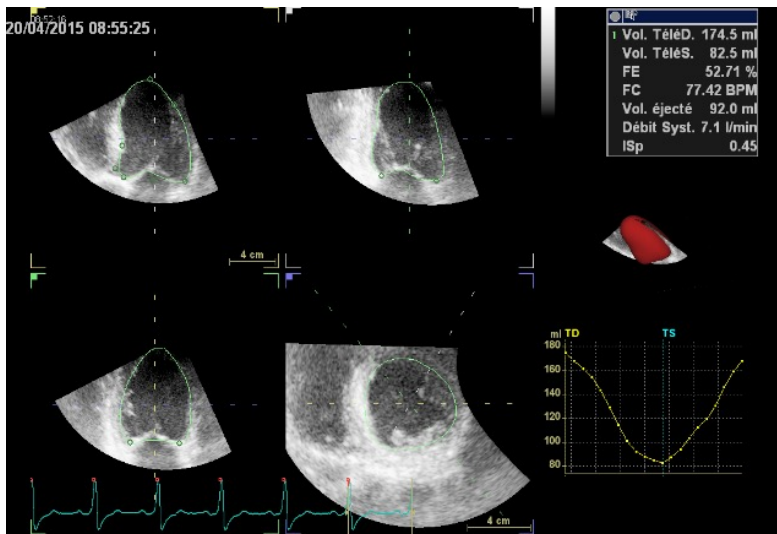




**Inserm**  
French Institute  
of Health and Medical Research



# Particularités de la prise en charge cardio-oncologique de l'enfant et jeune adolescent



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7 juin 2024

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Per thérapeutique

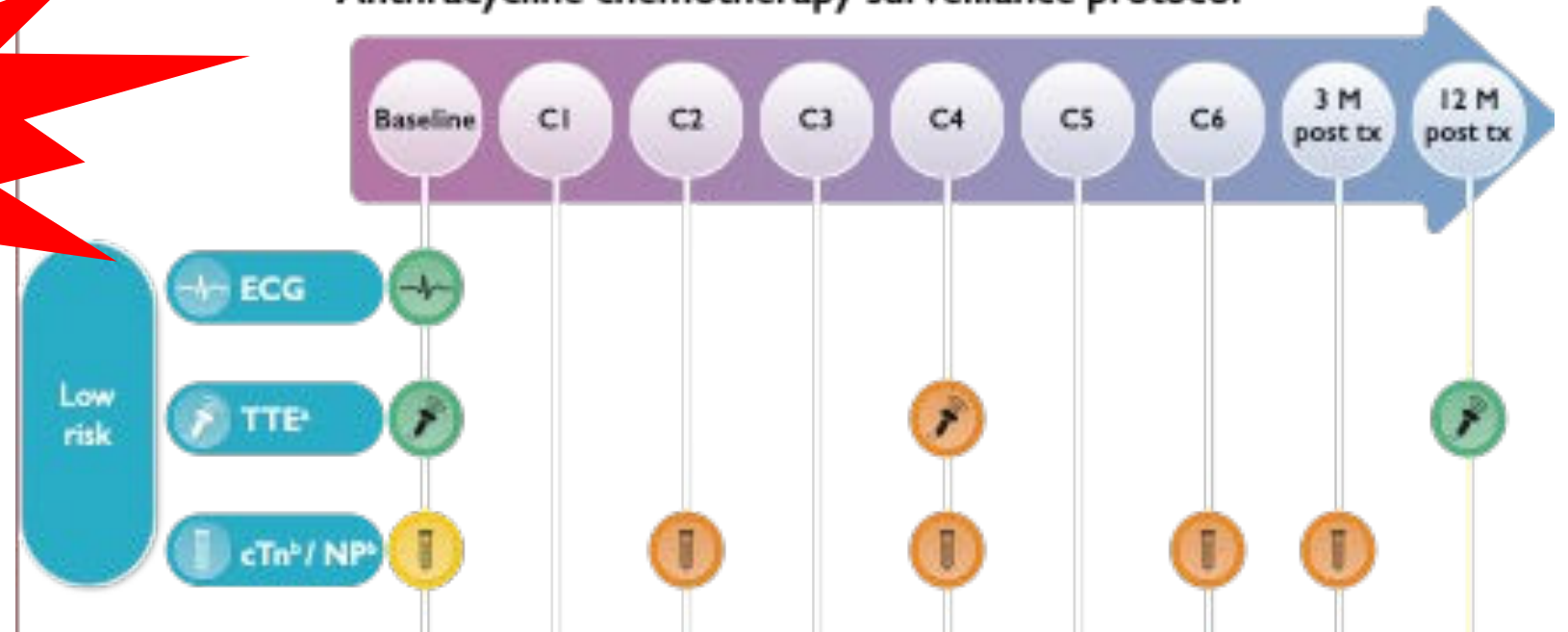
# Surveillance per-thérapeutique sous anthracyclines

## IC-OS stratification de risque

Baseline CV toxicity risk factors	Anthracycline chemotherapy
<b>Previous CVD</b>	
HF/cardiomyopathy	
Severe valvular disease	
MI or PCI	
Stent	
Arterial hypertension	
Albuminuria	
pressure index	
PH	–
Arterial thrombosis with TKI	–
Venous thrombosis (DVT/PE)	–
Arrhythmia <sup>a</sup>	–
QTc $\geq$ 480 ms	–
450 $\leq$ QTc < 480 ms (men);	–
460 $\leq$ QTc < 480 ms (women)	–
Prior PI CV toxicity	–
Prior IMiD CV toxicity	–

Non applicable chez les enfants

## Anthracycline chemotherapy surveillance protocol

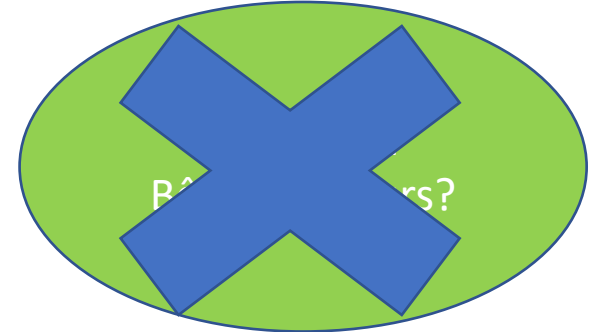


Rythme de surveillance chez les enfants/adolescents ?

