



Cardiotoxiciteit

Olivier Manintveld, cardioloog

Disclosures Olivier Manintveld

(Potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk ...	- Vergoedingen voor adviesraden en sprekersvergoedingen aan mijzelf dan wel aan Erasmus MC: Abbott, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Novo Nordisk en Siemens - -

10 STAPPEN PLAN

1. Waarom cardio-oncologie?
2. Doel cardio-oncologie
3. Behandeldoelen hartfalen/kanker
4. Wat kan er van het hart aangetast worden?
5. **Overzicht cardiovasculaire bijwerkingen anti-kanker therapie uit de cardio-onco richtlijn**
6. Hoe stel je hartfalen vast?
7. Welke zijn behandelmogelijkheden van de cardioloog?
8. Is hartfalen nu ernstig?
9. Wat is de invloed van co-morbiditeiten?
10. Take home messages

1. WAAROM CARDIO-ONCOLOGIE?

Kanker en HVZ delen veel dezelfde risicofactoren!



Patienten met maligniteit die mogelijk cardio-toxische behandeling krijgen die nog **niet** cardiaal bekend zijn

Patienten met maligniteit die mogelijk cardio-toxische behandeling krijgen die al **wel** cardiaal bekend zijn

Niet alleen van kanker neemt de overleving toe, maar ook van hart- en vaatziekten! Daardoor neemt de kans op beiden ziektes echter verder toe...

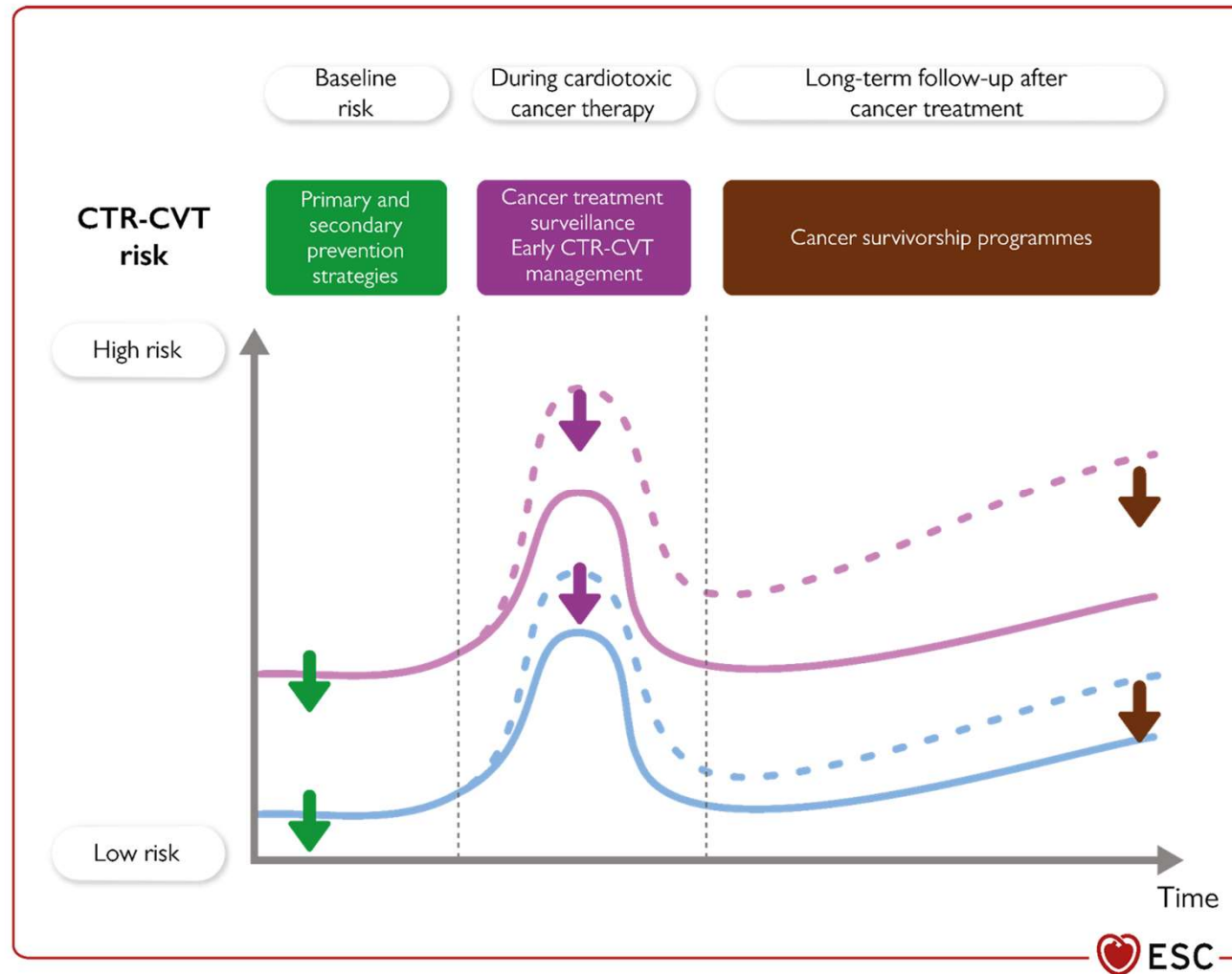
2. DOEL CARDIO-ONCOLOGIE

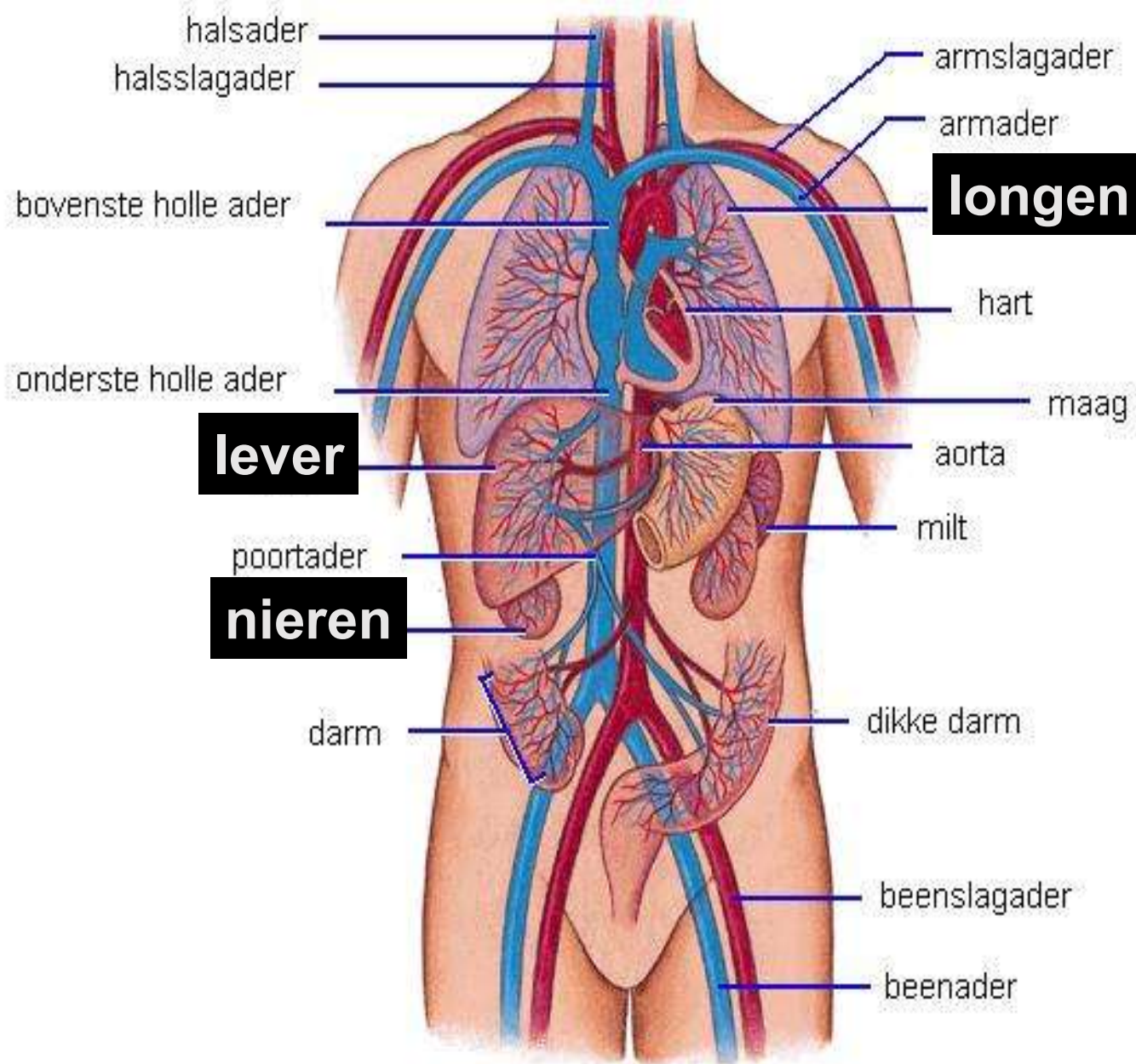
Voorkomen, indentificeren en behandelen van CV complicaties van anti-kanker therapie

CV risico management van cardiale patienten die cardiotoxische behandeling ondergaan

Screening voor lange termijns effecten na kanker behandeling

DYNAMICS OF CV TOXICITY RISK IN CANCER PATIENTS OVER TIME

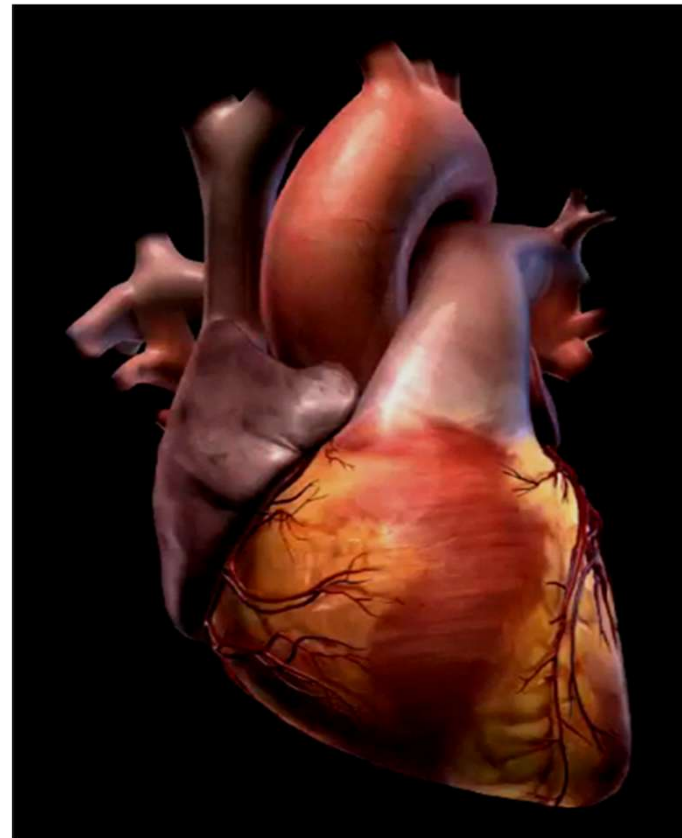




HET HART HEEFT MAAR 1 MISSIE IN HET LEVEN!

Bloed rondpompen om alle andere organen van bloed te voorzien zodat:

- O₂ en voedingsstoffen worden aangevoerd en
- CO₂ en afvalstoffen worden afgevoerd.

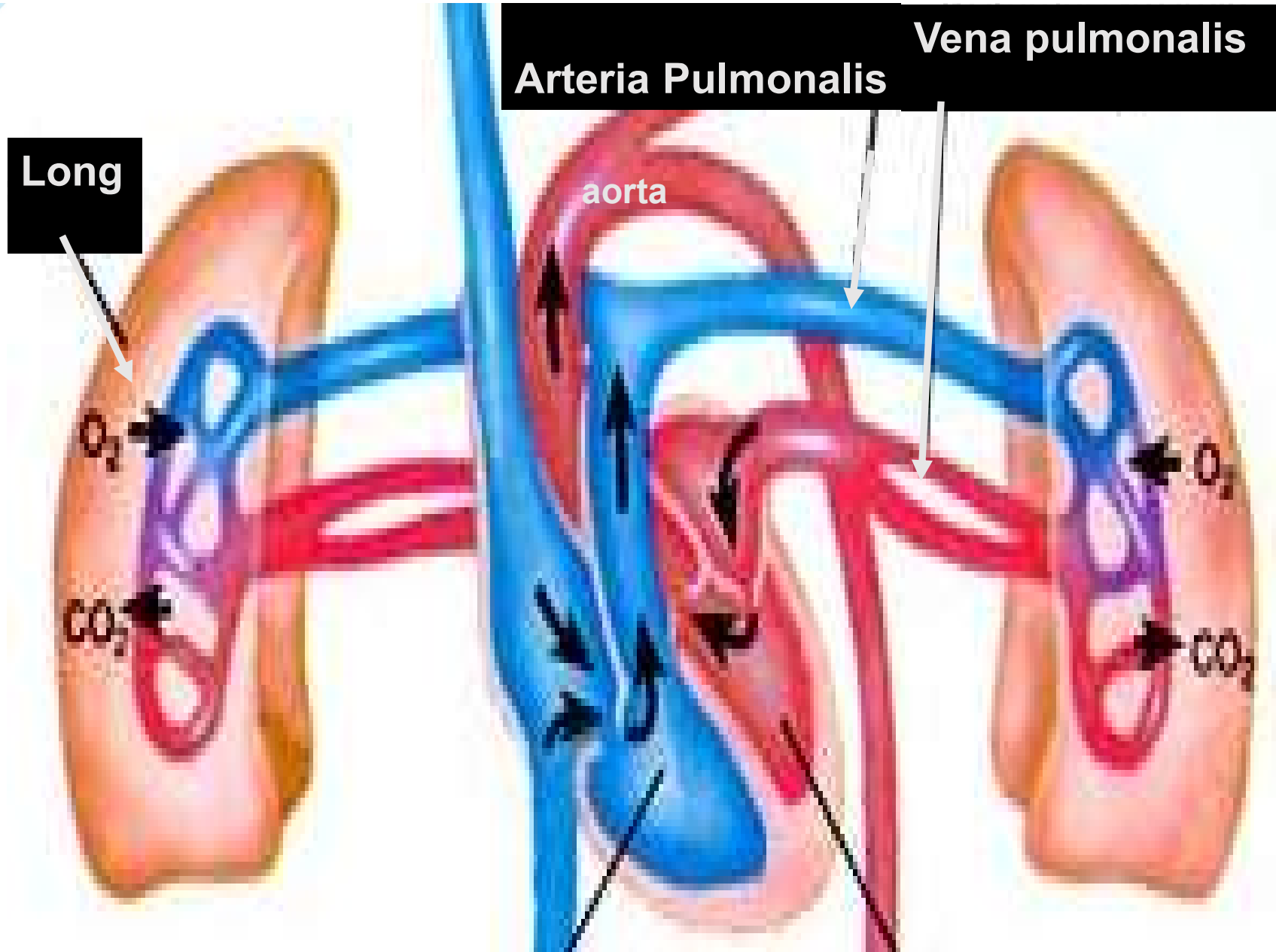


Long

Arteria Pulmonalis

Vena pulmonalis

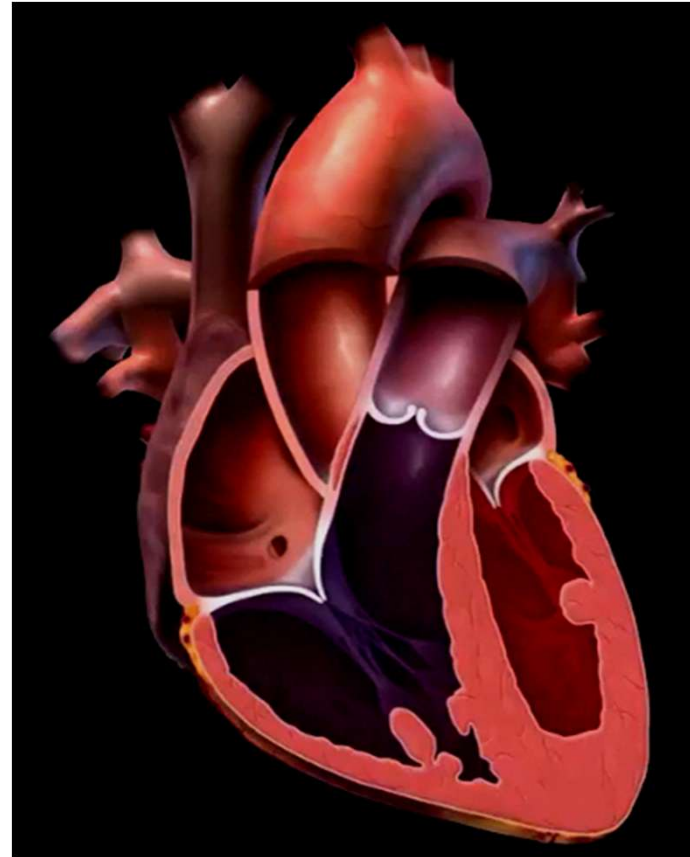
aorta



ECHTER...

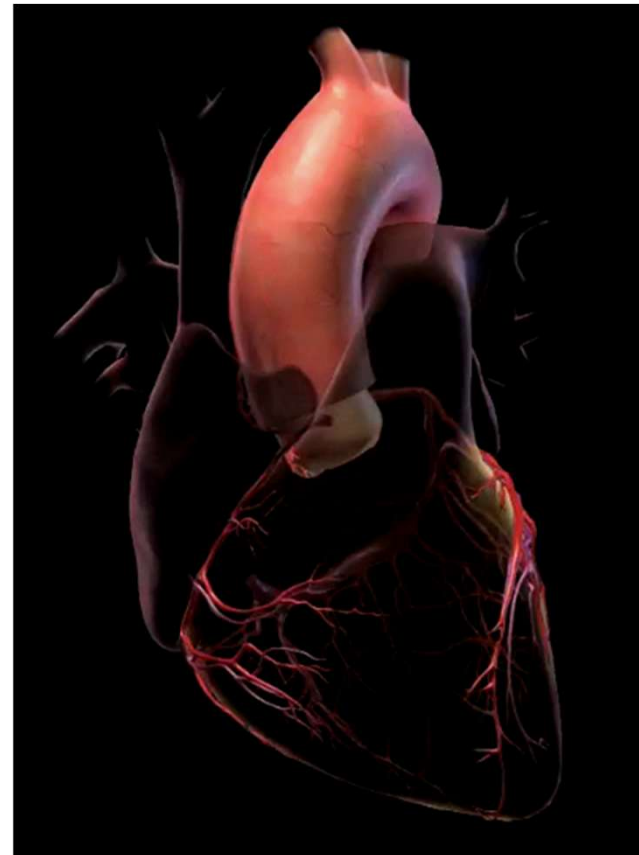
Deze pomp levert continue arbeid en heeft daarvoor energie en zuurstof nodig.

Het kan dat niet halen uit het bloed wat door het hart wordt gepompt.



