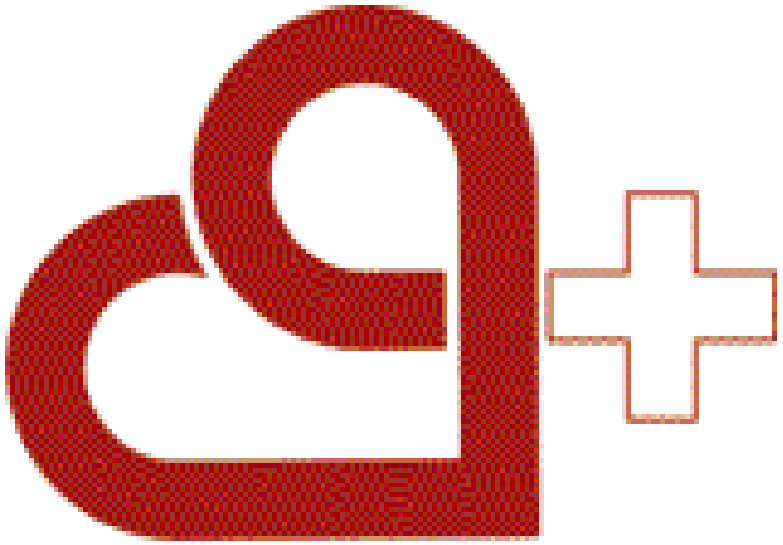

Swiss Cardio-Oncology Booklet 2021/22

Edition 1.1

Swiss Cardio-Oncology

Introduction:

It is now more than 40 years since Daniel von Hoff and colleagues first published “Risk Factors of Doxorubicin-Induced Congestive Heart Failure” – a pivotal paper in the field of cardio-oncology. We have come a long way since then, and now understand the mechanisms of cardiovascular toxicities for many cancer drugs and also radiation therapy. An important concept is that some cancer drugs may cause irreversible cardiovascular damage, whereas others induce reversible cardiac dysfunction. Therefore, the careful assessment of at-risk cancer patients and appropriate surveillance is critical in order to avoid irreversible cardiovascular damage arising from cancer therapy. Nowadays, many oncological diseases can be successfully controlled, reaching remission or remaining stable for years. Additionally, since oncological therapies have become increasingly efficacious, the number of long-term cancer survivors is steadily growing. It is important to understand that many cancer-related cardiovascular side effects become manifest only years after the initial cancer treatment, typically after discharge from the treating oncologist. Therefore, general practitioners and internists also need to be aware of the long-term consequences of cancer therapy.
A group of dedicated Swiss cardiologists and internists have written this comprehensive document on cancer-therapy-associated cardiovascular side effects. The target audience is cardiologists, oncologists, internists and general practitioners. The document aims to inform treating physicians about the potential cardiovascular side effects of cancer therapy. Furthermore, it should help to plan and optimize the long-term care of any patient that has survived an oncological disease.

Thomas Suter

Swiss Cardio-Oncology

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Disclaimer:
This booklet represents the view of this Swiss Cardio-Oncology group and was produced after careful consideration of the scientific and medical knowledge and the evidence available. The group is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the recommendation in this booklet and other official recommendations or guidelines. These recommendations are a pragmatic approach, which also consider the limited resources of the Swiss health care system.
The recommendations in this booklet do not override, in any way, the individual responsibility of health care professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver.
These suggestions do not exempt health care professionals from taking into full and careful consideration the relevant official updated recommendations or managing each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health care professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

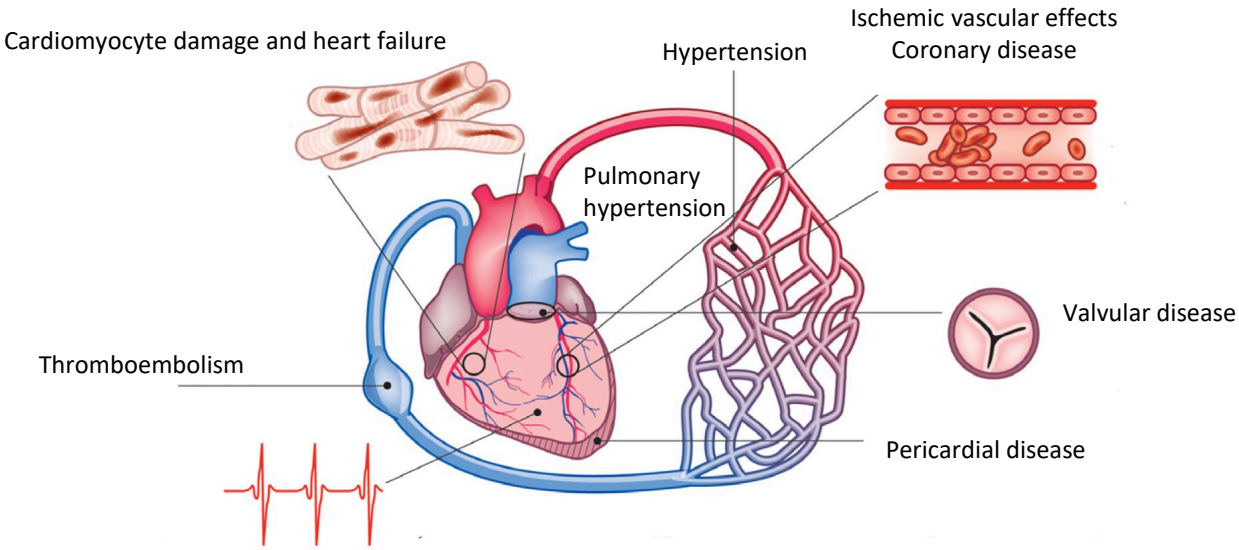
Cardio-Oncology

Abbreviations

AAD	Antiarrhythmic Drug	GL	Guideline
ACEi	Angiotensin-Converting Enzyme inhibitors	GLS	Global Longitudinal Strain
AC	Anticoagulation	GnRH	Gonadotropin-Releasing Hormone
ACR	Albumin-Creatinine Ratio	Gy	Gray
ACS	Acute Coronary Syndrome	HAS-BLED	HTN, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly
AE	Adverse Event	HCM	Hypertrophic Cardiomyopathy
AF	Atrial Fibrillation	Her2	Human epidermal growth factor receptor 2
AL	Amyloid Light-chain	HF / HF-Tx	Heart failure / Heart failure Therapy
ANT	Antracycline	HFpEF/HFmrEF/HFrEF	HF with preserved/mildly reduced/reduced EF
Anti FXai	Anti Xa Inhibitor	HR	Heart rate
ARB	Angiotensin (II) Receptor Blockers	HSCT	Hematopoietic Stem Cell Transplantation
ARNi	Angiotensin Receptor-Neprilysin inhibitors	HTN	Hypertension
ASCVD	Atherosclerotic Cardiovascular Disease	H/o	History of
ATO	Arsenic Trioxide		
ATTR	Transthyretin Amyloidosis	ICI	Immune Checkpoint Inhibitor
a/o	and/or	ICD	Implanted Cardiac Defibrillator
A2C/A3C/A4C	Apical 2/3/4-Chamber	IVC	Inferior Vena Cava
BAV	Bicuspid Aortic Valve	IVUS	Intravascular ultrasound
BB	Beta Blockers	LAA-C	Left Atrial Appendage Closure
BP	Blood Pressure	LDL	Low-density Lipoprotein
b.p.m.	Beats per Minute	LQTS	Long QT Syndrome
BRAF	Proto-oncogene «murine sarcoma viral oncogene homolog B»	LVSD	Left Ventricular Systolic Dysfunction
btw	between	LVEF	Left Ventricular Ejection Fraction
b/c, b/o	because, because of	MEK	Kinase Enzyme («mitogen-activated protein kinase kinase»)
Ca	Cancer	MGUS	Monoclonal Gammopathy of Undetermined Significance
CABG	Coronary Artery Bypass Graft Surgery	MRA	Mineralocorticoid Receptor Antagonist
CAC	Coronary Artery Calcium	mth/mthly	Month/monthly
CAD	Coronary Artery Disease	NP (BNP/NT-proBNP)	Natriuretic Peptide (BNP / NT-proBNP)
CAR-T	Chimeric Antigen Receptor-T	OAC	Oral Anticoagulation
CAT	Cancer-Associated Thrombosis	OMT	Optimal Medical Therapy
CCB	Calcium Channel Blocker	PAD	Peripheral Artery Disease
CCS	Childhood Cancer Survivor	PCI	Percutaneous Coronary Intervention
CHA2DS2-VASc	Congestive HF, HTN, DM, Stroke, Vascular disease, Age, Sex category	PE	Pulmonary Embolism
CIED	Cardiac Implantable Electronic Device	PM	Pacemaker
CKD	Chronic Kidney Disease	Pt/Pts	Patient/Patients
CMP	Cardiomyopathy	PTP	Pre-Test Probability
CMR	Cardiovascular Magnetic Resonance imaging	PY	Pack Years
CRT	Cardiac Resynchronization Therapy	q.3 (…) / q.6 (…)	every 3 (…) / every 6 (…)
cTn	Cardiac Troponin	RAAS	Renin-Angiotensin-Aldosterone System
CV	Cardiovascular	RCT	Randomized Controlled Trial
CVAE	Cardiovascular Adverse Event	ROI	Region of Interest
CVRF	Cardiovascular Risk Factors	RR	Relative Risk
Cx	Cancer therapy	RT	Radiotherapy
DAPT	Dual Antiplatelet Therapy	SCD	Sudden Cardiac Death
DDI	Drug-Drug Interaction	SGLT2i	Sodium-Glucose Cotransporter-2 inhibitors
DDx	Differential Diagnosis	TTE	Transthoracic Echocardiography
DM	Diabetes Mellitus	TKI	Tyrosine Kinase Inhibitors
DOAC	Direct Oral Anticoagulant	Tc	Thrombocytes
DVT	Deep Vein Thrombosis	Tx	Treatment/Therapy
EF	Ejection Fraction	UFH	Unfractionated Heparin
e.g.	for example	ULN	Upper Limit of Normal
EHRA	European Heart Rhythm Association	VEGF/R	Vascular Endothelial Growth Factor/Receptor
ESC	European Society of Cardiology	VHD	Valvular Heart Diease
FH	Familial Hypercholesterolemia	VKA	Vitamin K Antagonist
FLC	Free Light Chain	VTE	Venous Thrombembolism
FUP	Follow-Up	w/ and w/o	with and without
GI/GU	Gastrointestinal / Genitourinary	wks	weeks
		y	Year/years

2. Cardio-Oncology Overview

Cardio-oncology is more than just heart failure!



Adapted from Lenneman C, et al. *Circ Res*, 2016

Definition
Cardio-oncology is a subspecialty of cardiology taking care of the patient's cardiovascular health before, during and after cancer treatment in order to allow optimal and complete anti-tumoral therapy.

Special considerations

Time of consultation	• Time of consultation with respect to oncological treatment (pre-; during; after treatment?)
Risk stratification	• Classic cardiovascular risk factors • Malignancy-related • Treatment-related
Surveillance modalities	• Classic cardiovascular surveillance modalities • Advanced imaging (GLS +/- 3D echocardiography) • Consider other imaging modalities (e.g. staging CT, cardiac MRI) • Lab
Treatment options	• Treatment options for cardiovascular disease • Treatment options for cancer disease
Decision making	• Close collaboration with the oncology team • Consider patient preference and involve patient in the risk–benefit balance
Take-home message	**Cardio-oncology is a team effort**

3.1 Risk Stratification

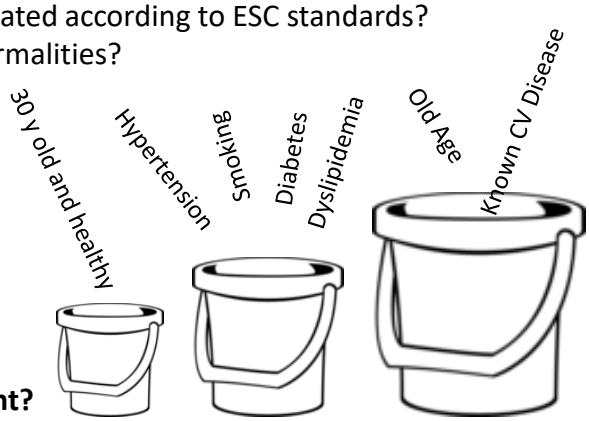
1. Check for patient-related risk factors

1. Cardiovascular baseline risk assessment

a) Assess the cardiovascular risk profile according to ESC guidelines
b) Is pre-existing cardiovascular disease treated according to ESC standards?
c) Are there baseline ECG, lab or TTE abnormalities?

Information gained from:

- Patient history
- Clinical exam
- Vitals (especially BP)
- Basic labs (see page 9)
- ECG
- TTE (before certain Cx, page 7)



2. Is there prior exposure to oncological treatment?

2. Check for therapy-related risk factors

- Depends on Cx compounds, the combination of compounds and the planned dose (in particular with anthracyclines) (see surveillance part).
- Take into account the history of oncologic treatments (previous chemotherapy and/or radiotherapy) and previous cardiac complications related to oncologic treatments

3. Choose the final risk category according to therapy-related risk factors AND patient-related risk factors.

The **highest** score determines the overall risk category

RISK	Therapy-related factors	Patient-related factors
Low		
Medium		
High		

4. Decide on follow-up intensity depending on chosen risk category and take the first patient-centered measures

3.1.2 Cardiovasular Baseline Risk Assessment

Cardiovascular risk stratification should occur at the first patient visit, ideally before starting cancer therapy irrespective of the modality, as well as in cancer survivors.

Patient check list

Prior to therapy
(or at first contact if therapy is already initiated)

Patient history:

- ❑ Pre-existing cardiovascular disease (coronary, hypertensive, valvular, other)
- ❑ History of heart failure
- ❑ Kidney disease, renal failure
- ❑ Cardiovascular risk factors:
  - ❑ Age >65 y
  - ☐ Age <18 y
  - ❑ Art. Hypertension
  - ❑ Smoking:
    - ❑ Current
    - ❑ Former, until:…….
      PY……..
  - ❑ Dyslipidemia
  - ❑ Diabetes
    - ❑ IDDM
    - ❑ NIDDM
  - ❑ Positive family history
  - ❑ Obesity, BMI……

Blood testing:

- ❑ Routine hematogram
- ❑ Routine chemogram
- ❑ Lipid status
- ❑ HbA1c
- ❑ TSH
- ❑ High sensitivity Troponin (T or I)
- ❑ NTproBNP (or BNP)

Standardized Blood Pressure measurement:

- ❑ 3’/2’/2’ algorithm (average of second and third recording)

ECG:

- ❑ Baseline ECG (including appropriate digital storage in the electronical health record) is recommended for all patients undergoing cancer therapy

Echocardiography:

- ❑ Routinely before cardiotoxic chemotherapy (including anthracyclines, Her2-targeting therapies), VEGF/VEGF-R pathway inhibitors, immune-checkpoint-inhibitors (only if 2 ICI are prescribed or 1 ICI with another cardiotoxic treatment), stem cell transplant, Car-T, before BRAFi and MEKi
- ❑ In all patients with pre-existing cardiovascular disease, abnormal ECG or elevated cardiac biomarkers
- ❑ Consider in patients with arterial hypertension, diabetes or >1 cardiovascular risk factor

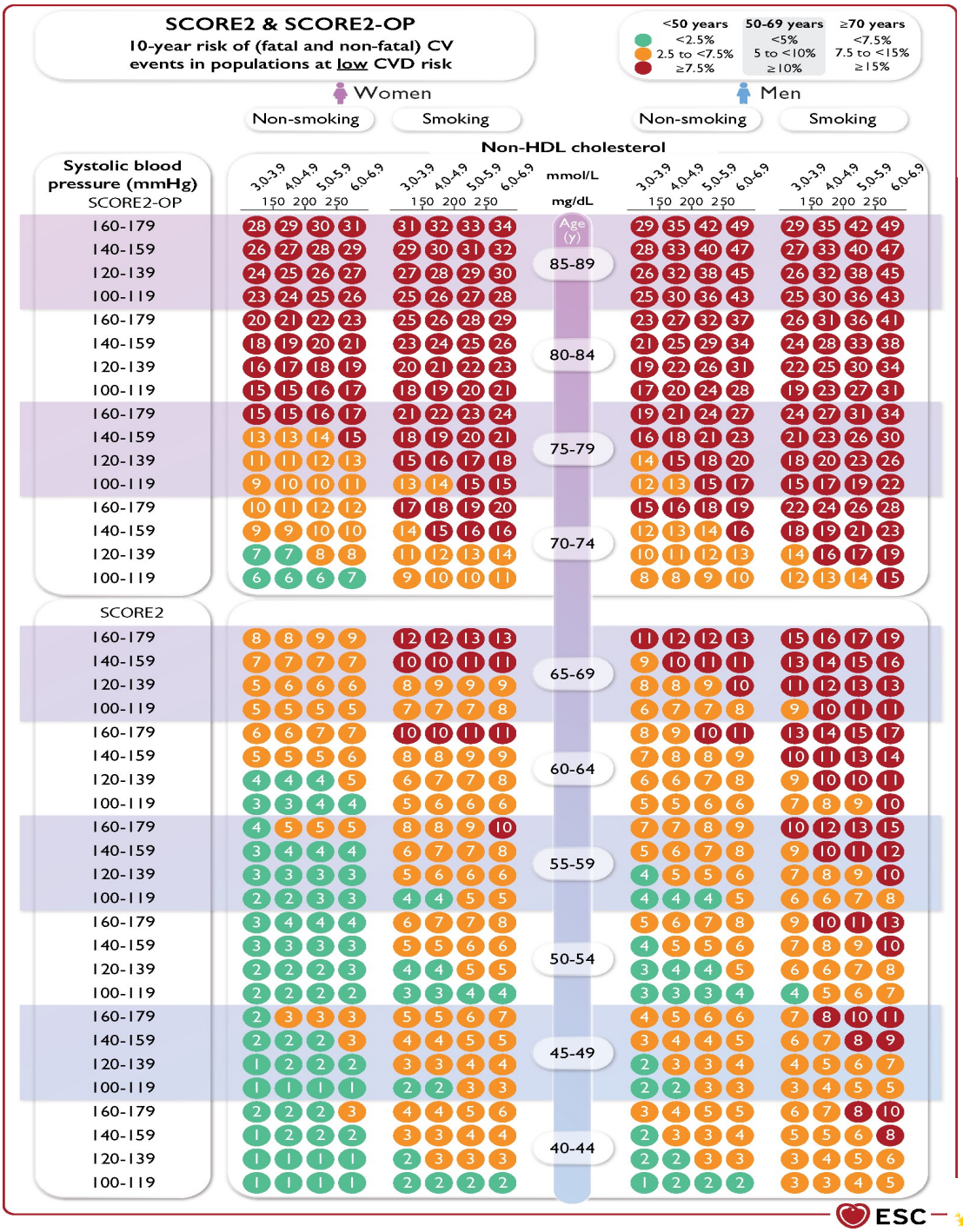
Refer to cardio-oncology if:

- **Pre-existing cardiovascular disease**
- **hs-Troponin > ULN**
- **Uncontrolled grade 2 (or higher) hypertension (>160/100 mmHg)**
- **LVEF <50%**

3.1.2 CV-Risk Estimation (ESC Guidelines)

Key points

- CV-risk estimation in apparently healthy people (w/o established ASCVD (event or plaque), type 2 DM, CKD, FH).
- CVD morbidity (non-fatal myocardial infarction , non-fatal stroke) combined with CVD mortality better reflects the total burden of ASCVD. The updated SCORE algorithm—**SCORE2** and **SCORE2-OP**— estimates an individual's 10-year risk of **fatal and non-fatal CVD events** (MI, stroke) in apparently healthy people aged 40–69 y (and 70–89 y using SCORE2-OP) with risk factors, untreated or stable for several y.
- SCORE2 and SCORE2-OP are calibrated to 4 clusters of countries (low, moderate, high, and very-high CVD risk).

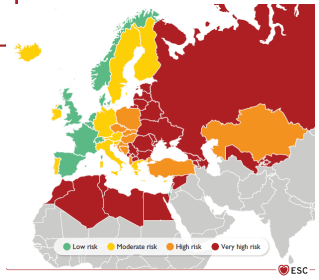


SCORE2 and SCORE2-OP risk chart for fatal and non-fatal (MI, stroke) ASCVD

Low CVD Risk countries

Different absolute risk threshold for age categories

Low-risk Countries: Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, Switzerland, the Netherlands and the United Kingdom (UK). **Moderate-risk**: Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia and Sweden. **High-risk**: Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia and Turkey. **Very high-risk**: Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Russian Federation, Serbia, Syria, The Former Yugoslav Republic (Macedonia), Tunisia, Ukraine and Uzbekistan.



3.1.2 CV-Risk Estimation (ESC Guidelines)

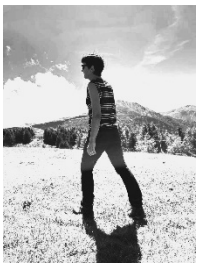
Patient category		Suggestions (risk stratification (SCORE2, LIFE-CVD) and pt preferences)
Apparently healthy individuals (w/o established ASCVD, DM, CKD, FH)		
<50 y	Low- to very high risk	Risk <2.5%: consider life-modifier Risk 2.5–7.5%: treatment should be considered (see below) Risk >7.5%: SBP <140mmHg, <130mmHg if tolerated (Cl. I), LDL-C <2.6mmol/l (Cl. IIa) Intensified therapy based on SCORE2, LIFE-CVD, comorbidities. SBP <130mmHg if tolerated (Cl. I) *and* LDL-C <1.8mmol/l if high-risk (Cl. IIa) LDL-C <1.4mmol/l if very high-risk (Cl. IIa)
50–69 y		Risk <5%: Consider life-modifier Risk 5–10%: treatment should be considered (see goal below) Risk >10%: SBP <140mmHg, <130mmHg if tolerated (Cl. I), LDL-C <2.6mmol/l (Cl. IIa) Intensified therapy based on SCORE2, LIFE-CVD, comorbidities.
>70 y		Risk <7.5%: no additional prevention goals Risk 7.5–15%: treatment should be considered (see below) Risk >15%: Consider life-modifier, comorbidities, frailty, polypharmacy, treatment benefit. If feasible: SBP <140mmHg, <130mmHg if tolerated Class I) LDL-C <2.6mmol/l (Class IIb)
Pts with Chronic Kidney Disease (CKD) without diabetes or ASCVD		
Moderate CKD: - eGFR 30−44mL/min/1.73 m2 + albumin/crea <30 - eGFR 45−59 mL/min/1.73 m2 + albumin/crea 30−300 - eGFR ≥60 mL/min/1.73 m2 + albumin/crea >300	High-risk	Risk factor treatment should be considered
Severe CKD: eGFR<30 mL/min/1.73 m2 *or* eGFR 30−44 mL/min/1.73 m2 and ACR >30	Very high	Risk factor treatment generally recommended.
Familial Hypercholesterolemia (FH)		
Associated w/ markedly elevated cholesterol levels	High risk	Risk factor treatment should be considered
Pts with type 2 Diabetes mellitus (DM)		
Pts with well-controlled short-standing DM (e.g. <10 y), no evidence of target organ damage (TOD) and no additional ASCVD risk factors	Moderate risk	Consider life-modifier Risk factor treatment generally not recommended
Pts with DM without ASCVD and/or severe TOD, not fulfilling moderate risk criteria.	High-risk	Risk factor treatment should be considered
Pts with DM w/ established ASCVD and/or severe TOD: - eGFR <45 mL/min/1.73 m2 - eGFR 45–59 mL/min/1.73 m2 and microalbuminuria (ACR 30–300 mg/g) - Proteinuria (ACR >300 mg/g) - Microvascular disease >3 different sites (e.g. microalbuminuria, retinopathy, neuropathy)	Very high risk	Risk factor treatment generally recommended. Residual 10-year CVD risk estimation after general prevention goals: - ADVANCE risk score - DIAL model
Pts with established atherosclerotic cardiovascular disease (ASCVD)		
Documented ASCVD, clinical or on imaging: - Previous MI, ACS, CAD, stroke and TIA, aortic aneurysm and PAD.	Very high risk	Risk factor treatment generally recommended. Residual CVD risk estimation after general prevention goals: - SMART risk score for pts with established CVD, 10-y - EUROASPIRE risk score for patients with CHD, 1- or 2-year - SMART-REACH model/DIAL model if diabetes

3.2 Patient-Centered Measures

Key points
- Optimize the cardiovascular profile as early as possible.
- Advise the oncologist of treatment choice if needed.
- Anticipate and initiate CV protection.

1. Support a healthy lifestyle and regular physical activity

Inform patient about:
- A healthy diet
- The importance of regular physical activity (also during treatment)
- Smoking cessation



2. Assess the cardiovascular risk profile according to ESC guidelines

- Treat individual CVRF according to the global risk profile
- Lifestyle adaptation and pharmacological treatment if indicated

ESC Guidelines

3. Treat pre-existing cardiovascular diseases according to ESC guidelines

- Is optimal medical treatment established?
- Are there urgent necessary interventions required before initiation of cancer treatment?

ESC Guidelines

4. Check for therapy-related risk factors

Inform oncologist about:
- Possible side effects and discuss treatment options if severe cardiotoxic side effects expected

Inform patient about:
- Possible cardiac side effects and their manifestation

5. Initiate cardioprotective medication if needed

4.1 Cardiovascular iImaging

Comparison of imaging techniques commonly used in cancer patients

	Echo	CMR	SPECT	PET	CT-Coro
Availability	👍👍👍	👍	👍👍	👍	👍👍👍
Cost	$	$$	$$$	$$$$	$$
Radiation	0	0	☢☢	☢(☢)	☢☢
Impact of irregular rhythm	👎	👎👎	0	0	👎👎
Impact of severe obesity	👎	0	(👎)	0	0
Impact of severe renal failure	0	👎	0	0	👎👎👎
Impact of claustrophobia	0	👎👎	👎	👎	(👎)
Impact of selected metallic devices	0	MR	0	0	0

Definition of Cancer Therapeutics-Related Cardiac Dysfunction (According to IC-OS 2021 Consensus)

	Mild	Moderate	Severe	Very Severe
Asymptomatic CTRCD (with or without additional biomarkers, LVEF values are based on 2D echocardiography	LVEF >_50% AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers§	New LVEF reduction by >_10 percentage points to an LVEF of 40–49% New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers	New LVEF reduction to <40%	
Symptomatic CTRCD (with LVEF and supportive diagnostic biomarkers)	Mild HF symptoms, no intensification of therapy required	Need for outpatient intensification of diuretic and HF therapy	HF Hospitalization	Requiring inotropic support, mechanical circulatory support or consideration for transplantation

Caution:
We recommend repeating TTE within 3 weeks in asymptomatic patients with LVEF decline or GLS-reduction >15% from baseline, before defining an asymptomatic CTRCD!