# Quid de la prévention primaire cardiovasculaire?

Primary cardioprotection with dexrazoxane in patients with childhood cancer who are expected to receive anthracyclines: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Esmée C de Baat, MD • Elvira C van Dalen, PhD • Renée L Mulder, PhD • Prof Melissa M Hudson, MD • Matthew J Ehrhardt, MD • Frederike K Engels, PharmD • et al. [Show all authors](#) • [Show footnotes](#)



**Dexrazoxane en prévention primaire si la dose totale cumulée prévue d'équivalent doxorubicine  $\geq 250\text{mg}/\text{m}^2$**

THE LANCET  
Child & Adolescent Health



BASE DE DONNÉES PUBLIQUE  
DES MÉDICAMENTS

## 4.1. Indications thérapeutiques ↴

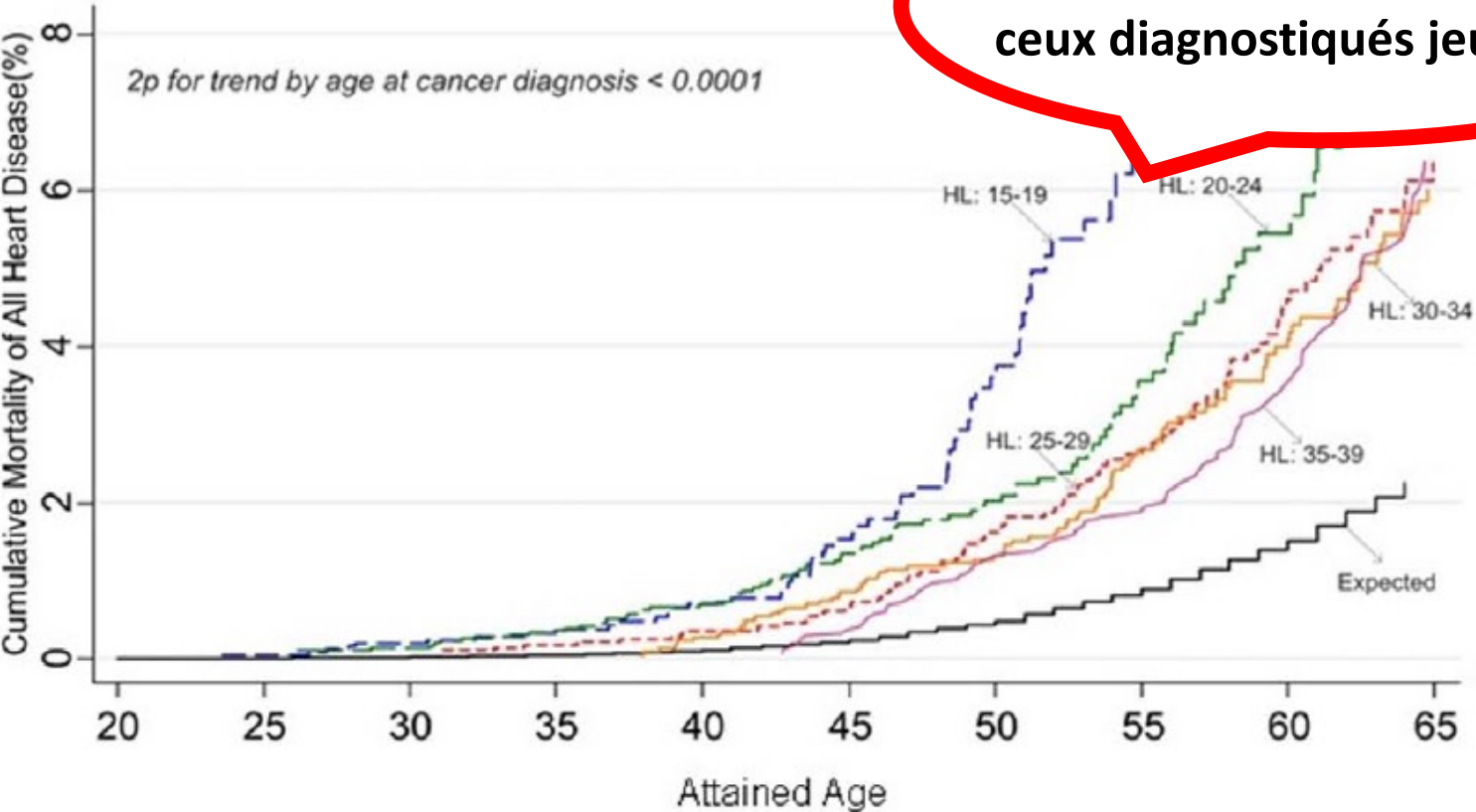
Cardioxane est indiqué chez les adultes pour la prévention de la cardiotoxicité chronique cumulative causée par l'administration d'anthracycline chez des patients atteints d'un cancer du sein avancé et/ou métastatique, ayant déjà reçu une dose cumulée antérieure de  $300\text{ mg}/\text{m}^2$  de doxorubicine ou de  $540\text{ mg}/\text{m}^2$  d'épirubicine, lorsqu'un autre traitement par une anthracycline est nécessaire.

A distance

# Cardiac Mortality Among 200 000 Five-Year Survivors of Cancer Diagnosed at 15 to 39 Years of Age

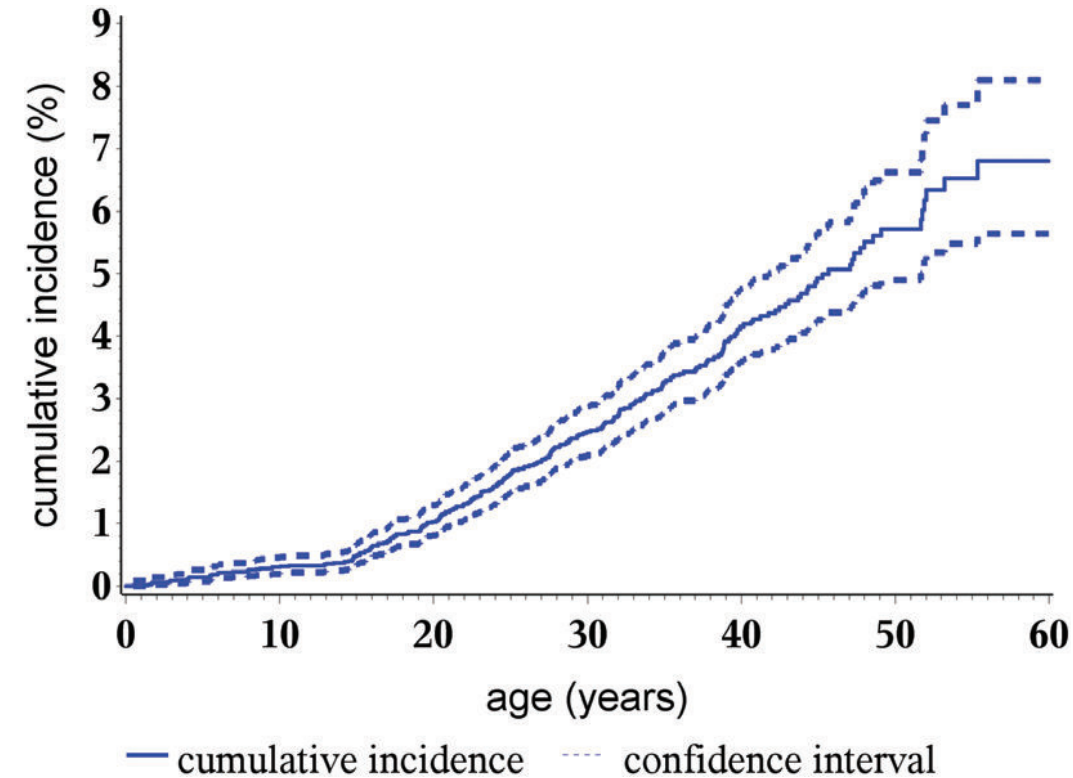
The Teenage and Young Adult Cancer Survivor Study

