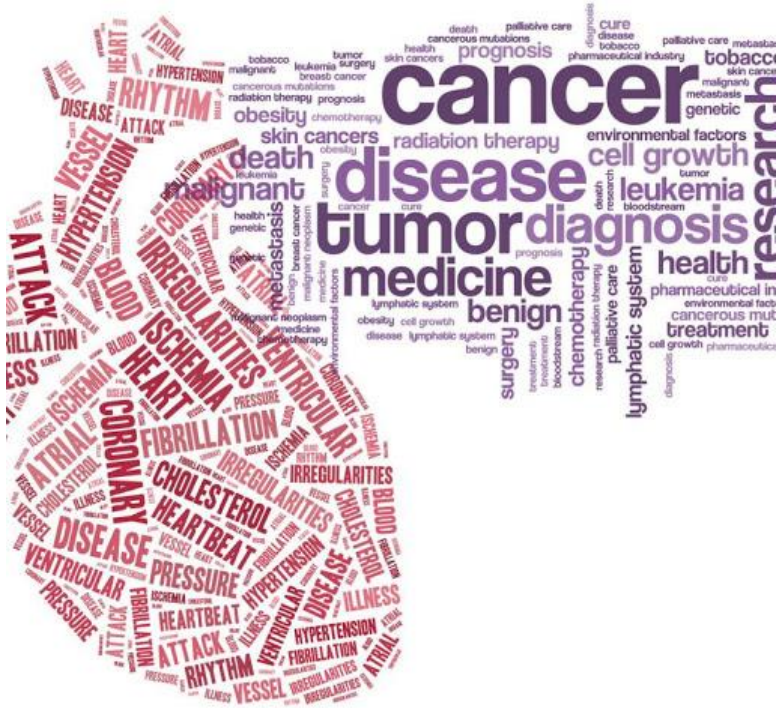
Les progrès dans les thérapies anticancéreuses : le rôle du cardiologue.



Nana Poku
Cardiologie

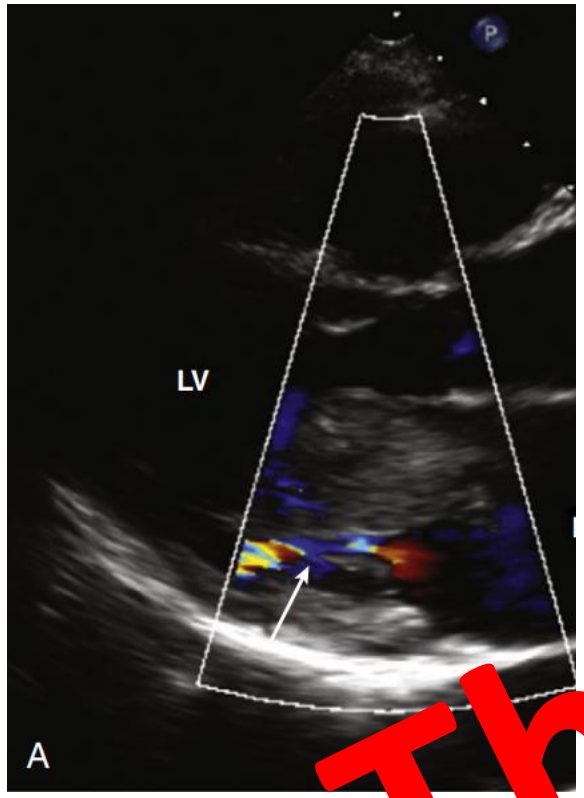
Laure Thouvenin
Nita Usdin
Oncologie

3 juin 2021

Plan

- What is cardio-oncology ?
- General cancer epidemiology
- Cardiotoxicity profile and cardiac assessment for specific cancer treatments
  - Fluoropyrimidine therapy
  - Anthracyclines
  - Anti HER2 therapy
  - Radiotherapy
  - Anti-androgen therapy
  - Tyrosine Kinase therapy
  - Immunotherapy
- Clinical cases
- Impact of a cardio-oncology unit
  - A multidisciplinary approach

What is cardio-oncology ?



RA/SVC	
Thyroid ca	1
Inflammatory pseudotumor	1
Total	**2**

RA	
Myxoma	5
Thrombus	2
Melanoma	1
Adrenocortical ca	1
Total	**9**

RA/IVC	
Hypernephroma	7
Rhabdomyoma	
Hepatoma	1
Total	**9**

RV	
[illegible]oma	2
Echinococcus cyst	1
Thrombus	1
Melanoma	1
Total	**5**

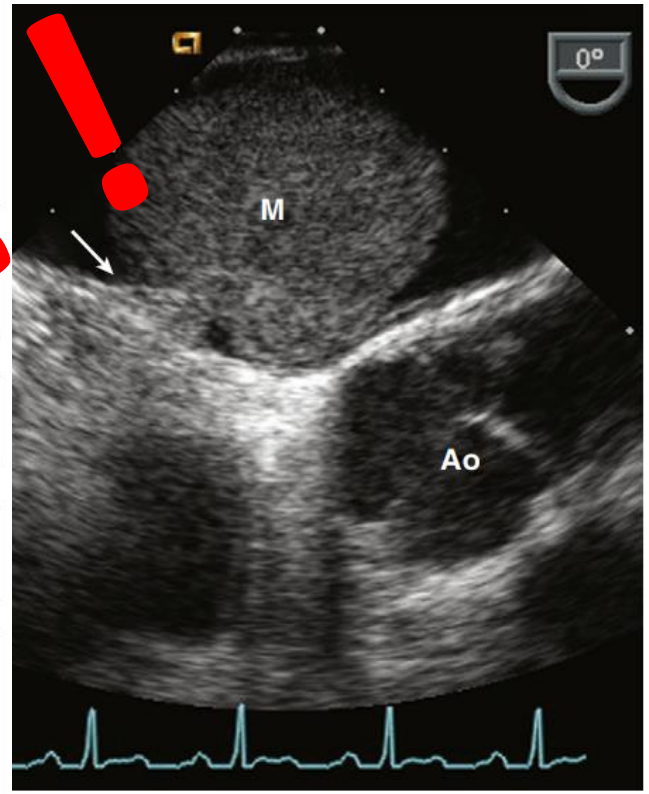
LA	
Myxoma	24
Thrombus	6
Sarcoma	3
Rhabdomyo	1
Total	**34**

[illegible]A	
Fibroelas[illegible]na	1

MV	
Fibroelastoma	3

Aortic valve	
Fibroelastoma	5

LV	
Thrombus	3
Fibroma	2
Met breast ca	1
Total	**6**



This is not it !

Dujardin KS et al : The role of intraoperative transesophageal echocardiography in patients undergoing cardiac mass removal. J Am Soc Echocardiogr 13:1080-1083, 2000

What is cardio-oncology ?

Definition

Cardio-Oncology is a subspecialty of cardiology that aims to optimize the cardiovascular health of cancer patients to guide and support them during and after necessary cancer treatment.

Among the main goals :

✓ to allow for optimized cancer therapy with minimal cardiac “collateral damage”

✓ to minimize unnecessary treatment interruption

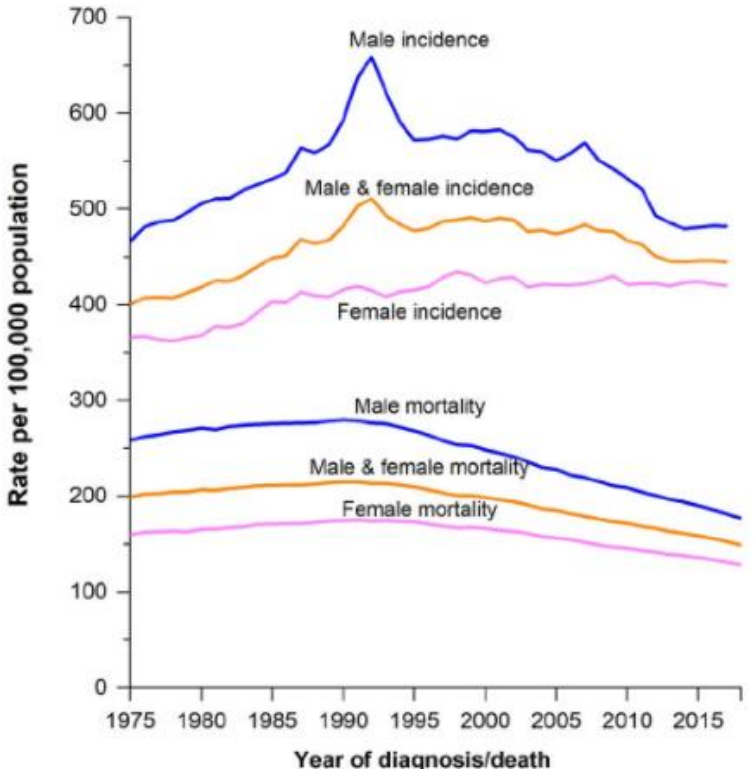
✓ to maximize treatment completion

Source : swiss cardio-oncologie working group (COS, cardio-oncology switzerland)

What is all the fuss about ?

→Oncology patients do live longer

→ there are around 50 000 000 patients worldwide *(cancer patients + survivors)*



Incidence et mortalité liée au cancer aux USA (1975-2018)

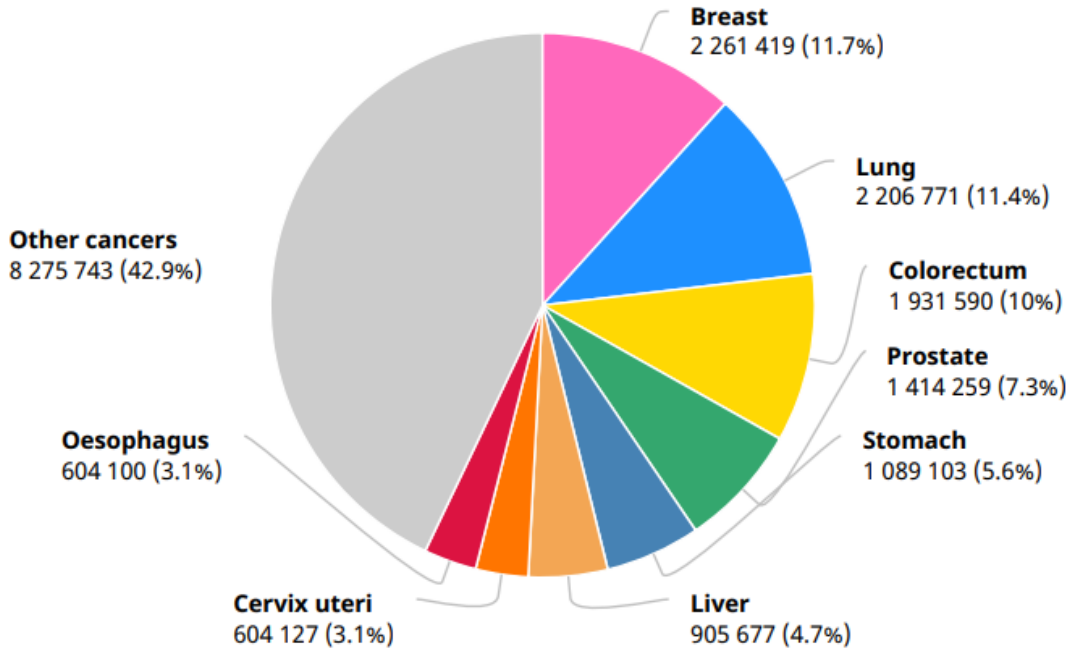
Site	1975 (%)	2018 (%)	% augmentation
Prostate	67	98	31
Mélanome	77	93	16
Sein	75	90	15
Colon	51	65	14
Poumon	12	21	9

Survie à 5 ans tous stades confondus

Siegel, Cancer statistics, 2020

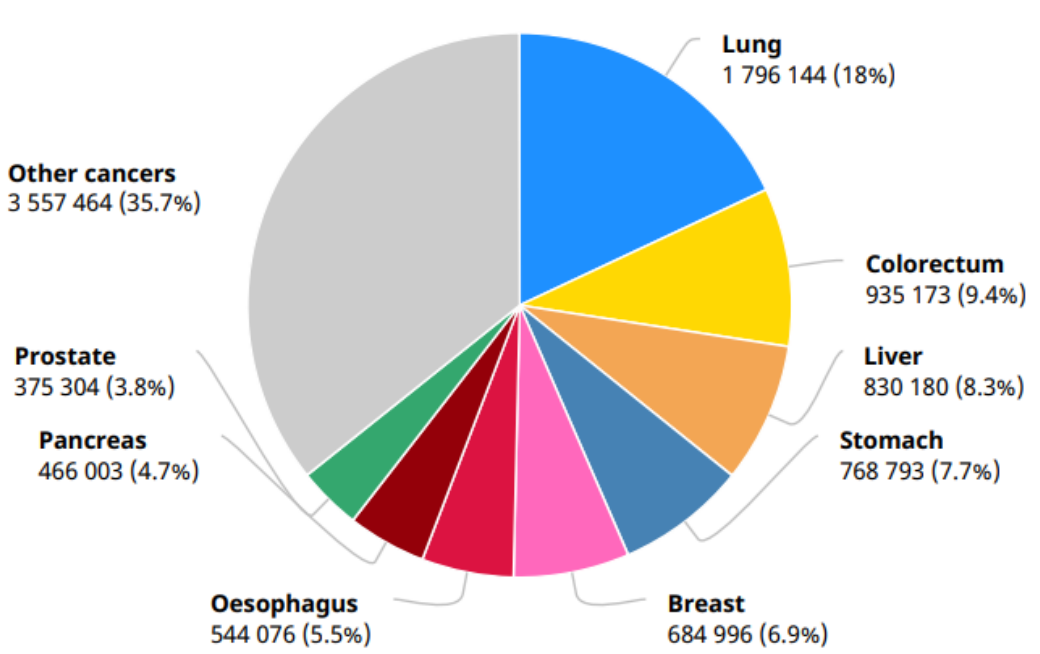
Cancer burden in 2020 - WHO

Number of new cases in 2020, both sexes, all ages



Total: 19 292 789 cases

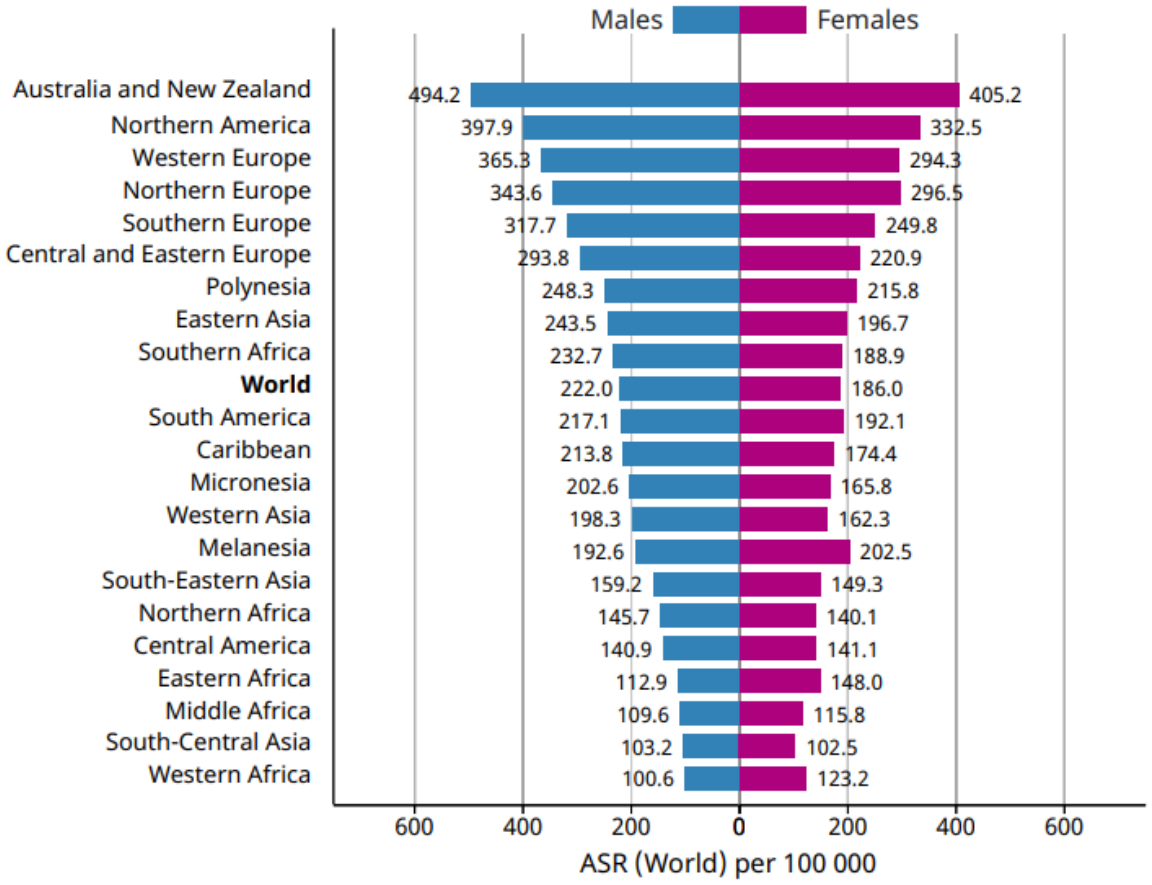
Number of deaths in 2020, both sexes, all ages



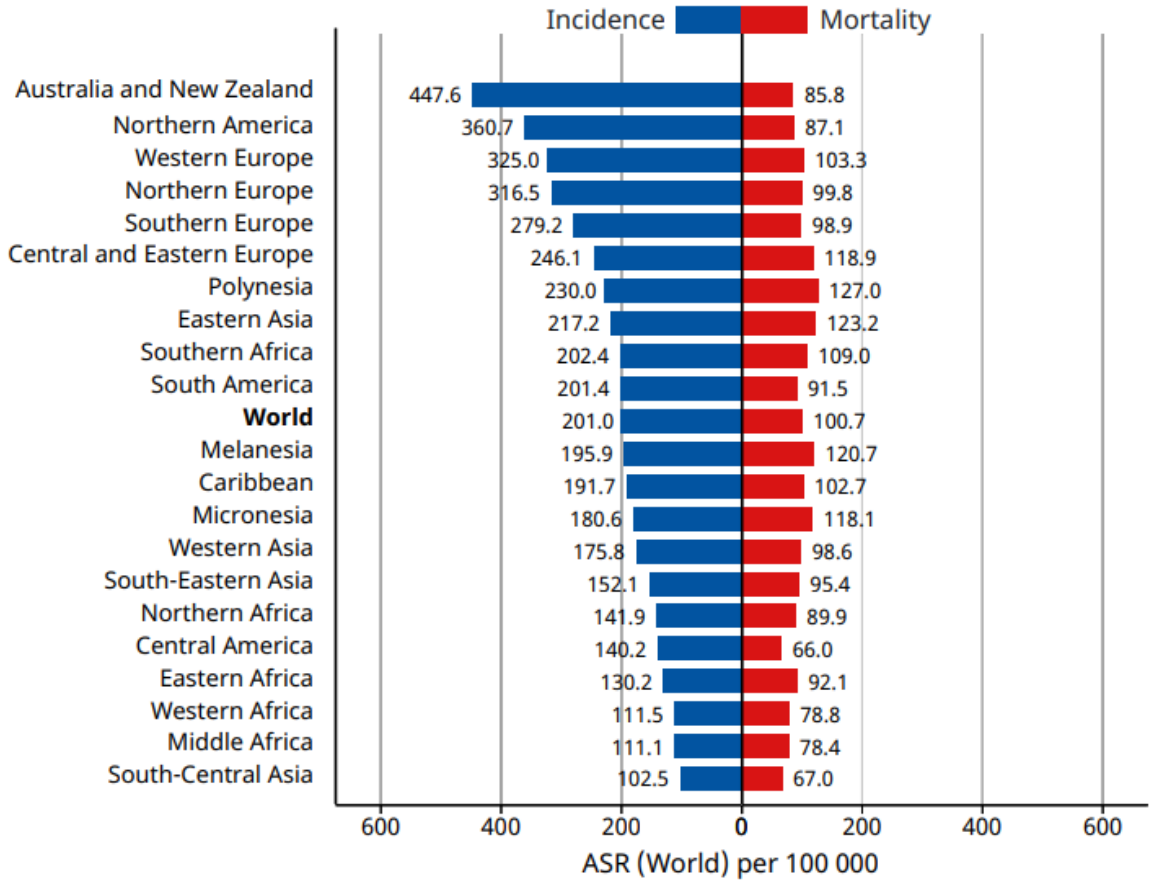
Total: 9 958 133 deaths

Cancer burden in 2020 - WHO

Age standardized (World) incidence rates, all cancers, by sex

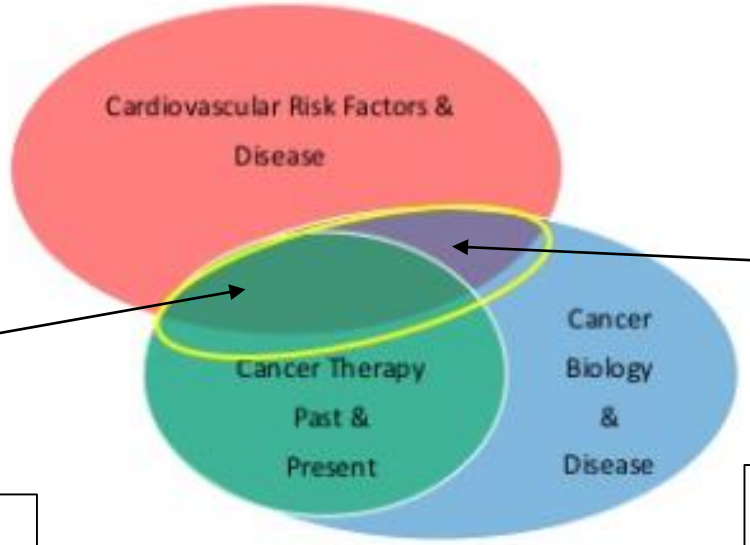


Age standardized (World) incidence and mortality rates, all cancers



Qu’est ce que la cardio-oncologie?

Travail conjoint entre cardiologues et oncologues pour éviter/prévenir les effets indésirables cardiovasculaires de certaines chimiothérapies, en particulier chez les patients les plus à risque.



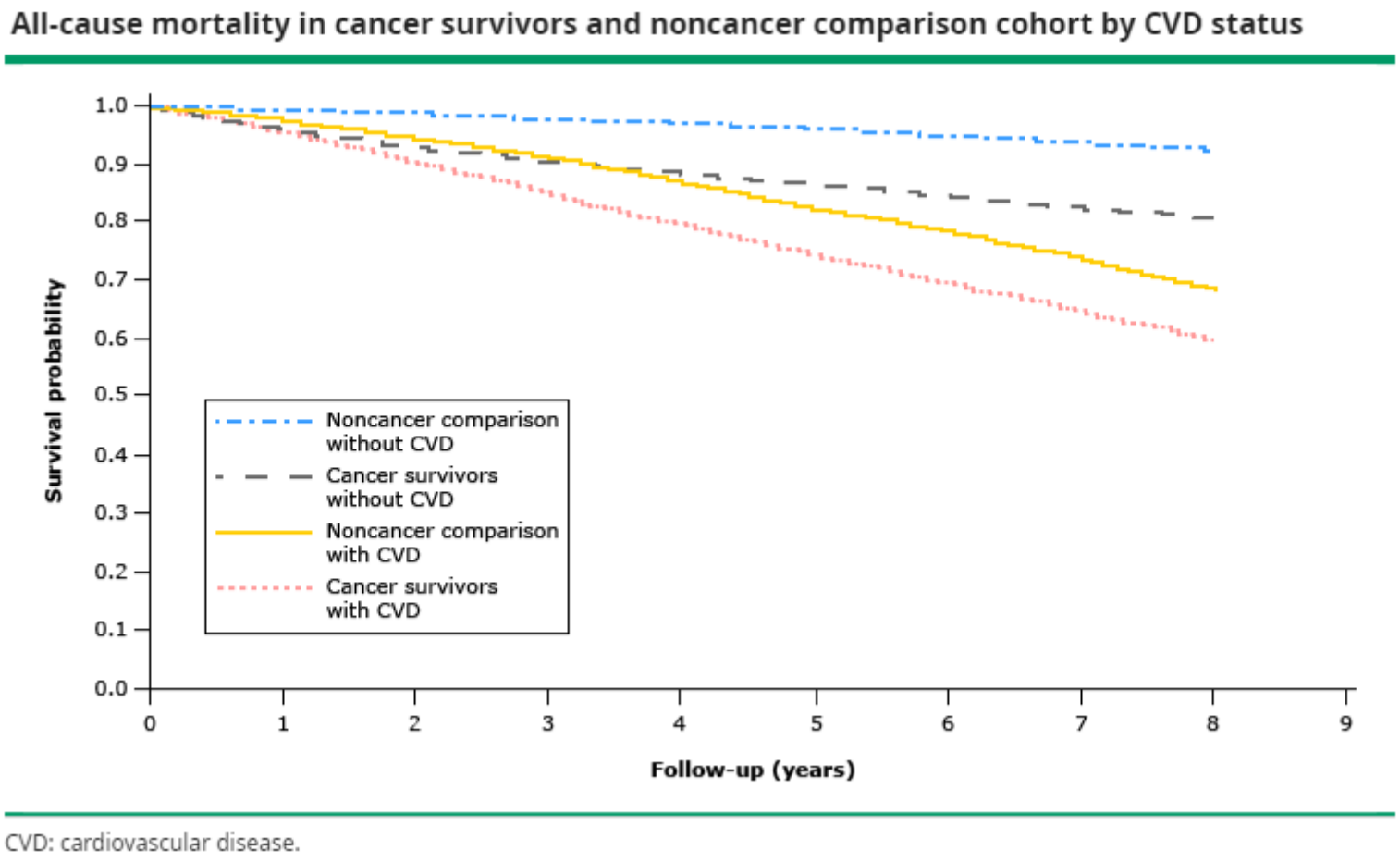
Liens entre CV et cancer

- Une pathologie CV peut **pré-exister** au traitement anticancéreux ou peut être **induite/exacerbée** par celui-ci
- FdR communs notamment âge

Cardiotoxicité liée au traitement

- La **toxicité aigüe** peut limiter l’accès à des traitements potentiellement curatifs
- La **toxicité chronique** peut impacter la survie, la morbidité et la QdV

Pourquoi la cardio-oncologie?



CVD: cardiovascular disease.

Armenian, 2016

TABLE 1 Baseline Demographic and Clinical Characteristics

	Total Cohort (N = 20,305)	Incident Cancer (n = 2,548)	No Cancer* (n = 17,757)
Age, yrs	50 ± 14	59 ± 12	49 ± 14
Men	9,426 (46)	1,328 (52)	8,098 (46)
SBP, mm Hg	126 ± 19	132 ± 20	125 ± 19
DBP, mm Hg	75 ± 10	77 ± 10	75 ± 10
HTN treatment	3,097 (15)	624 (25)	2,473 (14)
BMI, kg/m^2	26.5 ± 4.8	27.0 ± 4.7	26.4 ± 4.8
DM	839 (4)	171 (7)	668 (4)
Former smoker	6,750 (33)	1,035 (41)	5,715 (32)
Current smoker	5,822 (29)	786 (31)	5,036 (28)
Total cholesterol, mg/dl	210 ± 42	215 ± 42	209 ± 42
HDL, mg/dl	52 ± 16	50 ± 16	52 ± 16
Statin therapy	820 (4)	140 (6)	680 (4)
eGFR, ml/min^1/1.73 m^2	85 ± 25	74 ± 21	87 ± 26
10-yr ASCVD risk, %	8.2 ± 11.9	13.9 ± 13.5	7.4 ± 11.4

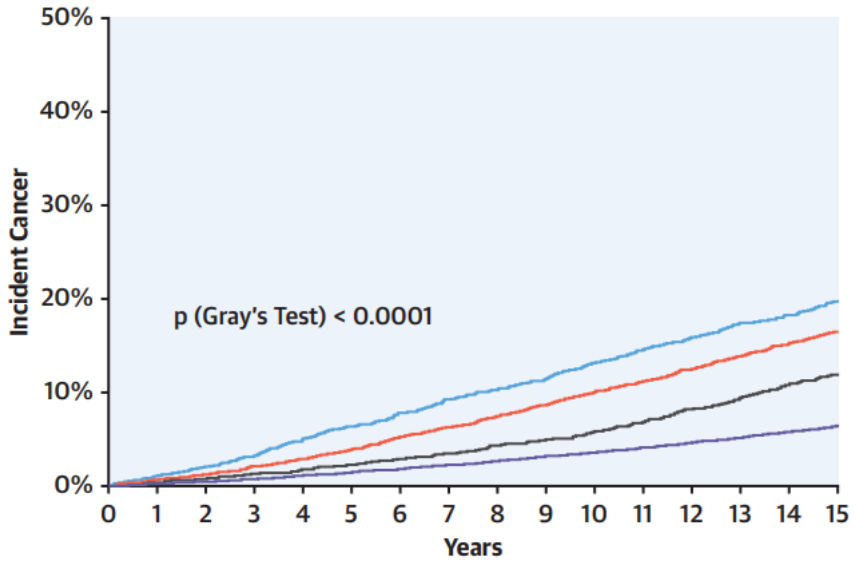
TABLE 2 Association of CV Risk Factors, Biomarkers, and CVD With Cancer

	Cancer (n/N = 2,548/20,305)	
	HR (95% CI)	p Value
CV risk factors*		
Age	2.12 (2.00–2.26)	<0.001
Male	1.39 (1.28–1.51)	<0.001
SBP	0.99 (0.94–1.03)	0.49
HTN treatment	1.10 (1.00–1.22)	0.06
BMI	1.03 (0.99–1.08)	0.20
DM	1.10 (0.94–1.30)	0.24
Former smoker	1.30 (1.18–1.43)	<0.001
Current smoker	1.74 (1.57–1.93)	<0.001
TC/HDL	0.96 (0.91–1.00)	0.048
Statin use	0.92 (0.77–1.10)	0.36
Risk scores†		
10-yr ASCVD risk	1.16 (1.14–1.17)	<0.001
Low	Ref.	
Borderline	1.88 (1.63–2.18)	<0.001
Intermediate	2.70 (2.44–3.00)	<0.001
High	3.71 (3.29–4.19)	<0.001
Biomarkers*		
NP tertile 1	Ref.	p_{trend} = 0.02
Tertile 2	1.10 (0.90–1.34)	0.35
Tertile 3	1.40 (1.02–1.91)	0.035
NP × time interaction‡	0.87 (0.81–0.95)	0.001
Continuous	1.26 (1.12–1.41)	<0.001
hs-cTn tertile 1	Ref.	p_{trend} = 0.47
Tertile 2	1.24 (1.01–1.53)	0.043
Tertile 3	1.16 (0.84–1.61)	0.37
hs-cTn × time interaction‡	0.95 (0.88–1.03)	0.18
Continuous	1.10 (0.99–1.21)	0.07
Previous events*		
CVD, n = 1,020	0.96 (0.82–1.12)	0.61
MI, n = 793	1.03 (0.87–1.22)	0.71
HF, n = 116	0.66 (0.37–1.17)	0.15
Interim events*		
CVD, n = 1454	0.99 (0.85–1.16)	0.91
MI, n = 687	0.99 (0.79–1.25)	0.95
HF, n = 681	1.07 (0.84–1.36)	0.59

Lau, E.S. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):48–58.

Cancer and Heart disease : shared risk factors

CENTRAL ILLUSTRATION Risk of Future Cancer by ASCVD Score



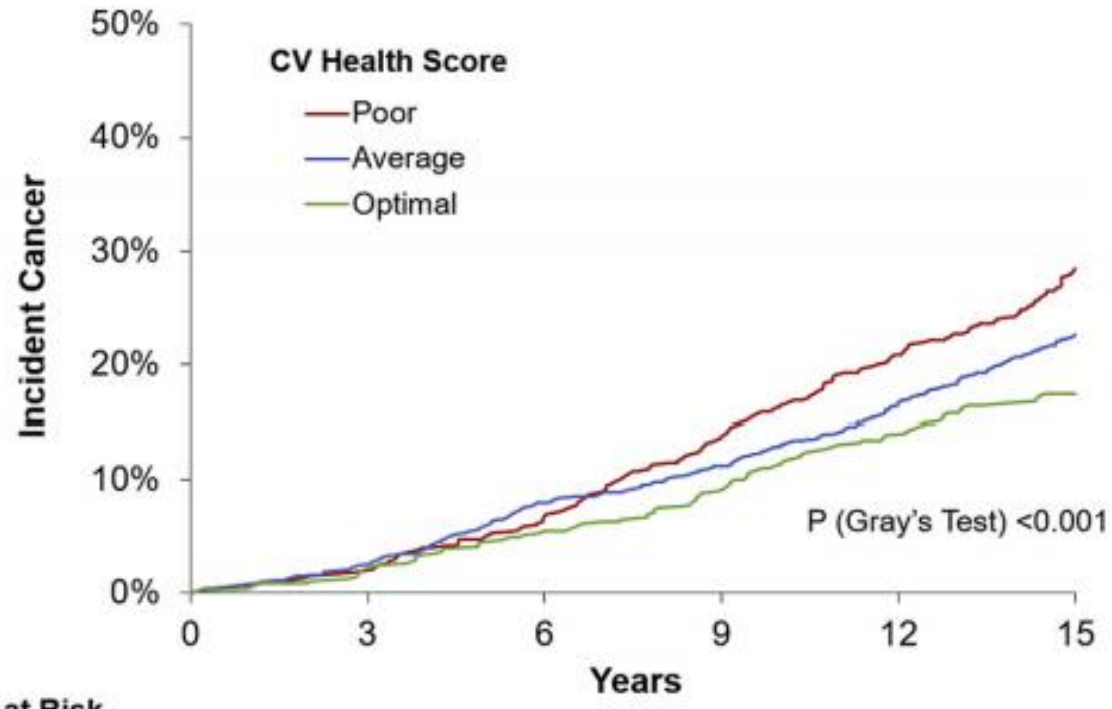
Number at Risk:

ASCVD 10-Year Risk						
ASCVD >20%	2,554	2,366	2,055	1,757	1,453	1,163
ASCVD 7.5%-20%	3,985	3,865	3,651	3,428	3,151	2,735
ASCVD 5%-7.5%	1,744	1,705	1,678	1,609	1,505	1,289
ASCVD <5%	12,022	11,916	11,725	11,454	10,970	7,712

Lau, E.S. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):48-58.

Incident cancer among subjects classified as atherosclerotic cardiovascular disease (ASCVD) low risk (<5%) **(purple)**, borderline risk (5% to 7.5%) **(gray)**, intermediate risk (7.5% to 20%) **(red)**, and high risk (>20%) **(blue)** for developing cancer.

FIGURE 1 Time to Incident Cancer by Categories of the AHA's Life Simple 7 CVH Score

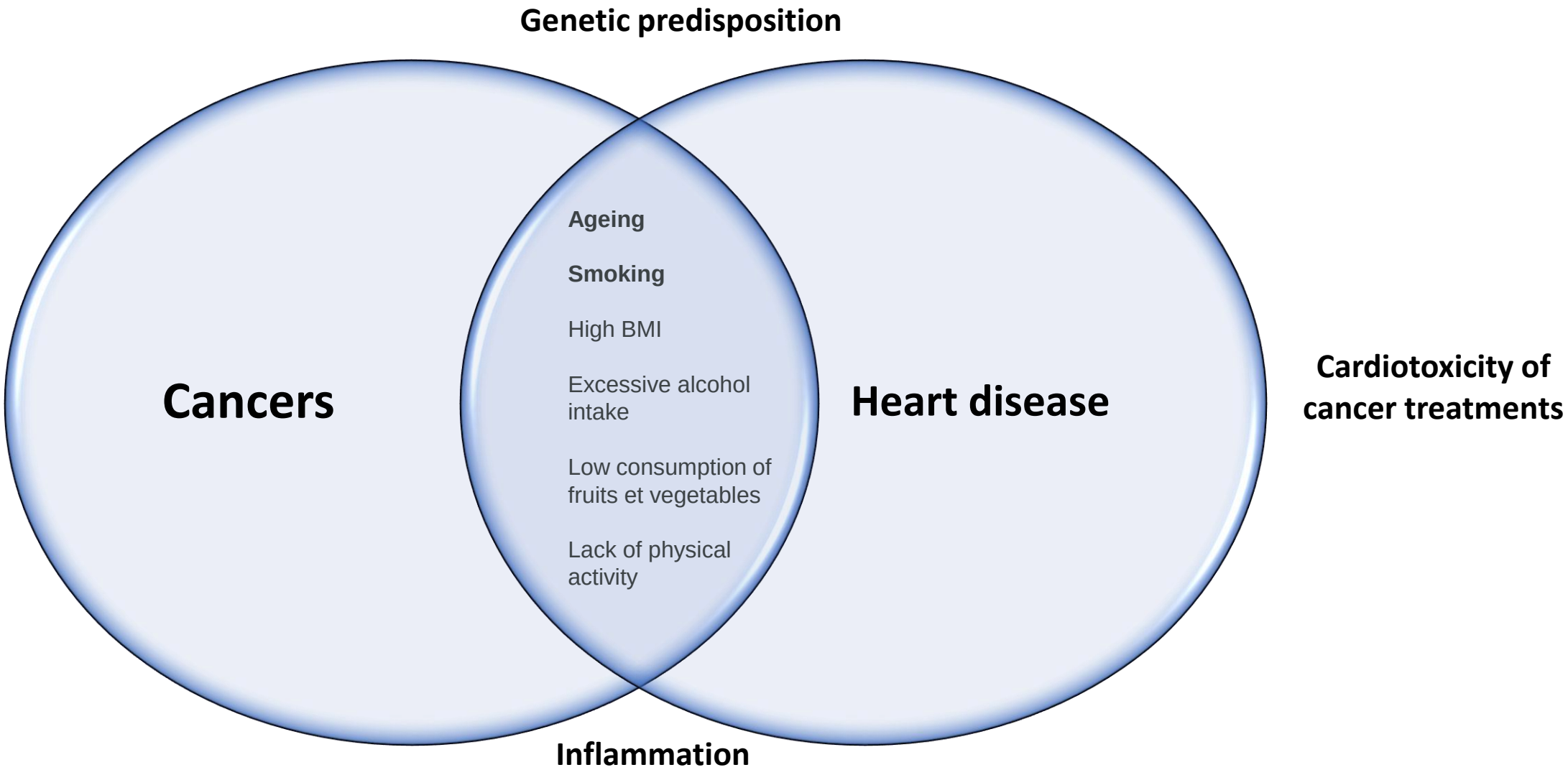


Number at Risk

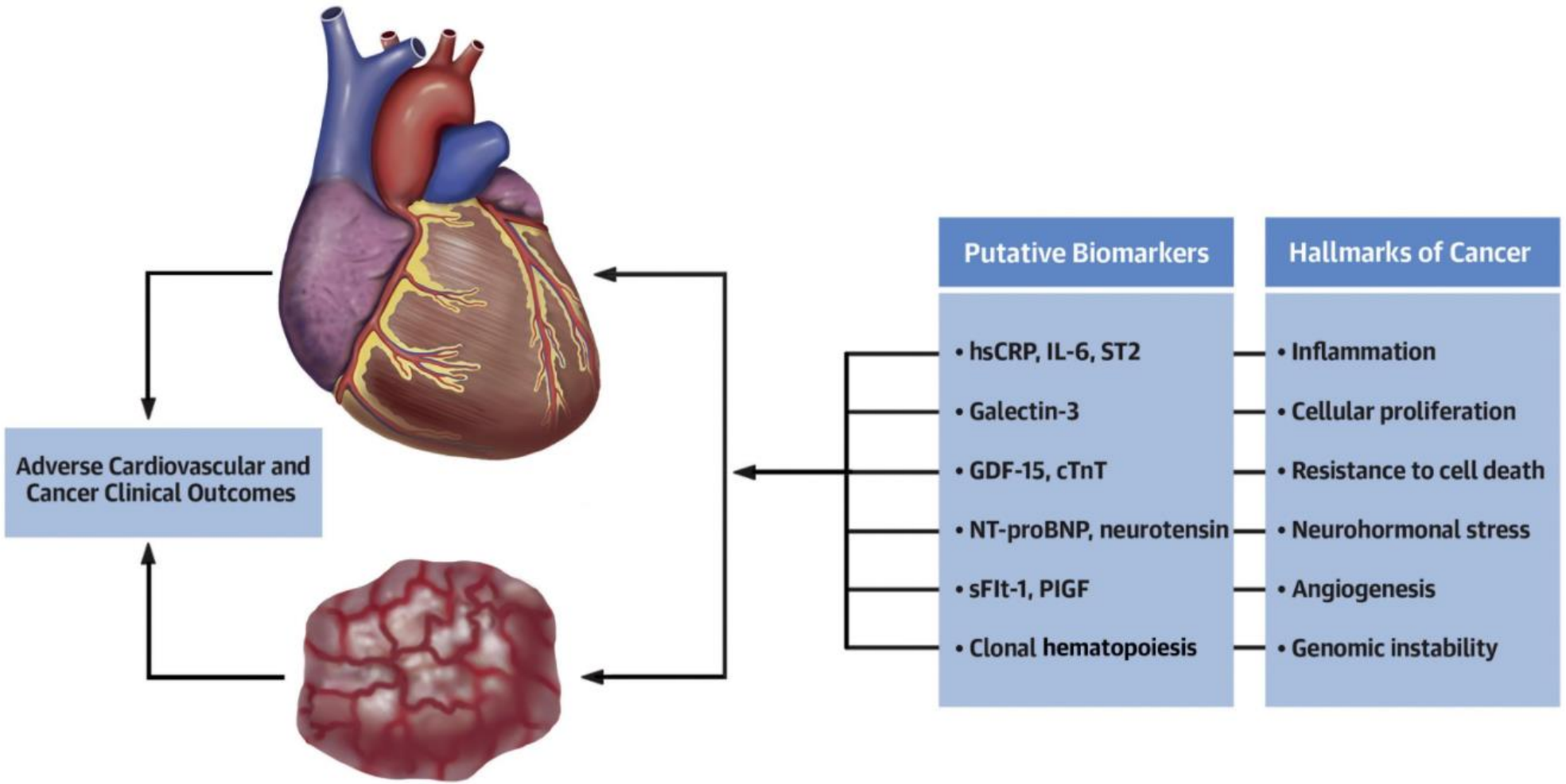
Poor	532	522	487	440	390	329
Average	1301	1259	1177	1118	1016	905
Optimal	493	482	461	438	480	379

Lau, E.S. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):48–58.

