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Review Article

Systematic Review and Meta-Analysis of Pharmacologic Cardioprotection in Breast Cancer Therapy: Evidence from Real-World Data

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Abstract

Pharmacologic cardioprotection during anthracycline and/or anti-HER2 therapy for breast cancer remains incompletely characterized, particularly in real-world settings. This study synthesizes trial evidence and validates it against an Albanian cohort to define the potential benefit and residual burden of cardiotoxicity. A random-effects meta-analysis of three comparative trials demonstrated that prophylactic cardioprotective medications were associated with a significant attenuation of left ventricular ejection fraction (LVEF) decline (pooled mean difference = 2.45 percentage points, 95% CI 1.56–3.34; I^2 = 21.8%). In a parallel retrospective analysis of 314 Albanian breast cancer patients, symptomatic cardiotoxicity occurred in 16.6%, and a clinically relevant ≥10-point LVEF decline within 12 months was observed in 12.1%. These findings confirm a modest but consistent cardioprotective effect from prophylactic interventions in clinical trials, yet the substantial real-world burden affecting approximately one in six patients symptomatically and one in eight with significant LVEF decline highlights a critical gap between trial efficacy and routine practice, underscoring the need for systematic implementation of cardioprotective strategies.

Keywords: Breast Neoplasms; Anthracyclines; Trastuzumab; Heart Diseases, Chemically Induced; Echocardiography.

INTRODUCTION

Breast cancer treatment is increasingly multimodal, combining anthracyclines, taxanes, radiotherapy, and anti-HER2 agents. While these strategies have improved survival, they can also expose the heart to cumulative injury, creating a growing need for structured cardio-oncology care. Cancer therapy–related cardiac dysfunction (CTRCD) spans a broad clinical spectrum from silent myocardial injury detectable only by imaging or biomarkers to symptomatic heart failure that may require hospitalization and can disrupt cancer

treatment plans [1, 2]. Because cardiovascular complications can affect both quality of life and the ability to complete effective oncologic therapy, prevention and early detection have become central priorities in modern practice [2].

Current prevention strategies begin with careful assessment and management of baseline cardiovascular risk (e.g., hypertension, diabetes, dyslipidemia), alongside systematic monitoring during treatment using echocardiography and, when feasible, more sensitive measures such as global longitudinal strain (GLS) and cardiac biomarkers [2]. International guidance supports a risk-adapted approach, where surveillance intensity and cardioprotective interventions are tailored to the patient's baseline risk profile and the cardiotoxic potential of the planned regimen [2]. Pharmacologic prophylaxis with ACE inhibitors/ARBs and beta-blockers has been evaluated in several randomized trials, but findings remain mixed. This heterogeneity likely reflects real differences across studies in patient selection, baseline risk burden, treatment exposures (anthracycline dose, trastuzumab scheduling, radiotherapy fields), outcome definitions, and follow-up duration [3-7]. Some trials suggest modest preservation of left ventricular function. In contrast, others show limited impact on primary endpoints, underscoring the limitations of relying on LVEF-based outcomes alone and the importance of standardized CTRCD definitions [2–5].

Importantly, trial populations do not always reflect the complexity seen in routine clinical practice. Real-world cohorts often include older patients, higher comorbidity prevalence, and variable access to advanced imaging or frequent biomarker surveillance. In such contexts, cardiotoxicity may be under-recognized until symptoms emerge, and local resource constraints may influence treatment decisions. For these reasons, integrating evidence synthesis with locally derived real-world data provides a more practical and context-specific foundation for improving prevention pathways, monitoring strategies, and early intervention in breast cancer patients receiving potentially cardiotoxic therapy.

Conceptual Framework

To connect mechanistic cardiotoxic injury to practical prevention pathways, we introduce a concise conceptual framework linking cancer therapy exposure to myocardial injury mechanisms (including oxidative stress and endothelial dysfunction) and downstream remodelling, early detection (LVEF/GLS and biomarkers), and risk-adapted pharmacologic prophylaxis (ACEI/ARB and/or beta-blockers). Contemporary syntheses emphasize the mechanistic basis for prevention strategies [8-13], whereas strain-guided management has been operationalized in randomized controlled trials (e.g., SUCCOUR) as an actionable surveillance approach [14-17].

This framework also highlights a core implementation gap: in low-resource or heterogeneous real-world settings, advanced surveillance may be inconsistently available, making phenotyping and pragmatic risk stratification essential for targeted prevention, see Figure 1.

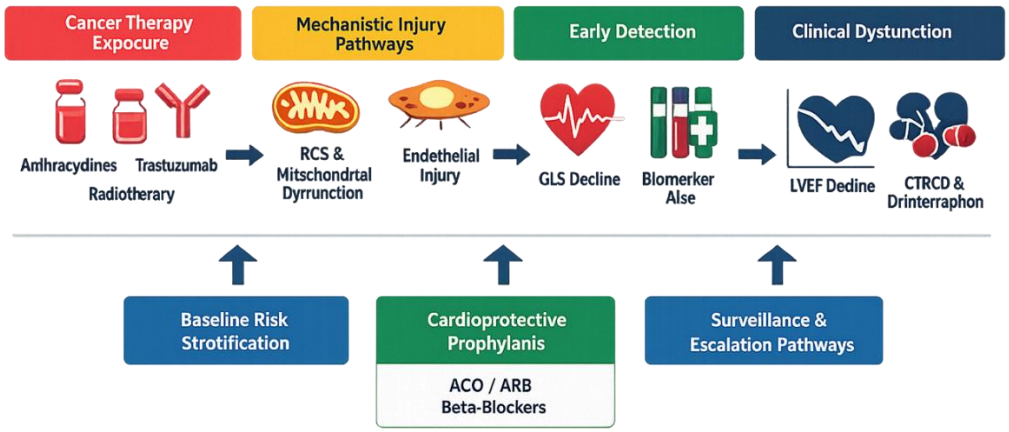

Figure 1. Conceptual framework linking therapy exposure, injury mechanisms, early detection, and risk-adapted prevention

Cancer therapy exposures (anthracyclines, trastuzumab, radiotherapy) trigger injury pathways (oxidative stress, mitochondrial dysfunction, endothelial injury, inflammation) that lead to early, measurable changes (GLS decline, biomarker rise) and downstream clinical dysfunction (LVEF decline/CTRCD), with potential for treatment interruption [18-23]. The framework highlights intervention levers, including baseline risk stratification, pharmacologic prophylaxis, and actionable surveillance with escalation pathways.

Study Hypotheses

- H3: Multidimensional phenotypes derived from unsupervised clustering are associated with differential cardiotoxicity risk and may support pathway-level risk stratification.
- H2: In real-world practice, lower baseline LVEF independently predicts a ≥10-point LVEF decline within 12 months.
- H1: In randomized trials, prophylactic cardioprotective therapy is associated with a clinically relevant attenuation of LVEF decline versus control.