Mortalité CV: 7% à 60 ans chez ceux diagnostiqués jeunes



# The role of irradiated heart and left ventricular volumes in heart failure occurrence after childhood cancer

European Journal of Heart Failure (2018)  
doi:10.1002/ejhf.1376



- Nested case-control matched study
- Cases: 239; controls: 1024
- Mean age at HF diagnosis: 25.1 yo
- HF: symptomatic in 85% of which 17% had died of HF
- Majority: no heart valve or coronary artery disease
- Factors associated with HF:
  - Radiation dose to the heart
  - Heart volume >10% receiving >30Gy
  - Chemotherapy: anthracyclines (dose effects+++), alkylating agents

# Modèles prédictifs

Supplemental table 2. Validated risk prediction models for cardiotoxic events in long-term childhood cancer survivors.

	Chow et al 2015	Chow et al 2018	Chen et al 2020	Oikonomou 2018
<b>Outcome</b>	Heart failure at age 40	Ischemic heart disease at age 50	Heart failure and ischemic heart disease at age 50	Cardiovascular mortality
<b>Sample size</b>	Derivation: 13,060 Validation: 3,421	Derivation: 13,060 Validation: 3,204	Derivation: 7,076 Validation: 7,075	Derivation: 22,374 Validation: 6,437
<b>Prediction timepoint</b>	5 years after diagnosis	5 years after diagnosis	Age 20-35 years	5 years after diagnosis
<b>Predictor selection</b>	Stepwise backwards selection, based on p-value	Stepwise backwards selection on p-value	A priori	P<0.05 in multivariable Cox regression with 1000 bootstrap analysis
<b>Predictors</b>	<b>Female sex, age at cancer diagnosis, anthracycline dose, chest-RT dose</b>	<b>Male sex, chest-RT dose</b>	<b>Heart failure: Male sex, age at diagnosis, anthracycline dose, chest-RT dose, diabetes, dyslipidemia, hypertension</b>  <b>Ischemic heart disease: Female sex, chest-RT dose, diabetes, dyslipidemia, hypertension</b>	<b>Age at diagnosis, male sex, lymphoma history, any radiation, race</b>
<b>Discrimination</b>	C-statistic 0.68-0.82	C-statistic 0.66-70	C-statistic 0.69-0.70 (both events)	C-statistic: 0.75 derivation, 0.72 validation
<b>Calibration</b>	Not performed	Not performed	Good calibration	Not performed
<b>Validation</b>	External in another cohort	External in another cohort	Internal (split sample analysis)	Internal (split sample analysis)
<b>Clinical impact analysis</b>	Not performed	Not performed	Not performed	Not performed