Cancer and Heart disease : shared risk factors



CENTRAL ILLUSTRATION: Shared Pathophysiological Mechanisms Between Cardiovascular Disease and Cancer



Narayan, V. et al. J Am Coll Cardiol. 2020;75(21):2726-37.

Cancer treatment : the other obvious link between cancer and cardiovascular disease

CANCER RESEARCH UK

Together we will beat cancer

Cancer drugs A to Z list

There are many cancer drugs and cancer drug combinations. They have individu
targeted cancer drugs and bisphosphonates. The drugs are listed in alphabetica

A to Z list of cancer drugs including combination treatments

Start typing ...

A
ABVD
AC
Abemaciclib (Verzenois)
Abiraterone (Zytiga)
Abraxane
Abstral
Actinomycin D
Actiq
Adriamycin
Afatinib (Giotrif)
Afinitor
Aflibercept (Zaltrap)
Aldara
Aldesleukin (IL-2, Proleukin or interleukin 2)
Alectinib (Alecensa)
Alemtuzumab (Campath, MabCampath)
Alkeran
Amsacrine (Amsidine, m-AMSA)
Amsidine
Anastrozole (Arimidex)
Ara C
Aredia
Arimidex

F
FEC
FLOT
FMD
FOLFIRINOX
Faslodex
Femara
Fentanyl
Firmagon
Fludara
Fludarabine (Fludara)
Fludarabine, cyclophosphamide and rituximab (FCR)
Fluorouracil (5FU)
Fluorouracil (5FU) and mitomycin C
Fluorouracil, epirubicin, cyclophosphamide and docetaxel (FEC-T)
Flutamide
Folinic acid, fluorouracil and irinotecan (FOLFIRI)
Folinic acid, fluorouracil and oxaliplatin (FOLFOX)
Fulvestrant (Faslodex)

G

O
Obinut
Octreo
Olapar
Oncovi
Onkotr
Opdivo
Oramo
OxCap
Oxalipl
Oxalipl

P
PC (pa
PCV
PE
PMitCE
POMB/
Paclita
Paclita
Palboc
Pamidr
Panad
Panitu
Parace

FEC

FEC is the name of a combination of chemotherapy drugs.

What is FEC?

The FEC chemotherapy combination includes:

- F – fluorouracil (5FU)
- E – epirubicin
- C – cyclophosphamide

It is a treatment for breast cancer.

https://www.cancerresearchuk.org/

CAPE-OX
CAPOX
CAV
CCNU
CHOP
CMF
CMV
CVP
…l (Jevtana)
…nib (Cometriq, Cabometyx)
…ine (Xeloda)
…n and etoposide
…n and paclitaxel
…e (BCNU)
…Zykadia)
…) (Erbitux)
…cil (Leukeran)
…nd capecitabine (CX)
…nd fluorouracil (5FU)
…etoposide and ifosfamide (VIP)
…fluorouracil (5FU) and trastuzumab
…(Leustat, LITAK)
…ab (Imfinzi)
…ib (Braftovi) and Binimetinib
…ide (Xtandi)
…(Pharmorubicin)
…, carboplatin and capecitabine
…, cisplatin and capecitabine (ECX)
Erbitux
Eribulin (Halaven)
Erlotinib (Tarceva)
Erwinase
Estracyt
Etopophos
Etoposide (Etopophos, Vepesid)
Everolimus
Evoltra
Exemestane (Aromasin)

IL-2
IPE
Ibandronic acid (Bondronat)
Ibrutinib (Imbruvica)
Ibuprofen (Brufen, Nurofen)
Iclusig
Idarubicin (Zavedos)
Idelalisib (Zydelig)
Ifosfamide (Mitoxana)
Imatinib (Glivec)
Imiquimod cream (Aldara)
Inotuzumab ozogamicin (Besponsa)
Instanyl
Interferon alfa (IntronA, Roferon-A)
Interleukin
Intron A
Ipilimumab (Yervoy)
Ipilimumab and nivolumab
Iressa
Irinotecan (Campto)
Irinotecan and capecitabine (XELIRI)
Irinotecan de Gramont
Irinotecan modified de Gramont

J
Javlor
Jevtana

K
Kadcyla
Kapake
Keytruda

M
Morphine
Myleran
Myocet
m-AMSA

N
Nab-paclitaxel
Nab-paclitaxel (Abraxane)
Navelbine
Nelarabine (Atriance)
Neratinib (Nerlynx)
Nexavar
Nilotinib (Tasigna)
Nintedanib (Vargatef)
Nipent
Niraparib (Zejula)
Nivolumab (Opdivo)
Novgos
Nurofen

RICE
Raloxifene
Raltitrexed (Tomudex)
Regorafenib (Stivarga)
Revlimid
Ribociclib (Kisqali)
Rituximab (Mabthera, Rixathon, Truxima)
Rucaparib (Rubraca)
Ruxolitinib

S
Sevredol
Sodium clodronate (Bonefos, Clasteon, Loron)
Solpadol
Sorafenib (Nexavar)
Steroids (dexamethasone, prednisolone, methylprednisolone and hydrocortisone)
Streptozocin (Zanosar)
Sunitinib (Sutent)
Sutent

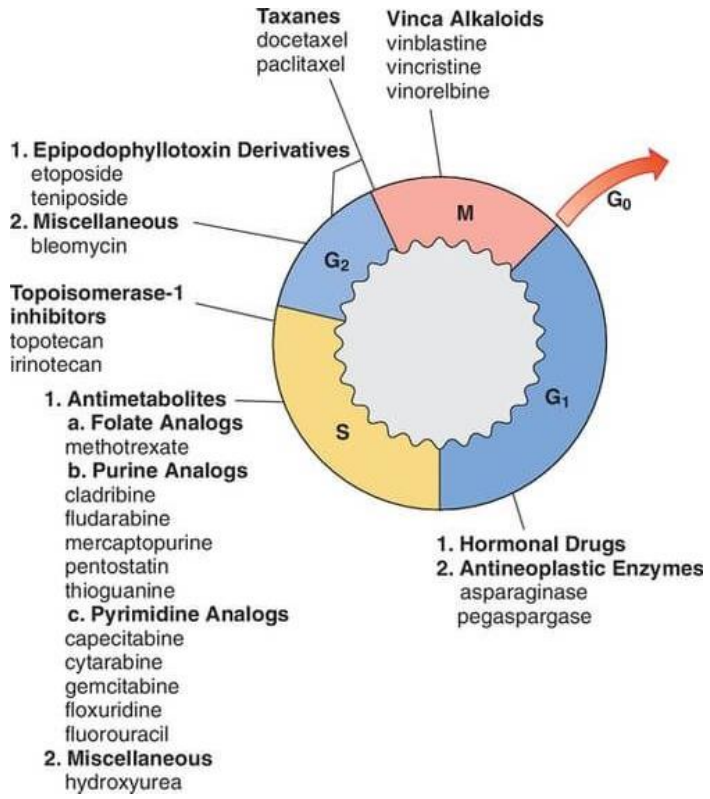
T
TAC
TIP
Tafinlar
Talimogene laherparepvec (T-VEC)
Tamoxifen
Tarceva
Targretin
Tasigna
Taxol
Taxotere
Taxotere and cyclophosphamide (TC)
(VAD)
Vindesine (Eldisine)
Vinorelbine (Navelbine)
Votrient

X
XELOX
Xalkori
Xeloda
Xgeva
Xtandi

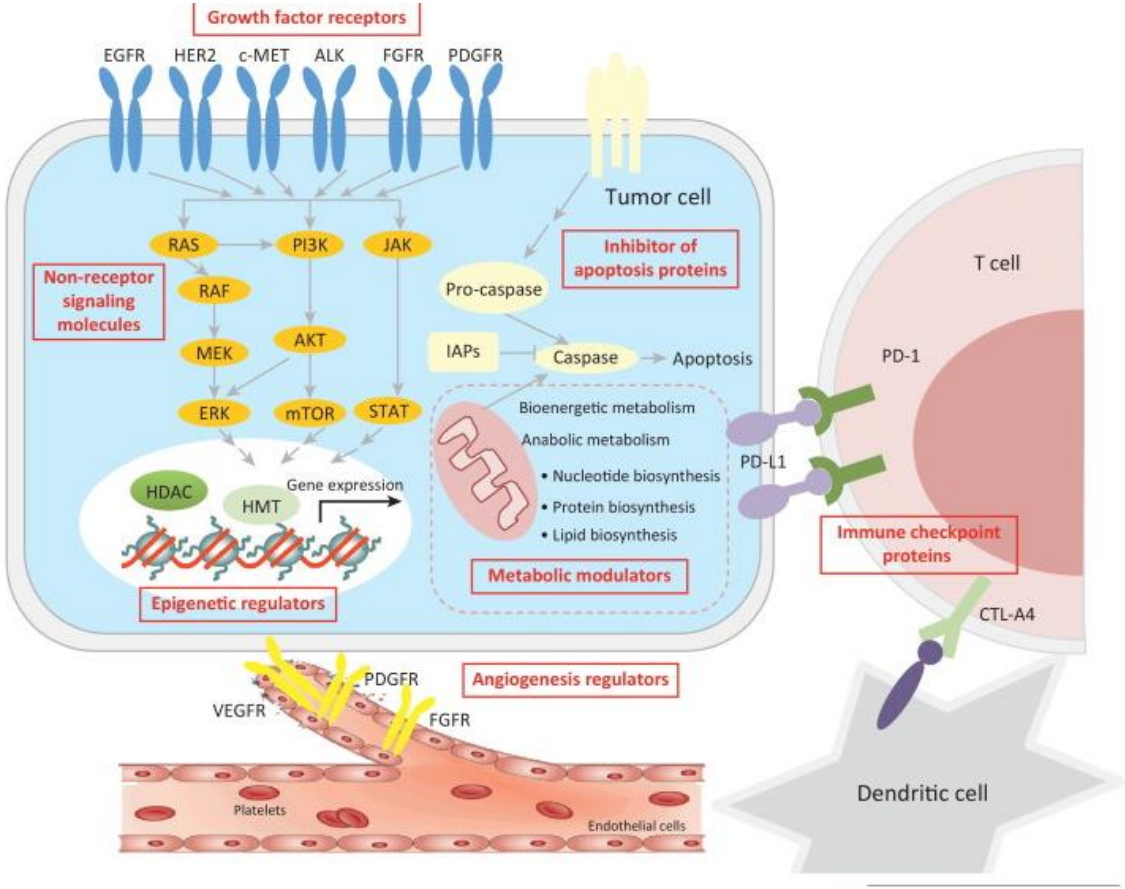
Y
Yervoy
Yondelis

Z
Zaltrap
Zanosar
Zavedos
Zelboraf
Zevalin
Zoladex (breast cancer)
Zoladex (prostate cancer)
Zoledronic acid (Zometa)
Zometa
Zomorph
Zydelig
Zytiga

A myraid of anti-cancer treatments



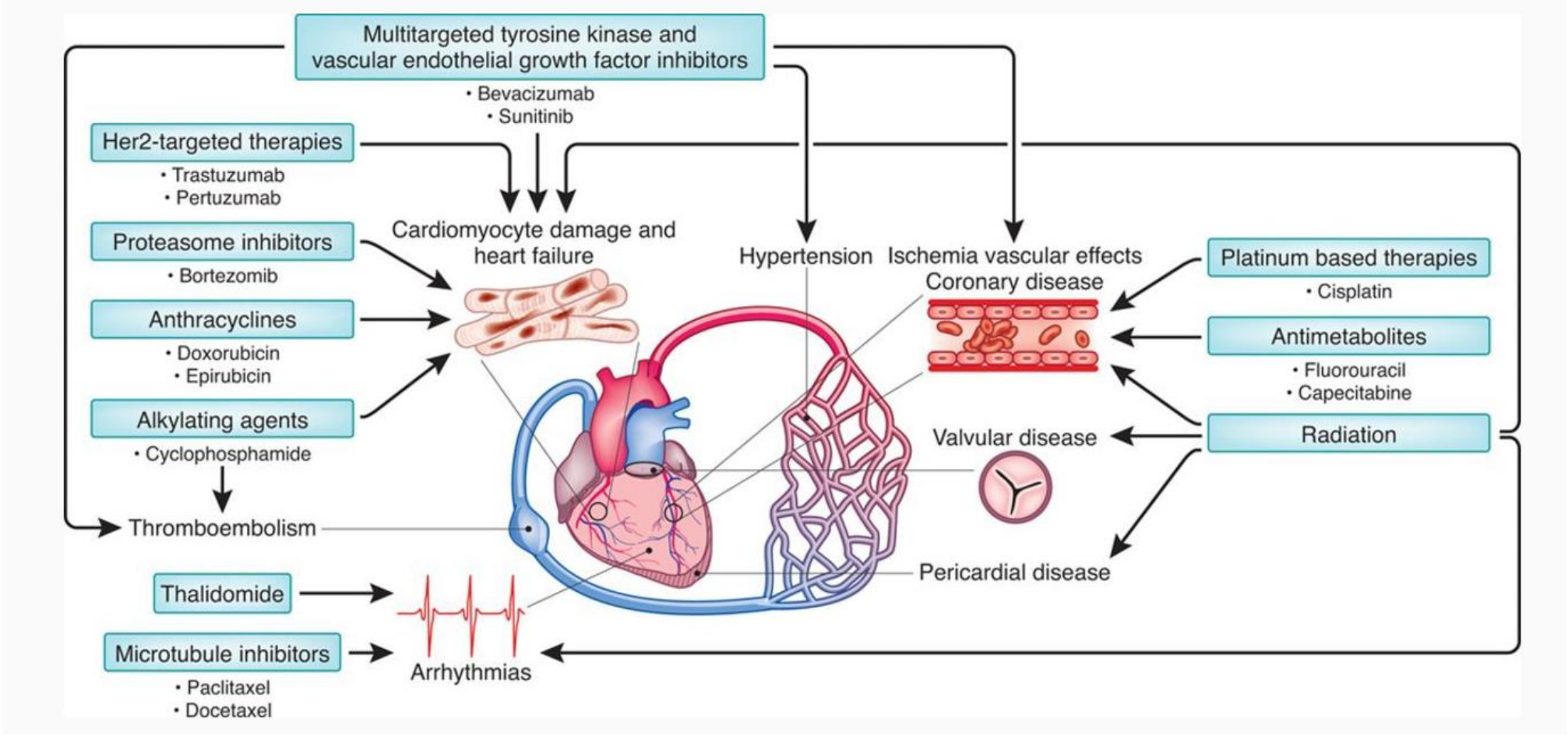
Cytotoxiques



Thérapies ciblées/immunothérapie

Epomedicine 2016, Huang 2014

A diverse cardiotoxicity profile



Lenneman, 2016

How to get around this vast heterogeity ? Concept of risk of cardiotoxicity

Facteurs de risque de cardiotoxicité	
Facteurs de risque liés au **traitement**	Facteurs de risque liés au **patient**
• **Risque haut** (score 4) : anthracyclines, cyclophosphamide, ifosfamide, clofarabine, trastuzumab • **Risque intermédiaire** (score 2) : docétaxel, pertuzumab, sunitinib, sorafénib • **Risque bas** (score 1) : bévacizumab, dasatinib, imatinib, lapatinib • **Risque très bas** (score 0) : par exemple, étoposide, rituximab, thalidomide	• Cardiopathie ou insuffisance cardiaque connues • Maladie coronarienne significative ou équivalent (artériopathie oblitérante) • Hypertension artérielle • Diabète • Antécédent de traitement par anthracyclines • Radiothérapie thoracique actuelle ou dans les antécédents • Âge < 15 ans ou > 65 ans • Sexe féminin

Calcul du risque global (CRS– Cardiotoxicity Risk Score)
(score du risque thérapeutique + nombre de facteurs de risque liés au patient)

Catégories de risque	**Proposition de suivi**	**Traitement cardioprotecteur (avant et pendant la chimiothérapie)**
Risque très haut	• ETT avec mesure du strain longitudinal global avant chaque cure (ou 1 sur 2) ; à l'arrêt du traitement, à 3-6 mois et 1 année • Optionnelle : ECG et dosage Tn avant les ETT prévues	• Introduction IECA/sartan, carvédilol, statine • Commencer la chimiothérapie 1 semaine après l'introduction du traitement • Majoration jusqu'aux doses maximales tolérées
Risque haut	• ETT avec mesure du strain longitudinal global toutes les 3 cures, à l'arrêt du traitement, à 3-6 mois et 1 année • Optionnelle : ECG et dosage Tn avant les ETT prévues	Introduction IECA/sartan, carvédilol, ± statine
Risque intermédiaire	• ETT avec mesure du strain longitudinal global à la moitié du traitement, à l'arrêt du traitement, et à 3-6 mois après l'arrêt • Optionnelle : ECG et dosage Tn au milieu du traitement	Discuter l'introduction du traitement cardioprotecteur (balance risque/bénéfice)
Risque bas	Optionnelle : ETT avec mesure du strain longitudinal global ± ECG et dosage Tn à l'arrêt du traitement	
Risque très bas	Suivi clinique	

Plan

- What is cardio-oncology ?
- General cancer epidemiology
- Cardiotoxicity profile and cardiac assessment for specific cancer treatments
  - **Fluoropyrimidine therapy**
  - Anthracyclines
  - Anti HER2 therapy
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5-fluorouracile

- Antimétabolite : Analogue pyrimidique
- Chimiothérapie du CCR, estomac, pancréas, foie, sein, endomètre, col utérin…
- Incidence de cardiotoxicité entre 1 et 18%, mortalité entre 2 et 13%
- Augmentation du risque en cas de radiothérapie thoracique concomitante, d'association avec d'autres traitements oncologiques et de pathologie cardiaque préexistante (CAD, cardiomyopathie…)
- Principalement lors d'une administration continue vs bolus

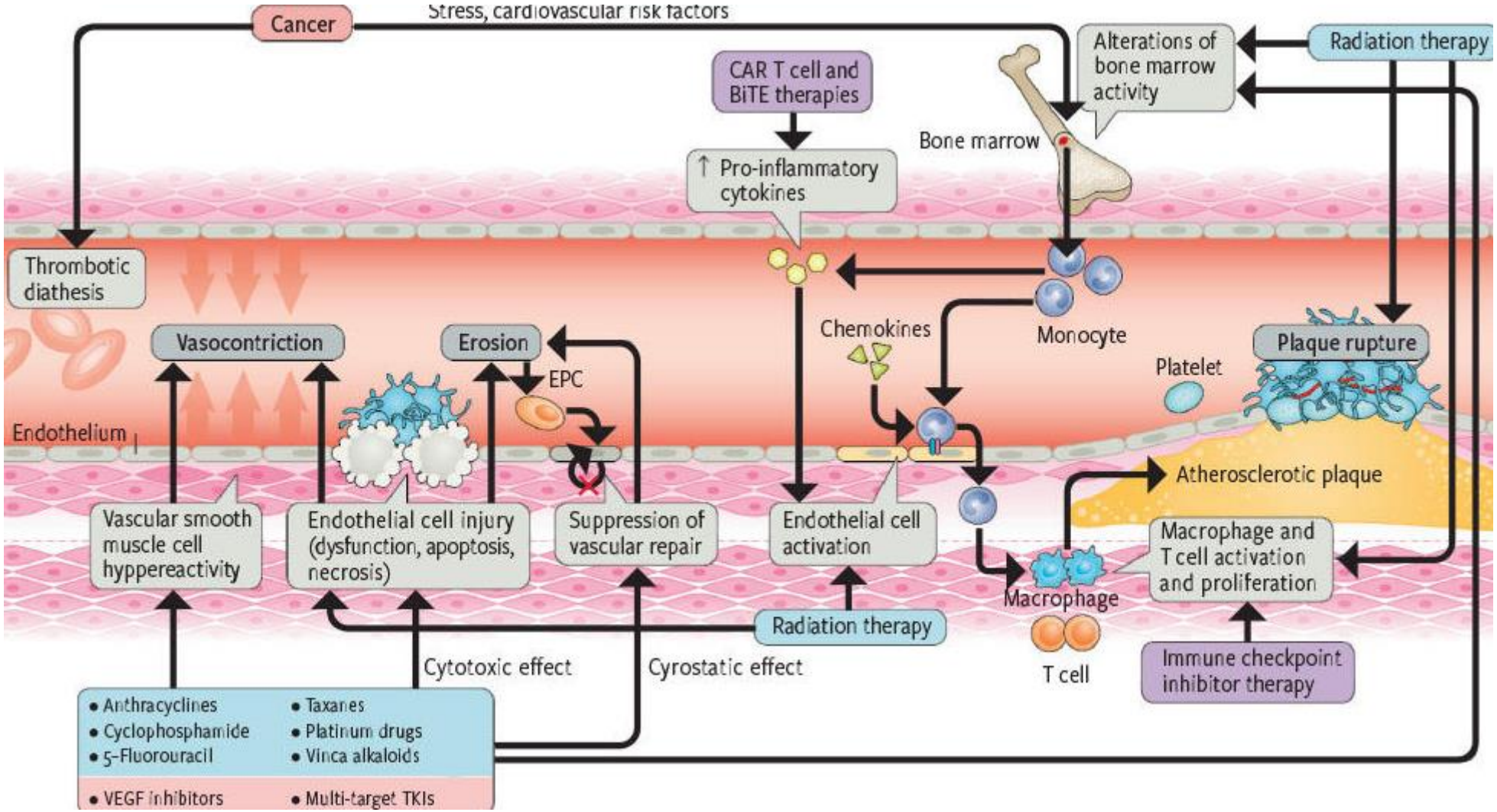
Cardiotoxicité liée au 5-fluorouracile

Clinique
Infarctus du myocarde
Cardiomyopathie
Myocardite
Péricardite
Arythmie
Mort subite

ECG
Tachycardie supraventriculaire
Tachycardie ventriculaire
Allongement QT
Changements ischémiques (ondes T et segment ST)
PARFOIS NORMAL+++++

Monitoring par ETT + sensible que les biomarqueurs cardiaques pour détecter la cardiotox

Mécanismes principaux de l'ischémie

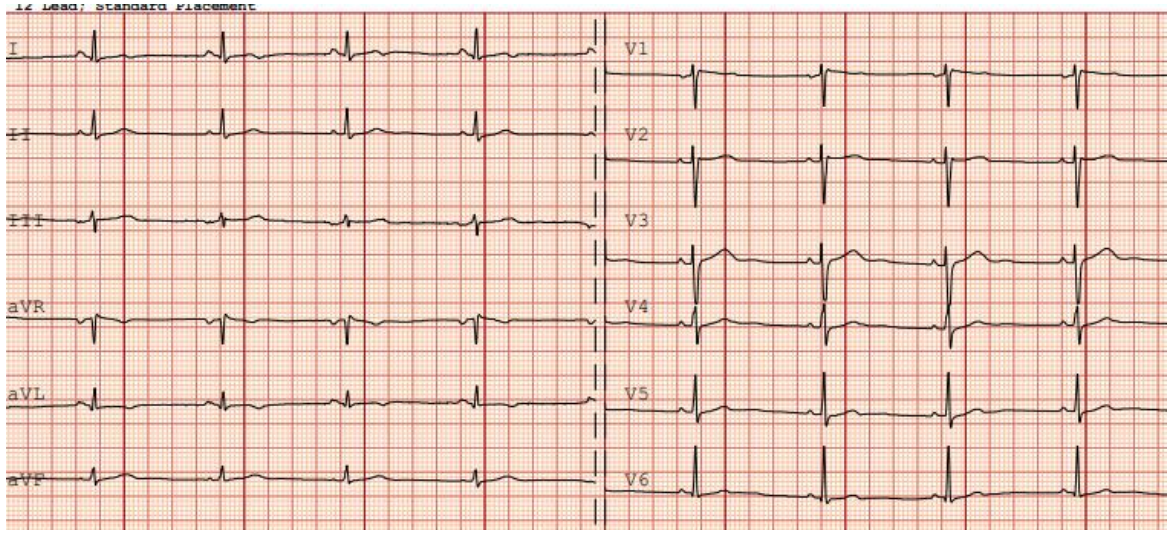


Cardiotoxicité liée au 5-fluorouracile

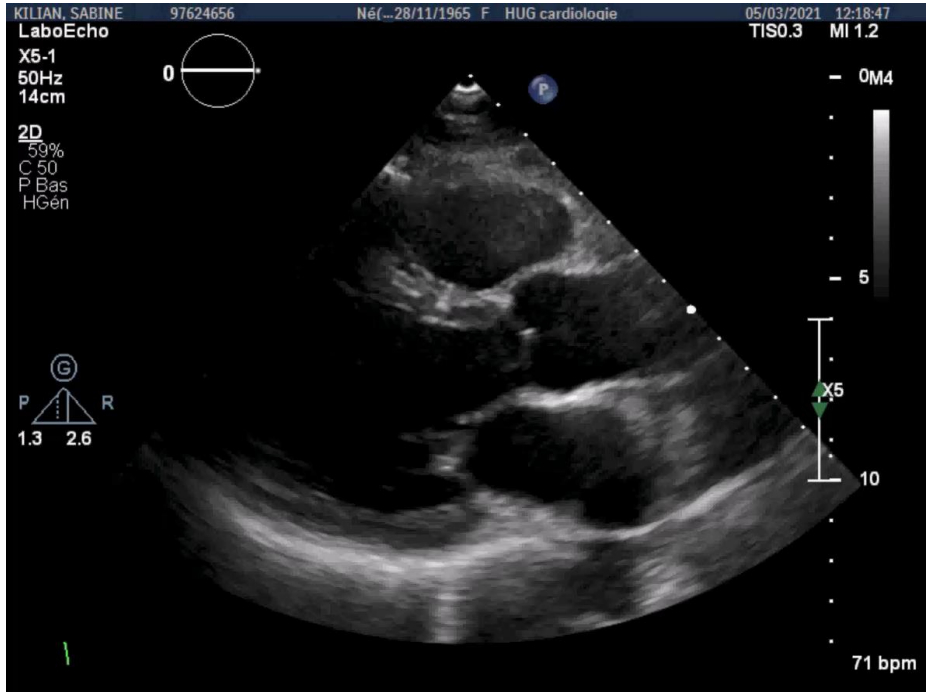
- Pas de recommandation de prise en charge
- Consensus actuel d'arrêt du 5FU dès qu'une cardiotoxicité est suspectée
- Traitement symptomatique aigu avec dérivés nitrés et inhibiteur calcique (efficace dans 70% des cas)
- Semblerait être réversible en l'absence de pathologie CV sous jacente
- Réduction du risque CV avec arrêt du tabac, optimisation tensionnelle, ttt par statine et contrôle glycémique
- Antidote : Vistogard® (uridine triacetate)
- 82 à 100% de récidive en cas de rechallenge et 13% de risque de décès

Cas clinique : Mme K, 55 ans

- Aucun FdRCV ni ATCD
- ADK caecal métastatique synchrone hépatique bilobaire, KRAS muté, MSS diagnostiqué en février 2020
- 1er cycle d'OCFL le 01.03: DRS oppressive 12h après le début du baxter de 5FU sans modification ECG ni élévation des troponines.



- Consultation de cardiologie le 5.3.2021 (J5)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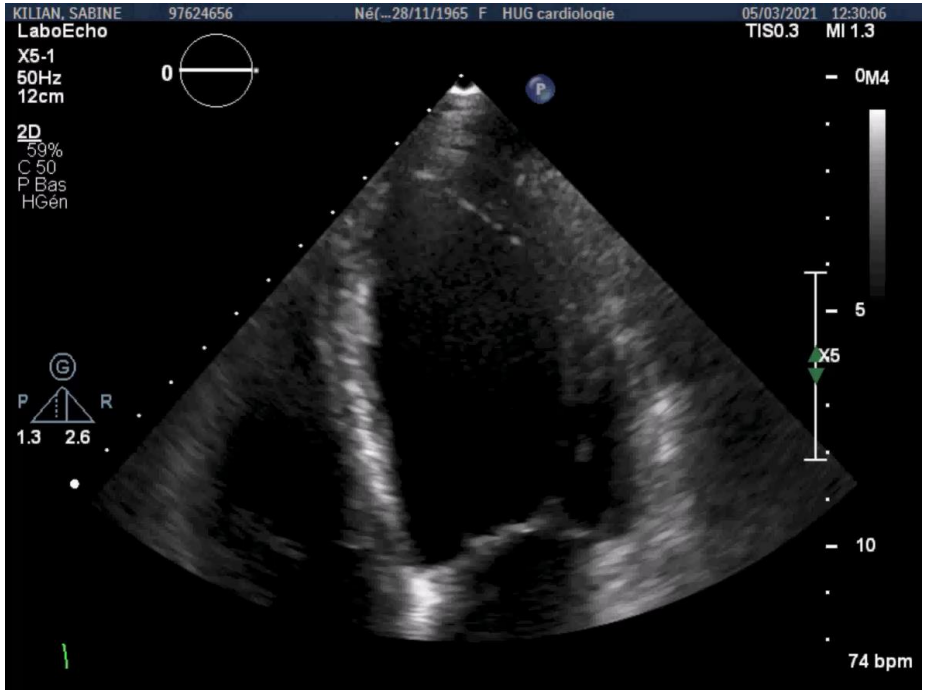
LaboEcho TIS0.3 MI 1.2
X5-1
50Hz
14cm
2D
59%
C 50
P Bas
HGén
0M4
5
X5
10
1.3 2.6
71 bpm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59%
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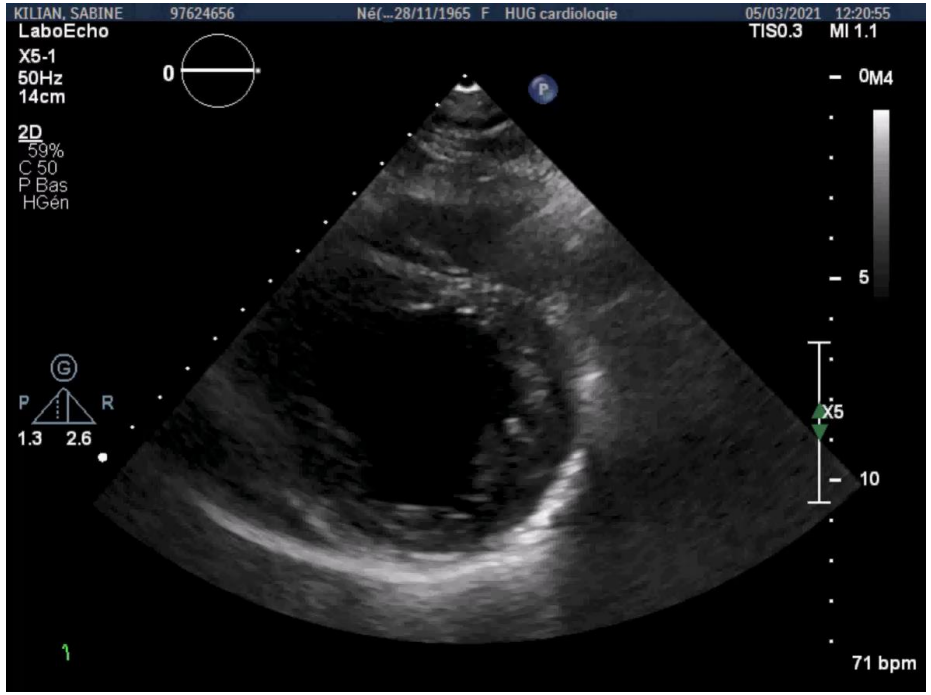
HGén
0M4
5
X5
10
1.3 2.6
74 bpm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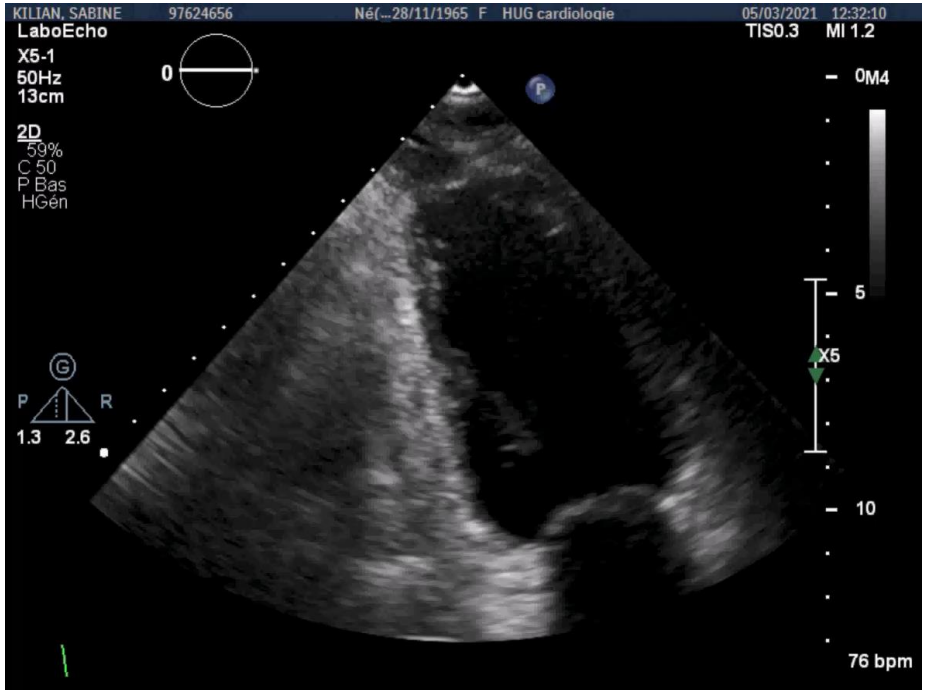
X5
10
1.3 2.6
71 bpm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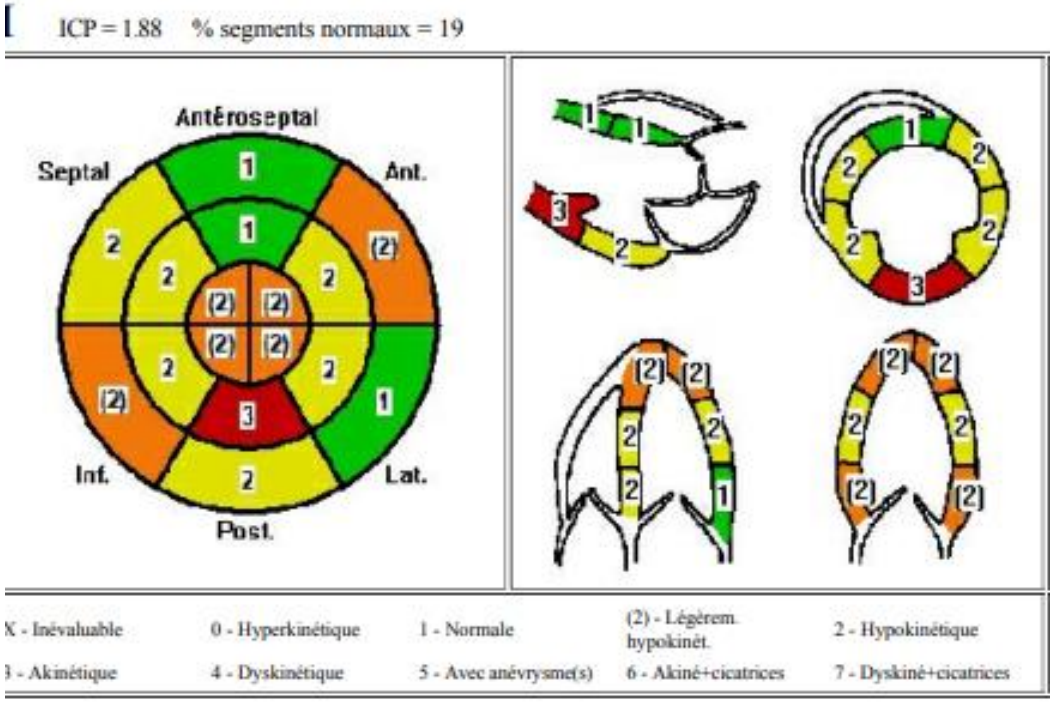
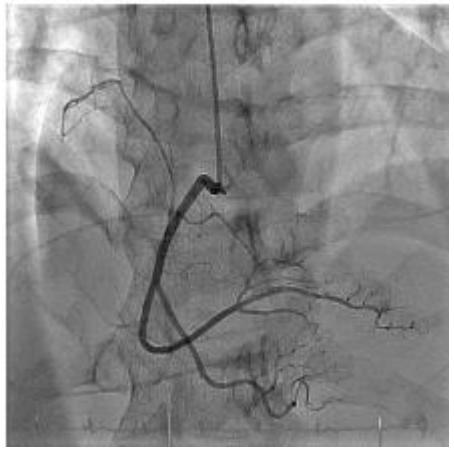
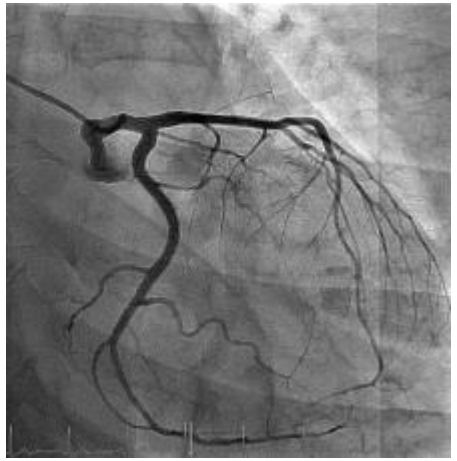
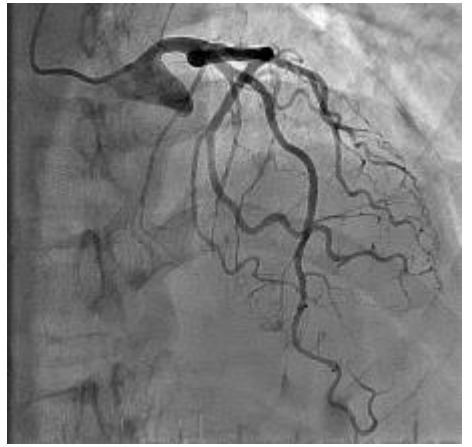
X5-1
50Hz
13cm
2D
59%
C 50
P Bas
HGén
0M4
5
X5
10
1.3 2.6
76 bpm

