Anthracycline-Induced Heart Failure

A Journey from Diastolic Dysfunction to Precision Cardio-Oncology

Diastolic Dysfunction → **Early Diagnosis** → **Biomarkers & CMR** → **Personalized Cardioprotection** → **Precision Cardio-Oncology**

Dr. Tora Sadigova, MD PhD FESC

Azerbaijan Medical University, Baku, Azerbaijan

Based on: JACC CardioOncology (2023, 2024) · Prog Cardiovasc Dis (2024) · Curr Oncol Rep (2024) · Cardiovasc Toxicol (2024) · Cardiovasc Res (2025)

Why This Matters: The Growing Burden

>65%

of malignancy regimens contain anthracyclines

2.5×

higher HF mortality vs idiopathic dilated cardiomyopathy (JACC CO 2024)

57%

subclinical LV dysfunction at cumulative dose ≥ 300 mg/m²

#2 cause

of death in long-term cancer survivors (after cancer itself)

The Paradigm Challenge

- With >16 million cancer survivors globally, long-term cardiac consequences are the next major public health frontier.
- JACC:CardioOncology 2024 (Herrmann et al.): HF after anthracyclines carries significantly worse prognosis than HF from other etiologies — demanding a prevention-first approach.

Herrmann J et al. JACC CardioOncology 2024; DOI: 10.1016/j.jaccao.2024.07.016 · Ewer MS et al. Prog Cardiovasc Dis 2024; DOI: 10.1016/j.pcad.2024.07.002

Cancer Therapy–Related Cardiac Dysfunction (CTRCD)

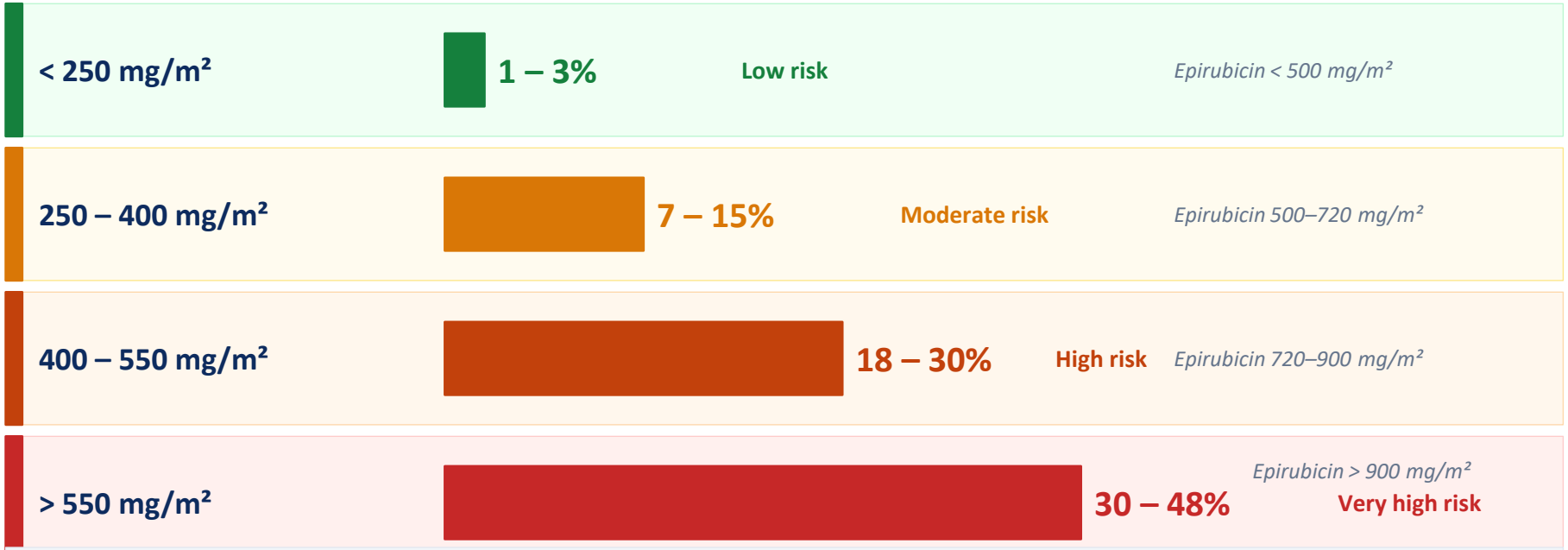
Heart failure represents the final stage of CTRCD progression