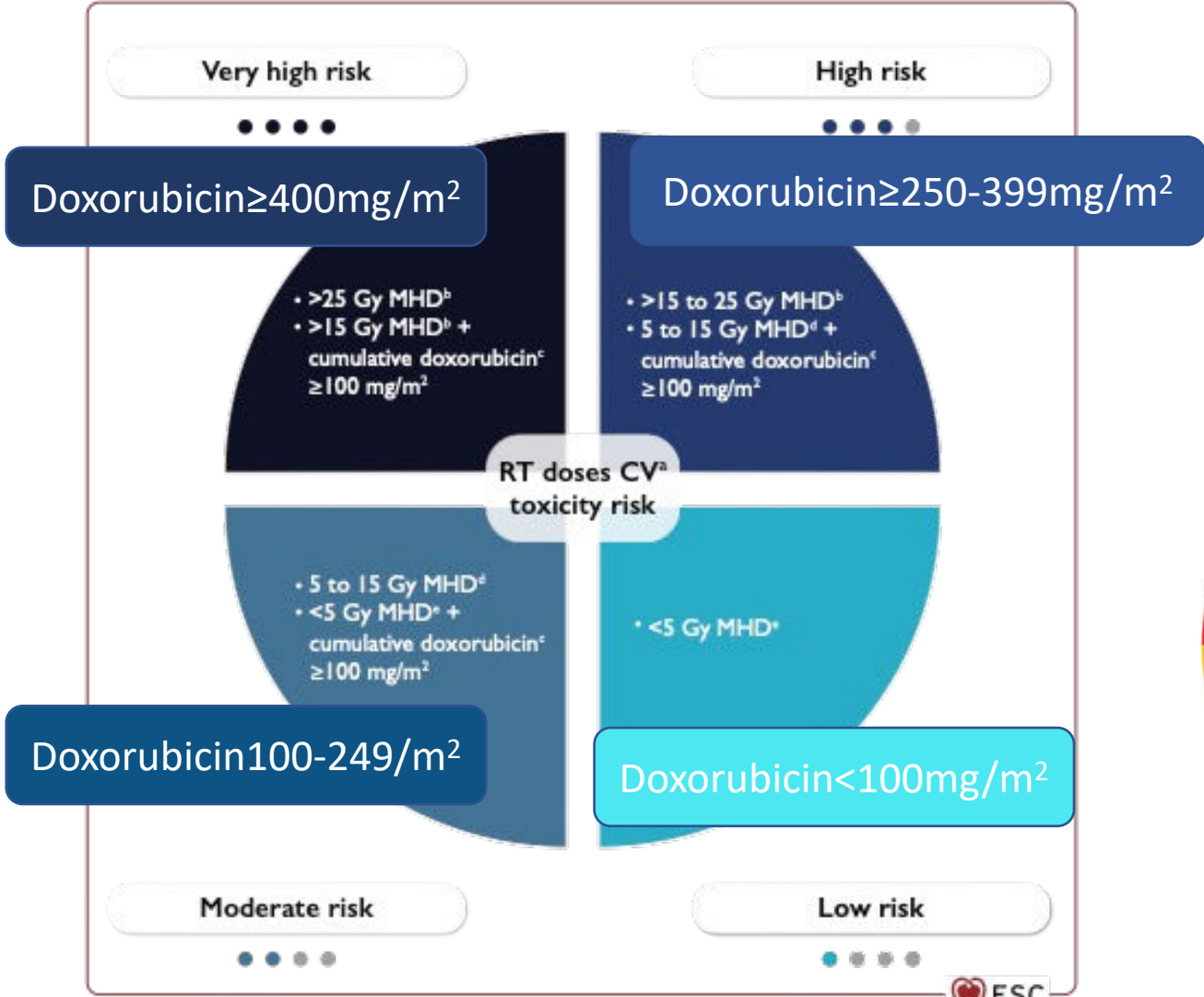
Age au diagnostic

Dose anthracyclines

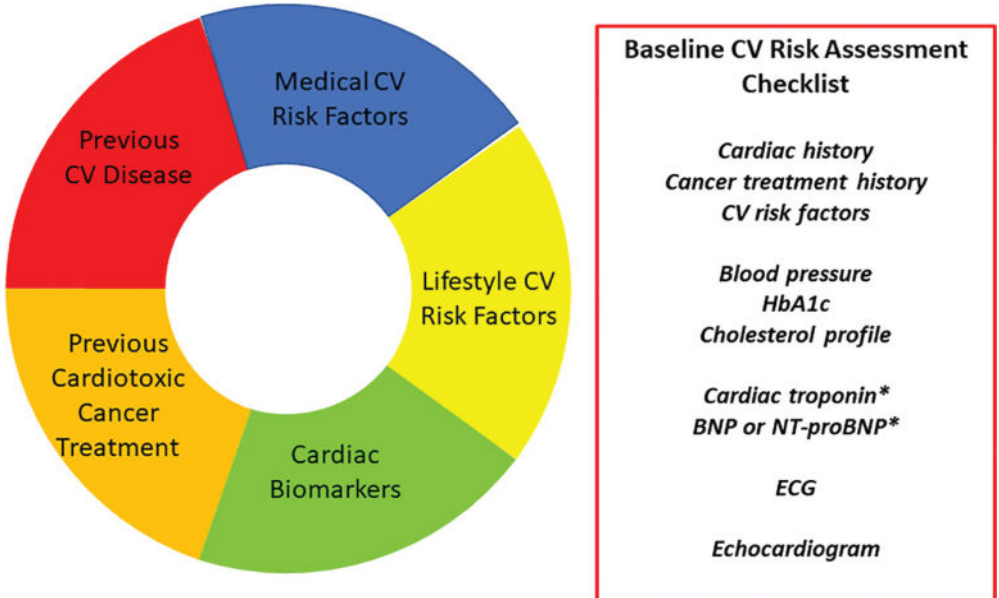
Dose radiothérapie



# Stratification du risque de cardio-toxicité

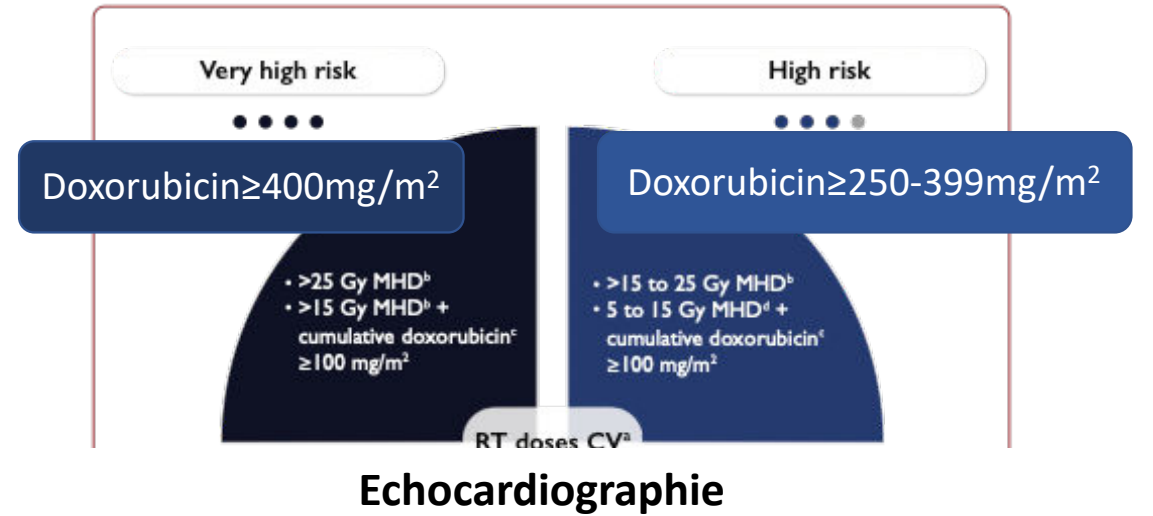
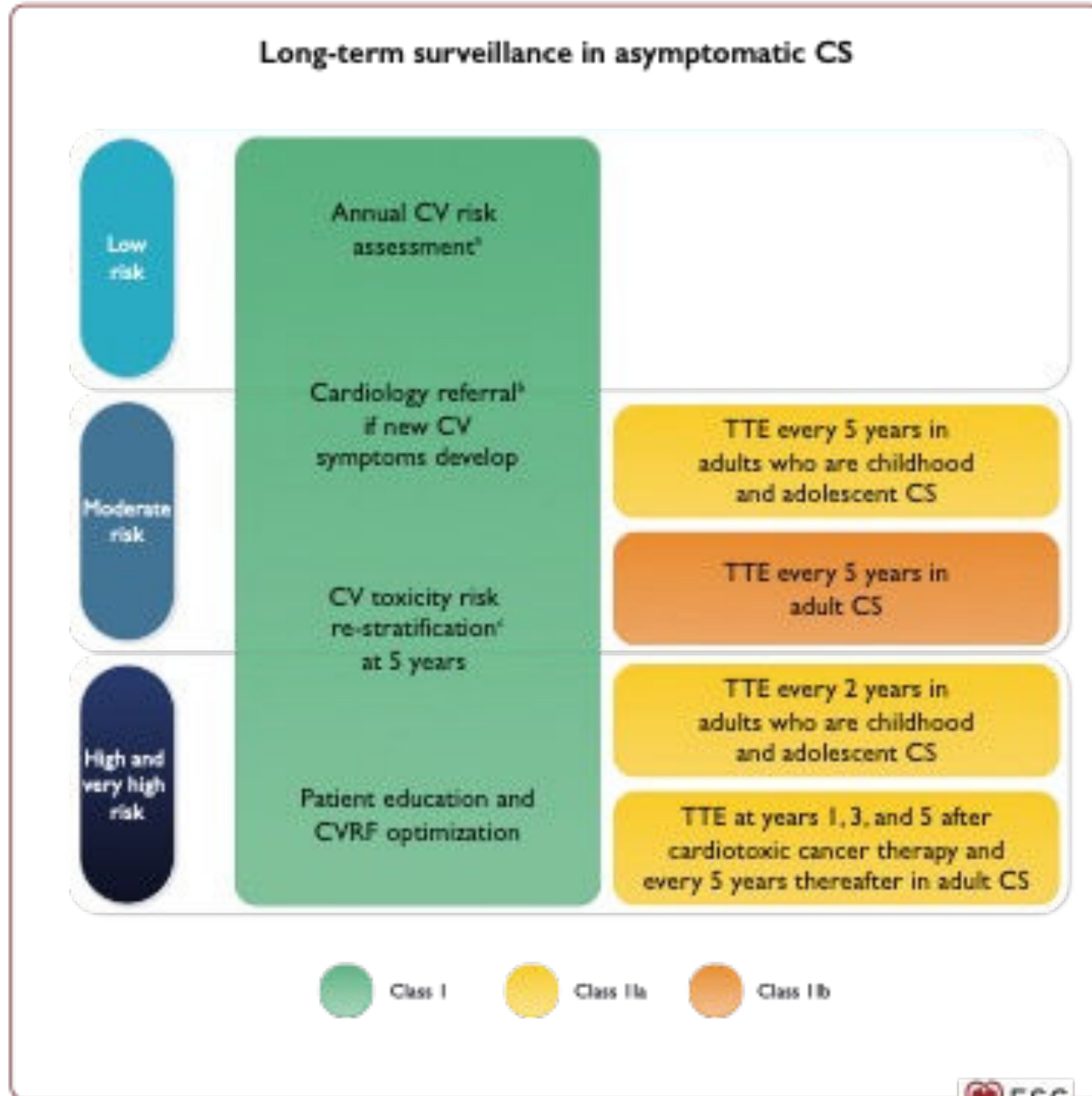


Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society



Lyon et al. Eur Heart Fail J 2020

# Suivi à vie



→ Tous les 5 ans si faible risque

→ Tous les 2 ans si haut risque

**Ne pas oublier la prévention primaire, en luttant contre : l'obésité, la sédentarité, le tabagisme, l'HTA, le diabète**

# Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group

*Lancet Oncol 2023*

Matthew J Ehrhardt\*, Jan M Leerink\*, Renée L Mulder, Annelies Mavinkurve-Groothuis, Wouter Kok, Anju Nohria, Paul C Nathan, Remy Merks, Esmée de Baat, Ogechukwu A Asogwa, Roderick Skinner, Hamish Wallace, E A M Lieke Feijen, Maëlle de Ville de Goyet, Maya Prasad, Edit Bárdi, Vesna Pavasovic, Helena van der Pal, Brice Fresneau, Charlotte Demoor-Goldschmidt, Ulrike Hennewig, Julia Steinberger, Chris Plummer, Ming Hui Chen, Arco J Teske, Nadia Haddy, Elvira C van Dalen, Louis S Constine, Eric J Chow, Gill Levitt, Melissa M Hudson, Leontien C M Kremert, Saro H Armenian†

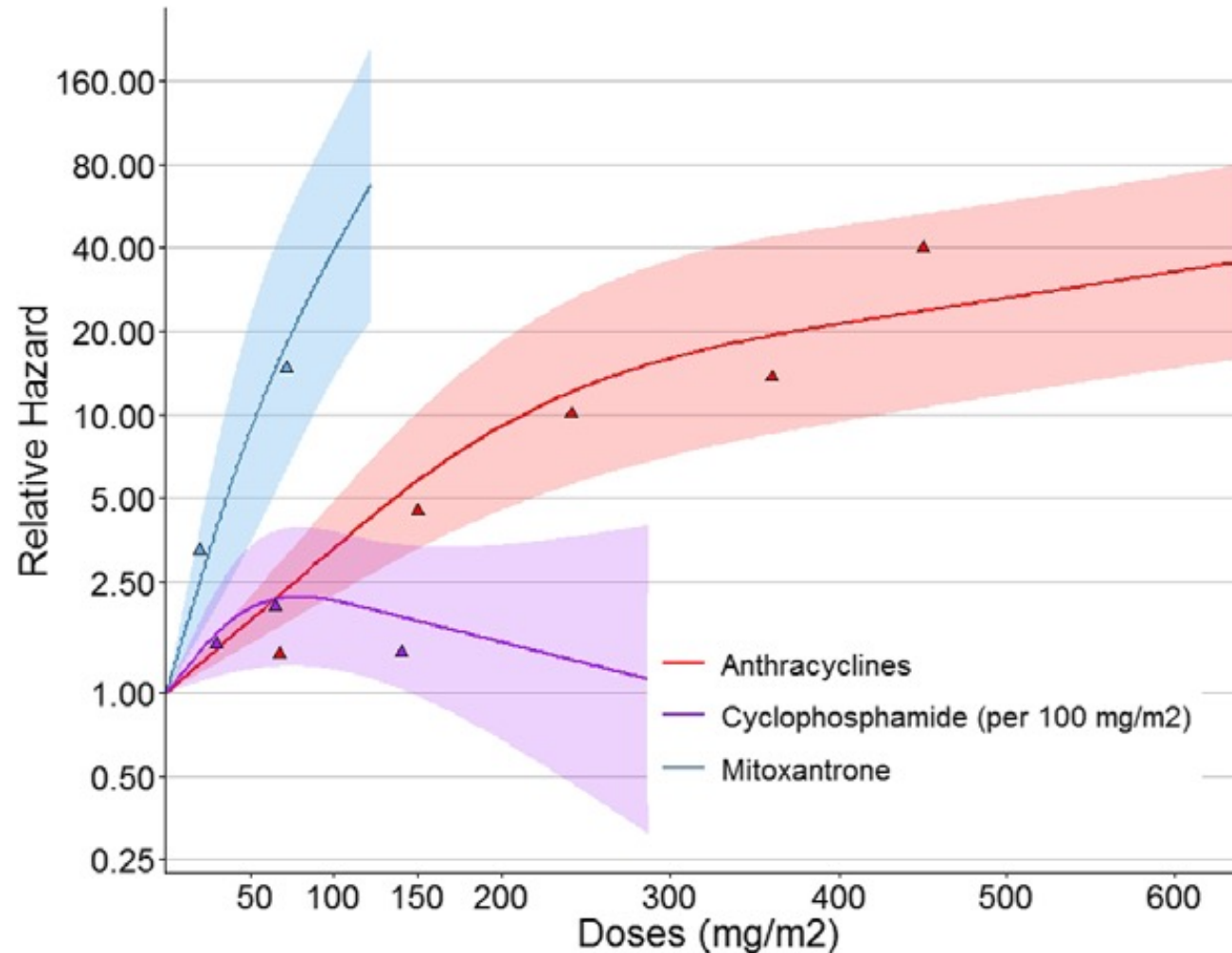
	Echocardiography (3D or 2D LVEF)	CMR	Blood biomarkers
High risk (anthracyclines $\geq 250$ mg/m <sup>2</sup> , chest-directed radiotherapy $\geq 30$ Gy, or a combination of anthracyclines $\geq 100$ mg/m <sup>2</sup> and chest-directed radiotherapy $\geq 15$ Gy)	+ High risk of heart failure (>3.5 times) + Widely available, cheap, and cost-effective at 2-year intervals – Reasonable agreement with CMR*	+ High risk of heart failure (>3.5 times) + High reproducibility, cost-effective at 5-year intervals – Costs, availability, wide use, interpretability by non-specialists, and burden for survivors	– Poor diagnostic value of biomarkers
Moderate risk (anthracyclines 100–249 mg/m <sup>2</sup> , or chest-directed radiotherapy 15–29 Gy, no combined treatment)	+ Risk of heart failure (>1.6 times) + Widely available, cheap, cost-effective at 5-year intervals – Reasonable agreement with CMR*	+ Risk of heart failure (>1.6 times) + High reproducibility, cost-effective at 10-year intervals – Costs, availability, wide use, interpretability by non-specialists, and burden for survivors	– Poor diagnostic value of biomarkers
Low risk (anthracyclines $< 100$ mg/m <sup>2</sup> and chest-directed radiotherapy <15 Gy)	– No increased risk of heart failure	– No increased risk of heart failure	– No increased risk of heart failure