A J5
ECG
ETT
coronarographie









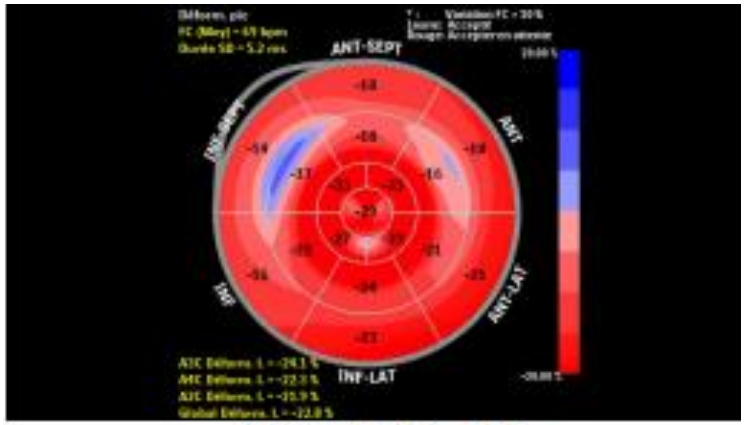
Cas clinique : Mme K, 55 ans

- J8 d'OCFL en intrahosp sous Holter ECG et nifédipine
- Durant la perfusion, boit un verre d'eau froide déclenchant à nouveau des DRS avec NV et ECG per-critique: négativation des ondes T V1-V3
- Analyse du holter: ondes T pointues 1h avant les douleurs puis négativation pendant 4h, normalisation 2h après la DRS et arrêt du 5FU

- Options possibles:
    1. changer de mode d'administration : durée de perfusion, bolus...
    2. différer la prochaine perfusion de 5FU avec prétraitement d'anticalciques et sous monitoring cardiaque (JUL53)
    3. finir le cycle actuel sous surveillance rythmique aux soins intermédiaires de cardiologie, sous nitrés iv et anticalciques po.
    4. choisir une alternative mais d'équivalence au 5FU incertaine

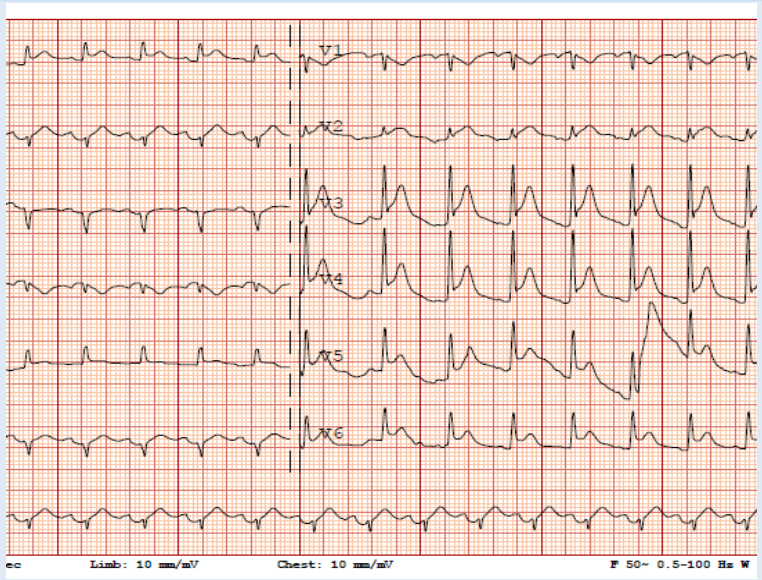
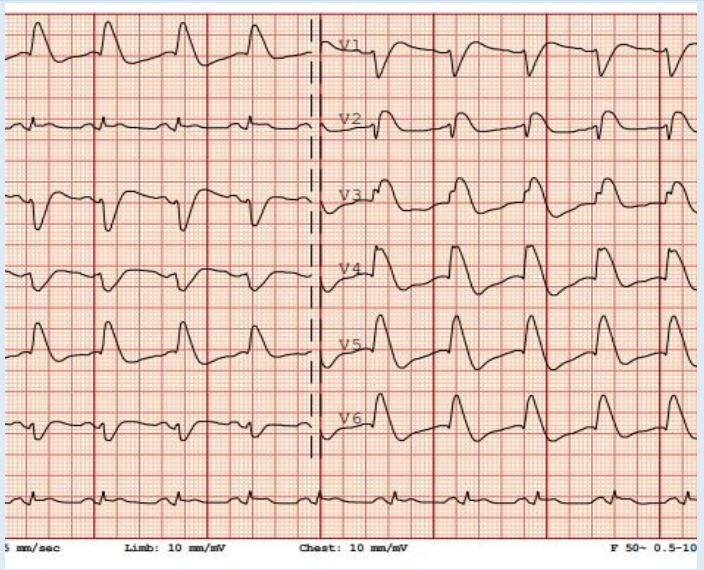
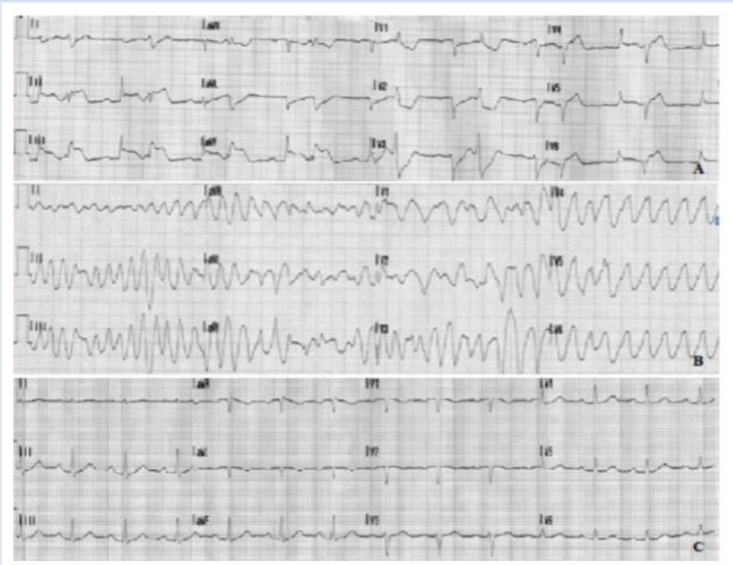
Cas clinique : Mme K, 55 ans

- Changement du 5FU pour du Raltitrexed
- ETT de contrôle à 2 mois : normale, FFEVG 55-60%, strain -23%

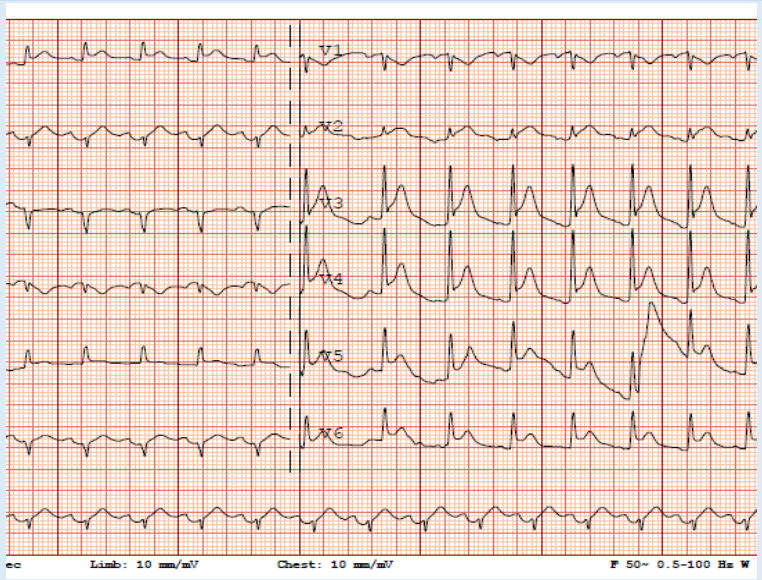
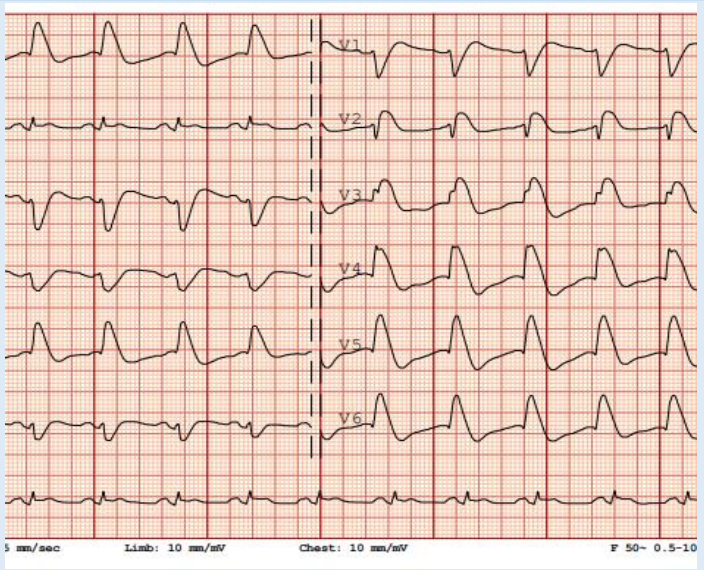
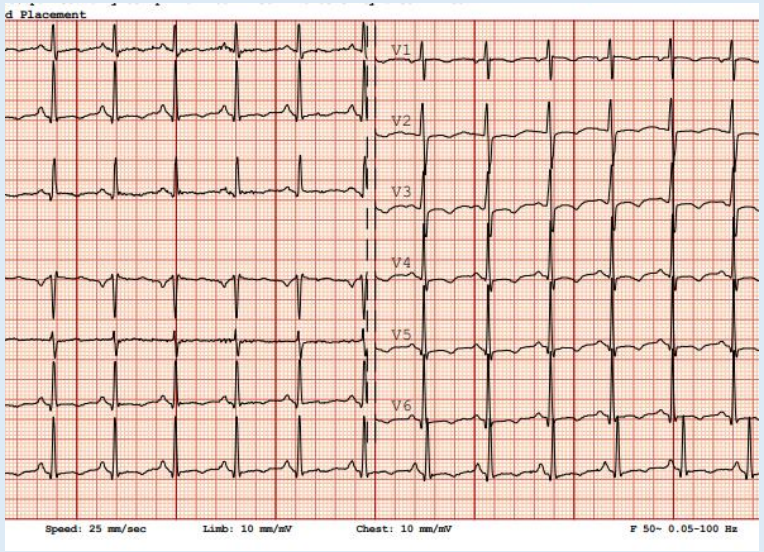


GLS normal à -23%

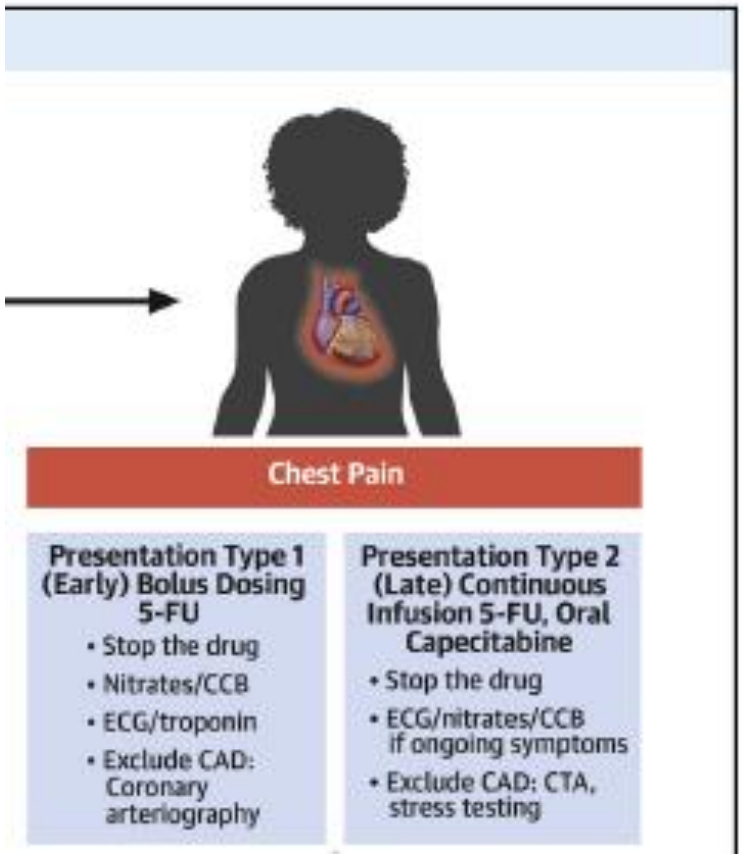
Other cases of fluoropyrimidine toxicity

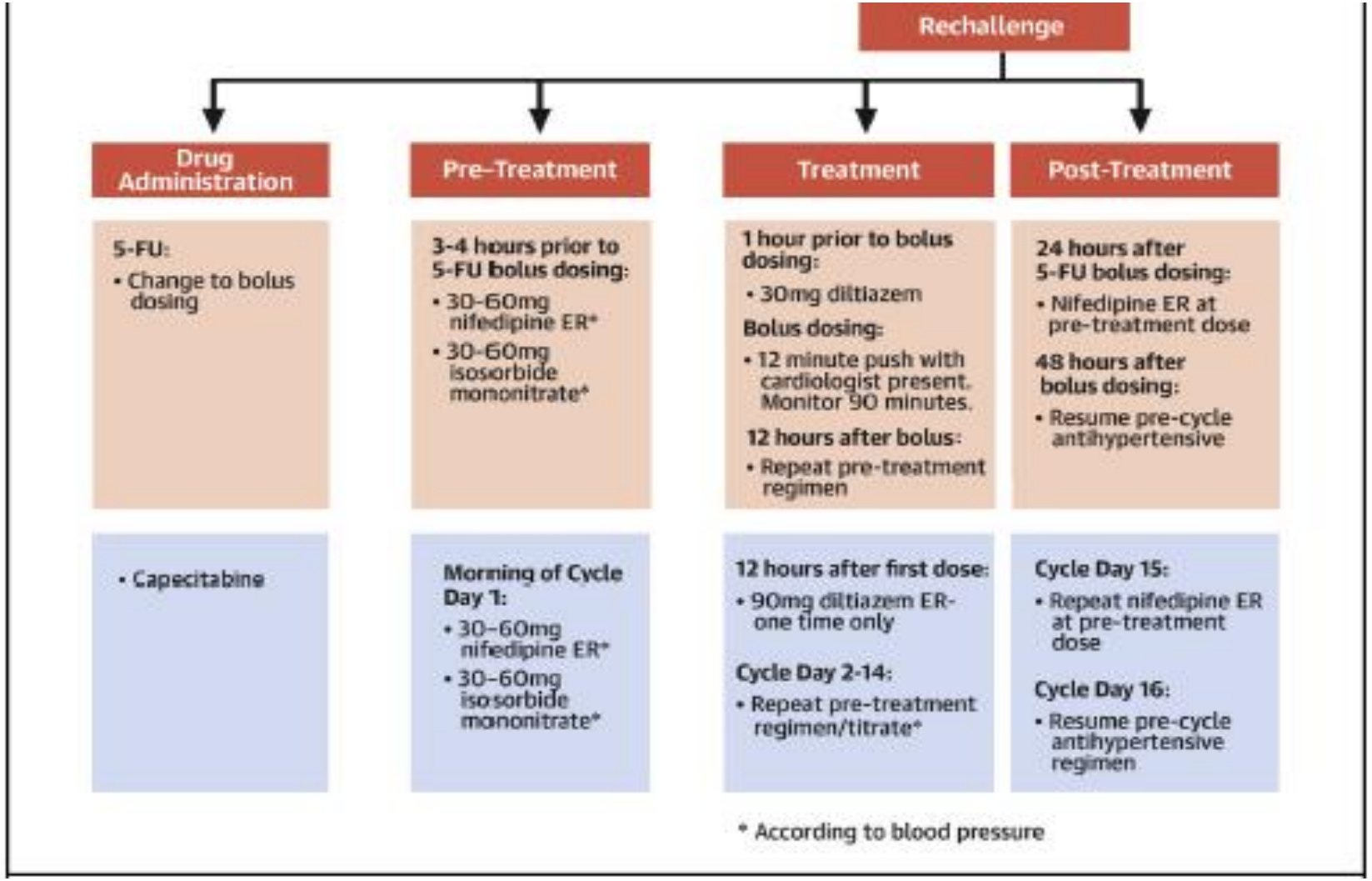
59 yr old man **0 comorbidities, no tabaco** **Pancreatic cancer (stage VI)** **Day 1 of FOLFIRINOX protocol** **Malaise, no chest pain, cardiac arrest, VF**	**71 yr old woman** **COPD, atrial flutter, past smoker** **Colorectal cancer (stage IV)** **Day 1 of OCFL-B protocol** **No chest pain, cardiac arrest, VF, ROSC after 10 external chocs**	**56 yr old woman** **CPOD, active smoker** **Syncope**
		
Echo : global hypokinesia, antero-septo-apical akinesia, LVEF 30% Discrete troponin elevation, normal CK level Mid LAD 50-70% stenosis, vasospastic segment **Normalisation of LVEF at 2 months**	Echo : global hypokinesia, LVEF 25% No obstructive coronary lesion Discrete troponin elevation, normal CK levels **Normalisation of LVEF at 6 months ,** GLS -18%	Echo : inferior wall akinesia, FEVG 50% Normal coronary angiogram

Other cases of fluoropyrimidine toxicity

59 yr old man **0 comorbidities, no tabaco** **Pancreatic cancer (stage VI)** **Day 1 of FOLFIRINOX protocol** **Malaise, no chest pain, cardiac arrest, VF**	**71 yr old woman** **COPD, atrial flutter, past smoker** **Colorectal cancer (stage IV)** **Day 1 of OCFL-B protocol** **No chest pain, cardiac arrest, VF, ROSC after 10 external chocs**	**28 yr old woman** **0 comorbidities** **Colorectal cancer (polyposis)** **Capecitabine/Oxaliplatine protocol** **Chest pain 3 days after the 1st dose**
		
Echo : global hypokinesia, antero-septo-apical akinesia, LVEF 30% Discrete troponin elevation, normal CK level Mid LAD 50-70% stenosis, vasospastic segment **Normalisation of LVEF at 2 months**	Echo : global hypokinesia, LVEF 25% No obstructive coronary lesion Discrete troponin elevation, normal CK levels **Normalisation of LVEF at 6 months ,** GLS -18%	Echo : LVEF 65% Normal coronary angiogram Discrete troponin elevation, normal CK levels

Is fluoropyrimidine rechallenge feasible ?

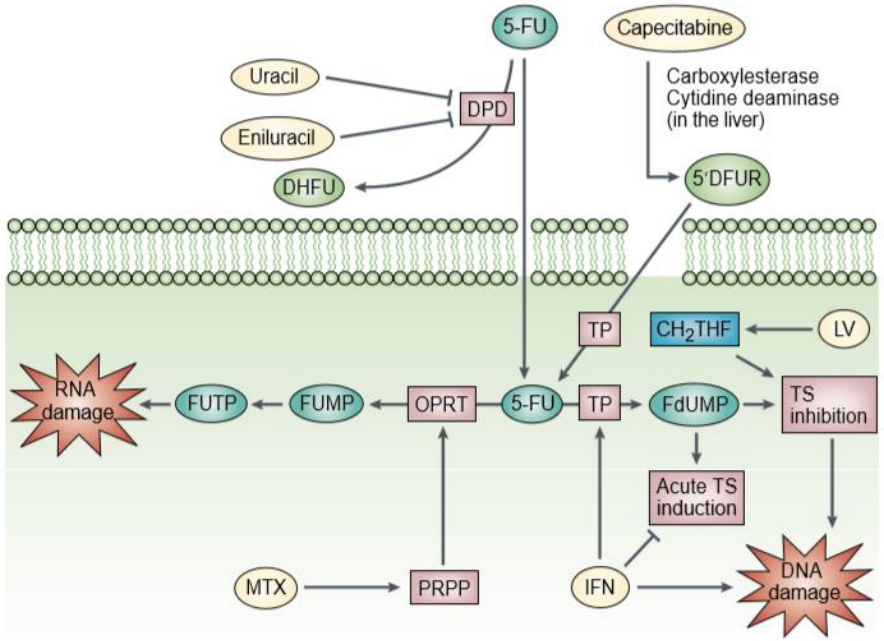




Padegimas and Carver Fluoropyrimidine-Induced Chest Pain, JACC 2020

Systematic DPD testing before fluoropyrimidine exposure

DPD testing
- either the enzyme activity of **dihydropyrimidine dehydrogenase** (DPD)
- or the DPYD genotype



Résultat et Conclusion (2)

Génotype DPYD : *1/*9A

Présence du variant ***DPYD*9A*** (rs1801265, c.85T>C) à l'état hétérozygote.

Absence des variants recherchés: ***DPYD*2A*** (rs3918290, c.1905+1G>A), ***DPYD*3*** (rs72549303, c.1898delC), ***DPYD*4*** (rs1801158, c.1601G>A), ***DPYD*5*** (rs1801159, c.1627A>G), ***DPYD*6*** (rs1801160, c.2194G>A), ***DPYD*7*** (rs72549309, c.299_302delTCAT), ***DPYD*8*** (rs1801266, c.703C>T), ***DPYD*10*** (rs1801268, c.2983G>T), ***DPYD*11*** (rs72549306, c.1003G>T), ***DPYD*12*** (rs78060119, c.1156G>T), ***DPYD*13*** (rs55886062, c.1679T>G), rs67376798 (c.2846A>T), rs115232898 (c.557A>G), rs56038477 (c.1236G>A), et rs75017182 (c.1129-5923C>G).

Longley DB, et al 5-Fluorouracil: mechanisms of action and clinical strategies. *Nature Rev Cancer*. 2003;3(5):330-8.

Fluoropyrimidines : cardiology workup and follow up

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 alterative cancer treatment with at least similar efficacy and impact on survival, patients with a history of fluoropyrimidine cardiac toxicity should be evaluated for the possibility of rechallenge.
- In patients with overt and/or life-threatening toxicities, administration of an antidote (uridine triacetate) might be useful.

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**

Plan

- What is cardio-oncology ?
- General cancer epidemiology
- Cardiotoxicity profile and cardiac assessment for specific cancer treatments
  - Fluoropyrimidine therapy
  - **Anthracyclines**
  - **Anti HER2 therapy**
  - **Radiotherapy**
  - Anti-androgen therapy
  - Tyrosine Kinase therapy
  - Immunotherapy
- Clinical cases
- Impact of a cardio-oncology unit
  - A multidisciplinary approach

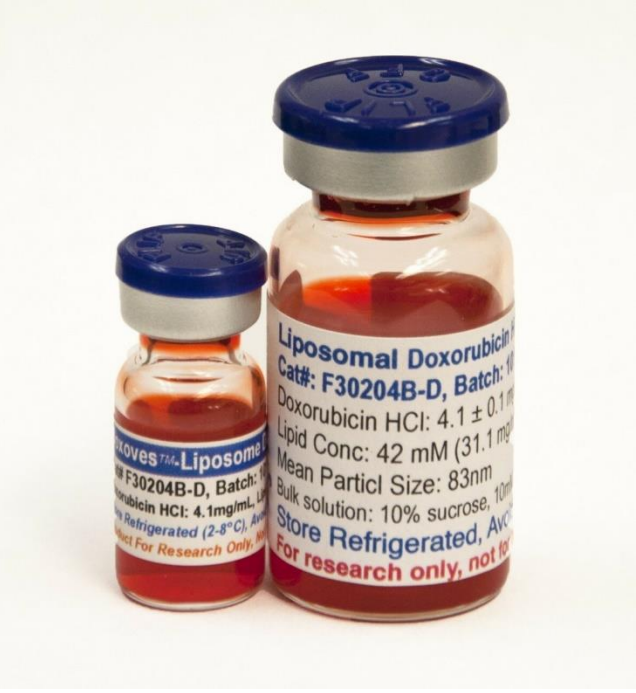
Cardiotoxicité

Today's cancer patients
are
tomorrow's cardiac patients

Anthracyclines

Cancers du sein néoadjuvant/adjuvant/métastatique
Sarcomes
Cancers **gynécologiques**
Hémopathies malignes

50-60% enfants survivants



Cardiotoxicité des anthracyclines

Mécanismes potentiels multiples :

- Formation de radicaux libres
- Dysfonction mitochondriale
- Cassure double brin ADN (effet anti-topoisomérase 2) -> apoptose

Cardio-toxicité :

. aiguë (< 1 an) / tardive (en moyenne 7ans)

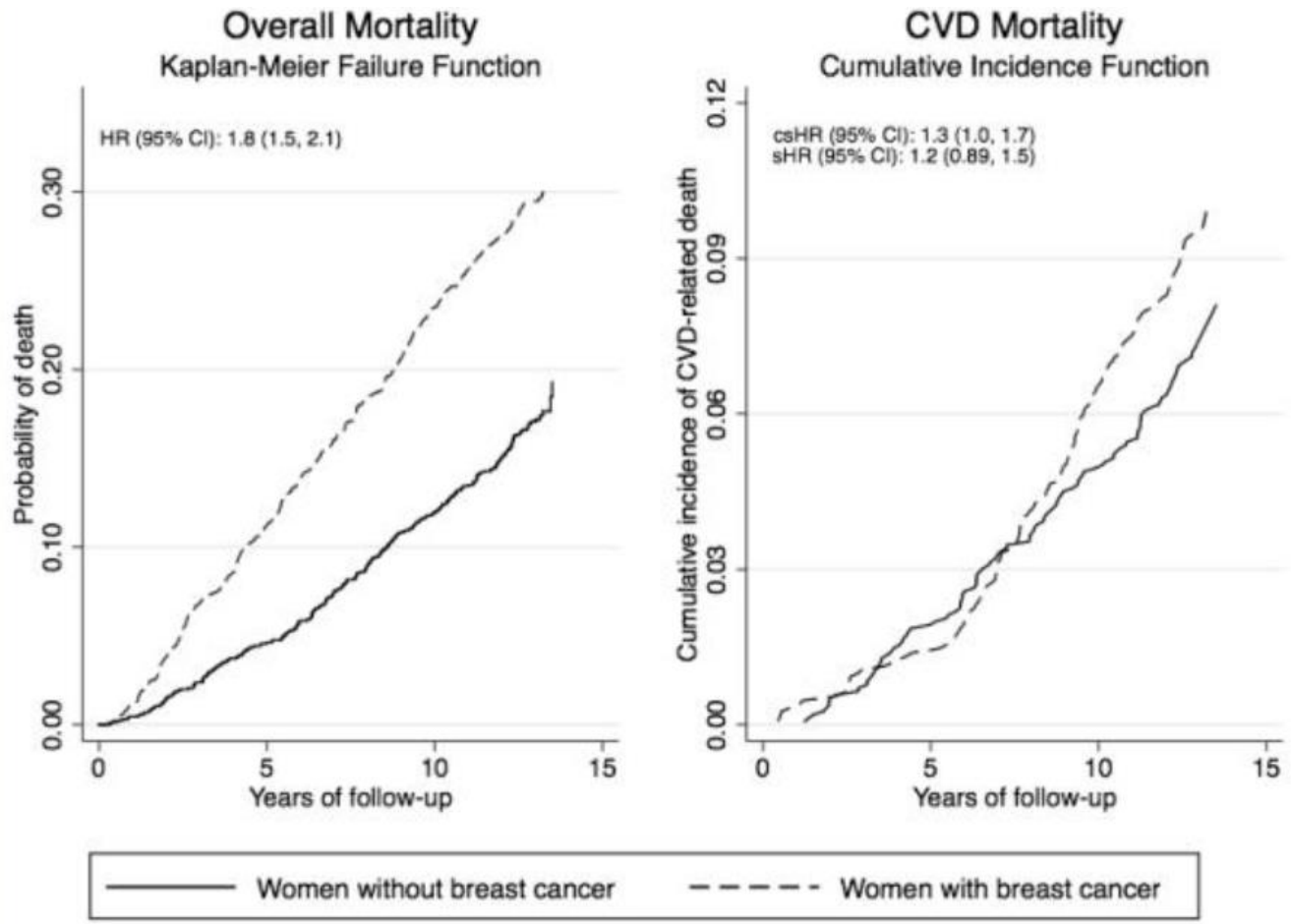
. CUMULATIVE

. de type I (permanente) ---> *Obsolète ?*

Anthracyclines	Dose cumulative maximale	Conversion isotoxique	Dose cumulative maximale si radiothérapie médiastinale
Doxorubicine	450-550mg/m2	x 1	400mg/m2
Epirubicine	900mg/m2	x 0,67	
Daunorubicine	600mg/m2	x 0,5	
Idarubicine	93mg/m2	x 5	
Mitoxantrone	160mg/m2	x 4	

McGowan, Cardiovasc Drugs Ther, 2017 ; compendium

Avec le temps, mortalité CV devient très importante.

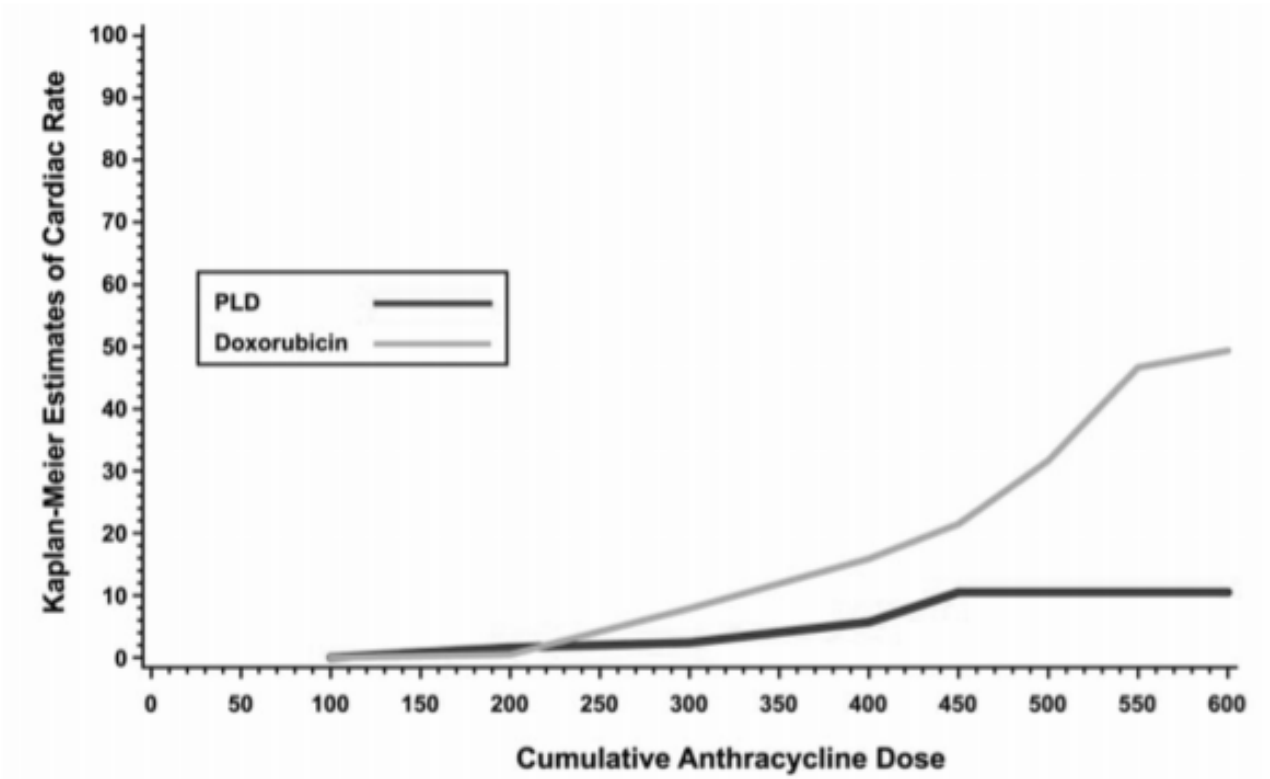


A + 9ans suivi post cancer sein : Plus de risque de décès d'origine CV qu'oncologique.
Enfants : 13% mortalité CV à > 45ans.

McGowan, Cardiovasc Drugs Ther, 2017 ; Bradshaw, Epidemiology, 2016

Diminuer la cardiotoxicité des anthracyclines

- **Doxorubicine liposomale (Caelyx)** moins cardiotoxique, permet «plus de doses»



O'Brien, Annals of Oncol, 2004 ; McGowan, Cardiovasc Drugs Ther, 2017 ; Bosch, JACC, 2013 ; Cardinale, Circulation, 2015 ; Gulati, Eur Heart J, 2016 ; Reichardt, Future Oncol , 2018 ; Liesse, J Pediatr Hematol Oncol, 2018

Diminuer la cardiotoxicité des anthracyclines

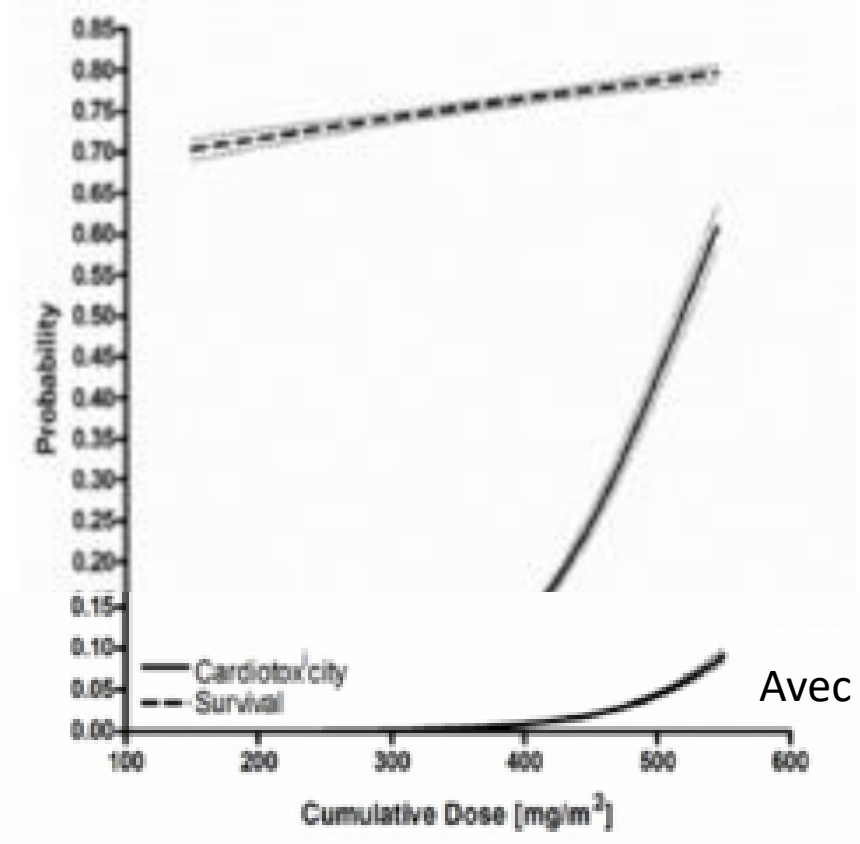
- **Doxorubicine liposomale (Caelyx)** moins cardiotoxique

- **Dexrazoxane**

. AC haute dose (> 300mg/m2) ou dans cancers pédiatriques

. Diminution cardiotoxocité

. AE possible : myélosuppression, cancer 2nd, pas de diminution effet antitumorale



Avec Dexrazoxane

O'Brien, Annals of Oncol, 2004 ; McGowan, Cardiovasc Drugs Ther, 2017 ; Bosch, JACC, 2013 ; Cardinale, Circulation, 2015 ; Gulati, Eur Heart J, 2016 ; Reichardt, Future Oncol , 2018 ; Liesse, J Pediatr Hematol Oncol, 2018

Diminuer la cardiotoxicité des anthracyclines

- **Doxorubicine liposomale (Caelyx)** moins cardiotoxique

- **Dexrazoxane**
. AC haute dose (> 300mg/m2) ou dans cancers pédiatriques
. Diminution cardiotoxocité
. AE possibles : myélosuppression, cancer 2nd, pas de diminution effet antitumorale

- Prophylaxie primaire*/secondaire par **BB – IEC/Sartan**
. Débattue
. Timing introduction ?
. Initiation rapide -> récupération FEVG plus importante et rapide

**OVERCOME trial (carvedilol + enalapril vs cô) : moins de diminution FEVG*
**PRADA trial (Sartan +/-BB) : pas effet du BB, mais absence de diminution FEVG avec sartan (vs 2,6%)*
Cardinale trial (IEC et carvedilol) : amélioration FEVG + rapide et + complète

⇒ NE PAS DEPASSER DOSE CUMULEE MAXIMALE
⇒ FU ETT AVANT, PENDANT et POST traitement

O'Brien, Annals of Oncol, 2004 ; McGowan, Cardiovasc Drugs Ther, 2017 ; Bosch, JACC, 2013 ; Cardinale, Circulation, 2015 ; Gulati, Eur Heart J, 2016 ; Reichardt, Future Oncol , 2018 ; Liesse, J Pediatr Hematol Oncol, 2018 ; Lin, Cardiology, 2020

Anti-HER2

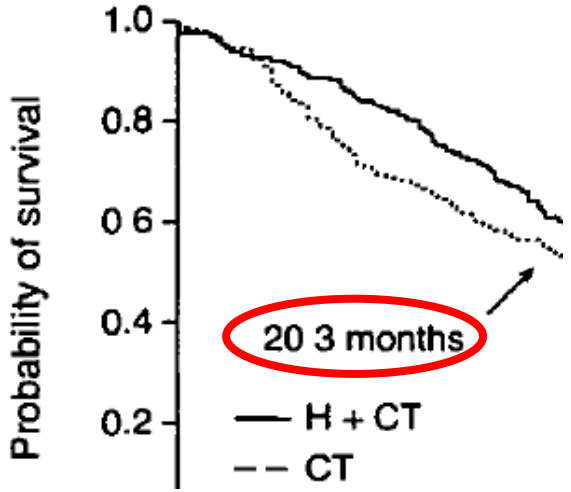
Cancer du **sein HER2 amplifié** (15-30% cancer sein) : Néoadjuvant ; Adjuvant ; Métastatique

Cancer de l'**estomac HER2 amplifié** : Métastatique *(études pour autres stades)*

Autres cancers HER2 amplifié

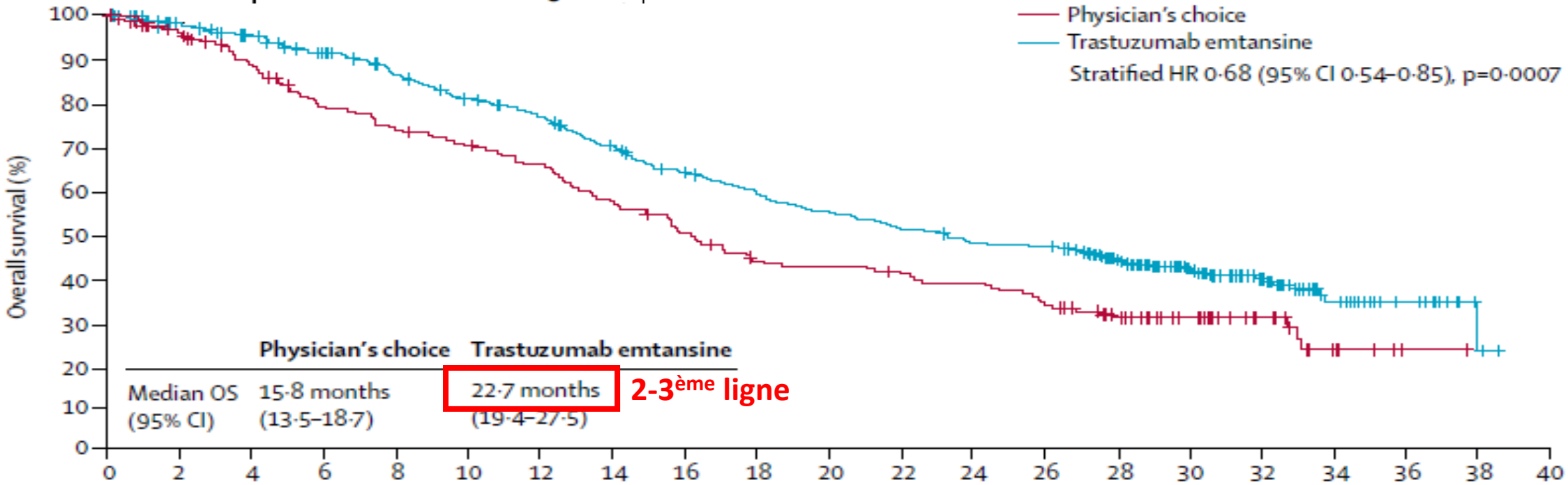
Et encore beaucoup d'autres…

Cancer du sein métastatique HER2 amplifié



1ère ligne

mOS 56,5 mois



2-3ème ligne

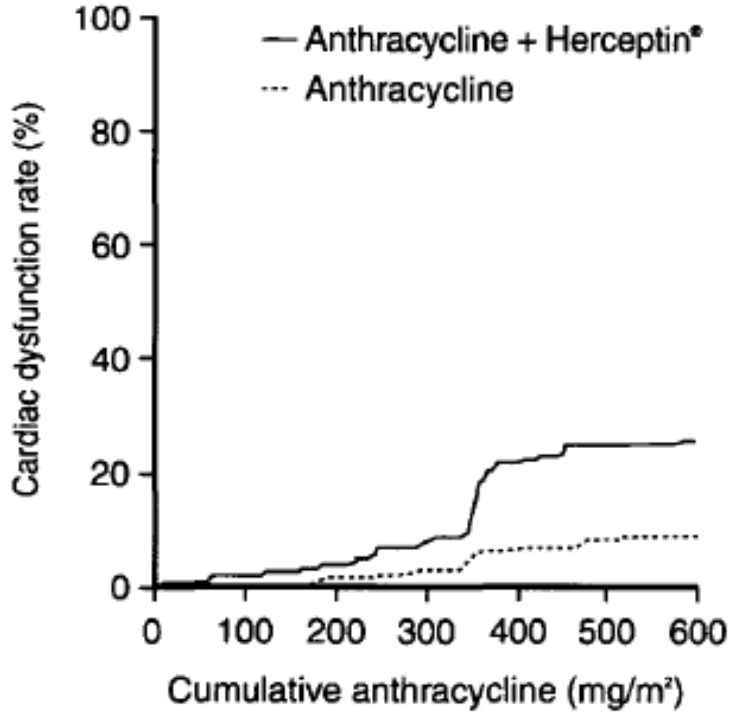
Eiermann, Annals Oncol, 2001 ; Swain, NEJM 2015 ; Krop, Lancet Oncol, 2017