Category	LVEF Status	Symptoms	Biomarkers
Subclinical (Pre-CTRCD)	≥ 53% (preserved)	None	**↑ hs-Troponin or ↓ GLS > 15%**
Mild CTRCD	Drop ≥ 10 pp to 50–52%	Absent	**Normal or mildly ↑**
Moderate CTRCD	40–49% (drop ≥ 10 pp)	May be present (dyspnea, fatigue)	**↑↑**
Severe CTRCD	< 40% (± symptoms)	Present or cardiogenic shock	**↑↑↑**

Key principle: Symptomatic Heart Failure = Moderate-to-Severe CTRCD. Early detection at subclinical or mild stage is the therapeutic window. (ESC Cardio-Oncology Guidelines 2022)

Dose-Dependent Risk of Anthracycline Heart Failure

Doxorubicin cumulative dose thresholds and equivalent doses



Ewer MS et al. Prog Cardiovasc Dis 2024; 10.1016/j.pcad.2024.07.002 · Anjos M et al. Cardiovasc Toxicol 2024; 10.1007/s12012-024-09866-1

Risk modifiers: Concurrent trastuzumab (risk ×2–5) · Liposomal doxorubicin (risk ↓ ~50%) · Infusion rate (slow infusion reduces peak Cmax) · Female sex, age >65, pre-existing CV disease.

How Our Understanding Evolved: 1970s → 2025

1970s–80s

"Accept the trade-off"

- Dose-dependent, irreversible
- Only end-stage HF recognized
- No prevention strategies

1990s–2000s

"Dose limits & LVEF"

- Cumulative dose ceilings established
- Echocardiographic surveillance begins
- Dexrazoxane introduced (EMA 1999)

2010s

"Subclinical detection"

- GLS outperforms LVEF for early injury
- hs-Troponin rises from Cycle 1
- ESC monitoring protocols (2022)

2020s →

"Precision prevention"

- Individual risk phenotyping
- SGLT2i cardioprotection data
- Multidisciplinary cardio-oncology

Ewer MS, Ewer SM et al. Prog Cardiovasc Dis 2024; 10.1016/j.pcad.2024.07.002

Diastolic Dysfunction: The Canary in the Coal Mine

Normal LVEF does NOT exclude significant myocardial injury

Temporal Sequence of Injury

Cycle 1–2	hs-Troponin rise (subclinical)
1–3 months	↓ GLS > 15% relative; LVEF still normal
3–6 months	Diastolic dysfunction grade I–II (↑ E/e')
6–12 months	LVEF begins to drop; HFpEF phenotype
> 1 year	HFrEF; dilated cardiomyopathy pattern

Key Diastolic Parameters to Monitor

E/e' ratio:	> 14 → ↑ LV filling pressure; gold standard for diastolic stress
LAVI:	> 34 mL/m² → chronic LA pressure overload
Septal e':	< 7 cm/s → impaired LV relaxation (tissue Doppler)
TR Vmax:	> 2.8 m/s → elevated pulmonary pressure
GLS:	> −16% (absolute) → high-risk subclinical toxicity

Anjos M et al. Cardiovasc Toxicol 2024; 10.1007/s12012-024-09866-1 · Pudil R et al. JACC CardioOncology 2023; 10.1016/j.jaccao.2023.12.009

Heart Failure Phenotypes After Anthracycline Therapy

Understanding the phenotype guides treatment strategy

HFpEF — Heart Failure with Preserved EF — LVEF ≥ 50%

Prevalence: ~ 60–70% of early AIHF

Mechanism

- Diastolic dysfunction dominant
- Impaired LV relaxation (↓ e')
- ↑ LV filling pressures (↑ E/e')
- Subclinical systolic impairment (↓ GLS)

Treatment Approach

- SGLT2i: best evidence (HFpEF)
- ACEi/ARB: may slow progression
- Diuretics for symptoms
- Treat comorbidities aggressively

HFmrEF — Heart Failure with Mildly Reduced EF — LVEF 40–49%

Prevalence: ~ 15–20% of AIHF

Mechanism

- Transitional phenotype
- Mixed systolic-diastolic injury
- Significant biomarker elevation
- Can recover or progress to HFrEF

Treatment Approach

- ACEi + BB: may promote LVEF recovery
- SGLT2i: emerging evidence
- MRA: consider in symptomatic pts
- Reassess LVEF every 2–3 months

HFrEF — Heart Failure with Reduced EF — LVEF < 40%

Prevalence: ~ 15–25% of AIHF

Mechanism

- Dilated cardiomyopathy pattern
- Severe contractile dysfunction
- Type I injury: cardiomyocyte death
- Interstitial fibrosis (LGE on CMR)