X

The balance between desirable and undesirable consequences is closely balanced or uncertain    + Balance of benefits  
 Desirable consequences clearly outweigh undesirable consequences in most settings    – Balance of harms  
 Undesirable consequences clearly outweigh desirable consequences in most settings  
 Desirable consequences probably outweigh undesirable consequences in most settings

# Insuffisance cardiaque: au -delà des anthracyclines et de la radiothérapie

Risk and Temporal Changes of Heart Failure Among 5-Year Childhood Cancer Survivors: a DCOG-LATER Study



# Au-delà de l'insuffisance cardiaque: coronaropathie

Coronary artery disease surveillance among childhood, adolescent and young adult cancer survivors: A systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group

European Journal of Cancer 156 (2021) 127–137

Concordances and discordances among existing guidelines for CAYA cancer survivors.<sup>a</sup>

	North American Children's Oncology Group [9]	Dutch Childhood Oncology Group [10]	Scottish Intercollegiate Guidelines Network [11]	UK Children's Cancer and Leukaemia Group [12]	Concordant/discordant
<b>Who needs surveillance?</b>					
<b>Anthracyclines</b>	No	No	No	No	Concordant
<b>Mitoxantrone</b>	No	No	No	No	Concordant
<b>Radiotherapy exposing the heart</b>	Yes	Yes	Yes	Yes	Concordant
<b>Higher risk</b>	Radiation dose $\geq 20$ Gy to chest; TBI; combined with radiomimetic chemotherapy (e.g. doxorubicin, dactinomycin); combined with other cardiotoxic chemotherapy (anthracyclines, cyclophosphamide conditioning for HCT, amsacrine)	Not specified	$\geq 30$ Gy radiotherapy exposing the heart; minimal protective cardiac blocking and younger age at irradiation	Not specified	Discordant
<b>Highest Risk Factors</b>	Anteriorly weighted radiation fields; lack of subcarinal shielding; doses $\geq 30$ Gy in patients who have received anthracyclines; doses $\geq 40$ Gy in patients who have not received anthracyclines; longer time since treatment	Not specified	Not specified	Not specified	Discordant
<b>What surveillance modality should be used?</b>					
<b>ECG</b>	Yes	Yes	No	No	Discordant
<b>Modifiable risk factors</b>	Yes	Yes	Yes	Yes	Concordant
<b>At what frequency should surveillance be performed?</b>					
<b>ECG</b>	Baseline at entry LTFU, repeat as clinically indicated	Baseline at 5 years following diagnosis, repeat if clinical concerns	–	–	Discordant

Risque de coronaropathie:

- $\geq 15$ Gy dose moyenne;
- Absence d'association : chimiothérapies (anthracyclines ou mitoxantrone)

Conduite à tenir: Clinique + ECG

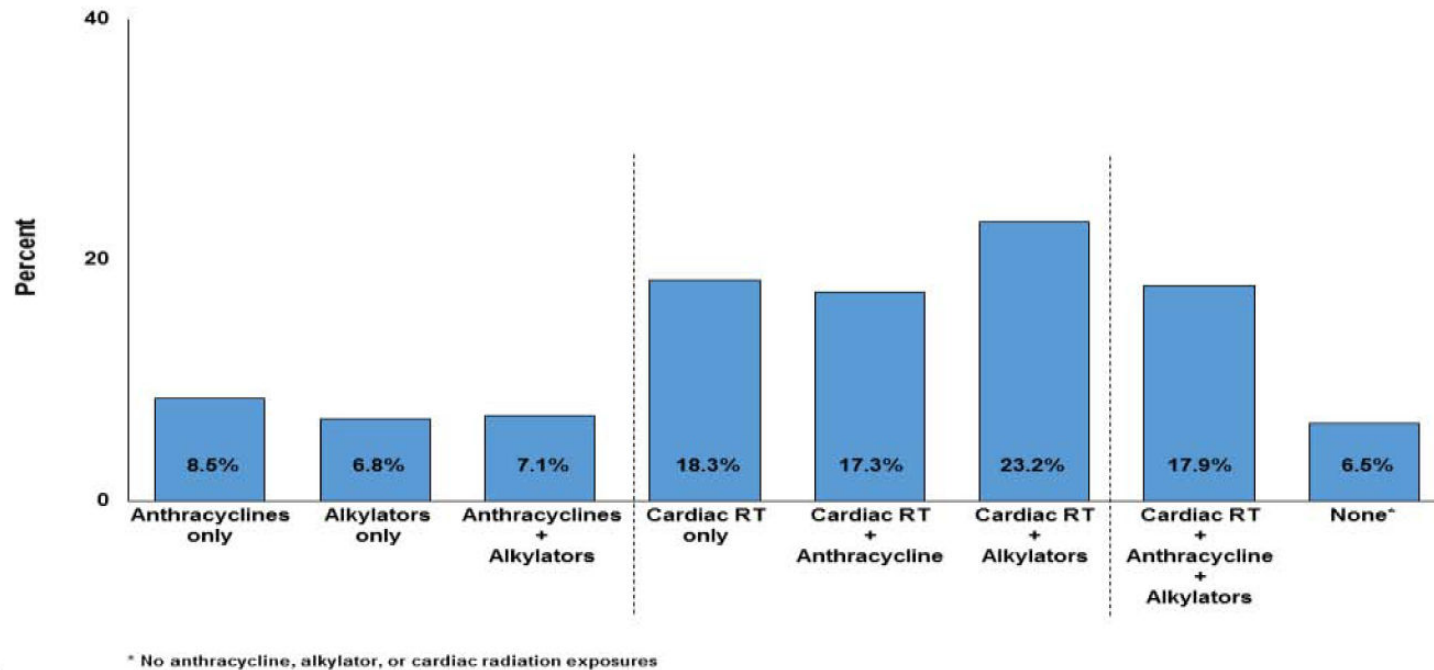
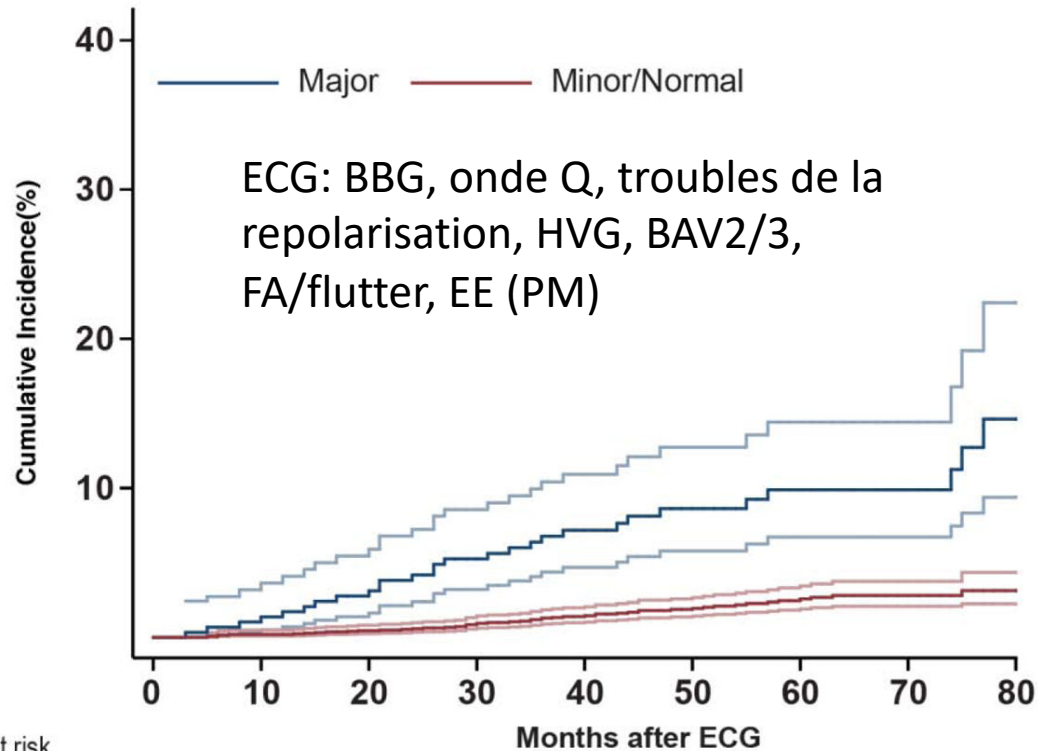
Le cofacteur significatif: HTA

