AZERBAIJAN CARDIOLOGY FESTIVAL

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13 DECEMBER, 2024, BAKU

Heart failure in cancer patients — a problem of the 21-st century. Common pathogenesis and approaches to treatment

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IC-OS
International Cardio-Oncology Society

European Heart Journal (2016) 37, 2768–2801
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)

Authors/Task Force Members: Jose Luis Zamorano* (Chairperson) (Spain), Patrizio Lancellotti* (Co-Chairperson) (Belgium), Daniel Rodriguez Muñoz (Spain), Victor Aboyans (France), Riccardo Asteggiano (Italy), Maurizio Galderisi (Italy), Gilbert Habib (France), Daniel J. Lenihan† (USA), Gregory Y. H. Lip (UK), Alexander R. Lyon (UK), Teresa Lopez Fernandez (Spain), Dania Mohty (France), Massimo F. Piepoli (Italy), Juan Tamargo (Spain), Adam Torbicki (Poland), and Thomas M. Suter (Switzerland)

ESC European Society of Cardiology

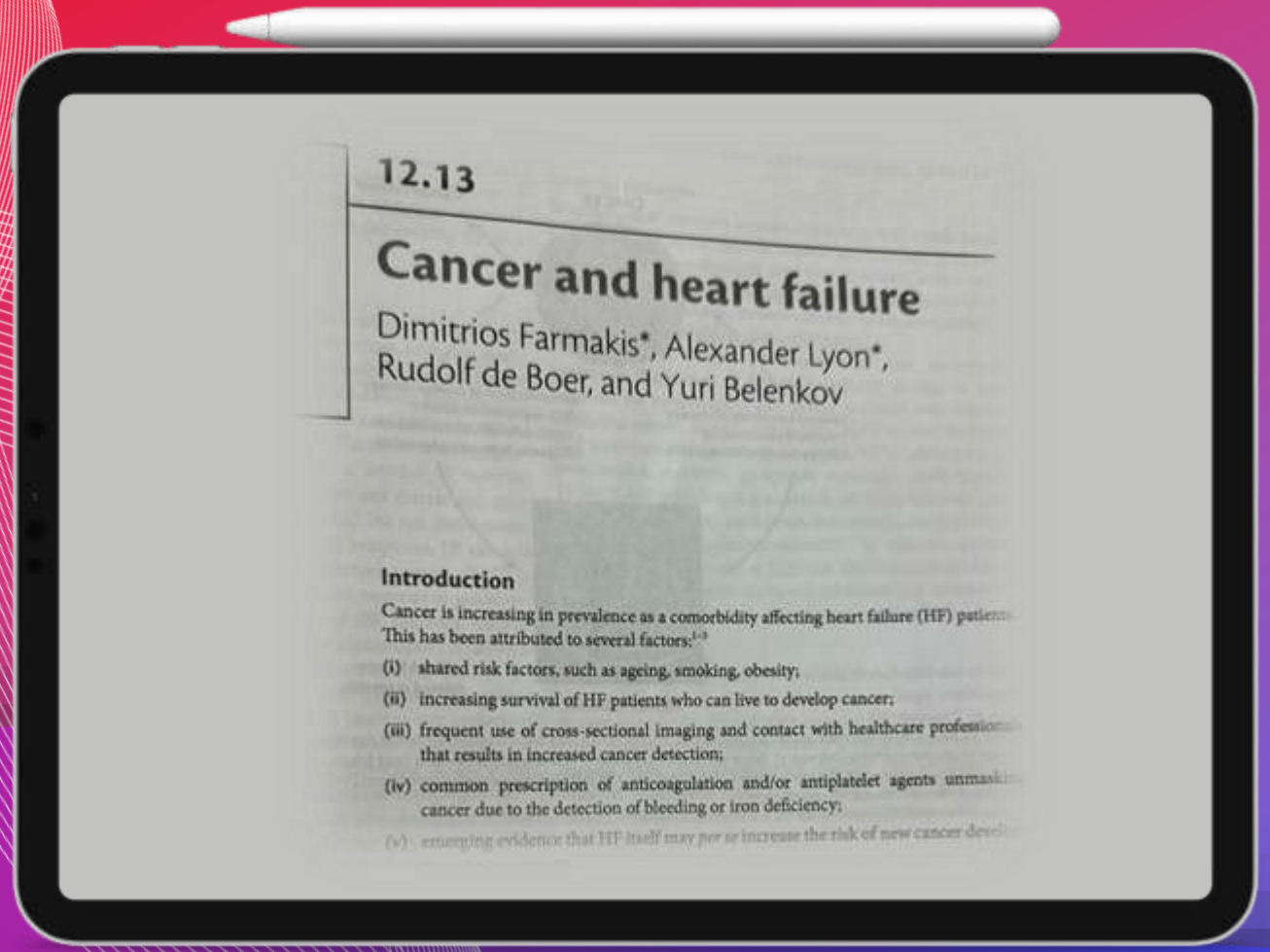
European Heart Journal (2022) 00, 1–133
https://doi.org/10.1093/eurheartj/ehac244

ESC GUIDELINES

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

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

A unique edition.
Fundamental work on heart failure 2023



12.13

Cancer and heart failure

Dimitrios Farmakis*, Alexander Lyon*,
Rudolf de Boer, and Yuri Belenkov

Introduction

Cancer is increasing in prevalence as a comorbidity affecting heart failure (HF) patien
This has been attributed to several factors:[1–3]

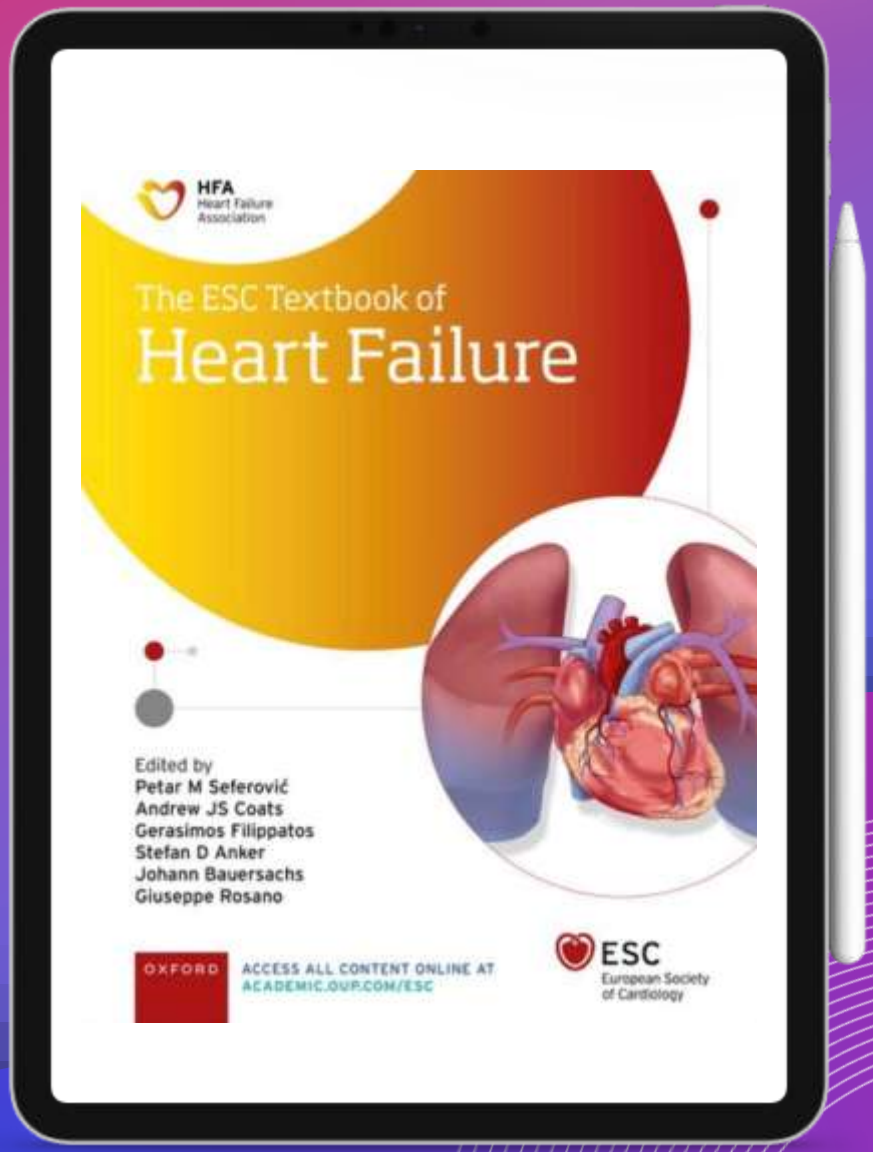
(i) shared risk factors, such as ageing, smoking, obesity;

(ii) increasing survival of HF patients who can live to develop cancer;

