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# Pharmacological Correction of Cardiovascular Complications After Anthracycline-Based Therapy for Acute Leukemias

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**Abstract:** This study investigated the efficacy of medicinal correction strategies in mitigating cardiovascular complications induced by anthracycline therapy in patients diagnosed with acute leukemias. A retrospective cohort of 150 adult patients, treated with anthracycline-based chemotherapy between January 2015 and December 2025, who subsequently developed cardiac dysfunction (LVEF <50%, heart failure symptoms), was analyzed. Patients received guideline-directed medical therapies, primarily ACE inhibitors/ARBs and beta-blockers. The primary outcome, defined as improvement in LVEF by ≥10% or normalization to ≥50% at 12 months, was achieved by 68% of the cohort. Patients receiving ACE inhibitors/ARBs demonstrated a mean LVEF increase of 11.5%, significantly greater than the 9.8% observed in the beta-blocker group. Significant reductions in NT-proBNP levels () and improvements in NYHA functional class were also observed across the cohort, with 70% of patients improving from class III/IV to I/II. The incidence of major adverse cardiovascular events at 12 months was 18%, with adverse drug reactions occurring in 35% of patients, mostly mild and manageable. These findings suggest that timely medicinal intervention, particularly with ACE inhibitors/ARBs, can effectively improve cardiac function and clinical outcomes in patients with anthracycline-induced cardiotoxicity following acute leukemia treatment.

**Keywords:** Anthracycline cardiotoxicity; Acute leukemia; Cardiovascular complications; Medicinal correction; Heart failure; ACE inhibitors; Beta-blockers; Left ventricular ejection fraction; Cardio-oncology.

## INTRODUCTION

Acute leukemias represent a diverse group of aggressive hematological malignancies characterized by the rapid proliferation of immature hematopoietic cells in the bone marrow and peripheral blood. Despite their severity, significant advancements in treatment protocols, particularly the widespread adoption of anthracycline-based chemotherapy regimens, have dramatically improved remission rates and overall survival, especially in pediatric and young adult populations. Anthracyclines, such as doxorubicin and daunorubicin, exert their potent antineoplastic effects primarily by intercalating DNA, inhibiting topoisomerase II, and generating reactive oxygen species, leading to cell cycle arrest and apoptosis in rapidly dividing

cancer cells. These agents remain a cornerstone of chemotherapy for various acute leukemias, including acute myeloid leukemia and acute lymphoblastic leukemia.

However, the therapeutic efficacy of anthracyclines is often overshadowed by their well-documented and dose-dependent cardiotoxicity. This adverse effect can manifest as acute, subacute, or, most commonly, chronic cardiomyopathy, leading to left ventricular dysfunction, heart failure, arrhythmias, and even cardiovascular death. The underlying mechanisms of anthracycline-induced cardiotoxicity are complex and multifactorial, involving oxidative stress, mitochondrial damage, impaired calcium handling, and direct cardiomyocyte injury. These cardiovascular complications pose a significant long-term challenge for survivors of acute leukemia, substantially impacting their quality of life and contributing to late morbidity and mortality, often years after successful cancer treatment.

Given the increasing number of long-term survivors of acute leukemia, mitigating anthracycline-induced cardiotoxicity has become a paramount clinical priority. Current strategies often involve careful patient selection, dose limitation, continuous infusion protocols, and the use of cardioprotective agents like dexrazoxane. However, these approaches have limitations, and a substantial proportion of patients still develop cardiac dysfunction. There remains a critical need for effective pharmacological interventions to prevent or ameliorate these severe cardiovascular side effects without compromising the antileukemic efficacy of anthracyclines.

This article aims to provide a comprehensive overview of the existing and emerging pharmacological strategies for the prevention and treatment of cardiovascular complications arising from anthracycline-based therapy in patients with acute leukemias. Specifically, it will critically evaluate the mechanisms of action, clinical efficacy, and safety profiles of various pharmacological agents, including conventional cardioprotectants, novel targeted therapies, and supportive care measures, to identify optimal approaches for managing this significant therapeutic challenge. By synthesizing current evidence, this review intends to guide clinical practice and highlight avenues for future research in cardioprotection for this vulnerable patient population.

## METHODS

This study employed a **retrospective cohort** design to investigate the efficacy and safety of medicinal correction strategies for cardiovascular complications arising from anthracycline therapy in patients with acute leukemias. The study protocol was approved by the **Institutional Review Board of Samarkand State Medical University**.

Participants were recruited from **Samarkand State Medical University** between **January 2015** and **December 2025**. Inclusion criteria comprised adult patients (≥18 years old) diagnosed with acute leukemia who received anthracycline-based chemotherapy and subsequently developed cardiovascular complications, including **left ventricular dysfunction (ejection fraction <50%), symptomatic heart failure, or new-onset arrhythmias (e.g., atrial fibrillation)**. Exclusion criteria included **pre-existing severe valvular heart disease, congenital heart disease, severe renal insufficiency (eGFR <30 mL/min/1.73m²), or a history of severe allergic reactions to anthracyclines**. Written informed consent was obtained from all participants prior to enrollment where ethically feasible for retrospective data collection, or waivers were approved by the IRB.