4.1 Cardiovascular Imaging

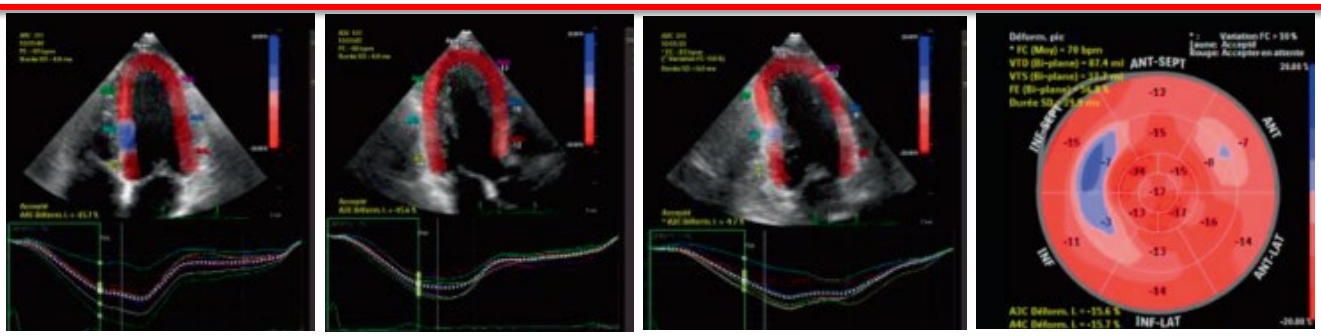
Key points:
- Use the same imaging modality to evaluate LVEF whenever possible during long-term follow-up.
- High-resolution imaging quality is needed for correct measurement of strain and LVEF.

Imaging modality	Parameters	Indications and clinical settings	Comment
Trans-thoracic echocardiography	**1. Ventricular function assessment methods:** LV ejection fraction, LV diameter/LV volume, Global Longitudinal Strain (GLS), LV diastolic function, RV function, **3D echo has better reproducibility**	• Screening for pre-existing LV dysfunction in every patient starting potentially cardiotoxic treatment • Monitoring of LV function during cardiotoxic treatment • Detection of late cardiac toxicity after cardiotoxic treatment	• Don't only consider LVEF-drop, but also look for significant changes in GLS (subclinical dysfunction). Page 11 • **3D echo should be favored whenever possible**
	2. Detection of pericardial effusion/tamponade Measure of effusion thickness Echocardiographic criteria of tamponade	• Most commonly with lung or breast cancer, lymphoma or leukemia, or shortly (wks) after thoracic radiation • Signs/symptoms of pericarditis	• Clinical signs for tamponade
	3. Detection of late complications after radiation therapy Systolic and diastolic function, strain analysis, constriction physiology, valve pathology, wall motion abnormalities	• In case of cardiac symptoms • Screening at 5 y (high-risk) or 10 y (non-high risk), then every 5 y	• Constrictive physiology • Restrictive physiology • Aortic valve degeneration • Indirect signs for coronary artery disease

Additional value of echocardiography : longitudinal myocardial deformation imaging (« strain »)
Strain describes the fractional change in the length of a myocardial segment.

Echocardiography strain analysis in cancer patients: Tips and tricks
- ✓ Ensure that an optimal ECG signal with minimal heart rate variability is present across the three cardiac cycles.
- ✓ Maintain a frame rate of 40 to 90 frames/s at a normal heart rate.
- ✓ Focus on the LV with appropriate adjustment of width and depth.
- ✓ Use optimal gain settings and breath-holding techniques to clearly delineate the endocardial and epicardial borders.
- ✓ During post-processing, the ROI should be aligned as accurately as possible to reflect the 17-segment LV model.
- ✓ Consult individual machine/software technical guidelines for further guidance (for example the selection of appropriate region of interest, ROI, which is vendor-specific)
- ✓ Be careful to exclude the pericardium, especially if automated analysis software is used. Inclusion of pericardium will lead to an underestimation of strain).

For more information, see :
- The 7-step approach for myocardial strain measurement described by Negishi et al, JACC 2015
- BSE and BCOS Guideline for Transthoracic Echocardiographic Assessment of Adult Cancer Patients Receiving Anthracyclines and/or Trastuzumab, Dobson et al, JACC 2021

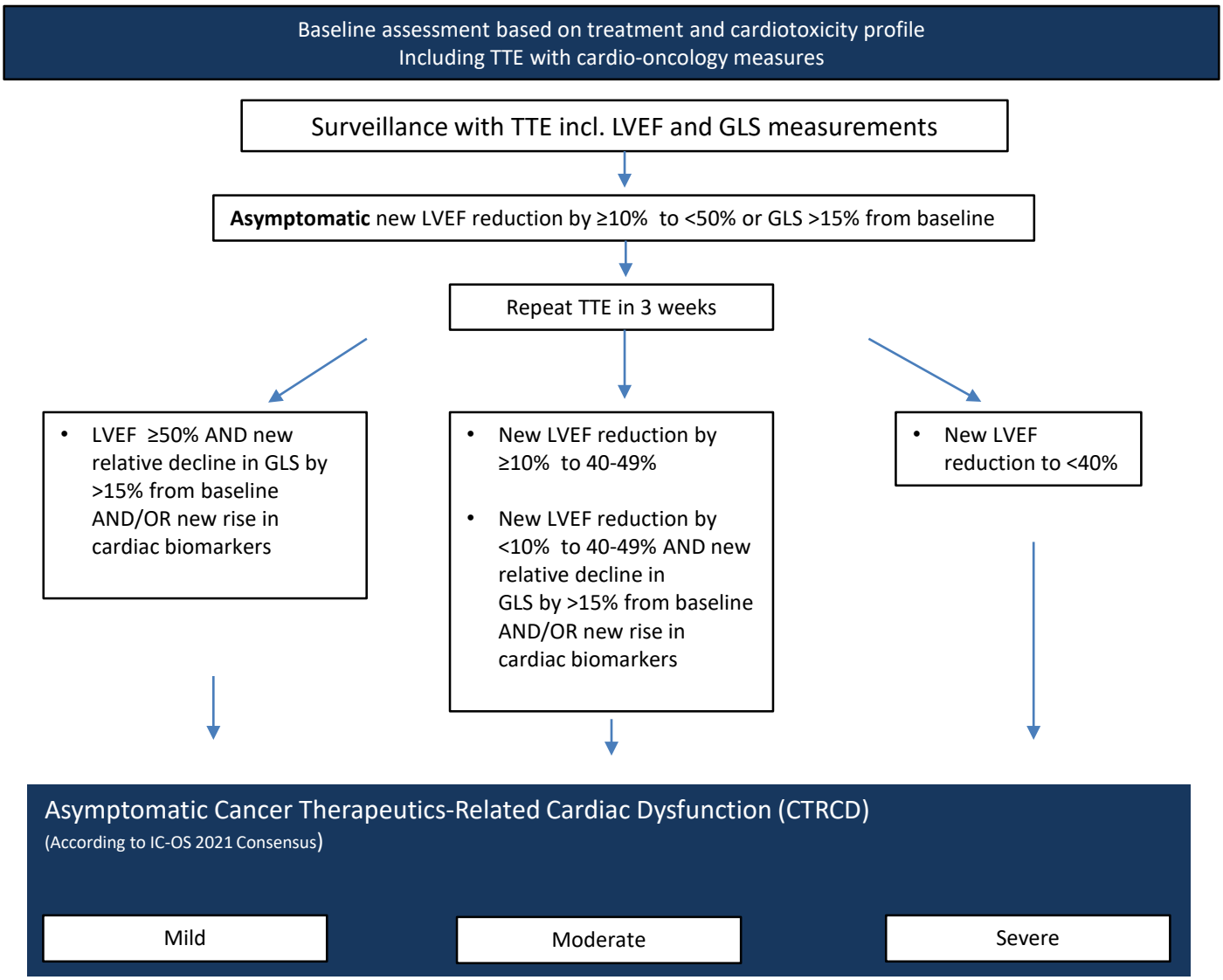


From left to right : Apical 4. 3 and 2 chamber views used for global longitudinal strain measurement, "bullseye" illustration of 17 segments

4.1 Cardiovascular Imaging

Key points:
- Use the same imaging modality to evaluate LVEF whenever possible during long-term follow-up.
- High-resolution imaging quality is needed for correct measurement of strain and LVEF.

Proposal of a surveillance algorithm based on echocardiography to detect cardiotoxicity integrating strain analysis of the left ventricle



4.1 Cardiovascular Imaging

CV Imaging modality	Parameters	Indications and clinical settings	Comments
Cardiac magnetic resonance	**1. Ventricular function assessment** Cine SSFP: LV volumes and ejection fraction LV mass RV volumes and ejection fraction	• Same as for transthoracic echocardiography, in case of poor image quality • Monitoring of LV function, if baseline assessment is done by cMR	• Cut off for cardiotoxicity by cMR: LVEF <53% in asymptomatic patients. • LV enlargement occurs together with dysfunction
	2. Myocardial tissue characterization Late gadolinium enhancement (macroscopic scar) T1 mapping/extracellular volume (microscopic fibrosis, amyloid infiltration) T2 mapping/T2-weighted imaging (myocardial oedema)	• Initial pretreatment assessment of high-risk patients with pre-existing cardiac disease/viability assessment • Optional advanced cardiotoxicity/radiation toxicity work-up • Suspected myocarditis with immune check-point inhibitors/ FUP after myocarditis • Suspected cardiac amyloidosis	• Assessment of pre-existing myocardial damage (e.g. infarction) • May detect replacement fibrosis and cardiomyocyte atrophy • Myocarditis defined as possible, probable or definite according to the clinical, biological, imaging and pathological results
	3. Pericardium-effusion-constriction Cine SSFP (effusion size/distribution) Black-blood T1-weighted +/- fat-saturation (pericardial thickness) Black-blood T2-weighted STIR (pericardial oedema) Late gadolinium enhancement (pericardial inflammation) Free-breathing real-time cine (respiratory septal D-shaping)	• Suspected pericarditis if clinical/ECG/echo workup not completely conclusive. • Pericardial assessment as part of suspected myocarditis work-up (see above) • Suspected pericardial constriction	• Pericardial thickening • Pericardial oedema/inflammation • Ventricular coupling (respiratory shift of the interventricular septum)
	4. Characterization of intracardiac masses Cine SSFP / T1w / T1w + Fat Saturation / T2w / T1 map / T2 map / resting perfusion / early gadolinium enhancement / late gadolinium, enhancement	• Detection of cardiac metastases • Characterization of primary cardiac tumors	• Cardiac metastases often have high T2 contrast • Melanoma metastases have shorter T1 due to melanin content
	5. Detection of myocardial ischemia		• ***See section on stress imaging on next page***
Coronary angiography and catheterization	• Angiography-relevant stenosis • Intracoronary physiology (FFR, iFR) • Intracoronary imaging (IVUS, OCT) • Intracardiac pressure measurements	• High probability of CAD in symptomatic patients • Long-term surveillance after RT. • Suspicion of vasospastic angina • New onset severe LV dysfunction • ACS presentation (DDx myocarditis vs NSTEMI)	• Prognostic ischemia • Proximal lesions
Coronary CT	• Coronary anatomy	• Chest pain work-up if no ACS • Screening for CAD • 5 y after radiotherapy	• Proximal CAD lesions • Valvular calcifications • Pericardial calcifications

4.1 Cardiovascular Imaging

Imaging modality	Parameters	Indications and clinical settings	Comments
Cardiac CT with calcium scoring (without contrast)	• Degree of coronary calcification • Degree of valve calcification	• CV risk stratification in asymptomatic individuals deemed at high risk • Planned exposure to cancer treatment associated with myocardial ischemia or accelerated atherosclerosis • High-dose radiotherapy on the thoracic region	CAC = 0, no intervention CAC = 1–99, consider statin CAC 100 = consider ASS and statin CV risk stratification during long-term follow up, especially in patients after treatment with potential for accelerated arteriosclerosis
Multigated Acquisition Scans (MUGA) Multigated Angiocardiography	LVEF	• Baseline LVEF evaluation prior to anthracycline exposure only if ETT/CMR not feasible or available • Monitoring during anthracycline therapy Suspect cardiotoxicity if there is a decline in LVEF by >10% from baseline and <50%	Historically in the initial anthracycline clinical trials in the 80s Protocol for LVEF evaluation only for anthracyclines Suspect cardiotoxicity if there is a decline in LVEF by >10% from baseline and <50%
Single-photon Emission Computed Tomography (SPECT)	3D evaluation of the LV and RV function Myocardial ischemia	• ***See section on stress imaging on page below***	Significant and prognostic myocardial ischemia
Positron Emission Tomography CT scan (PET-CT)	Myocardial ischemia Extensive fibrosis 18 FDG-PET search for patchy cardiac FDG uptake	Evaluation of cardiac viability Detection of radiotherapy-associated fibrosis along irradiated regions (FDG-PET/CT) Possible myocarditis (selected patients)	Significant and prognostic myocardial ischemia Caution: the cardiac PET protocol is different than the one for the oncology work-up
Nuclear bone scintigraphy techniques	using 99mTc-PYP and 99mTc-DPD tracers	Confirmation of ATTR cardiac amyloidosis. • for ATTR-amyloidosis only and after a thorough work-up to exclude monoclonal gammopathy (by serum protein electrophoresis, serum FLCs and immunofixation of the serum and urine • **Bone scintigraphy not necessary in work-up for AL-amyloidosis**	In the presence of MGUS, bone scintigraphy alone cannot be used to rule out AL-amyloidosis and a tissue biopsy is mandatory
Stress imaging	Perfusion CMR SPECT PET perfusion imaging dobutamine stress echocardiography	• Symptomatic (chest pain/dyspnea) patients with moderate (>15%) pretest probability of CAD/>5% pretest probability and high cardiovascular risk profile • High-risk patients/patient with poor exercise capacity before high-risk surgery • High-risk patients before administration of chemotherapy known to cause cardiac ischemia or androgen deprivation • Screening for coronary heart	Drugs associated with myocardial ischemia: go to page 39 Stress tests can be achieved either physiologically (physical activity) or pharmacologically. Pharmacological stress is often performed using dobutamine, adenosine/regadenoson depending on the test. The risk profiles of these «stressors» vary according to patient profiles. The choice of the stress test depends on

4.2 Cardiac Biomarkers

Troponin

Key points:
- **Evaluate troponin considering clinics, prior lab work, type of assay and troponin kinetics.**
- **Treatment decisions should never be based on troponin alone.**
- **Be aware of different troponin assays and their pitfalls.**

Conditions associated with cardiomyocyte injury (= cardiac troponin elevation)

ACS
Tachyarrhythmia
Cardiomyopathy (any), heart failure
Hypertensive emergencies
Myocarditis
Takotsubo syndrome
Valvular heart disease (e.g. aortic stenosis)
Cardiac contusion or cardiac procedures (CABG, PCI, ablation, pacing, cardioversion or endomyocardial biopsy)
Infiltrative disease (e.g. amyloidosis, hemochromatosis, sarcoidosis, scleroderma)

Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, Herceptin, snake venoms)
Pulmonary embolism, pulmonary hypertension
Rhabdomyolysis
Hypo- and hyperthyroidism
Extreme endurance efforts
Renal dysfunction and associated cardiac disease
Acute neurological event (e.g stroke or subarachnoid hemorrhage)
Critical illness (e.g.shock/sepsis/burns)

Special considerations in cardio-oncology patients:
- Tn elevation soon after high-dose chemotherapy is a strong predictor of cardiotoxicity and poor cardiological outcome, with the highest risk observed in patients showing a persistent (1 month) Tn increase.
- In patients with ICI-associated myositis or neurological disorders, troponin I is superior to hs-troponin T, as non-cardiac-specific increases in hs-troponin T occur.
- hs-troponin is used as a marker for surveillance and can be an early sign of cardiotoxicity
- The threshold of troponin rise to trigger further work-up has not yet been defined

NT-proBNP/BNP

Key points:
- They are used as quantitative markers of HF and provide the most accurate non-invasive tool for estimating intracardiac filling pressures and end-diastolic wall stress
- Primary use is to discriminate the cause of dyspnea (heart failure vs other causes) due to its high negative predictive value
- Obese patients have lower NP concentrations, mandating the use of lower cut-off levels (about 50% lower).
- NP concentrations have high prognostic accuracy for death and HF hospitalization in stable HF patients, myocardial infarction, valvular heart disease, atrial fibrillation and pulmonary embolism, however the use in cardio-oncology remains scarce

5. Surveillance During Cx—Principles

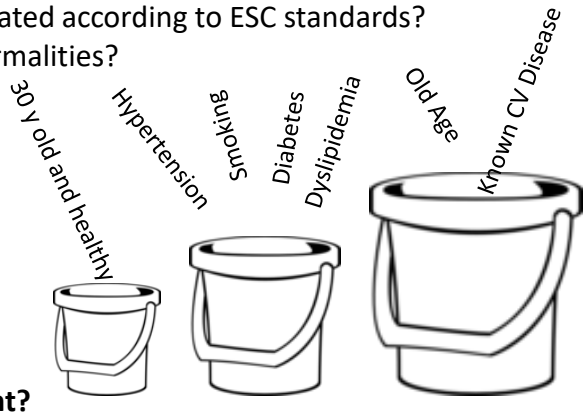
Key points
- Detect cardiovascular side effects as early as possible.
- Anticipate and initiate cardiovascular protection as early as needed.
- Support oncology for optimale duration and dose of Cx.
- Surveillance intensity and modalities (biomarkers, repetitive ECG, repeat TTE. etc.) depend on the pre-existing cv Risk **AND** on the planed Cx regime. It should be assessed and documented by the team in charge of Cx. **Risk-adapted surveillance intensity is a core principle of this booklet.**

1. Check for patient-related risk factors

1. Cardiovascular baseline risk assessment

a) Assess the cardiovascular risk profile according to ESC guidelines
b) Is pre-existing cardiovascular disease treated according to ESC standards?
c) Are there baseline ECG, lab or TTE abnormalities?

Information gained from:
- Patient history
- Clinical exam
- Vitals (especially BP)
- Basic labs (see page 9)
- ECG
- TTE (before certain Cx, page 7)



2. Is there prior exposure to oncological treatment?

2. Check for therapy-related risk factors

- Depends on Cx compounds, the combination of compounds and the planned dose (in particular with anthracyclines) (see surveillance part)
- Take into account the history of oncologic treatments (previous chemotherapy and/or radiotherapy) and previous cardiac complications related to oncologic treatments

3. Choose the final risk category according to therapy-related risk factors AND patient-related risk factors.

The **highest** score determines the overall risk category

RISK	Therapy-related factors	Patient-related factors
Low		
Medium		
High		

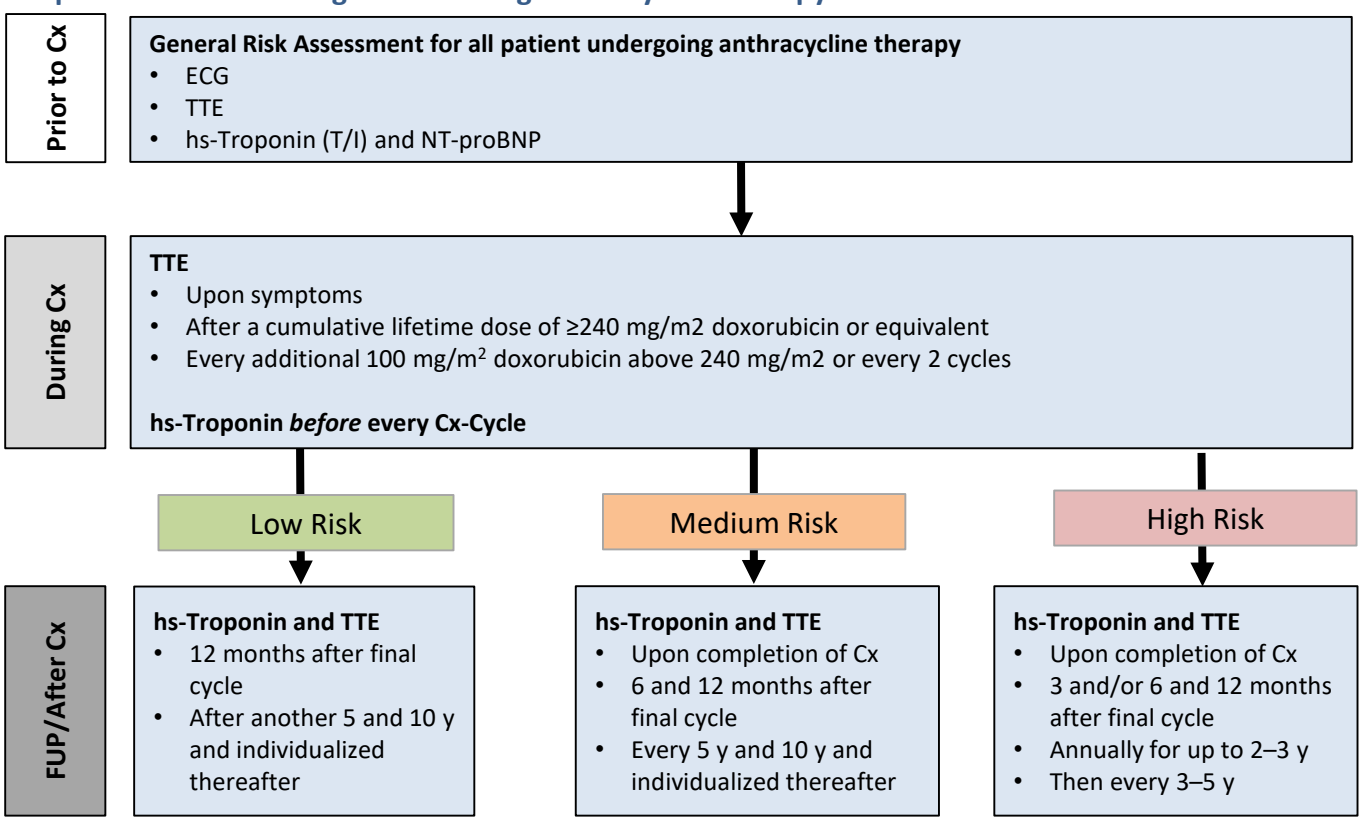
5.1 Surveillance During Cx—Anthracyclines

Key points

- Consider cumulative anthracycline (ANT) dose to group pts into risk categories. Be sure to sum up the different types of anthracyclines to estimate expected cardiac damage (e.g cum. dose of 120mg/m^2 mitoxantrone equal to 300mg/m^2 doxorubicin given by rapid infusion).
- A cumulative dose of 400mg/m^2 doxorubicin s.b.c. is the max. standard dose as the risk of congestive heart failure reaches a level of 5% or higher.
- Consider risk-lowering strategies in patients with expected high cumulative doses.

Risk	Therapy-related factors	Patient-related factors
Low	• Doxorubicin <200 mg/m^2 • Epirubicin <300 mg/m^2 • liposomal formulations	• Age >18, Age <50 y
Medium	• Doxorubicin 200–400 mg/m^2 • Epirubicin 300–600 mg/m^2 • ANT and Cyclophosphamide chemo followed by trastuzumab	• Age 50–64y • 1–2 CVRF (HTN, dyslipidemia, obesity, smoking, diabetes) • Elevated baseline troponin or BNP/NT-proBNP • Previous non-anthracycline based chemotherapy • Borderline LVEF 50–54%
High	• Doxorubicin ≥400 mg/m^2 • Epirubicin ≥600 mg/m^2 • Modest-dose ANT and Cyclophosphamide chemo plus left chest radiation therapy	• Age >65 y • >2 CVRF (HTN, dyslipidemia, obesity, smoking) • Underlying CVD • Reduced LVEF <50% • Prior ANT therapy • Prior radiotherapy to left chest or mediastinum

Proposed surveillance algorithm during anthracycline therapy



Refer to cardio-oncology if:

- **Increase of troponin of more than or equal to the ULN or 20% from baseline if abnormal at baseline**
- **Decrease in LVEF ≥10% points to <40–49%, or new LVEF reduction <50%**
- **Absolute global longitudinal strain (GLS) <-16%**
- **Relative decrease in GLS >15% from baseline**
- **Symptoms**

5.1.1 Cardioprotection During Treatment With Anthracyclines

Key points

- Five cardioprotection modalities that deserve consideration during anthracycline therapy:
  - Dose limitation
  - Schedule modification
  - Innovative delivery systems
  - Chemical and pharmacologic cardioprotection
  - Use of less toxic doxorubicine analogues.

Dose limitation

- Low dose 240–300mg/m2 (clinically relevant toxicity unusual if no underlying heart disease)
- Intermediate dose 300–400mg/m2
- High dose >400mg/m2 (greater risk for cardiotoxicity >5% even if no underlying heart disease)

Caution: cardiac toxicity vs reduced efficacy.