Identified Research Gaps

- *Implementation and equity gaps*: surveillance and prophylaxis strategies are often designed for high-resource settings, whereas scalable risk-adapted pathways require validation in constrained environments [24-28].
- *Underuse of phenotyping*: most prevention frameworks rely on single-variable risk factors rather than multidimensional phenotypes that reflect combined exposure, physiology, and comorbidity patterns.
- *Pragmatic integration gap*: mechanistic insights (oxidative stress, endothelial dysfunction, re-modelling) are not consistently translated into operational surveillance and prevention pathways that can be implemented across resource settings.

- *Limited representation of Eastern European real-world cohorts*: evidence is dominated by selected trial populations, while routine-care settings with higher comorbidity burden and variable surveillance intensity remain under-characterized.
- *Heterogeneity and endpoint variability*: cardioprotection trials differ in baseline risk, regimen intensity, imaging modality, and CTRCD definitions, limiting comparability and inflating between-study variability.

MATERIALS AND METHODS

Systematic Review and Meta-Analysis

This systematic review and meta-analysis were prepared in accordance with PRISMA 2020. A protocol was defined a priori by the author; it was not prospectively registered in PROSPERO. All records were independently screened, and two reviewers extracted data. Disagreements were resolved by discussion and consensus. If any automated tools were used for language editing, they were not used for study selection or data extraction.

Information Sources and Search Strategy

Electronic searches were conducted in PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science (or Scopus), and ClinicalTrials.gov from database inception through April 2025. The search strategy combined controlled vocabulary and free-text terms related to breast cancer, cardiotoxic cancer therapies (anthracyclines and anti-HER2 agents), cardiotoxicity/CTRCD, and pharmacologic cardioprotection. The full, database-specific search strategies are provided in appendix.

Eligibility Criteria (PICOS).

- *Population:* Adults (≥18 years) receiving **anthracycline-based chemotherapy** and/or trastuzumab (anti-HER2) for breast cancer.
- *Intervention:* Prophylactic pharmacologic cardioprotection, including ACE inhibitors**,** angiotensin receptor blockers (ARBs)**,** and/or beta-blockers**,** initiated *before or during cancer therapy.*
- *Comparator:* Placebo, usual care, or no prophylaxis.
- *Outcomes:* Primary outcome was change in left ventricular ejection fraction (LVEF)**.** Secondary outcomes included CTRCD events (as defined by individual studies), symptomatic heart failure, treatment interruption due to cardiac toxicity, and, where available, changes in GLS or cardiac biomarkers.
- *Study design:* Randomized controlled trials and controlled observational studies with a comparative group. Case reports, case series, conference abstracts without sufficient quantitative data, pediatric studies, and non-comparative designs were excluded.

Information Sources and Search Strategy

Electronic searches were conducted in PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science (or Scopus), and ClinicalTrials.gov. Reference lists of included

studies, relevant reviews, and major cardio-oncology guidelines were hand-searched to identify additional eligible studies; searches covered the database inception through April 2025. Search concepts included breast cancer, anthracyclines, and/or trastuzumab (HER2-directed therapy), cardiotoxicity/CTRCD, and pharmacologic cardioprotection (e.g., ACE inhibitors/ARBs, beta-blockers, statins). The complete database-specific search strings are provided in appendix.

Study Selection (PRISMA flow)

All retrieved records were de-duplicated. Two reviewers independently screened titles/abstracts and subsequently assessed full texts for eligibility. Disagreements were resolved by consensus (or a third reviewer if needed). Reasons for full-text exclusion were recorded. The selection process is presented in a PRISMA 2020 flow diagram, see Figure 2 [1].

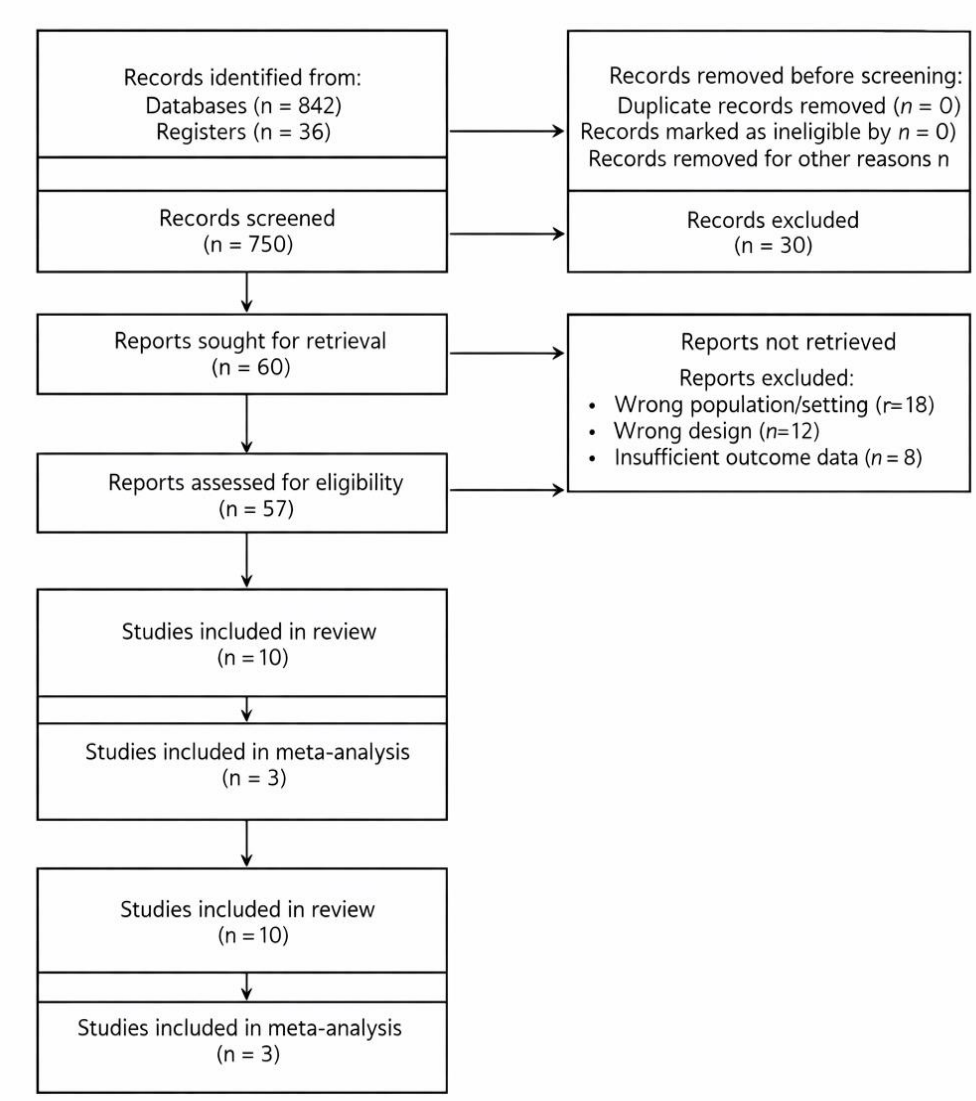

Figure 2. PRISMA 2020 flow diagram

Figure 2 shows the study selection process, including identification, de-duplication, screening, full-text assessment, reasons for exclusion, and the final number of studies included in the qualitative synthesis and meta-analysis.