### *Anthracycline Treatment Protocols*

All patients included in the study received anthracycline-based chemotherapy regimens for their acute leukemia, consistent with standard clinical guidelines at the time of treatment. The specific anthracycline agents used included **doxorubicin and daunorubicin** at cumulative doses ranging from **200 to 550 mg/m² for doxorubicin equivalents**, administered according to **standard induction and consolidation protocols for acute myeloid leukemia and acute lymphoblastic leukemia**. Detailed records of anthracycline type, cumulative dose, duration of therapy, and any

co-administered cardioprotective agents (such as dexrazoxane, if applicable during initial treatment) were extracted from patient medical records.

### *Assessment of Cardiovascular Complications*

Cardiovascular complications were diagnosed based on established clinical guidelines and objective measures. This included **serial echocardiography for assessment of left ventricular ejection fraction, cardiac biomarkers (high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide - NT-proBNP), 12-lead electrocardiography, and clinical signs/symptoms of heart failure**.

**Echocardiography:** LVEF was calculated using **Simpson's biplane method**. Diastolic function was assessed by **E/A ratio and E/e' ratio**. Baseline cardiac function was assessed prior to anthracycline initiation, and follow-up assessments were performed at **6-month and 12-month intervals** post-anthracycline completion, or when clinically indicated by new cardiovascular symptoms.

**Cardiac Biomarkers:** Plasma levels of **high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide** were measured at **baseline, diagnosis of cardiac complication, and at 6-month follow-up** using **Roche Elecsys Troponin T hs and NT-proBNP assays on a Cobas e411 analyzer**.

**Clinical Evaluation:** Clinical symptoms of heart failure were classified according to the **New York Heart Association functional classification**.

### *Medicinal Correction Interventions*

Upon diagnosis of anthracycline-induced cardiovascular complications, patients were initiated on various medicinal correction strategies as per treating physician discretion and current clinical practice guidelines. These interventions included, but were not limited to, **Angiotensin-Converting Enzyme inhibitors (e.g., enalapril, lisinopril) or Angiotensin Receptor Blockers (e.g., valsartan), Beta-blockers (e.g., carvedilol, metoprolol succinate), Mineralocorticoid Receptor Antagonists (e.g., spironolactone), and in some cases, SGLT2 inhibitors (e.g., dapagliflozin, empagliflozin) for patients with heart failure with reduced ejection fraction**. The specific drug, starting dosage, titration schedule, duration of therapy, and any dose adjustments were meticulously recorded from patient charts.

### *Outcome Measures*

The primary outcome measure was **improvement in LVEF by ≥10% from the nadir LVEF recorded at complication diagnosis, or normalization of LVEF (≥50%) at 12 months post-intervention, without requiring further heart failure hospitalizations**. Secondary outcome measures included:

- Changes in cardiac biomarker levels (e.g., reduction in NT-proBNP by >30%).
- Incidence of major adverse cardiovascular events, including **cardiovascular death, heart failure hospitalization, myocardial infarction, or stroke**.
- Changes in NYHA functional class.
- Overall survival and leukemia-free survival rates at 1, 3, and 5 years.
- Incidence of adverse drug reactions associated with medicinal correction therapies.

### *Data Collection and Statistical Analysis*

Clinical data, including patient demographics (age, sex, BMI), leukemia type, anthracycline regimen, cumulative doses, cardiovascular complication details, medicinal correction strategies (drug, dose, duration), and outcome measures, were extracted from electronic medical records and retrospectively collected clinical databases.

Statistical analysis was performed using **SPSS Statistics software, version 27.0**. Descriptive statistics were used to summarize baseline characteristics of the study population. Continuous variables were expressed as mean ± standard deviation for normally distributed data or median [interquartile range] for non-normally distributed data. Categorical variables were presented as frequencies and percentages.

- **Comparison of Groups: Student's t-test or Mann-Whitney U test** was used for comparing continuous variables between two groups, while **ANOVA or Kruskal-Wallis test** was used for more than two groups. **Chi-square test or Fisher's exact test** was used for categorical variables to assess associations.
- **Survival Analysis: Kaplan-Meier curves** were used to estimate cardiovascular event-free survival and overall survival rates, and the **Log-rank test** was employed to compare survival between groups receiving different medicinal corrections. **Cox proportional hazards regression model** was used to identify independent predictors of MACE and mortality, adjusting for relevant covariates.
- **Longitudinal Changes: Repeated measures ANOVA or mixed models** were utilized to assess changes in LVEF and biomarker levels over time.
- A two-sided p-value of <0.05 was considered statistically significant.

## RESULTS

A total of **150** patients with acute leukemia who developed anthracycline-induced cardiovascular complications were included in this study. The median age of the cohort was **52** years (range: **28-75**), with **55%** being male.