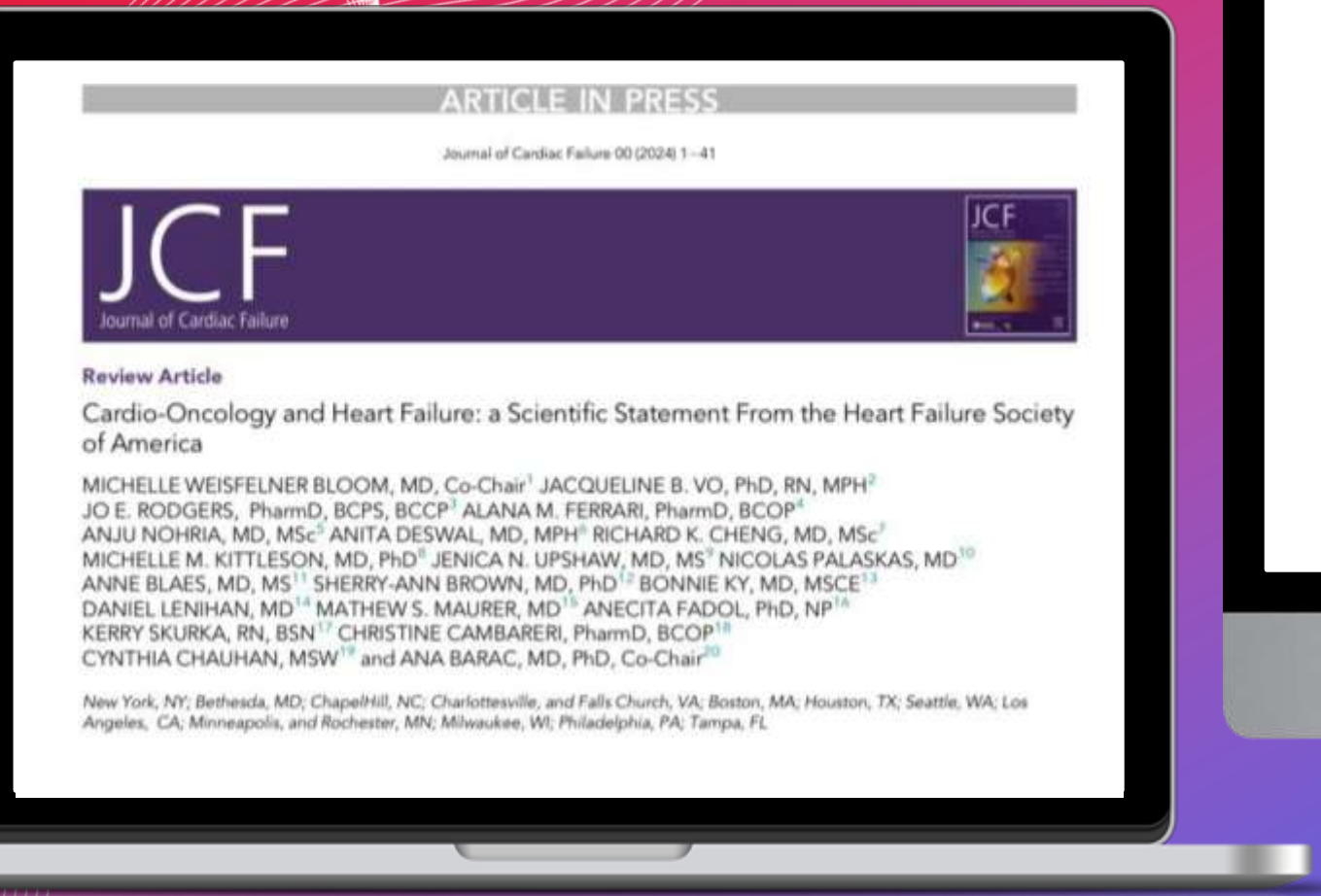
(iii) frequent use of cross-sectional imaging and contact with healthcare profession
that results in increased cancer detection;

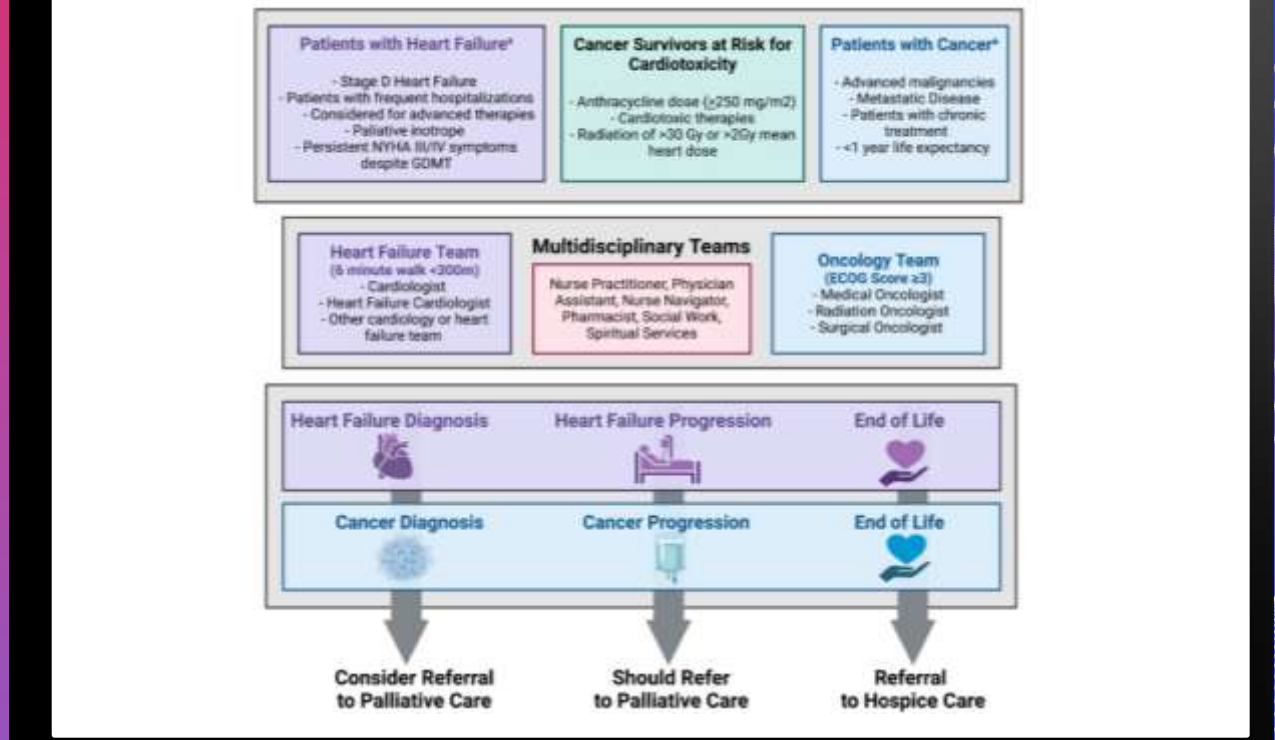
(iv) common prescription of anticoagulation and/or antiplatelet agents unmask
cancer due to the detection of bleeding or iron deficiency;

(v) emerging evidence that HF itself may per se increase the risk of new cancer devel



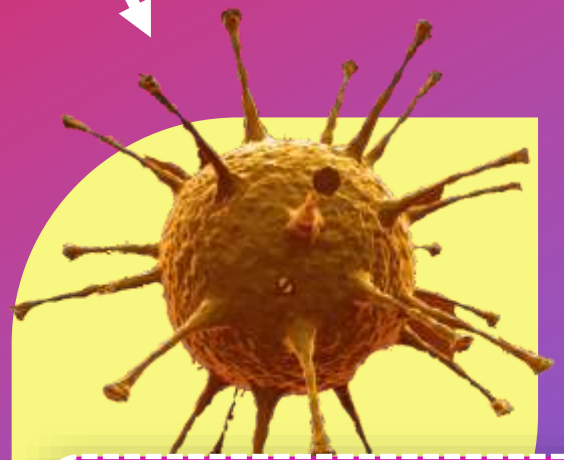
Scientific Statement from the Heart Failure Society of America 2024.





Cardiotoxicity

Chemotherapy (Anthracycline cardiomyopathy)



Oncological process

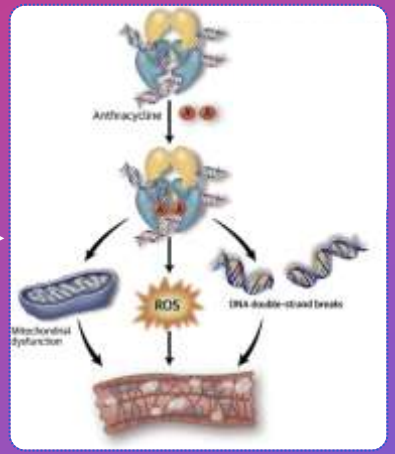
Radiation therapy

Specific antitumor therapy (polychemotherapy/radiation therapy)

Endothelial dysfunction (inhibition of proliferation and migration, apoptosis)

Cytokine imbalance (↑ TNF-α, TGF-β1, IL-1, IL-6)

Structural changes in cardiomyocytes (direct cardiotoxic effect, apoptosis)



Remodeling of the vascular wall, Including the microcirculatory bed

Vasculotoxicity

Myocardial remodeling

Cardiotoxicity

Tocchetti C.G. et al, Cardiovasc Res, 2020

McDonagh TA, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023 Aug 25:ehad195. doi: 10.1093/eurheartj/ehad195