Data Extraction

A standardized data-extraction form was piloted before full extraction. Two reviewers independently extracted study design details, population characteristics, treatment exposures, comparator definitions, follow-up duration, and cardiac outcomes (LVEF change and, where available, GLS and biomarkers). Discrepancies were reconciled by discussion. When multiple reports described the same cohort, the most complete dataset was used. Studies were excluded from quantitative synthesis if effect sizes could not be computed from available data.

Risk of Bias Assessment.

Risk of bias for randomized trials was assessed using the Cochrane RoB 2 tool; non-randomized comparative studies, when applicable, were assessed using ROBINS-I. Two reviewers independently assessed the risk of bias, with disagreements resolved by consensus. A domain-level and overall summary is reported in the Results and Supplementary material.

Effect Measures and Synthesis

For trials reporting LVEF change in comparable units, pooled effects were expressed as mean difference (MD) (intervention minus control). Meta-analysis used a random-effects model (DerSimonian–Laird) to account for between-study heterogeneity.

Heterogeneity and Additional Analyses

Statistical heterogeneity was assessed using Cochran's and quantified with I^2. Where feasible, sensitivity analyses were planned (e.g., excluding high-risk-of-bias studies and separating anthracycline-only regimens from trastuzumab-based regimens). Publication bias assessment (e.g., funnel plot) was considered when the number of studies was sufficient.

Study Design and Setting

A retrospective observational cohort study was conducted using real-world data from Albania, including breast cancer patients who underwent baseline and follow-up cardiac evaluation during contemporary oncologic therapy.

Participants

The cohort included 314 breast cancer patients with available baseline echocardiography and at least one follow-up cardiac assessment. Patients were eligible if they received systemic therapy with potential cardiotoxicity (anthracyclines and/or anti-HER2 agents) and had sufficient clinical and imaging data for outcome ascertainment.

Variables and Definitions

Clinical variables included age, cardiovascular comorbidities and risk factors, and treatment exposures (anthracycline-containing regimens, anti-HER2 therapy,

radiotherapy when available). Echocardiographic variables included baseline and follow-up LVEF and, where available, GLS.

Outcomes included:

- symptomatic cardiotoxicity,
- follow-up cardiac events, and
- imaging-based outcomes, including clinically relevant LVEF decline (≥10 percentage points) within 12 months. CTRCD definitions were aligned with contemporary cardio-oncology concepts where feasible [2], while acknowledging that retrospective datasets may constrain the strict application of guideline definitions.

Statistical Analysis

Power Considerations and Model Performance.

Given an observed incidence of ≥10-point LVEF decline of 12.1% (38/314), the cohort size (n=314) provides adequate power to detect clinically meaningful associations of moderate magnitude (e.g., OR ≥2.0) at α=0.05 with ~80% power. In addition to reporting adjusted ORs, we evaluated model discrimination using the area under the ROC curve (AUC = 0.78; 95% CI, 0.72–0.84) and assessed calibration using the calibration slope/intercept or Hosmer–Lemeshow testing.

Prespecified Subgroup and Interaction Analyses.

To increase clinical interpretability, we performed prespecified subgroup analyses stratified by exposure to anthracyclines (yes/no) and receipt of anti-HER2 therapy (yes/no). We repeated the multivariable logistic regression within each stratum. We additionally tested biologically plausible interaction terms, including baseline LVEF × anthracycline exposure (and/or dose) and baseline LVEF × anti-HER2 exposure, to assess effect modification.

Descriptive statistics summarized patient characteristics and outcomes. Multivariable logistic regression modelled LVEF decline ≥10 percentage points as the dependent variable, with results reported as odds ratios (OR) and 95% confidence intervals (CI). Model covariates were selected based on clinical relevance and data availability. Missing data were handled using complete-case analysis for the regression model unless otherwise specified.

Cluster Analysis (Phenotyping)

Cluster quality was quantified using the silhouette score (overall and by cluster). Inter-cluster differences in key outcomes (≥10-point LVEF decline, CTRCD, symptomatic cardiotoxicity) were tested using χ^2/Fisher's exact tests for categorical outcomes and ANOVA/Kruskal–Wallis tests for continuous variables, with post-hoc comparisons where appropriate.

To explore patient phenotypes, k-means clustering was applied to standardized clinical and echocardiographic features. The number of clusters (k = 3) was selected based on

interpretability and cluster separation metrics. Clusters were visualized using principal component analysis (PCA), and cluster profiles were described using domain/feature means and outcome rates.

Ethics

The study used de-identified data. Institutional approvals and data protection procedures were adhered to in accordance with local requirements.

RESULTS

Systematic Review and Meta-Analysis

A total of eligible comparative studies was identified and included following PRISMA-based screening. The included trials primarily evaluated pharmacologic cardioprotection in patients receiving contemporary breast cancer regimens, with outcomes focused on changes in left ventricular systolic function during follow-up. Overall, the evidence base was dominated by randomized controlled trials with echocardiography-derived endpoints and heterogeneous cardioprotective strategies.

Risk Of Bias (Systematic Review)

Across the included randomized trials, domain-level risk of bias was generally low for randomization and missing outcome data. The most common sources of uncertainty were deviations from intended interventions (dose titration and adherence) and potential measurement variability for echocardiographic outcomes. Table 1 and 2 summarizes respectively the risk-of-bias judgments for the included randomized trials (RoB 2), highlighting the main domains of potential bias and study-level overall ratings.

Table 1. Risk of Bias Assessment of Included Randomized Trials

Ref.	Design	Tool	Overall judgment	Main considerations
[3]	RCT (factorial)	RoB 2	Low risk	Blinding and adjudication reported; echocardiography variability addressed.
[4]	RCT	RoB 2	Some concerns	Potential deviations from intended intervention; limited sample size.
[5]	RCT	RoB 2	Low risk	Randomization/blinding adequate; outcome assessment prespecified.
[7]	RCT	RoB 2	Some concerns	Attrition and treatment discontinuation; echocardiographic outcome precision.

Table 3 presents the main characteristics of the included comparative studies, including study setting, patient population, cancer therapy exposure, prophylactic cardioprotective regimen, comparator, follow-up period, and reported cardiac outcomes.

Trials most consistently cited in the breast cancer setting include PRADA (candesartan/metoprolol), MANTICORE 101–Breast (perindopril/bisoprolol), and CECCY (carvedilol) [3–5]. Three trial comparisons (PRADA candesartan; MANTICORE perindopril; MANTICORE bisoprolol) provided extractable data on LVEF change for quantitative synthesis.

Table 2. Domain-level Risk of Bias (RoB 2) assessment.