Cardio-toxicité des antiHER2

Mal comprise
Non-cumulative
De type II (réversible)

Inattendue dans l'étude pilote 2001 du trastuzumab

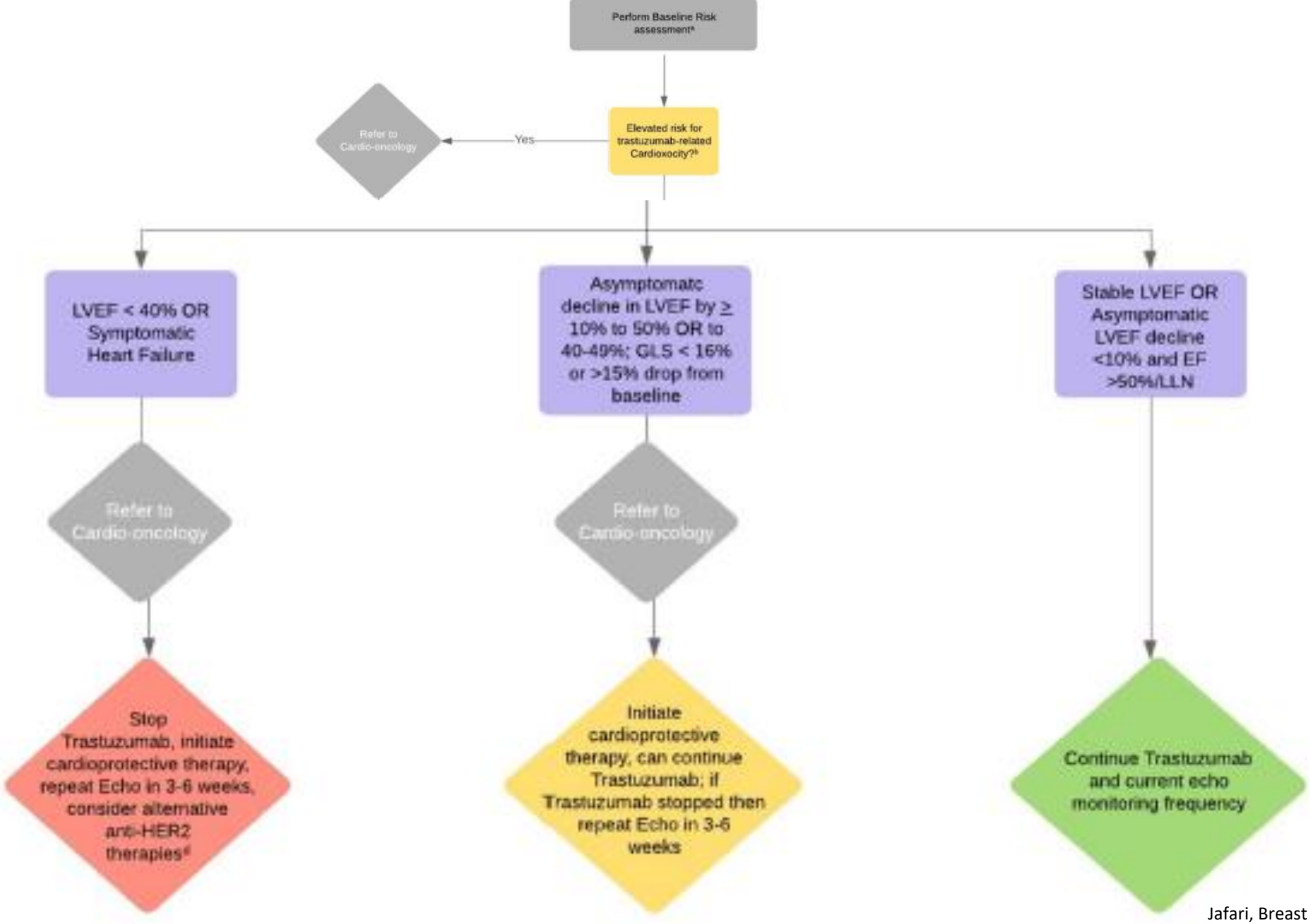
Risque augmentée avec anthracyclines concomitantes > antécédents AC > absence AC



Trials	Trastuzumab (2001)	T-Pertuzumab (2015)	T-DM1 (2017)	T-Deruxtan (2020)
Diminution FEVG	11-27*% *avec AC	6,6% (T seul : 8,6%)	2,5%	1,6%
Réversibilité	-	87,5% (T seul : 78,6%)	-	100%

⇒ JAMAIS AC + AntiHER2 CONCOMITANTS
⇒ FU FEVG /3 mois pendant ttt, et à la fin du traitement
⇒ SUSPENCION/ARRET antiHER2 en fonction

Gianni, Annals Oncol, 2001 ; Gianni, Annals Oncol, 2001 ; Swain, NEJM 2015 ; Krop, Lancet Oncol, 2017 ; Modi, NEJM, 2020



Jafari, Breast Ca Res and Treat, 2020

Rechallenge anti-HER2 post cardiotoxicité

Peu d'évidence pour antiHER2

Reprise du traitement à discuter :

. si amélioration partielle ou complète de la fonction cardiaque conservée à un contrôle à 4 semaines

. selon contexte clinique

. bénéfices attendus

. 60 patient avec diminution asymptomatique FEVG < 50% sous trastuzumab :

. 38% poursuivi traitement – 26% baisse FEVG supplémentaire ; 13% évènement CV

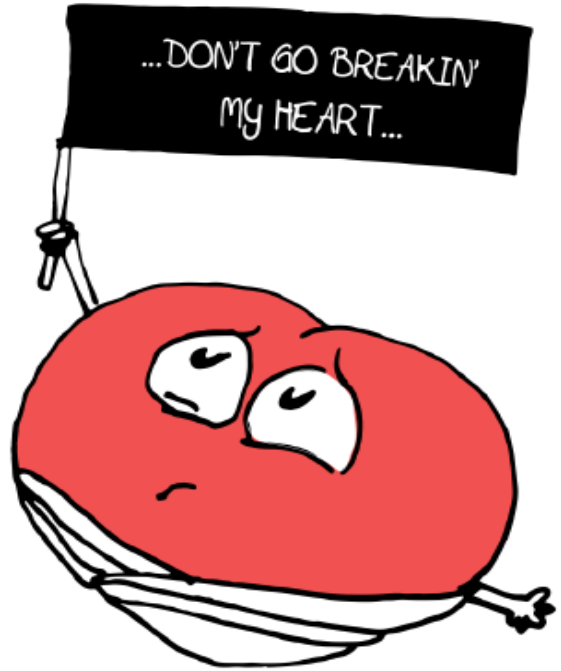
. 62% interrompu traitement – 41% rechallengé post amélioration

FU : pas de différence FEVG

Florido, JAHA, 2017 ; Hussain, Breast Ca Res and treat, 2019

Radiothérapie thoracique

- Cancer du sein adjuvant
- Cancer pulmonaire radio-chimiothérapie définitive
- Cancer œsophage radio-chimiothérapie définitive/radiothérapie palliative
- Hémopathies malignes (enfants !!)
- Lésions métastatiques



Radiation-Induced Heart Disease (RIHD)

. 0,5 – 55% patients traités par radiothérapie thoracique

. Plusieurs (10ènes) années post traitement

. Haut risque de morbi-mortalité :

Sténoses-artérioscléroses accélérées **coronariennes** – 85%
Calcification racine et valve aortique, sténoses **valvulaires**
Atrophies – **fibroses** myocardiques
Inflammations - adhésions/constrictions **péricardiques**
Troubles **conductions**

Cardiopathie ischémique	35% à 25ans Risque 3-5x >
Régurgitation aortique, mitrale	3-12%
Cardiomyopathie	10% (sous estimée)
Péricardite aigüe	*80% - anciennement*
Péricardite constrictive	6-10%
Arythmies	5%

Banfill, J Thor Oncol, 2020 ; Wang, Int J Biol Sci, 2019

Prévention «primaire» :

- Amélioration technique radiothérapie (précision ; contournement ; division du cœur en sous-structures)
- Limiter dose au cœur : 30Gy sur < 46% volume cardiaque ; Dose cardiaque moyenne < 15 Gy
- Diminution exposition cardiaque (traitement en position ventrale ; inspirium bloqué)
- Traitement FRCV

SUIVI – très important LONG TERME

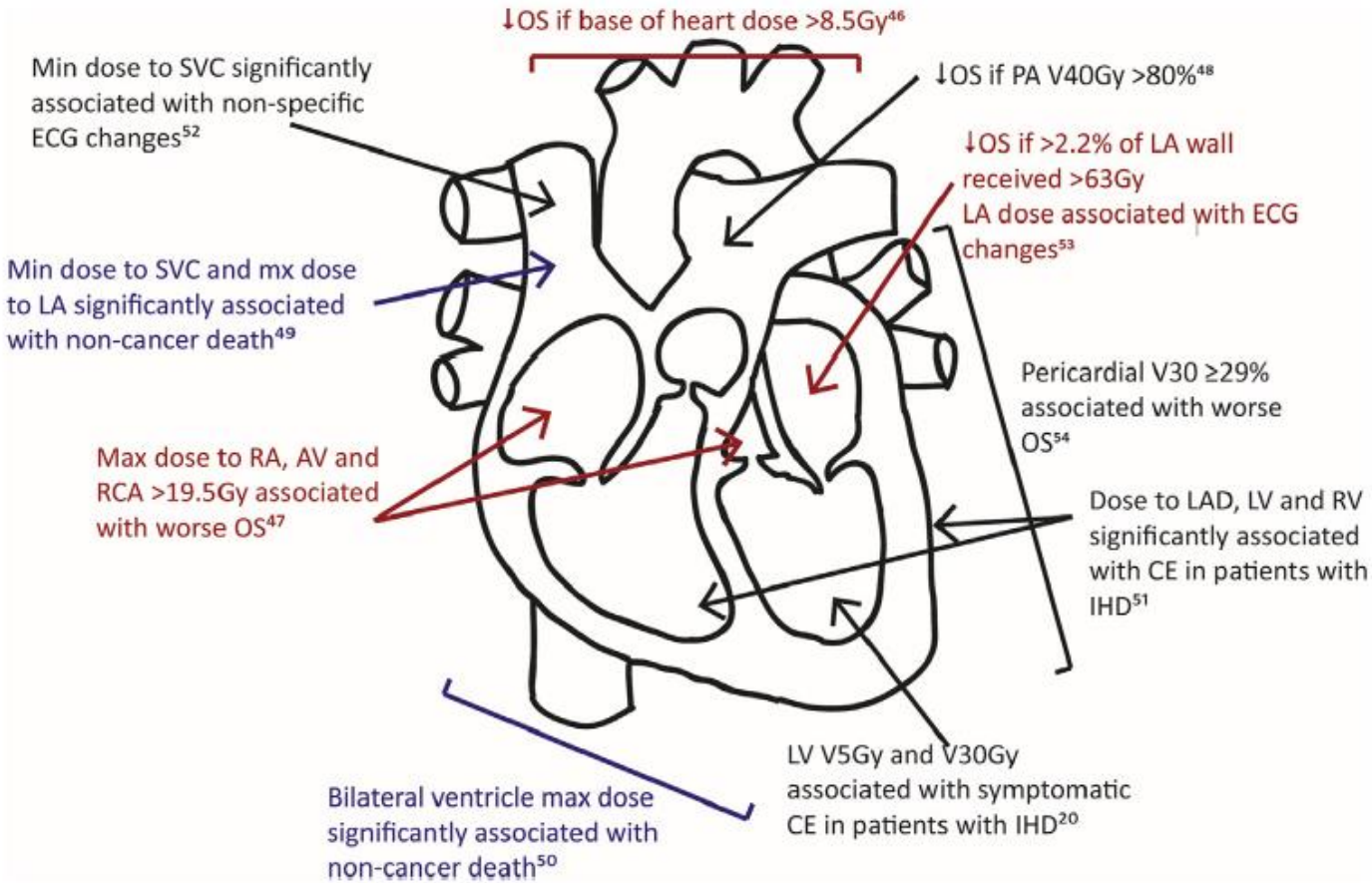
- ETT ou imagerie similaire

SCREENING

ECHO (or comparable imaging to evaluate cardiac function)

Recommended Frequency of Echocardiogram		
Anthracycline Dose*	**Radiation Dose****	**Recommended Frequency**
None	< 15 Gy or none	No screening
	≥ 15 - < 35 Gy	Every 5 years
	≥ 35 Gy	Every 2 years
< 250 mg/m²	< 15 Gy or none	Every 5 years
	≥ 15 Gy	Every 2 years
≥ 250 mg/m²	Any or none	Every 2 years

*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.
**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.



Banfill, J Thor Oncol, 2020

Anthracyclines : clinical case

- 46 yr old woman
- FRCV : slightly overweight, dyslipidaemia, positive family history for CAD, smoker until 2019
- Left bundle branch bloc

- Comorbidities :
  - Obstructive sleep apnoea treated by CPAP
  - Asthma

- Breast cancer in 2019 (Carcinome canalaire invasif droit)
  - with 1 metastatic site (L4 vertebrae)
  - Neoadjuvant chemotherapy (3 FEC 100, 3 Taxol)
  - Bilateral mastectomy
  - Stereotaxic radiotherapy on the L4 metastasis (35 Gy)
  - Adjuvant radiotherapy (right side of the thorax and lymph nodes), 40 Gy in 15 fractions
  - Hormonotherapy (LH-RH anti-aromatase analogue)

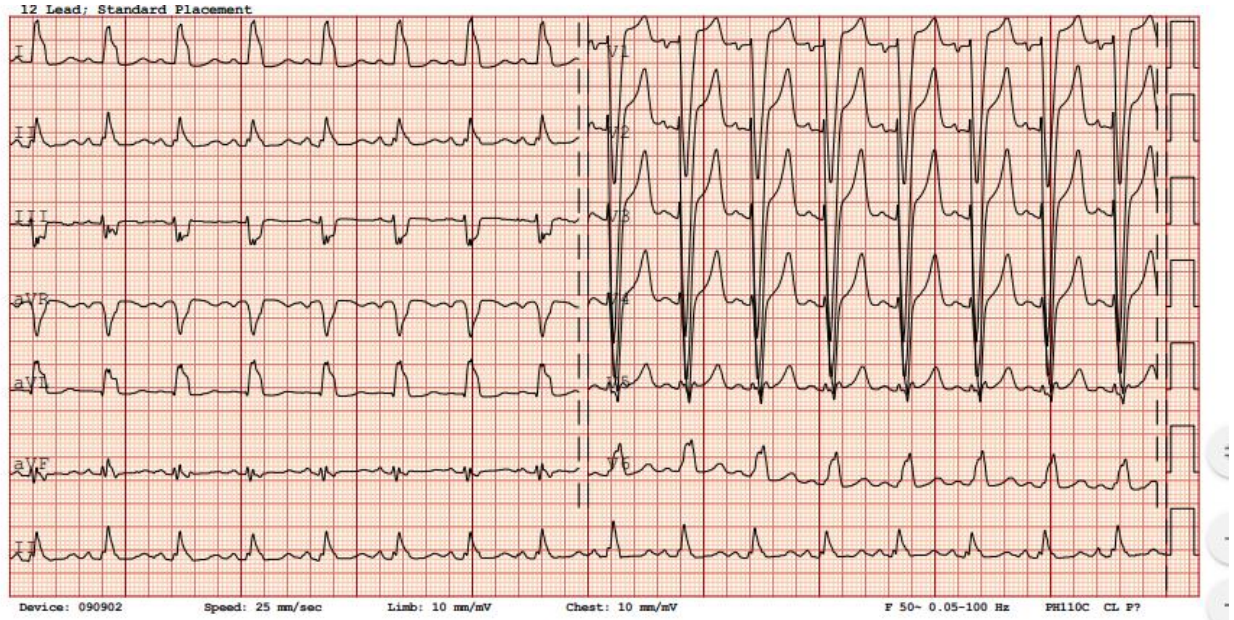
Anthracyclines : clinical case

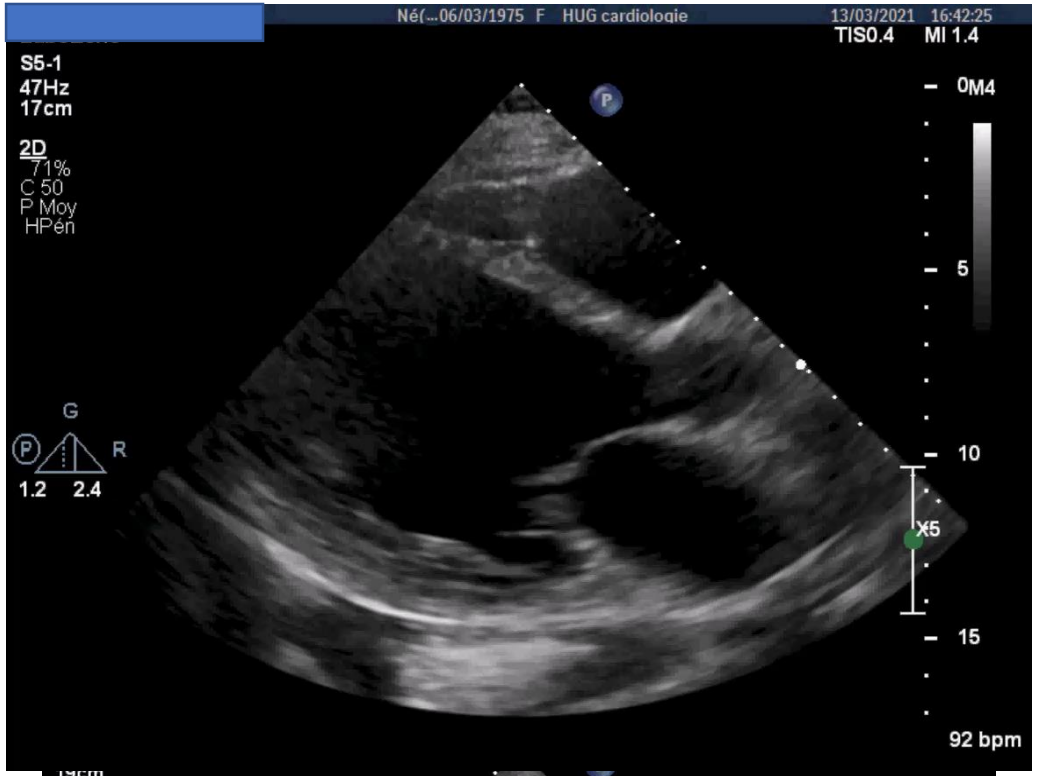
Pre chemotherapy	10 months after chemotherapy + Radiotherapy	
Intermittent LBB	Permanent LBB	
LVEF 65% in 2014	LVEF 50%	
No LV dilation	Discrete dilation of the LV	
No valvulopathy	Discrete MR	
	Asymptomatic	

Recent history (2 years after the cancer treatment)

- Dry cough and dyspnoea on exertion in 4 months ago with a positive COVID test

- Persistence of exertional dyspnoea despite recovery from the SARS Cov 2 infection
- Paroxysmal dyspnoea and orthopnoea
- Progression to NYHA stage IV and oppressive chest pain

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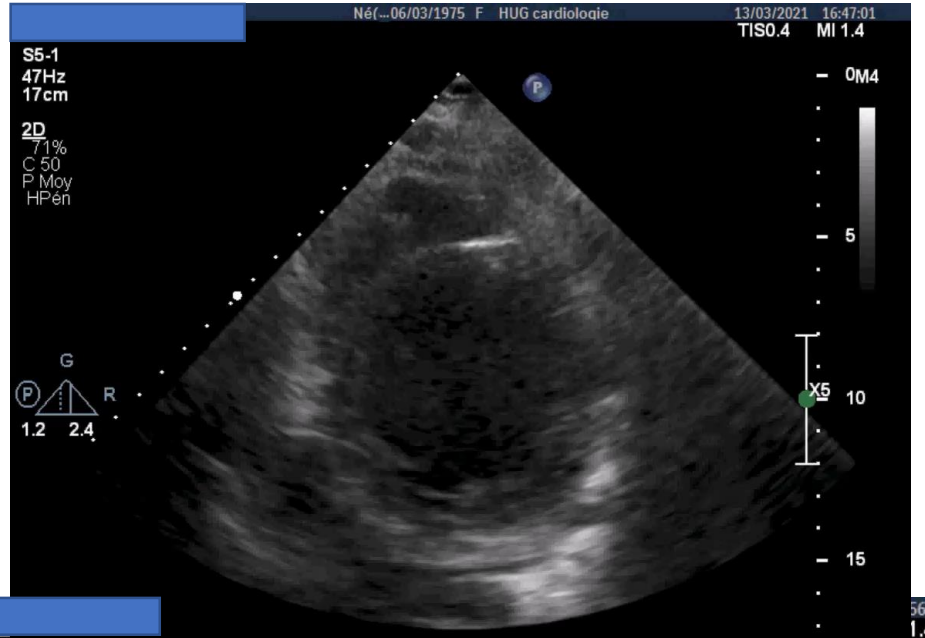
92 bpm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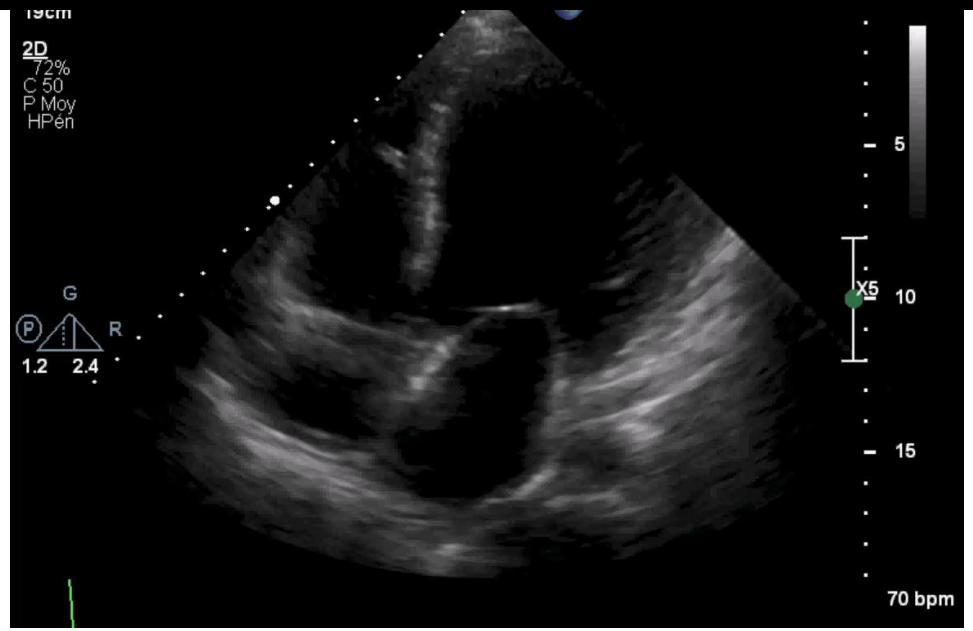
69 bpm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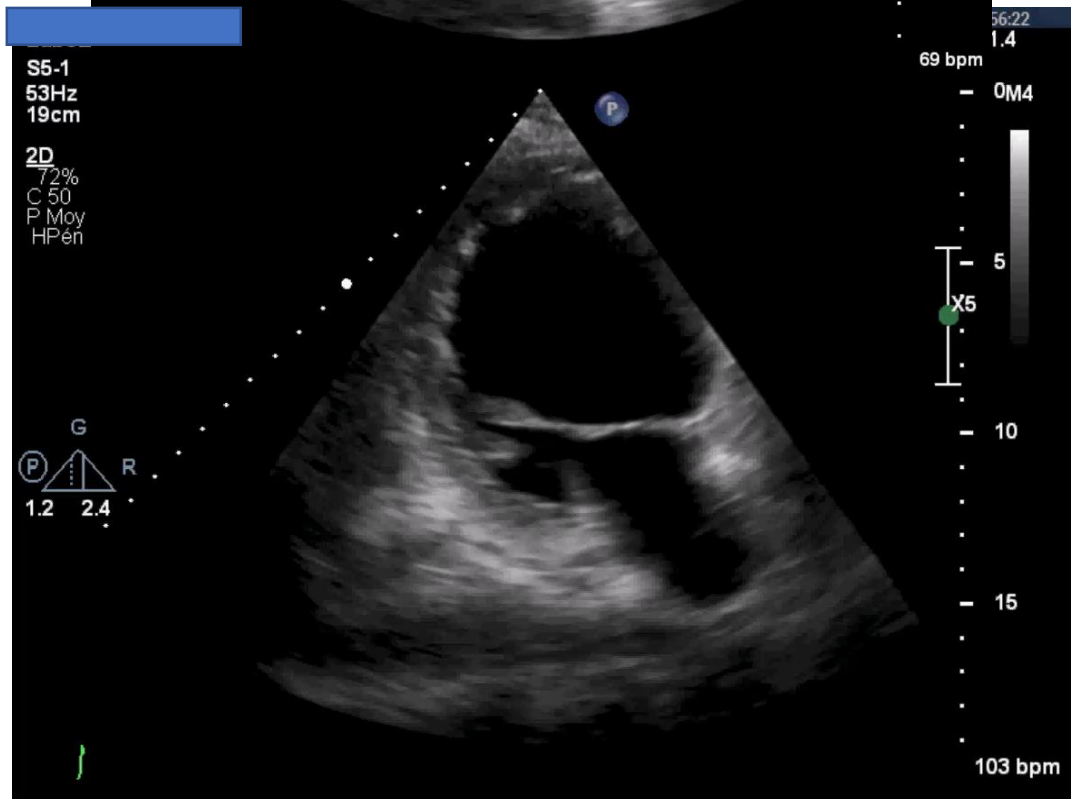
1.2 2.4
X5
70 bpm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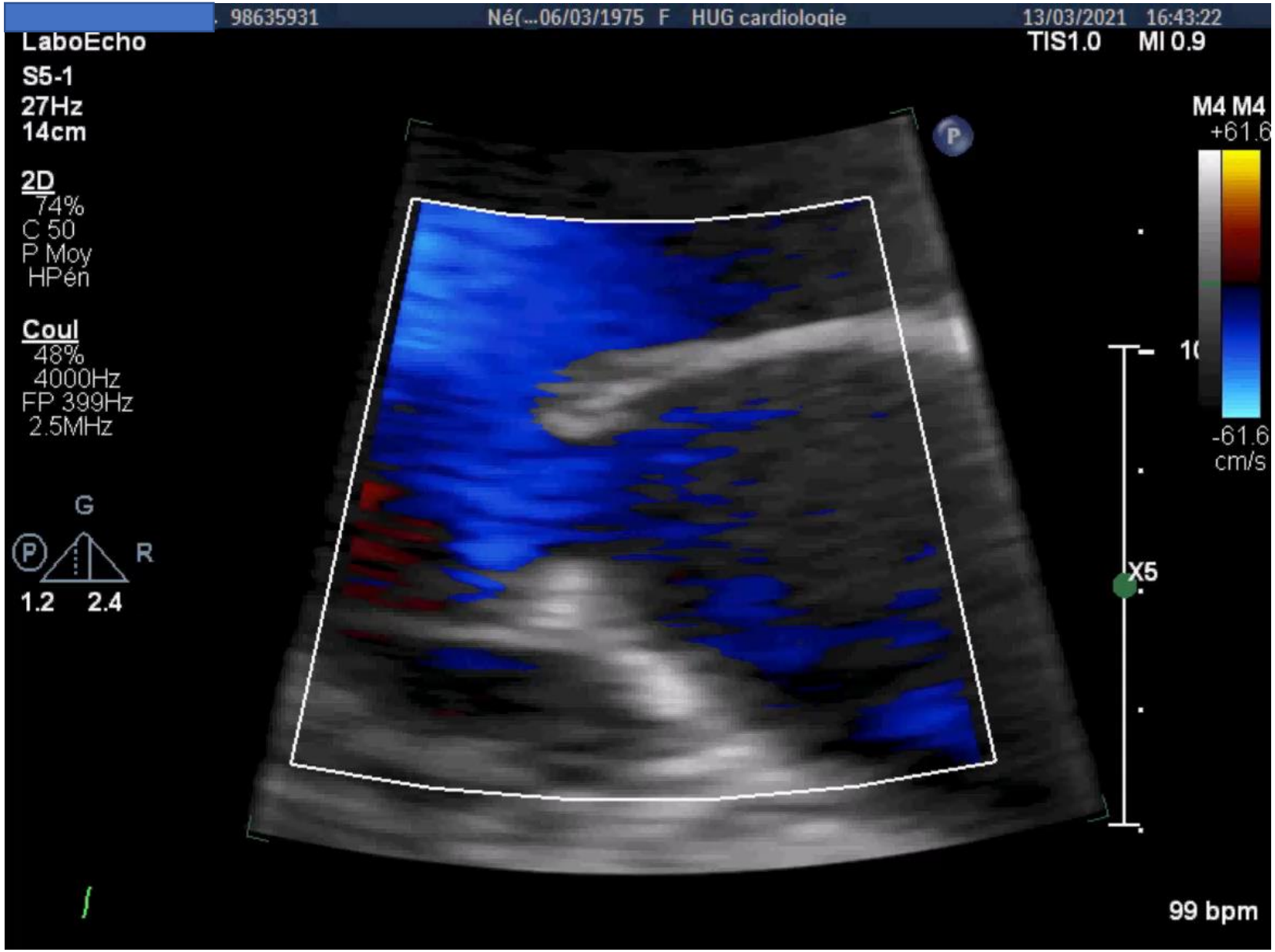
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2D
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C 50
P Moy
HPén
Coul
48%
4000Hz
FP 399Hz
2.5MHz
M4 M4
+61.6
-61.6
cm/s
G
P
R
1.2 2.4
X5
99 bpm

Anthracyclines : clinical case

Pre chemotherapy	10 months after chemotherapy + Radiotherapy	24 months after chemotherapy + Radiotherapy
Intermittent LBB	Permanent LBB	Permanent LBB (QRS duration of 180ms)
LVEF 65% in 2014	LVEF 50%	LVEF 10%
No LV dilation	Discrete dilation of the LV	Severe LV dilatation
No valvulopathy	Discrete MR	Moderate to severe MR
	Asymptomatic	NYHA IV, acute pulmonary edema

- Work up :
  - viral screening (no hepatitis, or HIV)
  - Normal thyroid function
  - No alcohol consumption
  - Coronary angiography : discrete atherosclerosis, but no significantly obstructed vessel
  - Cardiac MRI : severely dilated cardiomyopathy with LVEF measured at 18%. No sign of abnormal contrast uptake compatible with infiltrative disease, myocarditis or a myocardial infarct)

- Diagnostic : Dilated and non ischemic cardiomyopathy, probably due to late anthracycline cardiotoxicity (+/- radiotherapy), genetic underlying predisposition ?

Anthracyclines : clinical case

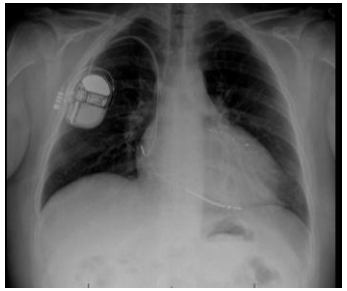
Pre chemotherapy	10 months after chemotherapy + Radiotherapy	24 months after chemotherapy + Radiotherapy
Intermittent LBB	Permanent LBB	Permanent LBB
LVEF 65% in 2014	LVEF 50%	LVEF 10%
No LV dilation	Discrete dilation of the LV	Severe LV dilatation
No valvulopathy	Discrete MR	Moderate to severe MR
	Asymptomatic	NYHA IV, acute pulmonary edema

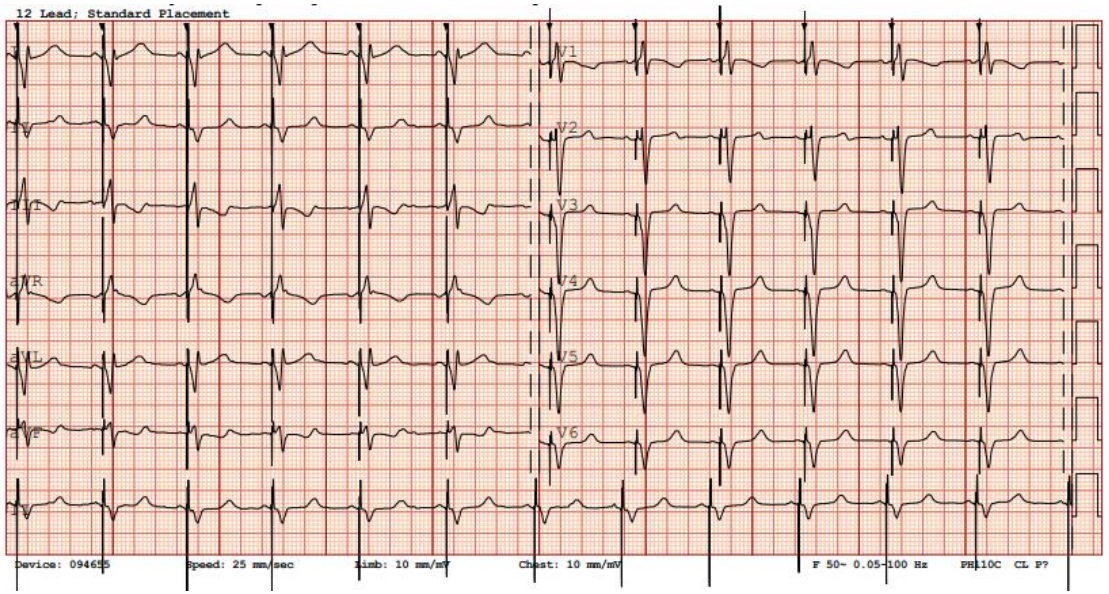
Current treatment :

- Spironolactone 25mg 1x/j
- Aspirine cardio 100mg 1x/j
- Metoprolol 50 mg 1x/j
- Rosuvastatin 10mg 1x/j
- Saccubutril-Valsartan 75 mg 2x/j
- Dapaglfozine 10mg 1x/j

- Escitalopram 10 mg 1x/j
- Arimidex cpr 1mg 1x/j

BNP (admission) 5059 ng/l
BNP after 2 months : 1176ng/l
NYHA IV to II
FEVG 25-30%, LV dilated





Anthracycline and anti-HER2 : identification of the patient at increased risk of cardiotoxicity

Lower risk	Increased risk
Therapy-related risk factors	
Lower lifetime dose of anthracycline < Doxorubicin 250 mg/m² or equivalent	Increased lifetime dose of anthracycline > Doxorubicin 250 mg/m² or equivalent – high risk > 400 mg/m² or equivalent – very high risk
No previous anthracycline/trastuzumab-related cardiotoxicity	Prior anthracycline/trastuzumab-related cardiotoxicity
Absence of sequential anthracycline and trastuzumab therapy	Sequential anthracycline and trastuzumab therapy
Low-dose radiation therapy to central chest including heart in radiation field < 30 Gy	High-dose radiation therapy to central chest including heart in radiation field ≥ 30 Gy
Patient-related risk factors	
Male	Female
Age < 50 years	Age 50 to 64 years – high risk and ≥ 65 years – highest risk
Absence of traditional cardiovascular risk factors: hypertension, smoking, obesity, dyslipidemia, insulin resistance	Presence of traditional cardiovascular risk factors: hypertension, smoking, obesity, dyslipidemia, insulin resistance
Past medical history:	Past medical history:
Normal baseline LVEF	Reduced or low-normal LVEF (50 to 54%) pre-treatment
Absence of pre-existing cardiovascular disease (e.g. CAD, PAD, cardiomyopathy, severe valvular heart disease, heart failure, or diabetes)	Presence of pre-existing cardiovascular disease (e.g. CAD, PAD, cardiomyopathy, severe valvular heart disease, heart failure, or diabetes)
Normal kidney function or chronic kidney disease stage 1	Chronic kidney disease stage 2 + (eGFR < 78 mL/min/1.73 m²) (84)
Biomarkers:	Biomarkers:
Normal baseline troponin and/or NT-proBNP	Elevated* baseline troponin and/or NT-proBNP
Normal cardiac troponin or NT-proBNP during cancer therapy	Elevated* cardiac troponin or NT-proBNP during cancer therapy

Dobson R, Ghosh AK, Ky B, et al. British Society for Echocardiography and British Cardio-Oncology Society guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab. *Echo Res Pract*. 2021;8(1):G1-G18.

Anthracycline and anti-HER2 : Frequency of echocardiographic montoring according to published guidelines.

Guideline, year (Ref. #)	**Recommendation for frequency of echocardiography during therapy**
HFA-EACVI, 2020 (15)	
Anthracyclines	Low risk*: after cycle of cumulative dose 240 mg/m^2 doxorubicin or equivalent, then every additional 100 mg/m^2 or every two cycles Medium risk*: following 50% of planned total treatment and after cycle of cumulative dose 240 mg/m^2 doxorubicin or equivalent High risk*: every two cycles, consider after every cycle above 240 mg/m^2 doxorubicin or equivalent
Anti-HER2 (neoadjuvant and adjuvant)	Low risk*: every four cycles (12 weeks) Medium risk*: every three cycles (9 weeks), then reduce to every four cycles if stable at 4 months High risk*: every two cycles (6 weeks), then reduce to every three cycles if stable at 4 months
Anti-HER2 (long term)	Low risk*: every four cycles in year 1, every six cycles in year 2, then reduce to every 6 months Medium risk*: every three cycles, then if stable reduce to every 6 months High risk*: every two or three cycles for 3 months, then reduce to every four cycles in year 1, then reduce frequency
ESMO, 2020 (26)	
Anthracyclines	After a cumulative dose of 250 mg/m^2 doxorubicin or equivalent, then after each additional 100 mg/m^2
Anti-HER2	Every 3 months (higher-risk patients may require more frequent monitoring)
Anti-HER2 (long term)	General surveillance, which may include cardiac imaging
ASCO, 2017 (16)	
Anthracyclines	Frequency of surveillance should be determined by health care providers; routine surveillance imaging may be offered in patients considered to be at increased risk of cardiac dysfunction
Anti-HER2	Frequency of surveillance should be determined by health care providers; routine surveillance imaging may be offered in patients considered to be at increased risk of cardiac dysfunction
CCS, 2016 (85)	
Anthracyclines	No recommendation made
Anti-HER2	Every 3 months
ESC, 2016 (10)	
Anthracyclines	After 200 mg/m^2 of doxorubicin or equivalent
Anti-HER2	Every four cycles
ASE, 2014 (33)	
Anthracyclines	After 240 mg/m^2 of doxorubicin or equivalent, then after each additional 50 mg/m^2
Anti-HER2	Every 3 months

Dobson R, Ghosh AK, Ky B, et al. British Society for Echocardiography and British Cardio-Oncology Society guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab. *Echo Res Pract*. 2021;8(1):G1-G18.