Clinical manifestations of cardio-vasculotoxicity

1. Myocardial dysfunction and heart failure
2. Atherosclerosis of the coronary arteries
3. Valve diseases
4. Arrhythmias and long QT syndrome
5. Arterial hypertension
6. Thrombo-embolic conditions
7. Peripheral arterial disease
8. Pulmonary hypertension
9. Pericardial lesions

Zamarano et al. EHJ. 2016

Cardio-Oncology Balance

Opposite Pathophysiology

CANCER

- Cell division
- Increased cell number
- Angiogenesis
- Increased metabolic activity
- Drug/toxin resistance

Heart failure

- Failure of cell division/ tissue repair
- Cell loss
- Ischaemia
- Impaired/decreased energetic efficiency
- Increased sensitivity to toxins

Cardio-Oncology Balance
Shared Pathophysiological Mechanisms

Oxidative stress
Predisposes to myocardial dysfunction and has an important role in cancer growth and progression

Chronic systemic inflammation
Impairs the immune system and increases susceptibility to various non-communicable diseases

Cardiac secreted factors
Circulating soluble factors produced by the diseased heart might accelerate tumour growth

Clonal haematopoiesis of indeterminate potential
A causal factor that promotes chronic inflammation

Cellular senescence
An ageing-related process that leads to cell-cycle arrest, which might be accelerated by shared risk factors, cancer therapy-related toxicity and cancer itself, leading to CVD

Gut microbial dysbiosis
Associated with atherosclerosis, thrombosis and inflammation in CVD, and with increased cell turnover, genotoxic metabolite production, impaired immune surveillance and chronic inflammation in cancer

Shared mechanisms of CVD and cancer

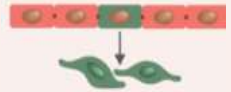
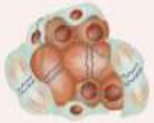
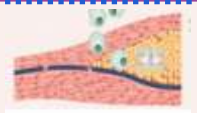
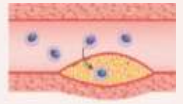
Hormonal effects
Imbalances in endogenous sex hormones and adverse effects of endocrine therapy for cancer are associated with adverse cardiovascular sequelae

Metabolic dysregulation
Altered metabolism in cancer cells extends beyond the tumour microenvironment, leading to the production of circulating oncometabolites and adverse cardiovascular remodelling

Wilcox et al Nature Reviews Cardiology

Chronic pro-inflammatory status: shared pathophysiological pathways

Cancer

Epithelial-mesenchymal transition		TGF-β, ↓FGF, VEGF		Epithelial-mesenchymal transition
Cancer and stromal cell proliferation		Oncogenes, proto-oncogenes (c-sis/PDGF), and dysregulated tumor supressors		Smooth muscle cell and macrophage proliferation
Dysregulated cell death		Bcl-2, NFkB, Mertk, CD47		Dysregulated cell death, defective efferocytosis
Leukocyte infiltration: innate and adaptive		Cytokines → adhesion molecules, chemokines		Leukocyte infiltration: innate and adaptive
Tumor angiogenesis, defective endothelial barrier function		Vascular endothelial growth factor (VEGF)		Plague angiogenesis, defective endothelial barrier function
Extracellular matrix remodeling (tumor expansion)		Interstitial collagenases (MMP-1, -8, -13), Elastases (MMP-12, Cathepsins S, L, K)		Extracellular matrix remodeling (compensatory enlargement)
Invasion and metastasis		Type IV collagenases (MMP-2), Interstitial collagenases (MMP-1,-8,-13)		Rupture and erosion

CVD

Libby P., Kobold S., CV Res, 2019

The link between heart failure and cancer risk factors

Common risk factors (smoking, diet, obesity, poor lifestyle)

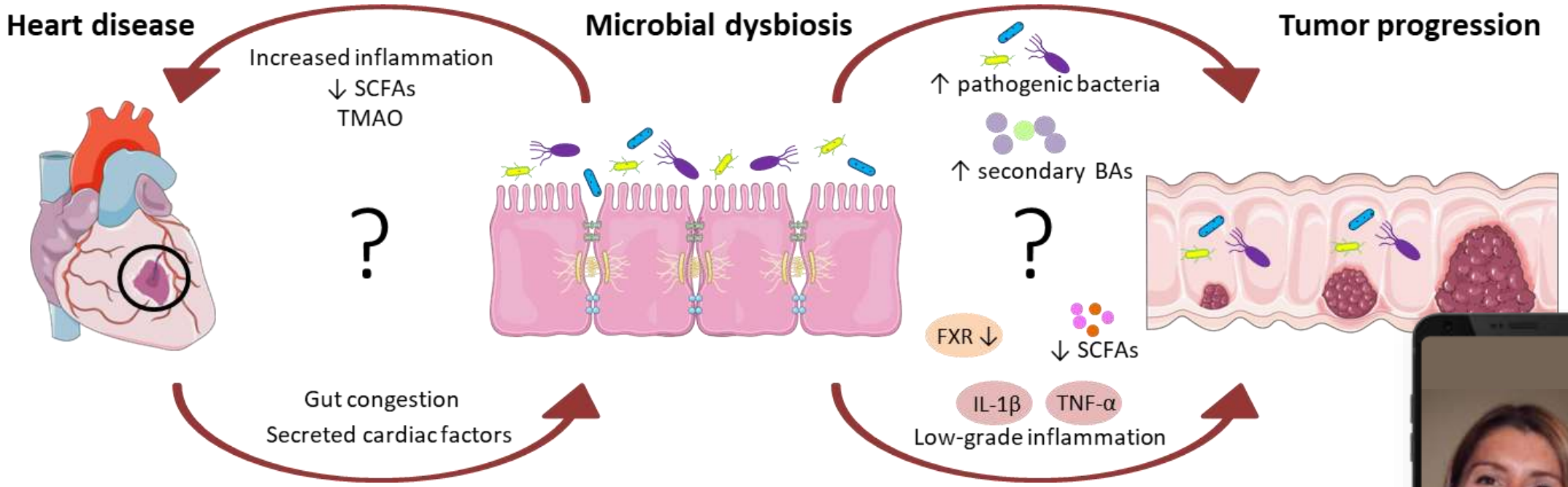
Shared pathophysiological pathways:

- Inflammation;
- Clonal hematopoiesis of indeterminate potential;
- Angiogenesis;
- Extracellular matrix/microbiome

Secreted /circulating factors

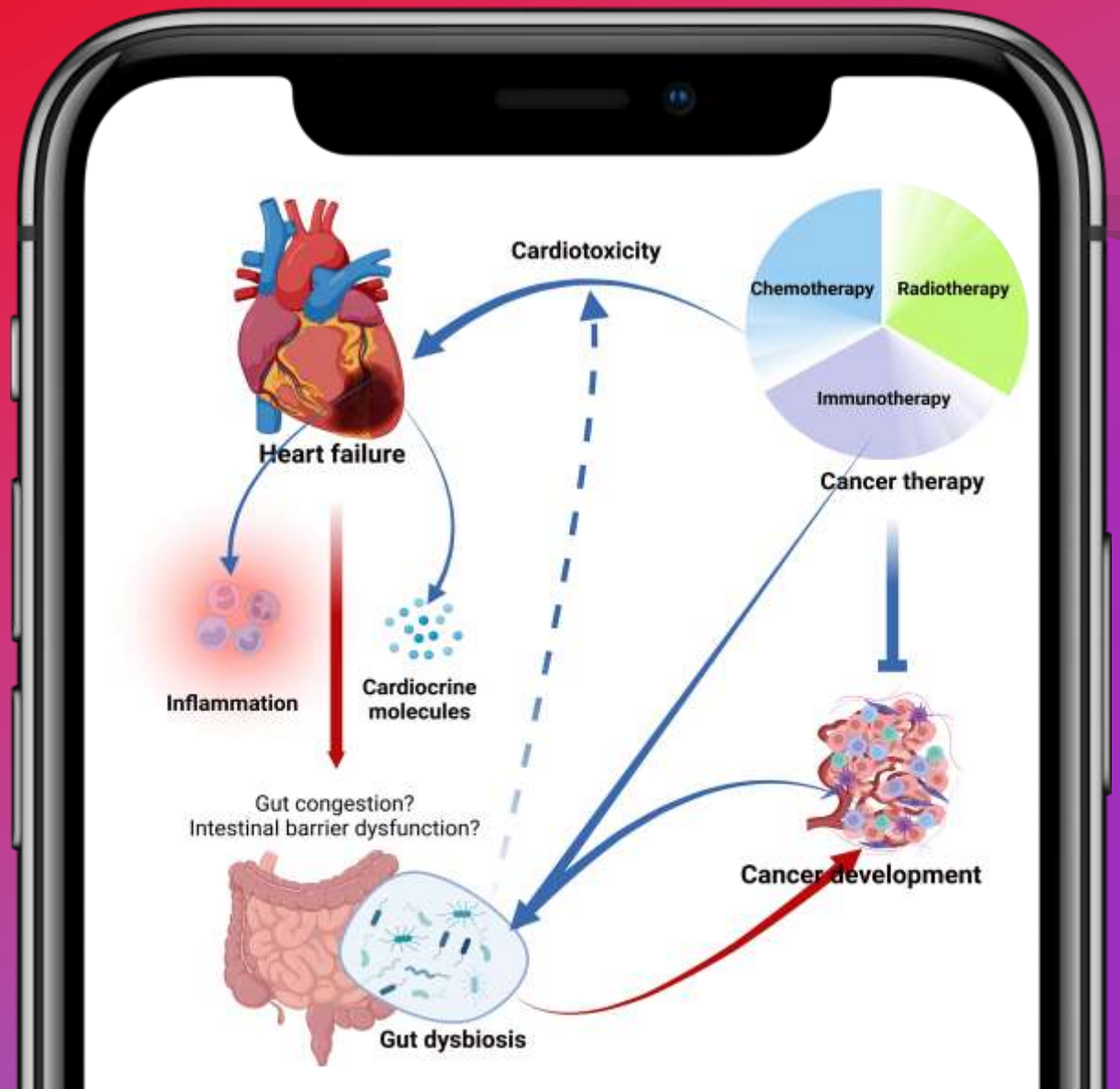
McDonagh TA, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023 Aug 25:ehad195. doi: 10.1093/eurheartj/ehad195