HET HART ZELF WORDT GEVOED DOOR DE KRANSSLAGADEREN

Deze liggen om het hart als een
kroon en heten ook wel coronairen



OM DEZE POMP TE LATEN FUNCTIONEREN HEB JE DE VOLGENDE ZAKEN NODIG

Kransslagaderen

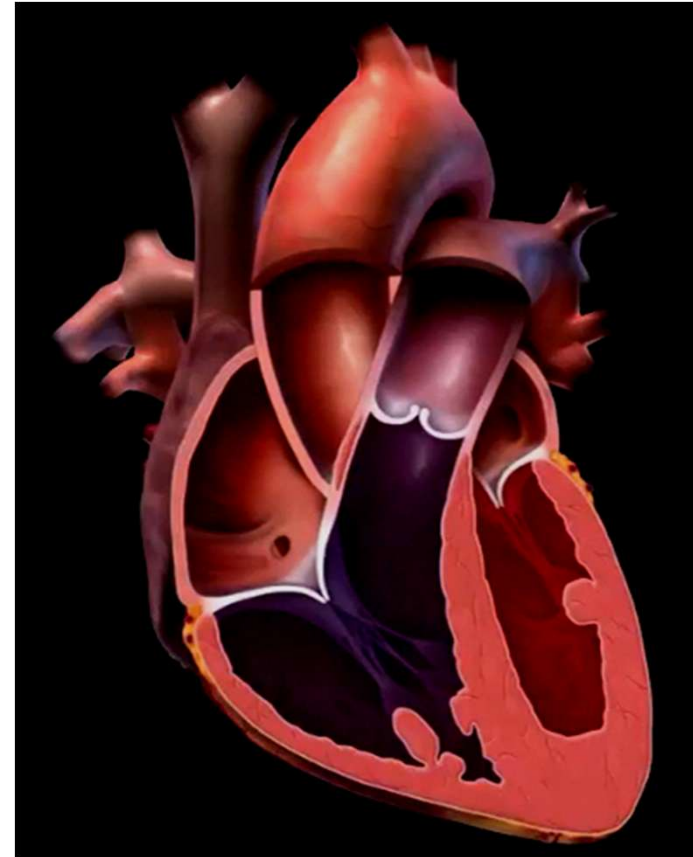
Hartspierweefsel

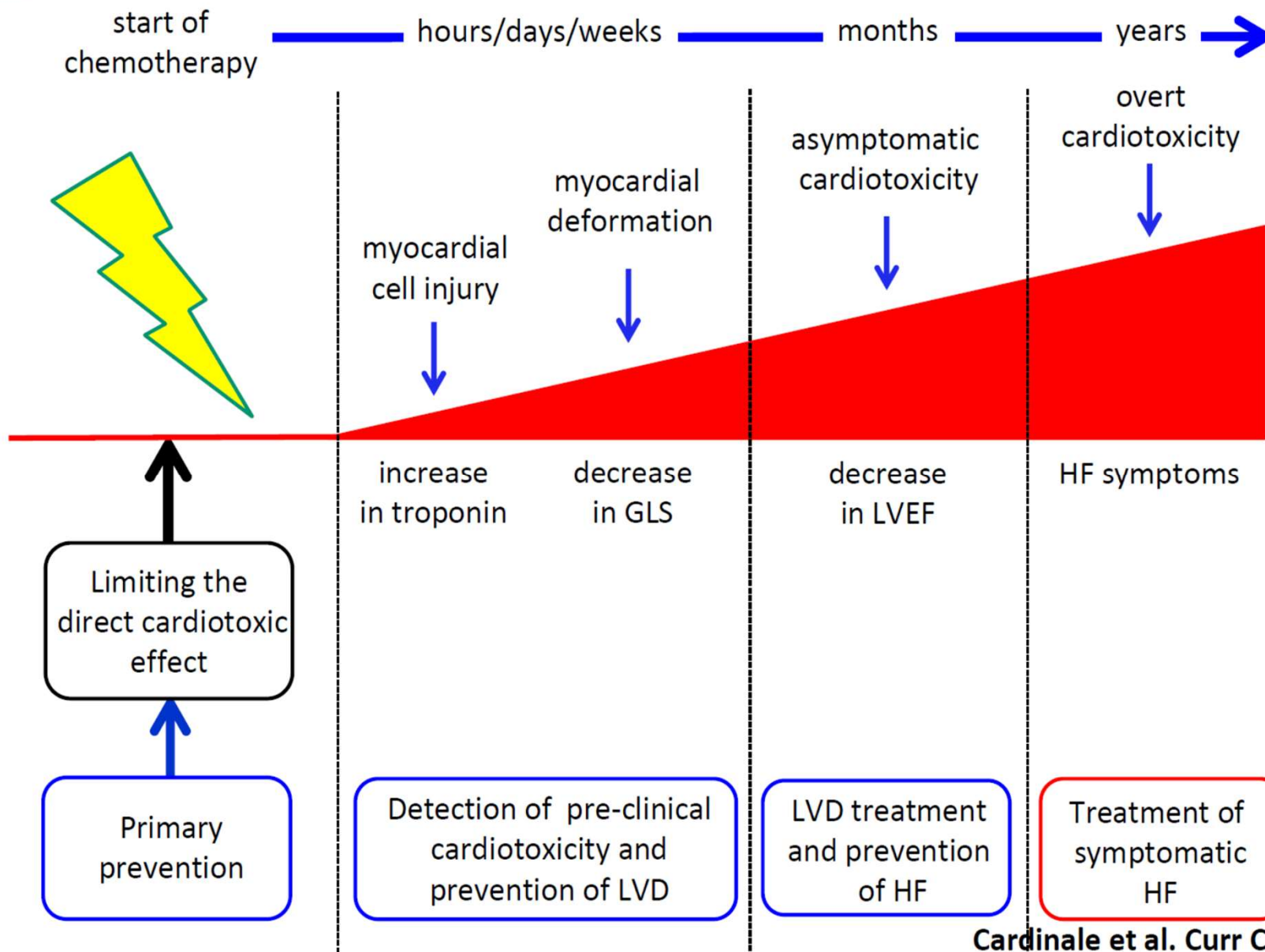
Hartkleppen

Electra (geleidingsweefsel)

Hartzakje

En op elk gebied waar dit niet normaal
functioneert kan het hartfalen geven!





Cardinale et al. Curr Cardiol Rep 2016.

3. WAT ZIJN JE BEHANDELDOELEN BIJ HARTFALEN?

1. Verlengen van de levensduur
2. Verminderen noodzaak ziekenhuisopname
3. Verhogen kwaliteit van leven

Maar de volgorde hangt af van de leeftijd en de co-morbiditeit!

3. WAT ZIJN JE BEHANDELDOELEN BIJ KANKER?

Bij consult voor cardiologie moet ook duidelijk genoteerd staan wat de behandeldoelen zijn. Dit is niet altijd duidelijk voor de cardioloog.

Dit geeft urgentie weer voor aanvullend onderzoek en behandeling. Hoe snel dit gaat hangt mede af van wat er aangetast is aan het hart.

Multidisciplinair overleg is dus belangrijk om met dezelfde taal te spreken en om aan verwachtingsmanagement te doen.

4. WAT KAN ER AANGETAST WORDEN?

Coronairen

Myocard

Kleppen

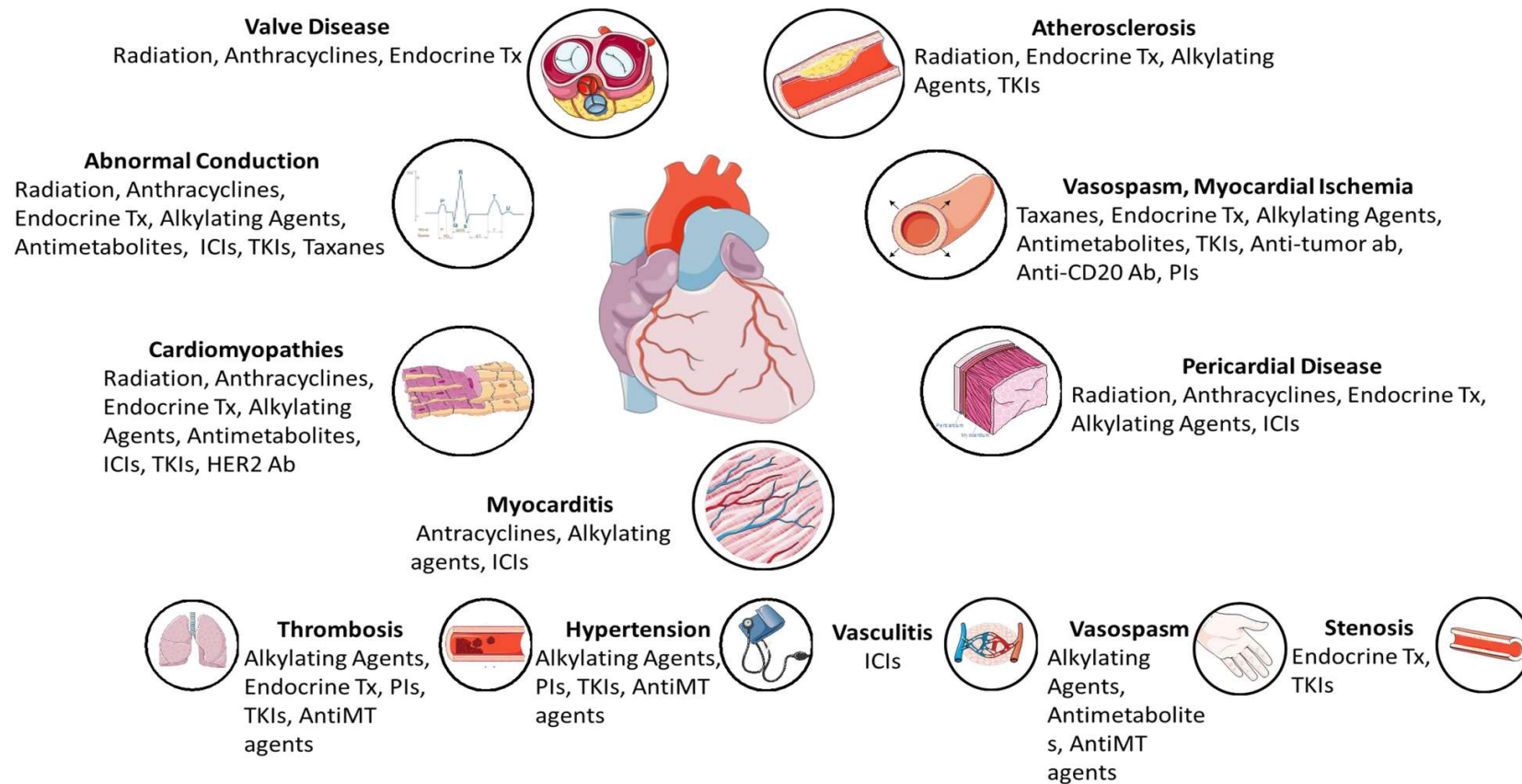
Geleidings- en/of ritmestoornissen

Pericard

Allemaal factoren leidend tot hartfalen!

NB hartinfarcten kunnen we (nog) niet goed voorspellen en dus niet voorkomen.....

5. OVERZICHT CARDIOVASCULAIRE BIJWERKINGEN VAN ANTI-KANKER THERAPIE





European Society
of Cardiology

European Heart Journal (2022) **43**, 4229–4361
<https://doi.org/10.1093/eurheartj/ehac244>

ESC GUIDELINES

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)

**Developed by the task force on cardio-oncology of the European
Society of Cardiology (ESC)**

GUIDELINE COMMITTEE



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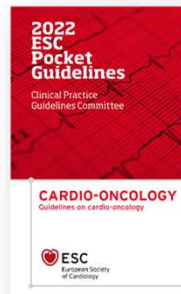
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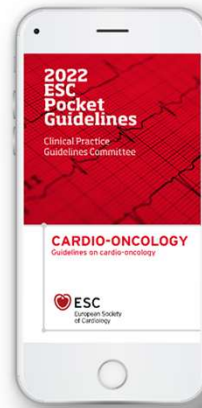
2022 ESC GUIDELINE CARDIO-ONCOLOGY

- ❑ 133 pagina's
 - ❑ +45 suppl
- ❑ 837 referenties
- ❑ 273 aanbevelingen

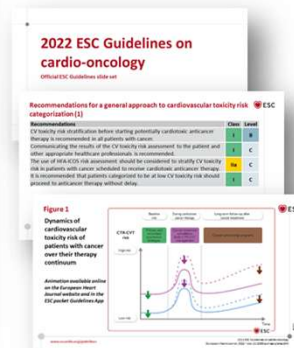
ESC Pocket Guidelines



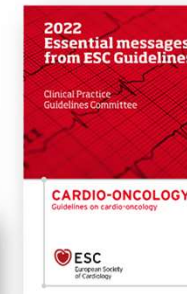
ESC Pocket Guidelines App



Official ESC Guidelines slide set



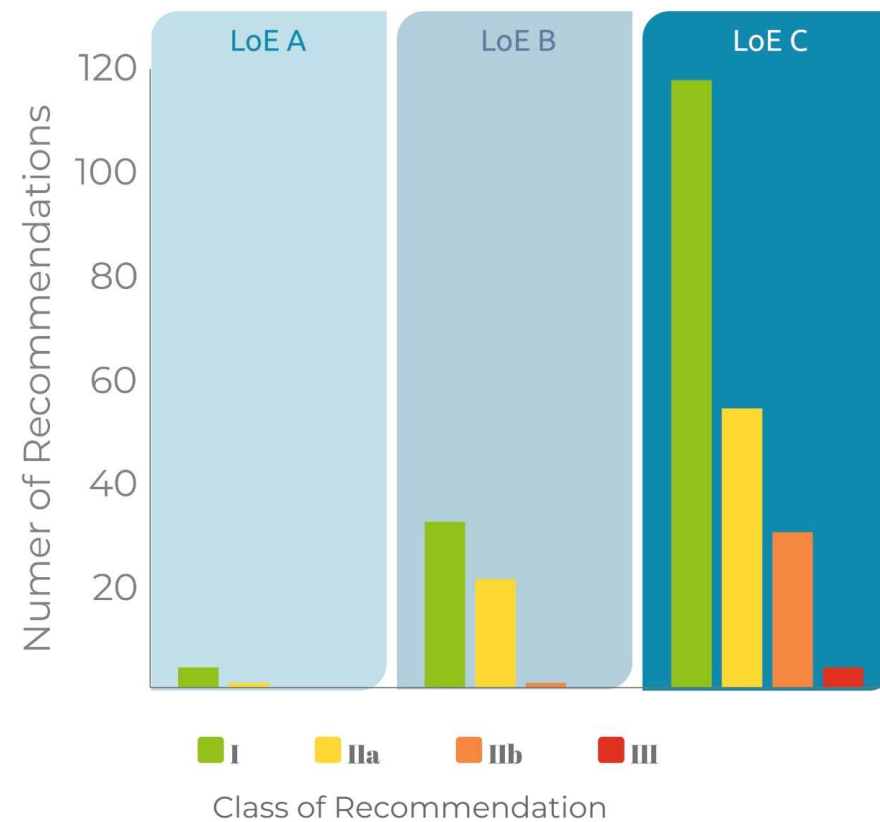
ESC Essential messages



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www.escardio.org/guidelines

ROBUSTE GUIDELINES?



UITDAGINGEN VOOR KLINISCHE IMPLEMENTATIE

- Geen leidraad tav effectieve verwijzing poli cardiologie
- Baseline risicostratificatie suboptimaal
 - Mist relevante factoren
 - Onpraktisch in klinische praktijk
- Adviezen tav screening in Nederlands zorgsysteem onhaalbaar (en onwenselijk)
- Ondanks omvangrijk document vele zaken niet behandeld
- Oncologisch veld is vol in ontwikkeling en dynamisch

MISSIE NVVC ENDORSEMENT GUIDELINE

- Haalbaarheid praktische uitvoering in de Nederlandse praktijk (time, resource, money)
- Afschalen overdiagnostiek bij gebrek aan bewijsvoering
- Nuancering aanbevelingen bij relevante patientengroepen
- Herverdeling aanbevelingen naar verantwoordelijke specialisme
- Afstemmen aanbevelingen met gepubliceerde richtlijnen
 - (hematologie / oncologie / BETER / LATER)

CTR-CVT: Cancer Therapy Related – Cardiovascular Toxicity

Asymptomatic

Severe

New LVEF reduction to <40%

Moderate

New LVEF reduction by ≥ 10 percentage points to an LVEF of 40–49% *OR*
New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either
new relative decline in GLS by >15% from baseline OR new rise in cardiac
biomarkers

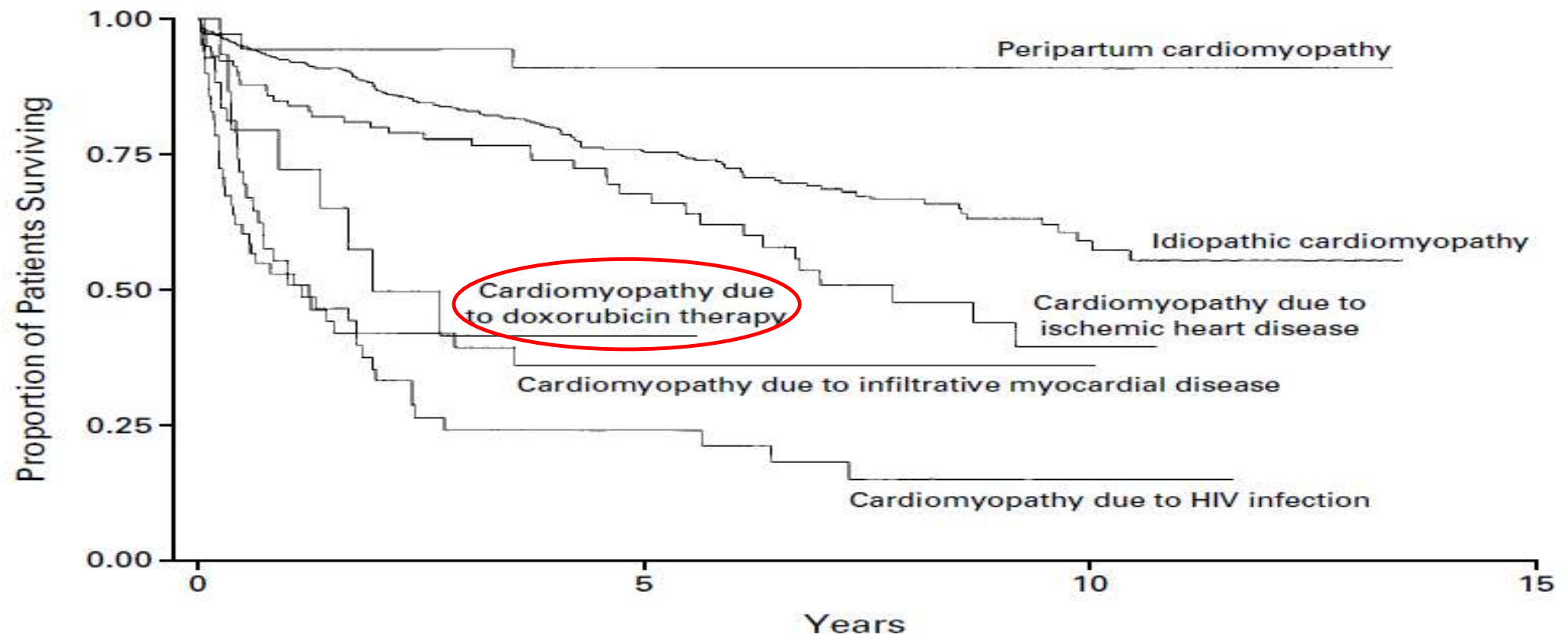
Mild

LVEF **$\geq 50\%$**
AND new relative decline in GLS by >15% from baseline
AND/OR new rise in cardiac biomarkers

CTRCD: TYPE I VS TYPE II

Type I	Type II
o.a. antracyclines	o.a. trastuzumab (herceptin)
Dosis-afhankelijk	Niet dosis-afhankelijk
Irreversibele schade	Meestal reversibel
Apoptose en necrose	Cellulaire dysfunctie

PROGNOSE CHEMO GEÏNDUCEERD HARTFALEN



Doel: Betere prognose indien vroege detectie van subklinische LVEF achteruitgang?