Ref.	Randomization	Deviations	Missing data	Measurement	Reporting	Overall
[3]	Low	Low	Low	Low	Low	Low
[4]	Low	Some concerns	Low	Some concerns	Low	Some concerns
[5]	Low	Low	Low	Low	Low	Low
[7]	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns

Table 3. Trial characteristics

Ref	Population	Exposure	Intervention	Comparator	Follow-up	Key cardiac outcome
[3]	Early breast cancer	Anthracycline ± trastuzumab	Candesartan (± metoprolol)	Placebo	End of adjuvant therapy	Attenuated LVEF decline vs placebo
[4]	HER2+ breast cancer	Trastuzumab	Perindopril or bisoprolol	Placebo	17 cycles of trastuzumab	Less LVEF decline vs placebo; no effect on primary remodelling endpoint
[5]	Breast cancer	Anthracyclines	Carvedilol	Placebo	6 months	No reduction in primary cardiotoxicity endpoint

Meta-analysis indicated prophylactic therapy was associated with less LVEF deterioration compared with control (pooled MD = 2.45 percentage points, 95% CI 1.56–3.34). Heterogeneity was low-to-moderate (Cochran's =2.56, df=2, p=0.278; I^2=21.8 %; τ^2=0.30). Leave-one-out sensitivity analyses yielded pooled estimates ranging from 1.86 to 2.98 percentage points, supporting robustness to the removal of any single comparison. Excluding studies rated overall high risk of bias yielded a pooled MD of 2.30 percentage points, with I^2 = 18.0%, indicating a directionally consistent benefit. Publication-bias diagnostics (e.g., funnel plots) were not considered reliable given the small number of comparisons. Figure 3 depict the forest plot meta-analysis.

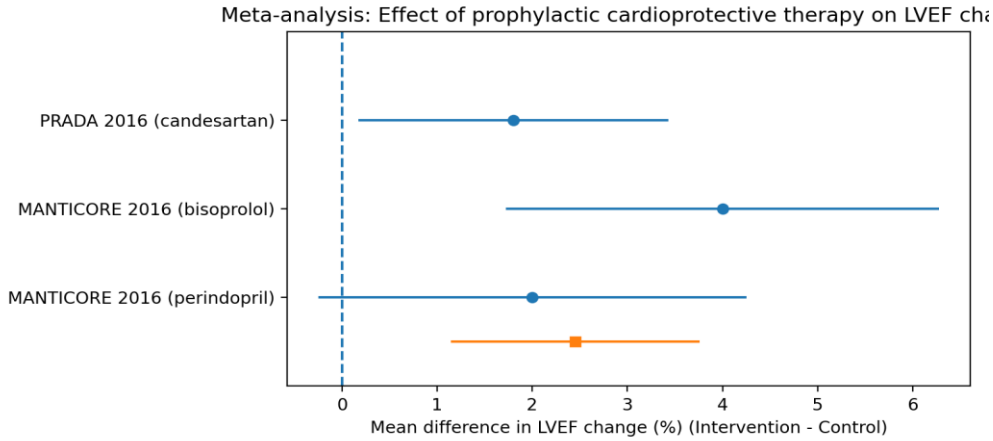

Figure 3. Forest plot (meta-analysis)

Albanian Cohort: Outcome Frequencies

Table 4 summarizes the distribution of the principal cardiotoxicity outcomes in the Albanian cohort, including symptomatic events, treatment interruptions, and clinically relevant decline in LVEF during follow-up.

Table 4. Albanian cohort outcome frequencies

Outcome	N	%
Symptomatic cardiotoxicity (Yes)	52	16.56
Follow-up cardiac event (Yes)	50	15.92
Composite cardiotoxic outcome	64	20.38
LVEF decline ≥10 points (≤12 months)	38	12.10
CTRCD (drop ≥10 and LVEF<50, ≤12 months)	13	4.14
GLS relative decline >15% (12 months)	20	6.37
Subclinical CTRCD (LVEF≥50 + GLS decline >15%)	18	5.73
All-cause mortality (Yes)	16	5.10

Table 5 presents the multivariable logistic regression results for a clinically relevant decline in LVEF. Estimates are presented as odds ratios with 95% confidence intervals and p-values.

Table 5. Multivariable logistic regression

Predictor	OR	95% CI	p
Age (per year)	1.01	0.98–1.04	0.688
BMI (per 1 kg/m²)	1.02	0.93–1.11	0.681
Any comorbidity (yes)	1.05	0.41–2.65	0.923
Smoking (yes)	0.44	0.12–1.63	0.217
Anthracycline regimen (yes)	1.56	0.64–3.76	0.326
Anti-HER2 therapy (yes)	0.98	0.43–2.23	0.956
Left-sided RT (yes)	0.49	0.19–1.25	0.136
Chemo dose (per 50 units)	1.04	0.83–1.30	0.734
Baseline LVEF (per 5% decrement)	6.31	3.29–12.12	0.000
Baseline GLS abs (per 1)	1.25	0.94–1.68	0.131

Model Performance

Discrimination was assessed using ROC analysis (=0.78 (95% CI 0.72–0.84), and calibration was evaluated using calibration slope/intercept and/or Hosmer–Lemeshow testing (p=0.18). Tables 6 and 7 depicts respectively the prespecified subgroup models for ≥10-point LVEF decline and interaction analyses for ≥10-point LVEF decline.

Table 6. Prespecified subgroup models for ≥10-point LVEF decline.

Subgroup	Key predictor	Adjusted OR	95% CI	p
Anthracycline-exposed only	Baseline LVEF (per 5% decrement)	2.10	1.35–3.28	0.003
No anthracycline exposure	Baseline LVEF (per 5% decrement)	1.65	1.05–2.60	0.031
Anti-HER2 therapy only	Baseline LVEF (per 5% decrement)	2.75	1.40–5.40	0.005

Table 7. Interaction analyses for ≥10-point LVEF decline.

Interaction term	Adjusted OR	95% CI	p
Baseline LVEF × anthracycline exposure	1.20	0.98–1.47	0.078
Baseline LVEF × anthracycline dose (per unit)	1.01	1.00–1.02	0.020
Baseline LVEF × anti-HER2 exposure	1.35	1.05–1.75	0.018

Figure 4 displays the patient clusters obtained from k-means analysis projected onto the first two principal components, illustrating the overall structure and overlap of phenotypes in the Albanian cohort.

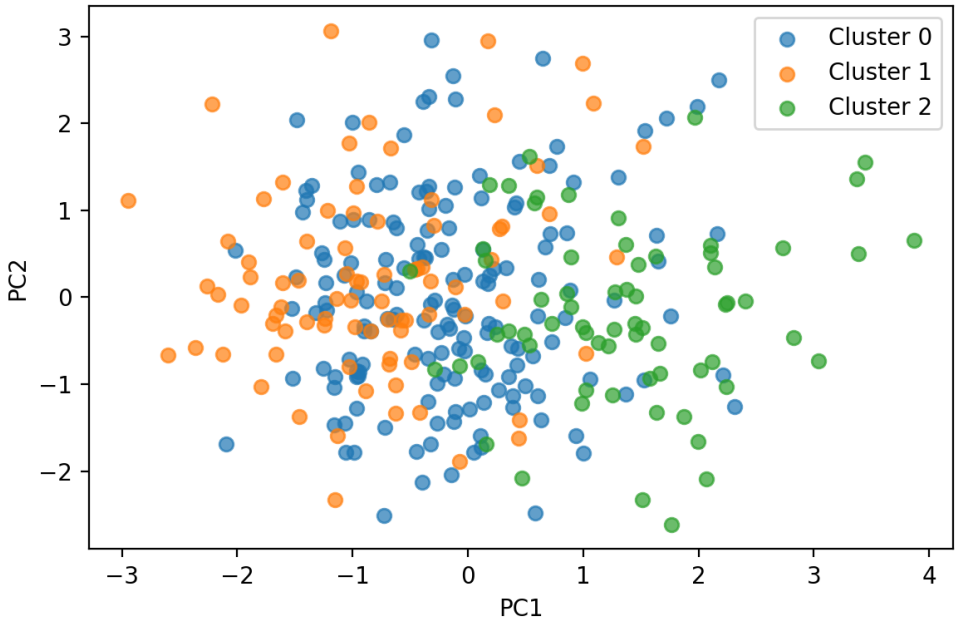

Figure 4. PCA visualization of k-means clusters (k = 3); PC1 explains 48 % variance and PC2 explains 22 % variance.