The relationship between CHF and microbiome



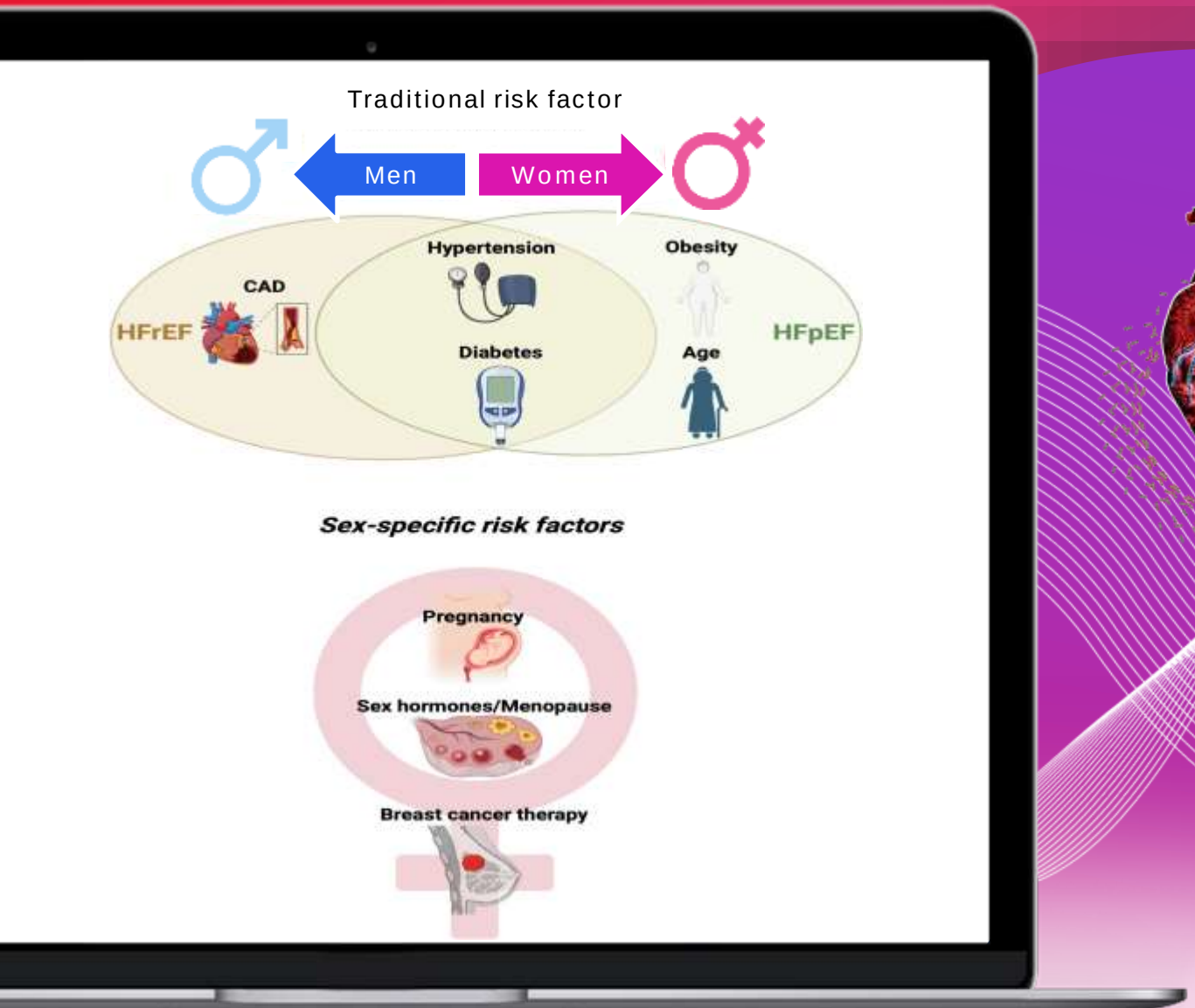
Tang WH, et al. *Nature reviews*. 2019; 16:137-154 Kurilshikov A, et al. *Circulation*. 2019 ;124:1808-1820 Gagnière J et al *World J Gastroenterol*. 2016; 22 501-508
Ahn J, et al. *JNCI*. 2013; 105:1907-1911

Interaction between HF, gut dysbiosis, cancer, and cancer therapy



Rangrez AY & Frey N. Cardiovasc Res. 2024; 120:561-562

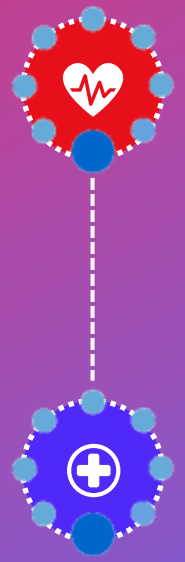
The main traditional and gender risk factors involved in the pathogenesis of HF with reduced and/or preserved ejection fraction



Шляхто Е.В., Беленков Ю. Н., Бойцов С.А., Виллевальде С. В., Галявич А. С., Глезер М. Г., ЗвартауН. Э., КобалаваЖ. Д., Лопатин Ю.М., Мареев В.Ю., Терещенко С.Н., Фомин И.В., БарбарашО.Л., Виноградова Н. Г., ДупляковД.В., Жиров И.В., Космачева Е. Д., Невзорова В. А., РейтблатО.М., Соловьева А.Е., Зорина Е.А.Проспективное наблюдательное многоцентровое регистровое исследование пациентов с хронической сердечной недостаточностью в РФ ПРИОРИТЕТ-ХСН): обоснование, цели и дизайн исследования. Российский кардиологический журнал. 2023;28(6):5456. doi:10.15829/1560-4071-2023-5456

Cardiovascular toxicity risk stratification before anticancer therapy

- Previous CVD
- Medical CVRF
- Lifestyle risk factors
- ECG, TTE, and cardiac biomarkers abnormalities
- Previous cardiotoxic therapies
- Age, sex, genetics



Clinical assessment

- Cancer treatment history
- CV history
- Cardiovascular risk factors
- Physical examination
- Vital signs measurement

Complementary tests

- cTn
- BNP or NT-proBNP
- Fasting plasma glucose / HbA1c
- Lipid profile
- Kidney function / eGFR
- ECG
- Transthoracic echocardiography

Recommendations	Class	Level
Baseline measurement of BNP/NtproBNP and/or cTnd is recommended in all patients with cancer at risk of cancer therapy-related cardiac dysfunction if these biomarkers are going to be measured during treatment to detect cancer therapy-related cardiac dysfunction	I	C
An ECG is recommended in all patients starting cancer therapy as part of their baseline CV risk assessment	I	C
In patients with an abnormal baseline ECG,c referral to a cardiologist is recommended	I	C

Lyon, Alexander R et al. European heart journal vol. 43,41 (2022): 4229-4361. doi:10.1093/eurheartj/ehac244

10-year risk of CV events

Low risk	there is no risk factor or 1 average risk factor	< 10%	• Routine oncology follow-up • Start the necessary anticancer treatment without delay • Cardiology referral if CV toxicity develops (Class I)
Moderate risk	the sum of the average risk factors is 2-4 points	10-19%	• Closer oncology follow-up • Cardiologya referral if CV toxicity develops (Class I), AND Cardiology referral (Class IIb)
High risk	the sum of the average risk factors 5 or more points or any high risk factor	20% or more	• Cardiologya referral erral (Class I) • Discussion of the risk/benefit balance of cardiotoxic anticancer treatment (Class I) • Cardioprotective strategies (Class IIa)
Very high risk	any very high risk factor	20% or more	