HFA ICOS RISICOCALCULATOR

1. Type anti-kanker therapie
- 2. CV belast**
3. Cardiale biomarkers
4. Leeftijd
5. CV risicofactoren (HT, DM, CKD)
6. Eerdere cardiotoxische therapie
7. Levensstijlfactoren (roken, overgewicht)

No history of cardiovascular disease

Heart failure or cardiomyopathy

Severe valvular heart disease

Myocardial infarction or previous coronary revascularisation

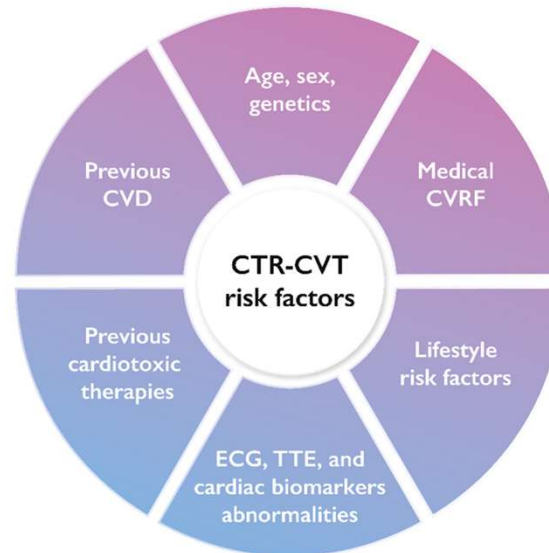
Stable angina

Baseline LVEF < 50%

Baseline LVEF 50-54%

BASELINE CV TOXICITY RISK ASSESSMENT

Baseline CV toxicity risk assessment checklist



Clinical assessment

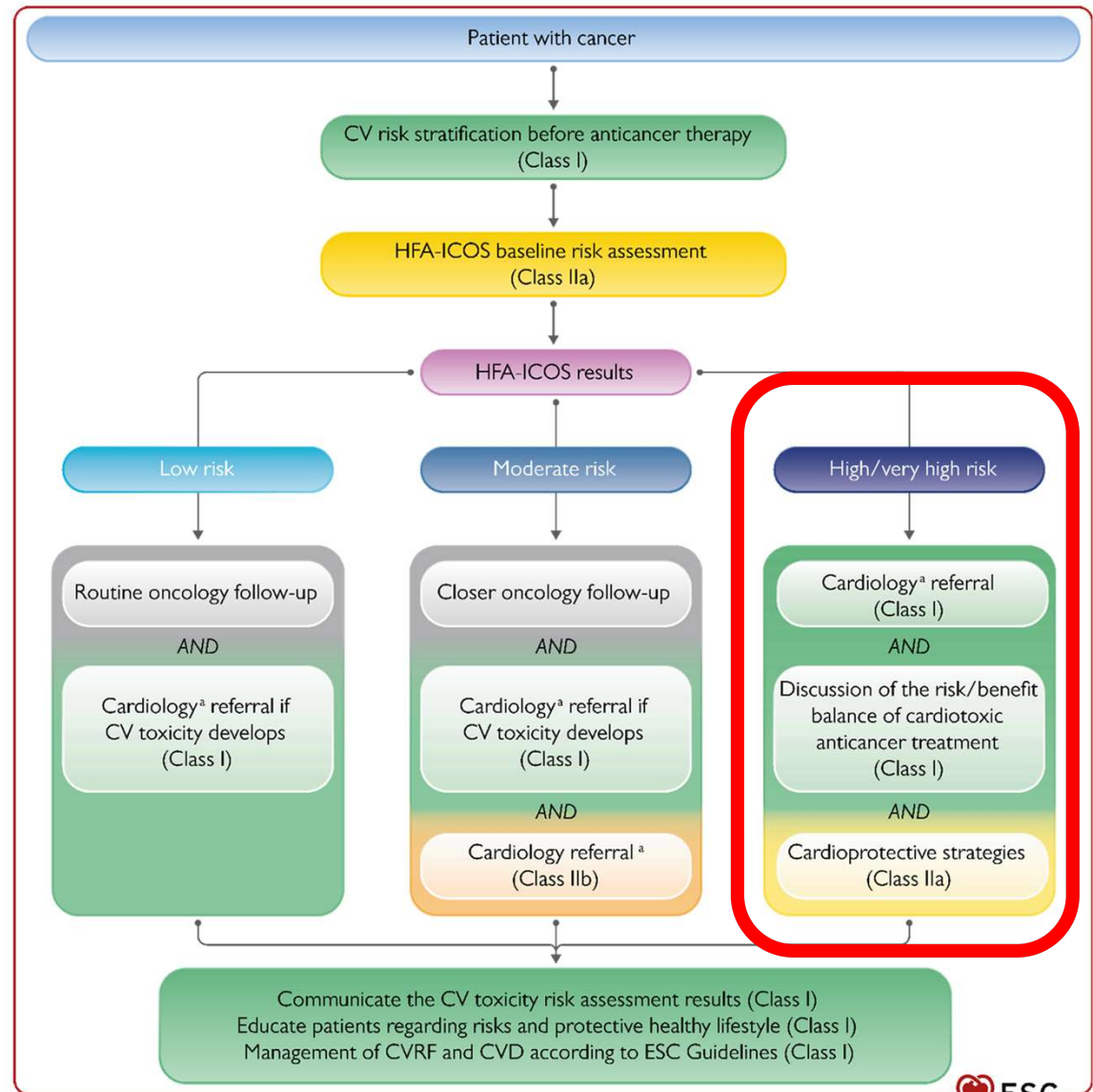
- Cancer treatment history
- CV history
- CVRF
- Physical examination
- Vital signs measurement^a

Complementary tests

- BNP or NT-proBNP^b
- cTn^b
- ECG
- Fasting plasma glucose / HbA1c
- Kidney function / eGFR
- Lipid profile
- TTE^c



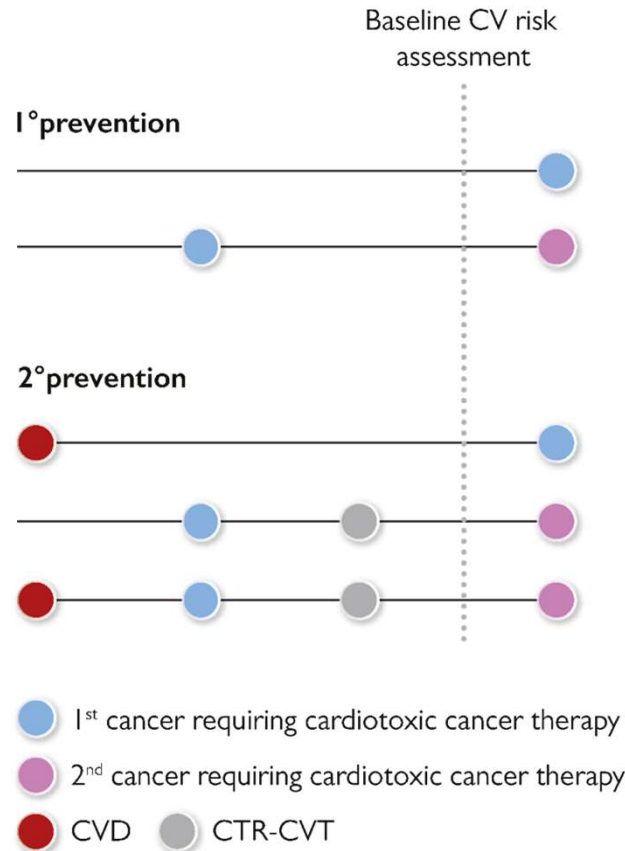
FLOW-CHART CARDIO- ONCOLOGY APPROACH



PRIMARY AND SECONDARY PREVENTION

Primary and secondary cancer-therapy related CV toxicity prevention strategies

Primary vs secondary prevention



Management of CVD and CVRF according to ESC Guidelines

In patients at high and very high risk of CTRCD

Minimize the use of cardiotoxic drugs

ACE-I/ARB and beta-blockers

Dexrazoxane/liposomal anthracyclines
(patients treated with anthracyclines)

Statins



Class I



Class IIa

Baseline screening - (very) high risk patients

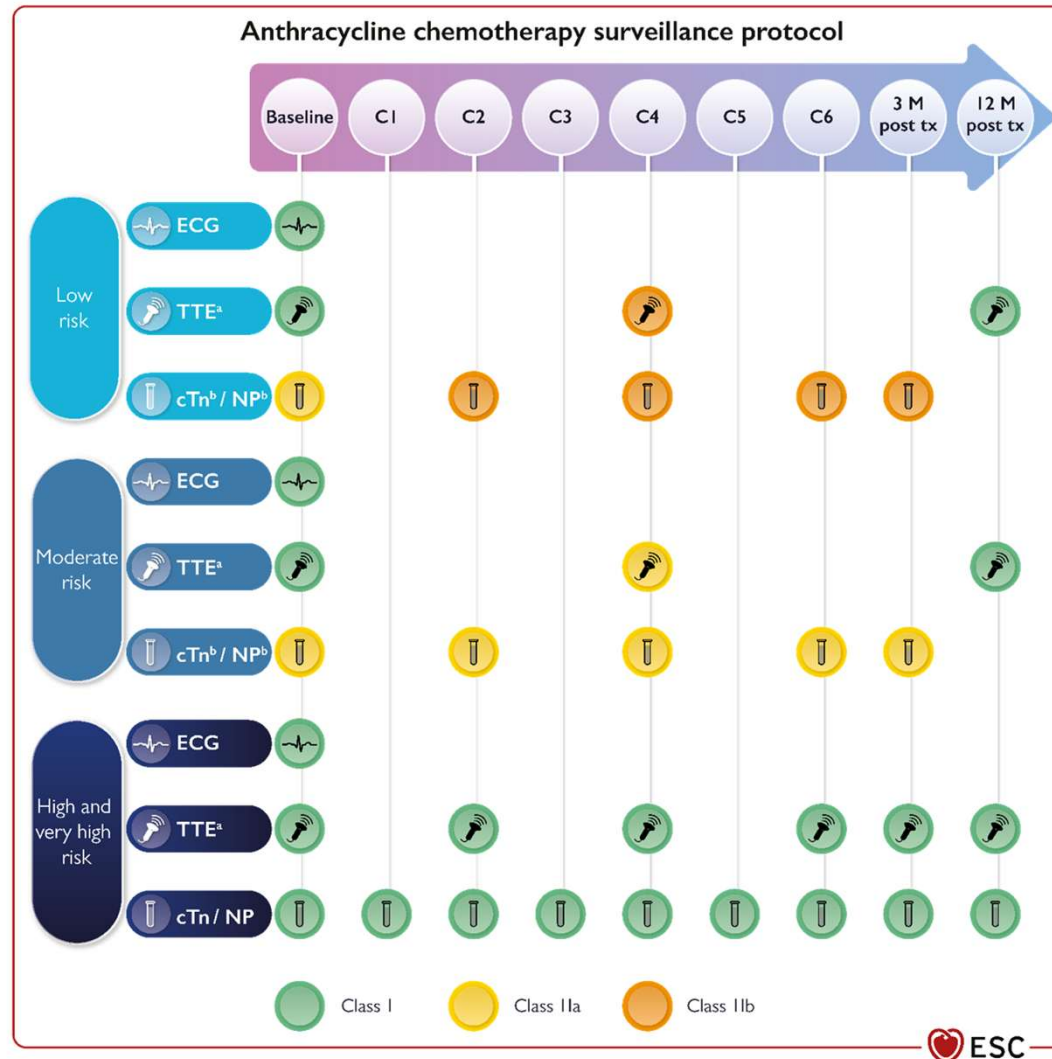
Baseline clinical CV assessment, physical exam and ECG are recommended in all cancer patients scheduled for cardiotoxic therapies ^a

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

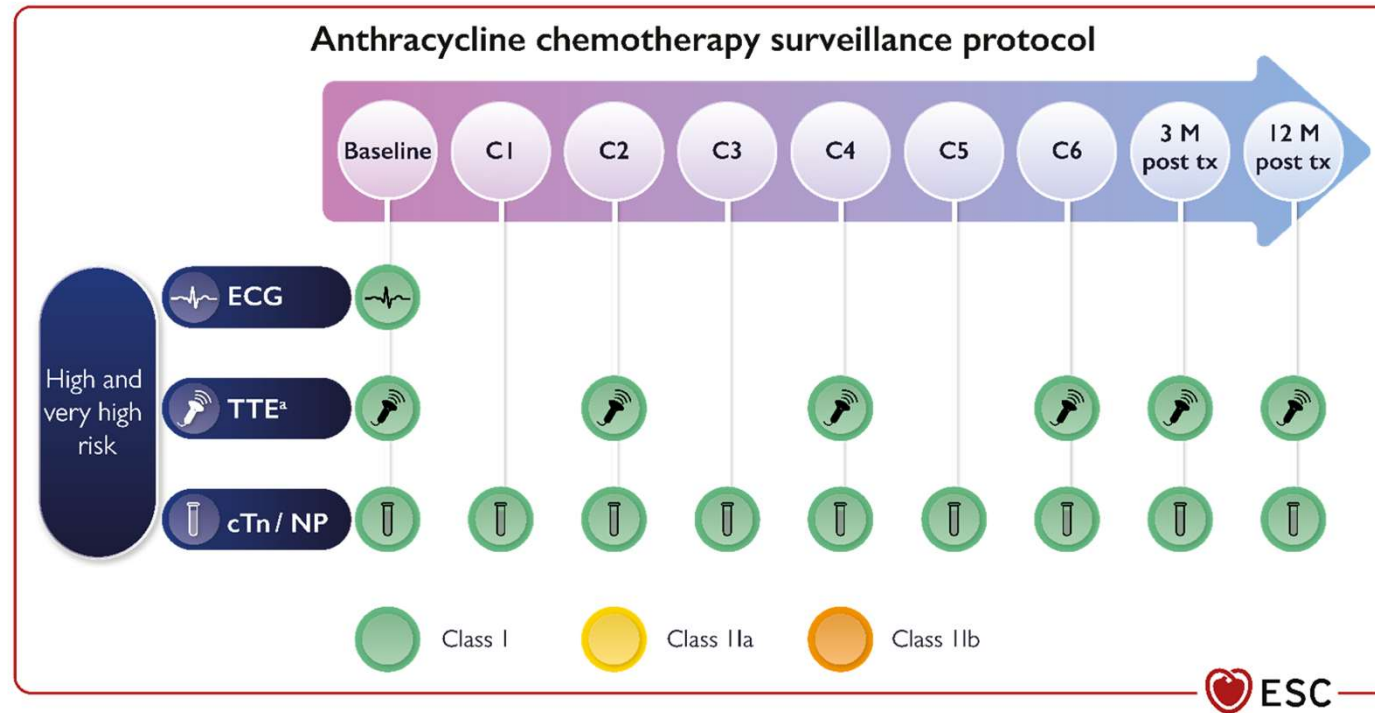
Very high risk Moderate risk Low risk Other conditions Class I Class IIa Class IIb
 ESC

ANTHRACYCLINES

CV toxicity monitoring - Anthracyclines



CV toxicity monitoring - Anthracyclines



TTE:

Baseline in all patients - IB

TTE after 12 months of Tx – IB

(very) high risk pt every 2 cycles and 3 months after Tx – IC

Moderate risk + >250mg/m² IIa-C

Low risk + >250mg/m² lib-C

Biomarkers:

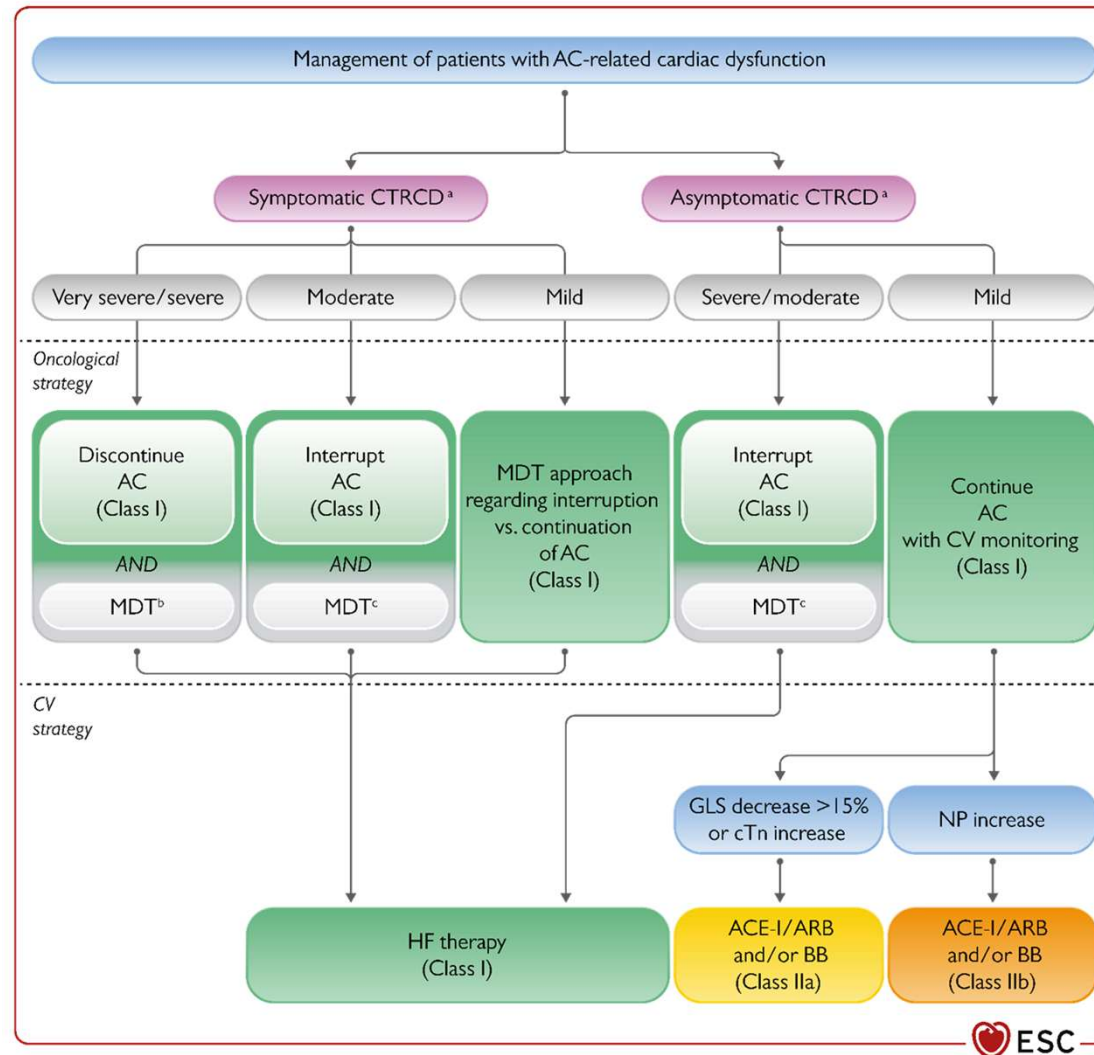
Baseline NP en cTn in (very) high risk patients - IB