Schedule modification

- Weekly doses vs 3-weekly doses
  - Cardiotoxicity may correlate more closely with peak plasma levels, while oncologic efficacy is more closely related to the area under the plasma concentration curve
- Longer continuous infusion time (72h vs 48h)
  - Caution: central catheter and infusion pumps needed, more time consuming, risk of paravation

Chemical and pharmacological cardioprotectors

- Dexrazoxane
  Caution: potential to interfere with anthracycline, therefore only use in patients that exceed max.dose and need further anthracycline treatment AND in combination with Etoposid possible risk for second malignancy
- There are no strong data for the use of B-adrenergic blockade or angiotensin-converting-enzymes as primary protection during anthracycline in otherwise healthy individuals, however follow section «Cardioprotection Under Anthracycline Therapy» if pathologic findings on echocardiography or cardiac biomarkers

Innovative Delivery Systems

- Liposomal anthracycline formulation (pegylated vs non-pegylated), e.g. Caelyx
  Caution: only approved for metastatic breast cancer, advanced/refractory ovarian cancer or multiple myeloma and AIDS-associated Kaposi sarcoma, but may be active in other cancers such as angiosarcoma

Use of less-toxic doxorubicin analogues

Drug	Relative mylosuppressive potency	Approximate relative cardiotoxicity	Cardiotoxicity Index	Recommended max.dose mg/m2
Doxorubicin	1	1	1	400
Daunorubicin	0.67	0.75	0.5	800
Idarubicin	5	0.53	2.67	150
Epirubicin	0.67	0.66	0.44	900
Mitoxantrone	5	0.5	2.5	160

Table modified from M.Ewer, Cancer and the Heart, 3rd Edition

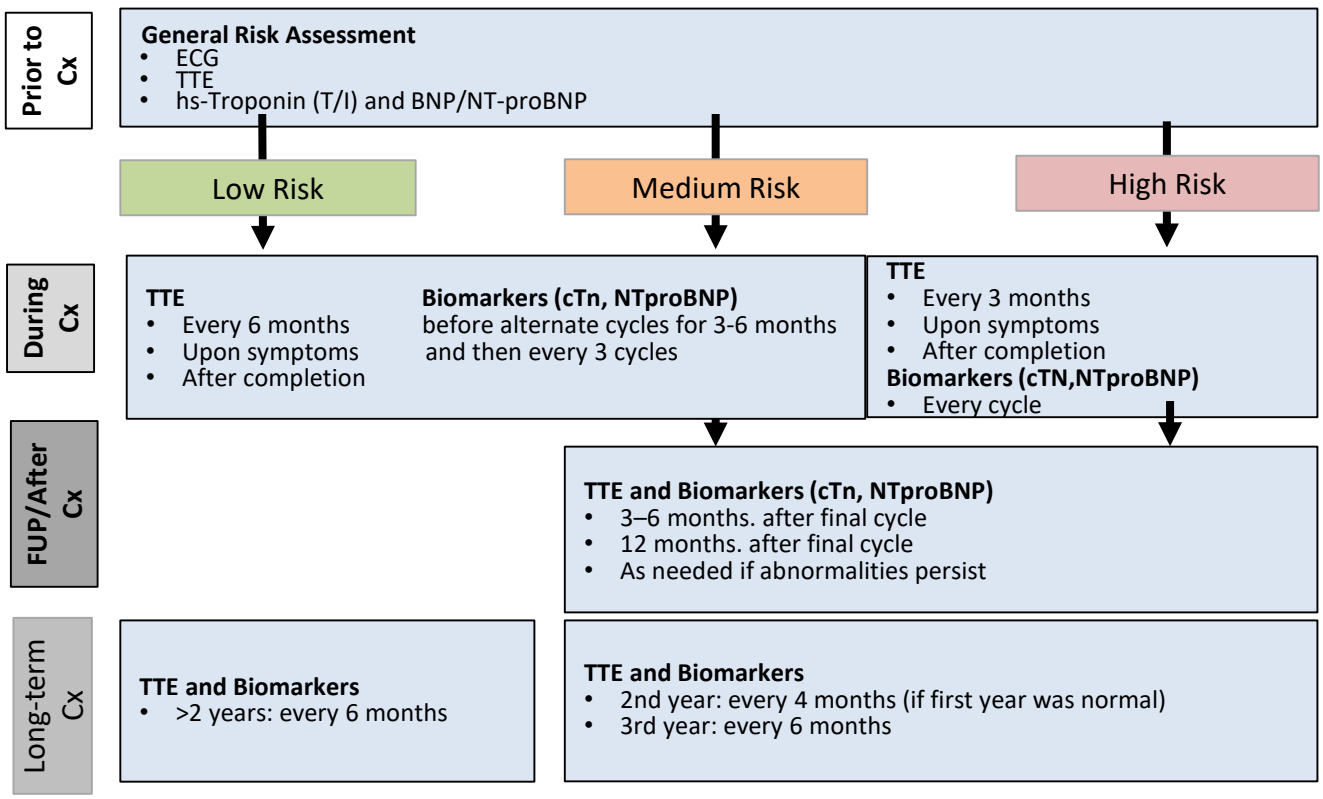
5.2 Surveillance During Cx—HER2

Key points

- Repeated echocardiographic exams and biomarker assessment for early detection of cardio-toxicity is recommended during and after treatment according to risk category.
- HER2-targeted therapies increase myocardium vulnerabilityto stressors (hypertension, anthracyclines), therefore previous or concomitant anthracycline and/or radiotherapy to the chest increases the risk of HER2-targeted toxicity.
- Under long-term/maintenance of HER2-targeted therapy, intervals can be prolonged, but follow-up should continue as toxicity may increase over time.

Risk	Therapy-related factors	Patient-related factors	
Low	• Trastuzumab without ANT and Cyclophosphamide chemo	• Age >18, Age <50 y	
Medium	• ANT and Cyclophosphamide chemo followed by trastuzumab	• Age 50–64y • 1-2 CVRF (HTN, dyslipidemia, obesity, smoking, diabetes) • Chronic kidney disease • Previous non-anthracycline-based chemotherapy	• Elevated baseline troponin or BNP/NT-proBNP without previous ANT • Borderline LVEF 50–54% • Arrhythmia
High	• Simultaneous ANT and Cyclophosphamide and trastuzumab • Elevated cardiac troponin post-AC prior to HER2-targeted therapy	• Age >65 y • >2 CVRF (HTN, dyslipidemia, obesity, smoking) • Underlying CVD	• Reduced LVEF <50% • Prior ANT therapy • Prior radiotherapy to left chest or mediastinum

Proposed surveillance algorithm during HER2-therapy



Refer to cardio-oncology if:

- **Increase of troponin of more than or equal to the ULN or 20% from baseline if abnormal at baseline**
- **Decrease in LVEF ≥10% points to <40–49%, or new LVEF reduction <50%**
- **Absolute global longitudinal strain (GLS) <-16%**
- **Relative decrease in GLS >15% from baseline**
- **Symptoms**

5.3 Surveillance During Cx

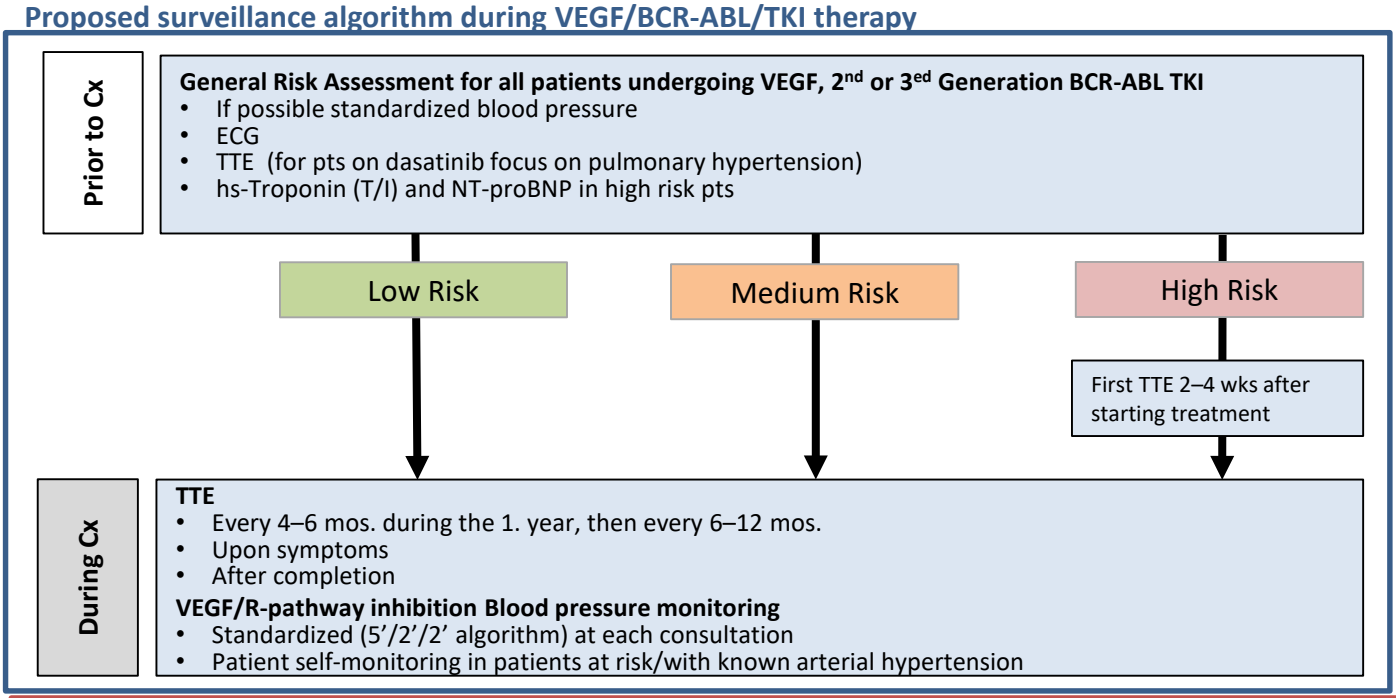
VEGF/R-pathway inhibition 2nd/3rd Gen. BCR-ABL TKI

Key points

- VEGF signaling inhibitors are associated with arterial hypertension and arterial thrombosis, but cardiac dysfunction and heart failure may likewise occur.
- VEGF signaling plays a role in the ischemic heart, rendering patients with pre-existing ischemic heart disease or cardiomyopathy more vulnerable.
- Various cardiovascular side effects have been reported under BCR-Abl inhibiting TKIs with cardiac dysfunction and heart failure as well as ischemic heart disease being named most frequently.

Risk	Therapy-related factors	Patient-related factors	
Low		• Age >18, Age <50 y	
Medium	• VEGF tyrosine kinase inhibitors • 2nd and 3rd generation Bcr-Abl tyrosine kinase inhibitors	• Age 50–64y • 1-2 CVRF (HTN, dyslipidemia, obesity, smoking, diabetes) • Chronic kidney disease • Proteinuria • Arrhythmia	• Elevated baseline troponin or BNP/NT-proBNP • Previous non-anthracyclin-based chemotherapy • Borderline LVEF 50–54% • 450ms≤QTc<480ms
High	• VEGF tyrosine kinase inhibitors following previous ANT and Cyclophosphamide chemo • Monoclonal antibodies: Bevacizumab	• Age >65 y • >2 CVRF (HTN, dyslipidemia, obesity, smoking) • Underlying CVD (incl. TIA, stroke, PVD)	• Reduced LVEF <50% • Prior ANT therapy • Prior radiotherapy to left chest or mediastinum • Venous thrombosis (DVT or PE) • Pulmonary arterial hypertension

Proposed surveillance algorithm during VEGF/BCR-ABL/TKI therapy



Refer to cardio-oncology if:

- **Increase of troponin of more than or equal to the ULN or 20% from baseline if abnormal at baseline**
- **Decrease in LVEF ≥10% points to <40–49%, or new LVEF reduction <50%**
- **Absolute global longitudinal strain (GLS) <-16%**
- **Relative decrease in GLS >15% from baseline**
- **Symptoms**
- **If arterial hypertension >160/90mmHg**

5.4 Surveillance During Cx—ADT

Key points

- Animal and human studies suggest an unfavorable coincidence btw medical androgen deprivation therapy (ADT) and cardiovascular toxicity in the form of an elevated risk of CVD and CV events (e.g.. CAD, MI, stroke).
- The mechanism is multifactorial but seems to be driven by a CV risk profile (dyslipidemia, insuline resistance, change in body composition or level of adipocytikines).
- Moreover, increased systemic inflammation may lead to destabilization of atherosclerotic plaque
- So far there are no clear consensus guidelines or recommendations for cardiotoxicity assessment during ADT (see box at the bottom "Level of evidence").
- ADT, in general, prolongs the QT interval and may increase the risk of arrhythmia, e.g. Torsades de Pointes (TdP) particularly in the presence of other concomitant QT-prolonging risk factors.

Risk	Therapy-related factors	Patient-related factors
Low		• Age >18, Age <65 y
Medium	• GnRH Receptor agonists: leuprolide, buserelin, goserelin, triptorelin • GnRH Receptor antagonists: degarelix, abarelix • 5a-reductase inhibitors: finasteride, dutasteride • nonsteroidal androgen-receptor antagonists: bicalutamide, flutamide, nilutamide	• 1–2 CVRF (HTN, dyslipidemia, obesity, smoking, insulin resistance, diabetes) • Borderline LVEF 50–54%
High	• Abiraterone • Apalutamide • Darolutamide • Enzalutamide	• Age >65 y • >2 CVRF (HTN, dyslipidemia, obesity, smoking) • Underlying CV disease: CAD, PAD, CMP, severe VHD, HF • Reduced LVEF <50 pretreatment • Prior cancer therapy

Proposed surveillance algorithm during androgen-deprivation therapy

Prior to Cx

General Risk Assessment for all patients

- **ABCDE** Approach and aggressive treatment of CVRF using/following the AGLA Recommendations (**A**wareness – **B**lood pressure – **C**holesterol and Cigarette – Diet and **D**iabetes – **E**xercise)
- Assess vital signs (standardized blood pressure), perform clinical examination
- Measure serum electrolytes, creatinine, TSH, HbA1c, Lipidprofil within the last 12 month
- ECG
- Check for concurrent medications b/o potentially increased risk of DDI-related adverse events

Low Risk | Medium Risk | High Risk

Identify pts who may benefit from additional evaluation or therapy (e.g. CHF), consider cardiology referral if not already in place

During Cx

- Check BP control at least twice a year
- Early after initiation of ADT conduct regular ECG monitoring (see QT-section). Later on, ECG once a year.
- Monitor pts taking medications that affect the p450 pathways due to potential DDIs
- Lipidprofil once a year
- Further diagnostics according signs and symptoms (ie. Holter ECG, Echo, cardiac biomarkers…)

Level of evidence

- GnRH agonists, GnRH antagonists, AR-targeting agent (ARTAAR) and orchiectomy for Prostata-Ca show positive associations with CV events and CV death.
- These effects are not consistently reproducible data. One reason is that pivotal trials excluded pts with significant CV comorbidities. But in fact, there is increasing evidence (meta-analysis, RCT and real-world data) that both treatment approaches have a clinically significant impact on CV complications, for which GnRH antagonists show an advantage over GnRH agonists.

5.5 Surveillance During Cx—ICI

Key points

- ICI-induced myocarditis is a rare adverse event (estimated 0.27–1.14%), but fulminant forms are associated with high mortality (up to 25–50%).
- Median delay from starting ICI is 30 days [18–60]: high clinical awareness is needed during the first 4 cycles.
- ICI often occurs in combination with peripheral myositis (25%) or myasthenia (10%).
- Exclude ACS when considering myocarditis.

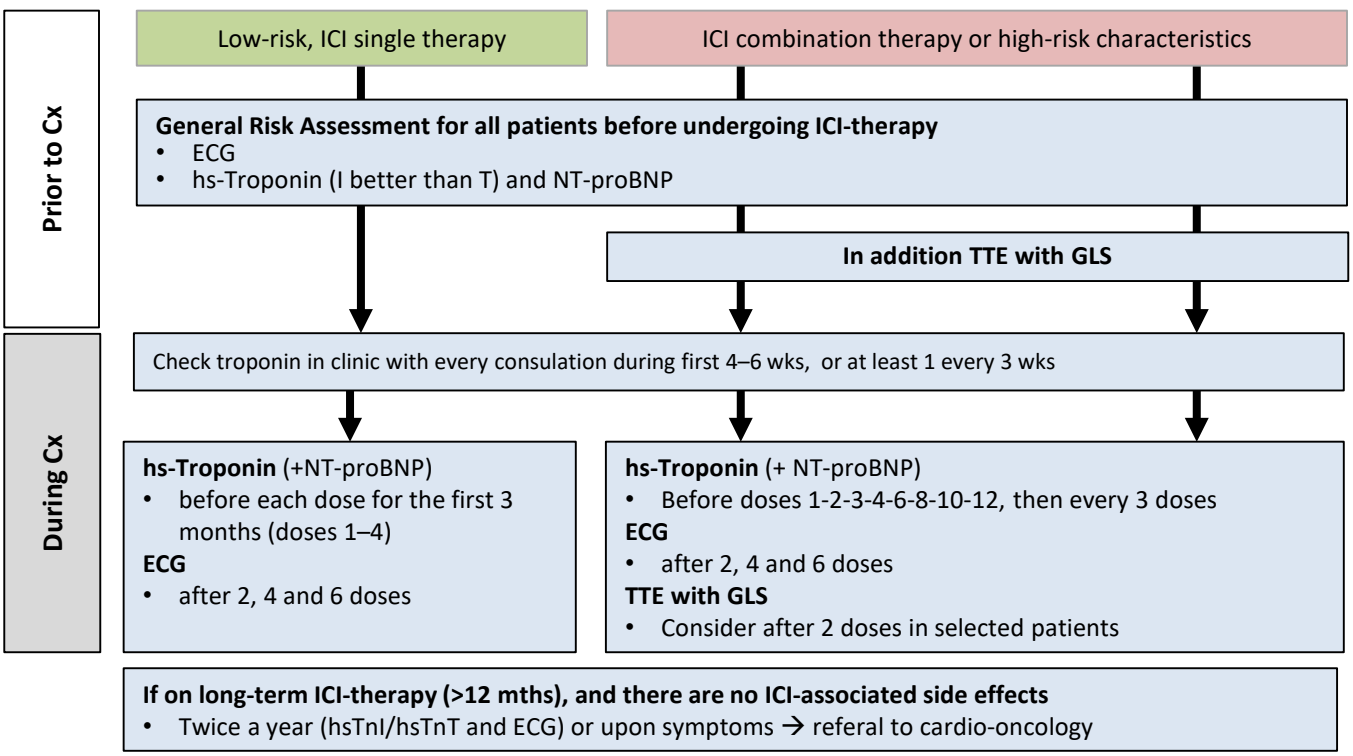
Risk	Therapy- related factors	Patient-related factors
Low	• ICI single therapy	• Age >18, Age <50 y
Medium		• Age 50–64 y • 1–2 CVRF (HTN, dyslipidemia, obesity, smoking, diabetes) • Underlying auto-immune disease
High	• ICI combination therapy (RR=4,3 vs single Tx) • ICI in combination with a second oncology drug with known cardiotoxicity	• Age >65 y • >2 CVRF (HTN, dyslipidemia, obesity, smoking) • Underlying CV disease: CAD, PAD, CMP, severe VHD, HF • Reduced LVEF <50 prior to cancer therapy

Suspected myocarditis:

Non-specific presentation with:

- Clinical: Chest pain, dyspnea, palpitations, dizziness, syncope or other immune-related adverse events (irAEs)
- ECG: Tachy-/bradyarrhythmia, AV conduction disturbance, bundle branch block, ST modification, T-wave inversion, low voltage
- Biomarkers: Increase in high-sensitivity troponins or CK; **TnI more specific than TnT (TnT may be released by skeletal muscle in case of myositis)**
  NT-proBNP/BNP elevation not specific for myocarditis but will reflect the degree of cardiac dysfunction
- TTE: Global/regional dysfunction (50% have normal LVEF), LV wall thickening, longitudinal strain reduction, effusion
- CMR: LGE, reginal wall motion abnormality, strain reduction (30–50% sensitivity in pts with myocarditis)
- FDG-PET: Look for increased metabolism (in cases with normal CMR but likely myocarditis)

Proposed surveillance algorithm during ICI therapy



If abnormal or patient symptomatic: consult section 5.5 Immune checkpoint inhibitor-associated myocarditis

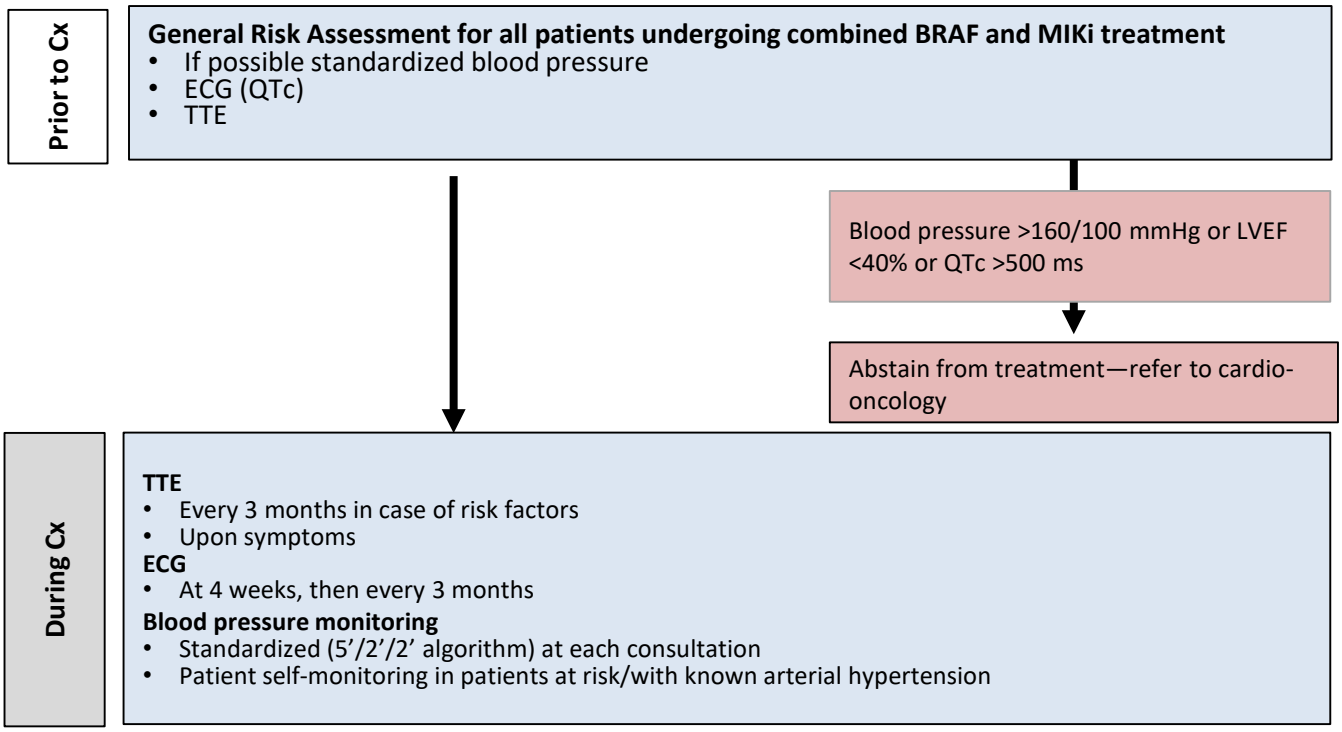
5.6 Surveillance during Cx—Combination of BRAF- and MEK-inhibitors

Key points

- BRAFi/MEKi is associated with HT (most frequent side effect), LVEF decrease (often asymptomatic and reversible) and QT interval prolongation (vemurafenib + cobimetinib).
- Toxicities are more a class effect than a substance effect.
- Published data on surveillance and treatment strategies is scarce (level of Evidence C).

Risk	Patient-related factors
Medium	• Age <65y • RF (HT, dyslipidemia, obesity, smoking, diabetes) • Prior arrythmias • Reduced or low-normal LVEF (50–54% pretreatment) • Elevated biomarkers • Prior Rx-therapy to chest or mediastinum
High	• Underlying CV disease: CAD, PAD, CMP, severe VHD, HF • Prior anthracycline exposure

Proposed surveillance algorithm during BRAFi/MEKi therapy



Refer to cardio-oncology if:

- **Increase of troponin at baseline**
- **Decrease in LVEF ≥10% points to <40–49%, or new LVEF reduction <50%**
- **Absolute global longitudinal strain (GLS) <-16%/relative decrease in GLS ≥15%**
- **QTc prolongation Δ 30-60 ms (treatment reduction advised)**
- **QTc >500ms or QTc Δ>60 ms or BP >160/100mmHg despite HT-therapy (treatment interruption advised)**

5.6 Surveillance—Radio-Therapy and Devices

Key points

- Clinical AE (adverse events) are uncommon. CIED (cardiac implantable electronic devices) malfunction rarely. AEs depend on the type of device and are mainly related to neutron-producing beams (*neutron contamination*).
- Radiation interaction w/ CIED is mainly based on a stochastic effect: even a dose <2Gy may be destructive.
- If the distance between treatment field edge and CIED is >10 cm, dose to CIED is probably <2 Gy.
- Risk-stratification: look for an interdisciplinary agreement with radio-oncologist.
- Promptly contact device manufactures (low threshold).

Proposed algorithm for device surveillance during Radio-therapy

LOW-risk	Characteristics	HIGH-risk
<2 (5) Gy	1. Cumulative dose to CIED	>5 Gy
Low	2. Risk of neutron contamination - Photon energy >10MV - Electron energy >20 MeV - Proton (any energy)	High
No	3. Pacing-dependency	Yes
No	4. ICD	Yes

Prior to RT

Whenever possible: plan RT in order to **minimize radiation exposure to CIED** and **lower neutron contamination**

If CIED location impacts optimal radiation delivery: consider CIED relocation prior to RT (shared decision making pt-treatment team). Not recommended for <5 Gy

Perform **CIED evaluation prior to initiation of RT –** consider contacting device manufacturer

Provide individual recommendations for RT according to patients' profile:

No ICD/not PM-dependent
- No reprogrammation
- No magnet use

PM-dependent
- Consider DOO/VOO reprogramming or magnet placement

ICD-patients
- Consider switch-off therapy or magnet placement for Tx (in latter case: PM-stimulation is not affected!).
- CRT: Check with manufacturer effect of magnet placement

During RT

Audio-visual contact with the patient during RT treatment
Monitoring with pulse oximetry
Pacemaker magnet and AED available at treatment unit

Access to external pacing (with trained staff) if PM-dependent
ECG monitoring if ICD-pt and recent anti-tachycardia treatments
Cardiologist available for pre/post Tx programming

CIED evaluation every week during RT

CIED evaluation at the end of RT

CIED evaluation at the end of RT

FUP/After

CIED interrogation:
- At 1 (eventually at 3) and 6 months after RT (remote monitoring or in person)

5.6 Surveillance—Radio-Therapy and Devices

Recommendation from different cardiovascular implantable electronic device manufacturers on radiation therapy to patients with devices. *From: ESC guidelines for heart failure, 2021*

	Abbott-St. Jude Medical	Biotronik	Boston	Medtronic	Microport
Max dose (Gy)	No exact threshold determined	≤10 MeV (≤2 Gy total dose) but no safe radiation dose	No safe radiation dose	500 cGy (except for older models)	Not mentioned (betatrons are contraindicated)
Shield	Not mentioned	Recommended	Recommended	Conventional X-ray shielding does not protect against neutrons effect	Recommended
Relocation	Recommended if the device is in the field	Not mentioned (avoid direct irradiation)	Recommended if the device is in the irradiation field	Recommended if the device in the irradiation field	Recommended if the device is in the field
Evaluation of reset	Not mentioned	The devices are unable to identify reset	"Safe check" and interrogation may not be possible to unveil reset	Magnet may induce electrical reset Pacemakers: asynchronous pacing rate 65 b.p.m. ICD: high/low tone	Not mentioned
Device check	Pacemaker-dependent: once or twice during the treatment or in case of symptoms	After the treatment (any course?)	After the treatment (depending on recommendation of the attending cardiologist)	After the treatment	Not mentioned
Web-based information	https://manuals.sjm.com	https://www.biotronik.com/en-de/ healthcare-professionals	http://www.bostonscientific.com/ manuals/manuals/landing-page/ EU-english.html	www.medtronic.com/ manuals	www.sorinmanuals.com

Bpm: beats per minute; cGy: centiGray; Gy: Gray; ICD: implantable cardioverter-defibrillator, MeV: megaelectron volt.