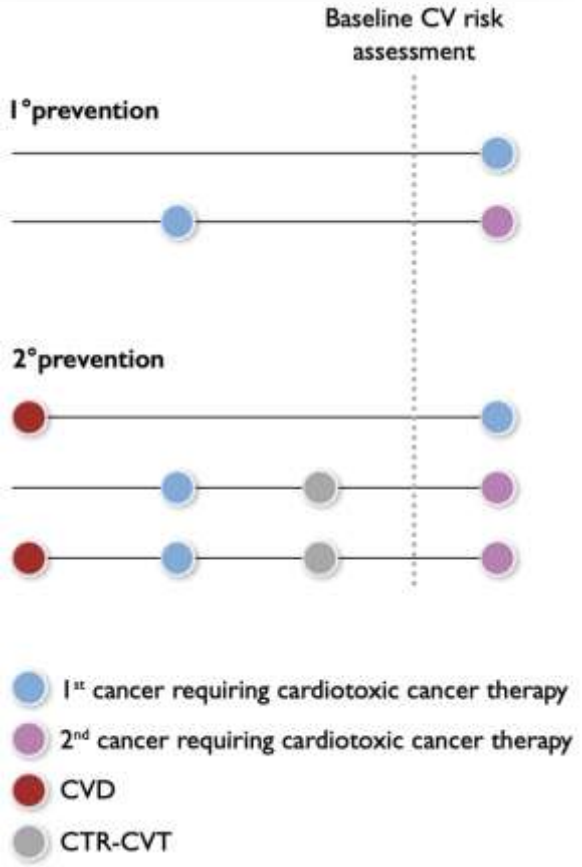
FOR ALL

- Communicate the CV toxicity risk assessment results (Class I)
- Educate patients regarding risks and protective healthy lifestyle (Class I)
- Management of CVRF and CVD according to ESC Guidelines (Class I)

Lyon, Alexander R et al. European heart journal vol. 43,41 (2022): 4229-4361. doi:10.1093/eurheartj/ehac244

Patient phenotypes and cancer-therapy related cardiovascular toxicity prevention strategies

Primary and secondary prevention



Management of CVD and CVRF according to ESK Guidelines

In patients with high and very high risk of CTRCD

- Minimize the use of cardiotoxic drugs
- ACE-I/ARB and/or BB
- Dexrazoxane/liposomal anthracyclines (patients treated with anthracyclines)
- Statins

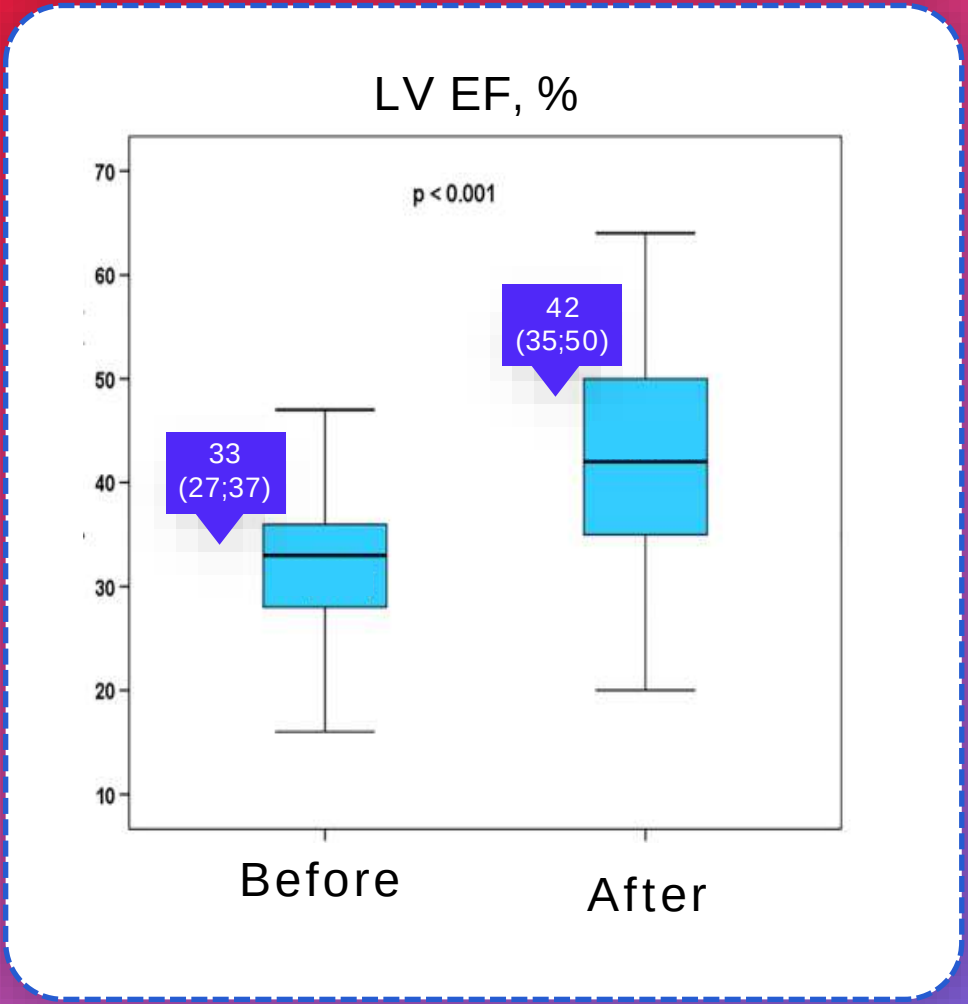
Management of CVRF according to the 2021 ESC Guidelines on CVD prevention in clinical practice is recommended before, during, and after cancer therapy (IC)