Baseline NP en cTn in low – moderate - risk patients - IIaC

(cTn and NP every cycle and 3 -12 months after

in (very) high risk patients - IB

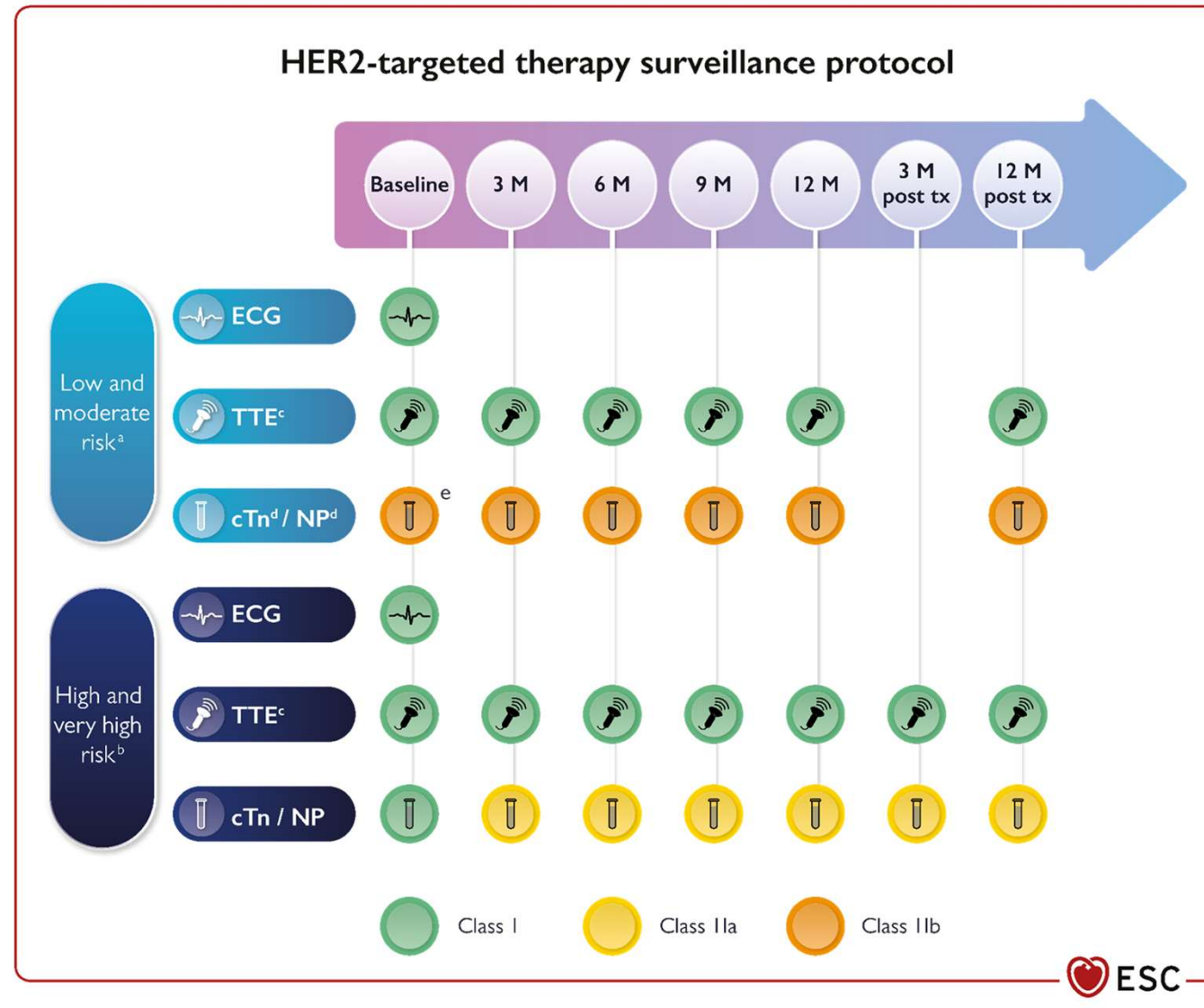
Management of anthracycline – CTR-CD



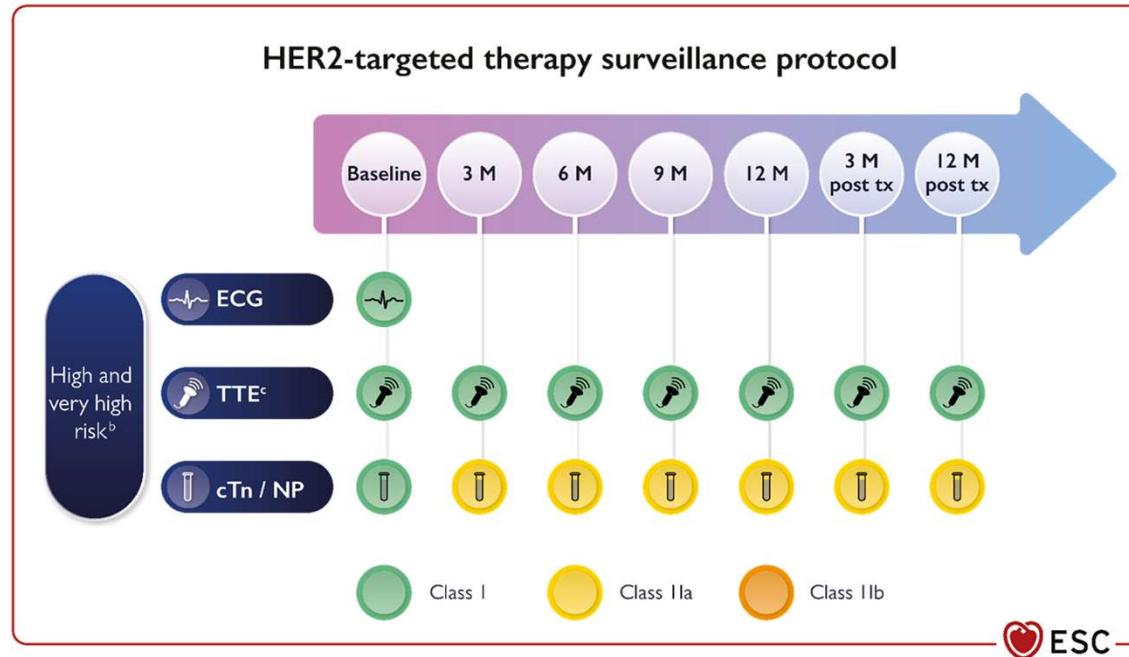


HER2 TARGETED THERAPY

CV toxicity monitoring – HER2 targeted Tx



CV toxicity monitoring – HER2 targeted Tx



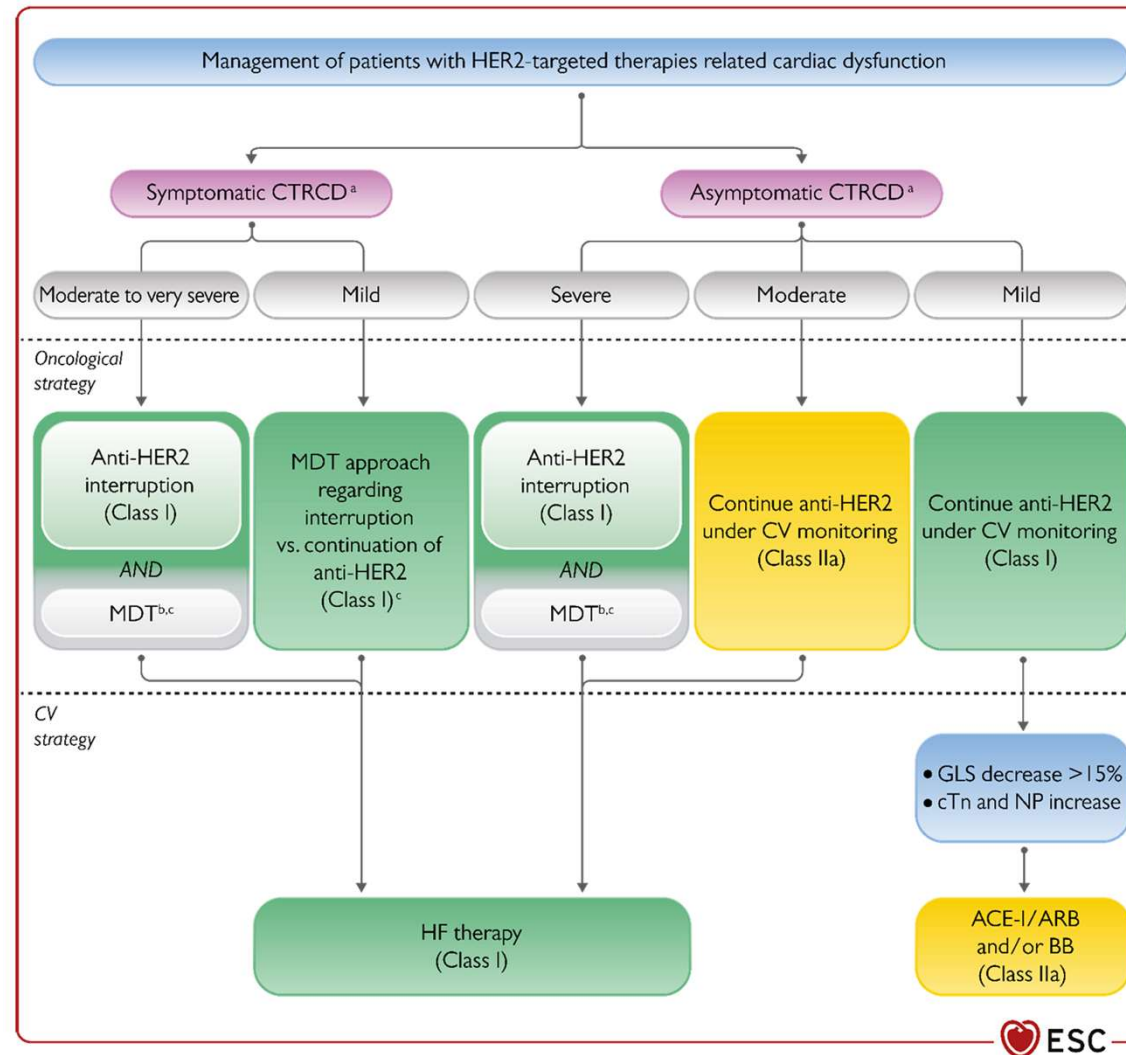
TTE:

Baseline in all patients - IB
HER2 as (neo)adjuvant TTE every 3 months and within 12 months after Tx – IB
4 months instead of 3 months in low-risk with normal TTE and no symptoms – IIBC
(very) high risk, more frequent TTE - IIaC

Biomarkers:

Baseline NP en cTn in (very) high risk patients - IB
Baseline NP en cTn in low – moderate - risk patients after anthracyclines - IIaA
(cTn and NP every 2-3 cycles and 3 -12 months after in (very) high risk patients - IIaC

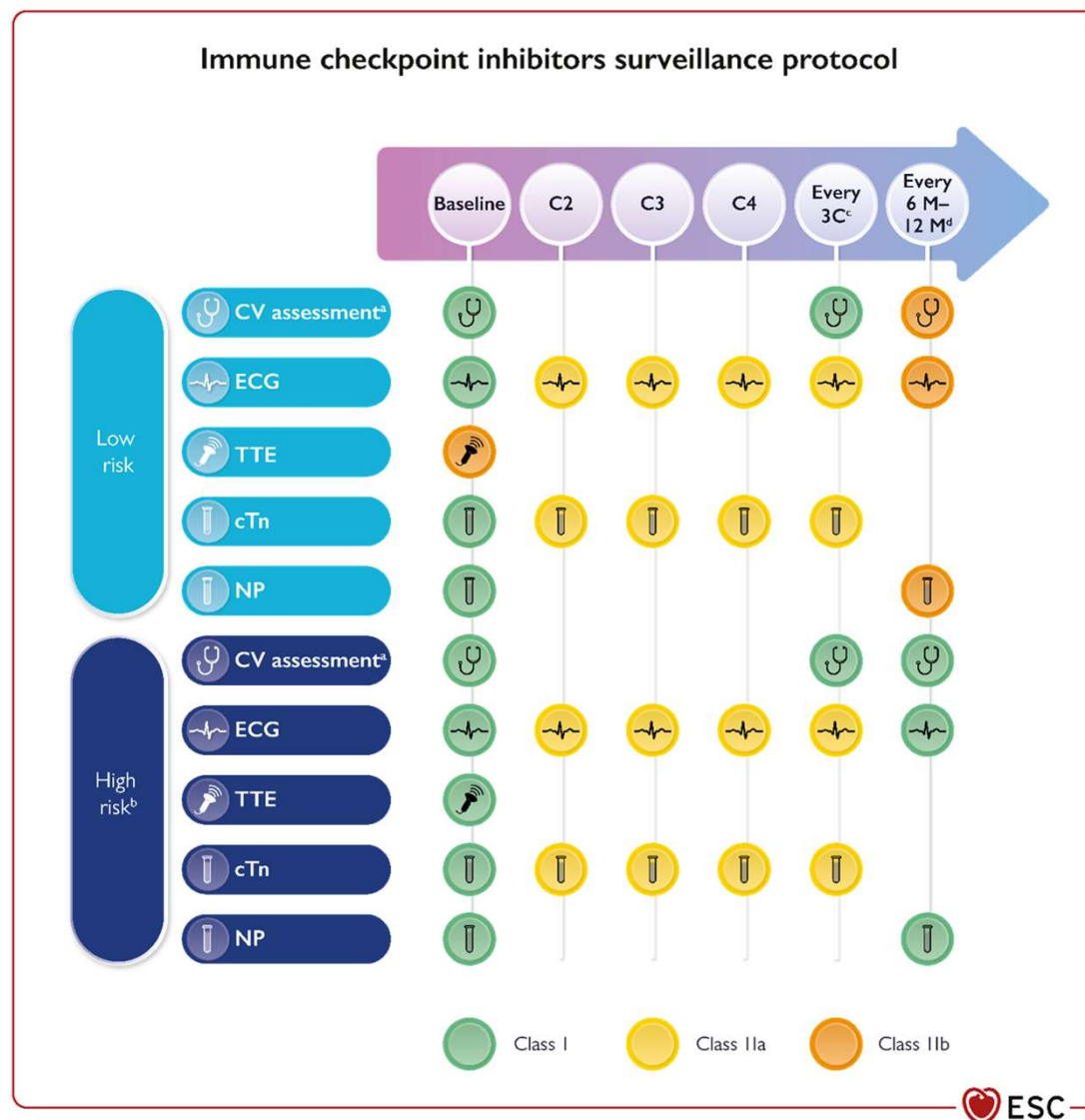
Management of HER2 – CTR-CD





IMMUNE CHECKPOINT INHIBITORS

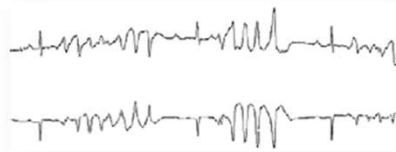
CV surveillance – Immune checkpoint Inhibitors



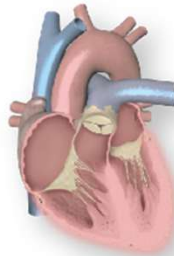
CV Toxicity – Immune checkpoint Inhibitors

