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Review Article

The Heart Under Targeted Therapy: A Review of Osimertinib-Associated Cardiotoxicity

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ABSTRACT

Osimertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has transformed the treatment landscape of EGFR-mutated non-small-cell lung cancer (NSCLC). Its ability to inhibit sensitizing EGFR mutations and the T790M resistance mutation, together with meaningful central nervous system activity and favorable systemic efficacy, has expanded its use across metastatic and adjuvant settings. As treatment duration and patient survival improve, however, the cardiovascular safety profile of osimertinib has become increasingly important. Reports from clinical trials, post-marketing surveillance, real-world cohorts, and case series describe a spectrum of cardiac adverse effects, including left ventricular dysfunction, heart failure, cardiomyopathy, QT interval prolongation, and arrhythmias. Although these events are relatively uncommon, their potential severity and the growing number of patients exposed to osimertinib make early recognition clinically important. The mechanisms remain incompletely defined but may involve off-target inhibition of HER2-related signaling, disruption of cardiomyocyte survival pathways, mitochondrial and oxidative stress, and electrophysiological effects that predispose susceptible patients to QT prolongation. This review summarizes the pharmacological basis of osimertinib therapy, the emerging clinical evidence for cardiotoxicity, proposed pathophysiological mechanisms, risk factors, diagnostic and monitoring approaches, and contemporary management principles. Particular emphasis is placed on integrating oncology and cardiology perspectives through a cardio-oncology framework. Persistent knowledge gaps include the absence of universally standardized surveillance protocols, uncertainty regarding optimal biomarkers and imaging intervals, and limited evidence guiding rechallenge after clinically significant cardiac toxicity. Future progress will depend on prospective cardiovascular phenotyping, risk stratification, real-world

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pharmacovigilance, and personalized monitoring strategies. A proactive approach to cardiac assessment can help preserve the oncological benefits of osimertinib while minimizing preventable cardiovascular harm.

INTRODUCTION

Lung cancer remains one of the leading causes of cancer-related mortality worldwide, and non-small-cell lung cancer (NSCLC) accounts for the majority of cases. The identification of actionable oncogenic drivers has fundamentally changed the management of NSCLC by enabling molecularly selected therapies that can achieve deeper and more durable responses than conventional cytotoxic chemotherapy in appropriately selected patients. Among these drivers, activating mutations in the epidermal growth factor receptor (EGFR) are particularly important. EGFR-mutated NSCLC is commonly treated with EGFR tyrosine kinase inhibitors (TKIs), and the development of successive generations of these agents illustrates the evolution of precision oncology from broad pathway inhibition toward increasingly mutation-selective treatment strategies. [1,6]

Osimertinib is a third-generation, irreversible EGFR-TKI designed to inhibit both common activating EGFR mutations and the T790M resistance mutation while demonstrating reduced activity against wild-type EGFR. Its clinical importance extends beyond resistance management. The drug has shown substantial efficacy in first-line metastatic disease, activity against central nervous system metastases, and benefit in the adjuvant treatment of resected EGFR-mutated NSCLC. These advantages have resulted in prolonged treatment exposure for many patients. Consequently, adverse effects that may have received less attention during earlier stages of drug development have become increasingly relevant in long-term clinical practice.[1-5]

The cardiovascular consequences of anticancer therapy are now recognized as a major component of survivorship and treatment safety. Historically, cardiotoxicity discussions focused largely on anthracyclines and HER2-directed therapies. The rapid expansion of targeted therapies has broadened this perspective. Small-molecule kinase inhibitors can influence cardiovascular physiology through direct myocardial effects, vascular toxicity, hypertension, metabolic disturbances, and alterations in cardiac electrophysiology. Importantly, targeted agents may produce toxicities through intended pathway inhibition, unintended off-target effects, or interactions between drug exposure and patient-specific susceptibility factors. [23-29,35]