Class I

Class IIa

Lyon A.R., 2022

Sacubitril/valsartan in the treatment of PHT-associated cardiotoxicity and CHF

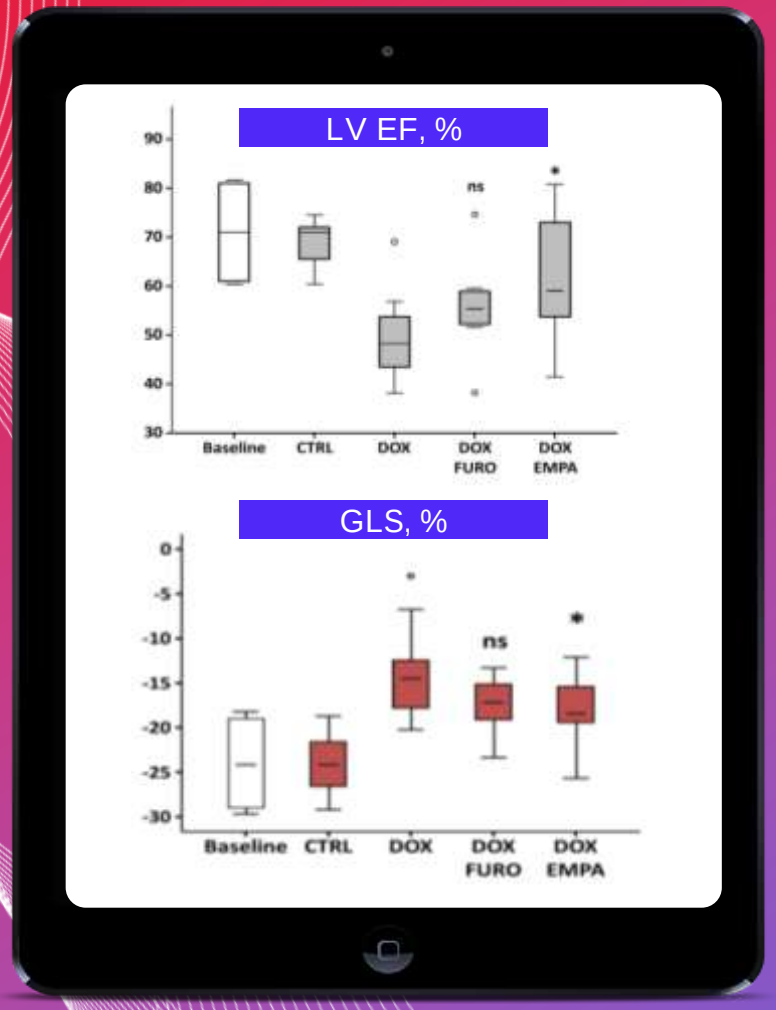


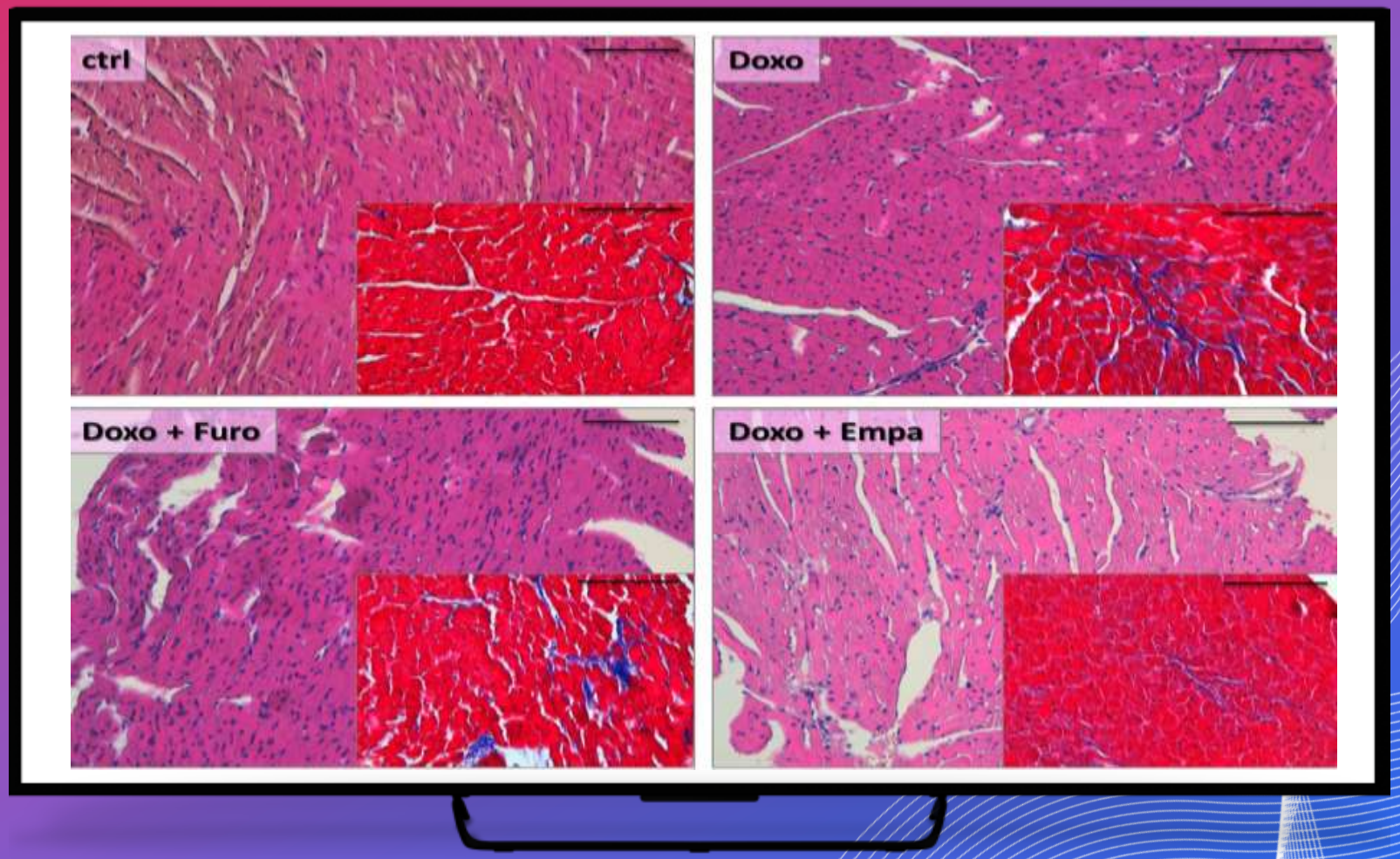
Criteria:

1. n = 67, breast cancer, lymphoma
2. PHT (70% with anthracyclines), RT
3. Median age 56.2±13.4 years
4. Cardiotoxicity with HF
5. Median LVEF 33%
6. 5 months follow-up
7. Combination therapy using sacubitril/valsartan

Martin-Garcia A. et al, E J Heart Failure, 2020

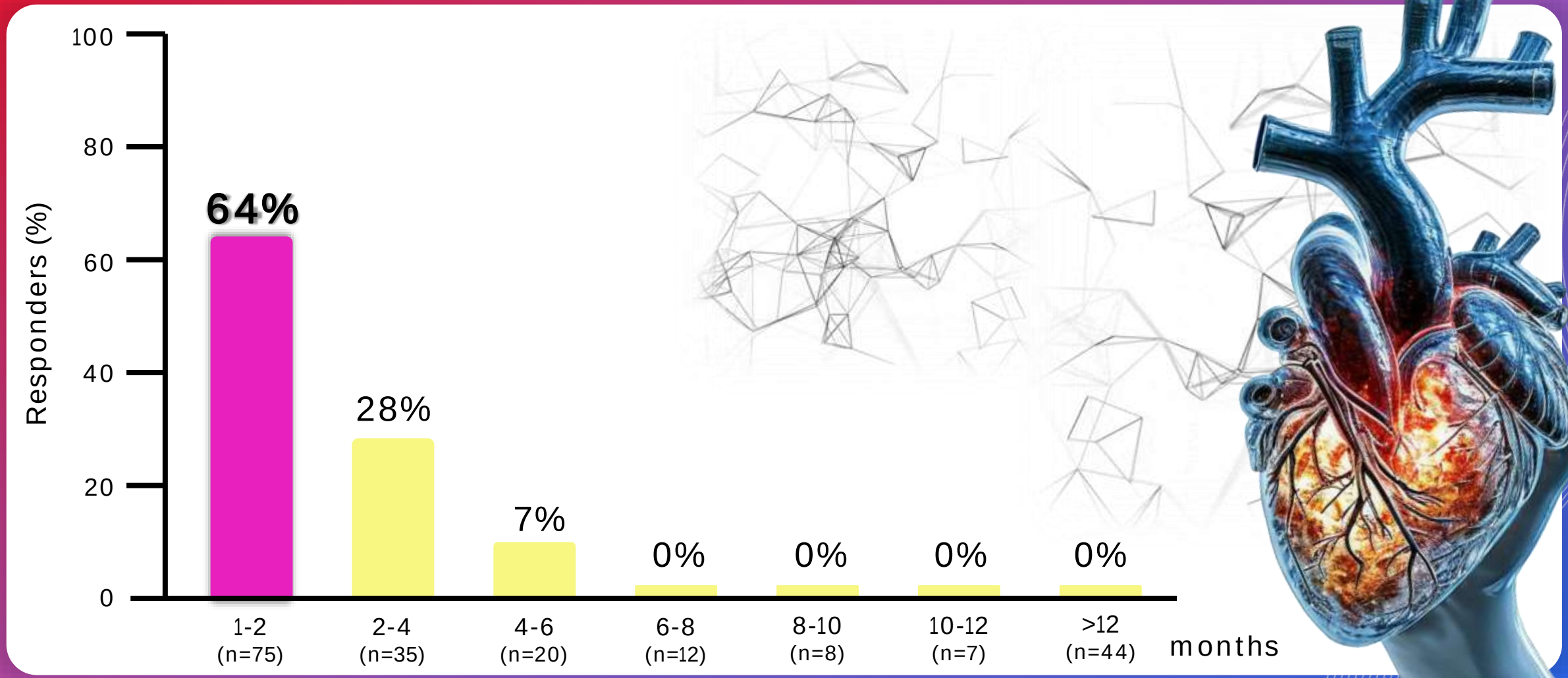
Empagliflozin for the prevention of DOX-associated cardiotoxicity (experimental model)





Sabatino J. et al, Cardiovasc Diabetol, 2020

Early detection of cardiotoxicity is the key to a good prognosis



Cardinale D. et al, JACC 2010;55:213-220

What is Reverse Cardio-Oncology?

Cancer driving heart disease

Heart disease driving cancer

	CVD	No CVD	*P* value‡
Sample size	4089	40 502	
Weighted sample size	127 809 316	1 610 614 001	
Age, y, median (IQR)	64.5 (53.7–74.1)*	41.1 (28.9–53.7)*	<0.0001*
Female sex, n (%)	59 525 877 (46.6)*	831 329 637 (51.6)*	<0.0001*

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RESEARCH ARTICLE | Originally Published 29 July 2024

Cardiovascular Diseases Increase Cancer Mortality in Adults: NHANES-Continuous Study

Omar M. Makram, MD, MPH, Tochukwu Okwuosa, DO, Daniel Addison, MD, Jorge Cortes, MD, Susan Dent, MD, Malcolm Bevel, PhD, MSPH, Sarju Ganatra, MD, Sadeer Al-Kindi, MD, Catherine C Hedrick, PhD, Neal L Weintraub, MD, Xiaoling Wang, MD, PhD, and Avirup Guha, MD, MPH

AUTHOR INFO & AFFILIATIONS

Journal of the American Heart Association • Volume 13, Number 15 • https://doi.org/10.1161/JAHA.124.035500

Conclusion (NHANES – Continuous Study 2024)

The study shows

All cardiovascular individuals are at higher risk of cancer mortality. Individual risk factors, including smoking, aging, and obesity, also significantly contribute to cancer mortality in individuals with CVD. Our findings highlight the potentially important role of obesity in the link between CVD and cancer mortality

The role of obesity in this relationship requires further exploration in future studies

Future research should examine the impact of CVD severity, such as heart failure stage and the effect of various cardiovascular medication intake on cancer mortality

	CVD (N=127 809 316)	No CVD (N=1 610 614 001)	*P* value
Median follow-up years (interquartile range)*	9.8 (5.3–16.3)‡	10.2 (5.9–15.6)‡	<0.0001‡
No. of deaths due to cancer, n (%)	4 084 613 (3.2)‡	11 221 492 (0.7)‡	<0.0001‡

https://www.ahajournals.org/doi/full/10.1161/JAHA.124.035500#:~:text=Journal%20of%20the,10.1161/JAHA.124.035500