Treatment Approach

- FULL GDMT: ARNI + ACEi + BB + MRA + SGLT2i
- ARNI (sacubitril/valsartan) preferred
- CRT if LVEF <35% + LBBB + QRS ≥130ms
- ICD for secondary prevention

Vergallo R et al. Curr Oncol Rep 2024; 10.1007/s11864-024-01238-9 · ESC HF Guidelines 2021 | ESC Cardio-Oncology Guidelines 2022

Early Diagnosis: Biomarkers and GLS

Catching the signal before the damage is done

hs-Troponin I / T

Cardiomyocyte injury marker

- Rises in 25–35% of patients after Cycle 1
- Persistent elevation (> URL at 1 month): 84% PPV for LV dysfunction
- Each 10× URL increase: HR 2.1 for HF events (JACC CO 2024)
- ESC Class I: measure at baseline + each cycle (high risk)
- Preferred: hs-TnT or hs-TnI (high-sensitivity assays)

NT-proBNP / BNP

Wall stress and HF precursor

- Sensitive to both systolic and diastolic dysfunction
- NT-proBNP ≥ 125 pg/mL: clinically significant threshold
- Rise > 2× baseline: independent predictor of MACE
- Complements troponin — different mechanistic pathway
- ESC Class I: measure at baseline + alongside troponin

GLS (Global Longitudinal Strain)

Subclinical systolic dysfunction

- Normal: GLS < −18% (absolute value > 18%)
- > 15% relative reduction from baseline = subclinical toxicity
- Detects injury 2–3 months before LVEF decline
- Meta-analysis 2024: AUC 0.87 for predicting HF progression
- ESC Class IIa: include in every surveillance echocardiogram

Vergallo R et al. Curr Oncol Rep 2024; 10.1007/s11864-024-01238-9 · Pudil R et al. JACC CardioOncology 2023; 10.1016/j.jaccao.2023.12.009

Cardiac MRI: The Gold Standard We Underused

When to use CMR and what it tells us that echo cannot

Indications for CMR in AIHF

Echo inadequate:	Obesity, COPD, poor acoustic window
Echo–symptom discordance:	Symptoms present but echo "normal"
Suspected acute myocarditis:	Tachycardia, ST changes, acute tox
High-risk structural workup:	Baseline CMR before high-dose anthracyclines
Fibrosis quantification:	Established AIHF — prognosis and CRT decision

T1 Mapping + ECV

ECV > 30% = diffuse interstitial fibrosis. Subclinical remodeling detectable before LVEF falls.

T2 Mapping

T2 > 55 ms = active myocardial edema. Identifies acute cardiomyocyte injury from anthracyclines.

Late Gadolinium (LGE)

Mid-wall pattern = non-ischemic fibrosis. LGE presence → ×3.2 risk of adverse events. (CVR 2025)

CMR-GLS + LVEF

LVEF reproducibility ±2% vs echo ±10%. CMR-GLS < −16% = high-risk for HF progression.

Plana JC et al. Cardiovasc Res 2025; 10.1093/cvr/cvaf179

ESC 2022 Surveillance: Before → During → After Therapy

BEFORE THERAPY	DURING THERAPY	AFTER THERAPY
☑ Echo: LVEF (biplane Simpson)	🔴 **HIGH RISK: every 2 cycles**	☑ All patients: 3 months post-therapy
☑ GLS (global longitudinal strain)	Echo + GLS + Tn + NT-proBNP	☑ All patients: 12 months post-therapy
☑ hs-Troponin I or T	🟡 **MEDIUM RISK: midpoint + end**	☑ High risk: annually × 5 years
☑ NT-proBNP	Echo + GLS + biomarkers	☑ Pediatric: lifelong surveillance
☑ Risk stratification (ESC tool)	🟢 **LOW RISK: end of treatment only**	☑ New symptoms: immediate echo + BM
☑ Optimize CV risk factors	Echo ± biomarkers	☑ HFpEF: continue SGLT2i + BB

⚠ **If CTRCD detected:** Initiate HF therapy immediately (Class I-A). Continue cancer treatment when benefit > risk. Joint oncologist + cardiologist decision.