Classification of cancer related cardiotoxicity

- Type 1 chemotherapy related left ventricular (LV) systolic dysfunction
  - caused by agents such as doxorubicin, epirubicin, idarubicin, cyclophosphamide, and docetaxel
  - usually, dose related
  - usually not reversible

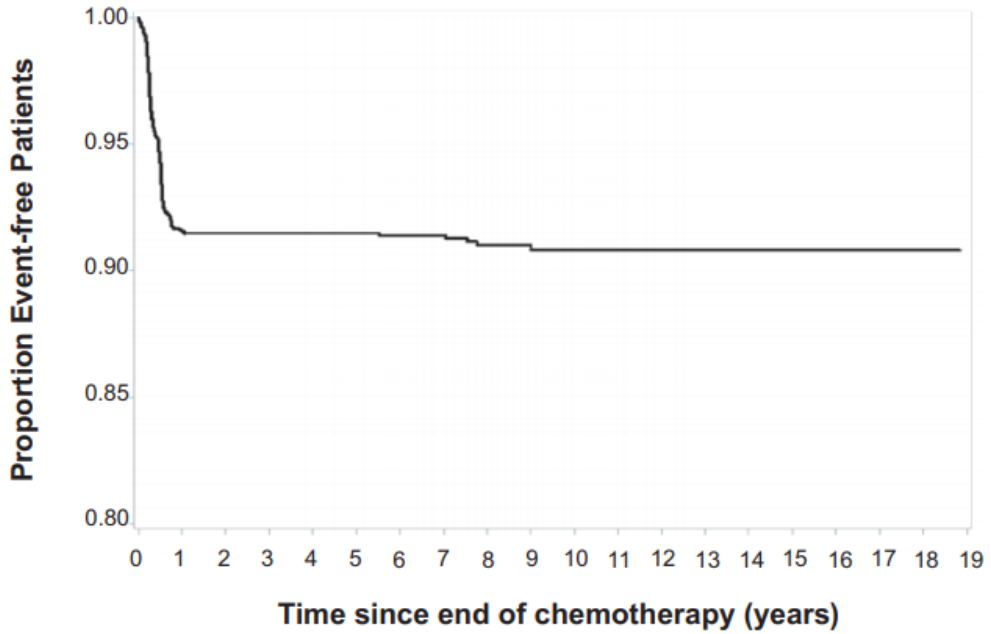
- Type 2 chemotherapy-mediated cardiotoxicity
  - results from agents such as trastuzumab, lapatinib, sunitinib, imatinib, and bevacizumab
  - generally not dose related
  - may be associated with reversible myocardial dysfunction

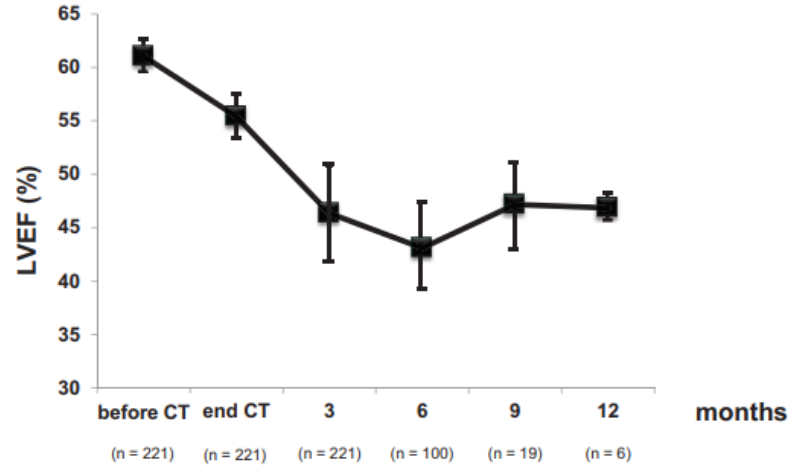
Anthracycline induced LV systolic dysfunction

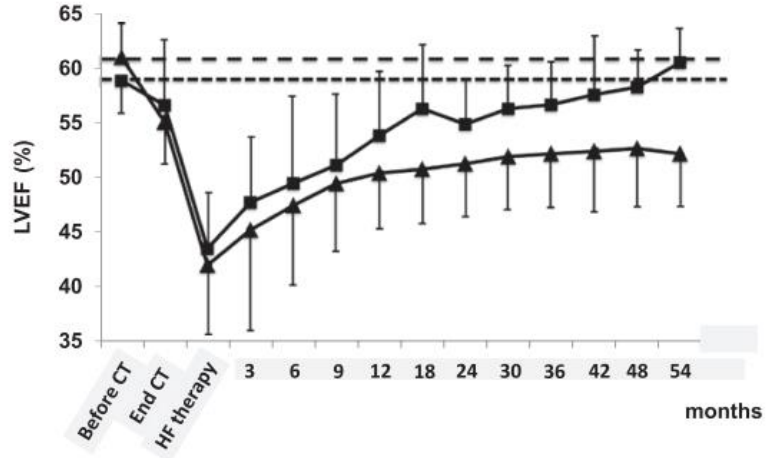
2399 patients planned exposed to anthracyclines
consecutive chemotherapy-naive patients
Excluded :

<18yrs, LVEF < 50%, valvulopathy, severe hypertension, life expectancy < 12wks, high ACT dose protocols, ACT followed by trastuzumab

1° endpoint : time to occurrence of cardiotoxicity (reduction in LVEF >10 percentage points from baseline AND <50%.





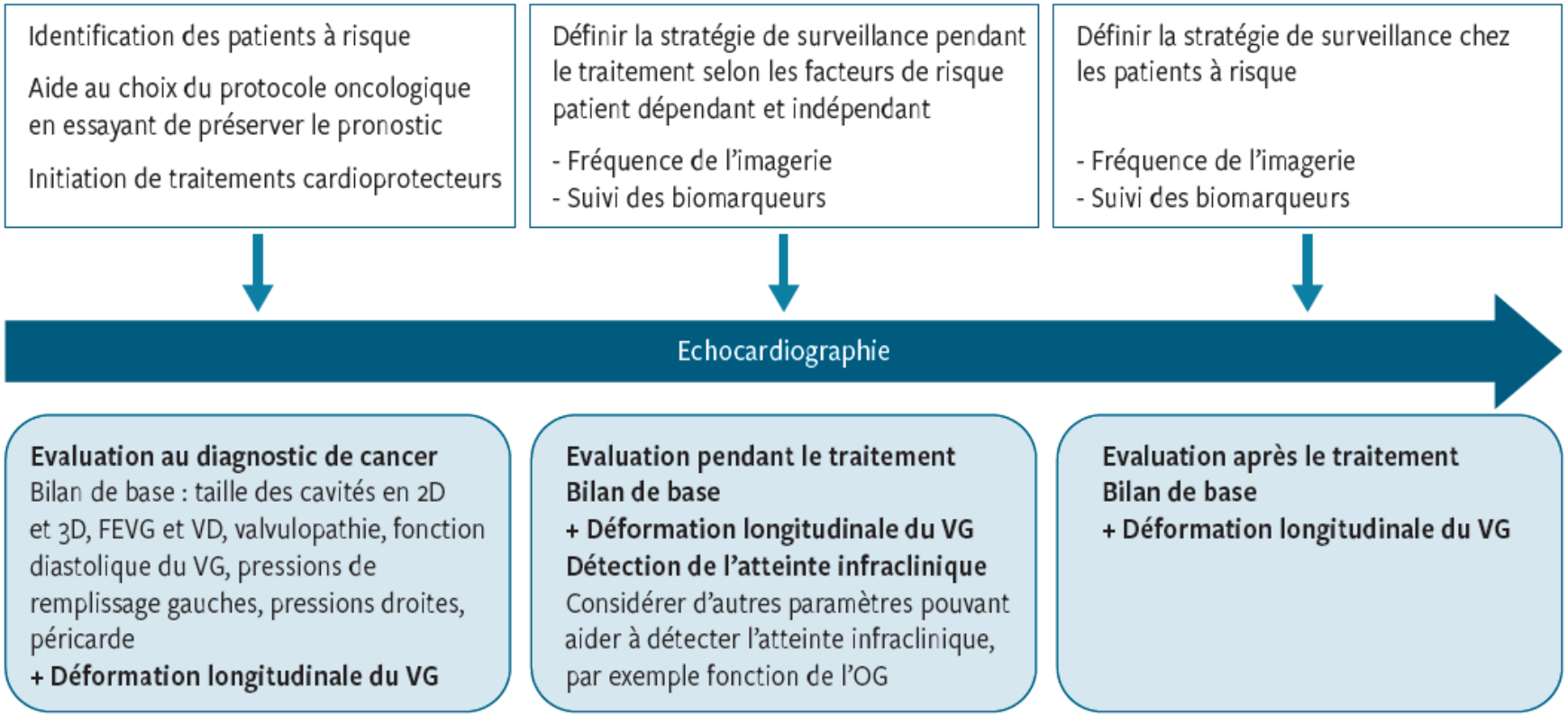


Cardinale D et al Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015 Jun 2;131(22):1981-8

Detection of subclinical and clinical cancer treatment related myocardial dysfunction

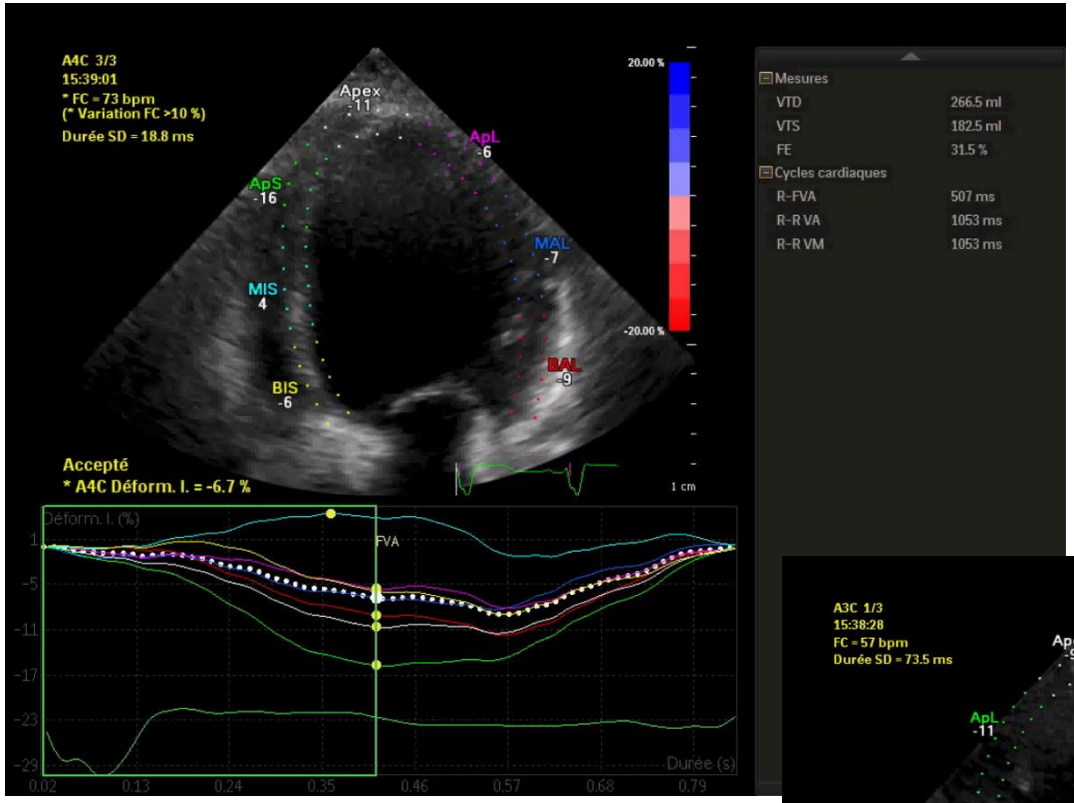
FIG 1 **Paramètres échocardiographiques à évaluer lors d'un traitement oncologique**

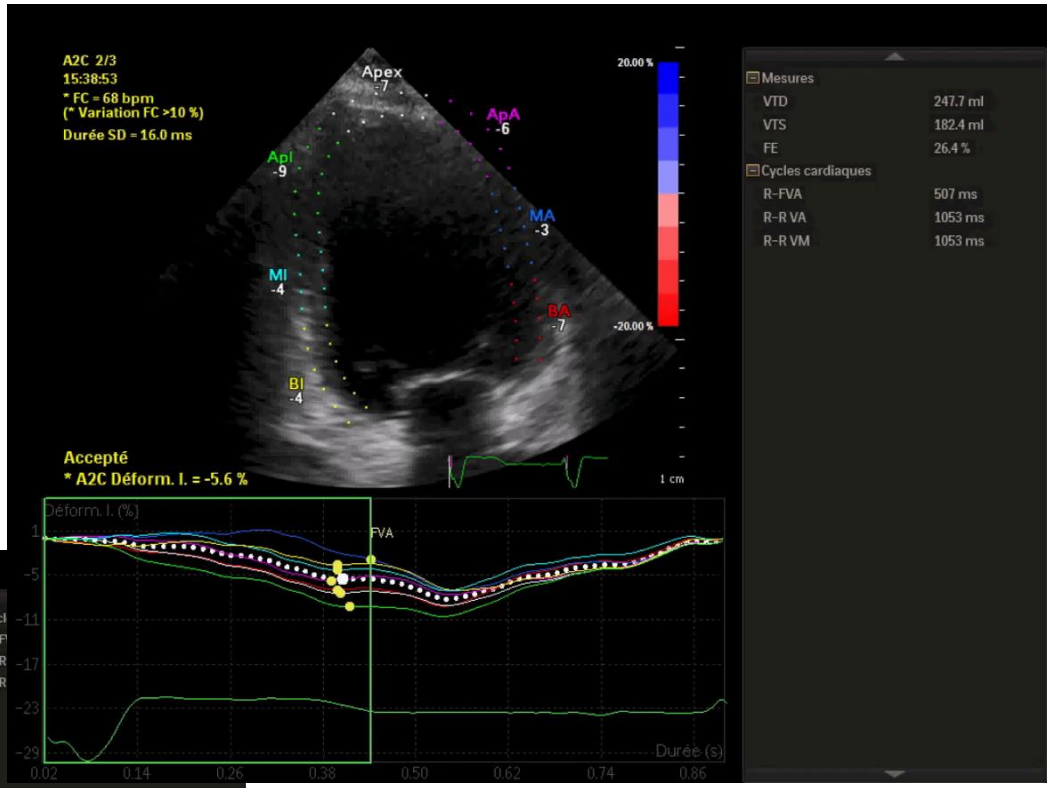
FEVG: fraction d'éjection du ventricule gauche; VD: ventricule droit; OG: oreillette gauche.

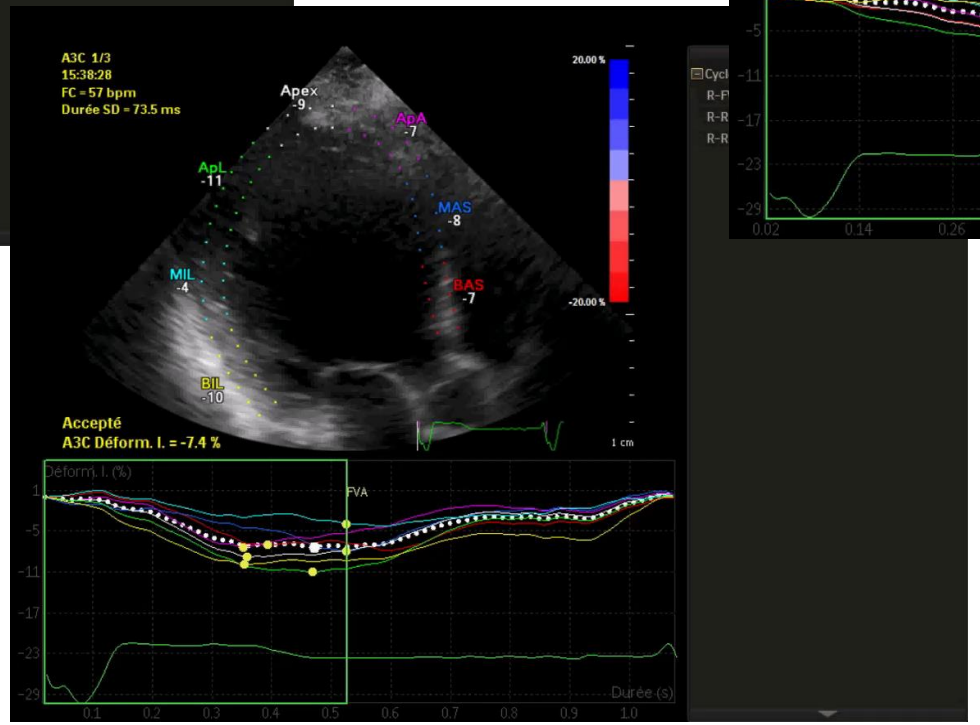


Poku NK et al, Rôle de l'échocardiographie avant, pendant et après un traitement anticancéreux. Rev Med Suisse. 2019 May 22;15(652)

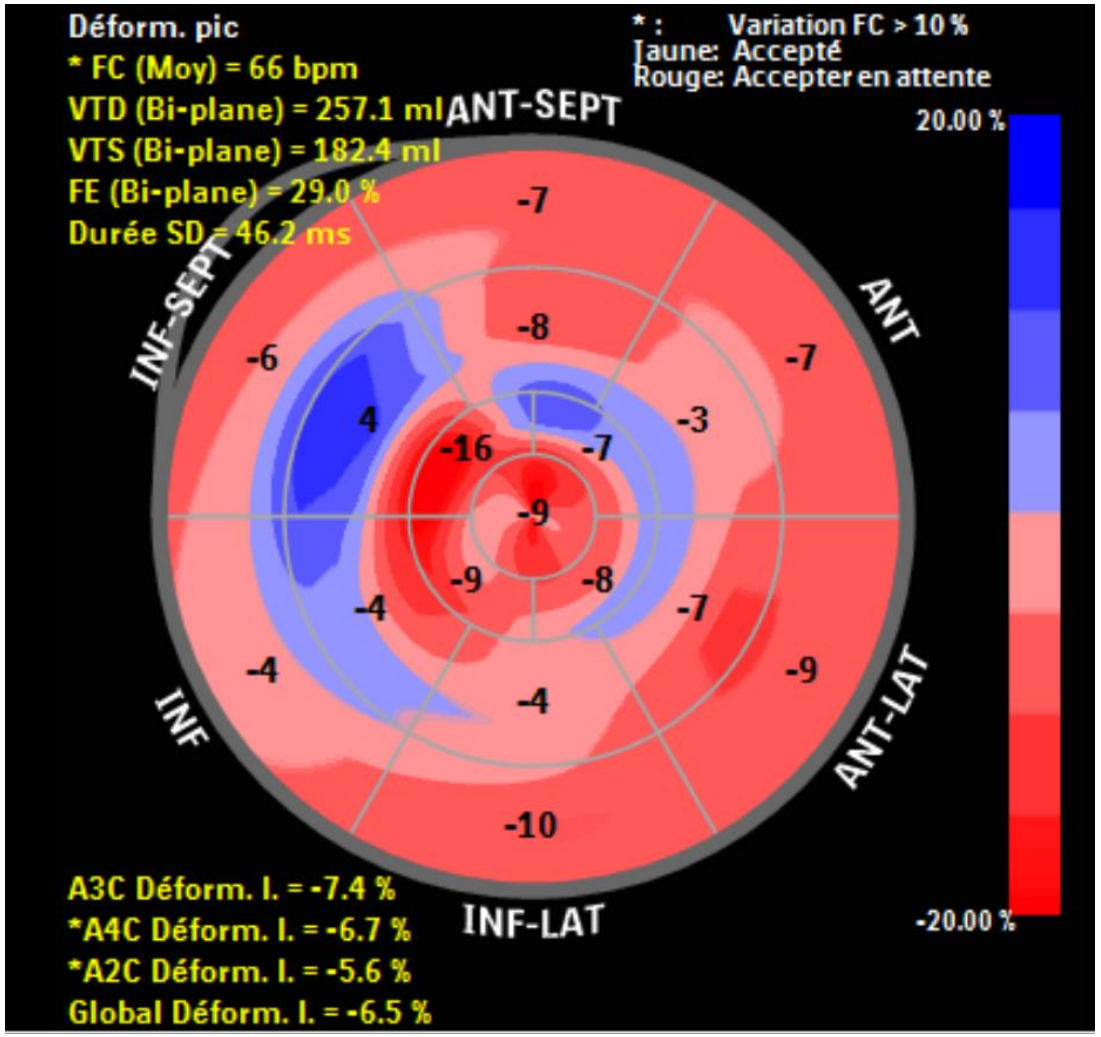
Detection of subclinical cancer treatment related myocardial dysfunction : LV deformation (strain) analysis







Detection of subclinical cancer treatment related myocardial dysfunction : LV deformation (strain) analysis



Tips for optimal Strain imaging :

- ✓ 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 (33) at a normal heart rate.
- ✓ Focus on the LV with appropriate adjustment of width and depth.
- ✓ The technique used to select the appropriate ROI is vendor specific (consult individual machine/software technical guidelines for further guidance)
- ✓ Two contours for speckle tracking are visible and should be aligned with the relevant area of interest :
  - ✓ the endocardial border (the inner contour of the myocardium)
  - ✓ and the epicardial border (the outer border of the myocardium).
- ✓ Be careful to exclude the pericardium, especially if automated analysis software is used. Inclusion of pericardium will lead to an underestimation of strain.
- ✓ 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.

Dobson R et al, British Society for Echocardiography and British Cardio-Oncology Society guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab. *Echo Res Pract*. 2021;8(1):

Current echocardiographic diagnostic criteria for cardiotoxicity

Cardiotoxicity or Probable/Possible Subclinical Cardiotoxicity

Cardiotoxicity:

- LVEF: A decline by >10 absolute percentage points to a value <50%

Probable subclinical cardiotoxicity:

- LVEF: A decline by >10 absolute percentage points to a value ≥50% with an accompanying fall in GLS >15%

Possible subclinical cardiotoxicity:

- LVEF: A decline by <10 absolute percentage points to a value <50%

OR

- LV GLS: A relative percentage reduction in GLS by >15% from baseline

Dobson R et al, British Society for Echocardiography and British Cardio-Oncology Society guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab. *Echo Res Pract*. 2021;8(1):

SUCCOUR randomized controlled trial : 1 year follow up results

Aim : to identify whether GLS-guided CPT prevents reduction in LVEF and development of CTRCD in high-risk patients undergoing potentially cardiotoxic chemotherapy, compared with usual care

Inclusion criteria :
Exposure to anthracycline-based chemotherapy with another risk factor for heart failure
- 28 centers from Australia, Asia, Europe, Canada, and the United States
- Enrollement between January 2014 and December 2019.

Additional heart failure risk factors in addition to receiving anthracycline included:
1) use of trastuzumab therapy in women with human epidermal growth factor receptor 2–positive (HER2þ) breast cancer
2) use of tyrosine kinase inhibitors (e.g., sunitinib)
3) cumulative doxorubicin dose of >450 mg/m2 or other isoequivalent anthracycline dose
4) any 2 traditional heart failure risk factors: age > 65 years, type 2 diabetes mellitus, hypertension, or previous cardiac injury (e.g., myocardial infarction).

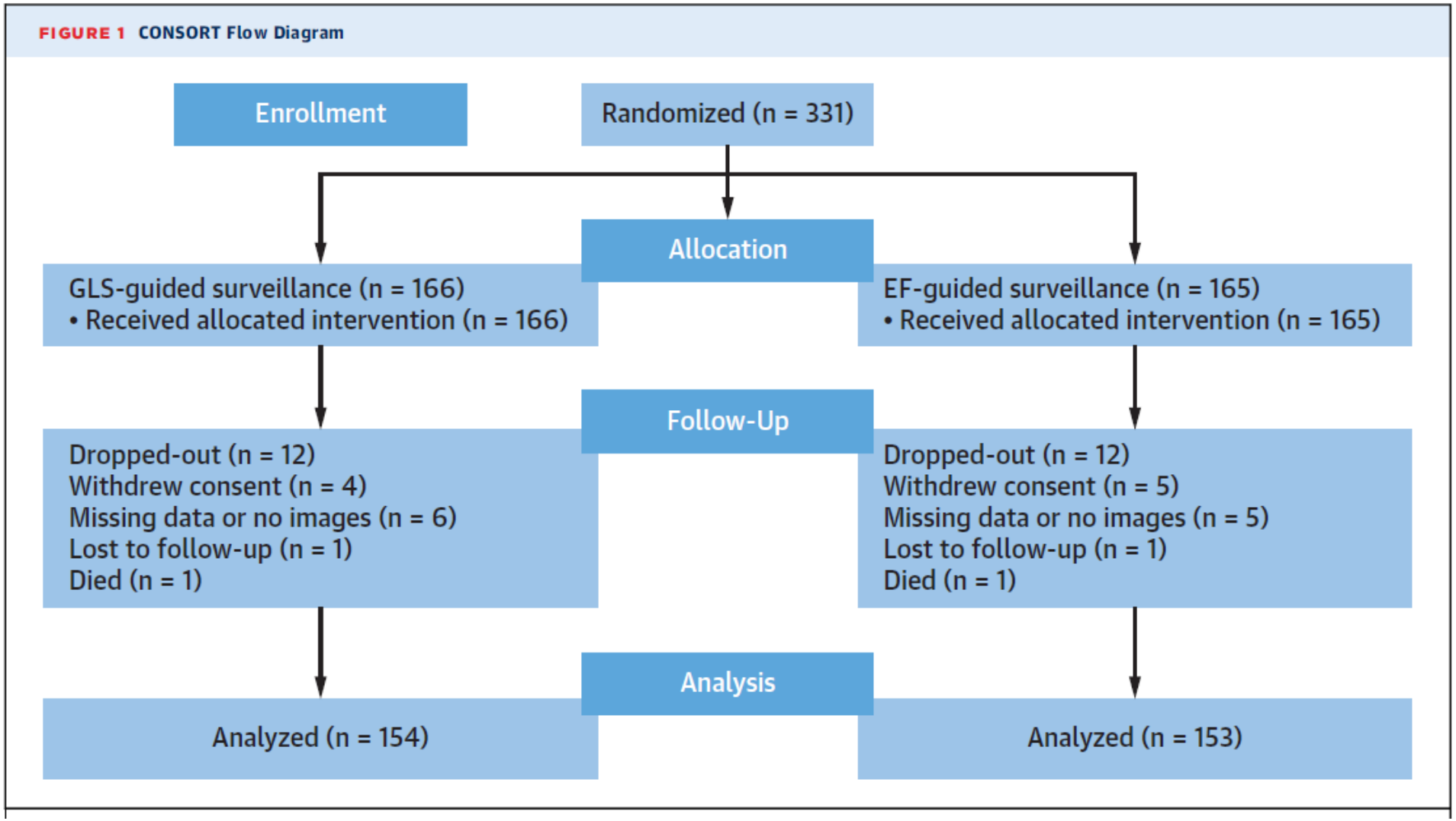
Exclusion criteria were:

1) **Baseline LVEF of <50%**
2) valvular stenosis or regurgitation greater than moderate in severity
3) history of previous heart failure
4) systolic blood pressure of <110 mm Hg
5) heart rate of <60 beats/min
6) inability to acquire interpretable images on baseline echocardiogram
7) contraindications to betablockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)
8) **current therapy with betablockers and ACE inhibitors or ARBs** (patients were eligible if they were on only a betablocker or ACE inhibitor/ARB)
9) Oncologic life expectancy of <12 months
10) unable to provide written informed consent
11) participating in another clinical trial where randomized treatment would be unacceptable

Primary endpoint : Development of CTRCD (symptomatic EF reduction of >5% or >10% asymptomatic to <55%) over 1 year

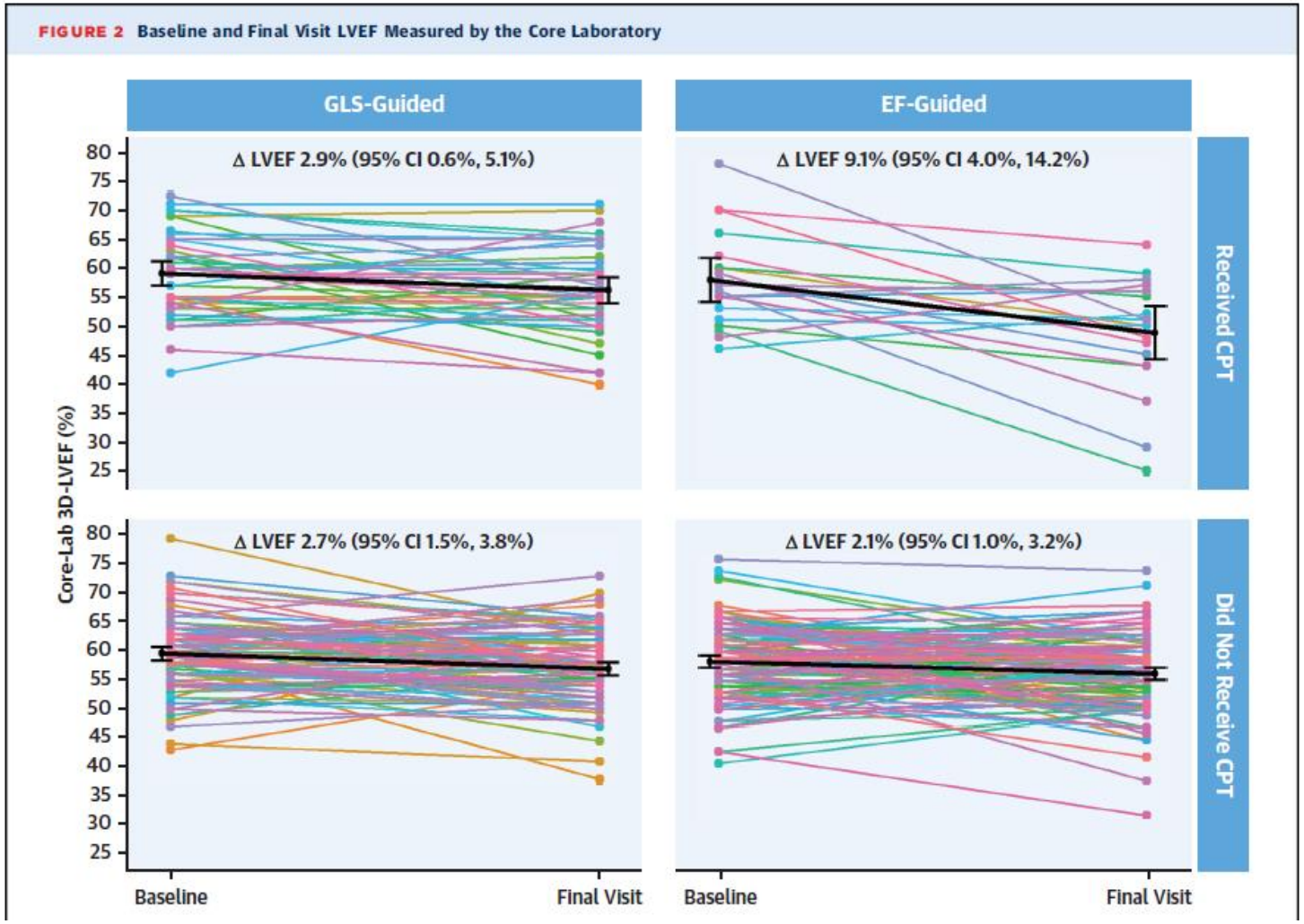
Thavendiranathan P et al SUCCOUR Investigators. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol. 2021 Feb 2;77(4):392-401.

SUCCOUR randomized controlled trial : 1 year follow up results



Thavendiranathan P et al SUCCOUR Investigators. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol. 2021 Feb 2;77(4):392-401.

SUCCOUR randomized controlled trial : 1 year follow up results



Thavendiranathan P et al SUCCOUR Investigators. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol. 2021 Feb 2;77(4):392-401.

SUCCOUR randomized controlled trial : 1 year follow up results

TABLE 2 Changes in LVEF and GLS Between Baseline and the 1-Year Follow-Up

	EF Guided			GLS Guided				
	n	LV Function, % (95% CI)	p Value*	n	LV Function, % (95% CI)	p Value*	Difference, % (95% CI)	p Value†
Core laboratory 3D EF, %								
Baseline	153	58 (57 to 59)		154	59 (58 to 60)		-1.2 (-2.6 to 0.2)	0.10
1 year	153	55 (54 to 56)		154	57 (56 to 58)		-1.5 (-3.0 to 0.0)	0.05
1 year - baseline	153	-3.0 (-1.8 to -4.2)	<0.001	154	-2.7 (-1.7 to -3.8)	<0.001	0.3 (-1.3 to 1.9)	0.69
Core laboratory GLS, %								
Baseline	153	-20.4 (-20.8 to -20.0)		154	-20.9 (-21.3, to -20.5)		0.49 (-0.05 to 1.03)	0.08
1 year	142	-19.0 (-19.5 to -18.6)		136	-19.6 (-20.0 to -19.2)		0.53 (-0.07 to 1.13)	0.08
1 year -baseline	142	1.5 (1.9 to 1.0)	<0.001	136	1.4 (1.8 to 1.0)	<0.001	-0.09 (-0.68 to 0.49)	0.75

TABLE 3 Cancer Therapy-Related Cardiac Dysfunction Treatment Details for the 2 Arms

	EF Guided (n = 153)	GLS Guided (n = 154)	p Value
Received ACE inhibitor/ARB	17 (11)	44 (29)	<0.001
Received BB	18 (12)	38 (25)	0.005
Received both	16 (10)	37 (24)	0.002
Maximal dose of ACE inhibitor/ARB achieved, %*†	31 (25-63)	50 (25-50)	0.81
Maximal dose of beta-blocker achieved, %*†	25 (12-50)	25 (12-50)	0.44

TABLE 4 Reasons for Interruption or Discontinuation of Cancer Therapy

	Interruption		Discontinuation	
	EF Guided (n = 8)	GLS Guided (n = 5)	EF Guided (n = 5)	GLS Guided (n = 9)
Adverse events/serious adverse effects	1	0	1	2
Left ventricular dysfunction	1	3	1	2
Chemotherapy side effect	3	1	1	4
Other reasons	3	1	2	1

Thavendiranathan P et al SUCCOUR Investigators. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol. 2021 Feb 2;77(4):392-401.

Proposal of an algorithm based on echocardiography surveillance of cardiotoxicity integrating strain imaging of the left ventricle, cardio-protection concepts

Baseline assessment based on treatment and cardiotoxicity profile
Including TTE with cardio-oncology measurements

LVEF and GLS analysis at regular intervals during treatment depending on risk for cardiotoxicity

Normal or no evidence of cardiotoxicity	Possible subclinical cardiotoxicity	Probable subclinical cardiotoxicity	Definite or highly probable cardiotoxicity
	LVEF decline by <10 absolute percentage points to a value <50% **OR** A relative reduction in GLS by >15% from baseline	LVEF decline by > 10 absolute percentage points to a value >/= 50% **WITH** an accompanying reduction in GLS by >15%	LVEF decline by > 10 absolute percentage points to a value <50%
True Normal	Borderline LVEF at baseline (50-54%)		

?

Consider referral to a cardio-oncology service

+

Initiation of “individualised” cardioprotective treatment

Personalized surveillance strategy during cancer treatment

Guideline directed OMT for HF, especially for symptomatic patients

TTE evaluation after completion of cancer treatment with repeat evaluation of cardio-oncology measurements for all

Personalized follow up strategy, especially in patients with possible, probable or definite cardiotoxicity.