- The majority of alterations is temporary, thus: perform frequent CIED controls
- Device memory is the component most likely to be affected by therapeutic radiation (beam or scatter particles)
- Some CIEDs perform self-diagnostic memory checks to correct errors, however, if the alteration is beyond the capability of self-correcting algorithms, the CIED may enter safety mode (basic PM and/or defibrillator therapy).

ICDs/ CRT-Ds	PM/ CRT-Ps	Potential Device Behaviors	Programming considerations
✓ .	✓ .	Altered device status (e.g. premature elective replacement indicator)	Perform regular CIED controls, as suggested in the earlier diagram
✓ .	✓ .	Altered pacing outputs (e.g. decreased pacing amplitude)	Perform regular CIED controls, adapt output parameters for pacing
✓ .	✓ .	Inhibition of pacing—pacing therapy not provided when needed	Initiate temporary asynchronous pacing (VOO/AOO/DOO)
✓ .		Altered tachyarrhythmia outputs (e.g. shock energy)	Manual capacitor reformation
✓ .		Inhibition of tachyarrhythmia therapy—shock therapy not provided when needed	CIED replacement may be necessary
✓ .		Inappropriate shocks—shock therapy provided when not needed	Deactivate tachy-therapy (tachy mode off) or place a magnet over the device to temporarily inhibit it
✓ .	✓ .	Complete loss of device function	CIED replacement may be necessary
✓ .		Reversion to a safety mode	Perform regular CIED controls, replacement may be necessary
✓ .	✓ .	Loss of remote monitoring	Perform regular CIED controls, replacement may be necessary

6.1 Hypertension During and After Cancer Therapy

Key points

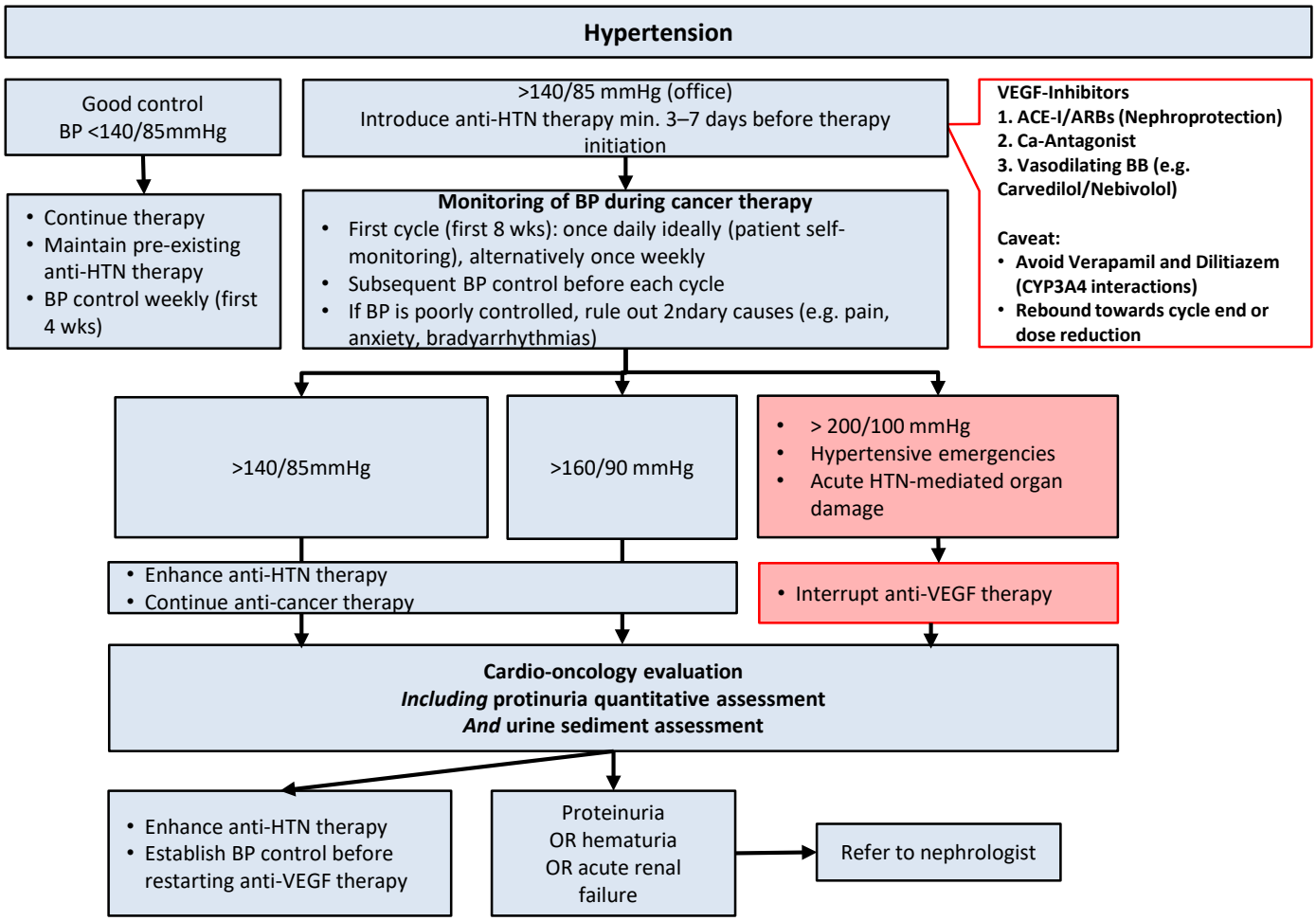
- Cancer patients and survivors are at a high risk for hypertension.
- Hypertension (HTN) likely contributes to the high burden of cardiovascular disease in cancer pts and survivors.
- In- and out-of-office blood pressure measurement is important in cancer pts and survivors.
- Target organ damage and treatment-specific morbidities should be considered when selecting antihypertensive agents.

Definition

Low Normal	Normal	High Normal	Stage 1	Stage 2	Stage 3	
<120 <80	120–129 80–84	130–139 85–89	140–459 90–99	160–179 100–109	>180 >110	Systolic Diastolic

Definition of Hypertension according to measurement method	SBP mm Hg	DBP mm Hg
• Automated Office BP (AOBP)	≥135	≥85
• Manual Office BP (MOBP)	≥140	≥90
• Ambulatory BP monitoring (ABPM)		
• Daytime (awake) mean	≥135	≥85
• Night-time (asleep) mean	≥120	≥70
• 24 hr mean	≥130	≥80
• Home blood pressure measurement (HBPM) mean	≥135	≥85

Proposed algorithm in case of hypertension during cancer therapy



6.1 Drugs Associated With Hypertension

Hypertension

Risk factors for hypertension and adverse CV events:
- Uncontrolled BP
- Organ damage (e.g. LV hypertrophy)
- CKD ≥stage 3
- Diabetes mellitus
- ≥3 CV risk factors
- Obstructive sleep apnoea
- Obesity
- Age ≥60–65

Cancer

High hypertension risk:
- VEGF-inhibitors
- mTOR inhibitors
- Cisplatin
- Ponatinib
- BRAFi/MEki

Risk–Benefit Assessment

Low/intermediate risk

Therapy initiation or intensification
- Ideally BP <120 mmHg, <130 mmHg minimal systolic goal
- BP assessment, preferably daily during first cycle, then weekly
- Instruct pts how to perform BP at home (resting for 5 min, then perform 3 measurements with 1 min pause between two measurements, different period of the day)

Antihypertensive drugs

Prohibitive risk

Prohibitive risk:
- Uncontrolled hypertension (BP >180/110 mmHg)

Reduce/pause Cx

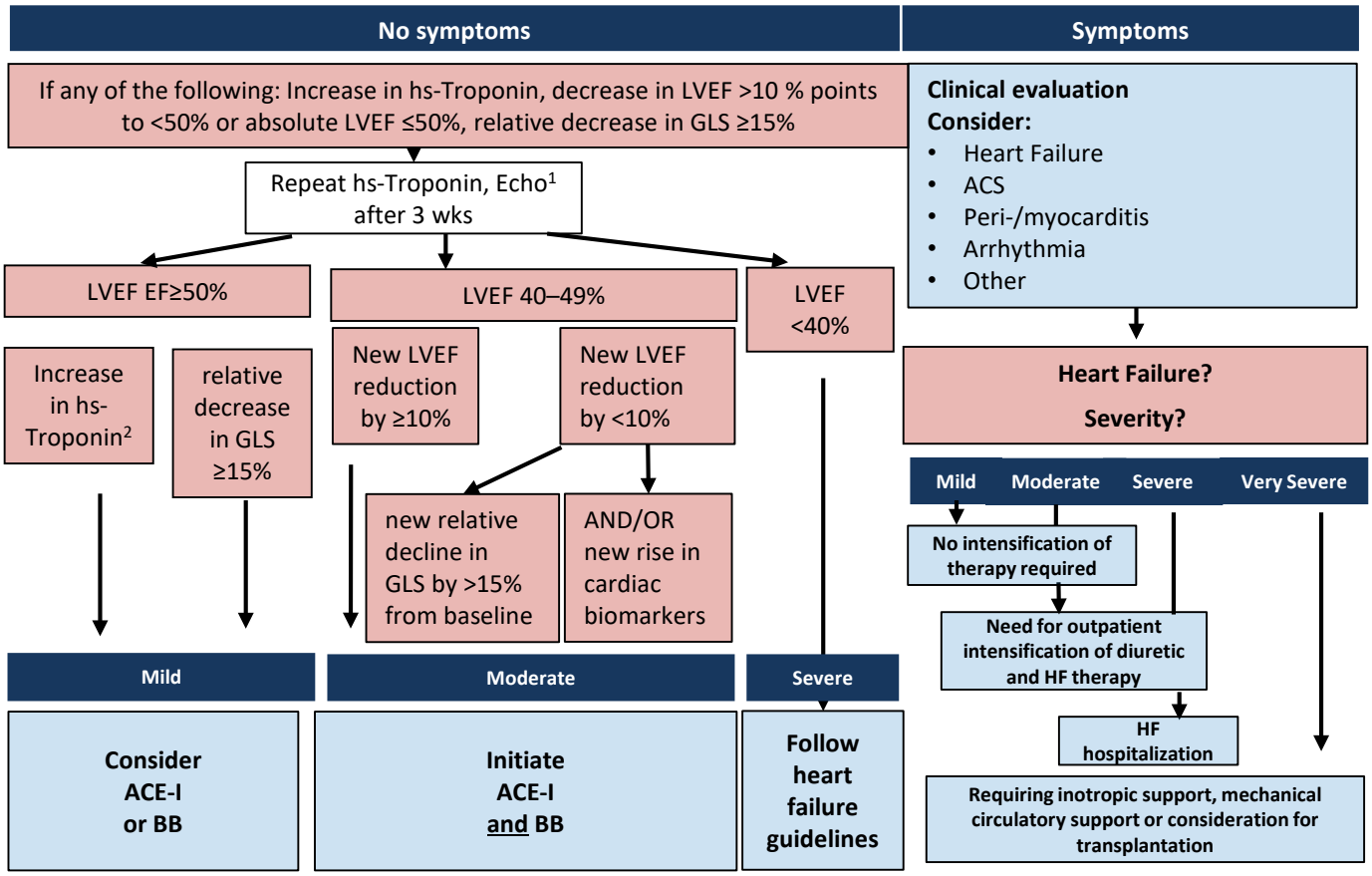
Drug class	Cx Agent	HTN incidence	Mechanism(s) of Blood Pressure Elevation	Recommendations
Alkylating agents and alkyl-like agents	• Cyclophosphamid • Ifosfamide • Cisplatin	14–53% (related to GFR) ~16%	• Vascular endothelial injury • Nephrotoxicity, dose-dependent, > in children • Nephrotoxicity and vascular endothelial injury	
Immuno-modulators	• Lenolidamid • Thalidomid	1–10%		
VEGF inhibitors	• Bevacizumab • Axitinib • Cabozatanib • Lenvatinib • Pazopanib • Sorafenip • Sunitinib	26–55% 40% 22–37% 41–68% 35–57% 17–48% 16–47%	– Increased vascular resistance – Reduced nitric oxide production Reduced angiogenesis – Impaired natriuresis – Endothelin-1–mediated vasoconstriction – Thrombotic microangiopathy	**1st line:** - RAAS inihibitors - Dihyropyridine Ca-antagonists (Amlodipine, Felodipine) **2nd line:** - BB (e.g. Nebivolol to counteract decreased NO signaling) **Avoid** Diltiazem/Verapamil (inhibition of cytP450). **Consider** dose reduction or discontinuation of VEGF-inhibitors if hypertension is not controlled. Restart once hypertension is under control.
Tyrosin kinase inhibitors BCR-ABL	• Bosutinib • Dasatinib • Imatinib • Ponatinib • Nilotinib	8% <10% 4% 67% 8–10%		
BRAFi/MeKi	• Dabrefenib +trametinib • Vemurafenib+ cobimetinib • Encorafenib +vemurafenib	11–26%		
Radiation				
• Abdominal radiation			Renal artery stenosis.	Treat accordingly and invasively, if necessary
• Head and neck radiation			Baroreflex failure with hypotension and/or hypertensive crises	Long-acting central sympatholytic drugs
Adjuvant therapies				
• Erythropoietin stimulating agents			↑erythrocyte mass Altered response to endogenous vasodilators + vasopressors	Treat pulmonary hypertension Phlebotomy
• Corticosteroids			Sodium retention due to mineralocorticoid receptor stimulation	Standard antihypertensive therapy according to comorbidities
• Calcineurin inhibitors	• Tacrolimus	22%	Systemic and renal vasoconstriction	Standard antihypertensive therapy according to comorbidities
• Nonsteroidal inflammatory drugs (NSAID)	• Ibuprofen • Diclofenac • Ac. mefaminic	<1% ~5% <1%	Impaired natriuresis due to reduction in prostaglandin inflammatory drugs synthesis	Suspend NSAID

6.2 Cardioprotection Under Anthracycline Therapy

Key points

- The proposed treatment algorithm applies to the time during (and up to 6–12 months after) Anthracycline therapy.
- Data on cardioprotection in pts with normal LVEF is still scarce. Best supported is the use of ACE-I upon Troponin increase. Less and contradicting data is available on BB; however, Carvedilol was most consistently associated with beneficial effects.
- Patients fulfilling criteria for HFrEF should always be treated according to HF guidelines.
- It is recommended that pts with a decline in LVEF >10 % points to <50% due to Anthracyclines should be started on ACE-I and BB. Similarly, pts with LVEF 40-50% (HFmrEF) may benefit.
- In any other case, decision on initiation of ACE-I and/or BB therapy should be made in a tailored fashion depending on the patient status and concomitant cardiovascular risk.

Proposed algorithm for initiation of cardio-protective treatment under Anthracycline therapy



[1] Consider cardiac MRI if:

- Poor image quality on echocardiography
- Before treatment interruption as secondary method for quantification of EF
- To discriminate ischemic from toxic etiology or other forms of cardiomyopathy (e.g. amyloidosis)
- For suspected myocarditis
- To assess pericardial pathology (e.g. post-radiation) or percardial or cardiac metastases

[2] Troponin rise:

- If normal at baseline: any increase above the ULN.
- If abnormal at baseline: 20% rise

ACE-I > BB
BB preferrably Carvedilol
Recommended treatment duration when asymptomatic with normal LVEF: 1 year

How to handle cancer treatment

- Multidisciplinary approach
  - Alternative treatment
  - Optimal cardiac treatment
  - Patient aware of risk
  - Overall prognosis

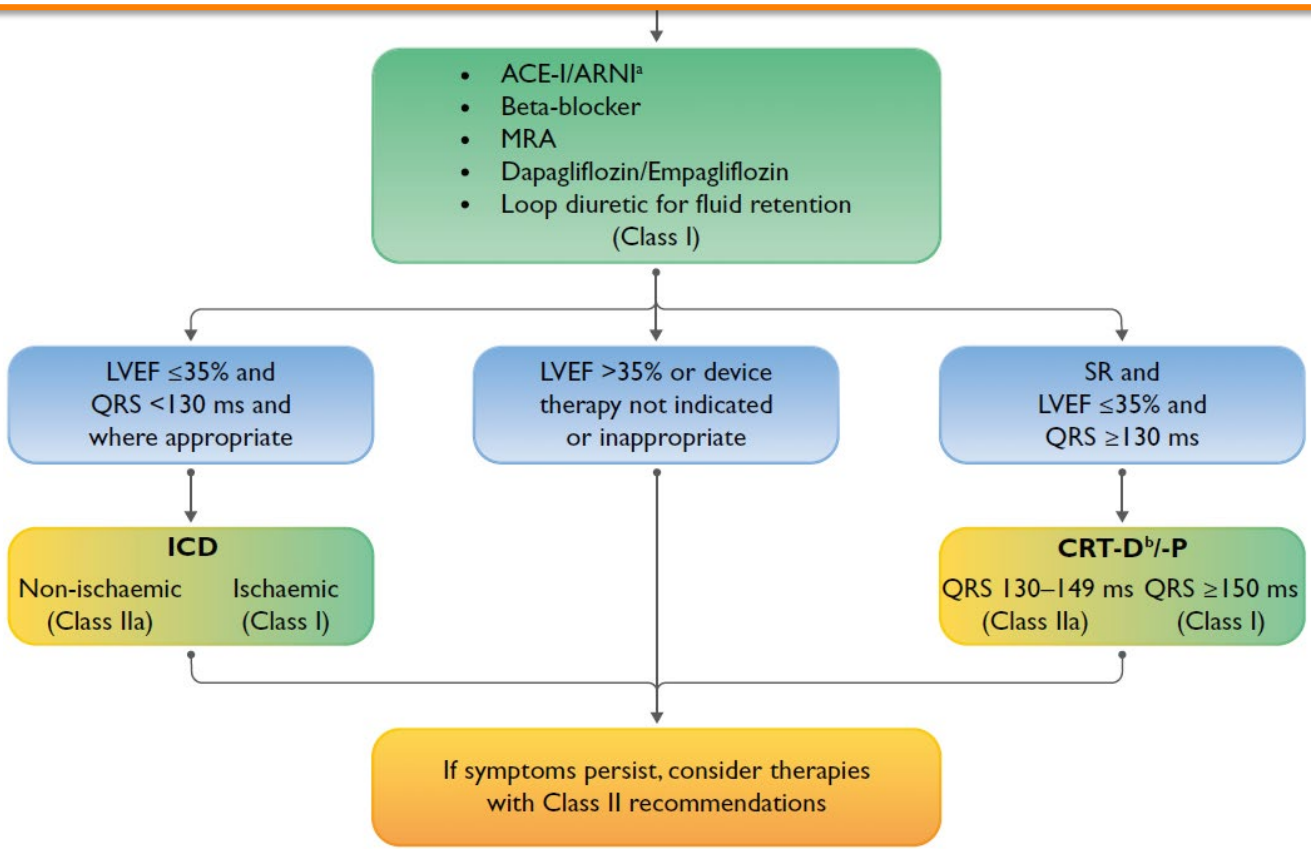
Check for potential drug interactions, in particular when patient under TKI
www.compendium.ch
(login via GLN Number)

6.2 Recommendations For Heart Failure (ESC Guidelines)

Key points

- The new ESC HF GL 2021 include a new category "heart failure with mildly reduced ejection fraction" (HFmrEF, EF: 41–49%), in between HFrEF (EF: ≤40%) and HFpEF (EF: ≥50%). The reason was: pooled data and retrospective analyses back up the therapeutic benefit for pts in this "grey area LVEF group", if they are treated analogous to HFrEF.
- Beyond the LVEF-based categories, keep in mind to search for specific causes of HF and choose an etiology-based treatment whenever possible, e.g. tachycardia-induced CMP, alcoholic CMP, valve CMP.
- All pts with HF should be in a multidisciplinary heart failure management program that provides strategies for strengthening self-empowerment and offers the opportunity to participate in a physical training program.

Management of pts with **HFrEF**



HFrEF treatment - approach:

- The 4-drug-approach, consisting of ARNI or ACE-I, BB, MRA and SGLT2i, is the new Class I recommendation, with SGLT2i regardless of the presence of DM. All 4 should be started simultaneously, or as close as possible
- Primary therapy with ARNI can also be considered
- Reassessing symptoms, LVEF and laboratory monitoring is needed periodically, it is especially important to recheck electrolytes and renal function after dose titration
- Preferential use of drugs proven to be beneficial in clinical trials is recommended
- All HF-pts should be in a multidisciplinary HF management program that provides strategies for strengthening self-empowerment and offers the opportunity to participate in a physical training program

ACE-I	ARNI	BB	Others
Captopril Enalapril Lisinopril Ramipril Trandolapril	Sacubitril/valsartan	Bisoprolol Carvedilol Metoprolol succinate Nevibolol	Candesartan Losartan Valsartan Ivabradine Vericiguat Digoxin Hydralazine/ISDN
	MRA	**SGLT2i**	
	Epleronone Spironolactone	Dapagliflozin Empagliflozin	

6.2 Approach To Patients With Heart Failure (ESC Guidelines)

Specific situation especially in HFrEF

- Avoid unnecessary and premature cessation or reduction of HF medication
- A 50% creat increase above baseline or creat ≤266 umol/l (≈ eGFR 25 mL/min/1.73 m2) can be tolerated before adjusting the dose of ACE-I, ARB or ARNI. HF-therapy should be paused/stopped only if beyond this.
- Hypotension: apart from loop diuretics, asymptomatic hypotension should not result in HF therapy reduction. In case of symptomatic hypotony, antihypertensive drugs that are not necessary should be stopped first.
- GL recommend reducing the MRA dose only if potassium is >5.5 mmol/l and stopping if potassium is >6.0 mmol/l (under close monitoring). A new option is the potassium binder Patiromer.
- If the LVEF improves from HFrEF range the HF therapy should be continued (exception for loop diuretics).

Management of patients with **HFmrEF**

Recommendation	Class	Level
Diuretics to alleviate symptoms and signs	I	C
ACE-I to reduce the risk of HF hospitalization and death	IIb	C
ARB to reduce the risk of HF hospitalization and death	IIb	C
BB to reduce the risk of HF hospitalization and death	IIb	C
MRA to reduce the risk of HF hospitalization and death	IIb	C
Sacubitril/Valsartan to reduce the risk of HF hospitalization and death	IIb	C

HFmrEF treatment - approach:

- The new ESC GL takes into account that pts may benefit from targeted therapies known to be beneficial in HFrEF, such as neurohormonal blockade
- However strong recommendations cannot be made about specific therapies at this point in time (IIb)
- The recently published EMPEROR-Preserved study showed significant advantage for patients with LVEF >40%, independent of the presence of diabetes and will lead to an updated therapy recommendation

Management of patients with **HFpEF**

HFpEF treatment approach:

- Diagnosis and treatment of HFpEF is still challenging. The identification of potential specific etiologies underlying HFpEF and thus targeted therapy of comorbidities is paramount (e.g. cardiac amyloidosis)
- Diagnosis is based on HFpEF:
- 1. Clinical signs
- 2. LVEFV ≥50% in combination with objective evidence (e.g. echo) consistent with the presence of LV diastolic dysfunction/raised LV filling pressures and
- 3. Increased levels of the NPs
- In general:
- Diuretics are used at signs of congestion recommended for symptomatic therapy
- The treatment of pts with DM and HF should contain an SGLT2i. An updated version for the administration of SGLT2i independent of DM can be expected in the near future

Don't withhold potential lifesaving cancer treatment unless there is a major cardiac adverse event. Cessation of cancer treatment must always be a team decision considering risk–benefit

6.3. Arrhythmia—Atrial Fibrillation (AF)

Key points

- AF is quite often seen in Cancer pts, in part due to the high degree of cancer-related systemic inflammation, oxidative stress and apoptosis present in malignancy, but also to certain cytotoxic agents used in cancer therapy regimens.
- Management might be complicated due to various DDI with Cx or a concomitant higher bleeding risk than in the normal population (e.g. thrombocytopenia, cerebral lesions, GI-Tumor, interruption for surgery).
- The general strategy for cancer Pts with AF should be based on the GL AF 2020 with individualized therapy adjustments.

Definition and Overview:
Atrial fibrillation (AF) is the most common sustained arrhythmia characterized by disorganized atrial electrical activity and contraction. According the GL, an episode lasting at least 30s is diagnostic for clinical AF.
The incidence and prevalence of AF is increasing. Lifetime risk over the age of 40 y is about 25%. Complications of AF include hemodynamic instability, cardiomyopathy, cardiac failure and embolic events such as stroke.

Classification is dependent on the presentation and duration of atrial fibrillation as below:

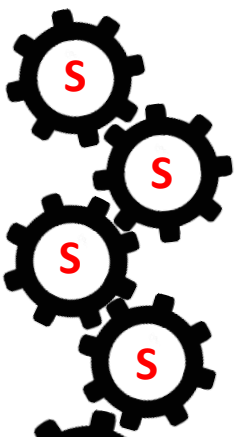
- First episode—initial detection of AF regardless of symptoms or duration
- Paroxysmal AF—self-terminating episode <7 days
- Persistent AF—not self-terminating, duration >7 days, also including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥7 days
- Long-standing, persistent AF ≥1 year
- Permanent (accepted) AF—duration >1 yr in which rhythm-control interventions are not pursued or are unsuccessful

The atrial fibrillation pathway adapted from the ESC AF guidelines 2020 central illustration

Confirm AF

12-lead ECG or a rhythm strip showing AF pattern for ≥30 s

Characterize AF
4S-AF scheme



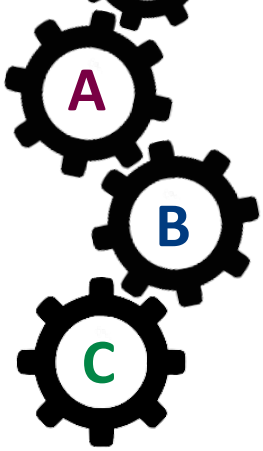
Stroke risk (St)
(e.g. CHA2DS2-VASc score)

Symptom severity (Sy)
(e.g. EHRA symptom score)

Severity of AF burden (Sb)
(duration, spontaneous termination)

Substrate severity (Su)
(age, comorbidities, atrial enlargement/fibrosis)

Treat AF
ABC pathway



Anticoagulation/Avoiding stroke

1. Identify low-risk pts CHA2DS2-VASc 0(m), 1(f)
2. Offer stroke prevention if CHA2DS2VASc ≥1(m), 2(f)
   - Assess bleeding risk, address modifiable risk factors
3. Choose OAC (DOAC or VKA with well-managed TTR)

Better symptom control

- Assess symptoms, Quality of life and patient's preferences
- Optimize rate control
- Consider a rhythm-control strategy (CV, AADs, ablation)

Comorbidities/ Cardiovascular risk factor management

- Manage risk factors
- Lifestyle changes (obesity reduction, regular exercise, reduction of alcohol use, etc.)