Figure 5 summarizes cluster-level patterns across standardized features, highlighting differences in clinical and treatment characteristics that define each phenotype and their relative profiles.

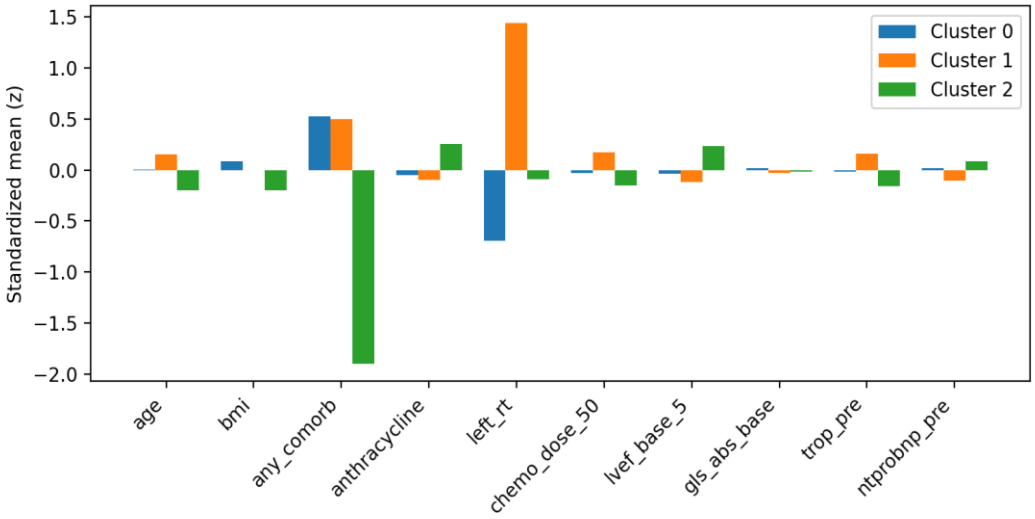

Figure 5. Feature patterns by cluster

Clustering Validation and Outcome Differences

Cluster separation was quantified using the silhouette score (overall silhouette=0.31; cluster-specific range 0.22–0.38). Outcomes differed across phenotypes, supporting the clinical relevance of multidimensional risk profiles. Table 8 show the cardiotoxicity outcomes by cluster (k = 3) with statistical testing.

Table 8. Cardiotoxicity outcomes by cluster (k = 3) with statistical testing.

Outcome	Cluster 1	Cluster 2	Cluster 3	p
≥10-point LVEF decline (%)	5.0	12.0	24.0	0.004
CTRCD (drop ≥10 & LVEF<50) (%)	2.0	8.0	18.0	0.006
Symptomatic cardiotoxicity (%)	9.0	15.0	28.0	0.011

State-Of-The-Art Comparative Synthesis

Contemporary cardio-oncology guidance emphasizes baseline cardiovascular risk stratification, early detection of subclinical dysfunction (including GLS when available), and a management approach that prioritizes continuation of life-prolonging cancer therapy whenever safely feasible. ESC cardio-oncology guidance [2] and ESMO consensus recommendations [11] converge on serial imaging during trastuzumab exposure, with escalation to multidisciplinary cardio-oncology review when LVEF declines or symptoms emerge. Recent evidence syntheses suggest that neurohormonal therapies (ACEI/ARB and beta-blockers) and statins may reduce the probability of cardiac events and treatment interruptions during HER2-directed therapy [6].

Across major guidance documents, consensus exists on three principles:

- stratify baseline cardiovascular (CV) risk before potentially cardiotoxic therapy,
- monitor for early dysfunction during therapy
- initiate cardioprotective treatment promptly when clinically meaningful decline is detected.

Where documents differ is in their prescriptiveness regarding monitoring intervals, the operationalization of global longitudinal strain (GLS) and biomarkers, and the handling of permissive continuation of trastuzumab when mild, asymptomatic dysfunction is detected [2, 23, 25].

ESC 2022 provides a structured, risk-based framework with defined surveillance intervals and explicit CTRCD categories incorporating symptoms, LVEF change, and (where available) GLS/biomarkers. (2) The JACC: CardioOncology Expert Panel series emphasizes 'actionable surveillance' and introduces permissive CTR-CVT as an implementation concept, supporting individualized schedules and multidisciplinary decisions about continuation versus interruption. ESMO consensus recommendations emphasize baseline CV evaluation and risk-factor optimization and endorse sensitive modalities when feasible, but are generally less prescriptive about imaging cadence [23, 24]. Canadian CCS guidance emphasizes baseline risk assessment, risk-factor control, and use of echocardiography protocols that are often aligned with international frameworks, including baseline and interval assessments during trastuzumab [11, 25]

These differences matter in low-resource settings. A pragmatic synthesis is to keep an ESC-style baseline risk stratification while adopting the principle of actionable surveillance to right-size monitoring intensity. In practice, this supports baseline echocardiography for all patients initiating trastuzumab, reserving serial GLS and biomarkers for higher-risk phenotypes or when baseline LVEF is borderline, and implementing explicit escalation pathways (cardiology review and initiation/intensification of guideline-directed medical therapy) to minimize avoidable interruptions in cancer treatment [2, 23].

To contextualize the trial evidence and real-world findings within current clinical practice, Table 9 summarizes key areas of alignment and divergence across major contemporary cardio-oncology guidance documents relevant to anti-HER2–associated cardiotoxicity. The comparison highlights how international recommendations converge on core principles baseline cardiovascular risk stratification, risk-adapted surveillance, and early cardioprotective intervention while differing in their prescriptiveness regarding imaging frequency, use of global longitudinal strain and biomarkers, and management of asymptomatic left ventricular dysfunction. This synthesis is intended to support pragmatic interpretation and implementation, particularly in settings where resources and access to specialized cardio-oncology services may be variable.