Source : swiss cardio-oncologie working group (COS, cardio-oncology switzerland)

Plan

- What is cardio-oncology ?
- General cancer epidemiology
- Cardiotoxicity profile and cardiac assessment for specific cancer treatments
  - Fluoropyrimidine therapy
  - Anthracyclines
  - Anti HER2 therapy
  - Radiotherapy
  - **Anti-androgen therapy**
  - **Tyrosine Kinase therapy**
  - Immunotherapy
- Clinical cases
- Impact of a cardio-oncology unit
  - A multidisciplinary approach

Androgen Deprivation therapy (ADT)

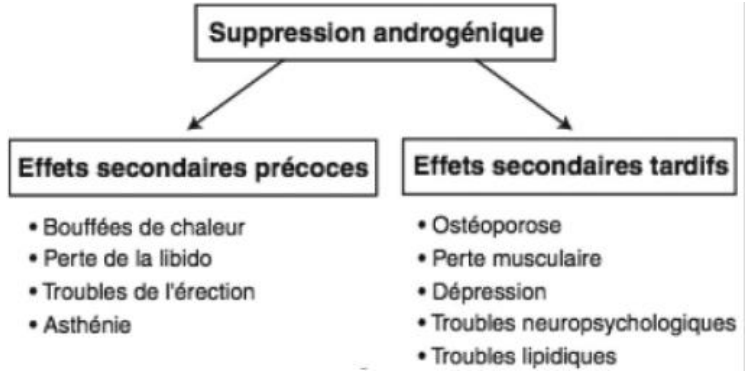
Les agonistes de la LH-RH :

- Leuproréline (Eligard, Enantone), formes injectables IM/SC ou per os
- Buséréline (Bigonist, Suprefact), formes injectables SC ou nasale (Suprefact)
- Gosséréline (Zotadex), formes injectables SC
- Triptoréline (Decapeptyl, Salvacyl), formes injectables IM/SC

L'antagonistes de la LH-RH :

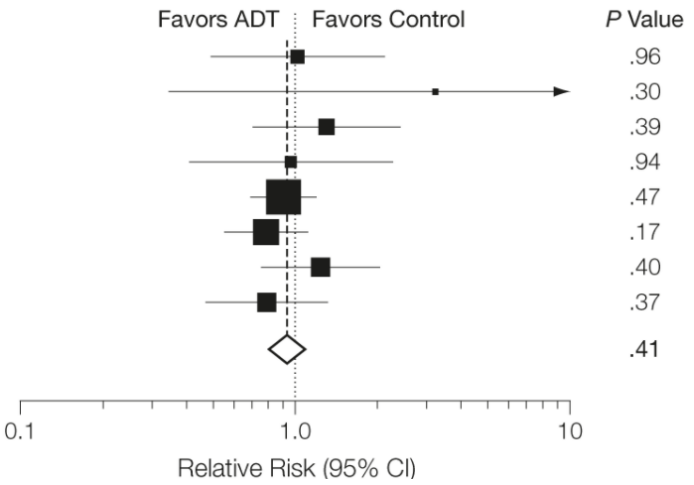
- Dégarélix (Firmagon), formes injectables SC

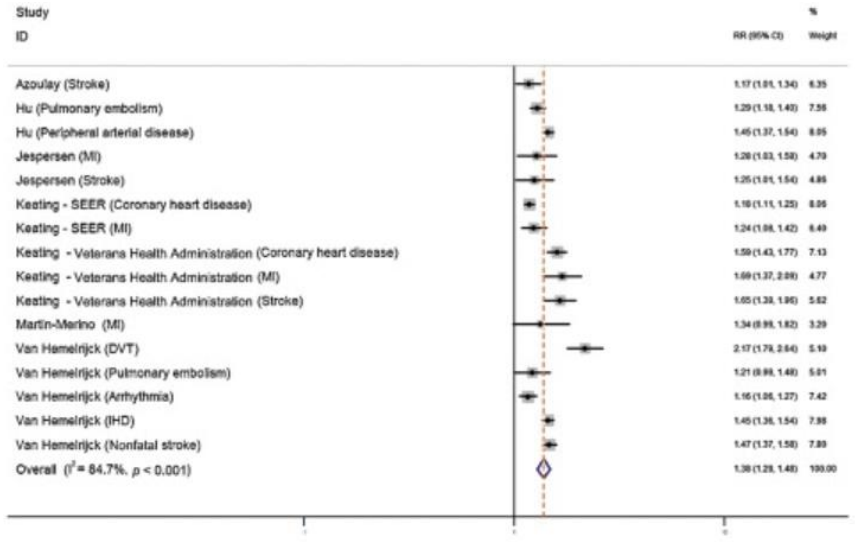
- Agoniste ou antagoniste LHRH (ou castration chirurgicale)
- Castration par diminution de la testostéronémie
- Initialement utilisé comme monothérapie dans le KP avancé ou M+ hormonosensible
- Désormais en combinaison en 1LM (+ Abiraterone/Enza-apalutamide/Docetaxel)
- Durée variable selon stade et hormonosensibilité : généralement plusieurs années

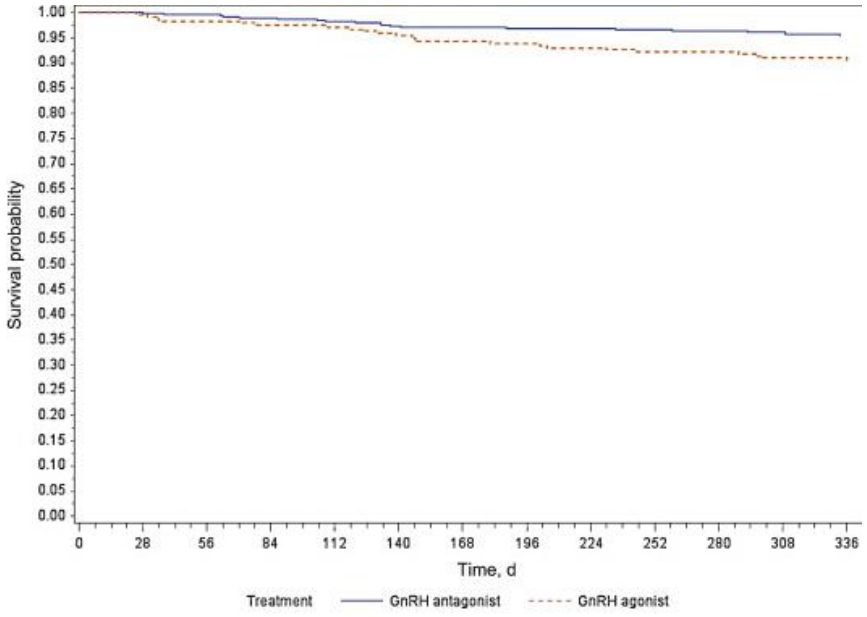


Cardiotoxicité de l'ADT : maladie CV

- Études contradictoires : ↗ morbidité/mortalité CV ?
- Majoration du risque en cas d'ATCD CV (≥2), surtout dans les 6 premiers mois du ttt
- Semblerait être moins important avec les antagonistes LHRH



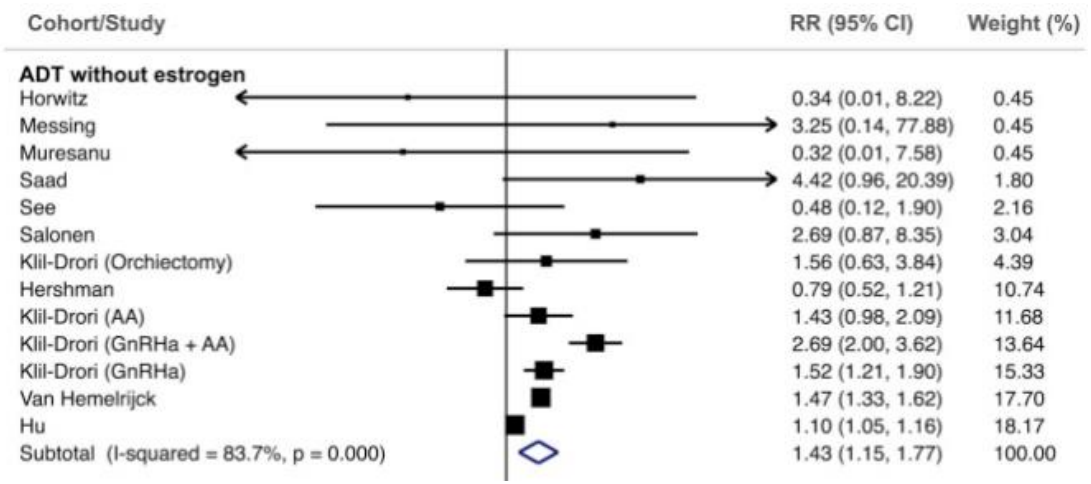




Nguyen JAMA 2011, Bosco Eur Urol 2014, Albertsen Eur Urol 2014

Cardiotoxicité de l'ADT : MTEV

- Majoration du risque d'événements thromboembolique (TVP, EP, AE)



	ADT (*N = 58,466*)			No ADT (*N = 96,145*)		
	No. Pts	**% of Pts**	**No. Events**	**No. Pts**	**% of Pts**	**No. Events**
Thromboembolic events						
Any event	8,829	15%	13,330	7,121	7%	10,318
Deep venous thrombosis	4,360	7%	6,623	3,564	4%	5,191
Arterial embolism	2,574	4%	3,834	2,011	2%	2,874
Pulmonary embolism	1,895	3%	2,873	1,546	2%	2,253

Nead urology 2018, Edhaie Cancer 2012

Cardiotoxicité de l’ADT

- Surveillance annuelle recommandée (AHA, AUA, ACA) :
  - Pression artérielle
  - Bilan lipidique
  - Glycémie à jeun

- Algorithme « ABCDE » :
  - Aspirine
  - Blood pressure
  - Cholesterol and Cigarette cessation
  - Diet and diabetes
  - Exercise

Cas clinique : M. V-C, 70 ans

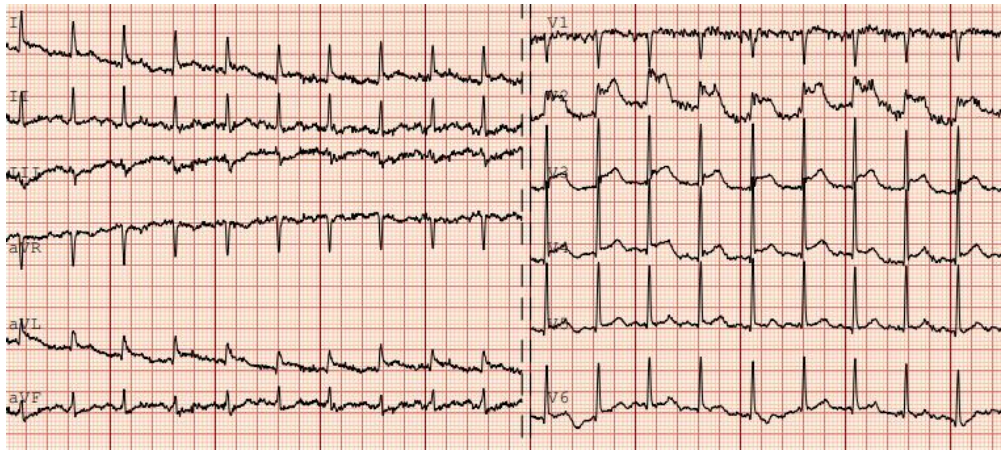
- Pas de FdRCV
- Sd de Lynch avec multiples ADK coliques opérés
- Myélome multiple IgG kappa depuis Jan 2019 traité par chimiothérapie (VRD puis daratumumab VMP)
- mHSCP depuis Juin 2020
  - ADT par agoniste LHRH + Abiraterone avec bonne efficacité sur PSA

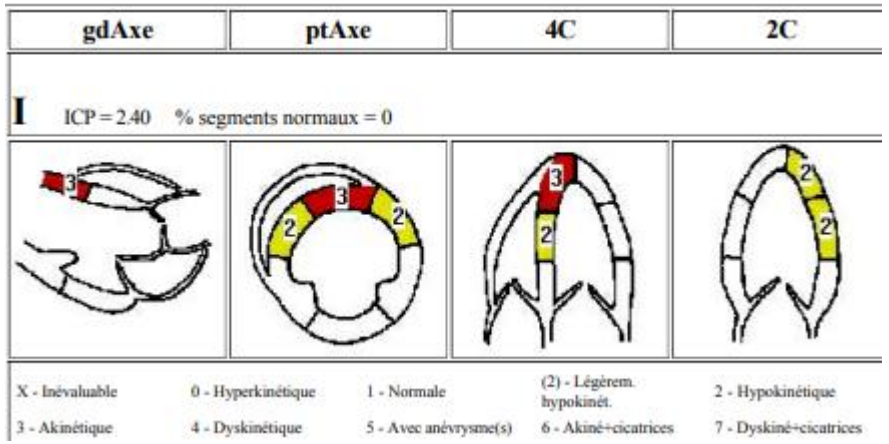
Fév 2021 : DRS oppressive + dyspnée + pic hypertensif avec ECG : sus ST V2-V4 puis résolution spontanée avec tropo ↗ de 59 à 900 ng/L.

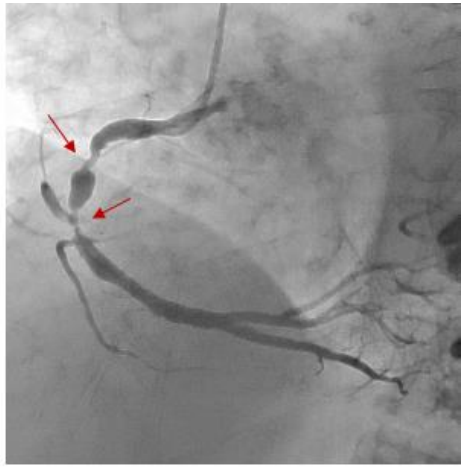
➔ ETT : akinésie antéroseptoapicale et hypokinésie inféroseptale moyenne et ant moyenne

➔ Coronarographie

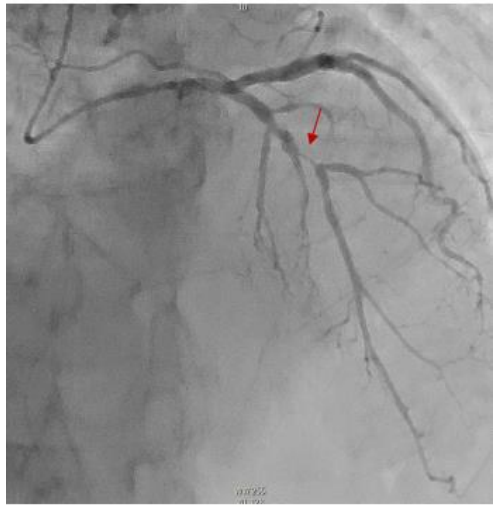
Cas clinique : M. V-C, 70 ans





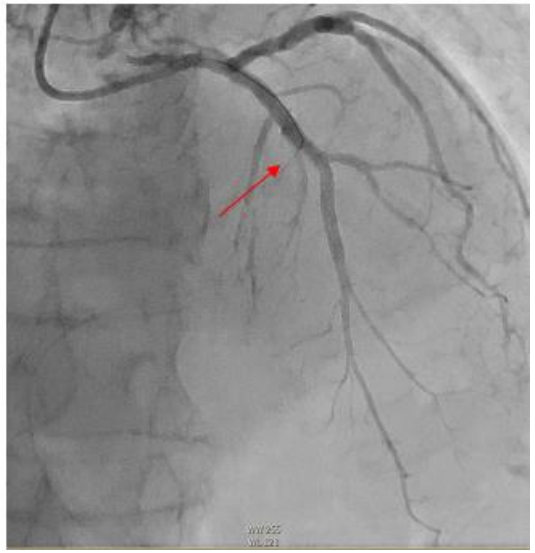


LÉSIONS CD

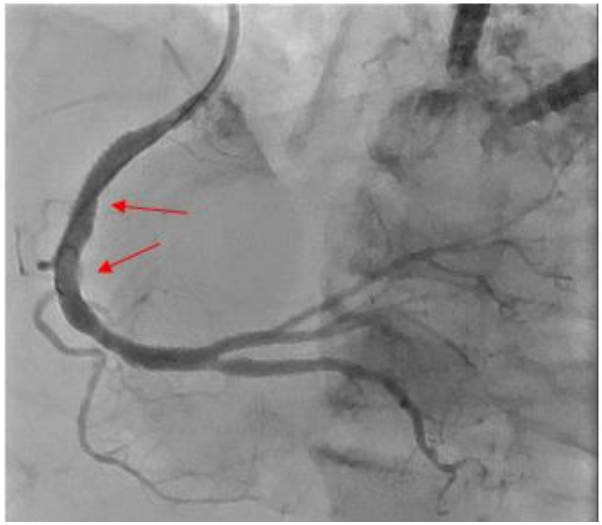


LÉSION IVA

APRÈS PCI IVA

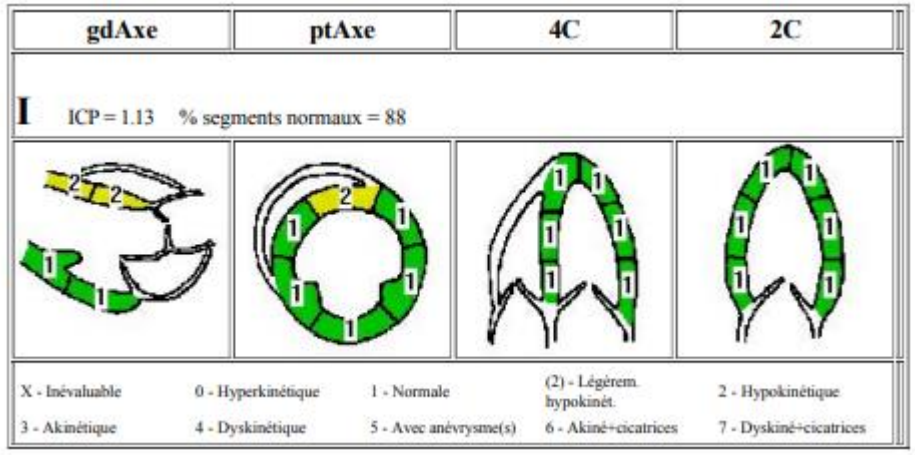


APRÈS PCI CORONAIRE DROITE



Cas clinique : M. V-C, 70 ans

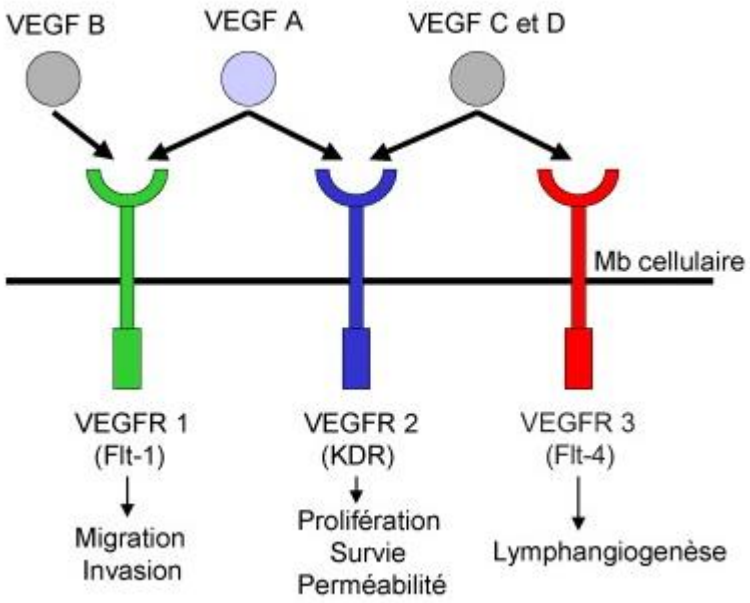
ETT post thérapeutique : FEVG 55-60%, strain -16%



➔ Décision de ne pas reprendre l'Abiraterone ni l'agoniste LHRH et de le remplacer par antagoniste de la LHRH

Antiangiogéniques

Bévacizumab (Avastin)	VEGF-A
Sorafénib (Nexavar)	VEGFR et PDGFR tyrosine kinase
Sunitinib (Sutent)	VEGFR, c-Kit et PDGFR tyrosine kinase
Pazopanib (Votrient)	VEGFR, c-Kit et PDGFR tyrosine kinase



- Inhibiteurs de tyrosine kinase
- Thérapie ciblée des cancers du rein, digestifs, CHC, SNC, poumon, GIST

- Cardiotoxicité
  - multifactorielle
  - Indépendante de la posologie
  - mais potentiellement réversible

Amram 2011, Mazeron 2008

Cardiotoxicité des antiangiogéniques

- HTA
  - ATCD HTA, âge > 60 ans, BMI > 25 kg/m² associés indépendamment
  - Pas de facteur prédictif
  - CAVEAT : verapamil/diltiazem avec sorafenib/sunitinib
- MTE veineuse ou artérielle
  - Pas d'anticoagulant ou antiagrégant en prophylaxie primaire
  - PEC selon standard of care – réintroduction à discuter
- Dysfonction VG et ischémie myocardique (sunitinib, axitinib++)
  - Dépistage par ETT et ECG (« stage A » heart failure patients) si ATCD MCV, sujet âgé, exposition aux anthracyclines
  - Moins cardiotoxiques : pazopanib, bevacizumab
- Dissection aortique et anévrisme
- Saignement
- Allongement QTc et arythmie (sunitinib++)

Plan

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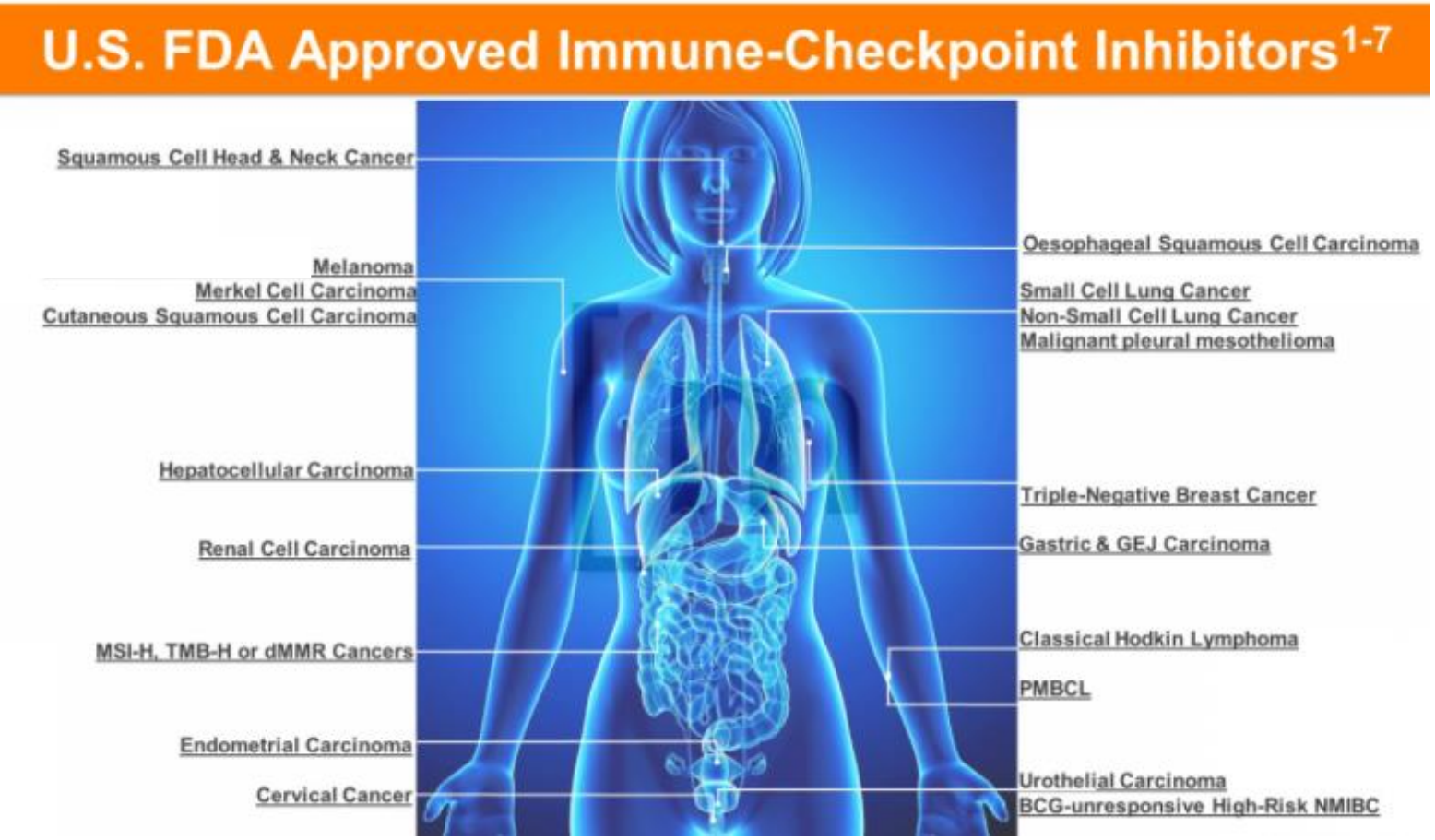
Immune Checkpoint Inhibitors - ICI



Anti-CTLA-4

Ipilimumab

Anti-PD-1

Nivolumab
Pembrolizumab
Cemiplimab

Anti-PD-L1

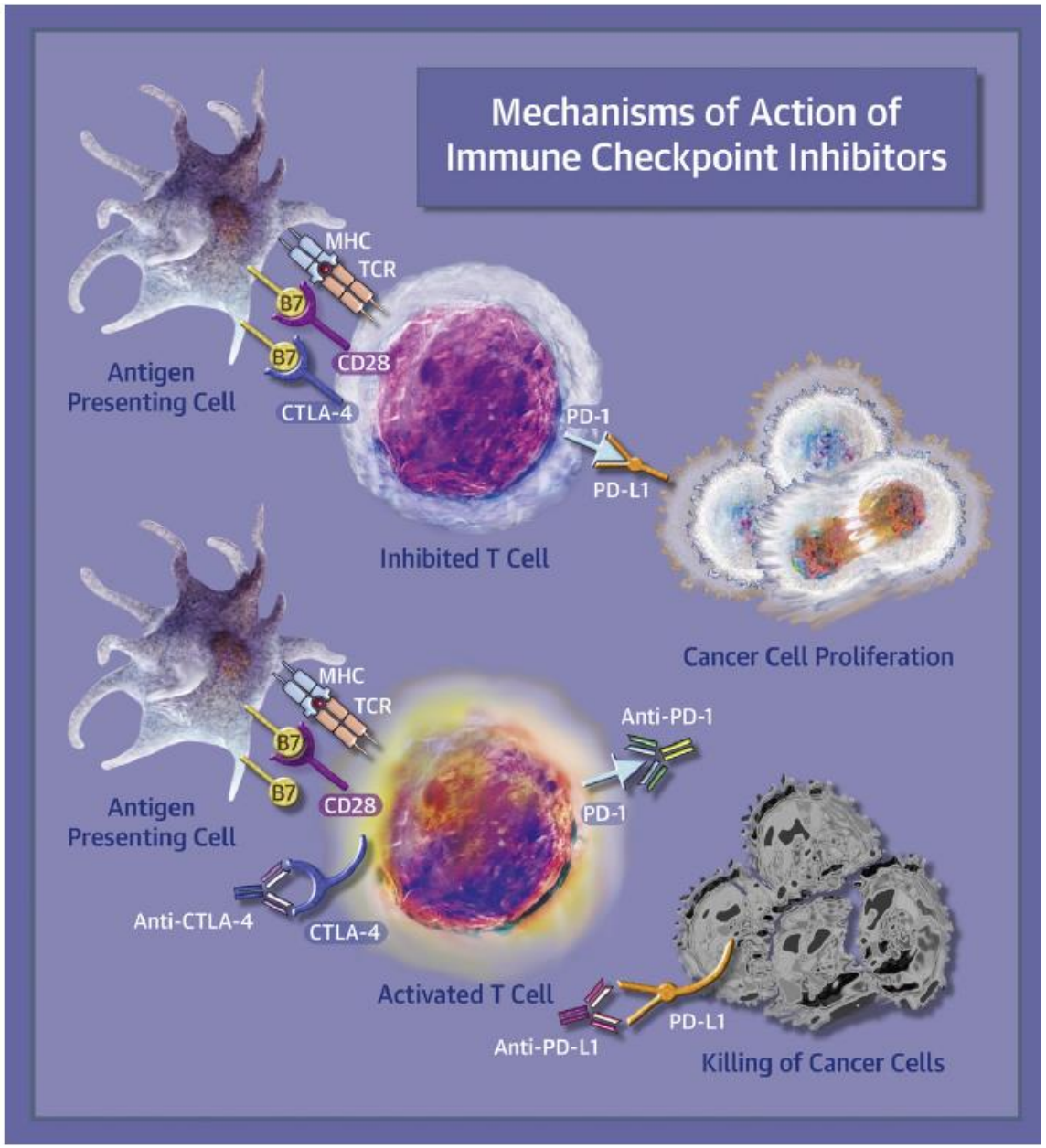
Atezolizumab
Durvalumab
Avelumab

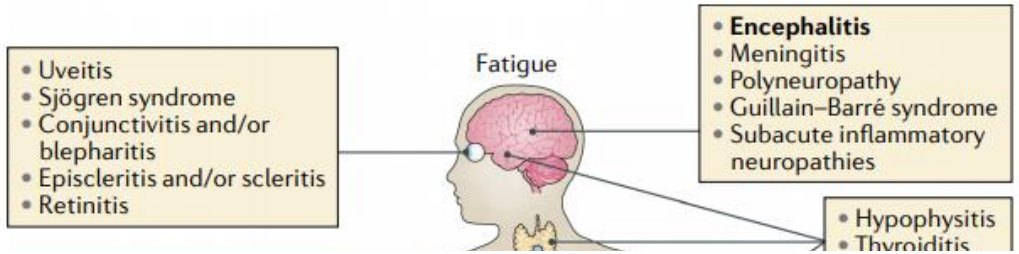
Et encore beaucoup en développement…

Seul ou en combinaison

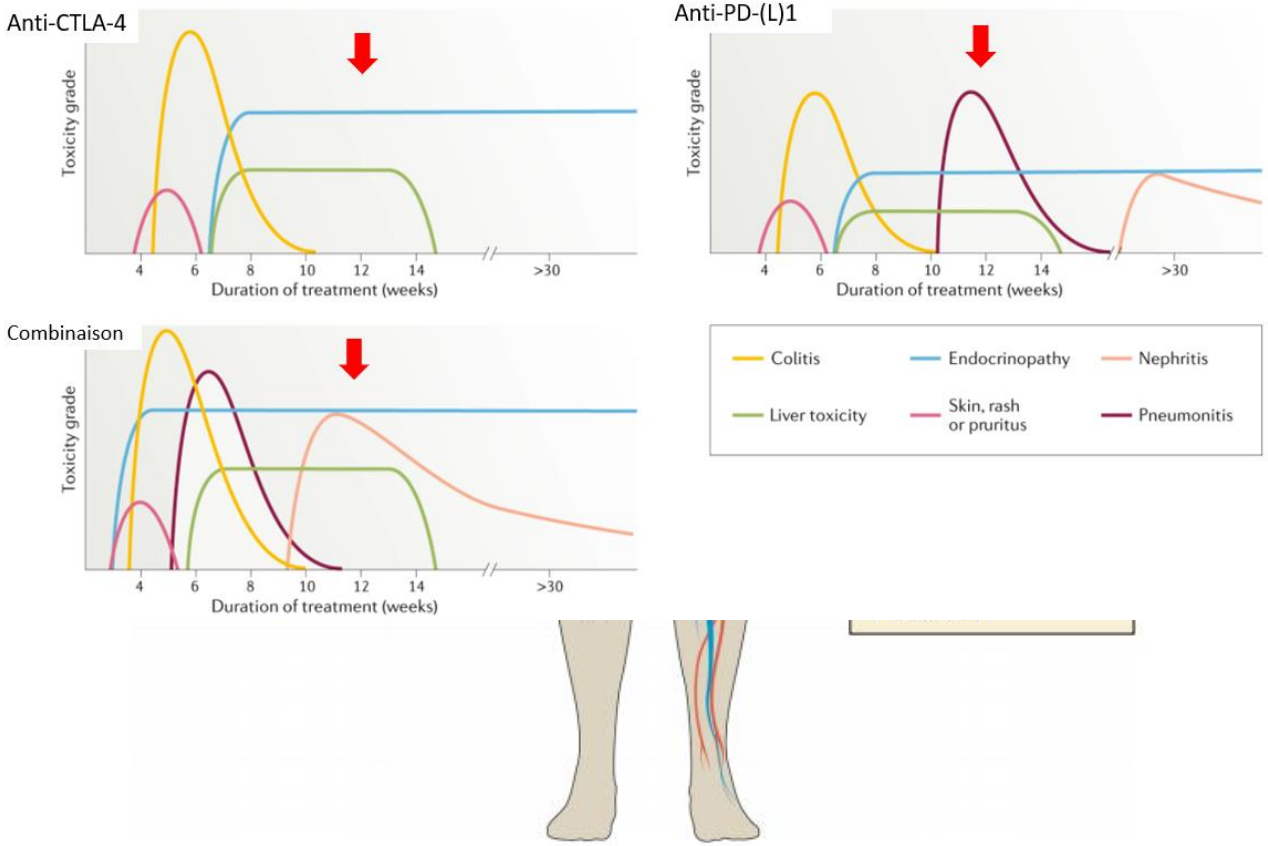
Association avec chimiothérapie, radiothérapie

Dans un contexte métastatique , adjuvant … *néoadjuvant*





IrAE : souvent dans les 3 premiers mois (+/- jours à mois)



Zhang, JACC, 2021 ; Martins, Nat Rev Clin Oncol, 2019

Grade selon CTCAE v5.

Grade 1 : Léger, asymptomatique

-> Observation, pas d'intervention

Grade 2 : Modéré

-> Suspendre ICI, intervention locale ou non invasive, souvent besoin faible dose orale stéroïde

-> Reprise ICI quand irAE ≤ G1

Grade 3 : Sévère, ou médicalement significatif mais non potentiellement mortel

-> Arrêt de l'immunothérapie, hospitalisation, haute dose de stéroïde

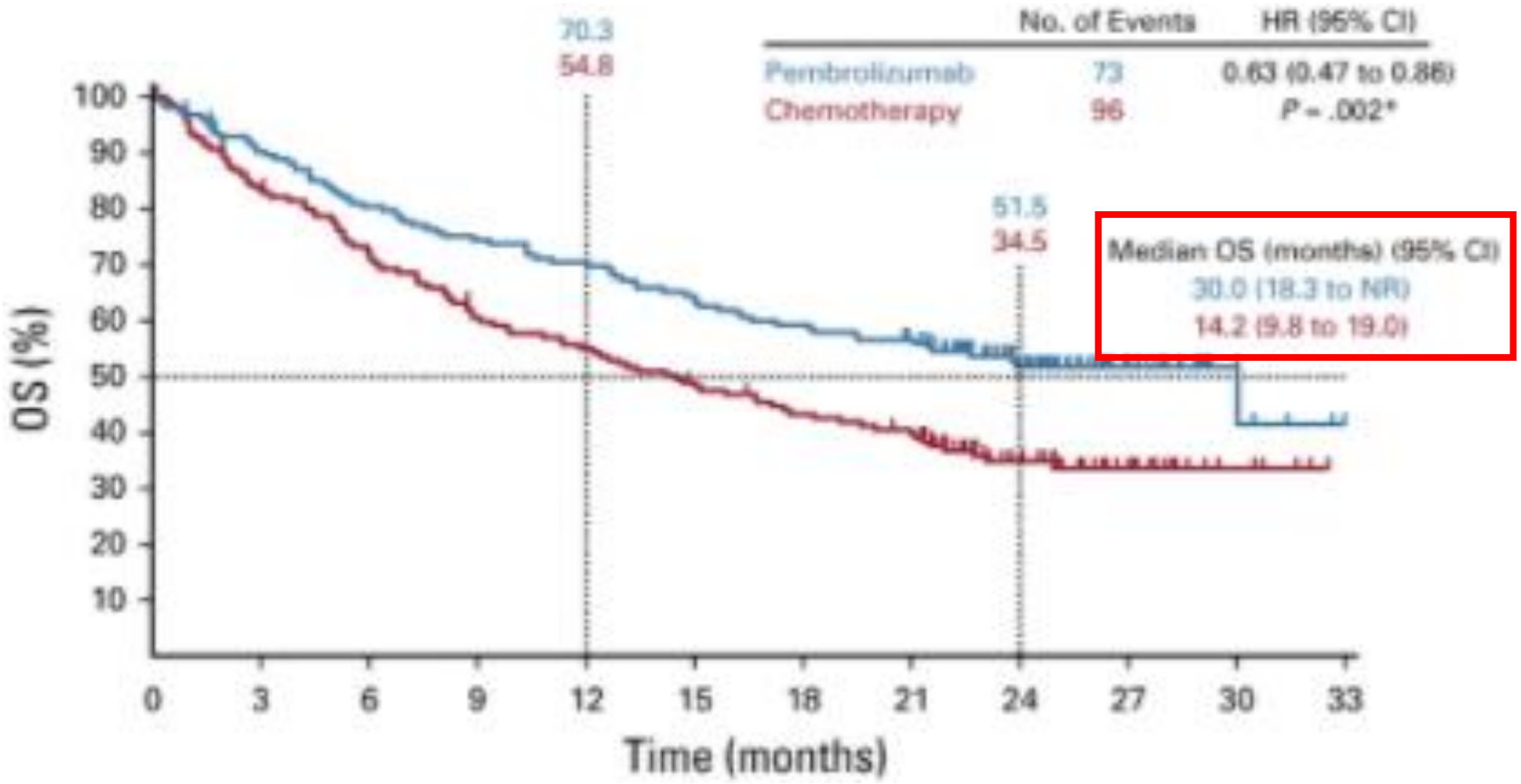
-> Reprise ICI à discuter quand irAE ≤ G1

Grade 4 : Conséquences potentiellement mortelles

-> Arrêt permanent ICI, intervention urgente nécessaire

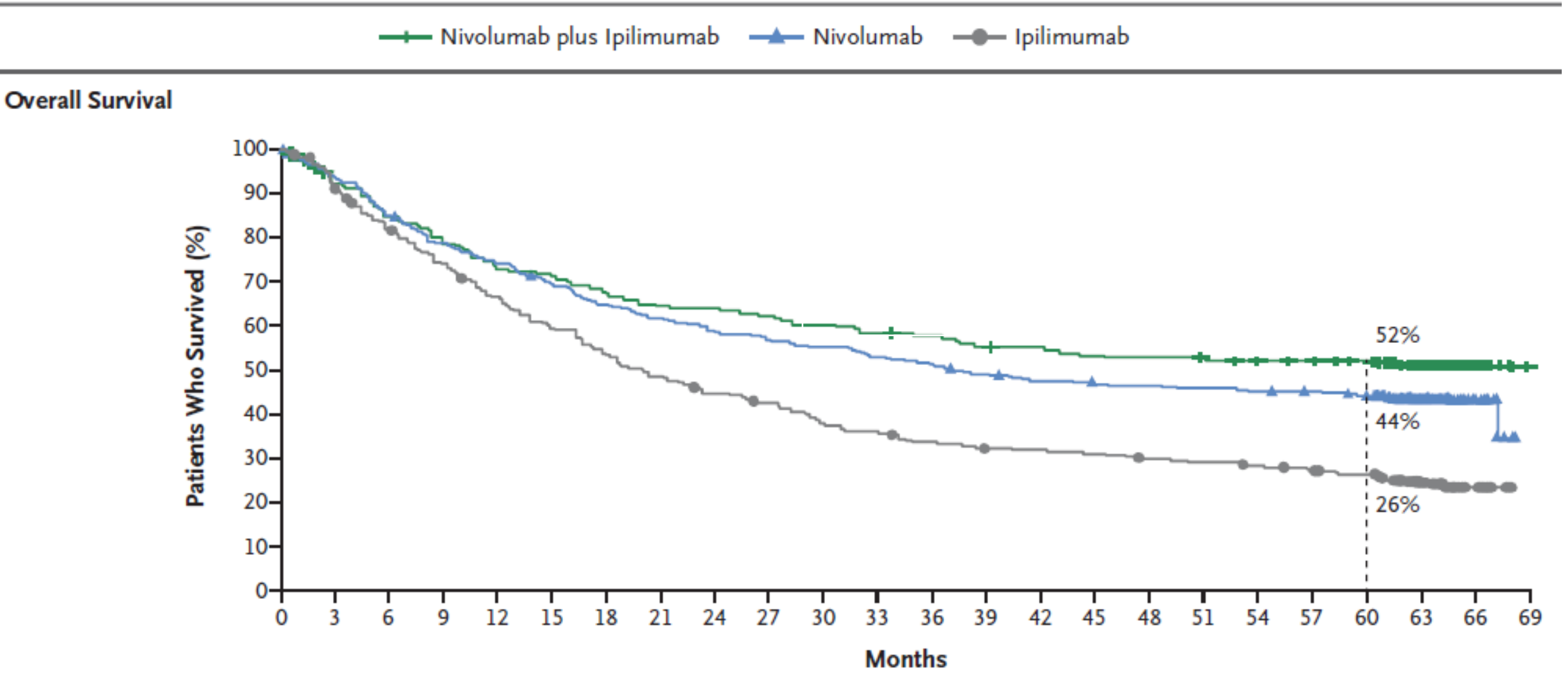
Grade 5 : décès

Cancer du poumon métastatique PD-L1 ≥ 50%



Reck, NEJM, 2016 ; Reck, JCO, 2019

Mélanome métastatique



Robert, NEJM, 2011 ; Larkin, NEJM, 2015 and 2019

Cardio-toxicité des ICI

Rare – probablement sous-estimée !

Non – cumulative ; souvent en début traitement (2-3 premiers mois).