Direct CV Toxicity

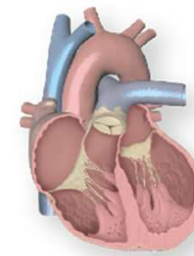
Arrhythmias



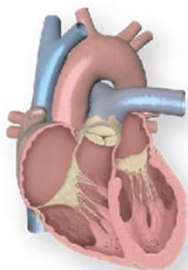
Myocarditis



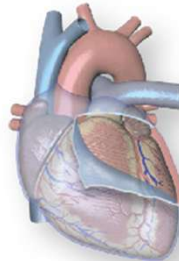
Non-inflammatory HF



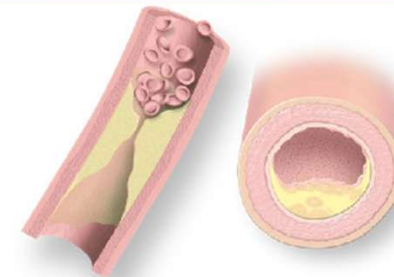
Takotsubo syndrome



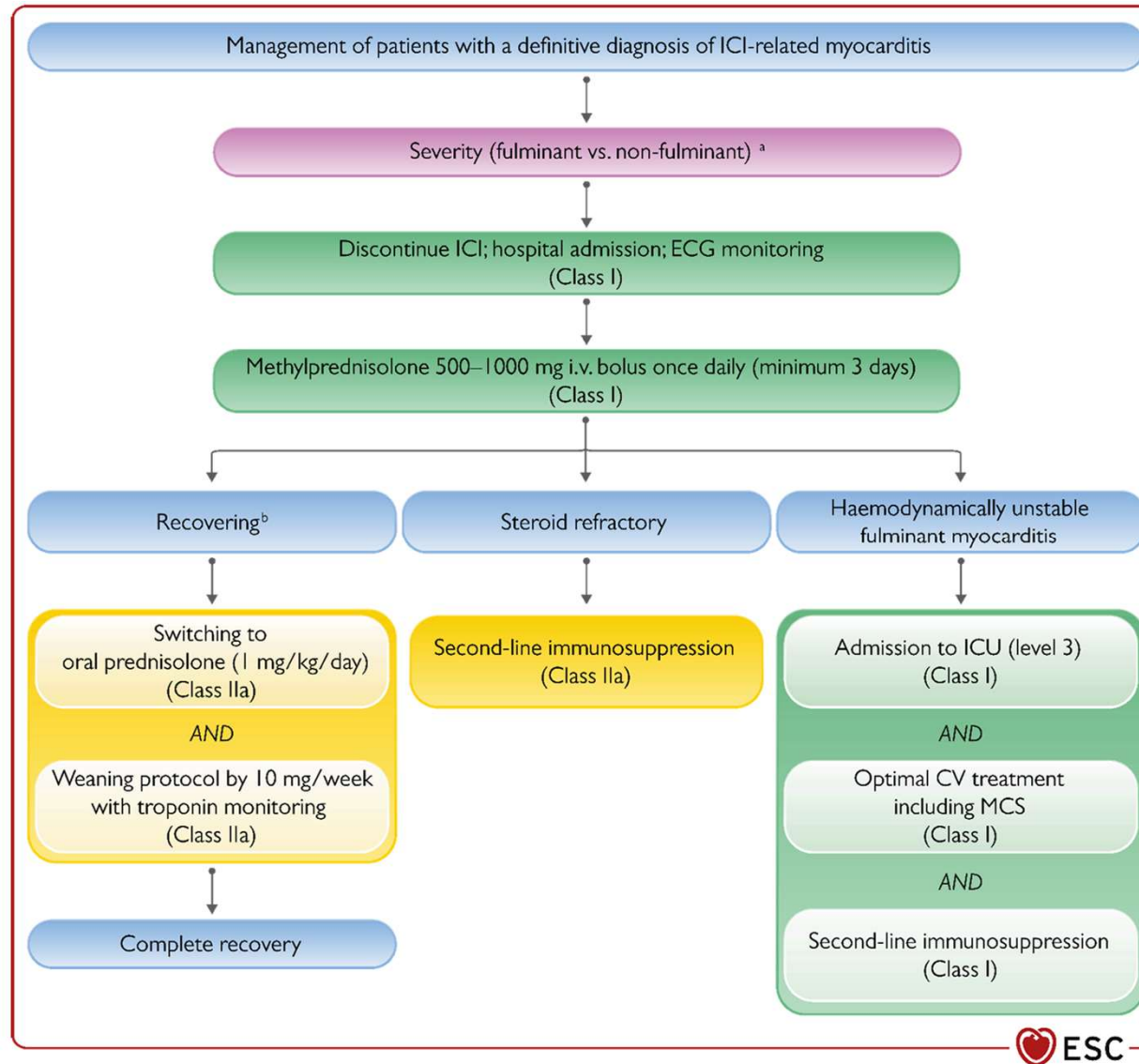
Pericarditis



Vascular



Diagnosis and management – ICI myocarditis

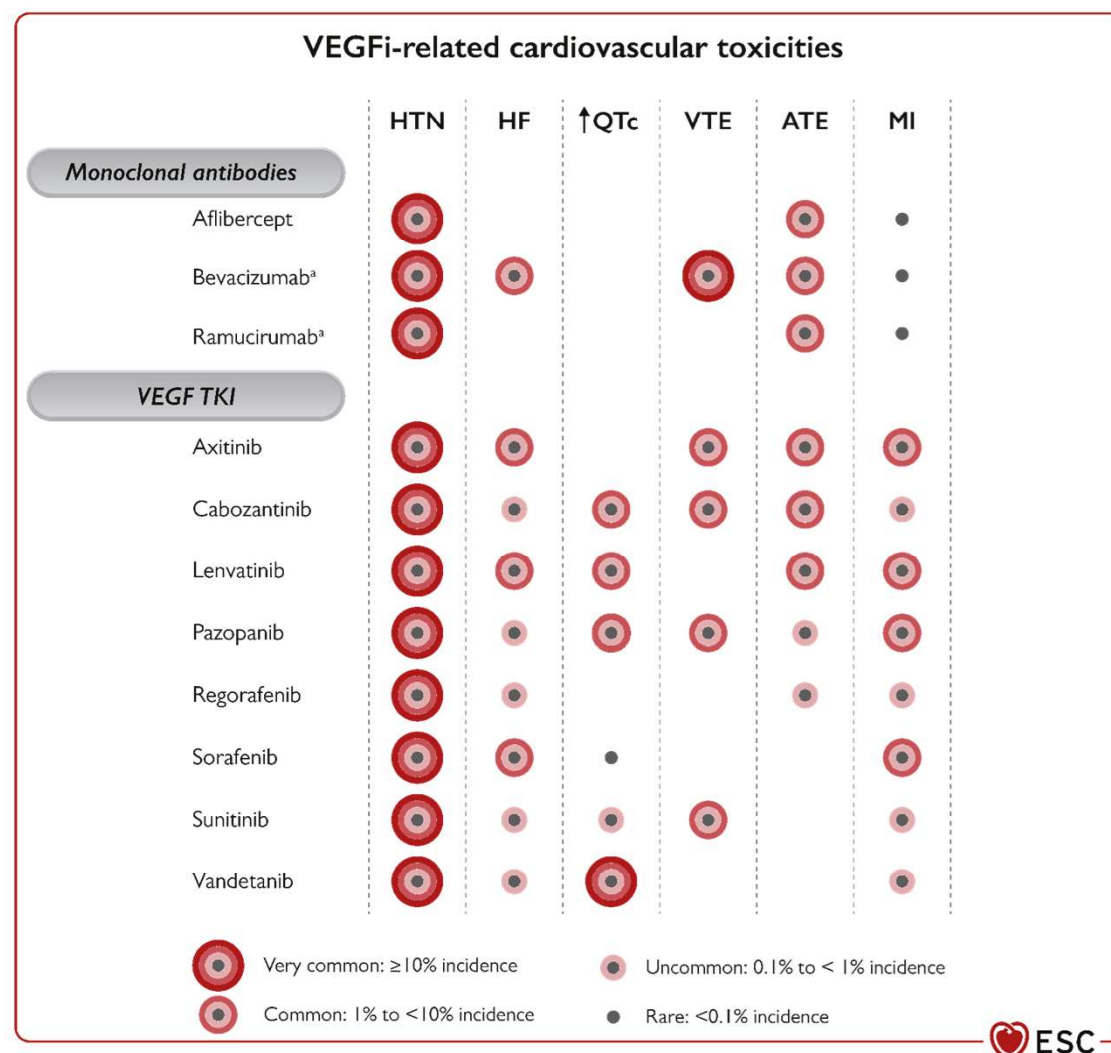




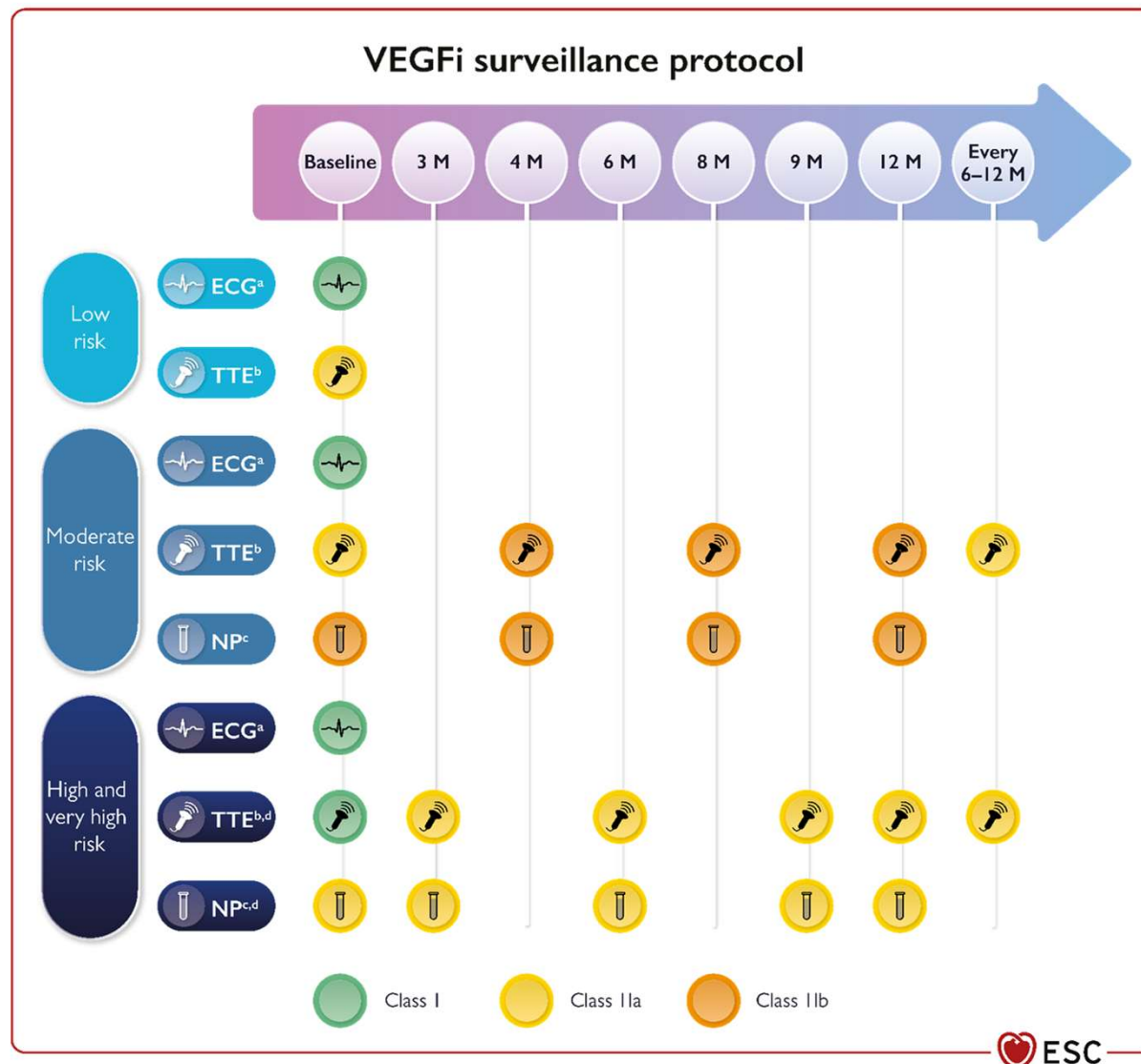
VEGFI

Figure 12

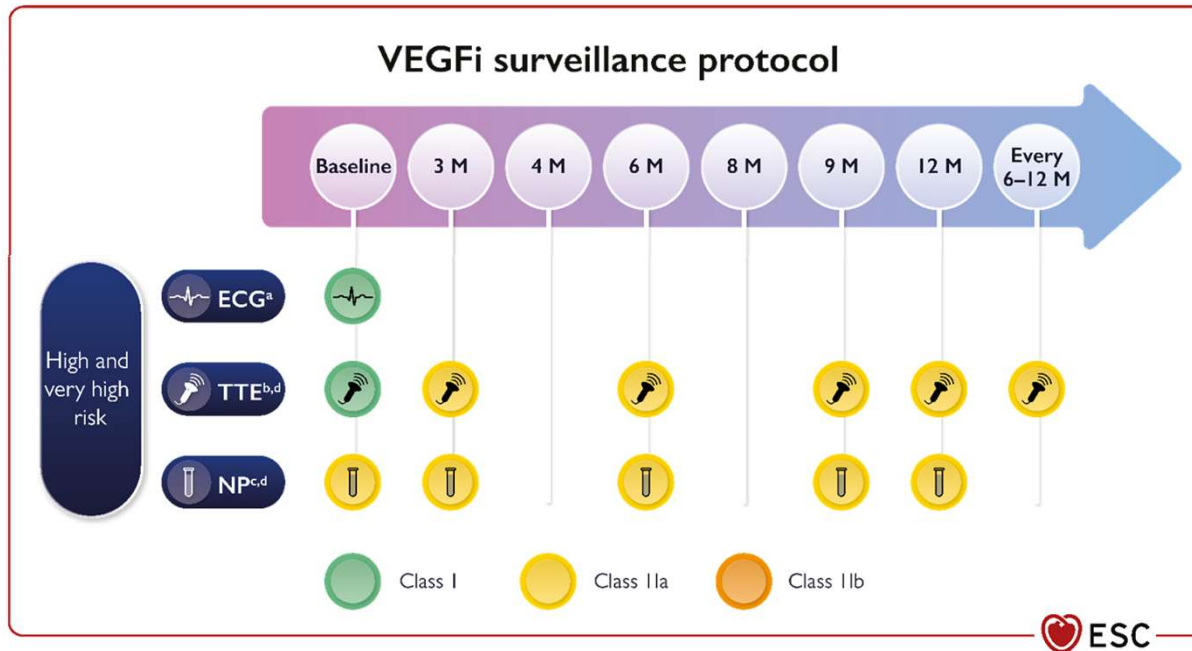
VEGFi-related cardiovascular toxicities



CV toxicity monitoring – VEGFi targeted Tx



CV toxicity monitoring – VEGFi targeted Tx



BP monitoring:

BP at every clinical visit – IC

Daily home monitoring (1^e cycle, any increase) – IC

ECG monitoring:

Risk for QTc prolongation, assess monthly till 3 months, thereafter 3-6 months – IC

TTE:

Baseline in (very) high risk patients - IC

Every 3 months in (very) high risk patients – IIaC

Baseline in low- and moderate risk patients – IIaC

Every 6-12 months in low- and moderate risk - IIaC

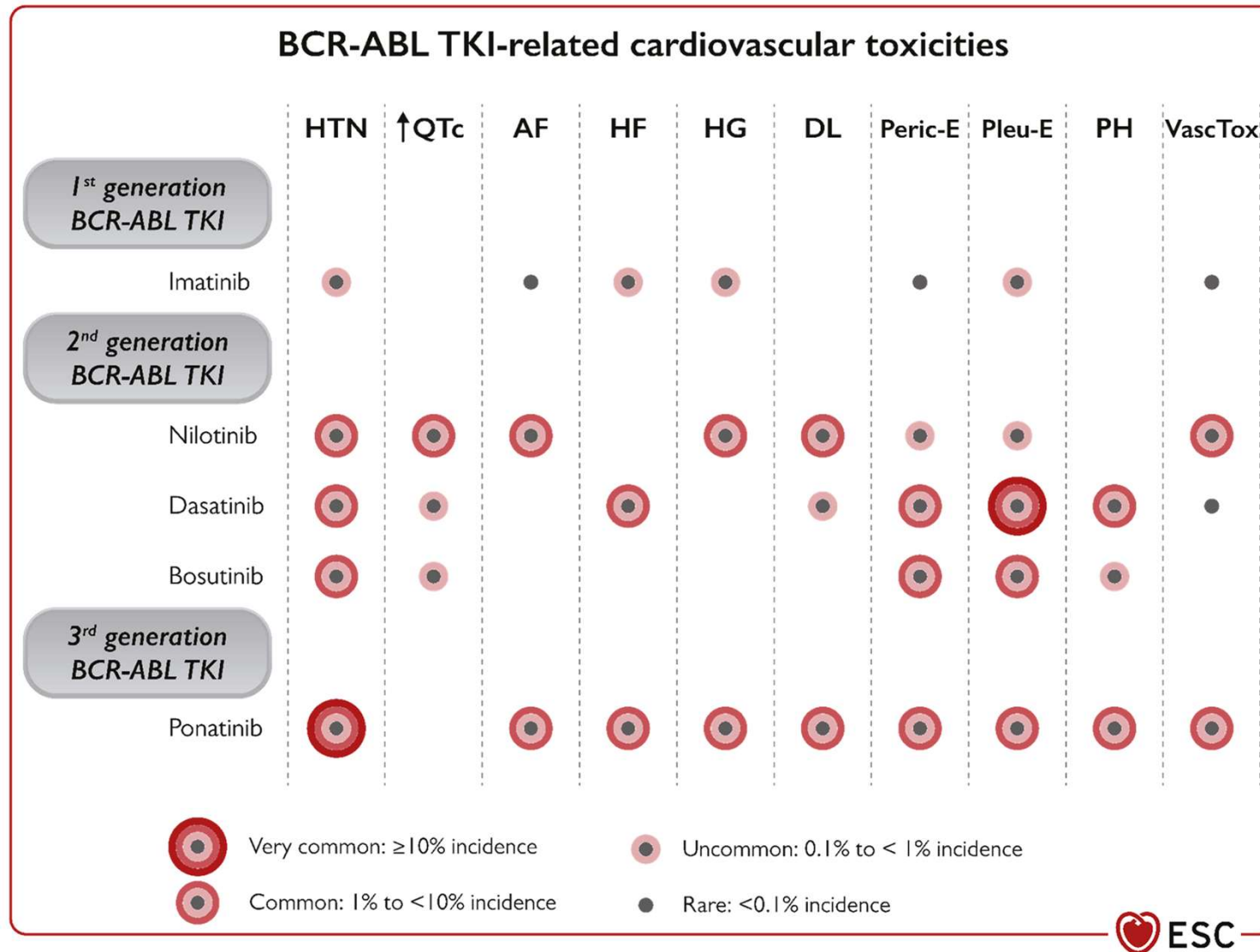
Biomarkers:

Baseline NP, 4 weeks and every 3 months in (very) high risk patients - IIaC

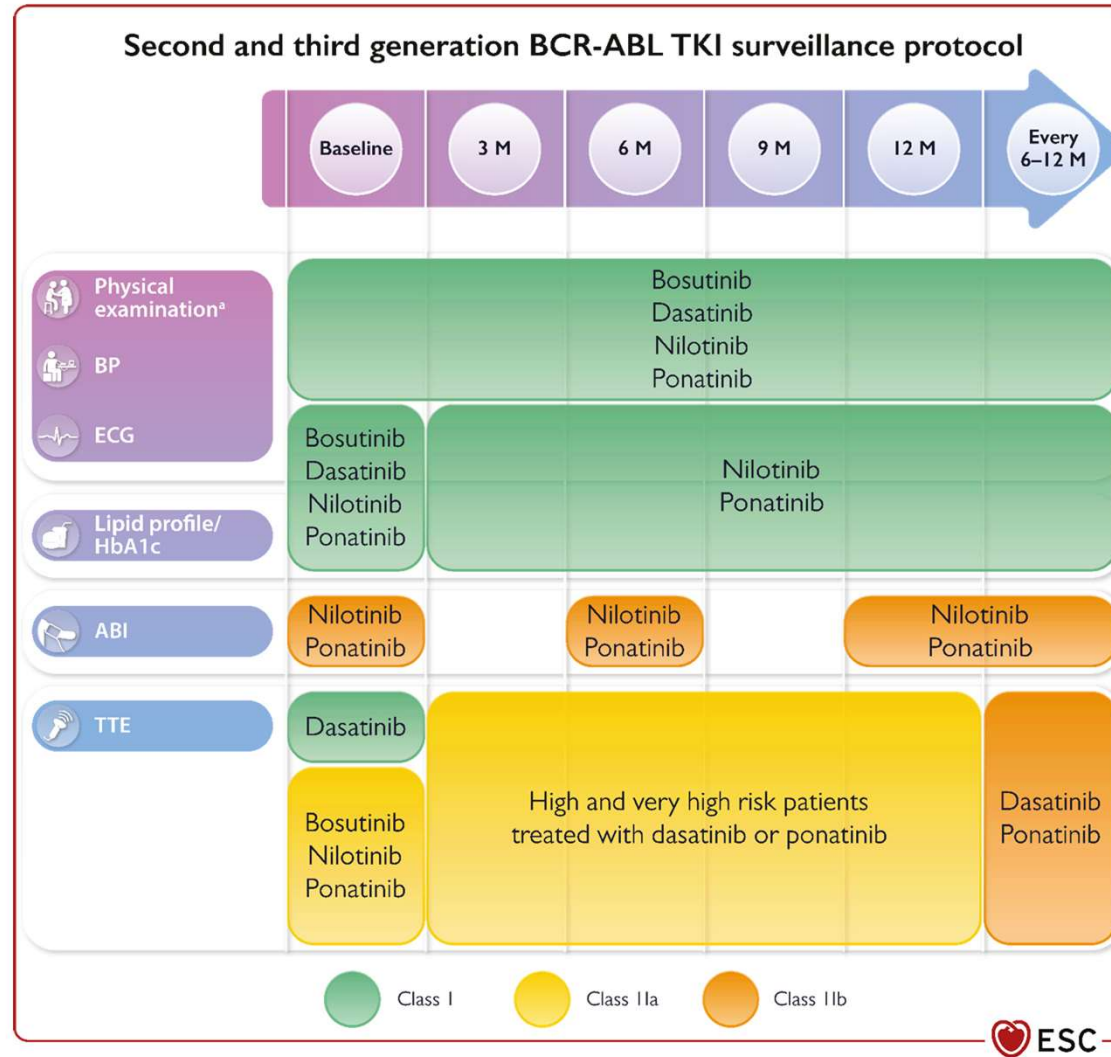


BCR-ABL

BCR-ABL TKI CV toxicities



CV toxicity monitoring – BCR-ABL TKI





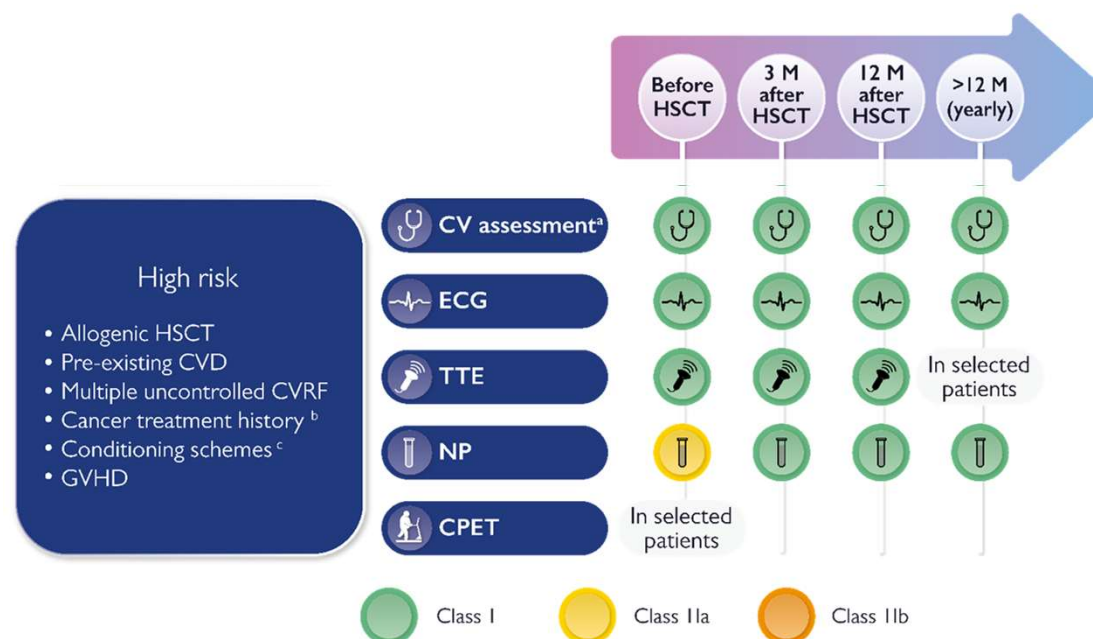
HAEMATOPOIETIC STEM CELL TRANSPLANTATION

CV Surveillance - HSCT

Cardiovascular surveillance in patients referred for haematopoietic stem cell transplantation