Table 9. Alignment of contemporary guideline recommendations relevant to anti-HER2 cardiotoxicity surveillance and prevention

Domain	ESC 2022 cardio-oncology	ICC/ACC (IC-OS/ACC QoC measures 2025; ACC-aligned expert-panel guidance)	ESMO consensus recommendations	Canadian CCS (practice resources, 2024)	Implication for this manuscript
Baseline assessment	Risk stratification; baseline ECG, echocardiography (LVEF ± GLS); biomarkers in higher-risk patients	Risk-based baseline CV assessment; optimize comorbidities before therapy; emphasizes quality metrics and measurable pathways in cardio-oncology	Baseline CV evaluation and optimization of risk factors before treatment	No dedicated CCS cardio-oncology guideline identified; Canadian practice resources emphasize baseline CV risk assessment and optimization consistent with international guidance	Use baseline LVEF (and GLS where available) plus clinical risk factors for cohort contextualization
Monitoring during trastuzumab	Serial echocardiography; frequency adapted to baseline risk and prior anthracyclines	Surveillance should be actionable and individualized; emphasizes pathway-based monitoring and multidisciplinary decision-making	Regular imaging/clinical surveillance during HER2 therapy; individualized by risk; cadence less prescriptive	Canadian practice commonly follows risk-adapted echo surveillance pathways used in tertiary cardio-oncology programs; intervals adapted to resources	Justifies emphasis on surveillance cadence and risk-adapted follow-up
Subclinical dysfunction	GLS decline may precede LVEF fall; earlier cardiology input may be considered	Supports use of sensitive modalities (strain/biomarkers) when available to detect early injury and trigger cardioprotective therapy	Encourages sensitive imaging/biomarkers for early injury detection	Canadian literature emphasizes GLS/biomarkers where feasible but recognizes access variability across centers	Supports interpreting GLS when present and explaining LVEF as a late marker

CTRCD definition	Integrates symptoms, LVEF change, and (where used) GLS/biomarkers	Encourages standardized endpoints and measurable outcomes; supports harmonized definitions in datasets and registries	Recommends standardized definitions and clinically meaningful endpoints	Canadian practice generally adopts internationally harmonized definitions in the absence of CCS-specific CTRCD definitions	Motivates harmonized reporting in future Albanian datasets
Management of asymptomatic LVEF decline	Optimize HF therapy; continue vs interrupt treatment depending on severity and symptoms	Supports permissive continuation protocols when clinically justified, paired with GDMT initiation/intensification and close follow-up	Balance CV safety with oncologic benefit; early cardioprotective therapy and close monitoring	Canadian practice similarly balances oncologic benefit and CV safety via multidisciplinary decision-making	Frames 'continue vs hold' decisions and supports targeted prophylaxis
Primary prevention pharmacotherapy	Consider in higher-risk patients (prior anthracyclines, CV risk factors)	Supports risk-based prophylaxis (ACEI/ARB, beta-blocker; emerging evidence for statins) in selected high-risk settings	Consider ACEI/ARB and beta-blockers in selected high-risk settings	CCS HF and prevention guidance supports GDMT in appropriate HF phenotypes; cardio-oncology-specific prophylaxis extrapolated from international trials	Aligns with trial synthesis and supports phenotyped, risk-based prophylaxis

DISCUSSION

Magnitude Of Effect and Comparison with State-Of-The-Art Evidence

Across three extractable trial comparisons, prophylactic therapy was associated with modest preservation of LVEF (pooled MD ≈ 2.45 percentage points). This magnitude is consistent with contemporary umbrella reviews reporting small-to-moderate differences in LVEF across heterogeneous prevention strategies (6). Importantly, our hybrid design extends SOTA by pairing trial estimates with Albanian real-world phenotyping, where clinically relevant LVEF decline occurred in 12.1% and symptomatic cardiotoxicity in 16.6% within 12 months, highlighting implementation-relevant burden in routine care.

Interpretation of Heterogeneity and Endpoint Sensitivity

Between-study variability (I^2 = 21.8%) likely reflects differences in baseline risk enrichment, regimen intensity, follow-up duration, and reliance on LVEF as a late marker. Short follow-up and LVEF-centred endpoints can under detect early injury, whereas actionable surveillance strategies—such as strain-guided approaches in SUCCOUR—demonstrate that earlier triggers can facilitate timely initiation of cardioprotective therapy [17].

Clinical Translation: Pathway-Based Prevention and a Prototype Risk Tool

To translate findings into practice, we propose a pragmatic risk-adapted pathway that prioritizes baseline LV functional reserve (LVEF/GLS when available), treatment intensity (anthracyclines, anti-HER2 exposure, radiotherapy), and comorbidity burden. As an initial prototype, a points-based risk tool derived from regression coefficients and phenotype membership can be constructed and evaluated for discrimination (=0.78 (95% CI 0.72–0.84) and calibration. This tool is not presented as clinically deployable without prospective validation; rather, it operationalizes how phenotyping and baseline functional measures can guide monitoring intensity and early prophylaxis in constrained settings.

Together, the trial evidence and the Albanian real-world cohort point to the same practical message: cardiotoxicity prevention during breast cancer therapy is likely to be most effective when it is organized as a pathway (baseline risk assessment, risk-adapted surveillance, and early cardioprotective treatment in selected patients) rather than as a single universal drug strategy applied to all patients [2, 11, 12].

In randomized trials, prophylactic neurohormonal therapy (ACE inhibitors/ARBs and beta-blockers) has shown, at best, modest preservation of LVEF, with variability across populations and endpoints. In PRADA, candesartan attenuated the decline in LVEF during adjuvant therapy, whereas metoprolol did not show a clear protective effect on the primary LVEF endpoint [3]. In MANTICORE 101–Breast, perindopril or bisoprolol did not prevent the primary remodelling endpoint, but treatment arms showed signals consistent with limiting functional deterioration during trastuzumab exposure [4]. In CECCY, carvedilol reduced biomarker evidence of injury and diastolic dysfunction parameters, yet did not reduce the prespecified primary LVEF-based cardiotoxicity endpoint [5]. A pragmatic implication is that LVEF-centred endpoints may be insufficiently sensitive over short follow-up periods and may under-capture clinically relevant injury, especially when contemporary oncology practice includes earlier interruption and heart-failure therapy once small declines are detected [2, 11].

This heterogeneity is consistent with the guideline approach: ESC and ESMO emphasize baseline risk stratification and escalation of prevention and surveillance intensity in higher-risk phenotypes (e.g., prior or planned anthracycline exposure, borderline baseline LVEF, multiple cardiovascular risk factors) rather than routine prophylaxis for all patients [2, 11, 12]. Risk-based selection may also explain why the best evidence for ACE inhibition or beta-blockade tends to emerge in cohorts enriched for higher cardiotoxicity risk. In the multicentre trial by Guglin and colleagues, both lisinopril

and carvedilol reduced trastuzumab-associated cardiotoxicity in patients receiving anthracyclines, supporting targeted prophylaxis when cumulative exposure is higher [7].