Atrial fibrillation and the risk of developing cancer in the future

ESC European Society of Cardiology

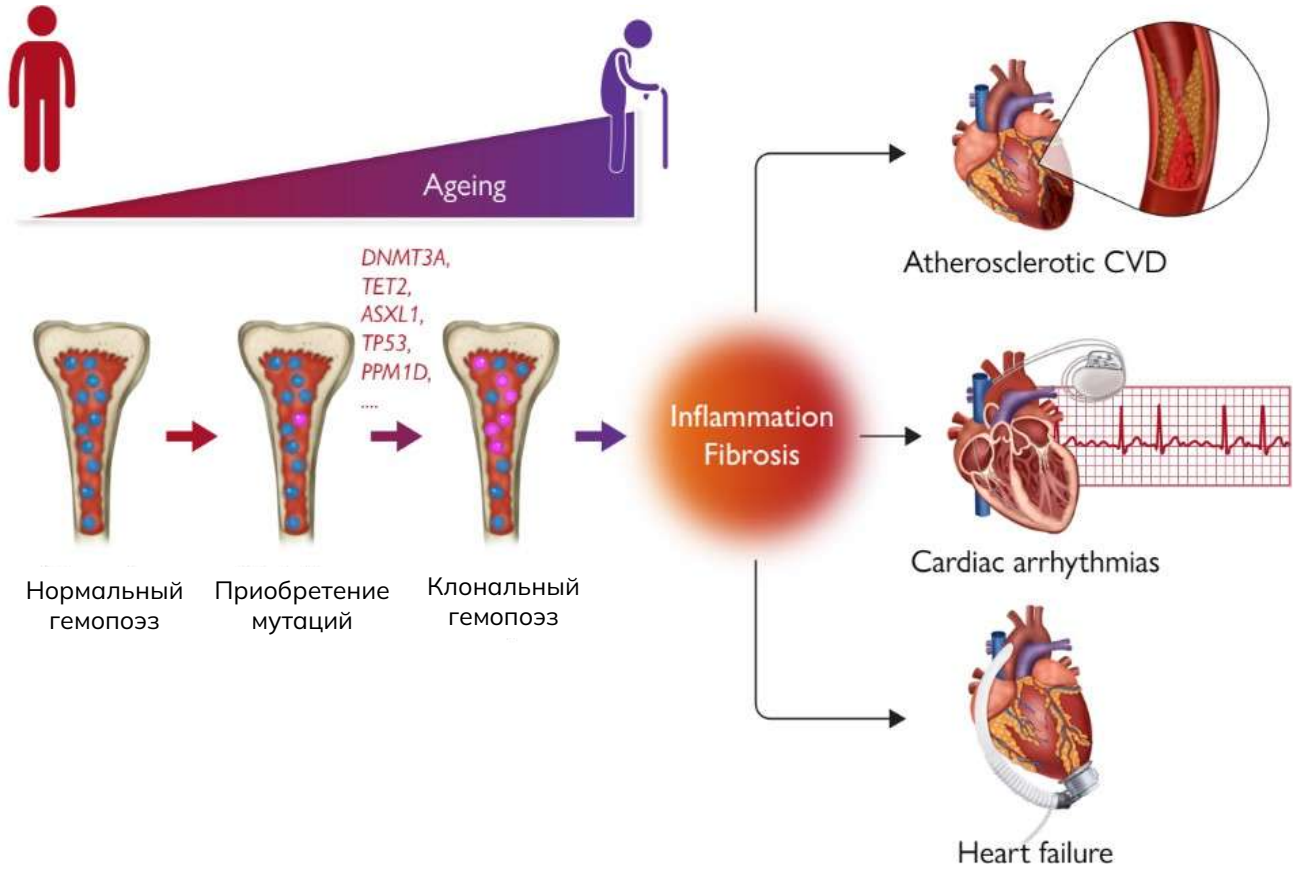
European Heart Journal (2024) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehae222

CLINICAL RESEARCH
Cardio-oncology

Coexisting atrial fibrillation and cancer: time trends and associations with mortality in a nationwide Dutch study

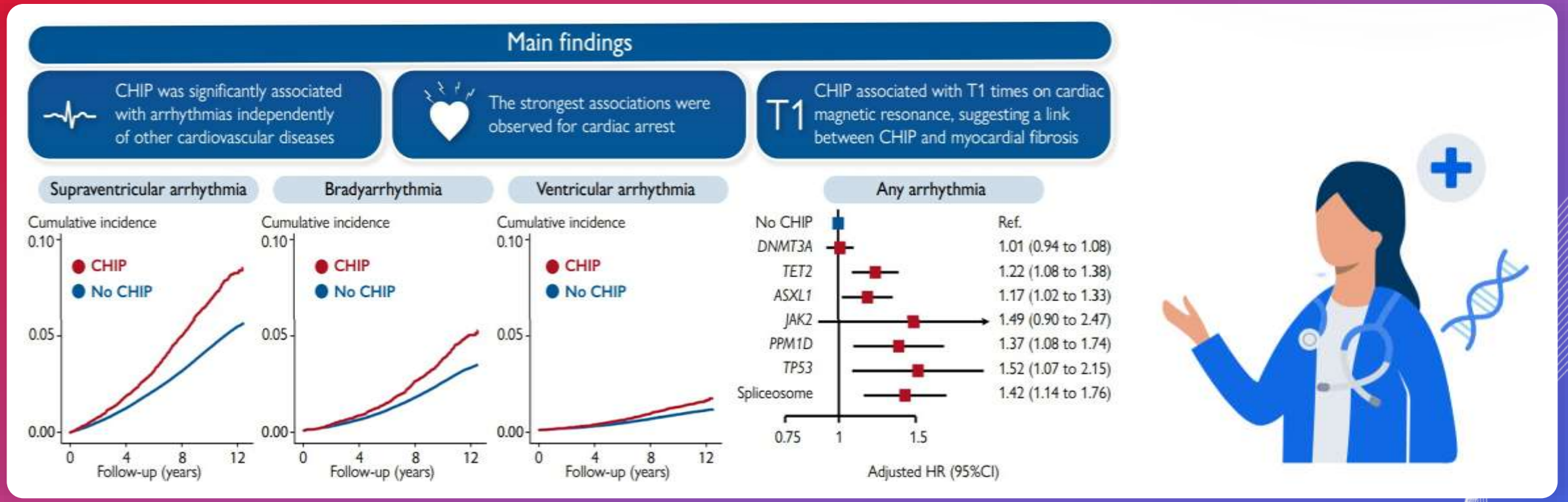
Qingui Chen [1]*, Nienke van Rein [1,2], Tom van der Hulle [3], Julius C. Heemelaar [4,5], Serge A. Trines [4], Henri H. Versteeg [6], Frederikus A. Klok [6], and Suzanne C. Cannegieter [1,6]

Clonal hematopoiesis is a new risk factor for the development of cardiac arrhythmias



European Heart Journal (2024) 45, 806–808

Clonal hematopoiesis is a new risk factor for the development of cardiac arrhythmias



Strong effects of mutations affecting the TP53 and PPM1D DNA damage response genes

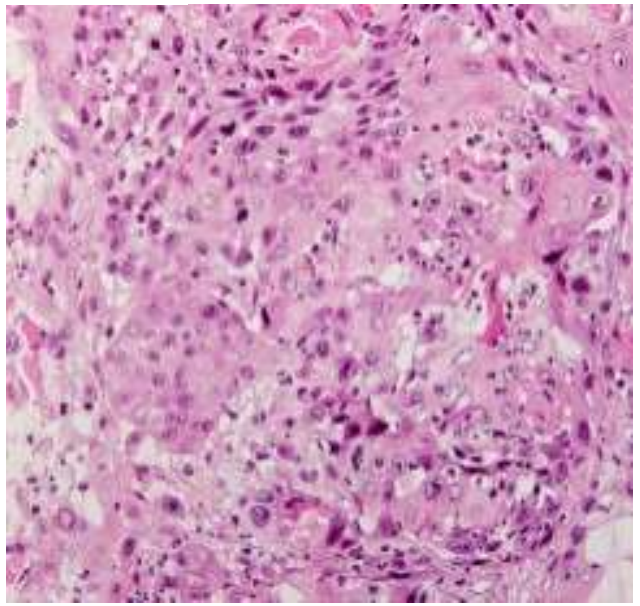
These mutations are especially common among cancer patients and survivors