Peut être fulminante

FR potentiels :

. Combinaison ICI
. Anti-CTLA4 (3,3% myocardite > 2,4% anti-PDL-1 > 0,5% anti-PD-1)
. Diabète
. Obésité
. Maladie autoimmune pré-existante
. Tabac
. HTA

Différentes atteintes possibles :

- Myocardite (+ fréquente)
- Arythmies
- SCA
- Vasculite
- Péricardite

Patel, Current Oncol Reports, 2021 ; Zhang, JACC, 2021

Immune-Related MYOCARDITIS

Rare (1,1-2,4% combinaison), mais probablement sous-estimée

Symptômes très variables : **A/paucy-symptomatique au Décès**

. Fatigue
. Myalgies (souvent associée à myosite)
. DRS
. Dyspnée
. Œdèmes
. Vertige/Syncope
. Palpitations/Arythmies
. Mort subite

Développement dans les **2-3 premiers mois de traitement.**

Complications majeures dans > 40-50% cas
(arythmies atriale ou ventriculaire, bloc complet, IC, choc cardiogénique, **décès (38-46%)**)
Plus ou moins **fulminante**

Patel, Cur Oncol Rep, 2021 ; Zhang, JACC, 2021

Démarche diagnostique

1. HAUT DEGRE DE SUSPICION - Exclure autres DD

- **ECG** : souvent anormal (89% cas) (mais normalité n'exclue pas myocardite)

- **Troponines** : majorées dans > 90% cas (mais peu spécifiques)
- BNP : peu utile

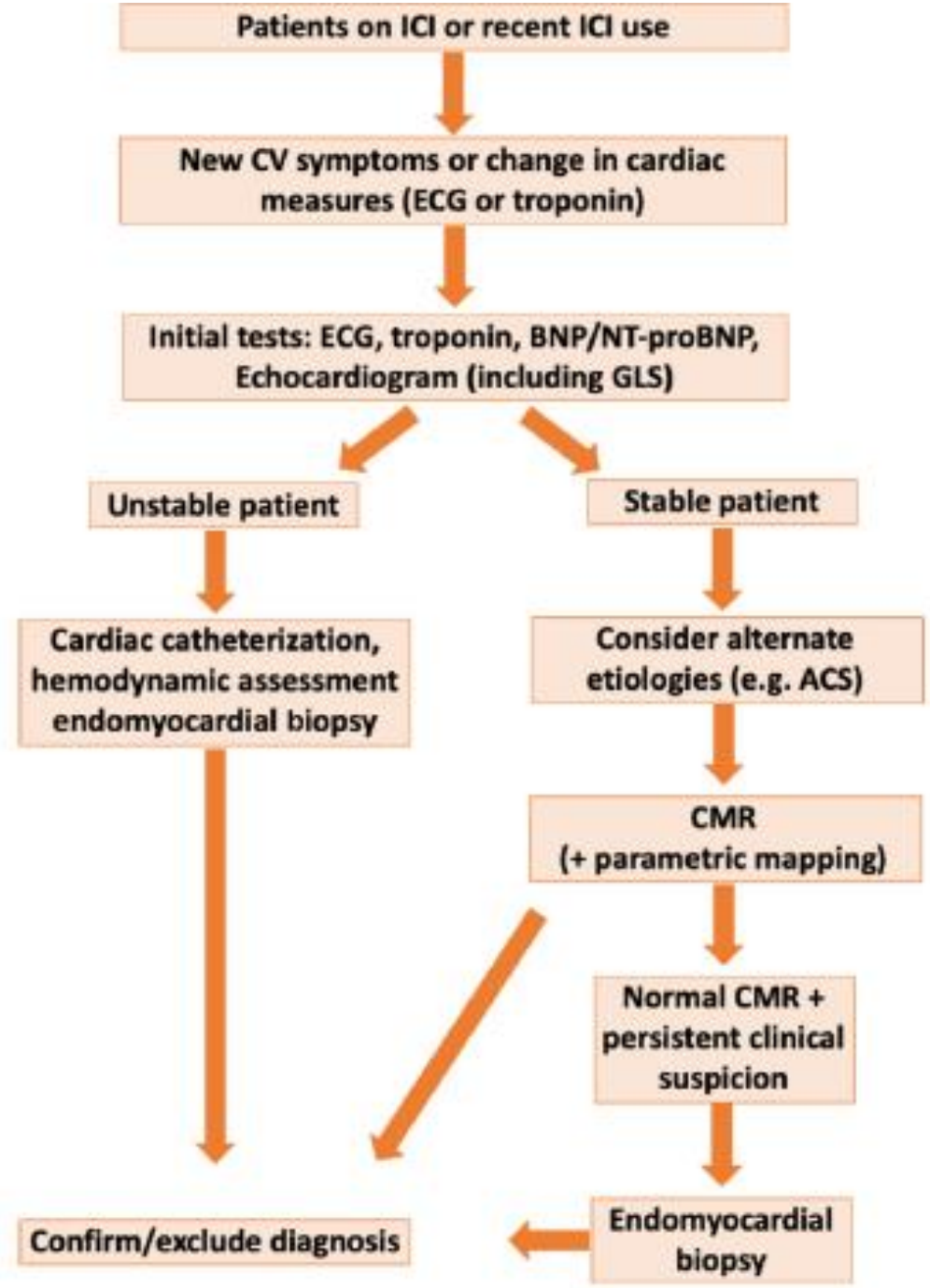
- **ETT** : FEVG normale dans > 50-60% cas
- **IRM cardiaque** : imagerie gold-standard

mais majorité FEVG N, et late gado enhancement dans seulement 28- 48%

- **Biopsie endo-myocardique** : LE + spécifique = GOLD STANDARD pour Dg.

Screening : Pas de routine pour le moment.

Mais ECG et troponines de base proposés avant l'ICI !!



Patel, Cur Oncol Rep, 2021 ; Zhang, JACC, 2021

Prise en charge – **MULTIDISCIPLINAIRE**

1. Mise en suspend des ICI
2. Selon grade/gravité

. Corticostéroides : (introduction rapide = amélioration outcome)
1gr IV/j 3j,
puis 1mg/kg/j IV puis po
puis dès disparition des symptômes : sevrage progressif lent sur > 4-6sem (voire +)

+ IVIG / plasmaphérèse si HD instable

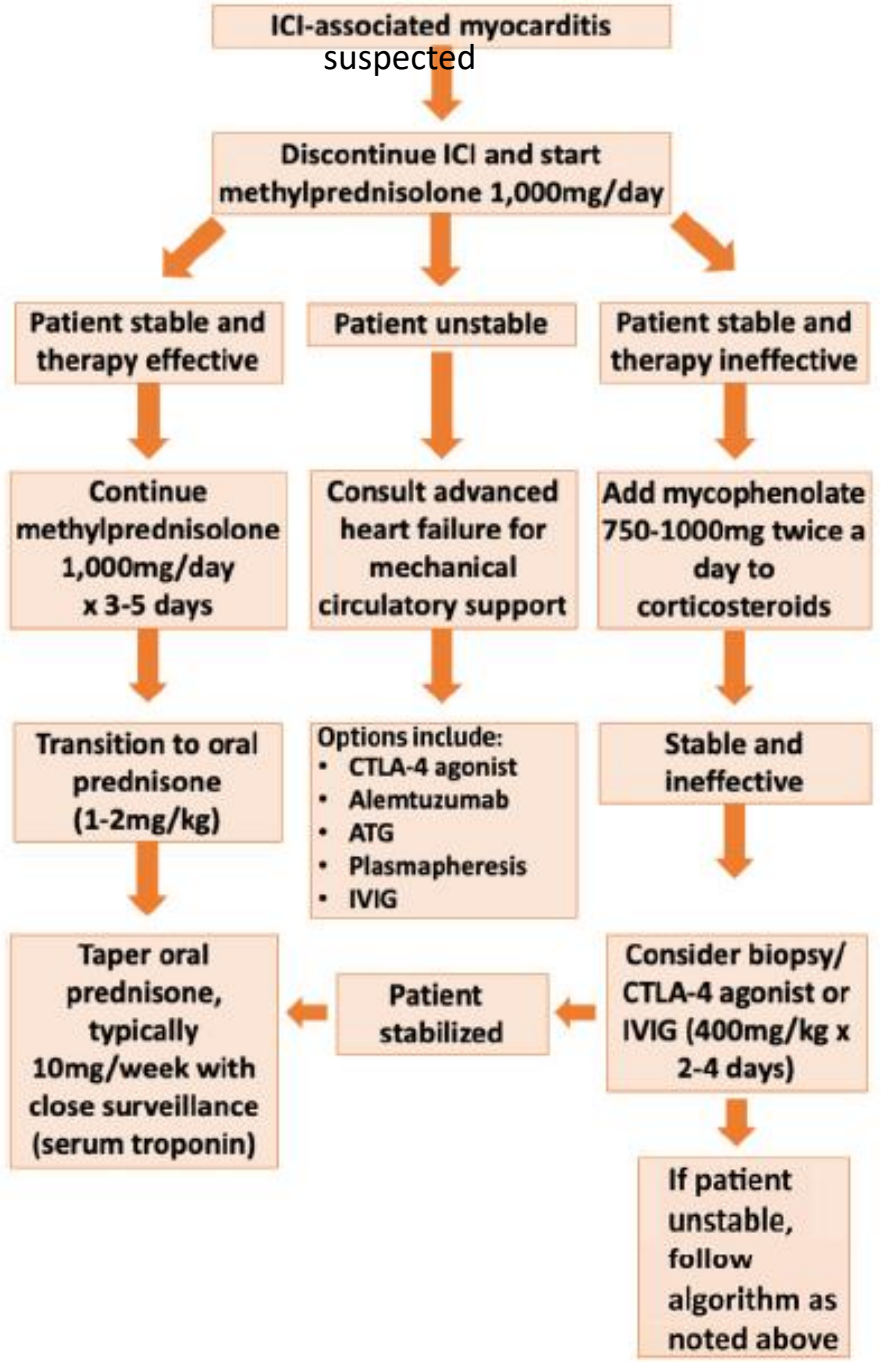
+ Tacrolimus / MMF si myocardite de haut grade à la bx

. En cas de résistance au stéroides => ajout autres immunosuppresseurs :

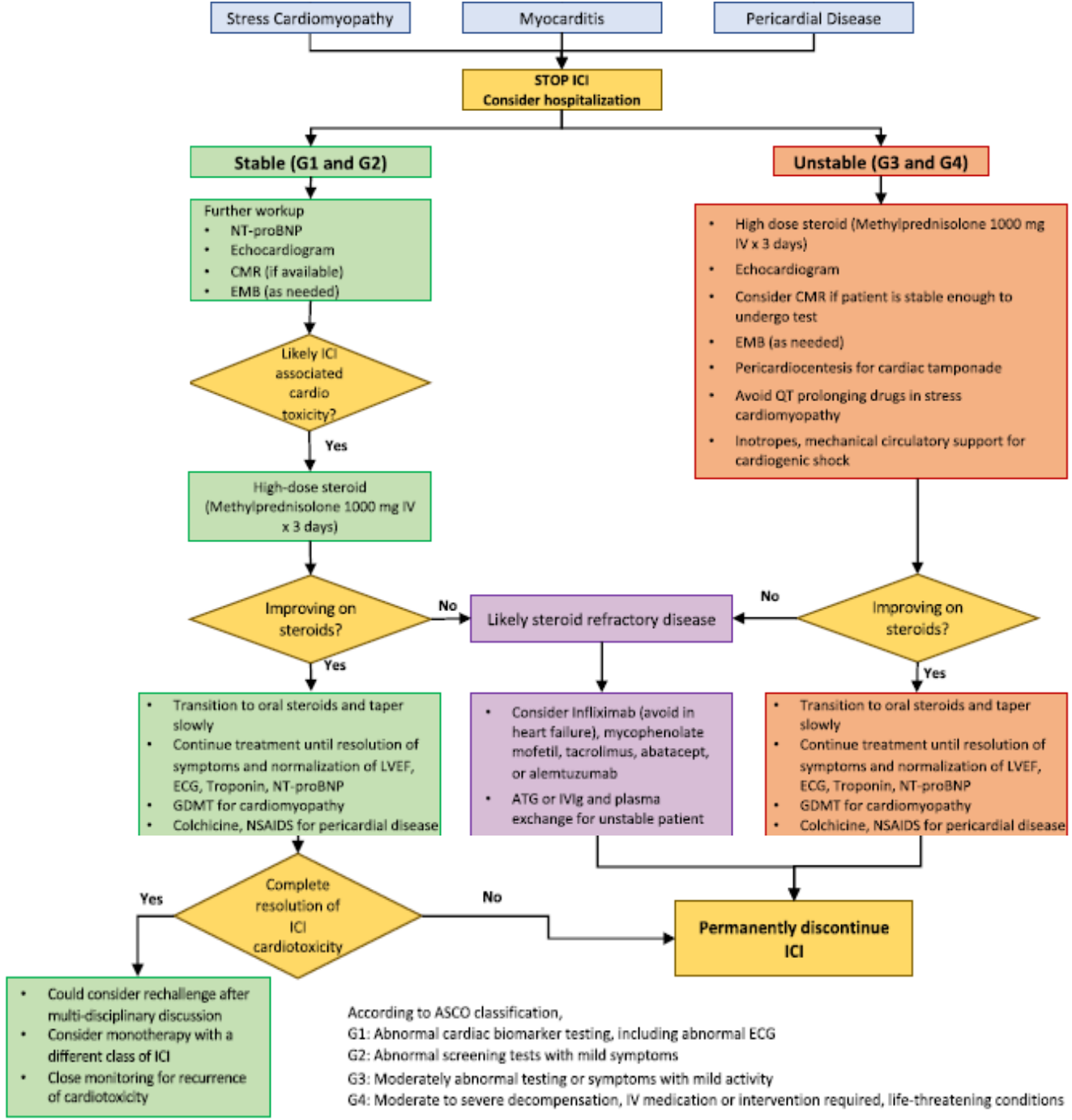
- Tacrolimus
- Mycophenolate Mofetil (MMF)
- IVIG et plasmaphérèse
- *Alemtuzumab (Ac anti CD52), Abatacept (agoniste CTLA4)*

Récupération partielle possible.

Rechallenge ?
Plutôt déconseillé…

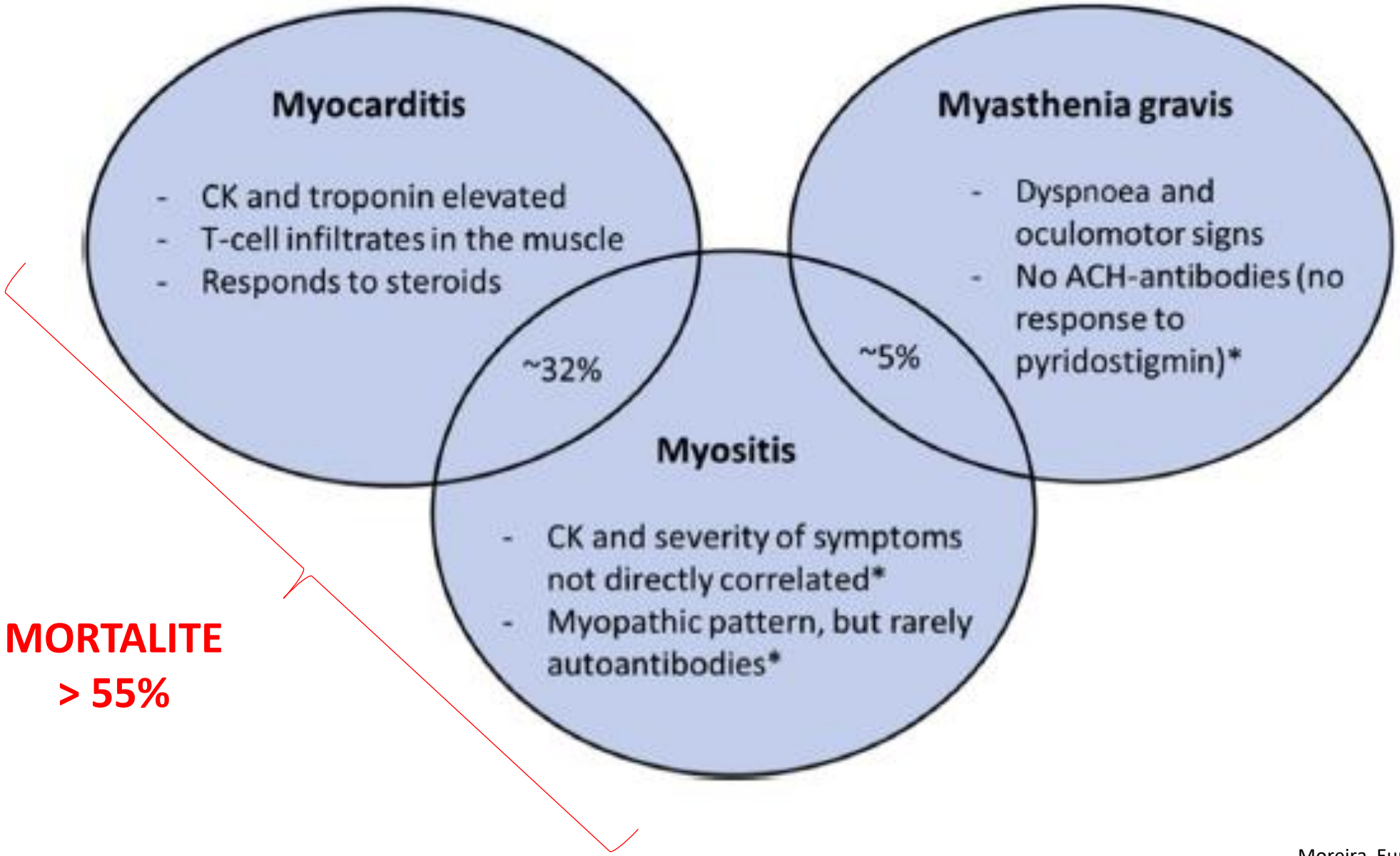


Patel, Cur Oncol Rep, 2021 ; Zhang, JACC, 2021



Patel, Cur Oncol Rep, 2021

Fréquemment associés à la myocardite



Moreira, Eur J Cancer, 2019

Autres toxicités cardio-vasculaires :

. Cardiomyopathie de stress (Takotsubo)

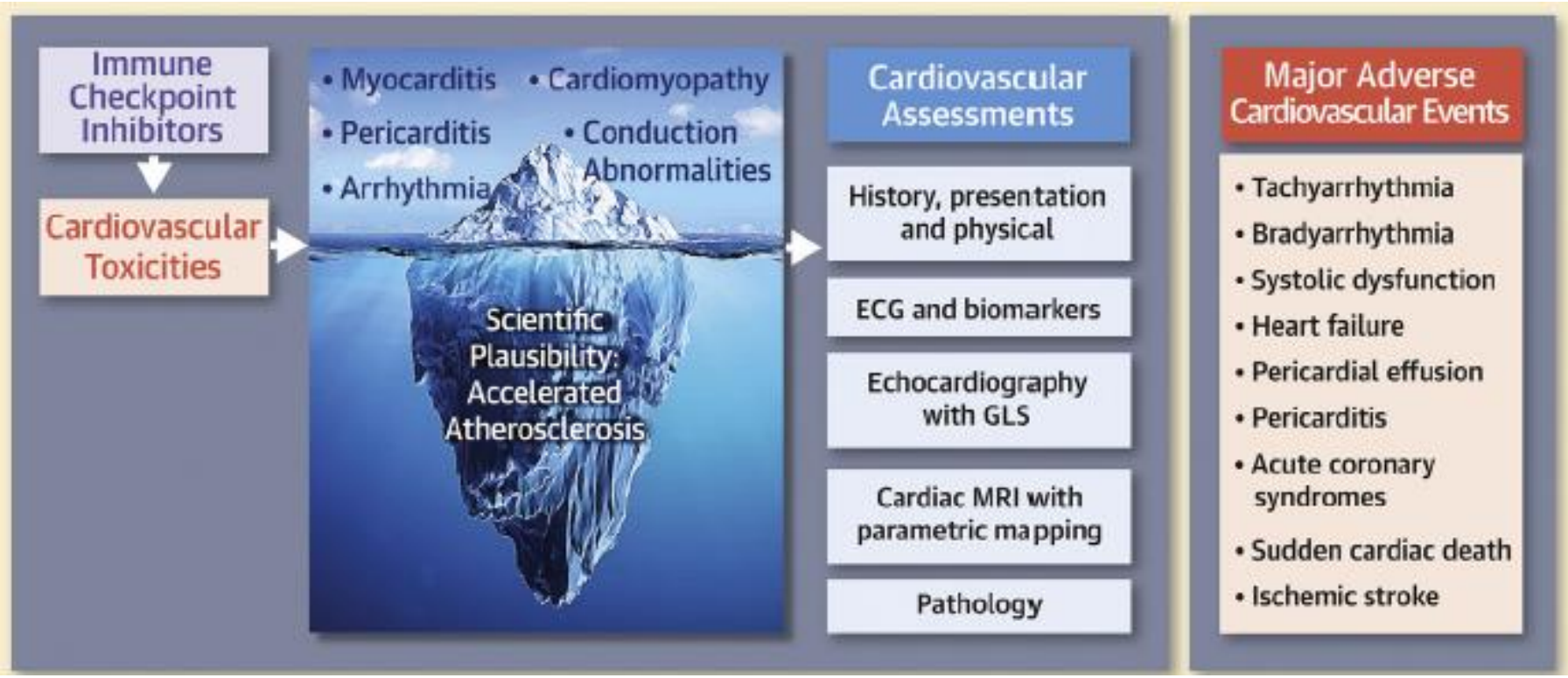
. Péricardite (2ème cardiotox en fréquence des ICI)

incidence 7-13,6%

mortalité 13-21%

peut être associée à la myocardite

. Anomalies de conduction



A long terme :

. 3x plus d'évènements CV post-ICI

. majoration en taille et de la rapidité de progression des plaques d'athérome

=> Screening FRCV !!!

Patel, Current Oncol Reports, 2021 ; Zhang, JACC, 2021

Cas Clinique – Mr B, 65 ans

Comorbidités : HTA, D2NIR, SAOS appareillé, tabagisme

Novembre 2020 – Carcinome pulmonaire à petites cellules, extensive disease (métastatique : pleurale, pulmonaire, cérébrale).

Du 17.11.20 au 28.12.2020 : 3C de chimiothérapie (carboplatine-etoposide) dont 2 avec **Atezolizumab**

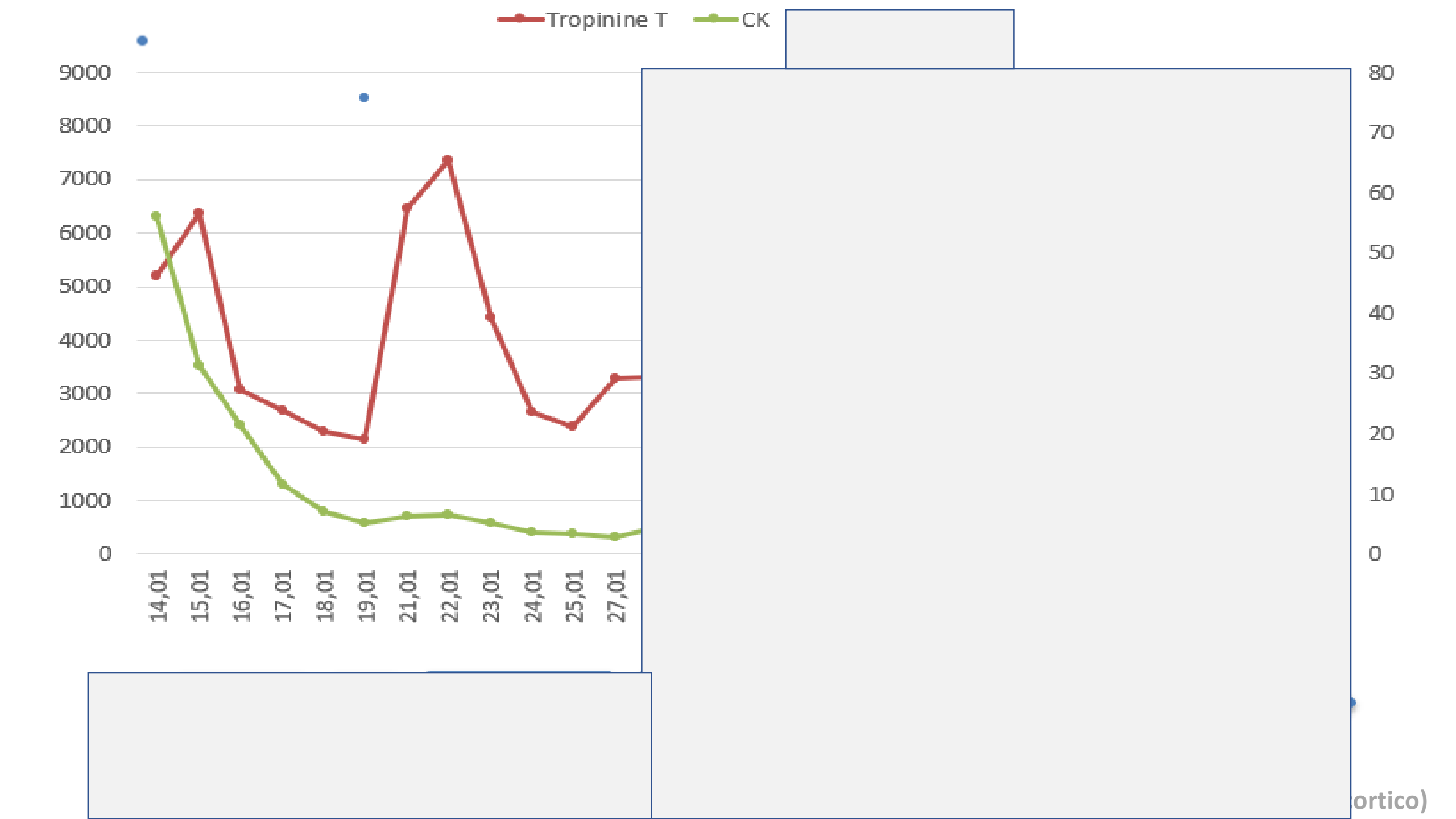
Début janvier 2021 : Asthénie
Difficulté à relever la nuque
Dyspnée (rapidement progressive sur quelques jours jusqu'à un stade III)

11.01.2021 – CT Thoracique : Exclusion EP, pas de signe de pneumonite ou BPN. Réponse partielle de l'atteinte tumorale.
-> Prednisone 90mg/j (1mg/kg/j) pour suspicion AE immunothérapie

14.01.2021 – Consulte aux urgences (Dyspnée IV)

. ECG : absence arythmie ou signe ischémie aigue.
. Gazo : Acidose respiratoire hypercapnique (pH 7,26, pCO2 8 kPa)
. Labo : CK tot 7045 U/L (N 47-222) ; Trop T us 5191ng/l (N<14) ; proBNP 263 ng/l (N<300)
. Radio thorax : pas épanchement pleural, pas de foyer, pas de signe de décompensation cardiaque.
. ETT : FEVG 70%, pas anomalie grossière cinétique segmentaire, pas de valvulopathie, pas épanchement péricardique.

=> IOT et transfert aux SI


Tropinine T
CK
9000
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70
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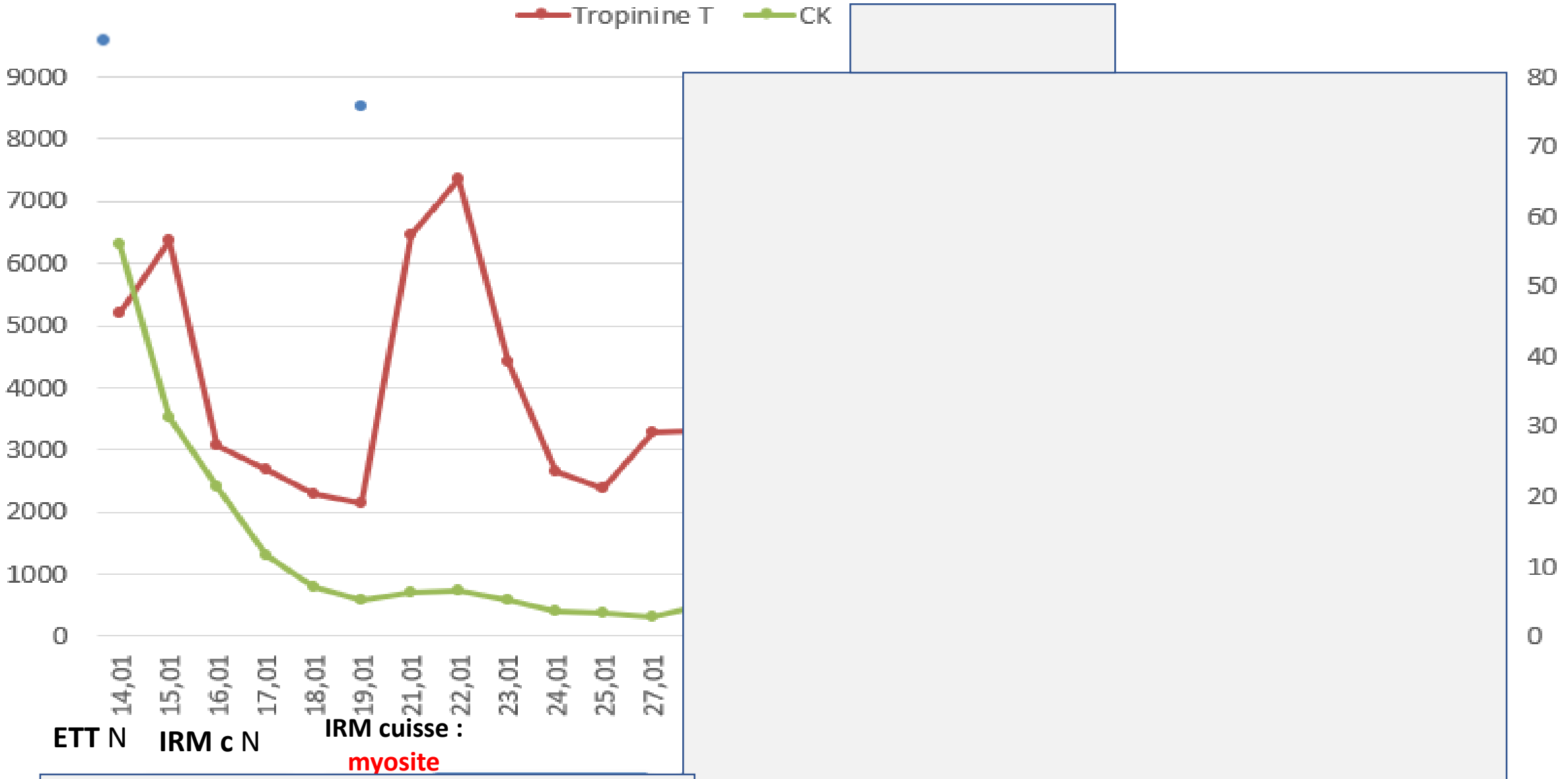
ortico)



ETT N **IRM c** N **IRM cuisse :**

myosite

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A case of false positive troponin ? by macrotroponin?

Table 4
Leading sources of false positive results in cardiospecific troponin testing.

- Patient and/or sample misidentification
- Spurious hemolysis
- Hyperbilirubinemia
- Turbidity
- Fibrin clots
- Microparticles
- Immunocomplexes
- Erroneous calibration
- Analyser malfunction
- Reagent deterioration
- Instrumental carry-over
- Inappropriate sample dilution
- Heterophilic antibodies
- Human anti-mouse antibodies (HAMA)
- Autoantibodies
- Rheumatoid factor

In a study of healthy blood donors :

9.9% had cTnT autoantibodies

12.7% had cTnI autoantibodies

more frequently seen with cTnI than cTnT

frequency comprised between 0.1 and 3.1% in the general population, which can be however remarkably increased, up to 50%, in specific category of patients such as those with persistent infection

Lippi G, et al Interference from heterophilic antibodies in troponin testing. Case report and systematic review of the literature. Clin Chim Acta. 2013 Nov 15;426:79-84.

How is macrotroponin confirmed ?

- Laboratory search for analytical interference
  - macro-troponine
    - Dilution tests
    - Treatment with polyethylene glycol in deionised water (PEG)
    - Exclusion of human anti-murine antibodies (HAMA)
    - Heterophilic antibodies
      - Heterophilic blocking reagent, and retest
  - **Measurement of troponin I**
  - Biotin interferance

- DDx:
  - Paraneopasltic syndrome
  - Cross reaction with auto-antobodies from feotal reversal in skeletal muscle « réversion fœtale »

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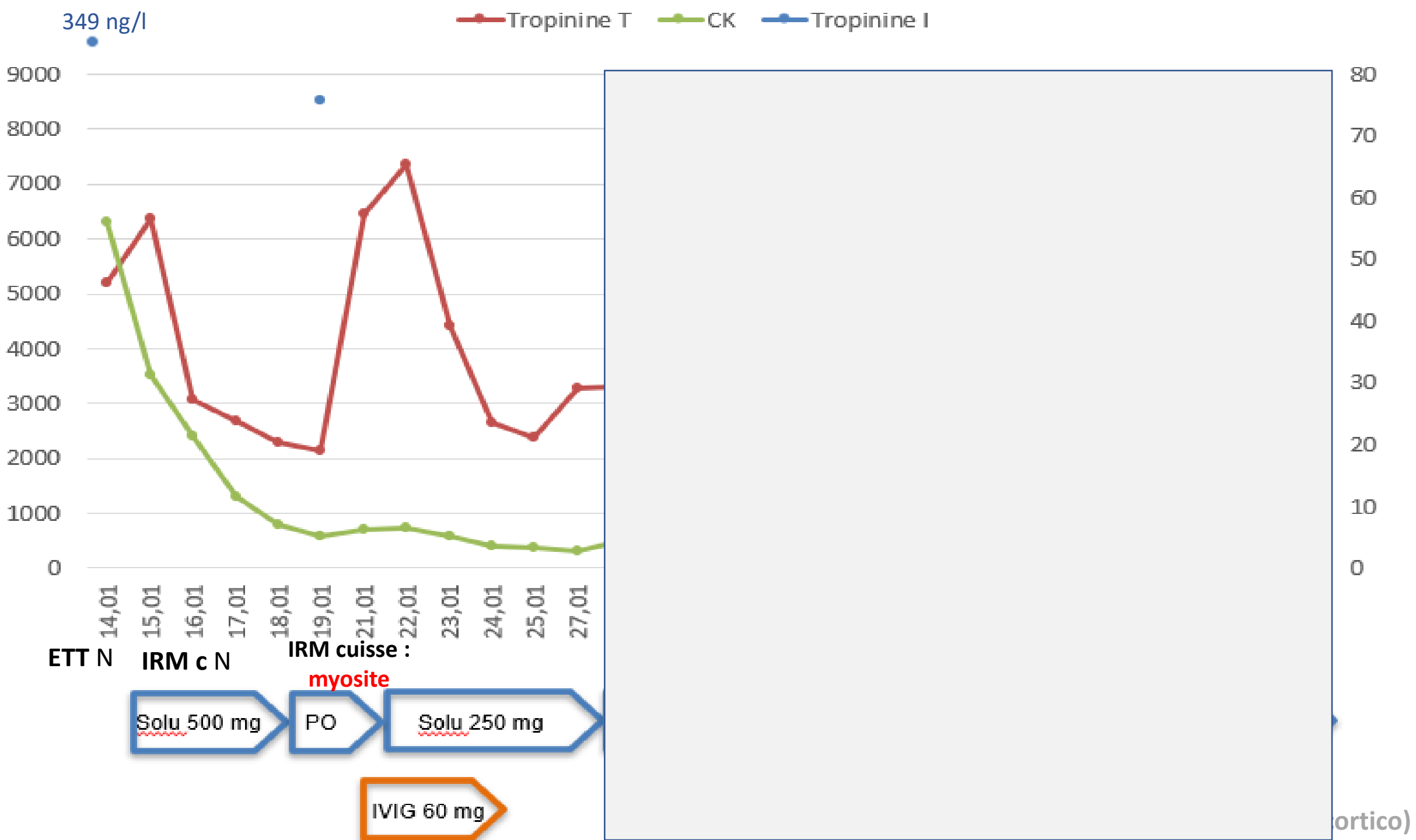
- Autoantibodies
- Rheumatoid factor

Lippi G, Aloe R, Meschi T, Borghi L, Cervellin G. Interference from heterophilic antibodies in troponin testing. Case report and systematic review of the literature. Clin Chim Acta. 2013 Nov 15;426:79-84. doi: 10.1016/j.cca.2013.09.004. Epub 2013 Sep 13. PMID: 24041812.


349 ng/l
Tropinine T
CK
Tropinine I
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
80
70
60
50
40
30
20
10
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14,01
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23,01
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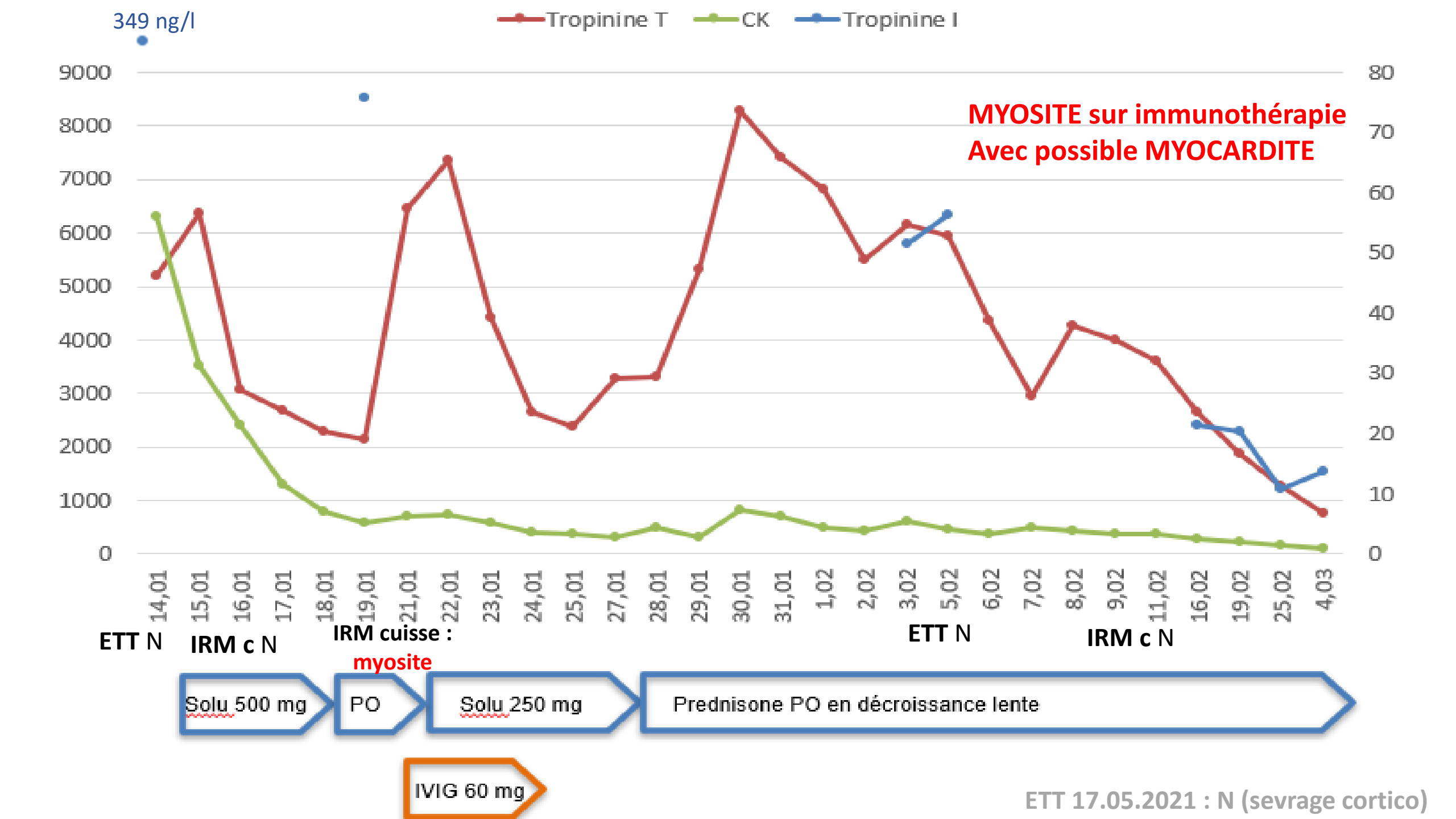
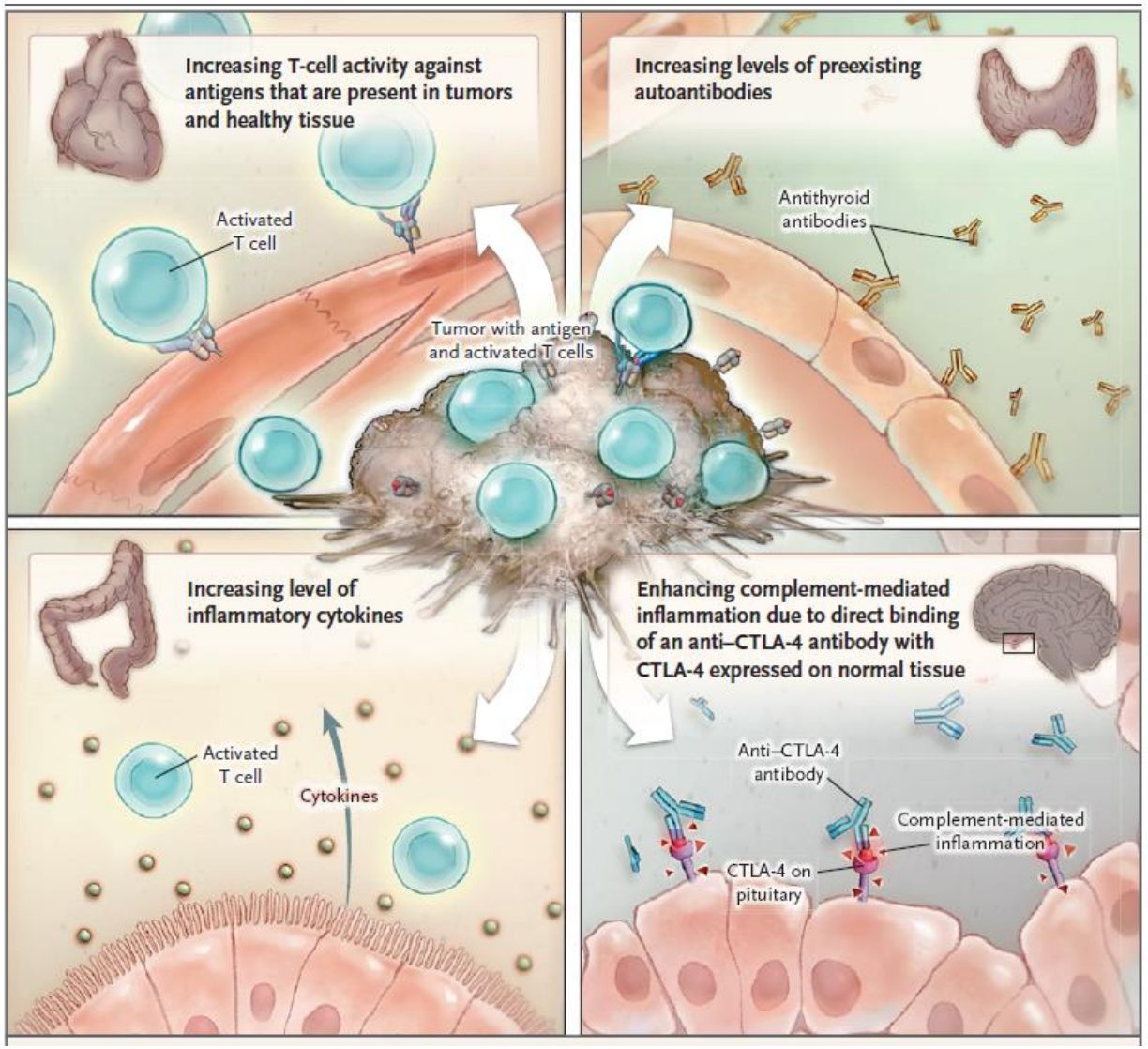
ETT N
IRM c N
IRM cuisse :
myosite
Solu 500 mg
PO
Solu 250 mg
IVIG 60 mg



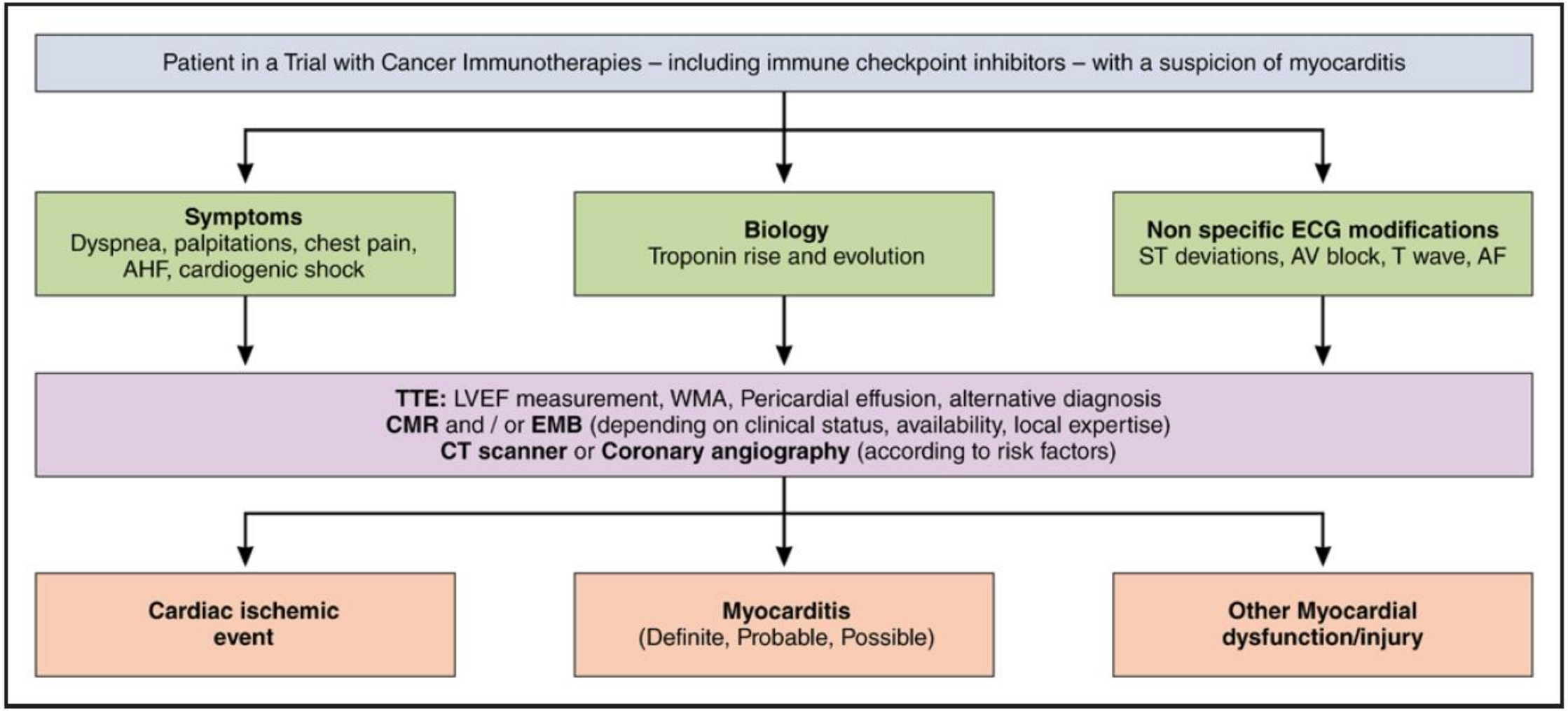
ETT 17.05.2021 : N (sevrage cortico)

Mechanisms of immunotherapy cardiotoxicity



Postow MA, et al Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018 Jan 11;378(2):158-168.