# L'ECG: prédictif de mortalité toutes causes

## Electrocardiographic Abnormalities and Mortality in Aging Survivors of Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study

*Am Heart J.* 2017 July ; 189: 19–27. doi:10.1016/j.ahj.2017.03.023.

Incidence de mortalité toutes causes

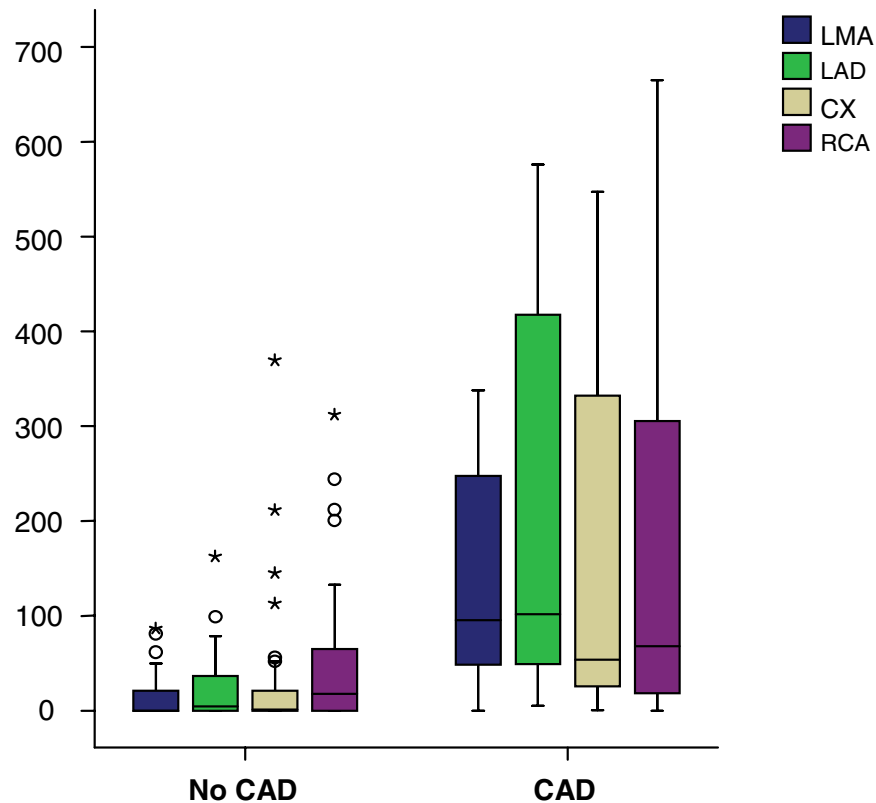


Parmi les 80 décès: 13 d'origine cardiovasculaire

Pourcentage ayant des anomalies ECG majeures selon modalités thérapeutiques oncologiques

# Relation of Coronary Artery Calcium Score to Premature Coronary Artery Disease in Survivors >15 Years of Hodgkin's Lymphoma