Lyon AR et al. ESC Cardio-Oncology Guidelines 2022. Eur Heart J 2022;43(41):4229–4361

Clinical Case: HER2+ Breast Cancer, Female, 45 Years

AC × 4 → Paclitaxel × 4 → Trastuzumab × 1 year

Patient: 45-year-old woman · HER2+ breast cancer (cT2N1) · No prior cardiac history · BMI 24 · BP 124/78 mmHg

BASELINE	AFTER CYCLE 2 (AC)	AFTER CYCLE 4 (AC)	END THERAPY	6-MONTH FOLLOW-UP
LVEF: 62%	LVEF: 60%	LVEF: 57%	LVEF: 55%	LVEF: 61%
hs-TnI: <URL	GLS: −18.5%	GLS: −17% (↓15%)	GLS: −18%	GLS: −19.5%
NT-proBNP: 58 pg/mL	**hs-TnI: 1.8× URL**	**hs-TnI: 2.3× URL**	hs-TnI: 1.2× URL	hs-TnI: normal
	NT-proBNP: 142 pg/mL	NT-proBNP: 198 pg/mL	NT-proBNP: 110 pg/mL	NT-proBNP: 62 pg/mL
Normal	**Subclinical CTRCD**	**Mild CTRCD → ACT!**	**Stabilised (Enalapril + Carvedilol)**	**RECOVERED No HF**

→ Enalapril 5 mg/day + Carvedilol 6.25 mg bid started after Cycle 4. Cancer therapy COMPLETED. No clinical HF at follow-up.

CASE DISCUSSION | *Would You Have Managed This Patient Differently?*

Q1
Should cardioprotective therapy have been started after Cycle 2?

Troponin: 1.8× ULN
NT-proBNP: 58 → 142 pg/mL
GLS: −20% → −18.5%
LVEF: preserved

YES
ACEi + β-blocker justified at this stage

Biomarker elevation precedes overt CTRCD

Q2
Should cancer therapy have been interrupted after Cycle 4?

LVEF: 57%
GLS reduction >15%
Troponin: persistently ↑
No HF symptoms

NO
ESC supports continuation with cardioprotection

Do not stop life-saving cancer therapy unnecessarily

Q3
What was the most important signal of cardiotoxicity?

✓ Persistent troponin ↑
✓ GLS reduction >15%

Both preceded LVEF decline

GLS + Troponin detect injury earlier than ejection fraction

GLS + troponin are early warning signals

Q4
Would you have performed Cardiac MRI?

Indications:
- Persistent biomarker ↑
- Progressive GLS decline
- Echo-symptom discordance

In this case: reasonable but not mandatory

REASONABLE
but not mandatory in this case

CMR valuable in selected high-risk patients

Q5
Should an SGLT2 inhibitor have been initiated?

FOR: early myocardial injury, emerging evidence

AGAINST: no DM, no CKD, no HF, LVEF >50%, no guideline indication

NOT YET
Promising but not yet guideline-based prophylaxis

SGLT2i: exciting future direction, not yet standard

CARDIOTOXICITY PATHWAY: Troponin ↑ → GLS ↓ → CTRCD → Heart Failure → PREV. ✓

CLINICAL MESSAGE

Do not wait for symptomatic heart failure. Troponin elevation and GLS deterioration identify myocardial injury months before LVEF declines. Early detection and early cardioprotection allow completion of cancer therapy while preserving cardiac function.

PREVENTION

Personalized Cardioprotection: Right Drug, Patient & Time

ACEi / ARB

Class IIa-A

- Enalapril: OVERCOME trial — LVEF preservation
- Candesartan: PRADA — HER2+ population
- Start prophylactically (high-risk patients)
- RAAS blockade → attenuates remodeling
- Continue throughout and after therapy

Beta-Blockers

Class IIa-B

- Carvedilol: α/β blockade + antioxidant properties
- Bisoprolol: cardioselective, well tolerated
- BB + ACEi: synergistic cardioprotection
- Most effective when started prophylactically
- Continue for ≥ 1 year after therapy

Dexrazoxane

Class IIa-A

- Iron chelation → ↓ Fenton reaction → ↓ ROS
- Cumulative dox > 300 mg/m²: start or early use
- JACC CO 2024: HF risk ↓ 45% vs control
- Dose: dox:DRZ = 1:10 ratio
- Underused: evidence supports earlier initiation

SGLT2 Inhibitors (Class IIb / emerging): Empagliflozin / Dapagliflozin — EMPA-HEART CardioOnc & DAPA-CardioOnc 2024: LVEF preservation + HF hospitalisation ↓ 25–38%. Meta-analysis 2025 (He et al.): cardiotoxicity risk ↓ 38%. *Anjos M et al. Cardiovasc Toxicol 2024; 10.1007/s12012-024-09866-1 · Vergallo R et al. Curr Oncol Rep 2024; 10.1007/s11864-024-01238-9*