6.3. Arrhythmia—Atrial Fibrillation (AF)

Risk	Therapy-related factors	Patient-related factors
Low	• No therapy with known AF risk	• Age <50 y • No CVRF
Medium	• ***Androgen deprivation tx**:* Abiraterone • ***Alkylating Agent(A)**:* Cisplatin, Melphalan, Cyclophosphamide, Ifosfamide, Dacarbazine • ***Anthracyclines**:* Dauno-, Ida-, Adriamycin • ***Antibody:*** Obinutuzumab, Rituximab • ***Antimetabolites**:* Azacitidine, Clofarabine, 5-FU, Leucovorin • ***Checkpoint inhibitors (I)**:* Ipilimumab • ***Proteasome I and Immunomodulating** A:* Bortezombib, Lena- , Pomalidomide • ***Taxane:*** Docetaxel, Paclitaxel, Gemcitabine • ***TKIs:*** Ponatinib, Cetuximab, Crizotinib, Sunitinib, Sorafenib, Nilotinib, Midostaurin	• Age 50–64y • 1–2 CVRF (HTN, dyslipidemia, obesity, smoking, diabetes) • OSAS • Inflammatory disease • COPD • Acute illness, surgery • Alcohol consumption • Post-stroke pts
High	• **Ibrutinib** (see page 35)	• Age >65 y • >2 CVRF (HTN, dyslipidemia, obesity, smoking, diabetes) • History of supraventricular arrhythmia • Pre-existing CV disease: CAD, PAD, CMP, at least moderate VHD, HFrEF and HFpEF • Reduced or low-normal LVEF (50–54% pretreatment)

Proposed surveillance algorithm for pts with AF or at risk for AF during Cx therapy

Prior to Cx

Low | **Medium** | **High**

General Risk Assessment for all pts
- Additionally: ask for alcohol, thyroid pathology, anemia, OSAS
- Baseline 12-lead ECG
- BP, when indicated 24-BP

Consider additional testing:
- **Echo**, if HF-symptoms
- **Holter-ECG-Monitoring**

Pt information and education about:
- The significance and treatment implications of detecting AF
- The use of various AF screening tools for AF detection: taking pulse or using health apps

During Cx

Low

Usually no specific FUP required

Respectively on demand

Medium | **High**

1. FUP after 3–6 Months and thereafter upon symptoms OR suspicious findings at clinical assessment
- 12-lead ECG
- Consider 24h-Holter-ECG in symptomatic pts or pts with elevated CHA_2DS_2-VASc Score [>1 (♂), >2 (♀)]
- Attention to good BP control

Documented AF at any time (conventional 12-lead ECG or 30-s ECG recording):

Approach with AF under Cx
- Evaluate AF-related symptoms, assess CHA_2DS_2-VASc/bleeding risk-score
- Consider acute trigger of AF and predisposing factors

→

- **Continue Cx if possible!**
- **Procedure in respect of GL AF 2020** with integrated ABC pathway and interdisciplinary approach (see next pages)

6.3 AF—The ABC Approach

'A' Anticoagulation/avoiding stroke

Managing Anticoagulation (AC): active cancer or Cx is NO contraindication but often involves special issues and considerations

Other indications for anticoagulation (AC):
- Due to VHD (valve prosthesis, moderate/severe mitral stenosis)
- Or other CVD (e.g. antiphospholipid syndrome)

Yes → (VKA), heparin

No

CHA_2DS_2-VASc* <1 (♂), <2 (♀)

Yes → No anticoagulation for AF (**)

* Note: score has not been validated in cancer pts

**BUT consider AC in pts with high embolic risk (pancreatic, lung or ovarian tumor) or on Tx with prothrombotics (Gemcitabine, 5-FU, Cisplatin, EPO, CSF)

No

CHA_2DS_2 – VASc*	CHA_2DS_2 – VASc*
= 1 (♂), = 2 (♀)	**>1(♂), >2 (♀)**
AC (Class IIA)	AC (Class IA)

Absolute contraindications to AC:
- According GL: Platelet Count <50 × 10^9
- Active bleeding
- Recent high-risk bleeding event (e.g. intracranial)

Yes → **Careful assessment of the risk–benefit-ratio**
- Cerebral imaging may help in pts w/ intracranial tumor
- Short-term thrombosis risk may be low, based on results in non-bridging arms of perioperative bridging studies
- Consider non-drug options

No

Bleeding risk Assessment:
- HAS-BLED score
- Cancer-related risk (***)
- History of cancer-related bleeding

Yes →
- Focus on modifiable bleeding RF
- Consider more fequently FUP or rare "off-label" DOAC dose reduction
- Consider non-drug options (LAA-C)

*** Intracranial Tumor, Cx interaction, non-compliance, coagulopathy, thrombocytopenia, anemia

No

- **DDI**? http:// www.cancer-druginteractions.com
- Patient preference?

Yes →
- VKA, with high time in therapeutic range, increased monitoring (self-management of VKA?)
- Heparin?

DOAC

'B' Better symptom control

Rate versus rhythm control in Pts with active cancer and AF

In general: similar to non-cancer pts, the decision is multifactorial, based on hemodynamic stability, chronicity, persistence of a potential trigger, symptoms, presence or absence of cardiomyopathy and heart failure and patient preference.

Prefer rate control strategy (target HR<110bpm), if:
- The active Cx causing AF is continued
- Advanced disease and palliative care, frailty

(BBs: first-line pharmacological class (no relevant DDI with Cx), particularly Atenolol and Nebivolol)

Prefer rhythm control strategy if:
- Pts remain symptomatic
- OR in case of hemodynamic instability
- Younger pts without structural disease
- AF secondary to correctable causes

Potential DDI and QTc prolongation must kept in mind

6.3 AF—Ibrutinib (IB)-Associated AF

Keypoints:

- AF in IB-treated pts is higher than in non-IB-treated pts and the normal population (incidence is about 4–16%). The management and treatment of AF in these pts implies a unique challenge.
- IB shows drug interactions with rate/rhythm controlling and anticoagulation agents. And there is a concern for bleeding, related to interference with platelet function and aggregation by IB itself. Disease-associated platelet defects and thrombocytopenia also play a role. Mostly low-grade bleeding AEs are observed (epistaxis, bruising). But potential simultaneous risk/occurrence of contrasting AEs such as CNS ischemic/hemorrhagic disorders must be kept in mind.
- IB has also been shown to increase bp (incidence of 78%), ventricular arrhythmias, HF and conduction disorder.

Proposed surveillance algorithm for pts on Ibrutinib

Prior to Cx

Special considerations:
- General baseline assessment
- Focus on ECG and blood pressure control
- Echo, if no recent work-up <6 mths

Medication history:
- Check DDI (P-gp / CYP450), http://medicine.iupui.edu/clinpharm/ddis/
- Evaluate pre-existing cardiac medication

Pt information/education about
- General recommendations
- Avoid: grapefruit, bitter oranges, NSAIDs, fish oils, vit E, polypharmacy, St. John's wort (*Johanniskraut*)
- Home BP monitoring

→
- Nondihydropidine **CCB** (Diltiazem and Verapamil): CYP3A4 inhibitory effect causes increased levels of Ibrutinib and resultant exacerbation of AF and bleeding, consider IB-dose ↓
- **Digoxin**: adjust Digoxin dose (↓) OR shifted intake (either 6 h prior to or after IB), frequent monitoring of digoxin levels
- **Amiodaron**, risk of IB-associated AE ↑
- **Antiplatelet therapy**: stop in case of primary prophylaxis OR reevaluate pts with low CV risk
- **Pts already under AC**:
  - Prefer FXa Inhibitor OR VKA with frequent monitoring
  - Avoid Dabigatran

During Cx

FUP every 3 mths for the first year, after that FUP every 6 mths **(or upon symptoms):**
- BP
- 12-lead ECG
- Symptoms like palpitations, dyspnoea, fatigue, effort intolerance (…)

→ Repeated **ECG-Monitoring** esp. in pts w/-elevated CHA_2DS_2-VASc Score (even if asymptomatic), otherwise choose additional testing modalities based on the clinical scenarios

Documented AF at any time (conventional 12-lead ECG or 30-s ECG recording):

Further Approach:
- Consider contributing causes
  - TSH
  - Structural disease (TTE)
  - Sleep study if appropriate
  - C2
- Evaluate
  - Need for anticoagulation
  - Rate control and symptom burden

→ **Continue or restart IB whenever possible**

→ **A: Avoid stroke**
- Evaluation stroke-/bleeding risk:

=> Consider AC if indicated by ESC guidelines
- Prefer FXa Inhibitor OR VKA with frequently monitoring
- Avoid Dabigatran

→ **B: Better symptom control**
- Prefer rate over rhythm control
- *BB* = first choice (safe)
  Avoid drugs that interact with IB (see above**)
- If needed add *Digoxin* OR add *CCB*: dose of IB should be reduced (discussion with hematologist)

NOTE Special situation: perioperative setting
- IB should be held for 3–7d prior to surgical procedures (depending on bleeding risk), restart 1–3 d post-op, holding IB alone means the antiplatelet effects should be partially reversed after 2.5 days
- low-bleeding-risk procedure: no IB-interruption necessary
- urgent/unplanned procedures: platelet transfusion, goal >50% fresh platelets might be considered

6.3 AF—'A': Anticoagulation

Agent		Dose-reduction criteria	Specifics	
DOACs	Rivaroxaban 1 x 20 mg/d	1 x 15 mg/d in pts with: – GFR 15 - 49 ml/Min – Concomitant use of P-gp and CYP3A4-inhibitors	DOACs: – Always consider DDI, e.g. http://www.cancer-druginteractions.com – Avoid if GFR <15ml/Min – measuring DOAC plasma level (only) recommended in rare situations (contact coagulation expert)	- Avoid concomitant use of Riboclib (if used at 600mg/d), Enzalutamide
	Apixaban 2 x 5 mg/d	2 x 2,5 mg/d in pts with: - ≥2 of 3 criteria: age ≥80y, weight ≤60kg, S-Creat ≥ 1.5 mg/dl (133 µmol/l) - concomitant use of P-gp and CYP3A4-inhibitors		- Avoid concomitant use of Riboclib (if used at 600mg/d), Idelalisib, Enzalutamide - Favored in pts with high risk for GI bleeding
	Edoxaban 1 x 60 mg/d	1 x 30 mg/d for pts with: - GFR 15 - 50ml/Min - Body weight <60kg or - concomitant use of P-gp inhibitors or inducers (e.g. Verapamil, Quinidine, Dronedarone)		
	Dabigatran 2 x 150 mg/d	2 x 110mg/d for pts with: - Age ≥80 y - Concomitant use of P-gp inhibitors, e.g. Verapamil - Avoid in pts with GFR <30 ml/Min.		Avoid with Ibrutinib, Ciclosporin, tacrolimus
LMWH 2x 1mg/kg KG/d			Alternative, e.g. pts who are unable to tolerate oral administration (nausea, vomiting), short-term treatment or in specific settings	
VKA INR goal 2–3		A target INR of 2.0–3.0 is recommended, with individual TTR ≥70%	Alternative, if either DOACs or LMWHs are not feasible	

6.3 QT-Interval Prolongation/Risk For TdP

QT-Interval Keypoints:

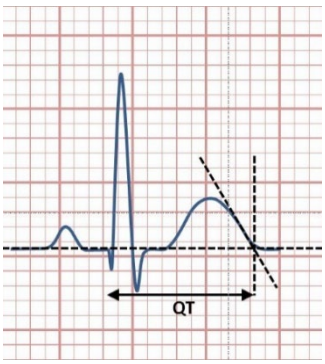
- Some cancer treatment drugs cause abnormalities in ventricular de- and repolarization resulting in QT prolongation
- The QT interval is inversely proportional to the heart rate (HR). Regardless of sex, a QT interval of >500 ms is considered abnormal and is associated with an increased risk of ventricular arrhythmia (torsade de pointes, TdP) and reports of SCD.
- The corrected QT interval (QTc) estimates the QT interval at a standard HR of 60 bpm. The Bazett formula (QTcB = QT/√RR) is most commonly used. The Fridericia formula (QTcF QT/ 3√ RR) might be more accurate at slower and faster HRs. Always use the same formula!
- The degree of prolonged QTc doesn't correlate with the incidence of TdP and SCD. Their reported incidence is very small.

How to measure the QT-Interval:

- Standard 12-lead-ECG: use leads II or V5-V6 OR the lane where the T-wave is best seen and can be seperated from the isoeletric line (picture).
- The end of the T wave is the intersection of a tangent to the steepest slope of the last limb of the T wave and the isoeletric line.
- Large U waves (>1mm, fused to the T wave) should be included in the measurement; smaller and separated U waves should be excluded.

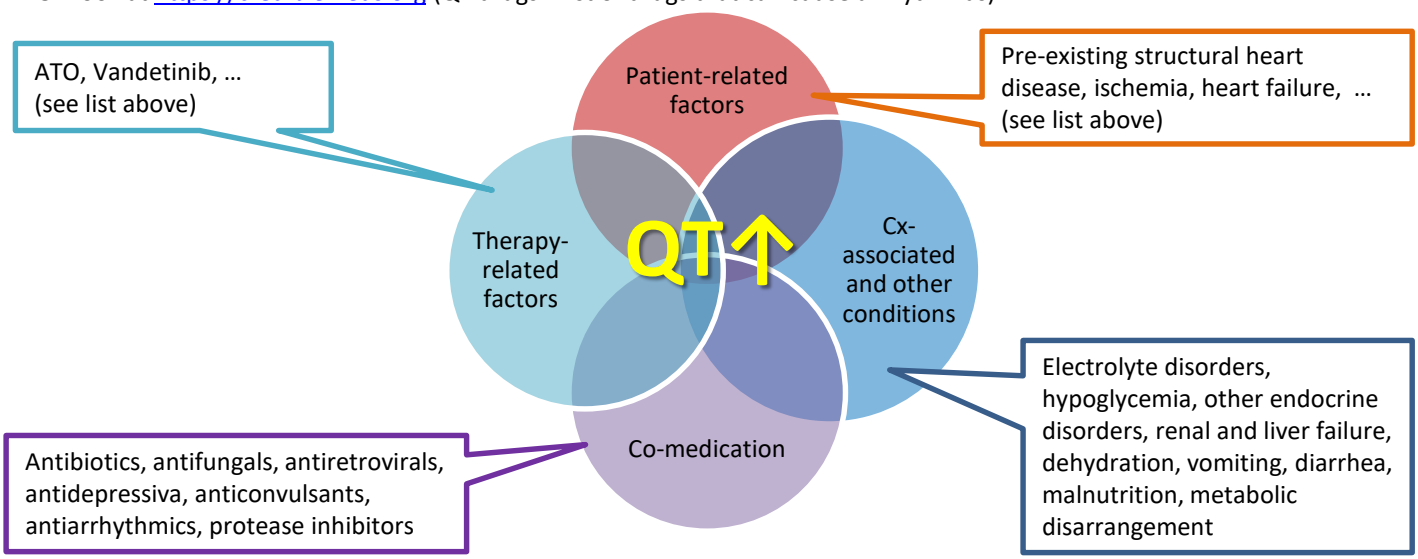
In pts with:

- **AF**: normal QT-Interval is assumed if R peak-T wave <50% of the corresponding R-R-Interval OR average the QT interval associated with the longest and shortest RR interval
- **Wide QRS**: pragmatic cut-off QTc >550 ms (#) OR use adjusted QTc-formula with QTc = QTc—QRS duration + 90 ms (same QTc-thresholds valid as in pts. w/o wide QRS)



Risk	Therapy-related factors	Patient-related factors
Low	• No medications which ↑QT	• No family history of SCD • No unexplained syncope • Known normal QTc in the past
Medium*	• **Antimetabolites:** Capecitabine • **Anthracyclines**: Epirubicin • **Antimicrotubule** agents: Paclitaxel • **TKI:** Bosutinib, Dasatinib, Lenvatinib, Nilotinib, Ponatinib, Pazopanib, Sorafenib/sunitinib • **Histone deacetylase inhibitors**: Panobinostat, Romidepsin, Vorinostat • **Proteasome inhibitors**: Bortezomib • **CDK 4/6 inhibitor**: Ribociclib • **B-Raf inhibitor:** Vemurafenib • **Androgen-deprivation therapy**: LHRH agonists (Goserelin, Leuprolide); LHRH antagonists (Degarelix); androgen inhibitors (Enzalutamide, Abiraterone)	• Female sex • Electrolyte-disorder • Bradycardia <50bpm, AF, heart failure • QTc >480 and ≤500 ms (regardless of sex) • Organ impairment: liver, kidney, sepsis, hypothyroidism, diarrhea, nausea and vomiting • Family history of SCD
High	• Vandetanib • Arsenic trioxide (ATO)	• QTc >500 (#) (regardless of sex) • LQTS OR history of TdP

*OR look at https://crediblemeds.org (QT drugs—list of drugs that can cause arrhythmias)



6.3 QT-Interval Prolongation/Risk For TdP

Algorithm in pts with active cancer under QT-interval-prolonging Cx

Prior to Cx

General Risk Assessment for all pts undergoing potential QT-prolonging drug therapy

- Patient history, medication history (check DDI), stopp unnecessary QT-prolonging drugs
- Baseline standard 12-lead ECG
- Assess renal and liver function, electrolytes: Ca++, Mg++, K+ (usually checked by oncologists in planning Cx)

Low	Medium		High	
QTc ≤480	QTc ≤480	QTc >480 and ≤500 (#)	QTc ≤500 (#)	QTc >500 (#)
	• Correct Ca++, Mg++, K+ • **Pt information/education about** worrisome cardiac signs/symptoms (e.g. syncope, dizzyness, rapid palpitations (*))			# 550 ms with intraventricular conduction delay
Start Cx	**Start Cx**	Re-Check ECG: QTc >480 and ≤500 (#) **Start Cx**	Recheck ECG: QTc ≤500 (#) **Start Cx**	Recheck ECG: QTc >500 (#) **Risk–benefit evaluation, consider alternative Cx** with oncologists

During Cx

Low	Medium	High
Usually no ECG FUP required during Cx	**FUP in week 1 and 2** • Recheck ECG / QTc • signs/symptoms (*)? • Assess electrolytes • Check co-medication	• Recheck ECG/QTc weekly • Ask for signs/symptoms (*) • Assess electrolytes • Check co-medication

ECG: QTc ≤480 no signs/symptoms **Continue Cx**	QTc >480, ≤500 ms (#) no signs/symptoms **Continue Cx**
Further FUP • mthly. during mth 1-3 OR after each cycle • After that q.3 mths	**Further FUP** • individualized, e.g. every 2 to 4 wks

If any of the following: new QTc >500 ms (#) OR QTc increased by ≥60 ms from baseline a/o signs/symptoms

Checklist:

- Pause Cx
- Optimize concomitant circumstances: co-medication? Correct electrolytes
- Discuss Holter ECG vs telemetry, prefer the latter if QT↑ PLUS symptoms (*) OR worrisome ECG-signs such as beat-to-beat-instability, frequent VES
- Further diagnostic if indicated (e.g. Echo)

Follow closely until QTc is corrected
Consider daily ECG for QTc

Resume Cx (maybe in reduced dose) if:	**Risk–benefit evaluation, if** persistent QTc >500 (#): Consider:
• QTc ≤500ms • NO signs/symptoms • NO electrolyte imbalance	• **Alternative Cx** with oncology colleagues • **Defintitely stop Cx** if symptoms clearly induced by Cx

After Cx

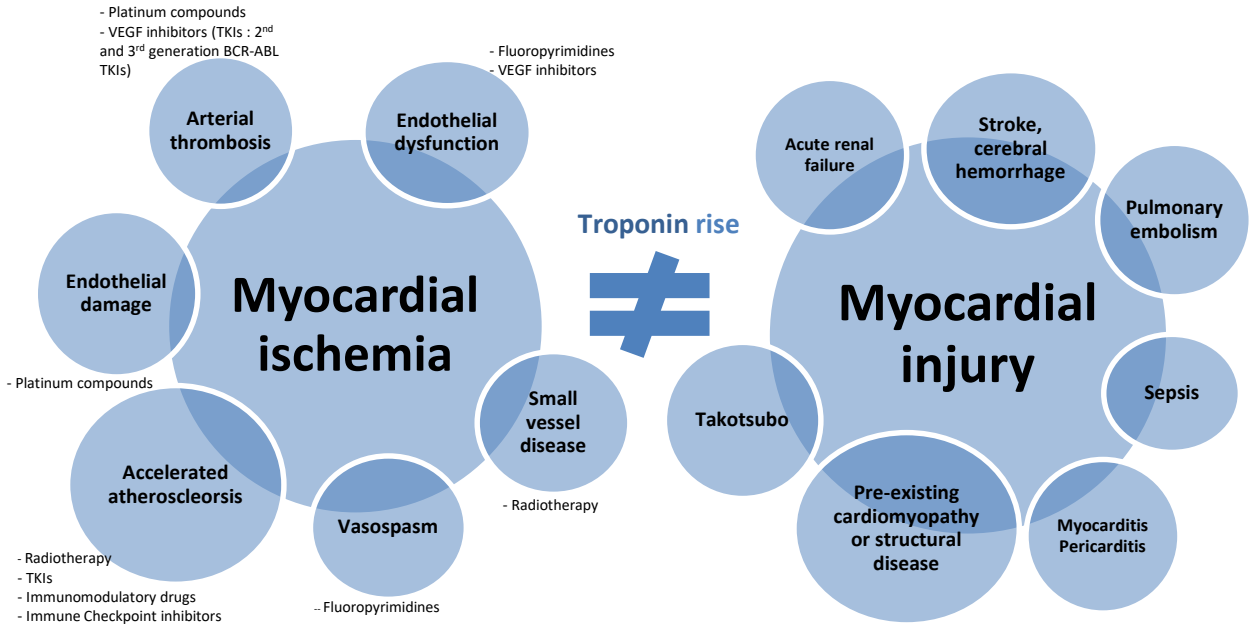
Usually no special checks necessary

6.4 Myocardial Ischemia During Cancer Treatment

Key points
- Myocardial ischemia should be distinguished from myocardial injury.
- Mechanisms involved in theses 2 separate entities are different and should be identified in order to guide specific management.

Definitions
- Myocardial injury is present when blood levels of cardiac troponin (cTn) are increased above the 99th percentile upper reference limit (ULN) – in the absence of peripheral myositis or peripheral myocyte damage
- Myocardial ischemia is defined as a mismatch between oxygen consumption and oxygen delivery to the myocardium.
- Prolonged myocardial ischemia may lead to myocardial infarction (myocardial necrosis of ischemic origin)

Mechanisms involved in myocardial ischemia and in myocardial injury in a cancer patient



NB: In clinical practice, multiple mechanisms of myocardial ischemia and/or myocardial injury can be involved in the same patient. For example, stress cardiomyopathy might overlap with myocardial injury and diffuse vasospasm

Causes of myocardial ischemia during cancer treatment which are unrelated to vascular wall anomalies		
Anemia Hypoxemia Hypotension/shock	Acute heart failure Tachy/bradyarrythmias Respiratory failure	Severe hypertension Sepsis

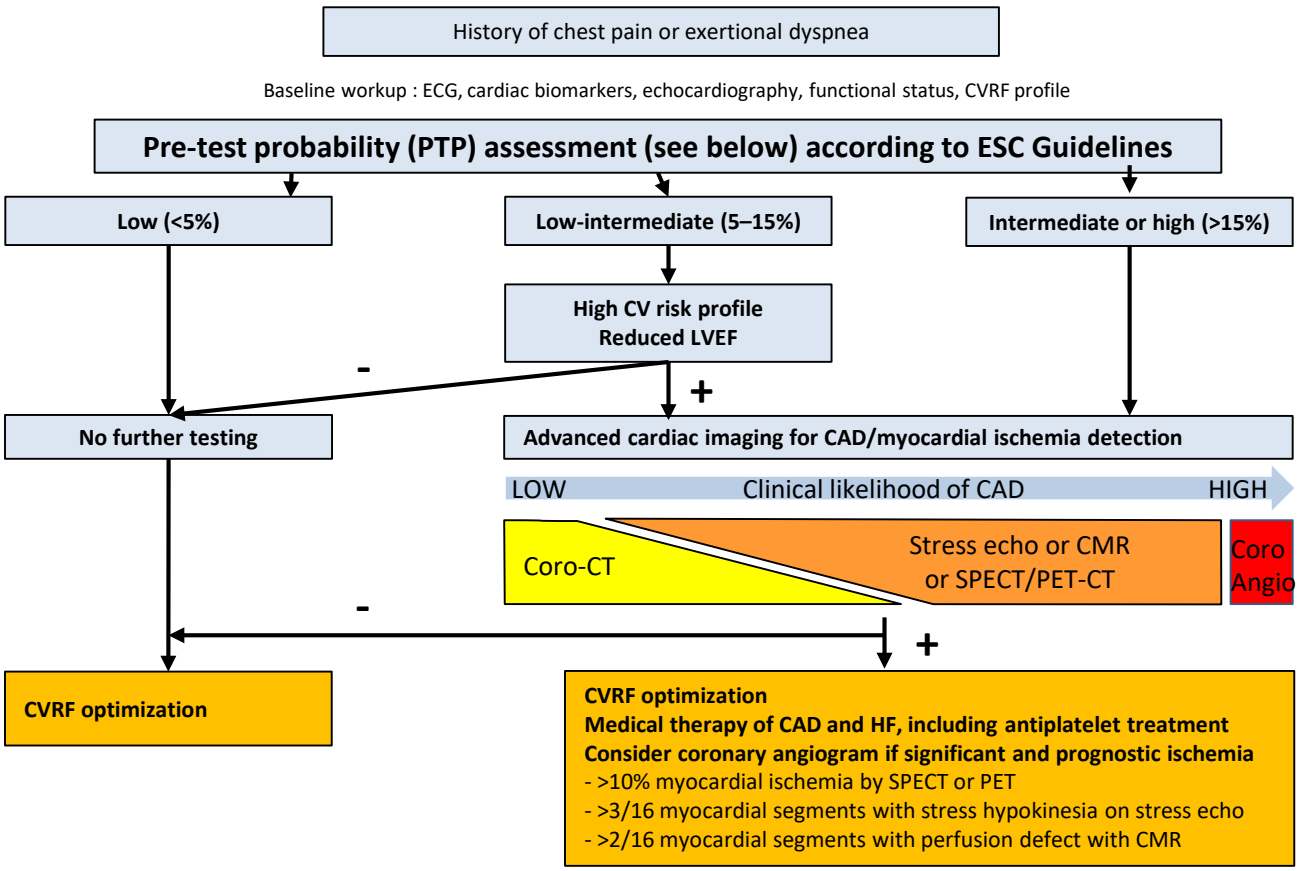
Clinical manifestations of myocardial ischemia and/or infarction :
- Symptoms : chest pain, palpitations, syncope, dyspnea (as an angina equivalent)
- New ECG changes : ventricular arrhythmias, ST segment and T wave changes, Q waves
- Dynamics in cardiac biomarkers (mainly troponin)
- New segmental wall motion abnormalities, LV dilatation

6.4 Ischemia Detection in Patients Requiring Cancer Treatment

Key points

- Newly diagnosed cancer patients with angina-related symptoms or heart failure should be screened for pre-existing CAD before cancer treatment including cancer surgery..
- CAD risk stratification should guide intensity of workup before cancer treatment.
- CAD risk stratification may identify pts at risk of an acute coronary event during cancer therapy.
- After cancer treatment, CAD risk should be re-evaluated considering not only patient-related factors but also therapy-related factors (see survivorship section and patient-centered measurements).