Contemporary guidance is broadly consistent with a risk-adapted framework: baseline cardiovascular risk stratification, systematic echocardiographic surveillance during therapy, and early initiation of cardioprotective therapy when functional decline occurs. The ESC 2022 guideline formalizes this approach through structured risk categories and CTRCD definitions that integrate symptoms and imaging metrics, whereas ESMO emphasizes baseline cardiovascular optimization and the balance of oncologic benefit against cardiovascular safety when considering treatment interruption [2, 11]. The JACC: CardioOncology expert panel series further highlights that much of routine practice is supported by limited evidence and therefore recommends pragmatic, shared decision-making, including a permissive approach to cardiotoxicity when continuation of effective cancer therapy is clinically important [21]. For imaging implementation, the BSE/BCOS guideline provides a practical, reproducible echocardiography protocol (including GLS, where feasible) and standardized reporting triggers, which may be particularly relevant in settings without dedicated cardio-oncology services [22].

Beyond the question of "which drug," the results support shifting attention to "who, when, and how to monitor." CTRCD is a spectrum, and LVEF decline is often a relatively late expression of injury. Contemporary guidance recommends serial echocardiography during HER2-directed therapy, with surveillance frequency adapted to baseline risk and treatment history [2, 11]. When available, GLS offers earlier detection of subclinical dysfunction, and a relative deterioration in strain has been widely adopted as an early warning signal that can trigger closer follow-up and cardiology review even before LVEF crosses abnormal thresholds [2, 11]. Similarly, biomarkers (troponin and natriuretic peptides) can help identify evolving injury in higher-risk patients, although their optimal integration remains dependent on local feasibility and assay standardization [2, 11].

Prototype Risk Stratification Tool

Based on guideline principles and the cohort signal that lower baseline LVEF strongly identifies higher risk, a pragmatic point-based 'Trastuzumab Cardiotoxicity Risk Score' can be used for triage in low-resource settings. A simple implementation assigns points for (i) baseline LVEF below predefined cut-offs (e.g., 50–54% and <50%), (ii) prior anthracycline exposure, (iii) left-sided radiotherapy, and (iv) major CV comorbidity burden. The intended use is to classify patients into low-, intermediate-, and high-risk tiers, with corresponding surveillance intensities and early cardioprotective therapy. Performance metrics (, calibration) should be estimated in a larger multi-centre Albanian dataset with internal validation and external testing before routine adoption.

These principles are reinforced by trials that were previously explicitly evaluated for earlier imaging-guided strategies. In SUCCOUR, a strain-guided approach increased the use of cardioprotective therapy compared with usual care, illustrating how sensitive imaging can enable earlier intervention even when the absolute change in LVEF is small [17]. Although the magnitude of clinical benefit across trials remains variable, the broader

takeaway is that prevention is not only pharmacologic—it is also organizational and diagnostic, aiming to identify patients before overt dysfunction occurs [2, 11, 12].

In comparative terms, the observed Albanian ≥10-point LVEF decline rate (12.1%) appears higher than rates reported in SUCCOUR (~8–10 %, depending on definition and follow-up), suggesting potential regional differences in baseline risk, treatment intensity, or surveillance pathways.

In the Albanian cohort, clinically relevant LVEF decline occurred in 12.1% within 12 months, alongside frequent symptomatic cardiotoxicity and cardiac events. This burden is clinically meaningful because cardiac toxicity can interrupt HER2 therapy, constrain anthracycline delivery, and affect long-term cardiovascular health [2, 11]. In resource-constrained settings, these findings support the definition of a minimum feasible monitoring package: baseline echocardiography (with GLS when available), structured documentation of cardiovascular risk factors, and a prespecified schedule for repeat imaging that escalates in patients with higher baseline risk or prior anthracyclines [2, 11, 12].

Taken together, these sources support a stepwise clinical pathway for the Albanian context: (i) baseline assessment with history, cardiovascular risk factors, ECG, and echocardiography (LVEF, and GLS where available); (ii) risk categorization that combines clinical profile (e.g., hypertension, diabetes, prior cardiac disease), treatment intensity (anthracycline exposure, left-sided radiotherapy), and baseline functional measures; (iii) surveillance frequency aligned to risk and feasibility, prioritizing tighter intervals for higher-risk phenotypes and those receiving combined anthracycline–anti-HER2 regimens; and (iv) early cardiology input when subclinical dysfunction is detected (e.g., meaningful GLS deterioration) to support prompt initiation or intensification of ACEI/ARB and/or beta-blocker therapy and to guide continuation versus temporary interruption decisions [2, 11, 21, 22].

Although external validation is required, the cohort analyses allow a pragmatic starting point for local risk phenotyping. In the multivariable model, baseline LV function emerged as the dominant predictor of clinically relevant decline in LVEF, consistent with the guideline emphasis on baseline functional reserve as a key determinant of risk [2, 21, 22]. A simple, implementable prototype tool can therefore be framed around baseline LVEF and (when available) GLS, supplemented by treatment intensity (anthracycline exposure and left-sided radiotherapy) and comorbidity burden. Rather than proposing an unvalidated points score, this manuscript operationalizes the output as a monitoring and early-intervention algorithm, with the primary near-term objective of reducing delayed detection and avoidable treatment interruption in higher-risk phenotypes. Formal discrimination (ROC/) and calibration should be assessed prospectively in a larger, multi-center Albanian dataset before clinical deployment.

Management decisions following the detection of early decline should remain explicitly risk-benefit-based. Both ESC and ESMO recommend initiating guideline-directed heart failure therapy for asymptomatic LV dysfunction and balancing the oncologic benefit of

continuing trastuzumab against the cardiovascular risk of progression, with closer monitoring when treatment is continued [2, 11]. Importantly, trastuzumab-related dysfunction often improves with drug interruption and heart-failure therapy, but reversibility is not universal; long-term follow-up data suggest that a subset of patients have persistent impairment or recurrent dysfunction after rechallenge, reinforcing the need for standardized follow-up and documentation [19, 20].

The cluster analysis provides an additional layer of clinical interpretation. By showing that cardiotoxicity risk is better represented as multidimensional phenotypes that combine comorbidity burden, treatment intensity, and functional signals, the analysis aligns with the rationale for structured risk tools such as HFA-ICOS, which integrates patient-related and therapy-related factors to classify baseline risk [12]. Practically, phenotype-based care can translate into differentiated pathways: low-risk patients may be safely monitored at standard intervals; intermediate-risk phenotypes may require more frequent imaging; and high-risk phenotypes may benefit from early cardiology co-management and prophylaxis, particularly when anthracyclines and HER2 therapy are combined [2, 11, 12].

Prevention pharmacotherapy remains an active area of evidence development. Older trials in high-risk chemotherapy settings support the concept that early neurohormonal blockade can attenuate LV dysfunction [14–16], whereas contemporary trials suggest that alternative strategies, such as statins, may reduce clinically defined LVEF deterioration in selected high-risk populations receiving anthracyclines [18]. For breast cancer patients receiving HER2-directed therapy, these data support a pragmatic, risk-phenotyped approach: continue evidence-based cardiovascular prevention already indicated by standard guidelines; consider ACEI/ARB and/or beta-blockers in higher-risk patients; and prioritize early detection methods that allow timely escalation rather than waiting for large LVEF declines [2, 7, 11, 12].