GDMT for Established Anthracycline-Induced Heart Failure

Guideline-Directed Medical Therapy (ESC HF Guidelines 2021)

Drug Class	ESC	Dosing	Clinical Note in AIHF
ARNI (Sacubitril/Valsartan)	I-A	49/51 mg bid → titrate to 97/103 mg bid	Preferred over ACEi for HFrEF; neprilysin inhibition + RAAS block; ↓ mortality 20%
ACE Inhibitor (Enalapril, Ramipril)	I-A	Enalapril 2.5 → 20 mg/day; Ramipril 5 → 10 mg/day	First-line if ARNI not tolerated; proven LVEF recovery in AIHF (OVERCOME trial)
Beta-Blocker (Carvedilol, Bisoprolol)	I-A	Carvedilol 3.125 → 25 mg bid; Bisoprolol 1.25 → 10 mg/day	Carvedilol preferred in AIHF (antioxidant properties); start low, titrate slowly
MRA (Spironolactone, Eplerenone)	I-A	Spironolactone 25–50 mg/day; Eplerenone 25–50 mg/day	Add when LVEF < 35% or persisting symptoms; monitor K+, eGFR
SGLT2 Inhibitor (Dapagliflozin, Empagliflozin)	I-A	Dapagliflozin 10 mg/day; Empagliflozin 10 mg/day	Added 2021 HF guidelines; cardiorenal protection; reduce HF hospitalisation

Device therapy: CRT (Class I) if LVEF < 35% + LBBB + QRS ≥ 130ms. ICD (Class I) for secondary prevention. Consider oncology status before ICD for primary prevention.

Precision Cardio-Oncology: The Next Frontier

Clinically relevant advances — not yet standard of care

Genomic Risk Stratification

- CBR3 V244M variant: 5.5× higher HF risk (actionable)
- SLC28A3 polymorphisms → doxorubicin exposure ↑
- HER2 gene variants → trastuzumab cardiotoxicity risk
- Pre-treatment genetic panels: clinical trials ongoing

AI-Assisted Early Warning

- ECG-AI: LVEF prediction from 10-lead ECG alone
- hs-Tn trajectory modeling: predict LVEF drop months ahead
- EHR integration: automated risk alerts per cycle
- Currently: research — not yet guideline-recommended

Multidisciplinary Cardio-Oncology

- >300 dedicated cardio-oncology clinics worldwide
- Joint oncology + cardiology board decisions
- Proven to reduce HF-related cancer therapy interruption
- ESC/ASCO joint guidance: implement NOW

Clinical message for today

While we await precision tools, every cardiologist and oncologist can act NOW: risk-stratify, monitor, start cardioprotection early, and treat established HF aggressively.

Herrmann J et al. JACC CardioOncology 2024; 10.1016/j.jaccao.2024.07.016 · Plana JC et al. Cardiovasc Res 2025; 10.1093/cvr/cvaf179

6 Points to Carry Out of This Session

01	**WHAT to measure:**	Echo (LVEF + GLS) + hs-Troponin + NT-proBNP — baseline in every patient before anthracyclines.
02	**WHEN to measure:**	High risk: every 2 cycles. All patients: 3 months and 12 months after completion. High-risk: annually × 5 years.
03	**WHO to monitor most closely:**	Cumulative dose ≥ 250 mg/m² · Age > 65 · Prior HF / cardiomyopathy · Concurrent trastuzumab · Baseline LVEF 50–54%.
04	**WHEN to start cardioprotection:**	High-risk: prophylactic ACEi + BB before or at start of anthracyclines. Subclinical CTRCD: start immediately. Do not wait for symptoms.
05	**HOW to treat established HF:**	Full GDMT (Class I-A): ARNI + BB + MRA + SGLT2i. Consider CRT (LVEF < 35% + LBBB). Continue cancer therapy when benefit > risk — joint decision.
06	**THE KEY PRINCIPLE:**	Treating the cancer AND protecting the heart are not competing goals. Cardio-oncology is not a subspecialty — it is the standard of care.

Herrmann J. JACCAO 2024 · Ewer MS. PCAD 2024 · Vergallo R. CurrOncolRep 2024 · Anjos M. CardiovascToxicol 2024 · Pudil R. JACCAO 2023 · Plana JC. CVR 2025