Ischemia detection in patients with angina or dyspnea before cancer treatment



Other specific indications for ischemia detection in oncology patients

1. Patients at high CV risk **before administration of drugs known to cause cardiac ischemia** (e.g. 5FU, Capecitabine, Bevacizumab, Nilotinib, Ponatinib)
2. Patients at high CV risk with poor functional status undergoing **high-risk surgery** (e.g. lung resection)
3. Screening for significant CAD **5–10 y after chest radiation therapy**

Pretest probability of CAD according to symptoms, age and gender

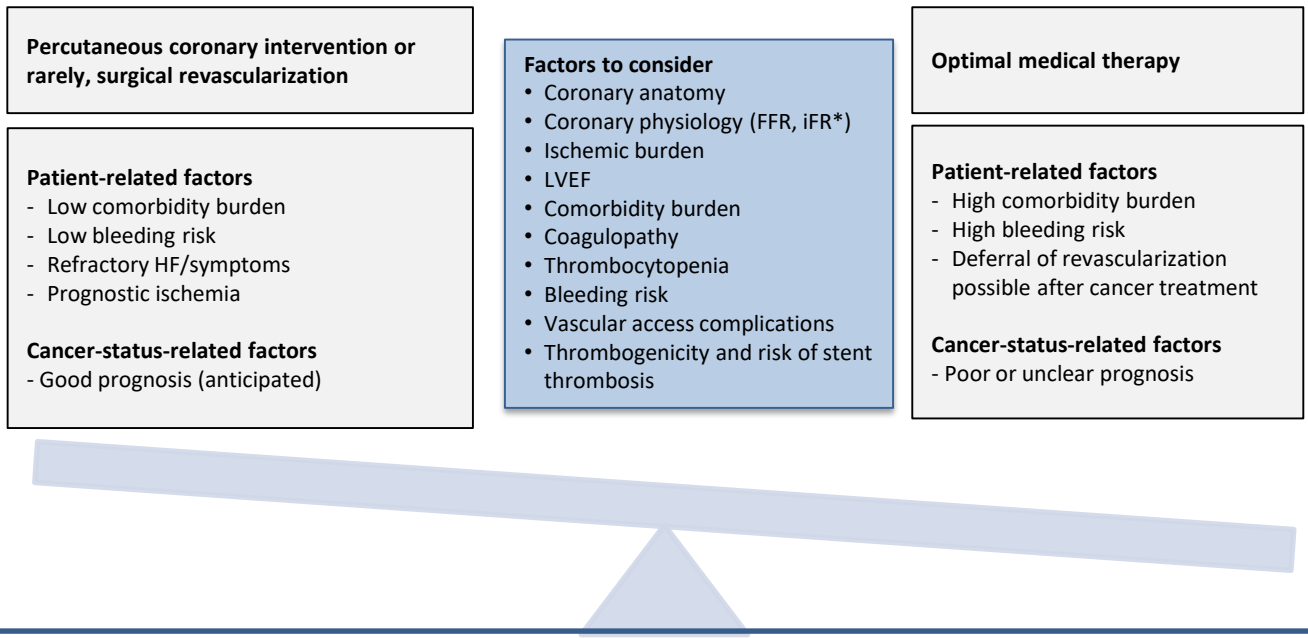
	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

6.4 Coronary Angiography And Coronary Revascularization Strategies in a Cancer Patient

Key points

- Invasive coronary investigation and coronary revascularization may induce considerable delay and increase the risk of prolonged interruption in the cancer treatment plan.
- The evaluation of the risk–benefit ratio of coronary interventions in a patient undergoing active oncological therapies should be done in a multidisciplinary manner (by a cardio-oncology team).
- Optimal medical treatment of CAD or deferral of CAD revascularization after Cx must be favored or even discussed if invasive revascularization options would result in delayed Cx.
- Choice of procedural and invasive strategies should aim to minimize impact on cancer treatment plan (e.g. choice of vascular access site, micro puncture technique, choice of type and length of stent, etc.).

Factors favoring revascularization of CAD vs medical treatment to be considered during multidisciplinary team discussion: cardio-oncology and heart teams



*FFR = Fractional Flow Reserve, iFR = Instantaneous wave-free ratio

Scenarios in which coronary angiography in a patient before/during active cancer treatment might be needed

Scenario	Comment
Acute myocardial infarction with ST segment elevation (STEMI)	Coronary angiography mandatory (potentially lifesaving). Consider intracoronary imaging study in case of absence of obstructive CAD to rule out a primary thrombotic event)
Acute myocardial infarction without ST segment elevation (NSTEMI)	High-risk features: heart failure related to ischemia, ventricular arrhythmias, refractory symptoms to optimal medical treatment
Severe and prognostic ischemia on a functional imaging test	After discussion with cardio-oncology team
Pre-op workup before surgical treatment of severe symptomatic valvular disease	Heart and cardio-oncology team discussion

6.4 Acute coronary syndrome (ACS) during cancer treatment

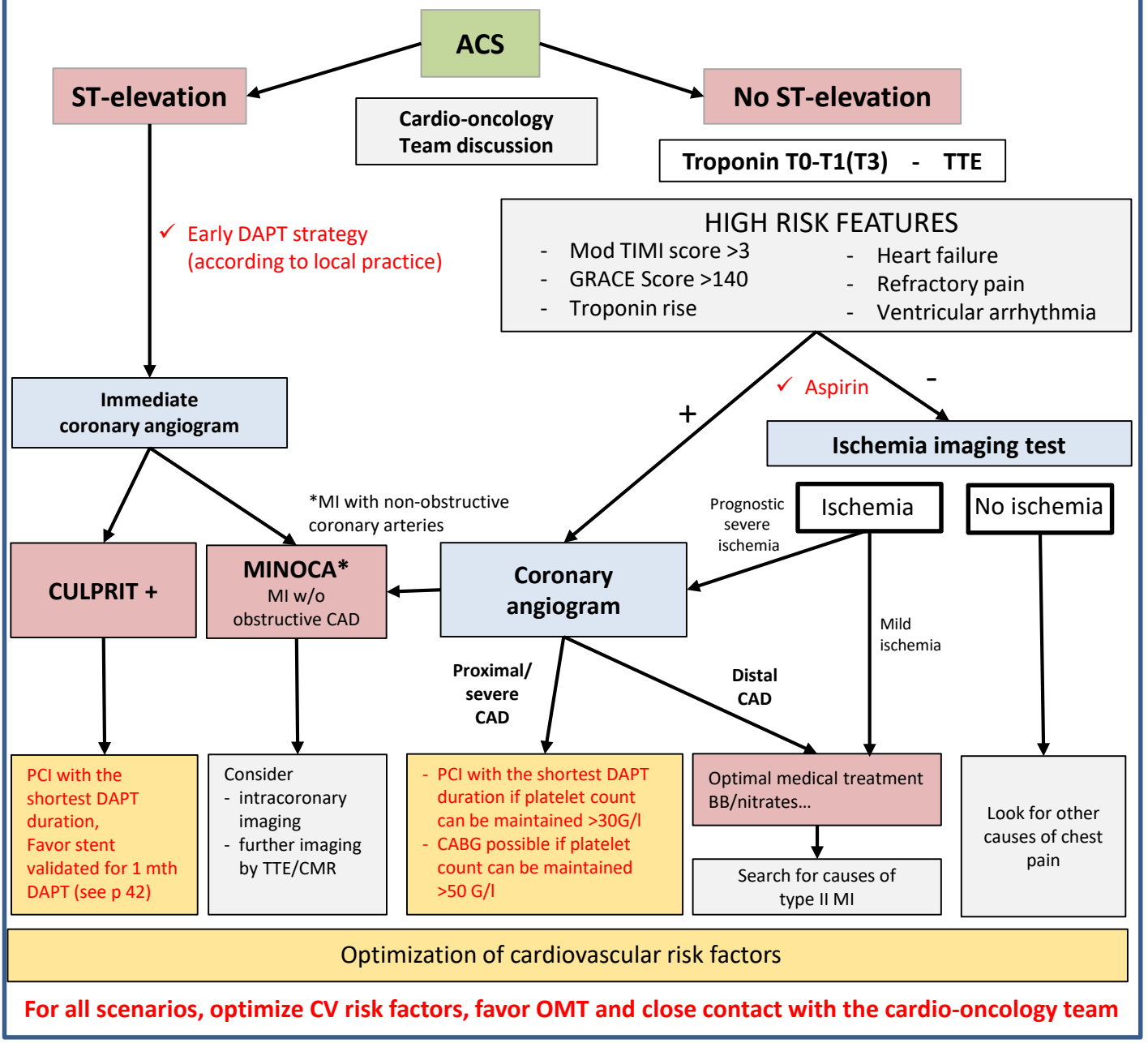
Key points

- Cancer patients undergoing active oncological therapies, with or without pre-existing CAD, are at increased risk of developing an ACS during cancer therapy.
- Mechanisms involved in this increased risk include not only the traditional CV risk factors, but also the increased pro-inflammatory state, therapy related factors, physical and psychological stressors.
- Prompt intervention for risk factor modification, early disease identification and early therapeutic intervention (with an emphasis on medical management) will improve prognosis.
- The cardio-oncologist has an essential role in coordinating intervention strategies in order to minimize disruption of the cancer treatment plan.

Antineoplastic agents associated with CAD and acute coronary events during cancer therapy

- **Antimetabolites** (5FU, Capecitabine)
- **Anitmicrotubules** (Paclitaxel, Docetaxel)
- **Monoclonal antibodies-based TKIs** (Bevacizumab)
- **Small molecule TKIs** (Erlotinib, Sorafenib, Sunitinib)
- **Nucleoside analogs** (Gemcitabine)
- **BCR-ABL targeted TKIs** (Nilotinib, Ponatinib)
- **Platinum compounds** (Cisplatin)

Proposed algorithm in case of ACS during cancer therapy



For all scenarios, optimize CV risk factors, favor OMT and close contact with the cardio-oncology team

6.4 Myocardial Ischemia: Fluoropyrimidines (Fluorouracil, Capecitabine)

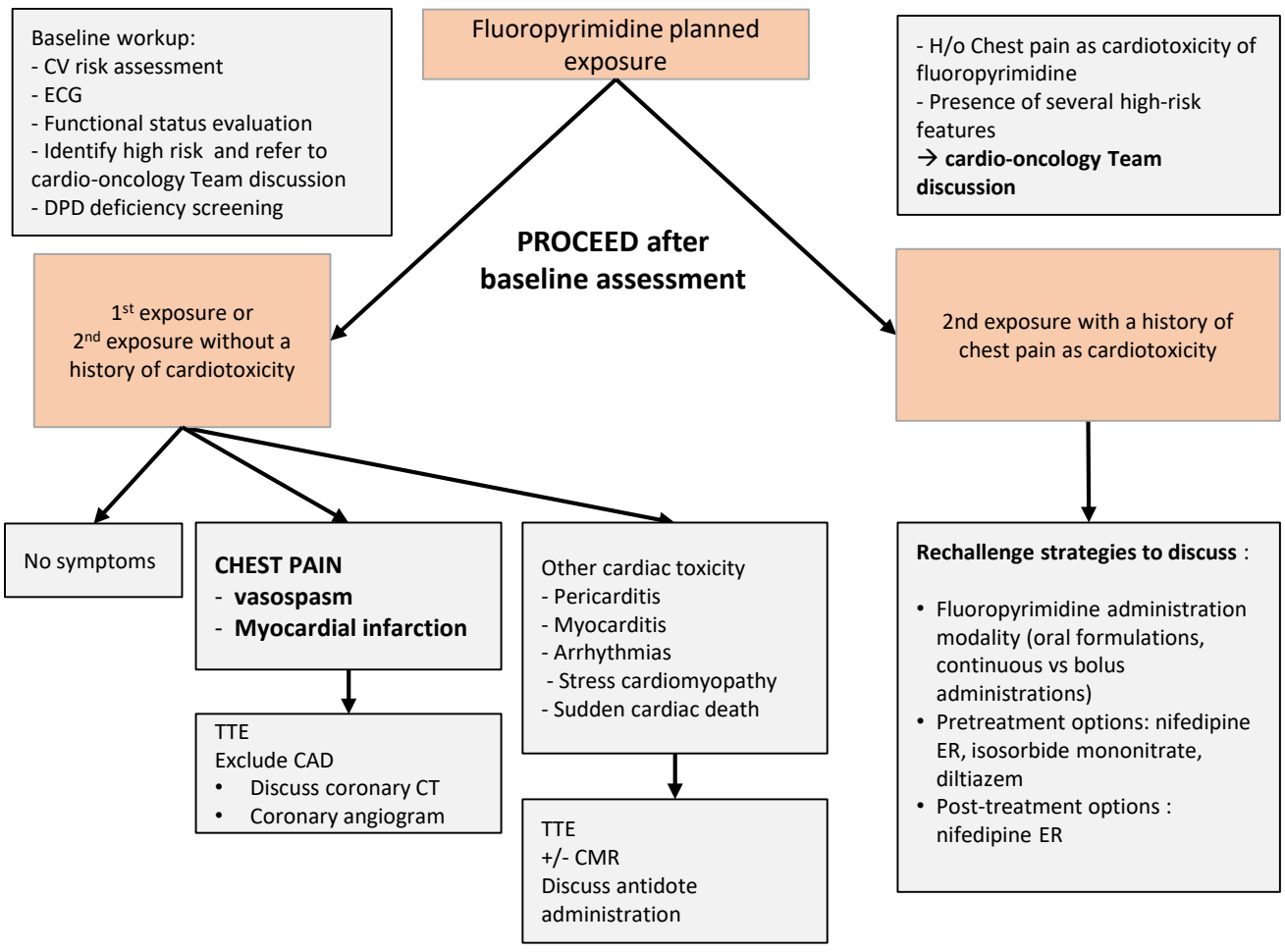
Key points

- Patients at presumed higher risk for fluoropyrimidine cardio-toxicity should be referred to cardio-oncology for optimization of medical treatment., and to establish a follow up strategy during and after cancer treatment.
- In the absence of an alternative cancer treatment with at least similar efficacy and impact on survival, pts with a history of fluoropyrimidine cardiac toxicity should be evaluated for the possibility of rechallenge.
- In selected pts with overt and/or life-threatening toxicities, administration of an antidote (uridine triacetate) might be useful. Screening for DPD deficiency in such pts may be considered.

Risk factors associated with fluoropyrimidine cardiotoxicity

Risk	Therapy - related factors	Patient - related factors
Low or Medium	• Short iv and/or low dose bolus • Short term infusion regimens • Topical or intraperitoneal administration • Oral formulations such as capecitabine	• No history of cardiotoxicity • No risk factors for vasospastic disease
High	• Combination therapies with cisplatin /leucovorin / radiotherapy • Radio sensitization with fluoropyrimidines during external beam radiotherapy • Continuous long infusions (>5 days)	• Dihydropyrimidine dehydrogenase (DPD) deficiency (polymorphisms) • Prior fluoropyrimidine cardiotoxicity Factors to consider, despite lack of clear evidence: • Pre-existing CAD • History of vasospastic angina • Risk factors for arterial vasospasm such as smoking

Fluoropyrimidine cardiotoxicity : management and rechallenge strategies



For all scenarios, optimize CV risk factors, and close contact with the cardio-oncology team

6.4 DAPT and Thrombocytopenia

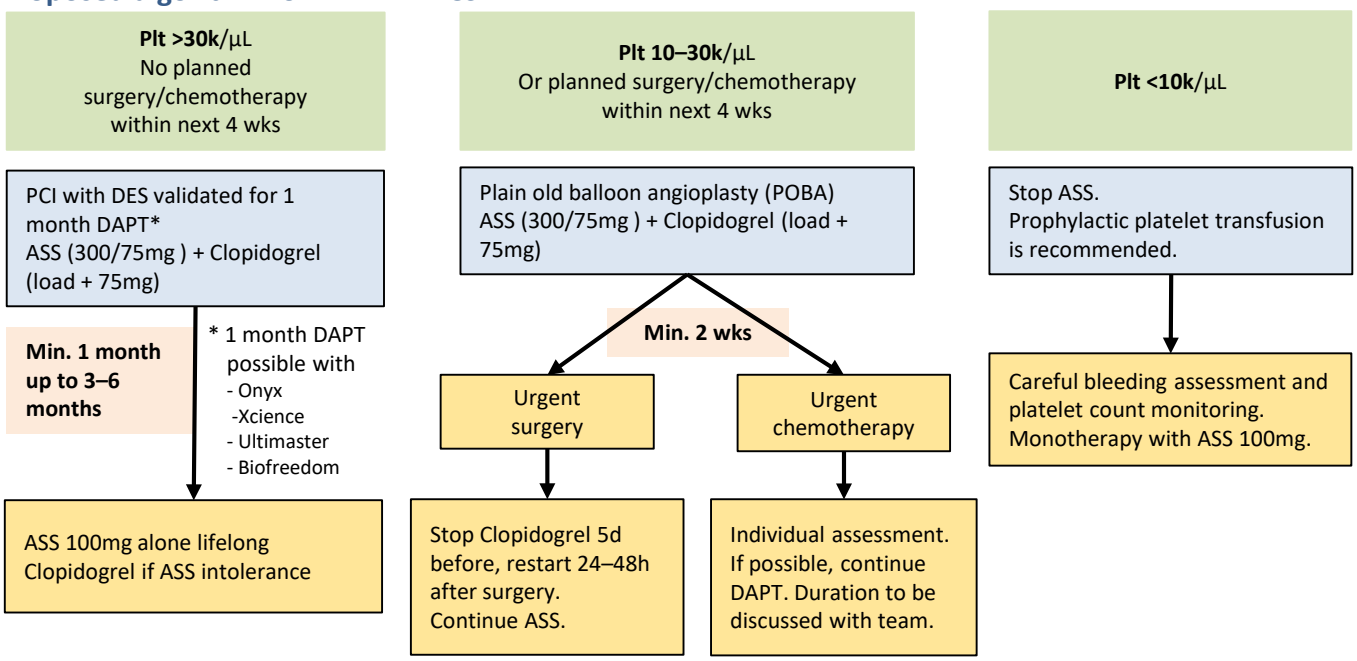
Key points

- Up to 15% of patients with ACS have concomitant cancer at various stages. Current guidelines for conservative and invasive treatment of ACS in this population are often not feasible.
- Up to 10–25% of cancer pts present with thrombocytopenia. Thrombocytopenia often coexists with thrombophilia.
- Several chemotherapies and radiation therapy are associated with an increased risk for ACS. On the other hand, cancer itself is related to a higher rate of reinfarction after PCI.
- Antiplatelet therapy should be individually tailored to the thrombotic and bleeding risks after considering the overall prognosis of the patient. Prefer transradial approach to heart catheterisation whenever possible.
- DAPT and its duration should be individualized based on bleeding risks, lesion characteristics and general thrombotic risk. Cooperation with hematologists and interventional cardiologists is essential.

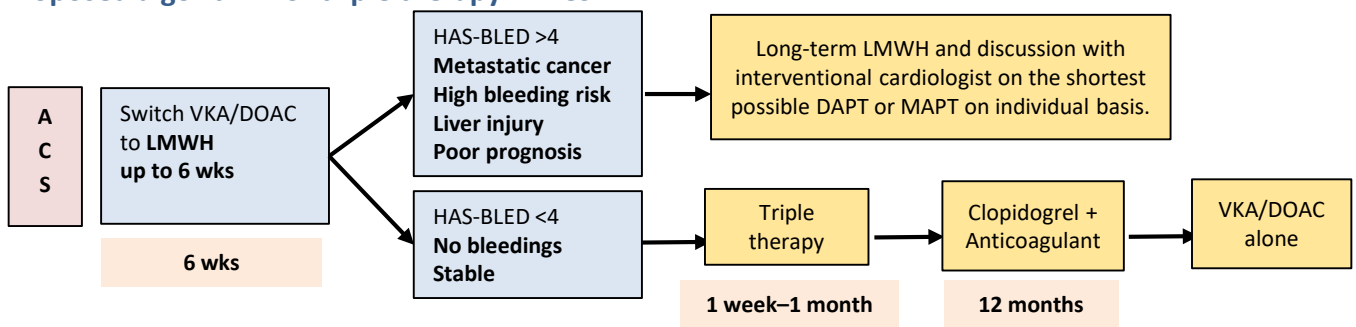
Thrombocytopenia

Platelet count	Suggestion
>50,000/µL	• All revascularization options and following DAPT are possible. • If conservative management is preferred: UFH dose of 50–70 U/kg and increase the dose if activated clotting time (ACT) <250s.
<50,000/µL	• Perform multidisciplinary evaluation and risk–benefit analysis. See schema below. • PCI is safer in absence of thrombotic disorders. Avoid Prasugrel, Ticagrelor and Glykoprotein (GP)-IIb/IIIa • Consider a short-DAPT regiment (4 wks, ASS alone thereafter). • If conservative management is preferred: UFH dose of 30–50 U/kg under ACT monitoring. Increase if ACT <250s. • In the presence of: platelet count <20,000/µL + high fever, leukocytosis, sudden decrease in platelet count, other coagulation disorders and/or active chemotherapy, a prophylactic platelet transfusion should be considered.

Proposed algorithm for DAPT in ACS



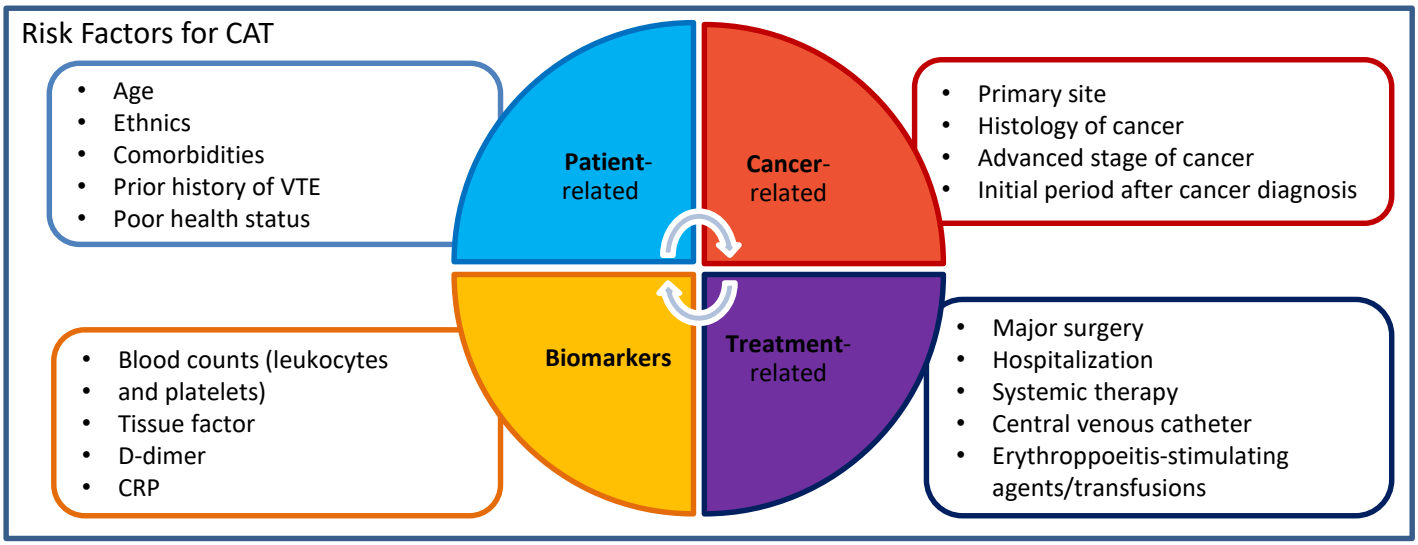
Proposed algorithm for triple therapy in ACS



6.5 Cancer-Associated Thrombosis (CAT)

Key points

- Cancer pts have a 4- to 7-fold increased risk of suffering a venous thromboembolism (VTE) and they also show a decisive risk for arterial thrombembolisms (ATE). Both VTE and ATE represent cancer-associated thrombosis (CAT) and are associated with worsened outcomes, hospitalization and mortality.
- Issues like the prevention and treatment of CAT mean that balancing the bleeding and thrombotic risks in cancer pts is always a unique clinical challenge.
- Upcoming data from randomized trials and real-world studies show the beneficial use of DOACs even in cancer pts, therefore different societies have adopted their guidelines and recommended management concerning CAT.