Osimertinib-associated cardiotoxicity has emerged as an important example of this evolving challenge. Reported manifestations include asymptomatic reductions in left ventricular ejection fraction (LVEF), symptomatic heart failure, cardiomyopathy, QT interval prolongation, and clinically relevant arrhythmias. The absolute incidence is lower than that associated with some traditional cardiotoxic regimens, but several characteristics warrant attention: cardiac events may be serious, symptoms may overlap with cancer-related fatigue or pulmonary disease, and many patients receiving osimertinib are older and may have baseline cardiovascular risk factors. Furthermore, clinical trial populations may underrepresent frail patients or those with significant pre-existing cardiovascular disease, making post-marketing and real-world evidence particularly valuable. [8-15,21]

The biological basis of osimertinib-associated cardiotoxicity remains incompletely understood. Experimental and pharmacological observations have raised the possibility that inhibition of HER2-

related signaling may contribute to myocardial dysfunction, because HER2 signaling is important for cardiomyocyte stress adaptation and survival. Additional hypotheses include mitochondrial injury, oxidative stress, altered calcium handling, and effects on cardiac ion channels. QT prolongation, meanwhile, may reflect drug-induced perturbation of ventricular repolarization in susceptible individuals, particularly in the presence of electrolyte abnormalities or concomitant QT-prolonging medicines. [7,22,25,26]

Recognition of these risks does not diminish the therapeutic value of osimertinib. Rather, it emphasizes the need to balance oncological benefit against cardiovascular safety. A modern cardio-oncology approach aims to identify vulnerable patients before therapy, detect early toxicity during treatment, manage established cardiac dysfunction promptly, and make individualized decisions regarding interruption, dose modification, discontinuation, or rechallenge. Such decisions require communication between oncologists, cardiologists, pharmacists, and patients because the consequences of stopping effective targeted therapy can be substantial. [27-30]

This review critically examines osimertinib-associated cardiotoxicity from mechanistic, clinical, diagnostic, and management perspectives. It discusses the spectrum of cardiac adverse effects, evidence from trials and real-world reports, potential risk factors, practical monitoring strategies, and future research priorities. The central objective is to support a proactive and clinically balanced approach in which effective cancer control is maintained whenever possible without overlooking potentially reversible cardiovascular injury. [8-15,27-35]

Osimertinib: Pharmacological Profile and Clinical Significance

Osimertinib is an oral, irreversible third-generation EGFR-TKI. It selectively targets activating EGFR mutations such as exon 19 deletions and L858R substitutions as well as the T790M resistance mutation that commonly limited the efficacy of earlier-generation EGFR inhibitors. The drug forms a covalent bond with mutant EGFR and suppresses downstream signaling pathways involved in cellular proliferation and survival. Its favorable activity against central nervous system disease is another clinically important characteristic, as brain metastases are common in EGFR-mutated NSCLC. [1,4,5]

The success of osimertinib has progressively expanded the duration and settings in which patients may receive the drug. This therapeutic success creates a paradox: as survival improves, delayed and cumulative toxicities become more visible. Dermatological and gastrointestinal adverse effects are well recognized, but cardiovascular complications require particular vigilance because they may be clinically silent initially and can progress to symptomatic dysfunction if not detected early. [8,11,12]

Feature	Clinical relevance
Drug class	Third-generation irreversible EGFR-TKI
Primary molecular targets	Sensitizing EGFR mutations and T790M resistance mutation
Major strengths	Systemic efficacy, CNS activity, use across metastatic and adjuvant settings
Cardiac concerns	LVEF decline, heart failure, cardiomyopathy, QT prolongation and arrhythmias
Clinical implication	Longer survival increases the importance of longitudinal cardiovascular surveillance