*The American Journal of Cardiology*

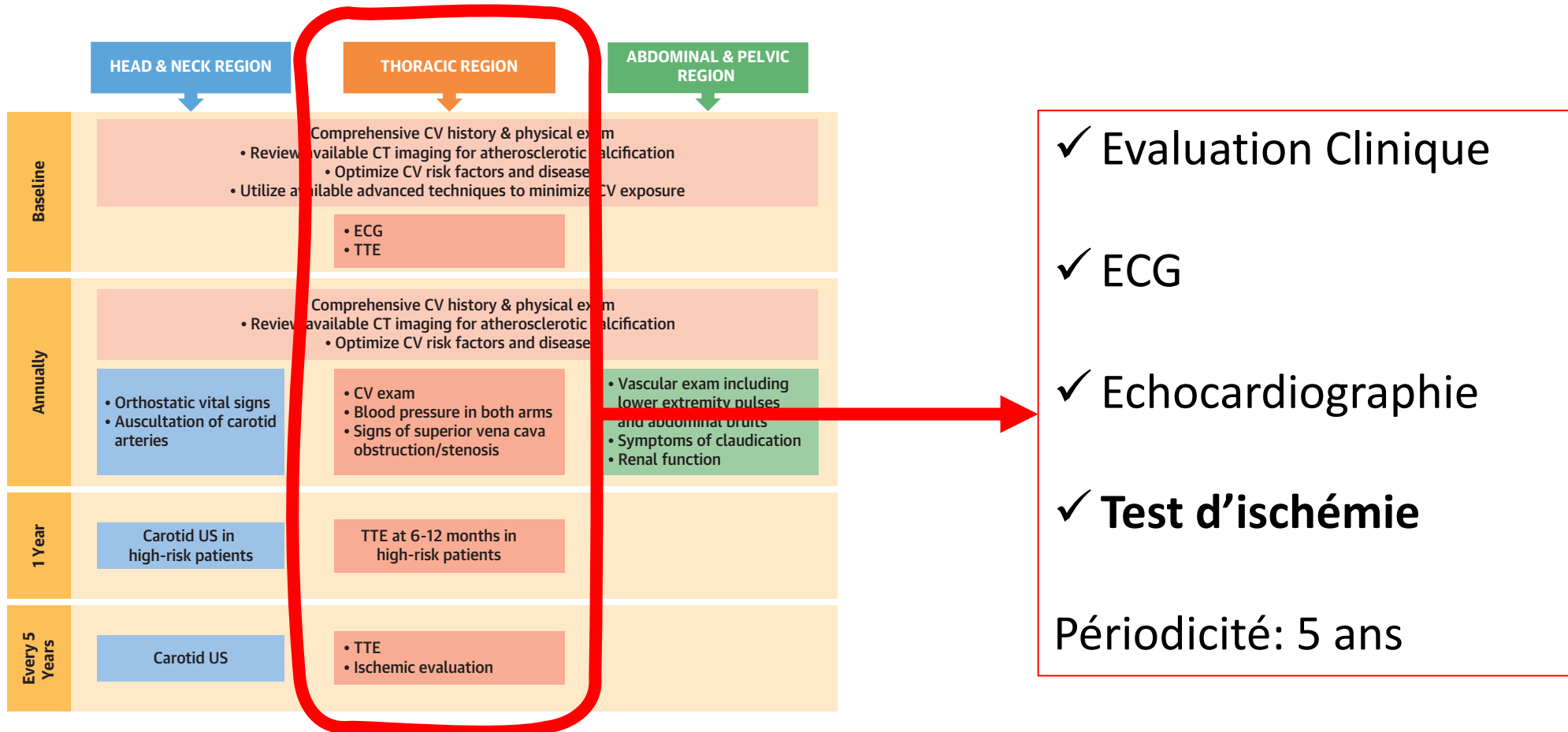


CAC Score (volume score)	HL Survivors With No Signs or Symptoms of CAD	HL Survivors With Documented CAD	Percentage With Documented CAD
0	8	0	0
1-199	27	2*	7
200-999	5	3	38
≥1,000	0	2	100

**Score calcique (volume): bonne valeur prédictive négative dans une population dont le seul facteur de risque est la RT et CT antérieure**

# Suivi après radiothérapie médiastinale

## International Cardio-Oncology Society guidelines

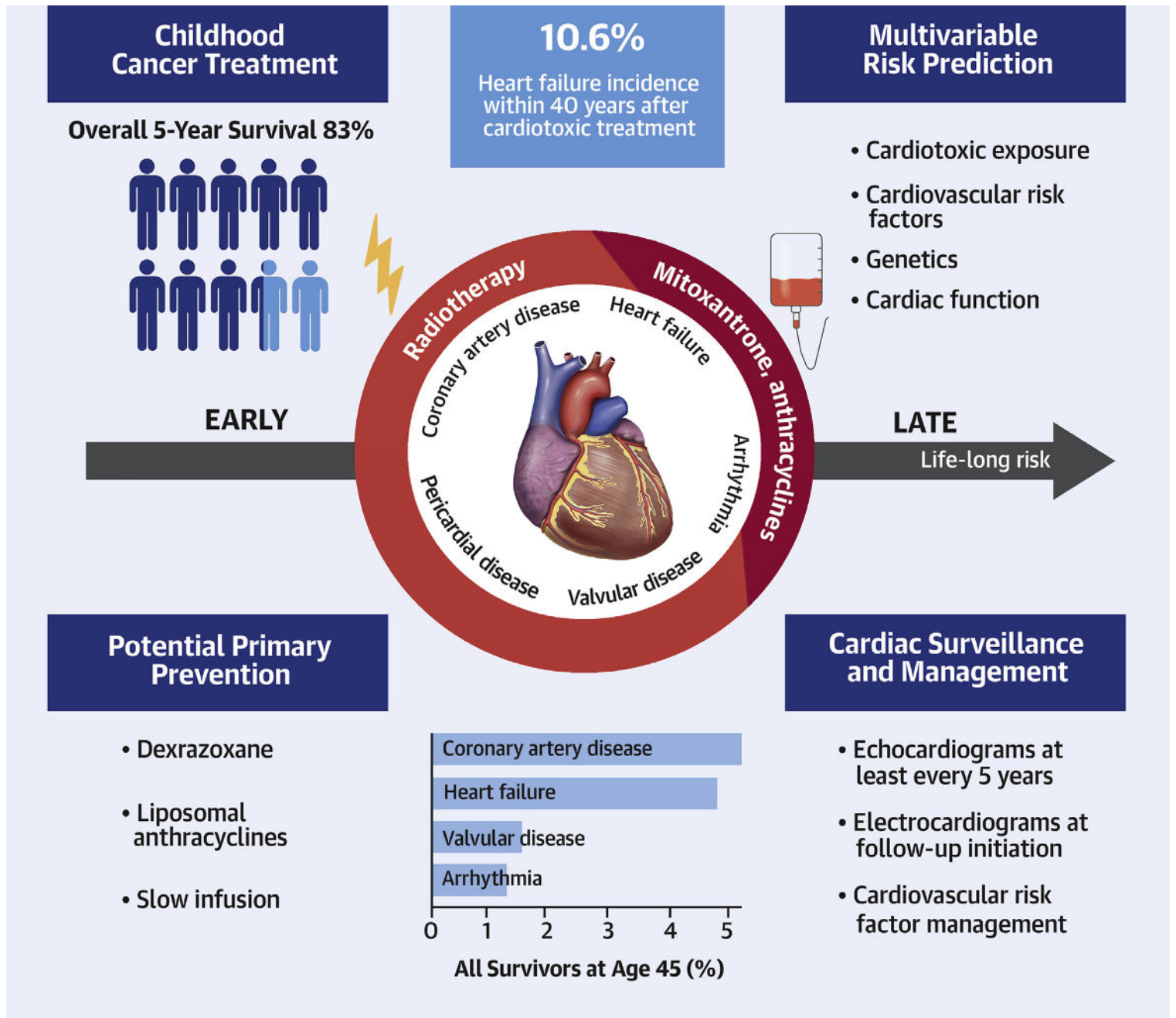




# Conclusions

## Surveillance

- Education
  - Choix oncologiques: réduction des doses, dexrazoxane
  - Prévention CV 1<sup>aire</sup> : HTA+++
  - Biomarqueurs:
    - Echocardiographie
    - ECG
    - Echocardiographie d'effort?
    - Score calcique coronaire?
  - Périodicité de l'échocardiographie:
    - /5 ans risque intermédiaire
    - /2 ans si haut risque
    - A priori non chez faible risque
- Ehrhardt et al. Lancet Oncol 2023*





Merci!

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