CV Surveillance - HSCT



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

OVERIGE MIDDELEN

Figure 16

Multiple myeloma drug-related cardiovascular toxicities

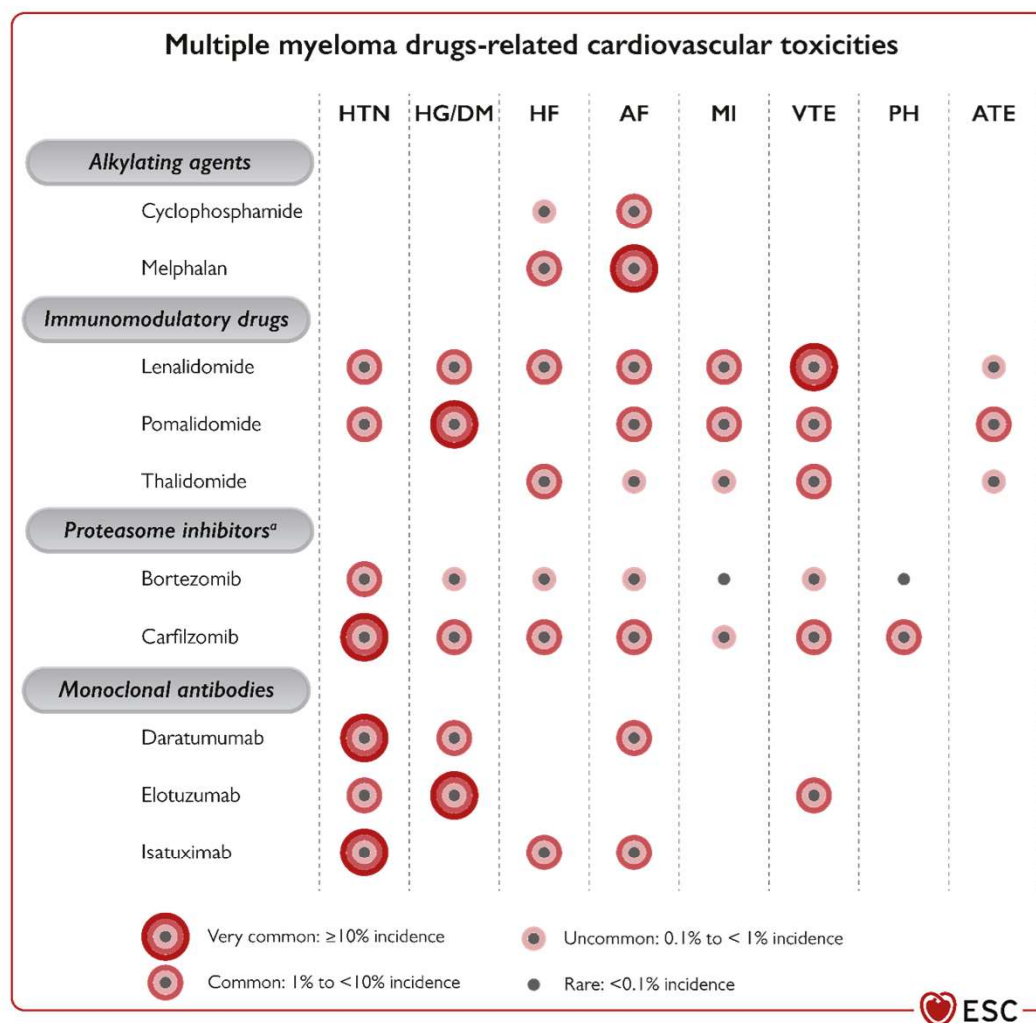


Figure 19

RAF and MEK inhibitor-related cardiovascular toxicities

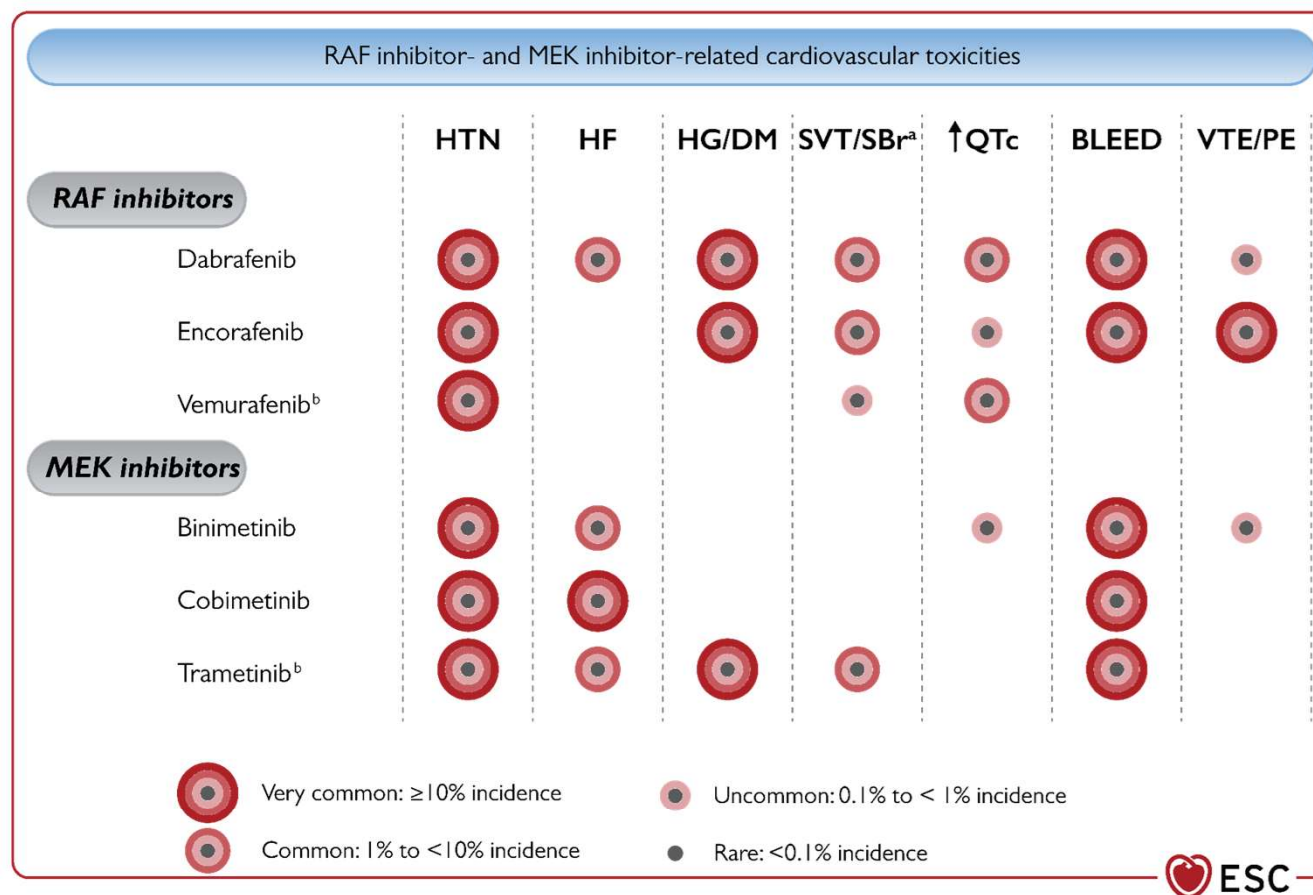


Figure 21

Androgen deprivation therapy-related cardiovascular toxicities

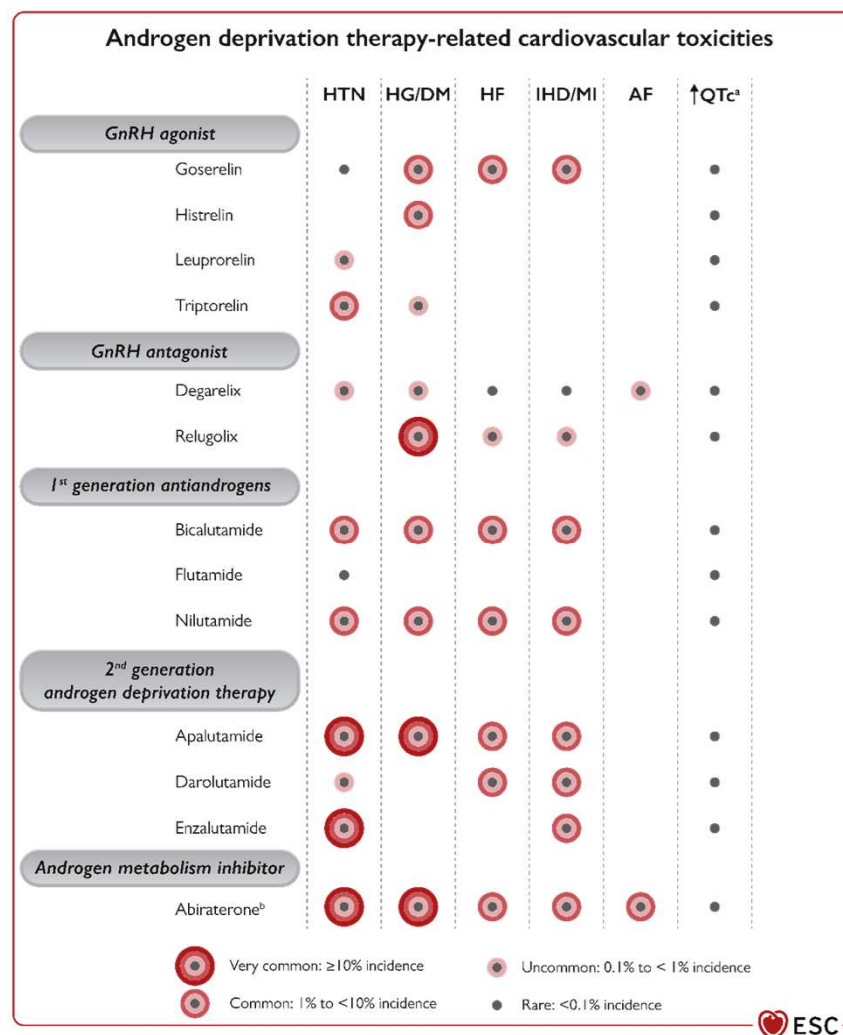
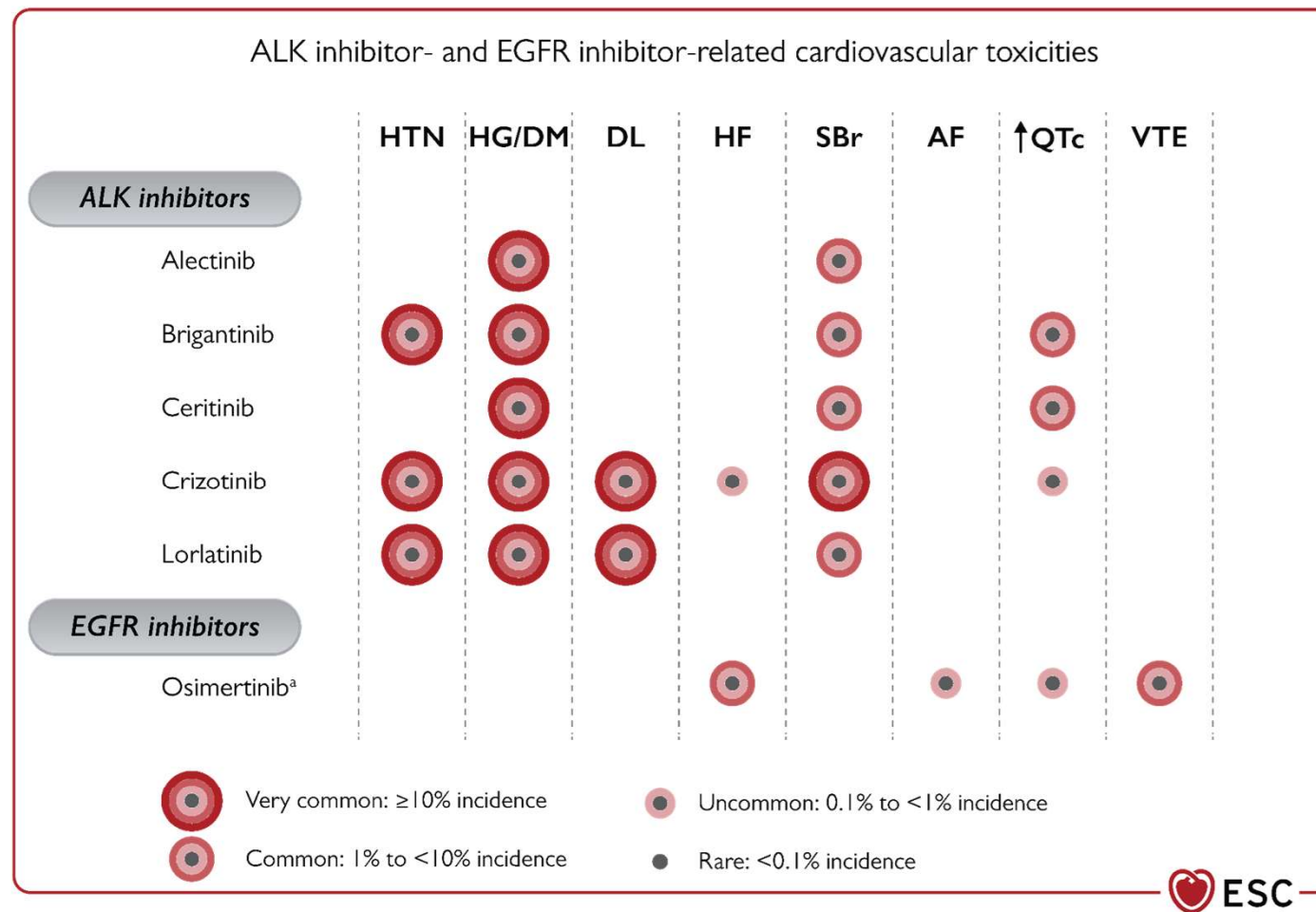
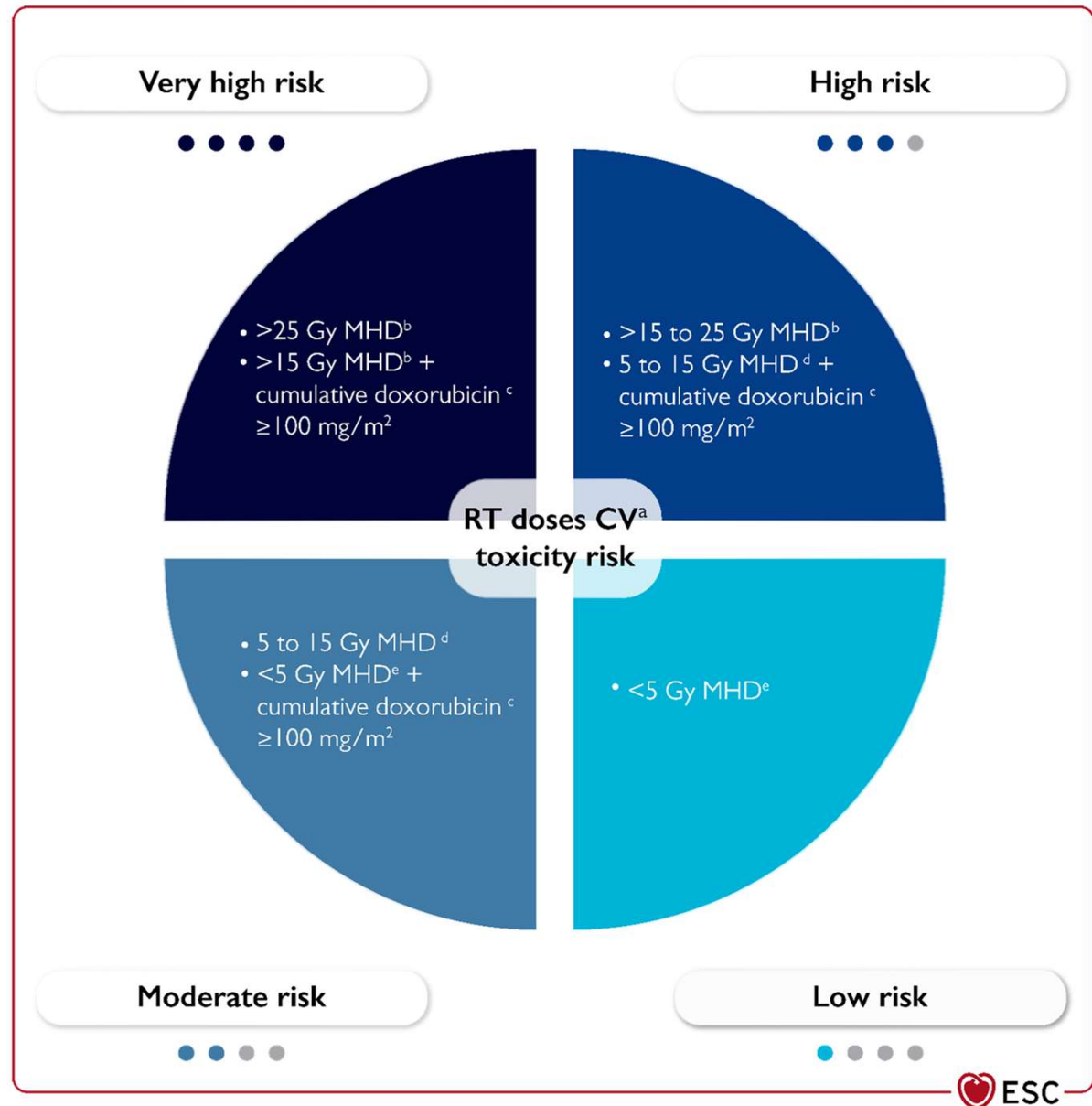


Figure 22

ALK and EGFR inhibitor-related cardiovascular toxicities



Radiotherapy dose associated with CV toxicity risk



Recommendation for adult cancer survivors with pericardial complications

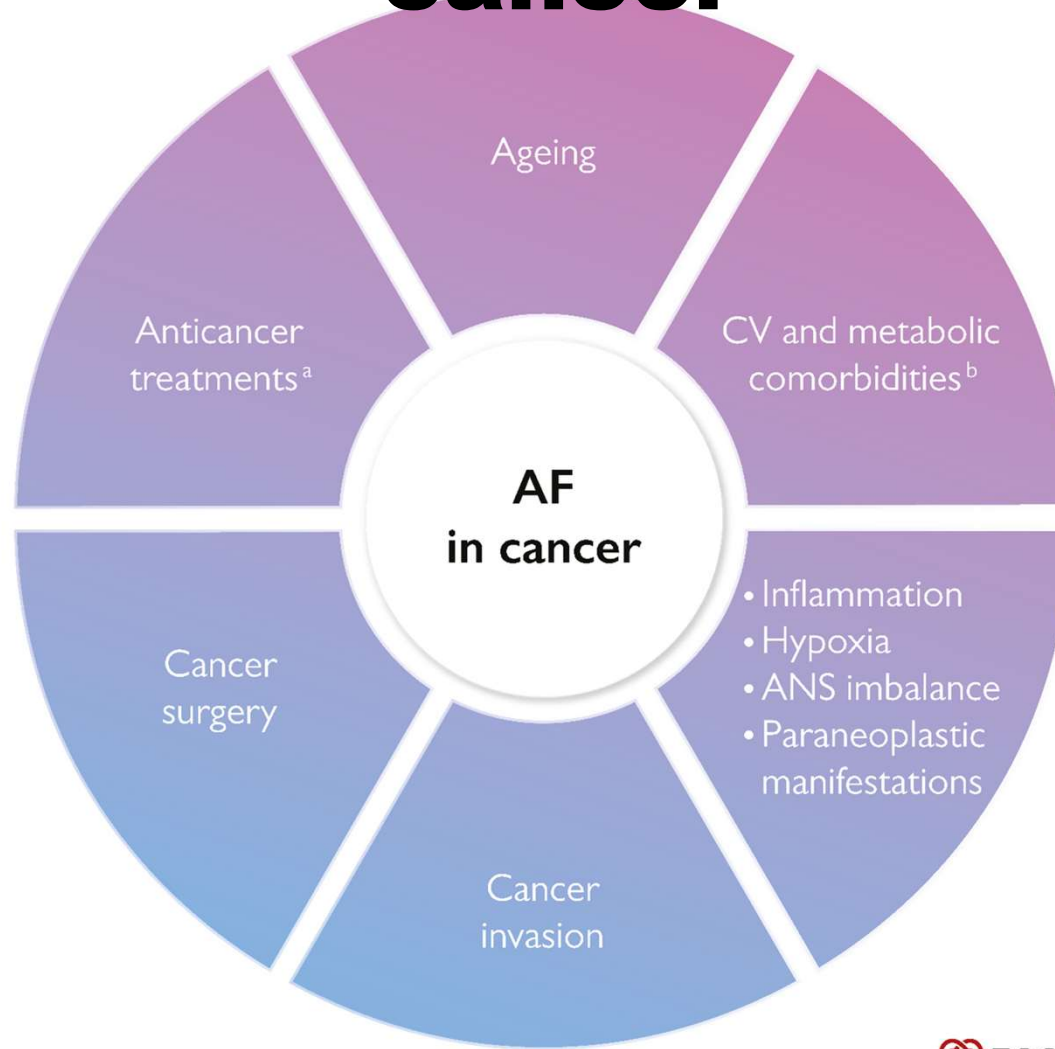


Recommendations	Class	Level
Patients with acute pericarditis during RT to a volume including the heart are at higher risk of developing chronic constrictive pericarditis, hence echocardiography surveillance every 5 years may be considered.	IIb	C



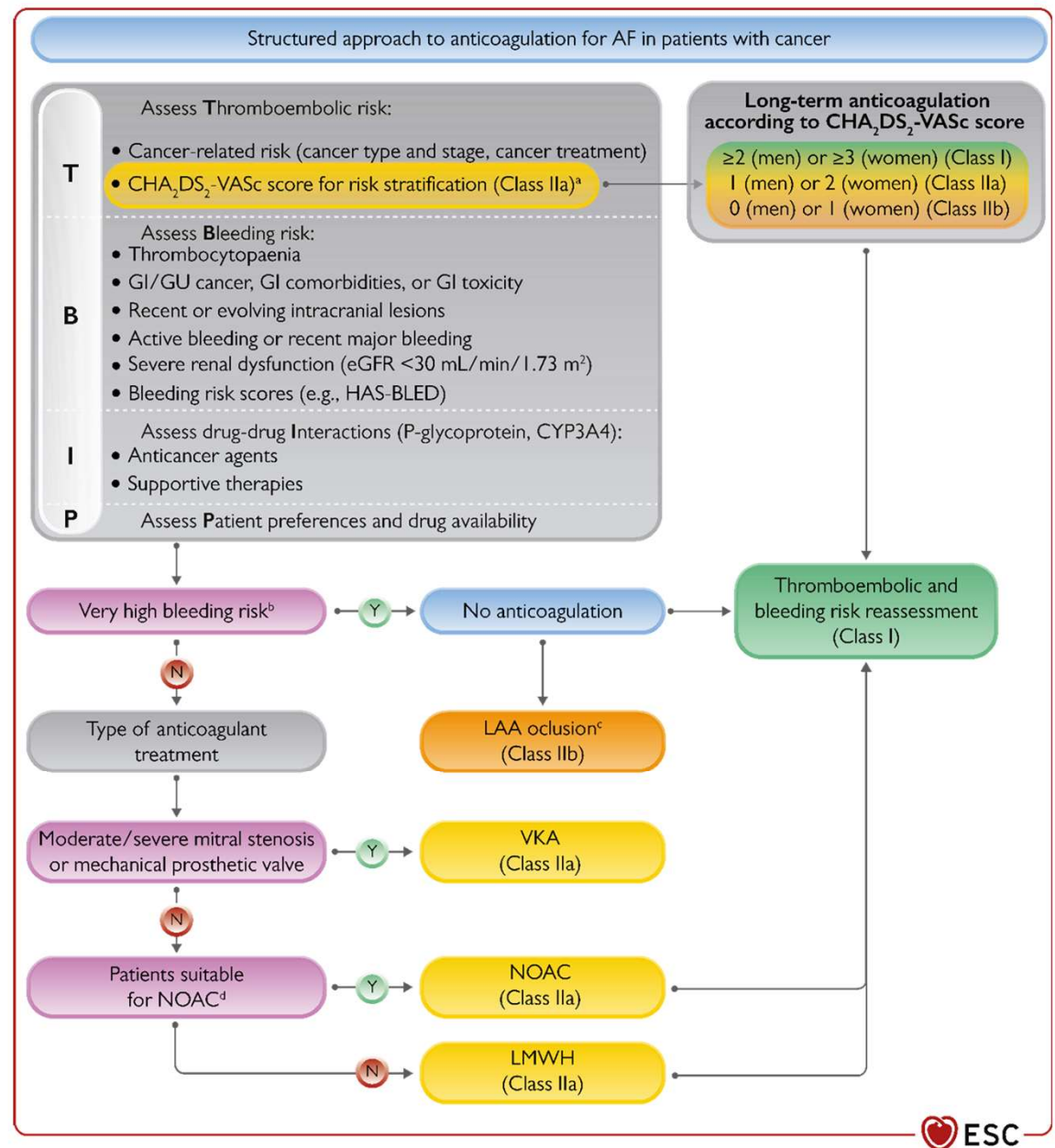
ATRIAL FIBRILLATION & CANCER

Pathophysiology of AF associated with cancer



Approach of AF in patients with cancer

Cancer patients have an increased thrombotic risk!