Myocarditis in the setting of immune check point blockade



Bonaca MP, Moslehi J., et al. Myocarditis in the Setting of Cancer Therapeutics: Proposed Case Definitions for Emerging Clinical Syndromes in Cardio-Oncology. Circulation. 2019 Jul 2;140(2):80-91.

Definition of myocarditis in the setting of immune check point blockade

Myocarditis – A Proposed Definition
Hierarchical definition accounting for different levels of evidence

Pathology	Imaging	ECG	Syndrome	Biomarkers

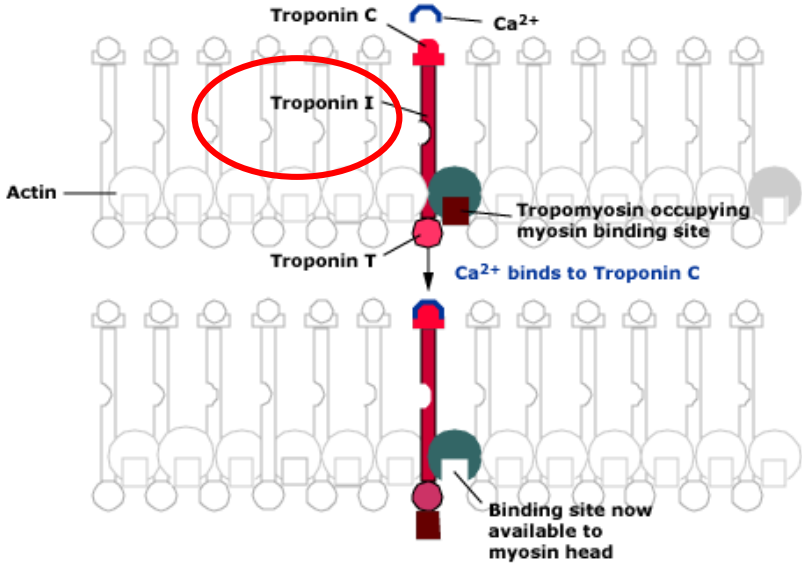
For all/other diagnosis/explanations (e.g. ACS) must be excluded

Definite Myocarditis:
- Pathology
  OR
- Diagnostic CMR + syndrome + (biomarker or ECG)
  OR
- ECHO WMA + syndrome + biomarker + ECG + negative angiography

Probable Myocarditis:
- Diagnostic CMR (no syndrome, ECG, biomarker)
  OR
- Suggestive CMR with either syndrome, ECG, or biomarker
  OR
- ECHO WMA and syndrome (with either biomarker or ECG)
  OR
- Syndrome with PET scan evidence and no alternative diagnosis

Possible Myocarditis:
- Suggestive CMR with no syndrome, ECG or biomarker
  OR
- ECHO WMA with syndrome or ECG only
  OR
- Elevated biomarker with syndrome or ECG and no alternative diagnosis

Troponin-tropomyosin complex



Bonaca MP, Moslehi J., et al. Myocarditis in the Setting of Cancer Therapeutics: Proposed Case Definitions for Emerging Clinical Syndromes in Cardio-Oncology. Circulation. 2019 Jul 2;140(2):80-91.

MRI in the setting of suspected myocarditis induced by immune check point blockade

international multicentre registry of ICI-associated myocarditis

23 sites across the USA, Canada, and Europe

The first case in the registry was diagnosed in November 2013, and cases were included in this report until April 2019

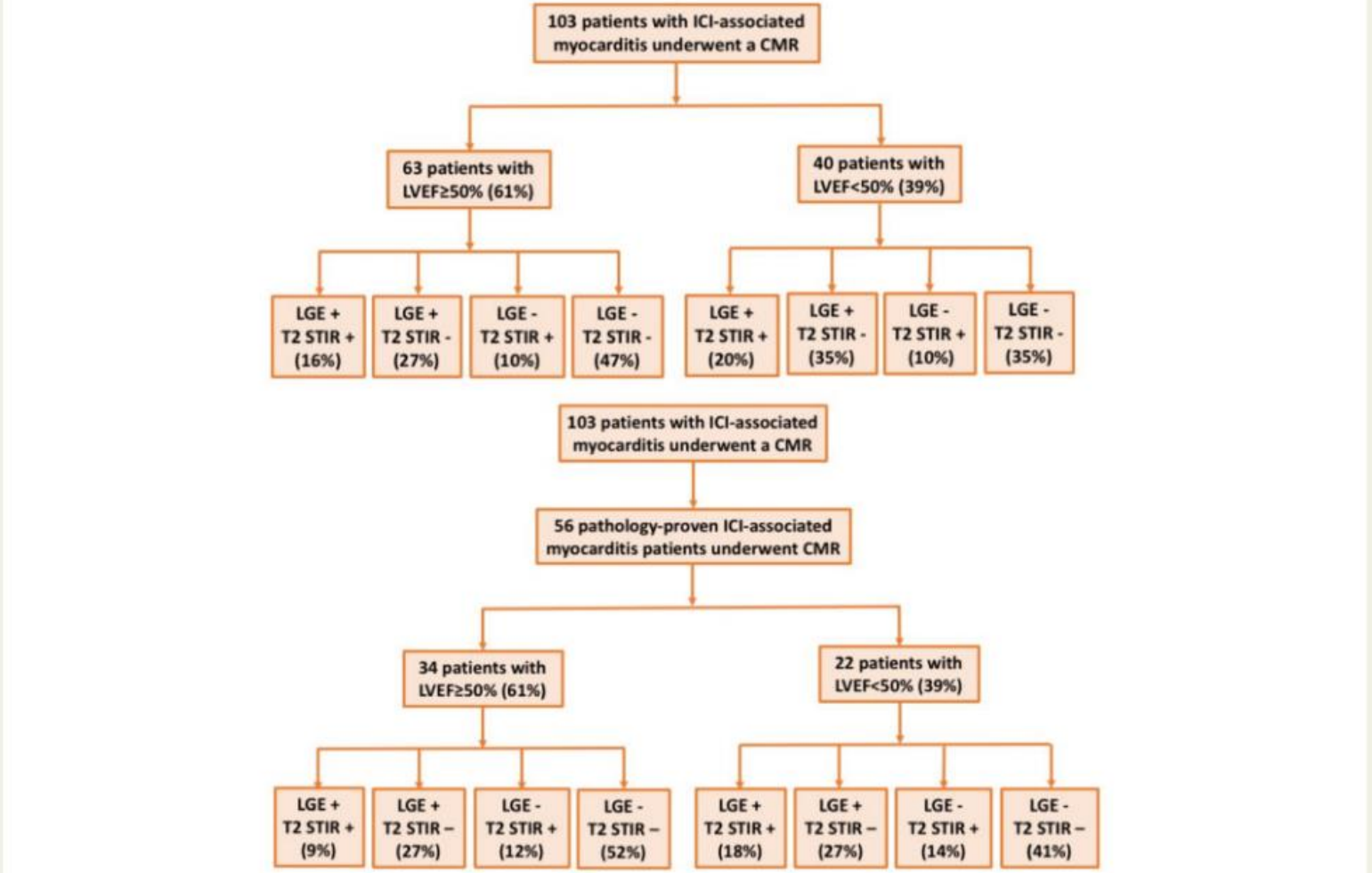


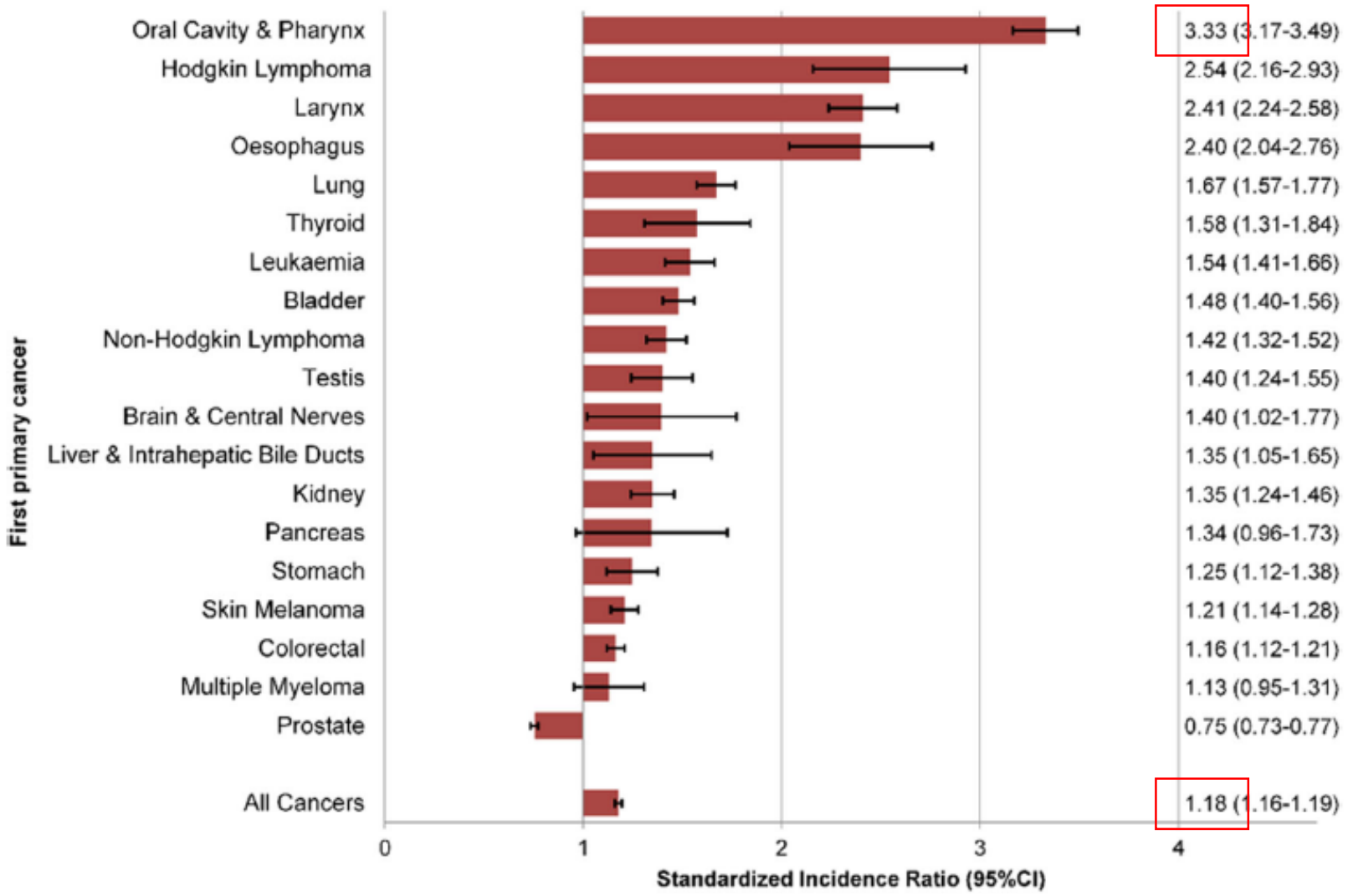
Figure 1 Patient cohort of immune checkpoint inhibitor-associated myocarditis. CMR, cardiovascular magnetic resonance; ICI, immune checkpoint inhibitors; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; STIR, short tau inversion recovery.

Zhang L, et al Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. Eur Heart J. 2020 May 7;41(18):1733-1743.

Characteristic	Cancer therapy-related cardiomyopathy		
	Type I	**Type II**	**Type III**
Definition	Direct impairing effect on the myocardium	Indirect impairing effect on the myocardium	Impairing effect owing to myocarditis
Risk with cancer therapy			
Doxorubicin	Yes	Yes	Yes (toxic or reactive)
Cyclophosphamide	Yes	Yes	Yes (toxic or reactive)
5-Fluorouracil	Yes	Yes	NR
HER2 (ERBB2) inhibitors	Yes	Unclear	NR
VEGF inhibitors	Yes (TKIs)	Yes	Unclear
ICIs	Possible	Possible	Yes (immunomediated)
Radiation therapy	Yes (at high dose)	Yes	Yes (toxic or reactive)
Diagnosis			
Imaging	Echocardiography, cardiac MRI, MUGA scan	(Stress) echocardiography, (stress) cardiac MRI, nuclear stress test, CT coronary angiography, vasoreactivity studies	Cardiac MRI, PET, echocardiography
Biomarkers	Cardiac troponins, natriuretic peptides (especially long term)	Thyroid function studies, cytokines, catecholamines ECG abnormalities (e.g. ST-segment shifts, T-wave inversions)	Cardiac troponins, natriuretic peptides, ECG abnormalities (e.g. heart block, ectopy)
Management			
Treatment	Stop cancer therapy, β-blocker (carvedilol), ACE inhibitor, ARB, spironolactone	Stop cancer therapy, therapy directed at the underlying cause (e.g. correction of myocardial ischaemia or valve disease)	Stop cancer therapy; for ICI therapy, anti-inflammatory and immunosuppressive therapy, supportive care as needed (e.g. ECMO)

Joerg Herrmann, Nature Reviews, 2020

Seconds cancers



FR pour 2ème cancer :

. Type de cancer primaire (tabac)

. < 50ans au 1er Dg

. Survie > 10ans

. Type de chimio-radiothérapie

FU oncologique

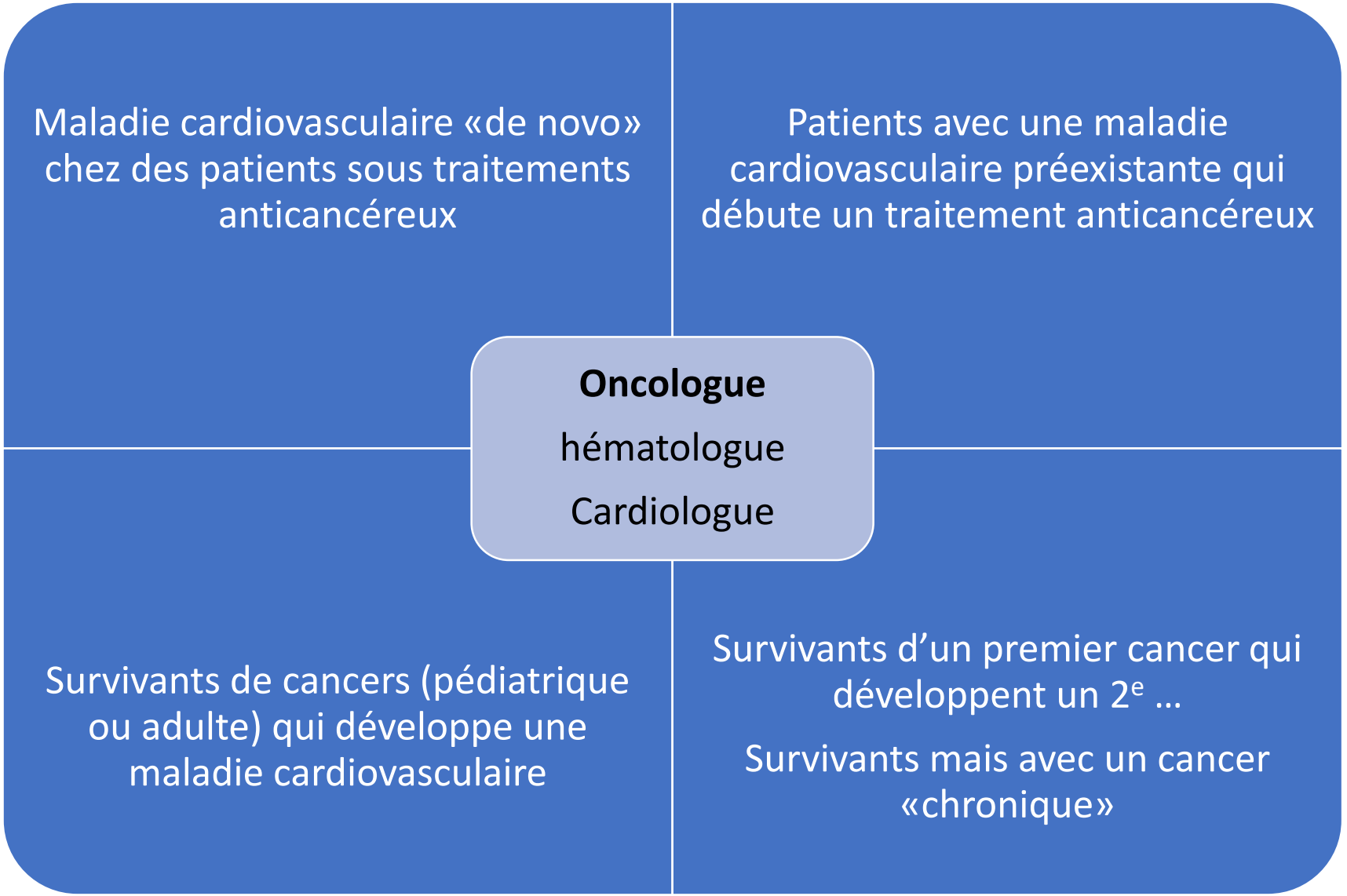
Amélioration du style de vie

Feller, BMC Cancer, 2020

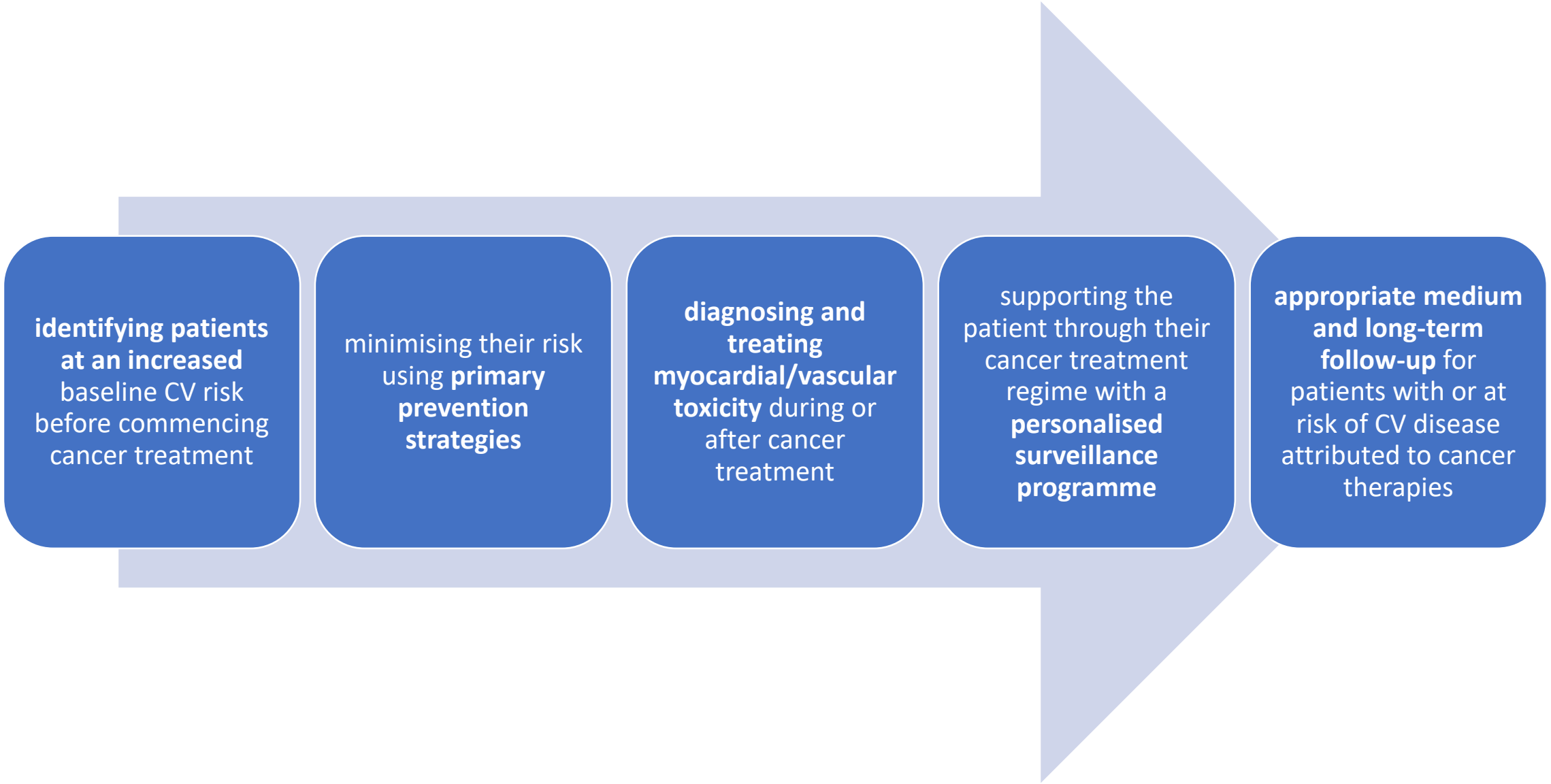
Plan

- What is cardio-oncology ?
- General cancer epidemiology
- Cardiotoxicity profile and cardiac assessment for specific cancer treatments
  - Fluoropyrimidine therapy
  - Anthracyclines
  - Anti HER2 therapy
  - Radiotherapy
  - Immunotherapy
  - Anti-androgen therapy
  - Tyrosine Kinase therapy
- Clinical cases
- Impact of a cardio-oncology unit
  - A multidisciplinary approach

Cardio-oncology or onco-cardiology ?



Cardio-oncology or onco-cardiology ?



5 years of activity in a cardio-oncology clinic

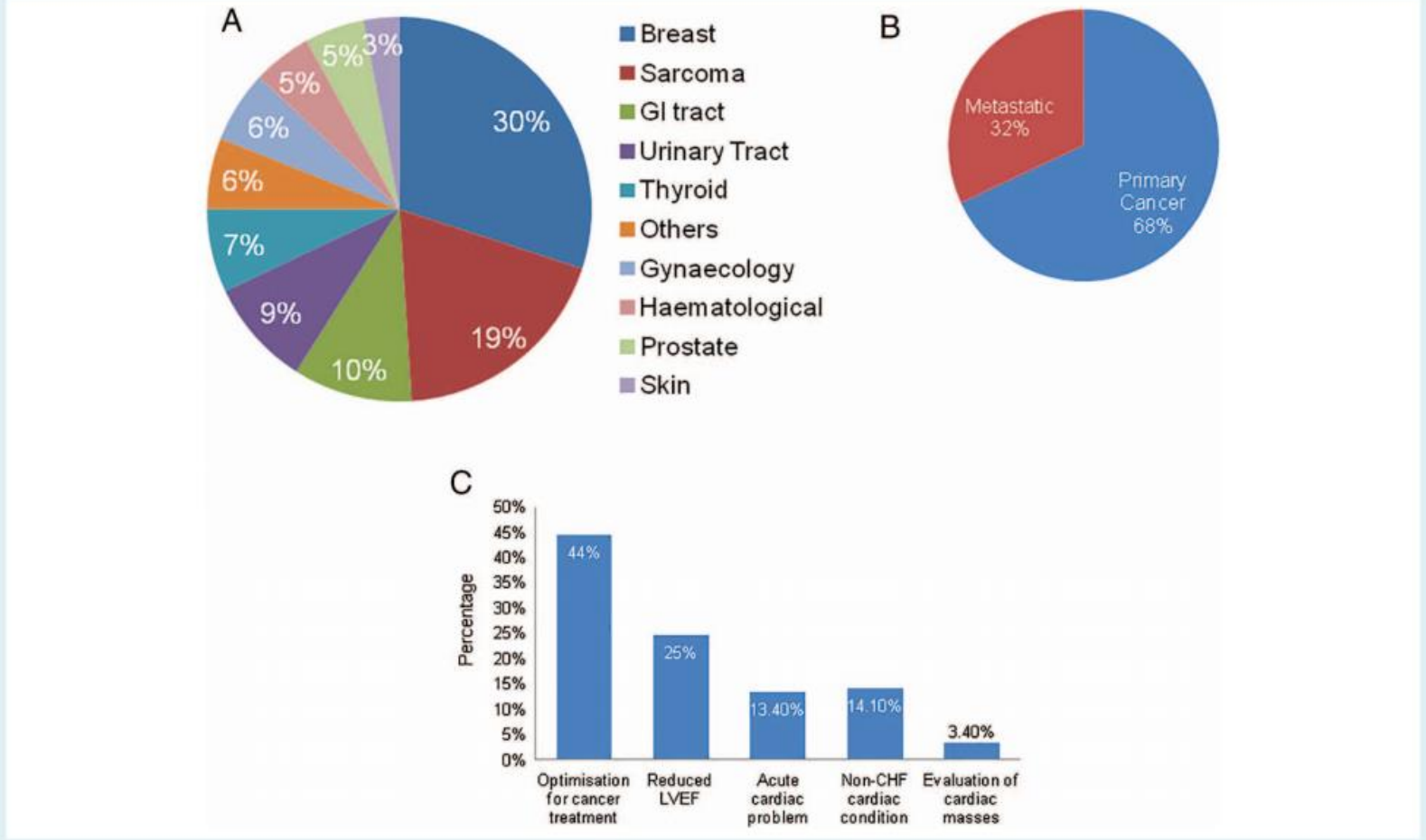


Figure 1 Study population cancer types and reasons for referral to the cardio-oncology service. (*A*) Types of primary cancers referred to our service. (*B*) Frequency of primary and metastatic cancers. (*C*) Reasons for referral to our service. CHF, congestive heart failure; GI, gastrointestinal; LVEF, left ventricular ejection fraction.

Pareek N, Lyon AR et al. Activity and outcomes of a cardio-oncology service in the United Kingdom-a five-year experience. Eur J Heart Fail. 2018 Dec;20(12):1721-1731.

5 years of activity in a cardio-oncology clinic

Table 2 **Management strategies and percentage of patients completing cardiotoxic cancer therapy according to Royal Brompton Hospital myocardial toxicity class**

Cardiotoxicity group	Classification	Definition	Management strategies	
			Oncology therapy	Cardiology therapy
1	Early biochemical cardiotoxicity	New BNP or troponin I rise but with normal cardiac imaging. (If normal at baseline, then any increase above the upper limit of normal. If abnormal at baseline, then 20% rise).	Continue	Cardio-oncology review. Consider closer monitoring, or start low-dose ACEI or BB cardioprotection.
2	Early functional cardiotoxicity	New reduction in GLS or grade III–IV diastolic dysfunction and normal biomarkers.	Continue	Cardio-oncology review. Consider closer monitoring, or start low-dose ACEI or BB cardioprotection.
3	Early mixed cardiotoxicity	Normal LVEF with abnormal biomarkers and GLS/diastolic dysfunction.	Continue	Cardio-oncology review. Start low-dose ACEI or BB cardioprotection.
4	Symptomatic HFpEF	Symptomatic HFpEF.	Interrupt and review risk/benefit*	Cardio-oncology review. Diuretic for fluid congestion. ACEI or BB cardioprotection if continuing cancer therapy.
5	Asymptomatic LVSD	New LVEF reduction to <50%, or a reduction in LVEF >10% to a LVEF <55%†.	Review and balance risk/benefit*	Cardio-oncology review. Start ACEI and/or BB and up-titrate to 50–100% target dose for HF as tolerated.
6	Symptomatic LVSD	Symptomatic reduction in LVEF <50%, or a reduction in LVEF >10% to a LVEF <55%†.	Interrupt and review risk/benefit*	Cardio-oncology review. Start ACEI and/or BB and up-titrate to 100% target dose for HF as tolerated‡#.

ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; BNP, brain natriuretic peptide; GLS, global longitudinal strain; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction.

*Continuing cardiotoxic cancer therapy may be suitable in selected cases depending on the risk/benefit ratio, severity of left ventricular impairment, symptoms, cancer stage and response.

†If LVEF fall is to >50%, then incorporate either biomarker elevation or GLS reduction (<−18% if normal at baseline, or <15% relative reduction of GLS if reduced at baseline).[11]

‡If ACEI or BB are not tolerated, or the patient is already taking these agents when cardiotoxicity is diagnosed, consider adding aldosterone antagonist.

#If LVEF <35% follow the European Society of Cardiology HF guidelines regarding eligibility for cardiac resynchronisation therapy, sacubitril/valsartan and ivabradine.

Pareek N, Lyon AR et al. Activity and outcomes of a cardio-oncology service in the United Kingdom-a five-year experience. Eur J Heart Fail. 2018 Dec;20(12):1721-1731.

5 years of activity in a cardio-oncology clinic

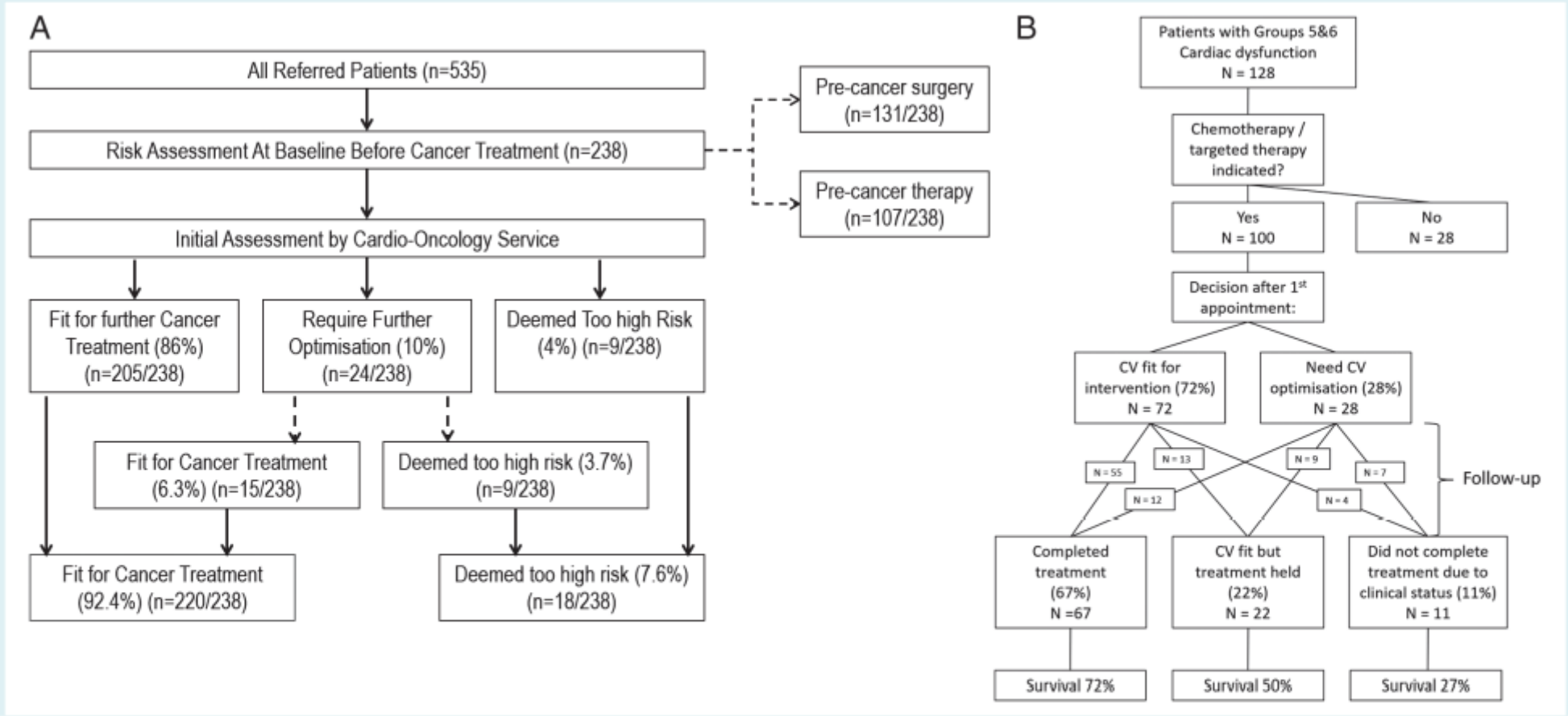


Figure 3 Diagrams of patient flows after assessment and optimisation by our service. (*A*) Diagram of decision making for patients referred for cardiovascular (CV) optimisation at baseline before current cancer treatment. (*B*) Diagram of decision making and outcome in patients with left ventricular systolic dysfunction (Groups 5 and 6 of our cardiac dysfunction classification) awaiting potential cardiotoxic therapy.

Pareek N, Lyon AR et al. Activity and outcomes of a cardio-oncology service in the United Kingdom-a five-year experience. Eur J Heart Fail. 2018 Dec;20(12):1721-1731.

Take Home Messages (1)

- *Cardio-oncology is an emerging field that focuses on the **management of cardiovascular disease at the time of cancer diagnosis, during cancer treatment and well beyond in cancer survivors**.*

- *There is a growing need in this field due to major improvements in cancer therapy and as a direct consequence the **rising numbers of cancer survivors at best and at the very least patients living with a chronic but well controlled cancer**.*

- ***Cancer and cardiovascular disease share common risk factors**. Among these factors traditional cardiovascular risk factors, especially when poorly controlled can not only disrupt cancer treatment but also these factors increase morbi-mortality in cancer survivors.*

- *The first step in cardioprotection is the **optimization of traditional cardiovascular risk factors**.*

Take Home Messages (2)

- *It is of paramount importance to **recognize patients at a higher risk of cardiotoxicity** in order to adequately utilize resources by :*
  - *determining an individualized cardioprotection strategy*
  - *and a personalized cardiovascular surveillance short term and long term strategy.*

- *The ultimate aim is to **increase cancer treatment completion rates, while at the same time minimising short term and long term cardiac collateral damage**.*
  - *Early detection of cardiotoxicity*
  - *Early management of cardiotoxicity*
  - *Minimizing treatment interruptions*

- *A **multidisciplinary approach** is key to success in the evaluation risk-benefit ratios in order to minimize cancer treatment interruptions and maximize survival rates.*

Coming soon !

Swiss Cardio-Oncology

Booklet 2021/22

European Heart Journal Advance Access published August 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

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

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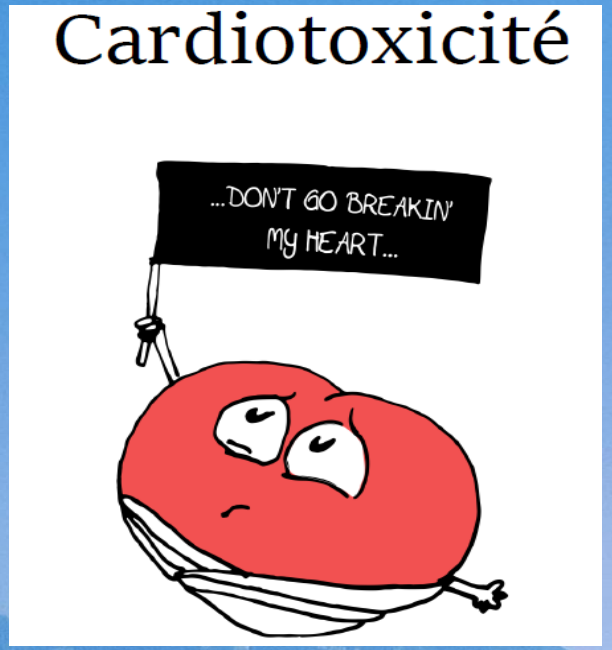
NEXT ESC GUIDELINES IN 2022

The end !



Today's cancer patients
are
tomorrow's cardiac patients

But

Today's cardiac patients
<u>should not be</u>
Tomorrow's cancer patients