tricuspid regurgitation velocity; ULN, upper limit of normal; VEGFi, vascular endothelial growth factor inhibitors; VHD, valvular heart disease; VTE, venous thromboembolism.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 16. Quality indicators for cardio-oncology

Quality indicators (QIs) are tools that may be used to evaluate care quality, including structural, process, and outcomes of care.<sup>835</sup> They may also serve as a mechanism for enhancing adherence to guideline recommendations, through associated quality improvement initiatives and the benchmarking of care providers.<sup>836,837</sup> As such, the role of QIs in improving care and outcomes for CVD is increasingly recognized by healthcare authorities, professional organizations, payers, and the public.<sup>835</sup>

The ESC understands the need for measuring and reporting quality and outcomes of CV care and has established methods for the development of the ESC QIs for the quantification of care and outcomes for CVD.<sup>835</sup> These methods were used to develop QIs pertinent to cardio-oncology in parallel with the writing of this Clinical Practice Guideline document and through the collaboration with patient representatives and domain experts. The QIs, alongside their measurement specifications and development process will be published separately.

## 17. Supplementary data

Supplementary data is available at *European Heart Journal* online.

## 18. Data availability statement

No new data were generated or analysed in support of this research.

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