CANCER & CORONARY ARTERY DISEASE

Cancer treatment that predispose to acute coronary syndrome

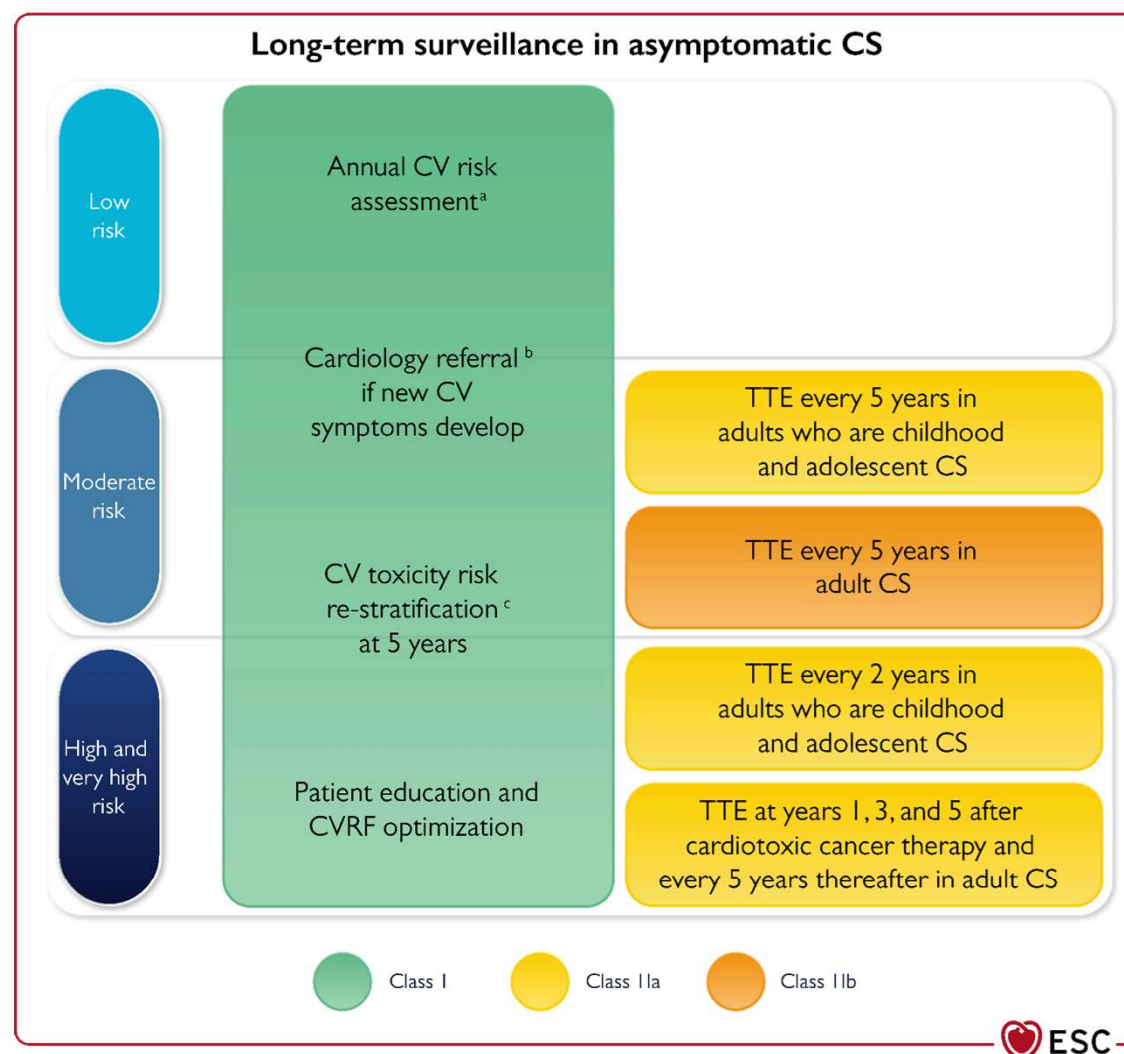
Accelerated atherosclerosis and plaque rupture	ADT (GnRH agonists), ICI, nilotinib, ponatinib, radiation therapy, VEGFi
Vasospasm	Bleomycin, fluoropyrimidines, taxanes, VEGFi, vinca alkaloids
Coronary thrombosis	Alkylating agents (cisplatin, cyclophosphamide), erlotinib, ICI, IMiD (lenalidomide, thalidomide),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



CANCER SURVIVORS

Figure 38

Long-term follow-up in cancer survivors



WAT DOE JE AAN ASYMPTOMATISCHE LV DYSFUNCTIONIE?

Recommendations for adult cancer survivors who develop cancer therapy-related cardiac dysfunction late after cardiotoxic cancer therapy



Recommendations	Class	Level
ACE-I/ARB and/or beta-blockers are recommended in adult CS with moderate asymptomatic CTRCD.	I	C
ACE-I/ARB and/or beta-blockers may be considered in adult CS with mild asymptomatic CTRCD.	IIb	C

WAT DOE JE AAN KLEPLIJDEN?

Recommendations for adult cancer survivors with valvular heart disease ESC

Recommendations	Class	Level
A MDT approach is recommended to discuss and define the surgical risk in CS with severe VHD.	I	C
TAVI should be considered for patients with symptomatic severe aortic stenosis caused by radiation at intermediate surgical risk.	Ila	B

WAT DOE JE AAN CORONAIRLIJDEN?

Recommendations	Class	Level
<i>Symptomatic radiation-induced CAD detected during surveillance</i>		
Pre-operative assessment of LIMA and RIMA viability, venous access, and sternal wound healing is recommended in CS with radiation-induced CAD where CABG is considered.	I	C
PCI may be considered in CS with radiation-induced CAD with severe left main or three-vessel disease with a high SYNTAX score (>22) in whom the procedure is technically feasible.	IIb	B

6. HOE STEL JE HARTFALEN VAST?

Electrocardiogram

Bloedonderzoek (NT-proBNP en hsTnT)

Echocardiografie

In geselecteerde gevallen:

CT coronairen/Coronairangiografie

MRI cor

Hartbiopt

Allemaal zoekend naar oorzaak en wat er aanvullend gedaan kan worden.

WAT IS NODIG VOOR DE DIAGNOSE ?

Klachten – symptomen

+

Dysfunctie van hart

- Moeheid
- Kortademigheid
- Vochtretentie
- Misselijkheid/verminderde eetlust
- *Hoge hartfrequentie*
- *Derde harttoon*
- *Crepitatie longen*
- *Oedeem*
- *Grote lever - ascites*
- *Bleekheid*

- Contracties verminderd
- Hoge vullingsdrukken
- Vulling gestoord
- Klepafwijkingen
- Dimensies abnormaal
- Wanddikten abnormaal
- *Geleidingsstoornissen*
- *Ritmestoornissen*

WAT ZIJN DE MEEST VOORKOMENDE OORZAKEN VAN HARTFALEN?

Myocardinfarct

Hypertensie

Cardiomyopathie

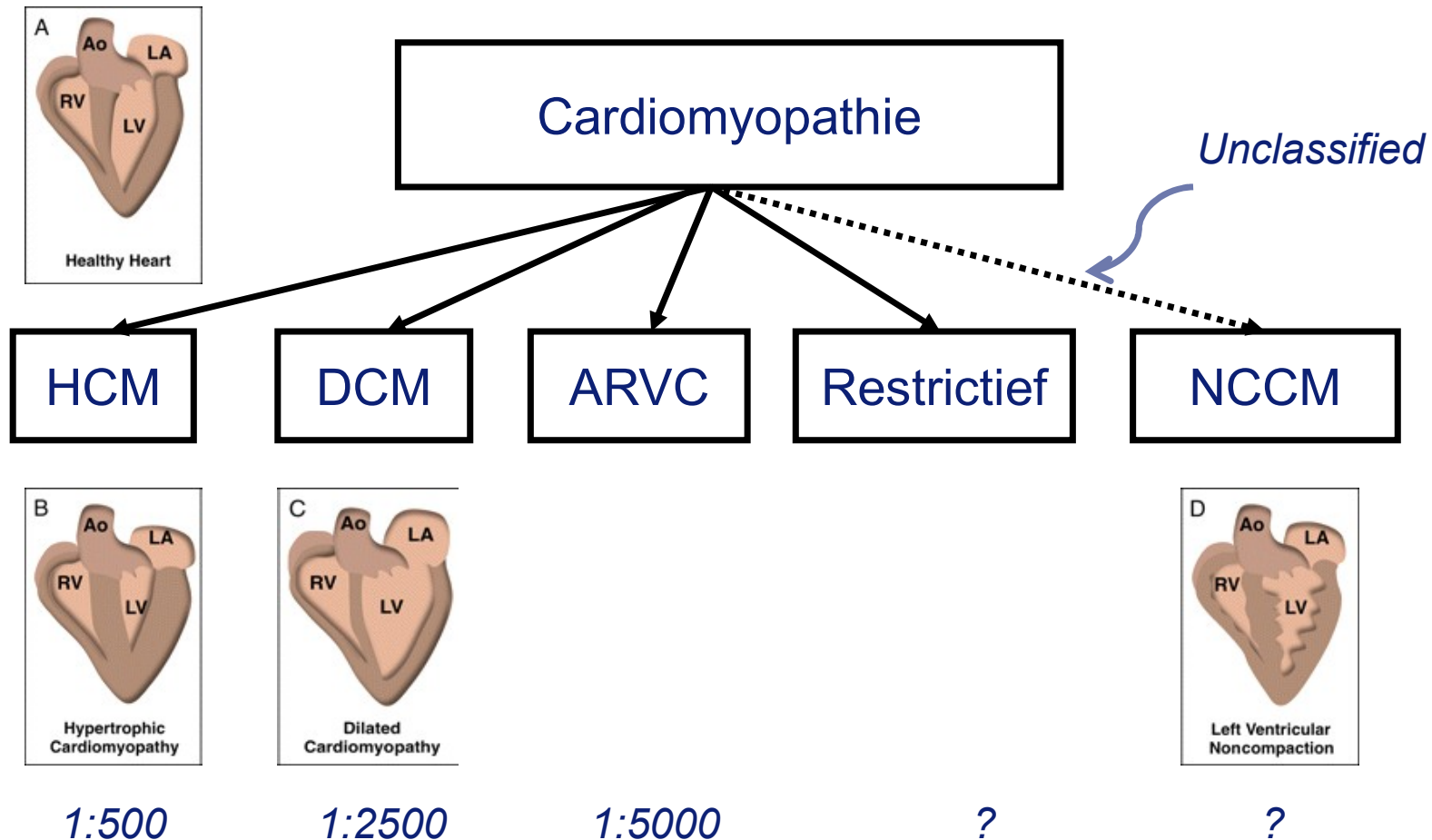
- *genetisch en niet genetisch*
- *stapelingsziekten*
- **toxisch**

Kleplijden

Myocarditis

En nog vele oorzaken meer

CLASSIFICATIE CARDIOMYOPATHIE



Elliott P et al. Eur Heart J 2008;29:270-276

7. WELKE BEHANDELINGEN HEEFT DE CARDIOLOOG?

Medicatie

Pacemaker/ICD

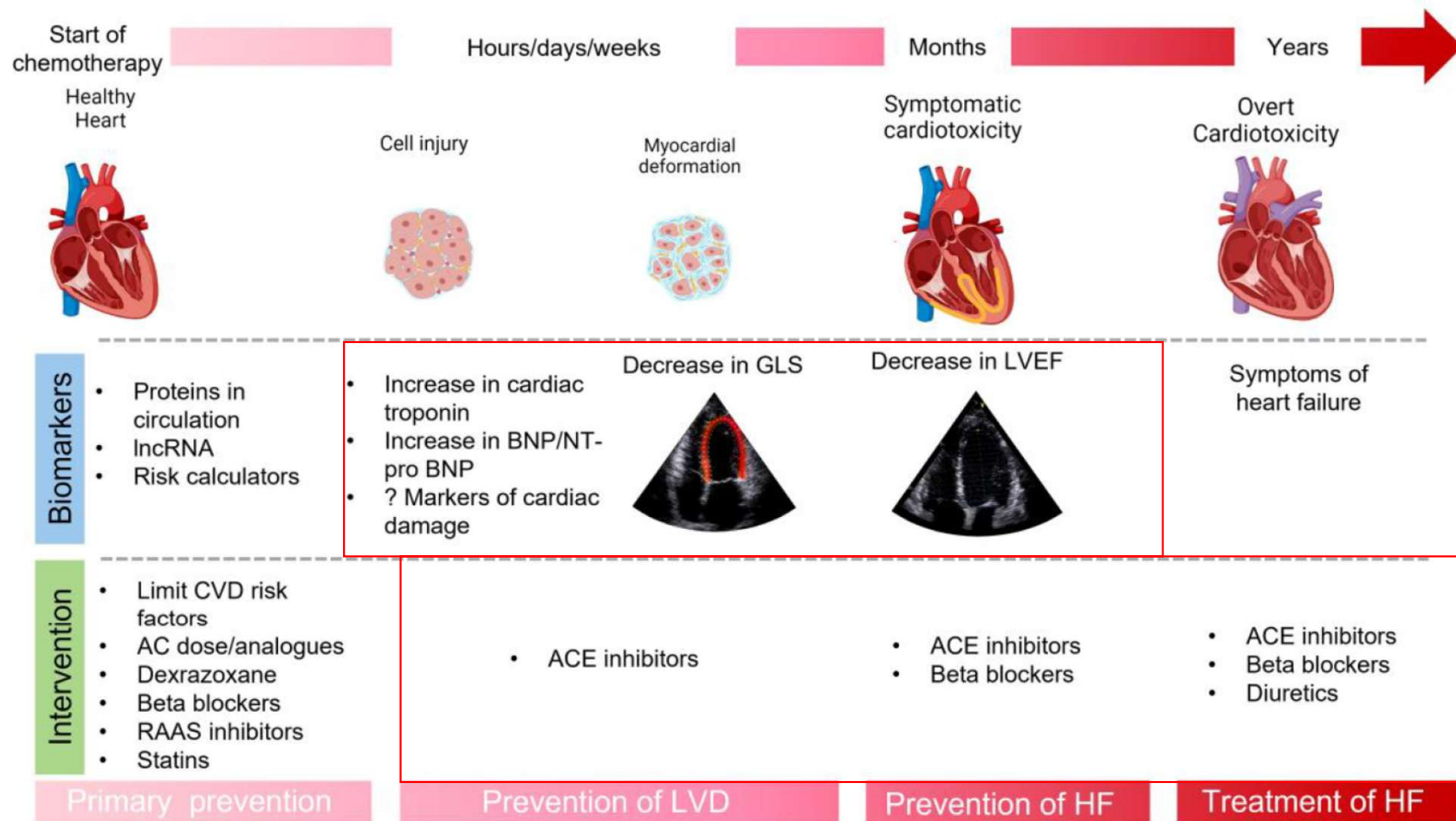
Coronaire stents

Klepinterventies

Ablaties

Levensstijl interventie (geen alcohol/roken, hartrevalidatie, evt vocht- en zoutbeperking)

Voorlichting over ziektebeeld



8. IS HARTFALEN NU ERNSTIG?



WHAT IS HEART FAILURE?

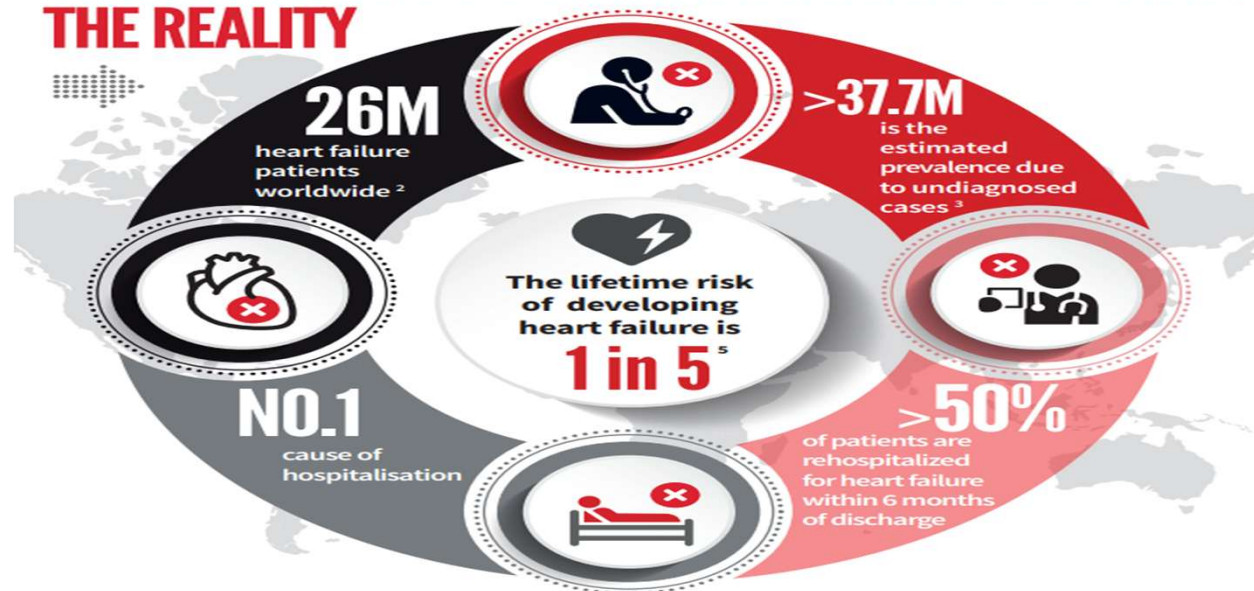
Heart failure is a severe failure of the heart to pump enough blood around the body
Symptoms include breathlessness, fatigue and swollen limbs

The global burden of heart failure is rising



THE REALITY
Quality of life survival is poor, with **45-60%** reported deaths within 5 years¹

THE REALITY



IMPACT VAN HARTFALEN IN NL

± 250.000 mensen in NL met hartfalen

Stijgt door vergrijzing, verbeterde overleving
post-infarct en meer co-morbiditeit

> 7000 mensen/jaar overlijden aan hartfalen

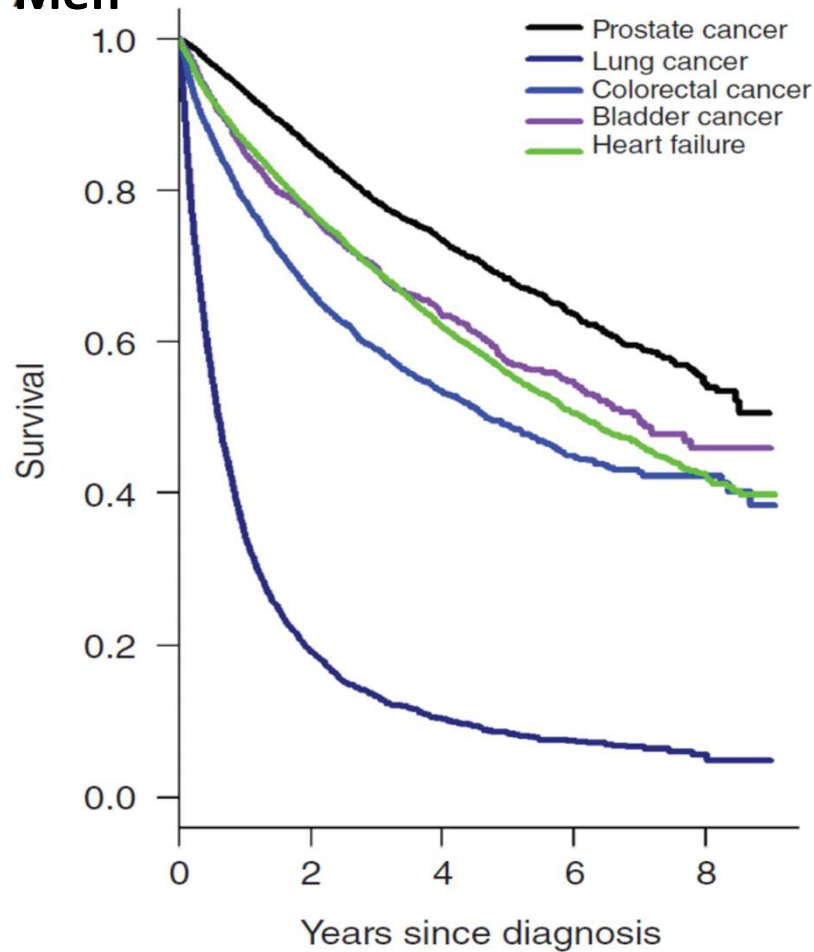
< 1990 5 jaars mortaliteit tot 70% en nu 40-50%!