VTE Prevention – different clinical settings

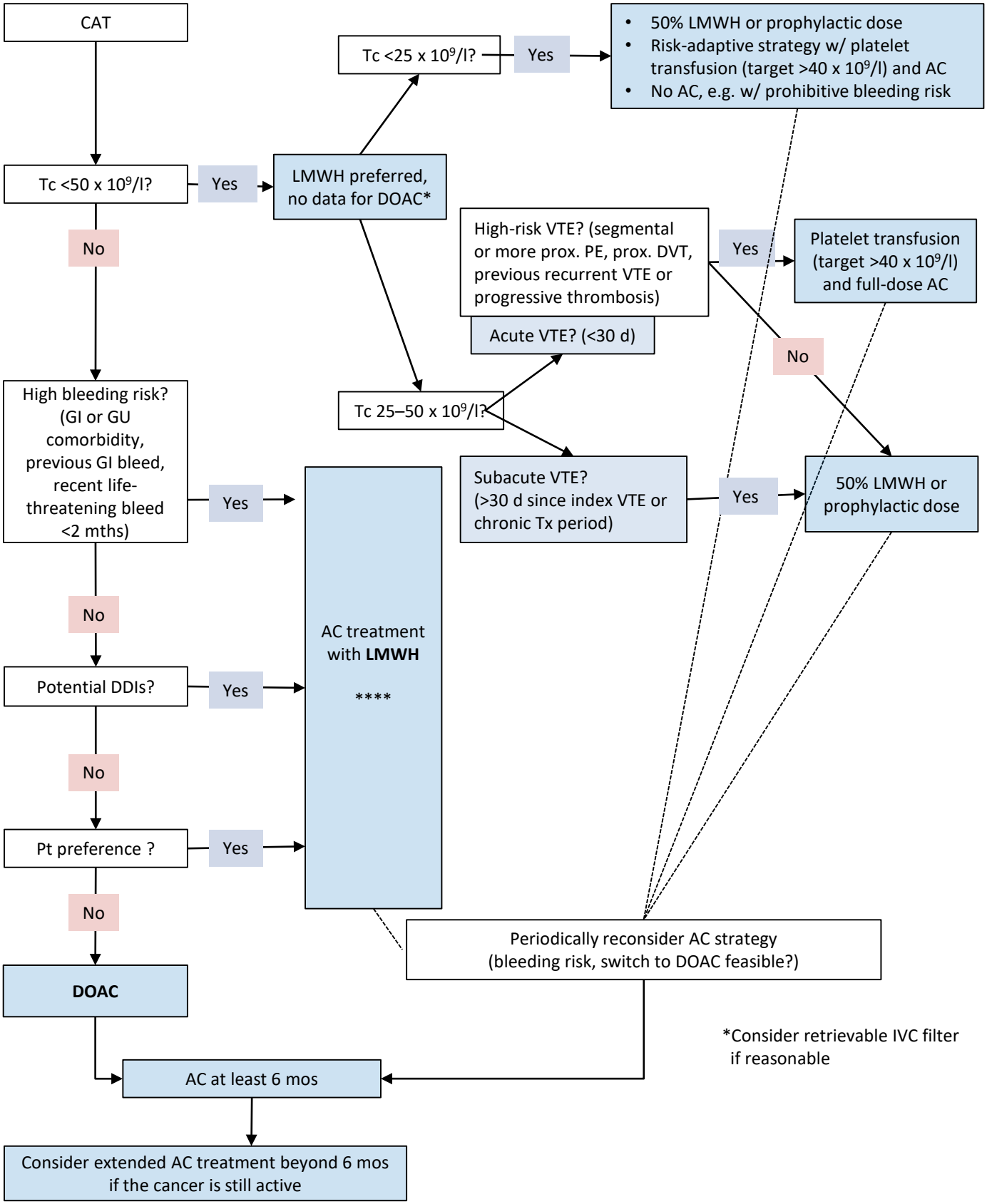
Outpatient Setting - NO routine prophylaxis, but risk-adapted - Duration: ≈ 12 wks after starting Cx	**Khorana risk stratification (in general)** Site of cancer – Stomach, pancreas – Lung lymphoma, gyn, bladder, testicular Pre-Cx platelet count ≥ 350 x 10^9/l Pre-Cx Hb <100 g/l or use of EPO Pre-Cx leucocyte count > 11 x 10^9/l BMI ≥ 35 kg/m^2	Score 2 1 1 1 1 1	Khorana Score ≥ 2 points AND low bleeding risk => Consider VTE prophylaxis with: - Apixaban: 2 x 2.5mg /d - Rivaroxaban: 1 x 10mg/d - LMWH
	Multiple myeloma - risk stratification: – Pt: age, history of VTE, obesity, inherited thrombophilia, comorbidities, immobility – Myeloma: disease burden, hyperviscosity – Therapy: Thalidomide, Lenalidomide, combined with Dexamethasone	Risk	Decision usually made by oncologist
		low	- Aspirin or LMWH
		high	- LMWH or VKA - DOAC if other indications
	CNS malignancy (high VTE risk assumed) (primary cancer or cerebral metastasis)	– LMWH or – DOAC e.g. Apixaban 2 x 2,5 mg/d	
	Central vein catheter	Not routinely	

Have in mind: before changing the patient's AC or platelet inhibitor therapy always consult the oncologist/oncology GL

Hospitalized Patients - Preferably use the internal hospital approach	**With major surgery:**	- Offer VTE-prophylaxis pre- and post-operatively - Continue for 7 to 10 days - Extended prophylaxis (for up to 4 wks) in pts w/- high-risk features (restricted mobility, obesity, history of VTE, others)
	Without major surgery	- Offer risk-adapted VTE-prophylaxis (pts w/- active cancer, acute illness or reduced mobility) - Not necessary in pts with minor procedures (chemotherapy infusion)
	Special situations	See the following pages

6.5 Anticoagulation in Cancer-Associated Thrombosis

Treatment algorithm for CAT—individualize treatment based on patient risk–benefit



NOTES

- Recommendation of an individualized treatment regimen concerning renal and liver function, feasibility due to problems of intake or absorption, patient's preference. Identify additional factors associated with higher bleeding risk, such as fever, hematocrit ≤25%, increasing bilirubin and prothrombin time or use of antithrombotic drugs.
- Regularly evaluate and reassess individual risk profiles during treatment and when considering extending treatment duration in all pts with CAT.

6.5 Anticoagulation in Cancer-Associated Thrombosis

Key point

- Although clinical practice GL for the treatment of CAT exist, recommendations for specific subgroups of pts (like the below) are limited and mostly refer to relatively small observational studies.
- The level of evidence should be considered weak for all, but these potential management suggestions could serve as helpful thoughts in daily practice.

VTE Treatment, specific clinical situations			Duration
SPECIAL SITUATIONS	Retrievable inferior vena cava (IVC) filters	Only in pts with: - Acute (<1 mth) proximal DVT or PE and absolute contraindications to AC (e.g. active bleeding, severe prolonged thrombocytopenia) - or: - as add-on therapy, VTE with progression (recurrent or extension) despite full-dose AC - as a combined regimen (pharmacologic + mechanical) in high-risk pts, perioperative, major surgery	- IVC should be removed as soon as AC can be resumed - Ideally, removal ≤30 d after insertion
	Renal impairment GFR ml/Min. 30–49	• Dabigatran: 2 x 150 mg or 110 mg/d * • Rivaroxaban: 2 x 15mg/d for 3 wks, then 1 x 20/d * • Edoxaban: 30 mg/d • Apixaban: 2 x 10 mg/d for 7 d, then 2 x 5 mg/d * consider reduced dose if bleeding risk is high	
	15–29	• Rivaroxaban: 2 x 15mg/d for 3 wks, then 1 x 20/d * • Edoxaban: 30mg/d • Apixaban: 2 x 10 mg/d for 7 d, then 2 x 5 mg/d • LMWH, monitoring anti-Xa-level 4–6 h after dose application * consider reduced dose if bleeding risk is high	
	<15	no LMWH, no DOAC recommended	
	VTE recurrence or progression under established AC	- Switch to alternative anticoagulant - Consider increase in dose: LMWH + 25%, check anti-FXa - Or: IVC filter as short-term add-on to full-dose AC	
	Cerebral lesions	DOAC or LMWH can be used (maybe with reduced dose) - Presence of prior intracranial bleeding?, pre-existing bleeding diathesis? - Appears safe, except for pts with untreated tumors such as melanoma, kidney, choriocarcinoma, thyroid or HCC.	
	Catheter-related thrombosis	- LMWH o. DOAC - Removal not mandatory (except: infected, improperly positioned, not functional or persistent symptoms under AC) - Catheter removal after 5–7d of anticoagulation	At least 3 mos, consider longer if catheter is still in situ
	Incidental VTE	• same Tx as for symptomatic PE, if: - Proximal DVT - Segmental PE - Multiple subsegmental vessels - Or single subsegmental pulmonary embolism in association with proven DVT (proximal or distal) • Splanchnic or visceral thrombosis: in favor of conventional VTE-Tx • Isolated distal DVT: in favor of conventional VTE-Tx • In case of decision against AC (for any reason or e.g. solely SSPE (w/o proven DVT) clinical FUP after 1 wk recommended, probably with an additional imaging test (ventilation scan, US …)	Consider long-term AC in pts with either a major persistent risk factor or unprovoked VTE
	Tc-penia >50 x 10^9/l	Full-dose AC	*no data
	Tc-penia <50 x 10^9/l no DOAC*	See diagram on previous page - Because of the higher risk of VTE recurrence during the acute phase (<30 days from the event), AC during that time is highly recommended.	Consider retrievable IVC filter (s.a.)
	Nausea	• LMWH recommended, if high risk of nausea/vomiting • If nausea/ vomiting occurs: - ≤2 h of DOAC administration, give dose-equivalent LMWH - >2h: no change or action necessary	

6.5 Anticoagulation in Cancer-Associated Thrombosis

Options for VTE Treatment

Anticoagulants	Dose	Specifics	Duration
Rivaroxaban	2 x 15mg/d for 3 wks, then 1 x 20/d		At least 6 months Consider extended AC treatment if the cancer is still active , e.g. not surgically removed, metastatic disease, hematological cancer not in complete remission or those receiving Cx.
Apixaban	2 x 10 mg/d for 7 d, then 2 x 5 mg/d	Reduced dose (50%) in pts with: - concomitant use of dual inhibitors of P-gp and CYP3A4	
Edoxaban	Start with LMWH or UFH for 5–10d, then 1 x 60 mg/d	1 x 30mg/d for pts with: - GFR 15 - 50ml/Min., - weight <60 kg or - concomitant use of P-gp inhibitors or inducers	
Dabigatran	Start with LMWH or UFH for 5–10d, then 2 x 150 mg/d	2 x 110mg/d for pts with: - GFR <50ml/Min - Or concomitant use of P-gp inhibitors	
LMWH	2 x 1mg/kg KG/d		
VKA	Start with LMWH or UFH, INR goal 2–3	Alternative if either DOACs or LMWHs are not feasible	

6.6. Myocarditis Associated With Immune Checkpoint Inhibitors

Key points

- Patients frequently present with unspecific symptoms. Increase in biomarkers, decline in LVEF, regional wall motion (WMA) abnormalities or ECG changes can all be missing and CMR is frequently normal.
- Consider ICI-myocarditis also in the absence of symptoms when other immune-related adverse events are present (in particular myositis or myasthenia gravis).
- Gold standard for diagnosis: endomyocardial biopsy, in particular when CMR is inconclusive (check risk–benefit).
- Depending on clinical presentation, ACS or other cardiovascular pathology need to be ruled out.

Definition of Myocarditis (proposed by Bonaca MP et al., Circulation 2019)

- **Possible myocarditis:**
  Suggestive CMR with no syndrome, ECG or biomarker OR TTE with WMA with syndrome or ECG only OR elevated biomarkers with syndrome or ECG and no alternative diagnosis
- **Probable Myocarditis:**
  Diagnostic CMR (no syndrome, ECG, biomarker) OR suggestive CMR with either syndrome, ECG or biomarker OR TTE WMA + syndrome (with either biomarker or ECG) OR syndrome with PET-CT scan evidence and no alternative diagnosis
- **Definite Myocarditis:**
  Pathologic OR diagnostic CMR + syndrome + (biomarker or ECG) OR
  TTE WMA + syndrome + biomarker + ECG + negative angiography
  Positive cardiac biopsy

Proposed diagnostic strategy in case of increase in troponin and new cardiac symptoms, ECG changes, or other irAEs

Urgent cardio-oncology assessment (<24h)/suspend ICI

- Severity of cardiac symptoms, change in vital signs
- ECG
- CK, CK-MB, TroponinT, Troponin I, NT-proBNP
- Full blood count, renal and hepatic function, thyroid function
- Echocadiography with GLS
- Cardiac magnetic resonance tomography with LGE (if Troponin I elevated)
- Consider coronary angiography if clinical presentation suggestive of acute coronary syndrome
- Consider cardiac biopsy/FDG-PET

Increase in troponin * without other pathology	**Increase in troponin with mild symptoms NYHA I–II or other irAEs**	**Hemodynamic instability NYHA III–IV**
Consider holding ICI	Hold ICI	Hold ICI
Consider troponin dynamics Re-check troponin Consider differential diagnosis (see section troponinemia)	Rhythm monitoring TTE CMR, consider biopsy Exclude alternative diagnosis	CCU or ICU TTE CMR, possible biopsy Exclude alternative diagnosis
Restart ICI if troponin is going down and follow-up closely	Prednisone 2 mg/kg/d with tapering according to symptoms/biomarkers Heart failure treatment if indicated	Methylprednisolone 1g/d IV for 3 days then switch to Prednisone 2 mg/kg/d Consider immunomodulators based on biopsy and soluble markers (e.g. Tocilizumab, Abatacept, Mycophenolat mofetil etc.)

*No definite threshold defined yet.
Increase in troponin 20% from baseline if already ULN at baseline
Increase above ULN if normal at baseline

- Assess the probability of myocarditis (and all differential diagnoses) before considering resuming ICI treatment
- Definite myocarditis grade III/IV usually contraindicates further ICI treatment, however in mild forms of myocarditis close collaboration with the oncologist will define further treatment options/choices

6.7 Cardiac Amyloidosis

Key points

- Amyloidosis derives from a deposition of fibrils composed by subunits of misfolded proteins in variable organs.
- >95% of cardiac amyloidosis is caused by light-chain deposits (AL) or transthyretin (ATTR, genetic or wild-type).
- The tissue infiltration leads to restrictive cardiomyopathy (usually HFpEF) and arrhythmias (AF and conduction abnormalities).
- Prompt classification of amyloidosis (first of all exclusion of AL Amyloidosis) is crucial to guide therapy.
- For more complete information go to «Expert recommendation from the Swiss Amyloidosis Network».

	AL-Amyloidosis	ATTR-Amyloidosis
Etiology	Deposition of monocloncal immunoglobulin light-chains produced by a plasma-cell dyscrasia	Misfolding of transthyretin, a liver-synthetized protein. Hereditary form: endemic in specific geographic regions or ethnic groups. Different mutations related to different age of onset Wild-type: age-related
Clinical presentation	Renal dysfunction with proteinuria Orthostatic hypotension Nondiabetic neuropathy Chronic diarrhea Hepatic dysfunction Hypothyroidism Macroglossia, periorbital purpura	Carpal tunnel, lumbal spinal stenosis Cardiomyopathy (HFpEF, AF, AV conduction abnormalities) Orthostatic hypotension Nondiabetic polyneuropathy (in familial type >sensory, EMG might be negative) Spontaneous biceps tendon rupture Ocular floaters

Diagnostic work-up—when to suspect amyloidosis

History	HFpEF, orthostatic hypotension, peripheral neuropathy, proteinuria, carpal tunnel syndrome (>bilateral) hypo/normotension if previously hypertensive	**TTE:** Unexplained LV hypertrophy, low-flow, low-gradient aortic, stenosis, RV hypertrophy, myocardial granular sparkling, atrial dilatation, diastolic dysfunction—restrictive physiology, reduced LV GLS (<-15%) with apical sparing, pericardial effusion
ECG	low-voltage QRS despite LV hypertrophy AV conduction disease	**CMR**: diffuse subendocardial LGE, elevated native T1 and ECV
Biomarkers	NT-proBNP elevation Persistent, unexplained Tn elevation	**^{99m}Tc-DPD-Scintigraphy :** Perugini grade 2 or 3 cardiac uptake (ATTR>>AL)

Diagnostic work-up to differentiate between AL and ATTR

1st step

AL-Amyloidosis?

Search for monoclonal protein:
- Serum/24h-Urine immunofixation electrophoresis
- Serum kappa/lambda free-light-chain assay

\+ → Hematological referral
Tissue biopsy (abdominal fat, salivary gland, bone marrow, affected organ)

\-

2nd step

AL-Amyloidosis excluded

Search for ATTR-Amyloidosis:
- 99mTc- DPDwhole body scintigraphy—highly sensivtive and specific for ATTR-amyloidosis in absence of monoclonal gammopathy. Positive for amyloidosis if Perugini grade score 2–3.
- Consider TTR gene sequencing (to differentiate between familial and wild-type).

CAVEAT: an immunohistochemical or proteomic typing of amyloid deposits should be performed to complete the dx and should be obtained in particular in those pts with suspected ATTR-amyloidosis and monoclonal components with unclear significance (MGUS).

6.7 AL-Amyloidosis

Cardiac screening in patients with monoclonal gammopathy

- Role of the cardiologist is to screen for cardiac involvement (40–50% of light-chain gammopathy), stabilize the heart function (diuresis, prevention of embolic events, management of arrhythmias and conduction disorders) and assess the cardiac response to treatment
  - Blood tests: NT-proBNP, hs-Tn-I or T (prognostic value)—see table
  - TTE: LVEF, global longitudinal strain (GLS), stroke volume index (prognostic)
- Misfolded light-chains may have toxic effects on cardiomyocytes (necrosis).
- Cardiac response to treatment is defined as >30% NT-proBNP reduction in pts with a baseline NT-proBNP >650ng/l.

Prognostic score

Staging system	Markers and Thresholds	Stages	Median Survival (months)
Revised Mayo Model (Kumar et al. JCO 2012)	NT-proBNP ≥1800ng/l TnT ≥0.025 ng/ml Difference between involved and uninvolved serum free light-chains >180mg/l	I. No markers > cut-off II. 1 marker > cut-off III. 2 markers > cut-off IV. 3 markers > cut-off	I. 94.1 II. 40.3 III. 14.0 IV. 5.8

Nonspecific therapy and follow-up

- Heart failure therapy: if restrictive cardiomyopathy avoid BB (fixed stroke volume, increase in heart rate as only possible to increase cardiac output). Caution with ACE-I (peripheral vasodilation and risk of orthostatic hypotension). Diuretics to control congestive symptoms.
- In case of atrial fibrillation: anticoagulate *independently* from CHA_2DS_2 VASc score (DOAC/VKA)
- Follow-Up: 24h-ECG (to search for atrial fibrillation and AV conduction anomalies), resting ECG and biomarkers every 6 mths and TTE annually.

Specific therapy for AL-amyloidosis

- Specific chemotherapy:
  - Alkylating agents ---------- Melphalan, Cyclophosphamide
  - Steroids
  - Proteasome inhibitors ---------- Bortezomib, Carfilzomib, Ixazomib
  - Immunomodulators ---------- Thalidomide, Lenalidomide, Pomalidomide
  - Immunotherapy ---------- Daratumumab
- Autologous hematopoietic cell transplantation (autoHSCT)

Cardiac consequences of AL therapy:

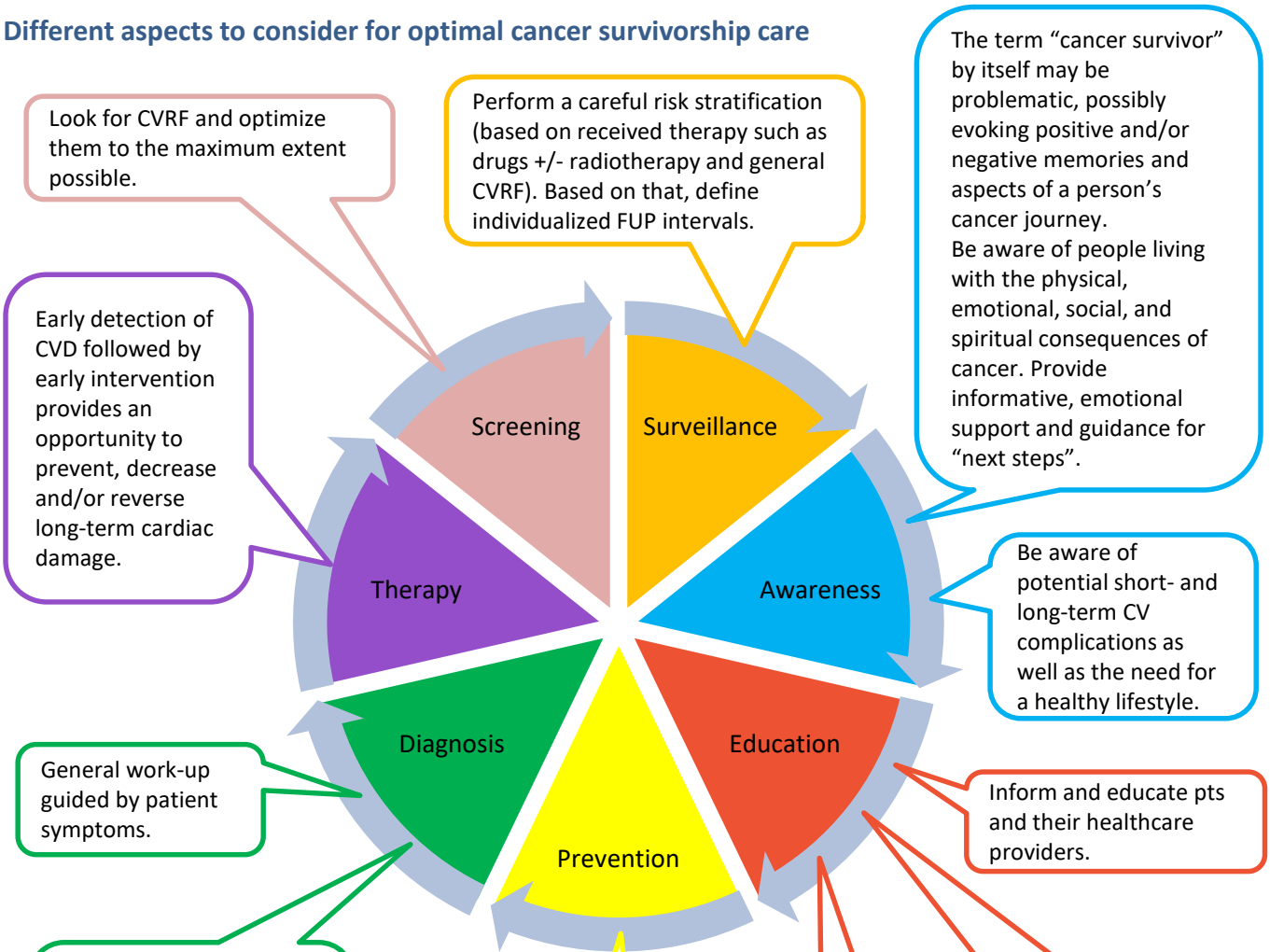
- CyBorD (Cyclophosphamide, Bortezomib and Dexamethasone): most commonly used first-line treatment
- Carfilzomib: second-line (relapse or refractory multiple myeloma), significant cardiac, renal and pulmonary toxicity
- Ixazomib: second-line, possible secondary cardiac structural damage/cardiotoxicity
- Lenalidomide: worsening of cardiac function, atrial fibrillation, hypotension
- Daratumumab: improved clinical outcome together with CyBorD
- Auto-HSCT: in AL is associated with higher morbidity and mortality compared to multiple myeloma alone

7 Cancer Survivors—Overview

Key points

- Long-term cancer survivors are at increased risk of CVD morbidity and mortality. To normal age-related physiological changes, Cx related effects (e.g. direct tissue damage, or e.g a decrease in physical activity) to the cardiovascular system must be taken into consideration.
- Periodical and lifelong FUP should be promoted in all Cancer Survivors, pediatric as well as adult. However, a good risk estimation based on cancer type, patient profile and type of received treatment is essential to provide a tailored surveillance.
- However, multiple Cx make it often very challenging to establish a tailored surveillance, simply because of not knowing the full-scale long-term effects of each drug.
- All these considerations together with the fear of over- and under-diagnosis and unsolved questions concerning adequacy of the therapeutic regimen or cardio-protection strategies make Cancer Survivorship really challenging. Close collaboration btw cardiologists, oncologists and general practitioners is required to achieve the most appropriate care.
- Main principle in survivorship care is the aggressive treatment of CVRF as the cornerstone in preventing cardiovascular events.

Different aspects to consider for optimal cancer survivorship care



7.2 Childhood Cancer Survivors (CCS)

Key points :

- Childhood cancer survivors (CCS) are those people diagnosed with cancer before the age of 19 y.
- CV sequelae are common in childhood cancer survivors (CCS) and are important contributors to the burden of later health outcomes. Consider late toxicity even two to three decades after Cx and be aware of premature CVD.
- Cumulative Anthracycline dose and chest-directed RT are well-known treatment-related factors affecting long-term CV outcomes. Existing risk scores and recommendations for screening and managing CV late effects in CCS predominately focus on these two factors. Best-known is the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers (Children's Oncology Group, Version 5.0). But newer therapies should be taken into consideration.
- Cancer treatment at a very young age (<5 y) and or intrauterine may act as a risk-enhancing modifier (ASCO GL 2018).

Risk	Therapy-related factors	Patient-related factors
Low	• No history of exposure to Cx with accelerated atherosclerosis or cardiotoxic potential • Very low-dose RT <15 Gy # or none	• No CVRF
Medium	• Lower-dose anthracyclines* (Doxorubicin (Doxo) ≤ 250 mg/m^2) alone • Lower-dose RT ≥ 15 - ≤ 35 Gy RT #	• 1–2 CVRF (HTN, dyslipidemia, obesity, smoking, insulin resistance)
High	• High-dose Anthracyclines* (Doxo ≥250 mg/m^2) • High-dose RT ≥ 35 Gy RT # • Lower-dose anthracycline* (Doxo ≤250 mg/m^2) PLUS lower-dose RT # • Autologous or allogenic HSCT	• Underlying CVD

Remarks:

*Conversion instructions for Doxorubicin isotoxic equivalent dose (LTFU Guidelines 2018, Version 4, adapted in 2019)

- Doxorubicin (Doxo) multiply total dose x 1
- Daunorubicin (Dauno) multiply total dose x 0.5
- Epirubicin (Epi) multiply total dose x 0.67
- Idarubicin (Ida) multiply total dose x 5
- Mitoxantrone (Mitox) multiply total dose x 4

e.g. cumulative Anthracyclines (calculation example) = ((Doxo x 1) + (Dauno x 0.5) + (Ida x 5) + (Epi x 0.67) + (Mitox x 4))

RT with potential impact to heart (RT to chest, abdomen, spine (thoracic, whole), total body)

Algorithm for Screening / Surveillance and Diagnosis of CVD in **CCS (general recommendation)**

Time

- **Long-term-FUP** starts usually about 5 y from diagnosis or 2 y from completion of Cx

FUP

- Present health
- Physical examination with specific emphasis on cardiac symptoms
- BP
- 1st FUP additional baseline ECG

Any CV symptoms or new findings?