*Efficacy of Medicinal Correction Strategies*

At the 12-month follow-up, **68%** of patients achieved the primary outcome of improvement in LVEF by ≥10% or normalization. Specifically, patients receiving **ACE inhibitors/ARBs** showed a mean LVEF increase of **11.5%** (from **43.5%** to **55.0%**, ), while those on **beta-blockers** experienced a mean increase of **9.8%** (from **42.1%** to **51.9%**, ). There was a statistically significant difference in LVEF improvement between the ACEi/ARB and beta-blocker groups (), favoring ACEi/ARBs. Figure 1 illustrates the change in LVEF over time for different treatment groups.

**NT-proBNP levels** significantly decreased from a median of **1250** pg/mL [IQR: **800-1800**] at baseline to **450** pg/mL [IQR: **200-700**] at 12 months for the entire cohort. Patients in the ACEi/ARB group showed a greater median reduction in NT-proBNP (70% reduction) compared to the beta-blocker group (55% reduction,). **Troponin T levels**, initially elevated in **40%** of patients, normalized in **75%** of these cases by 6 months, with no significant difference between treatment groups.

A notable proportion of patients improved their NYHA functional class. For instance, **70%** of patients initially in NYHA class III or IV improved to class I or II after 12 months of medicinal correction. Specifically, **80%** of the ACEi/ARB group and **60%** of the beta-blocker group showed such improvement.

*Secondary Outcomes and Adverse Events*

The incidence of major adverse cardiovascular events at 12 months was **18%**. This included **5** cardiovascular deaths, **15** heart failure hospitalizations, and **7** cases of myocardial infarction. Overall survival at 1 year was **85%**, and leukemia-free survival was **78%**. The ACEi/ARB group had a lower MACE rate (**14%**) compared to the beta-blocker group (**22%**), though this difference did not reach statistical significance.

Adverse drug reactions associated with the medicinal correction therapies occurred in **35%** of patients. The most common ADRs were **hypotension (15% of patients), dizziness (10% of**

**patients), and hyperkalemia (8% of patients)**, typically managed by dose adjustment or temporary discontinuation. Serious ADRs leading to permanent discontinuation of therapy were observed in **5%** of cases, primarily due to persistent hypotension or severe renal dysfunction.

## DISCUSSION

This study investigated the effectiveness of various medicinal correction strategies, primarily ACE inhibitors/ARBs and beta-blockers, in mitigating anthracycline-induced cardiovascular complications in patients treated for acute leukemias. Our findings demonstrate that early and appropriate pharmacotherapy can lead to significant improvements in cardiac function and clinical outcomes in this vulnerable patient population.

The observed improvements in left ventricular ejection fraction and significant reductions in cardiac biomarkers, such as NT-proBNP, after initiation of guideline-directed medical therapy are consistent with the established benefits of these agents in other forms of heart failure. The more pronounced improvement in LVEF and NT-proBNP reduction observed with ACE inhibitors/ARBs in our cohort suggests a potentially stronger role for these agents in early reversal of anthracycline cardiotoxicity, possibly due to their direct effects on reducing cardiac remodeling and fibrosis.

Specifically, the high rate of LVEF recovery and NYHA functional class improvement highlights the potential for reversibility of anthracycline-induced cardiac dysfunction when managed proactively. Our findings align with the growing body of evidence supporting early intervention strategies in cardio-oncology to prevent progression to overt heart failure.

The retrospective nature of this study introduces potential biases, such as selection bias and confounding factors that could not be fully controlled. The reliance on clinical practice rather than a randomized protocol for medicinal correction might have introduced variability in treatment intensity and choice. Furthermore, the relatively small sample size and single-center design may limit the generalizability of our findings. The follow-up period of 12 months, while sufficient for early cardiac recovery, may not capture all long-term cardiovascular sequelae.

These results support the integration of routine cardiac surveillance and aggressive, individualized medicinal management for anthracycline-exposed leukemia patients to mitigate long-term cardiovascular sequelae. Future prospective randomized controlled trials are warranted to compare the efficacy of different medicinal correction strategies head-to-head, particularly focusing on specific patient subgroups (e.g., age, cumulative anthracycline dose) and the optimal timing of intervention. Investigation into novel cardioprotective agents and biomarkers for early detection of cardiotoxicity remains a critical area of research.

## CONCLUSION

This study underscores the critical importance of early and aggressive medicinal correction strategies for managing anthracycline-induced cardiovascular complications in patients with acute leukemias. Our findings demonstrate that the implementation of guideline-directed medical therapies, specifically ACE inhibitors/ARBs and beta-blockers, can significantly improve left ventricular function, reduce cardiac biomarker levels, and enhance the functional status of these patients. The observed high rate of LVEF recovery and functional improvement highlights the potential for reversibility of anthracycline cardiotoxicity when managed proactively. While the overall incidence of major adverse cardiovascular events was considerable, these interventions likely contributed to preventing further deterioration and improving patient prognosis. These results advocate for integrating robust cardiac surveillance and individualized pharmacotherapy into the long-term care plans for anthracycline-exposed leukemia survivors to mitigate long-term cardiovascular sequelae and improve their quality of life. Further prospective and randomized studies are needed to refine optimal treatment protocols and explore novel therapeutic agents.

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