Schuermans A, et al. European Heart Journal (2024) 45, 791–805

Takostubo Syndrome and Cancer

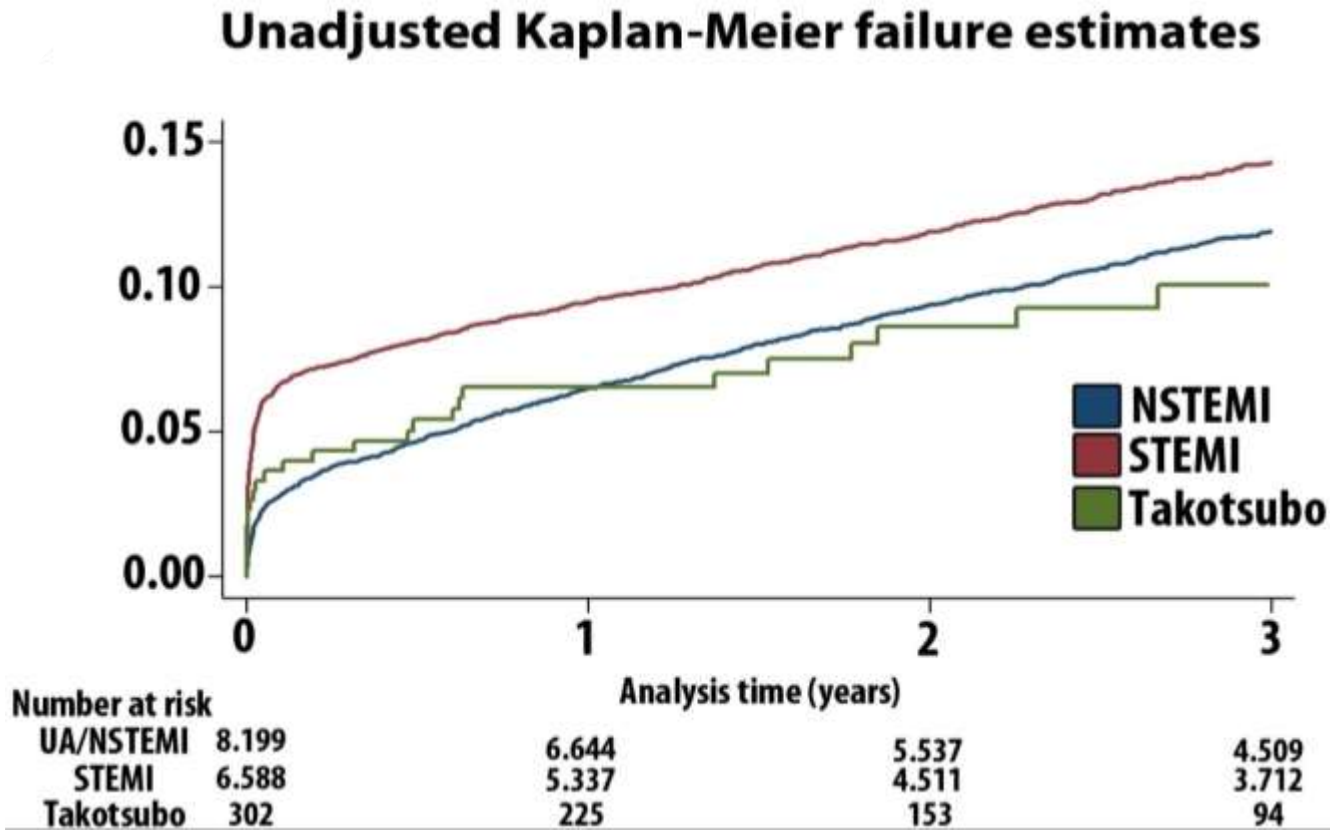
Prevalence of cancer in Takotsubo syndrome patients at presentation

Future cancer incidence in Takotsubo syndrome survivors



Mortality in Takotsubo syndrome is similar to mortality in myocardial infarction

Data from the SWEDEHEART registry



Redfors B et al Int. J. Cardiol. 2023;185:282-289

Long term mortality in patients with Takotsubo syndrome

Overall long term mortality for Takotsubo syndrome :

5,6%
mortality
per annum

in InterTAK registry

Overall
20-25%
10 year mortality

deaths from all causes

8%
3 year mortality

deaths from all causes
in SWEDEHEART registry

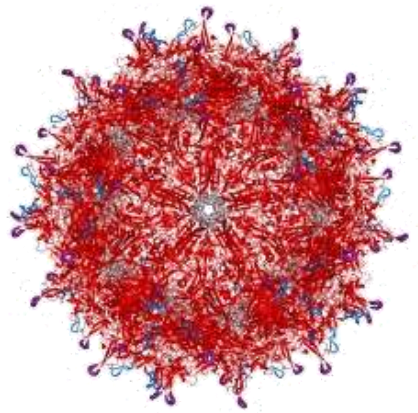
Non-CV causes
> CV causes

Increased incidence of de novo malignancies in patients with Takotsubo syndrome during long-term follow-up

~8% of cancer patients suffer from paraneoplastic syndrome

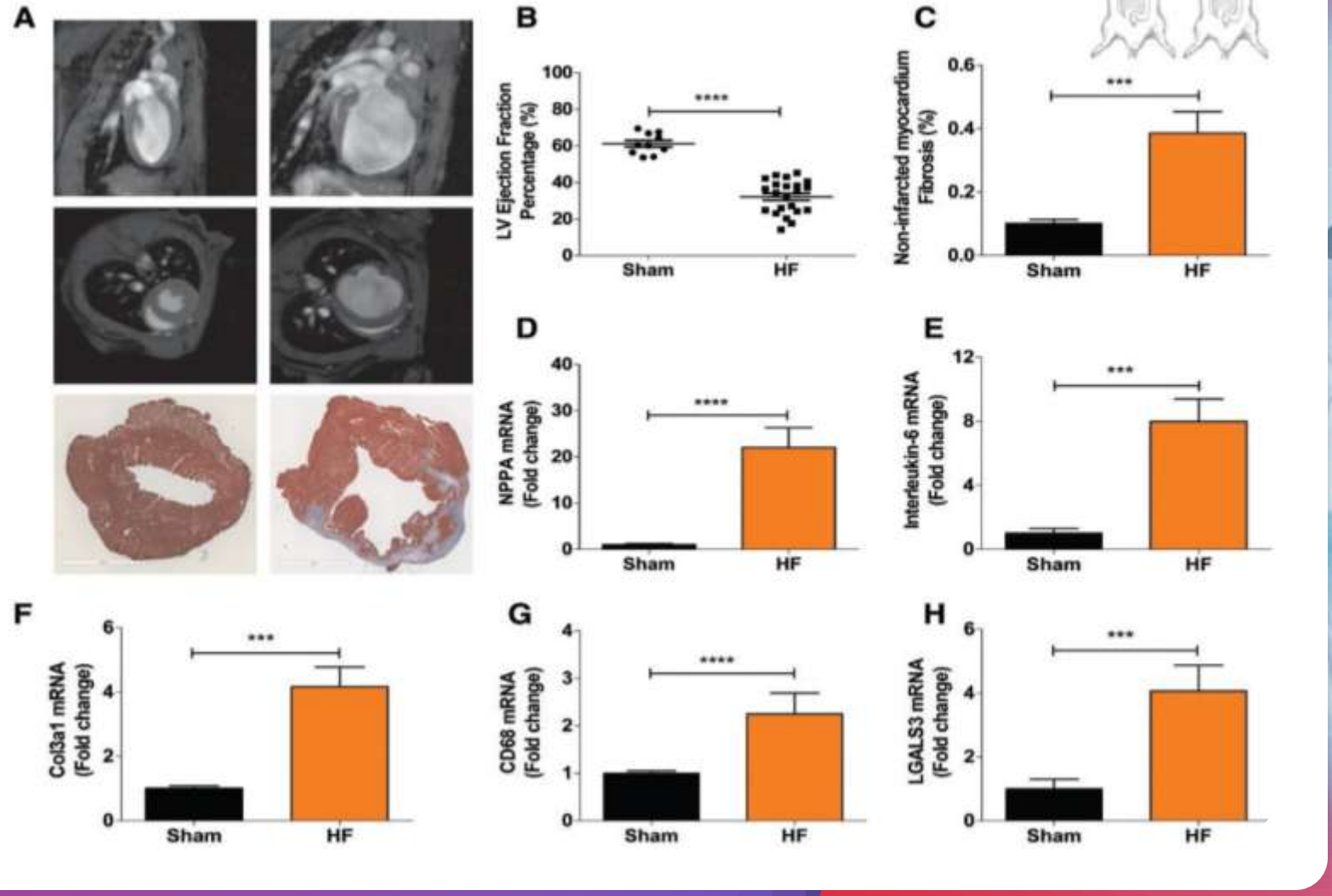
The diagnosis of a new malignancy appears to be more common in patients with Takotsubo syndrome during follow-up:

- Casuistic nature;
- Small cohorts: 50 patients with Takotsubo syndrome vs. 50 patients with IM, follow-up period 2.9+/-1.6 years;
- 14% (7/50) vs 0% incidence of new cancer in Takotsubo syndrome vs IM1;
- Requires prospective study;
- Is Takotsubo syndrome a paraneoplastic syndrome in some cases?
- Is there cancer screening in patients with Takotsubo syndrome?
- Atypical or unusual cases:
  - Spontaneous Takotsubo syndrome;
  - Male patients with Takotsubo syndrome;
- Long-term follow-up is appropriate



Burgdorf C et al Eur. J. Heart Fail. 2020;10(10):1015-1019

HF Promotes Tumor Growth



Meijers WC, et al. Circulation. 2018; 137:678-691

1. What mechanisms explain the Bidirectional Connection Between Cancer and HF?

2. Can we target these?

Shared Risk Factors
(smoking, obesity, sedentary lifestyle, diet)

HF Secreted/Circulating Factors

Shared Mechanisms:

- Inflammation
- Clonal Hematopoiesis of Indeterminate Potential
- Angiogenesis
- Extracellular Environment/microbiome

Summary

There is an increased risk of new cancer in a range of different CV populations MI, AF, ACHD, PH, Takotsubo syndrome

- Range of reasons
  - Shared risk factors
  - Shared pathophysiology
  - Increased medical investigations
  - Increased used of Anticoagulant or Antiplatelets and bleeding
- CV and Cancer survivorship both increasing

Azərbaycan Kardiologiya Cəmiyyəti

ESC European Society of Cardiology

HFA Heart Failure Association

OSSN

RUSSIAN SOCIETY OF CARDIOLOGY

IC-OS International Cardio-Oncology Society

Thank you for attention!