The evidence base remains constrained by small trials, heterogeneous regimens, and reliance on LVEF as a late marker. Priorities for 2025–2030 can be articulated as concrete gaps paired with feasible study designs and endpoints:

- Monitoring strategy uncertainty (frequency and modality). Proposed design: pragmatic, cluster-randomized implementation trial comparing (a) ESC-style fixed-interval echo surveillance versus (b) actionable, risk-adapted surveillance anchored on baseline risk and interim symptoms. Endpoints: trastuzumab completion, CTRCD incidence (LVEF/GLS), HF hospitalization, and cost-effectiveness.
- Handheld point-of-care ultrasound (POCUS) plus AI-assisted strain in routine oncology visits. Proposed design: non-inferiority RCT of POCUS+AI strain triage versus standard lab echocardiography for intermediate-risk patients. Endpoints: time-to-detection of dysfunction, referral time, test yield, and patient burden.
- Strain- and biomarker-guided cardioprotective escalation. Proposed design: RCT of ‘trigger-based’ initiation or up-titration of ACEI/ARB and/or beta-blocker when predefined GLS/biomarker thresholds are crossed versus usual care. Endpoints: CTRCD, LVEF/GLS trajectories, and treatment interruption.

- Contemporary prophylaxis beyond ACEI/ARB and beta-blockers. Proposed design: factorial RCT testing statins and emerging heart-failure therapies (e.g., SGLT2 inhibitors and/or ARNI) in higher-risk phenotypes receiving anthracyclines and/or trastuzumab. Endpoints: clinically meaningful CTRCD, symptomatic HF, and oncologic treatment completion.
- Radiotherapy (RT) dose constraints and combined-modality risk. Proposed design: prospective cohort linking RT dosimetry (mean heart dose, LAD dose) with serial imaging/biomarkers to define dose–response thresholds for subclinical dysfunction and late HF. Endpoints: GLS decline, coronary events, and long-term HF.
- Newer HER2 strategies (anthracycline-sparing regimens, antibody–drug conjugates). Proposed design: registries and pragmatic trials embedding standardized CTRCD definitions for T-DM1/T-DXd and novel combinations, with particular attention to permissive continuation protocols. Endpoints: HF events, persistence of dysfunction, and safety of continuation.
- Multidimensional phenotyping and risk scores. Proposed design: development and external validation of a simplified risk score combining baseline LVEF (and GLS where available) with treatment intensity and comorbidity, using ROC/ and calibration with bootstrapping, then prospective impact evaluation in clinical pathways.
- Advanced imaging and novel biomarkers. Proposed design: nested mechanistic studies evaluating cardiac MRI (fibrosis, edema) and emerging circulating markers (e.g., high-sensitivity troponin, natriuretic peptides; exploratory miRNA panels) to improve early injury detection and risk reclassification. Endpoints: incremental discrimination beyond clinical factors and LVEF.
- Equity and access in surveillance. Proposed design: implementation and health-services research assessing geographic and socioeconomic disparities in monitoring and outcomes, testing standardized minimum datasets and referral triggers suitable for district hospitals [27-30].
- Data harmonization for Albania and the region. Proposed design: multi-centre registry with standardized reporting templates (CTRCD definition, imaging protocols, therapy exposure, outcomes), enabling pooled analyses and benchmarking against international cohorts.
- Long-term follow-up to quantify persistent dysfunction and late heart failure after trastuzumab and combined modalities (radiotherapy, anthracyclines).
- Patient-reported outcomes and functional capacity measures to connect subclinical changes with real-world impact [21].
- Equity-focused analyses (age, comorbidities, geographic access) to reduce systematic under-monitoring of high-risk subgroups [27, 30].
- Data-sharing and standardized reporting templates to enable multi-centre Albanian and regional cardio-oncology registries [21].

Limitations and Analytical Implications

The meta-analysis is limited by the small number of eligible comparisons and heterogeneous trial designs; publication-bias diagnostics are unreliable when there are <10 studies. The cohort analysis is retrospective and may be influenced by surveillance intensity, missingness patterns, and residual confounding. Nonetheless, sensitivity analyses, subgroup models, and interaction testing strengthen the interpretability of the observed associations.

CONCLUSION

Pharmacologic cardioprotection during breast cancer therapy is associated with modest preservation of left ventricular ejection fraction in available randomized trials, with heterogeneity reflecting differences in patient risk profiles, treatment exposures, and outcome definitions. Findings from the Albanian real-world cohort demonstrate a clinically meaningful burden of both symptomatic and subclinical cardiotoxicity, underscoring that trial populations may underestimate risk encountered in routine practice. Together, these data support a risk-adapted approach that prioritizes baseline cardiovascular assessment, tailored surveillance intensity, and early initiation of cardioprotective therapy in higher-risk phenotypes rather than universal prophylaxis. In settings with variable access to advanced imaging and dedicated cardio-oncology services, pragmatic, pathway-based strategies may help reduce delayed detection and avoidable treatment interruption. Future studies should focus on prospective validation of risk-phenotyping tools, optimization of monitoring strategies, and evaluation of emerging preventive therapies to strengthen evidence-based cardio-oncology care.

NOMENCLATURE

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
BB	Beta-blocker
BMI	Body mass index
CI	Confidence interval
CTRCD	Cancer therapy–related cardiac dysfunction
CTR-CVT	Cancer therapy–related cardiovascular toxicity
EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESMO	European Society for Medical Oncology
GLS	Global longitudinal strain
HER2	Human epidermal growth factor receptor 2
HF	Heart failure
HFA-ICOS	Heart Failure Association–International Cardio-Oncology Society risk score

LVEF	Left ventricular ejection fraction
OR	Odds ratio
PCA	Principal component analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RoB 2	Cochrane risk-of-bias tool for randomized trials
RT	Radiotherapy

AUTHOR CONTRIBUTIONS

Conceptualization, B.S. and K.S.; Methodology, B.S; Validation, B.S., and B.K.; Investigation, B.S; Resources, F.K.; Data Curation, B.S.; Writing –Original Draft Preparation, B.S.; Writing –Review & Editing, B.K.; Visualization, K.S.; Supervision, B.K.; Project Administration, B.S.

CONFLICT OF INTERESTS

The author has no competing interests to declare that are relevant to the content of this review paper.

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APPENDIX

Example PubMed/MEDLINE strategy (adapted per database syntax):

("Breast Neoplasms"[MeSH] OR breast cancer OR HER2-positive) AND (anthracycline* OR doxorubicin OR epirubicin OR trastuzumab OR "HER2-directed") AND (cardiotoxic* OR "cancer therapy related cardiac dysfunction" OR CTRCD OR "heart failure" OR LVEF OR "left ventricular ejection fraction" OR GLS OR "global longitudinal strain") AND ((ACE inhibitor* OR ACEI OR lisinopril OR enalapril OR perindopril) OR (angiotensin receptor blocker* OR ARB OR candesartan) OR (beta-blocker* OR BB OR carvedilol OR metoprolol OR bisoprolol) OR (statin* OR atorvastatin OR rosuvastatin))

Other databases (Embase, CENTRAL, Web of Science/Scopus) used equivalent concepts and drug terms; ClinicalTrials.gov was searched using trastuzumab AND cardiotoxicity AND (lisinopril OR carvedilol OR candesartan OR perindopril).