— all →
- **Patient/survivor and parent education** to support effective self-management
- **Management of CVRF** and counseling on **healthy lifestyle are essential**

Yes → Further assessment, additional diagnostic steps (non-invasive/ invasive testings) according to pts presentation furthermore in respect of general GL recommendations

High / Medium

Asymptomatic pts:
Repeat FUP every 2-5 y
Check pts CV profile AND pay attention to strict CVD prevention

Low

No regulary FU recommended

Emphasize on general good Healthy lifestyle

ALWAYS:

- consider that CCS are prone to show a rapid progression or more aggressive course of specific cardiac condition.

Childhood Cancer Survivors (CCS)

Key points :

- Evidence on frequency of FUP examinations and treatment of cardiac conditions is scarce, however tables 1 and 2 show some common CV diagnostic tools and corresponding comments dealing with CCS surveillance (mainly based on Children's Oncology Group 2018)

Table 1 Commonly used and accepted: **Recommended Frequency of Screening—Echocardiogram (incl. 3D, GLS*)** Based on Children's Oncology Group 2018—Long-term Follow-Up Guidelines

Anthracycline Dose*	Radiation Dose**		Recommended Frequency
None	<15 Gy or none	Low	No regular screening echo recommended, ONLY upon symptoms
	≥15 – <35 Gy	medium	Every 5 y
	≥35 Gy	High	Every 2 y
<250mg/m2	<15Gy or none	medium	Every 5 y
	≥15 Gy	High	Every 2 y
≥250mg/m2	Any or none	High	Every 2 y

* Based on Doxorubicin isotoxic equivalent dose, see page before
** Based on radiation dose with potential impact to the heart (chest, abdomen, spine (thoracic, whole), total body)

Table 2 **Level of evidence, comments and usefulness for "daily"/routine practice**

MANAGEMENT OPTIONS			
	IMAGING		
	Echo	-	Often pediatric-specific data are lacking. Echo continues to be the most important imaging modality and advanced imaging techniques (GLS) appear to improve detection rates for cardiotoxicity
		+	A midrange LVEF (40–49%) is associated with an increased risk for a subsequent therapeutically relevant decreased LVEF <40%, surveillance might be refined at that time
	CMR	+	Consider if echo is not technically feasible/optimal or as a part of the further workup
		-	prognostic/therapeutic utility of fibrosis assessment in this disease and pt group is not documented
	ECG	+/-	Inexpensive test though cost-effectiveness of this screening strategy need to be confirmed
		-	Arrhythmias are extremely unusual, ECG is a poor tool for detecting Anthracycline cardiomyopathy
		-	No scientific evidence that screening picks up clinical meaningful changes.
	LABORATORY TESTS		
	CVRF	+	Increased prevalence of metabolic disorders in CCS, which contributes to the increased CV risk
	BNP / Trop	-	Routine use of biomarker is not recommended
		+/-	Baseline may be helpful in pts with borderline or reduced LVEF
		+	Only if the patient has signs suggesting volume overload
	STRESS TESTS, e.g. Velo-test, Stressecho		
		+	Additional stress test 5 to 10 y following RT, and after that as recommended by a cardiologist
		+	CCS often have other occult risk factors for CAD
		-	The yield for a stress test in pts in the absence of symptoms or other CVRFs is not clear
	MEDICATION		
		-	Based on data from other groups (pts with asymptomatic cardiomyopathy), treatment with ACE-I (+/- BB) may be reasonable
	Special considerations		
	Pregnancy	+	additional cardiology evaluation/monitoring should be provided (see section pregnancy)

7.1 Adult Cancer Survivors—Risk Categories

Key points :

- In recognizing the intersection of cancer and CVD, everybody would agree: “regular follow-up care is very important for cancer survivors”. But little is known about the best and most reasonable way.
- New cancer treatments come along with higher chances of reaching survivorship. At the same time, different cardiovascular side effects are observed during and after therapy. However, data about long-term outcomes in survivorship are often lacking. Additionally, multiple Cx make it even more challenging to establish a tailored surveillance, simply because of not knowing the full-scale, long-term effects of each drug.
- Cancer type, cancer treatment, age at cancer diagnosis, comorbidities as well as general cardiovascular risk profile all influence outcomes, especially mortality. Therefore, giving one single pathway would be wrong.
- Due to lack of evidence and the fact that both ESMO and the NCCN guidelines only provide scarce information, we decided to give only general recommendations on how to group and follow these patients.

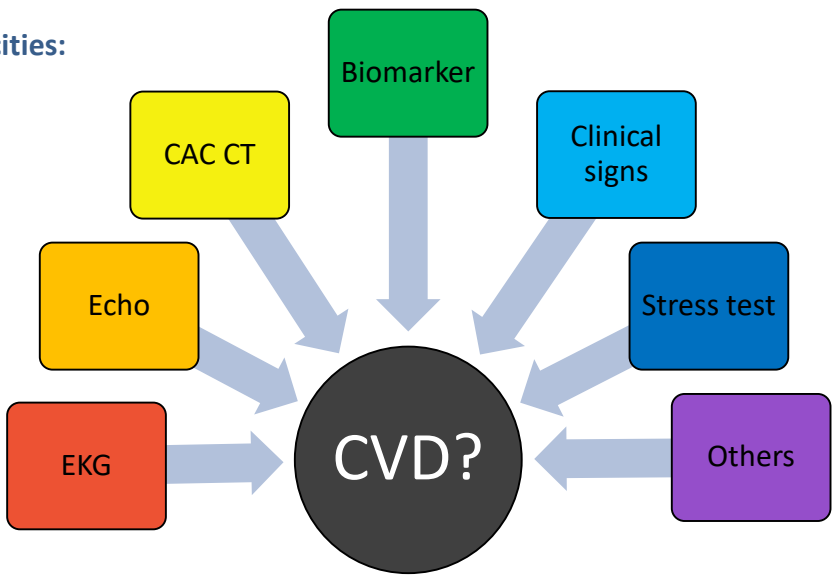
Defining risk for cardiovascular disease in survivorship according to NCCCN and ESMO Guidelines

Risk	Therapy-related factors	Patient-related factors
Low	• No history of exposure to cancer therapy with accelerated atherosclerosis potential	• Age <65 • No CVRF or one CVRF
Medium/ High	• Chemotherapy as e.g. ANT • Targeted therapy such as HER-2 targeted therapy • Higher doses of ANT and or Trastuzumab • Hormone therapy such as androgen deprivation therapy • Radiation therapy applied near the heart • Immunotherapy such as immune checkpoint inhibitors • Allogenic HSTX inkl TBI	• Age >65 years at cancer diagnosis • 1–2 CVRF (HTN, dyslipidemia, obesity, smoking (current/prior), DM) • Prior cardiovascular disease • Cardiovascular event during Cx • Reduced or low-normal LVEF (50–54% pretreatment)

Possible long-term cardiovascular toxicities:

- Cerebrovascular disease
- Conduction abnormalities, arrhythmia
- Coronary artery disease, vasospasm
- Left ventricular dysfunction, heart failure
- Hypertension
- Myocardial and pericardial disease
- Peripheral arterial disease
- Valve disease
- Thromboembolic disease

Because of the wide range of cardiovascular Complications, a multimodality surveillance is recommended in order to detect CVD at an early, subclinical stage.
For details see next pages.



7.1 Adult Cancer Survivors—Algorithm (1/2)

Proposed algorithm for screening/surveillance and diagnosis of CVD in adult cancer survivors

Time period: post-treatment year 1–4

Long-term-FUP usually starts ≥12 mths post-Cx

All

Define cardiac risk (page before)

Low | **Medium/high**

No regular FU recommended

General recommendations

- **Heart-healthy lifestyle:** healthy diet, smoking cessation, weight management, regular exercise (aerobic and resistance exercise, for ≥150 min/wk)
- **Adjust modifiable CVRF** according to ESC GLs
  - Use established CV risk calculators (Agla risk (Calculator) or ESC SCORE2 algorithm (SCORE2 and SCORE2-OP)), in the knowledge that CVD risk in cancer survivors might be underestimated
- **Blood pressure (BP):**
  - BP-target ≤65 y: <130/80 mmHg
  - BP-target >65 y: <140/80 mmHg
  - target may differ in special conditions (e.g. CKD)
- **Cholesterol management:**
  - Primary/secondary prophylaxis according to ESC GL
  - Consider additional diagnostic procedures like carotid US (arterial plaque burden?) or CAC scoring with CT to guide therapy decisions, especially in individuals at low or moderate risk.
- **Diabetes:** <HbA1c 6.5–7%
- **Nicotine:** smoking cessation

Yearly

- H/o present illness
- Clinical assessment
- Check and optimize CVRF
- After RT, yearly ECG (conduction abnormality?)
- Annually TTE for up to 2-3 y if high risk pts after ANT (see section 5.1)

- Annual Echo up to 2–3 y if high-risk pt after ANT Cx (see page xy)

Signs/symptoms for CVD?

- Shortness of breath?
- Ankle swelling?
- Angina?
- Reduced fitness level?
- Dizziness? Palpitations?
- Syncope?
- New murmur?
- Altered ECG or other imaging?

Yes

Further assessment, additional diagnostic steps (non-invasive/invasive) according to pts presentation

CVD confirmed?

Yes

No

- Management as general GL recommendations (e.g. HF, CAD), close collaboration w/ oncologist
- A proactive stance (e.g. starting medical Tx) might allow for better results in the FUP of pts

Differential diagnosis?

Note

- If chest CT performed for any reason consider assessment of CV findings (e.g. CAC Scoring)
- Troponin/NTproBNP is not routinely recommended, but might be reasonable in some situations

Asymptomatic and NO new aspects

Repeat yearly

Specific recommendations (1):

- **Pregnancy:** additional cardiology evaluation should be provided at a low-threshold base, e.g. in CCS:
  - ≥250 mg/m^2 ANT or
  - ≥35 Gy chest RT or
  - ANT (any dose) combined with chest RT (≥15 Gy)

  (for details have look at the **pregnancy section**)
- **PAD:** ankle–brachial-index screening should be performed annually on those who received RT to lower extremities
- **In pts under HF-based therapy (HF-Tx)** which was started b/c of LVSD or HF due to Cx, CV care including HF-Tx and regular cardiology review should be continued indefinitely, if tolerated, regardless of improvement in LVEF or symptoms. Only consider stopping HF therapy after a period of stability and no further active anticancer therapy.

Go to next page for ≥5 y

7.1 Adult Cancer Survivors—Algorithm (2/2)

Continuation of follow up ≥5 y post-treatment

Time period: post-treatment ≥5 y

Medium/high

Continue yearly FUP and pay attention to strict CVD prevention
- H/o present illness
- Clinical assessment
- Check and optimize CVRF
- After RT yearly ECG (conduction abnormality?)

Re-assess with TTE at least every 5 y in asymptomatic pts (consider earlier testing according to treatment-specific risk profile) AND at any time if a patient shows suspicious signs and symptoms

H/o chest-directed radiation?

Yes

Perform non-invasive (stress) test (CAD? Ischemia?), even if pt asymptomatic
Re-assess every 5–10 years

No

New findings?

Yes

- Further assessment, additional diagnostic steps (non-invasive/invasive) according to pt's presentation and disease severity
- This should adhere to established GLs, always considering a possibly rapid progression or more aggressive course of specific cardiac condition in cancer survivors

Specific recommendations (2):

- Always consider a closer FUP if it is reasonable in an overall view while at the same time the surveillance burden might be decreased in others

- **Carotid artery disease:** Carotid US screening 5 ys after supra-clavicular RT, repeat at least every 5 ys.
- **Pts treated with vasotoxic drugs** with persistent and enduring CV risk after therapy (e.g., Cisplatin, Nilotinib) could be considered for imaging screening tests for PAD every 1–2 y and additional non-invasive stress testing every 5 y
- **Discuss treatment options in heart team:** if feasible avoid surgery for CAD or CVD because of bad outcome, you definitely should avoid more than one surgery/re-do-operation (multiple cardiac lesions, porcelain aorta, fibrosis of left internal mammary and often RT-induced pulmonary dysfunction)

Repeat periodical, lifelong FUP

Caution:
- For some therapies, special long-term surveillance recommendations exist (e.g. ANT). Please consult the literature in these cases.
- Be aware, that we did not consider the exact dose of radiation e.g. to the coronaries as well as the newer cardioprotective techniques (e.g. breath holding during radiotherapy in breast cancer). Meaning long-term outcomes are expected to improve. We will probably include this in a later version of this booklet.

8 Pregnancy After Cancer

Key points:

- Pregnancy itself is characterized by significant hemodynamic and cardiovascular (CV) changes and as such is a period of elevated CV risk for women.
- For women with a history of anticancer treatment, pregnancy implies facing a period with increased risk of CV and obstetrical complications. CV problems can initially manifest or already pre-existing CV issues can worsen.
- Several risk stratification tools are available to estimate individual maternal CV risk in women with pre-existing CVD (CARPREG II, ZAHARA, mWHO)), which consequently guides CV monitoring and careful perinatal management. However these do not aid in women without known CVD.
- Diagnosis of any pathology can be challenging because the overlap of CV symptoms with those of normal pregnancy may lead to delays in diagnosis and subsequent care.

Risk	Therapy-related factors
Low	• No history of exposure to Cx w/- accelerated atherosclerosis or cardiotoxic potential • Very low-dose RT <15 Gy or none • Only surgical treatment of cancer
Medium	• Lower-dose Anthracycline* (Doxorubicin ≤250 mg/m2) alone • Lower-dose RT ≥ 15 – ≤ 30 Gy RT to the heart or surrounding tissues • VEGF Inhibitors

High	• High-dose Anthracycline* (Doxorubicin ≥250 mg/m2)
	• High-dose RT ≥30 Gy RT to the heart or surrounding tissues
	• Lower-dose RT ≥ 15 – ≤ 30 Gy in combination with Anthracycline chemotherapy (at any dose)
	  • Especially in RT before 2000
	  • Discuss with radio-oncologist
	• Total body irradiation (TBI)

Risk	**Patient-related factors** (use established risk calculators such as the mWHO Pregnancy Risk Classification for ♀ w/- pre-existing CVD)
Low **mWHO I**	• 1–2 CVRF • Advanced maternal age (>40) • Mild pulmonary stenosis, PDA, mitral valve prolapse • Successfully repaired simple lesions (ASD, VSD, PDA, anomalous pulmonary venous drainage) • Atrial or ventricular beats, isolated
Medium	• Unoperated ASD or VSD • Repaired ToF • Most arrhythmias (esp. supraventricular) • Turner syndrome w/o aortic dilatation
High	History of cardiotoxicity before pregnancy
mWHO II/III	• Mild LVSD (EF >45%) • HCM • Native or tissue VHD not considered WHO I or IV • Marfan/other HTAD syndrome w/o aortic dilatation • Aorta <45 mm in BAV pathology • Repaired coarctation • Atrioventricular septal defect
mWHO III	• Moderate LVSD (EF 30–45%) • Previous peripartum cardiomyopathy (PPC) w/o any residual LVSD • Mechanical valve • Systemic right ventricle w/- good or mildly decreased ventricular function • Fontan circulation: otherwise uncomplicated • Unrepaired cyanotic heart disease • Other complex heart disease • Moderate mitral stenosis • Severe asymptomatic aortic stenosis • Moderate aortic dilatation (see GL ESC 2018) • Ventricular tachycardia
Very high **mWHO IV**	• Pulomonary arterial hypertension • severe LVSD (EF <30%), NYHA III or IV • Previous PPC w/- any residual LVSD • VHD: severe MS and severe symptomatic AS • Systemic RV w/- moderate or severely decreased ventricular function • Severe aortic dilatation (see ESC GL 2018) • Vascular Ehlers–Danlos • Severe (re)coarctation • Fontan w/- any complication

mWHO: Pregnancy contraindicated, if pregnancy occurs, termination should be discussed

8. Pregnancy—General Considerations & Possible CV Problems

During Pregnancy

- Heart Failure
- Thrombembolism
- Preeclamsia
- Arrhythmia
- ACS
- Preterm delivery
- Aortic dissection

Changes in normal pregnancy:
- Cardiac Output ↑, Stroke Volume ↑, Heart rate ↑
- Plasma volume ↑
- Risk of thromboembolism ↑
- Systolic BP: minimal changes, diastolic BP ↓ / =

Echo:
- Chamber size and volume ↑ (within ULN)
- LV and RV mass ↑
- Diastolic dysfunction
- Valvular annulus dimension w/- regurgitation
- Small pericardial effusion may develop
- LVEF variable = / ↓

ECG:
- Left axis deviation, transient ST/T wave changes

Pregnancy in Female Cancer Survivors

Very-high-risk group not accounted

Prior to Pregnancy: Risk stratification - multidisciplinary team planning

Low	Medium	High
Routine pregnancy care Usually no special tests and FUP necessary	**Routine pregnancy care** • No clear evidence about necessary pre-conception CV assessment • Optimize medical status	**Pre-conception CV assessment recommended:** • BP • 12-lead ECG • Natriuretic peptide • Echo, GLS • Further diagnostics according suspicion and clinic (ie. Holter ECG, cardiac MRI, exercise stress testing)

Consider pre-conception CV assessment if fertility Tx or assisted reproduction is planned

Diagnostic testing, see box «high» risk group

Results ?

- normal → **No relevant OR small increased risk**
- abnormal → **Abnormal cardiac function OR high-risk features**

During Pregnancy
3rd trimester – 2nd trimester – 1st trimester

No fix CV monitoring recommended
- But repeat echo, BNP with CV signs and symptoms
- Stay vigilant and consider one or two FUP visits - echo, natriuretic peptide (esp. in 3rd trimester)

Cardiological FUP:
- Minimal 1x/trimester w/- Echo, BNP
- Frequency depends on underlying CV pathology and symptoms
- Close collaboration w/- obstetric team

Always look for red flags:
- Symptoms: inadequate dyspnoe, chest pain, sustained palpitations, syncope
- Signs: HR ≥120bpm, BP ≥160, SO_2 <95% (unless chronic), JVP↑, loud heart murmur, wheezing, crackles, marked edema

If yes: urgent evaluation

Labor and delivery: vaginal delivery usually preferred, consider pulse oximetry and telemetry, as indicated

Post-partum

Postpartum routine care AND:
- Consider echo and BNP 3–6 mths after delivery

Postpartum routine care AND:
- Plan echo and BNP 3–6 mths after delivery

8. Pregnancy After Cancer—CV Medication

	During Pregnancy	Postpartum/During Lactation
ACE-I		Captopril, Enalapril, Benazepril may be safe
ARB		
ARNI		
BB and Combined Alpha/BB	Prefer β1-selective Blocker b/o β2-mediated uterine relaxation + peripheral vasodilation	
• Atenolol	• cave	
• Metoprolol	• 1L HTN	
• Propanolol	• 2L HTN	
• Labetolol	• 1L HTN, small study: possible IUGR	• Conflicting data
• Carvedilol	• 1L HTN	
Alpha Adrenergic Agonists		
• α-Methyl-Dopa	• 1L HTN	
• Clonidin		• Clonidine probably safe
CCB		
• Verapamil	• Verapamil > Diltiazem for PSVT	
• Diltiazem		• Conflicting data
• Nifedipine	• 1L HTN, hypotension may develop w/- concomitant use of magnesium	
• Amlodipine	• Probably safe	• Probably safe
AAD		
• Adenosine		
• Propafenon	In general: should be avoided if possible during the 1st trimester, otherwise lowest dose should be attempted - only in women w/o structural heart abnormalities	
• Flecainid		
• Sotalol		• Conflicting data
• Amiodaron	• Only last line therapy, risk of fetal thyroid and neurodevelopmental abnormalities	
• Digoxin		
Vasodilatators		
• Hydralazine	• Note: risk for maternal lupus-like syndrome, reflex-Tc and fetal TZ ↓	• Hydralazine safe
• Nitro/ISDN		• Nitroglycerine probably safe
• Nitroprusside	• possible Bc, only use in refractory cases b/o potential for cyanide toxicity	

*Internet databases and manufacturers' instructions containing prescribing information are helpful in acquiring the most current information, see also: www.embryotox.de

8. Pregnancy After Cancer—CV Medication

	During Pregnancy		Postpartum/During Lactation	
Diuretic Agents • Loop diuretics • Hct • MRA				
Others: • Ivabradine • Sacubitril/Valsartan • Statin class				
Antiplatelet Agents: • ASS • P2Y12		• Risk of premature closure of fetal Ductus arteriosus • Clopidogrel: limited data, even less data for Praasugrel, Brilique		• Clopidogrel: limited data
Anticoagulants • VKA • LMWH • Intravenous UFH • DOAC		• Risk of Coumadin embryopathy, • Periodic evaluation of anti–FXa • Should be discontinued 4 to 6 hours before delivery		• Restart ≈ 4 to 6 hs after delivery
Thrombolytics		• Alteplase and Streptokinase, limited data		• Alteplase and Streptokinase, limited data

8. Diagnostic Testing During Pregnancy/Postpartum Care

Key points :

- Imaging of a pregnant woman is challenging as it involves both the mother and the fetus. Diagnostic findings may mimic CVD although sometimes they refer to physiological changes that occur during pregnancy.
- Concerning imaging, ultrasound and CMR are the modalities of choice during pregnancy. But theoretically, all currently available imaging modalities, correctly performed, may be used. The risk to a fetus from ionizing radiation is dependent on gestational age (GA) and the dose of radiation. The guiding principle of radiation safety "ALARA" (as low as reasonably achievable) should always kept in mind.
- In general all observations of significant IQ reduction and severe mental retardation are not expected to occur at an absorbed dose <100 mGy. Most commonly performed cardiac diagnostic and therapeutic imaging techniques are below this threshold (see table at the bottom). Furthermore, using low-exposure protocols can reduce dose exposure to the minimum amount while keeping diagnostic value.
- IVC compression syndrome must be taken into consideration during the 3rd trimester (drop of maternal CO by up to 30%).

Modalities WITHOUT ionizing radiation

	During Pregnancy		Postpartum	
Ultrasound	❖ Average Radiation Exposure (fetal dose): 0 mGy			
In general: - TTE		Recommended mechanical and thermal indexes should both be less than 1. • Prolonged high-power techniques (i.e. Doppler) should be avoided		
- TEE		• Can be safely performed • Majority of risk is related to required sedation—consider pregnant women's ≈ status to a full stomach		
i.v. echo contrast agent				
- Agitated saline		• Potential risk of placental infarction/fetal distress		
- LV enhancing Agent*		• No sufficient clinical data		
CMR	❖ Average Radiation Exposure (fetal dose): 0 mGy			
In general		**1st–3rd Trimester** • MR imaging magnet strength should be ≤3.0 Tesla • Primary concerns are heating; B0 strength, which may affect cell migration during the 1st trimester; acoustic noise, which may damage fetal hearing (important by 24 wks)		
Contrast Agent - Gadolinium*		• Should be avoided if possible		Breastfeeding safe w/o interruption

Modalities WITH ionizing radiation, general considerations during pregnancy

Leading clinical settings and indication for the use of ionizing radiation	
• Trauma	• Pregnant pts with positive findings on a FAST examination • Use dose reduction strategies if possible and advisable
• Suspected pulmonary emboli	In general: ionizing imaging should be performed after negative findings at bilateral lower extremity Doppler US b/- as many as one-third of pregnant pts with PE have DVT • Pulmonary CT angiography: provides a lower dose to the fetus when the fetus is small and farther from the field of view - equivocal or higher dose when gravid uterus is enlarged, closer to the diaphragm • V/Q scintigraphy: consider imaging w/o the ventilation portion especially if chest X-ray is normal

* In case of allergic reaction: Use Diphenhydramine and Prednisone or Dexamethasone b/c the majority of either medication is metabolized within the placenta before reaching the fetus.

8.Diagnostic Testing During Pregnancy/Postpartum Care

	During Pregnancy	Postpartum
Ionizing radiation	❖ If possible, procedures should be delayed until completion of major organogenesis (>12 wks GA)	
In general	**Potential effects on the embryo and fetus from radiation exposure** **Deterministic Effects** **<50 mGy fetal radiation dose** – 0–2 wks GA: – "all-or-non-effect" period – >2 wks GA: – Probably too subtle to be clinically detectable **>50–100 mGy:** Pregnancy termination not justified – 2–25 wks GA: – Teratogenic; organogenesis (e.g., congenital abnormalities, IUGR) *8–15 wks: * caution advised, CNS sensitive to radiation effects – >25 wks GA: – No teratogenic effect observed at doses <100 mGy **100–500 mGy:** risk of malformation, decision to abort fetus must be made individually **>500 mGy:** fetal damage (any pregnancy trimester) **Stochastic E. (risk of carcinogenesis):** no dose limit	No specific risk during breastfeeding
– Diagnostic X-ray	• Single diagnostic X-ray w/o relevant risk to cause AE	
– CT	• See table above, furthermore using low-exposure protocolls can reduce dose exposure to minimum amount although keeping diagnostic value	
Iodinated contrast agents*	• Potential risk of fetal hypothyroidism, check TSH levels at the time of birth; if normal, no extra attention • mMay increase radiation absorption	Breastfeeding safe w/o interruption
– Nuclear medicine Radiotracers	• Use of ^{131}I-NaI contraindicated. If diagnostic examination of the thyroid is essential, use ^{123}I or ^{99m}Tc instead	Temporary breast-feeding interruption, duration depends on the used pharmaceutical

* See remark concerning allergic reaction on previous page

Radiation Doses Associated with Common Radiologic Examinations (EXAMPLES!)		Fetal Dose (mGy)
Modality: **CT**	– Pulmonary angiography – CT Thorax – CT Abdomen – Aortic angiography of chest, abdomen, and pelvis, w/- or w/o contrast agent – Coronary artery angiography	0.01–0.66 0.1–1.0 1.0–10 6.7–56 0.1–3
Nuclear medicine	– Low-dose perfusion scintigraphy – V/Q scintigraphy – Technetium 99 (99mTc) bone scintigraphy – Myocardial perfusion with 99mTc-sestamibi	0.1–0.5 0.1–0.8 10–50 17
Radiography	– Chest radiography, two views	0.0005–0.01

Estimated dose varies according to protocol, radiotracer type and dosage, method of dose calculation and patient-dependent factors (e.g. weight or body habitus and percentage of glandular breast tissue)