1-jaars mortaliteit echter nog 10-20% oplopend tot 60%
bij NYHA klasse IV

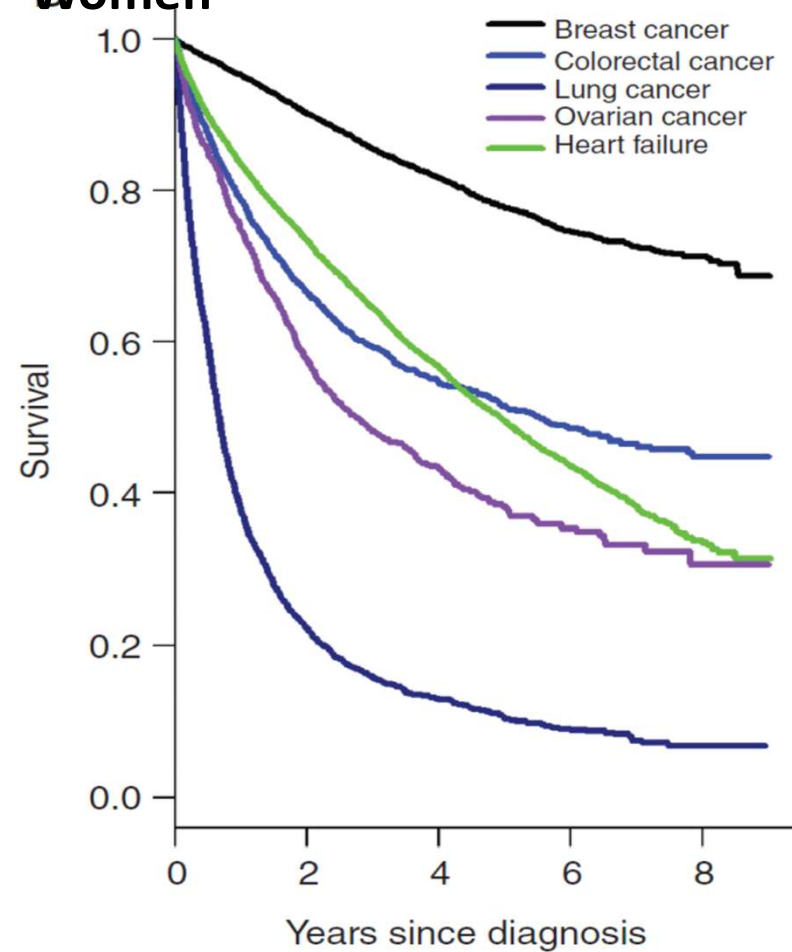
Elke opname voor hartfalen is stap dichterbij de dood

OVERLEIVING KANKER VS HARTFALEN

Men



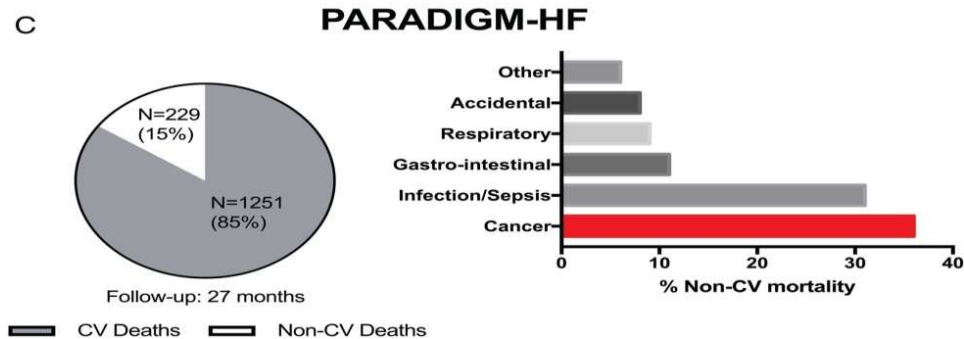
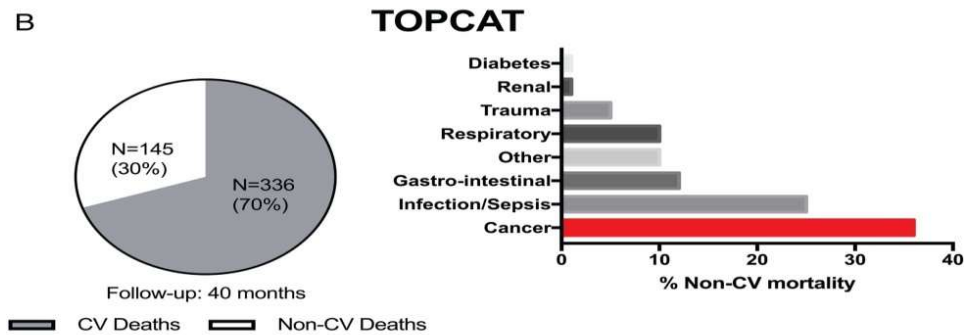
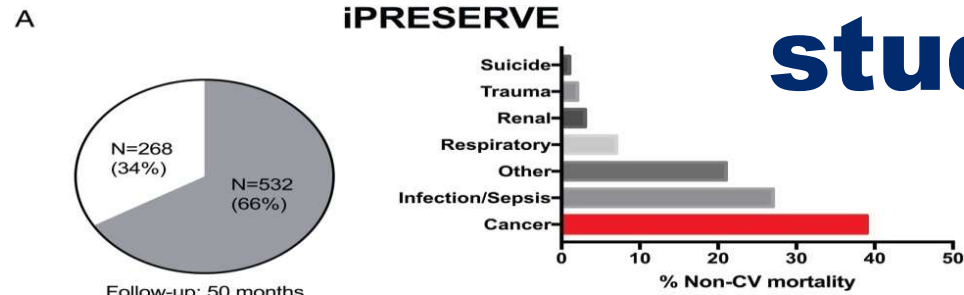
Women



Erasmus MC

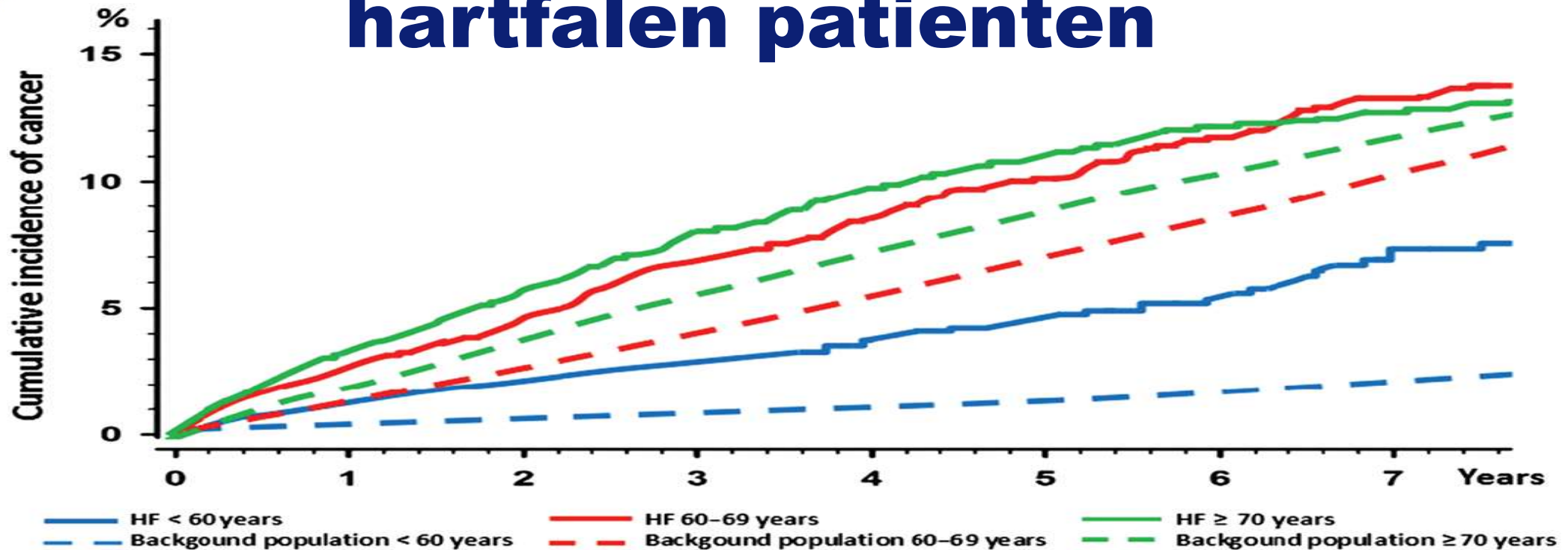
Erasmus

Non-CV sterfte in hartfalen studies



Kanker is de grootste oorzaak van non-CV sterfte bij hartfalen en maakt 35-40% van het totaal uit!

Registry toont meer kanker bij hartfalen patienten



- Deens hartfalen register: 9.307 patienten & 330.843 algemene populatie (controle groep)
- 975 kanker cases, follow up 4.5 ± 2.3 jaren

9. HARTFALEN BEHANDELING VEREIST EEN HOLISTISCHE AANPAK: “BALANS TUSSEN HOOFD, HART EN NIEREN”

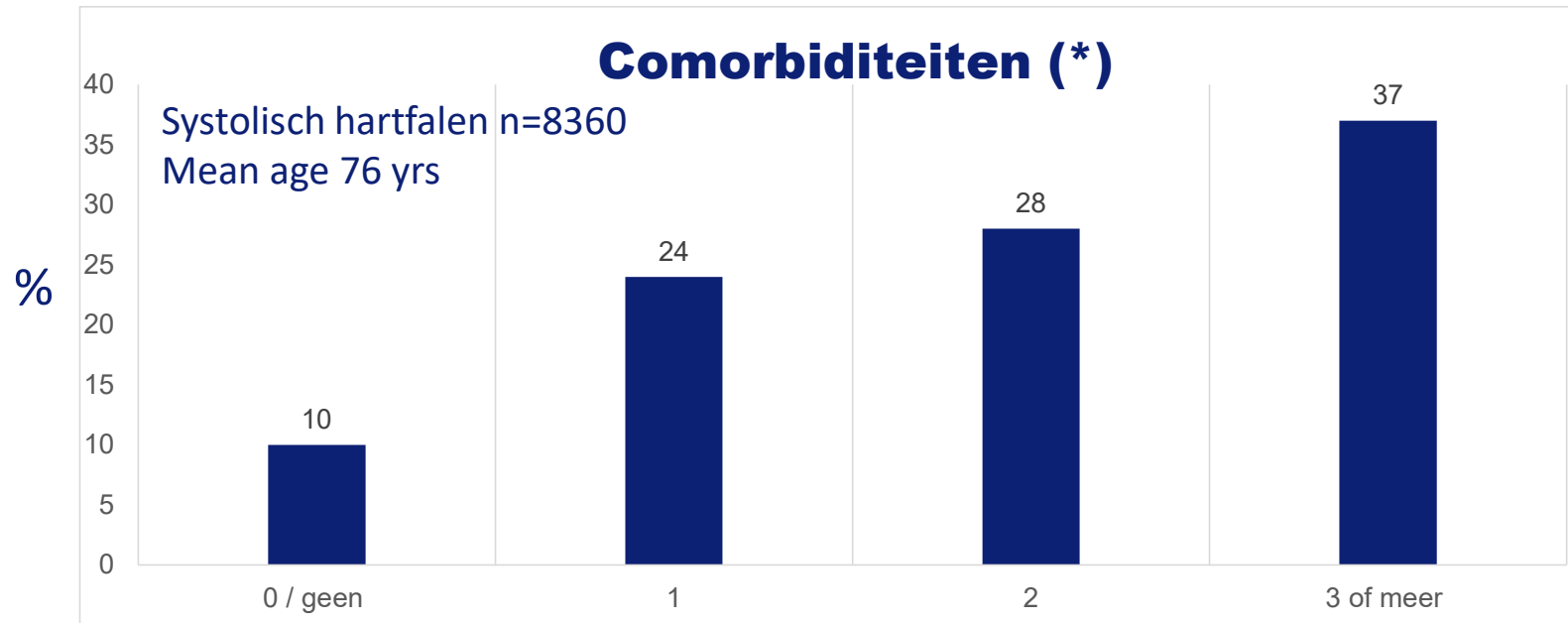
Ziekte van m.n. ouderen (mediane leeftijd in NL 76 jr)

Steeds complexere interactie met comorbiditeiten. Wie is regievoerder?

Relatie hartfalen, comorbiditeiten en opnames

Hartfalen hospitalisaties beïnvloeden prognose

HARTFALEN EN AANTAL COMORBIDITEITEN IN NEDERLAND

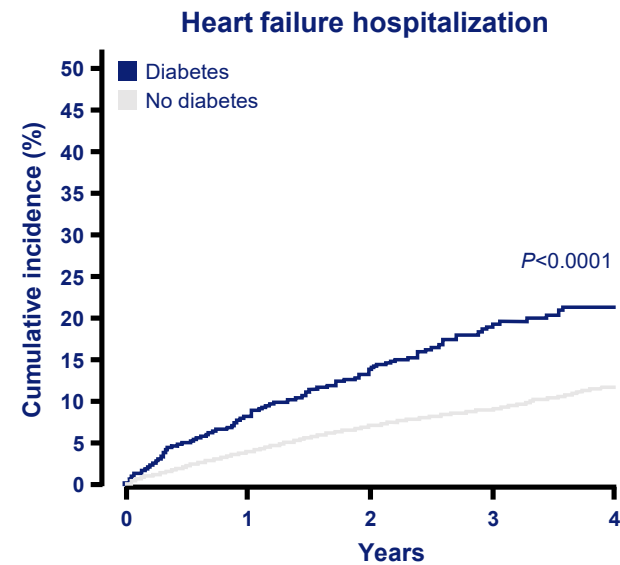
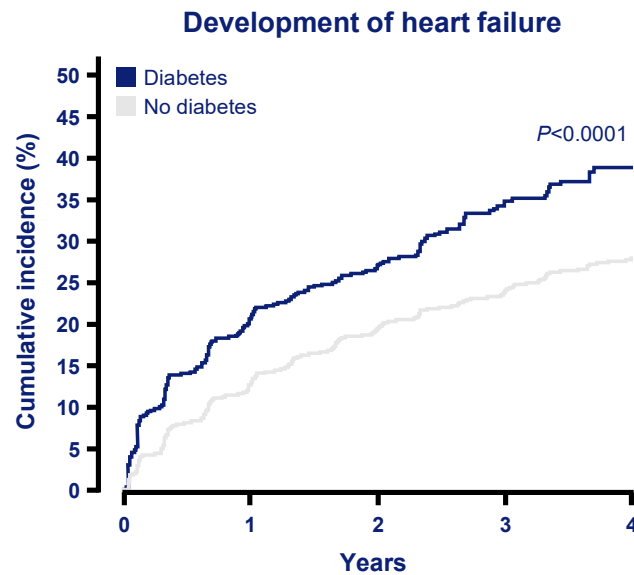


COPD, OSAS, diabetes mellitus, hypertensie, nierinsufficiëntie (eGFR<60), schildklier dysfunctie, anemie

Brugts JJ et al. Neth Heart J 2018

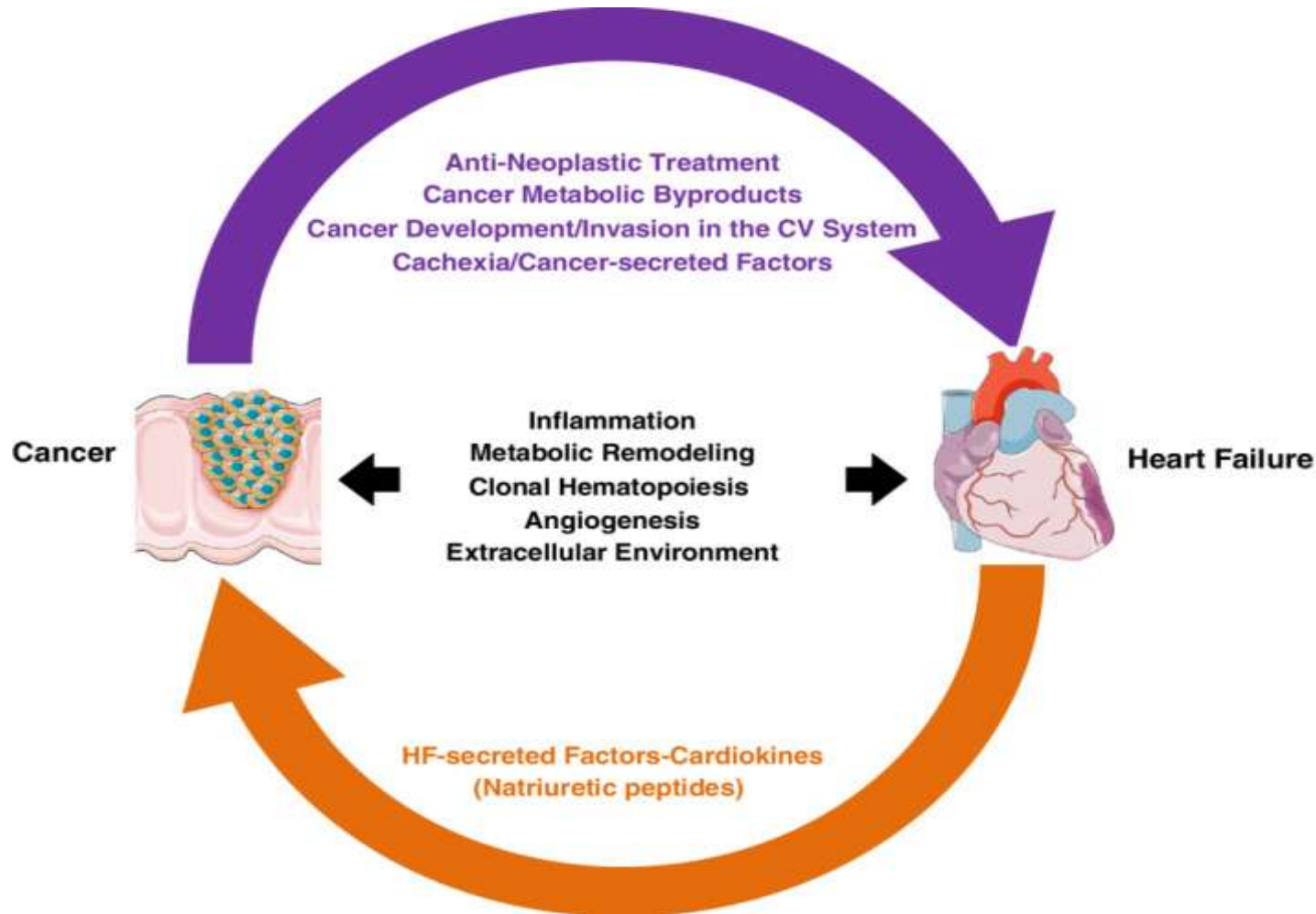
INVLOED VAN DIABETES MELLITUS BIJ HARTFALEN

Prevalentie DM-II bij hartfalen: 30% in 8360 systolisch hartfalen patienten



Brugts JJ et al. CHECK-HF Neth Heart J 2018
Rørth R, et al. *Diabetes Care* 2018;41:1285-1291

Kanker leidend tot hartfalen



Hartfalen leidend tot kanker

Eur J Heart Fail. 2020 Dec; 22(12): 2272–2289

10. TAKE HOME MESSAGES

- 1. Kanker en hartfalen hebben invloed op elkaar.**
- 2. Initiële diagnostiek naar hartfalen is niet ingewikkeld, maar er valt nog veel te winnen!**
- 3. Veel van wat we weten qua (bij)werking is nog van oudere medicatie, en effect van nieuwe medicatie qua (bij)werking is nog niet altijd duidelijk.**
- 4. Comorbiditeiten zijn van grote invloed op de uitkomst bij HF en screen hier dus ook op! Dit geldt zowel voor oncoloog als cardioloog...**
- 5. Kanker icm hartfalen heeft een slechtere prognose en verbind hieraan ook consequenties en bespreek dit.**