Spectrum of Osimertinib-Associated Cardiotoxicity

(a) Left Ventricular Dysfunction and Heart Failure

Left ventricular dysfunction is among the most clinically significant cardiac complications associated with osimertinib. It may present as an asymptomatic decline in LVEF detected on surveillance echocardiography or as overt heart failure characterized by dyspnea, fatigue, edema, orthopnea, and reduced exercise tolerance. In patients with lung cancer, these symptoms can be difficult to interpret because pulmonary tumor burden, infection, anemia, pleural effusion, and treatment-related pneumonitis may produce similar complaints. A low threshold for cardiovascular evaluation is therefore appropriate when new or unexplained symptoms develop. [8,10-12,16,18]

(b) Cardiomyopathy

Case reports and observational series have described potentially reversible cardiomyopathy occurring during osimertinib exposure. The temporal association with treatment, improvement after drug interruption, and response to guideline-directed heart failure therapy support a causal role in at least some patients. Nevertheless, causality must be assessed carefully because ischemic heart disease, uncontrolled hypertension, tachyarrhythmia, myocarditis, and other cancer therapies can also contribute to ventricular dysfunction. [11,12,16,18,20]

(c) QT Interval Prolongation and Arrhythmias

QT interval prolongation is a recognized electrophysiological concern. Prolongation of ventricular repolarization can increase susceptibility to malignant ventricular arrhythmias, particularly torsades de pointes in the presence of marked QTc prolongation. Risk is amplified by hypokalemia, hypomagnesemia, bradycardia, congenital long-QT syndromes, renal or hepatic impairment affecting exposure, and concomitant medications that prolong the QT interval. Although severe arrhythmias are uncommon, ECG surveillance and medication review are important in high-risk individuals. [7,9,17,19,21,22]

(d) Other Cardiovascular Manifestations

The broader cardiovascular spectrum reported in pharmacovigilance and clinical practice includes atrial arrhythmias and nonspecific cardiac symptoms. The heterogeneity of reported events highlights the importance of distinguishing direct drug toxicity from coincidental cardiovascular disease. Structured adjudication, temporal assessment, and objective testing remain essential. [9,13,19,21,29]

Proposed Mechanisms of Cardiotoxicity

The mechanisms responsible for osimertinib-associated cardiotoxicity are not fully established and are likely multifactorial. One leading hypothesis involves interference with HER2/ErbB signaling. The ErbB receptor family participates in cardiomyocyte survival and adaptation to stress. Experimental disruption of this pathway has been associated with impaired myocardial resilience, particularly when additional stressors are present. [26,35] Although osimertinib is designed primarily for mutant EGFR, off-target interactions with related pathways may contribute to cardiac vulnerability. [25,26]

Mitochondrial dysfunction and oxidative stress represent additional plausible mechanisms. Cardiomyocytes have high energy requirements and depend heavily on intact mitochondrial function. Drug-related disruption of energy production, reactive oxygen species balance, or calcium homeostasis could impair contractile

performance and contribute to progressive ventricular dysfunction. These hypotheses require further mechanistic validation in translational studies. [24,25,35]

Electrophysiological toxicity may arise through altered ion-channel activity and delayed ventricular repolarization. QT prolongation is clinically important because it represents a measurable intermediate marker of arrhythmia risk. However, QT duration alone does not determine clinical outcome; risk depends on the magnitude of prolongation, dynamic changes over time, patient susceptibility, electrolyte status, and interacting medicines. [7,17,19,22]

A multifactorial model is therefore most useful. Osimertinib exposure may create a background myocardial or electrophysiological stress that becomes clinically apparent when combined with age, pre-existing cardiovascular disease, metabolic abnormalities, prior cardiotoxic therapy, or acute illness.

Osimertinib exposure
↓
Potential HER2/ErbB pathway interference + mitochondrial dysfunction + oxidative stress + altered calcium/ion-channel handling
↓
Impaired cardiomyocyte survival and ventricular repolarization
↓
LVEF reduction, cardiomyopathy, heart failure, QT prolongation and arrhythmias

Figure 1. Proposed Mechanisms of Osimertinib-Associated Cardiotoxicity

Clinical Evidence and Emerging Safety Signals

Evidence for osimertinib-associated cardiotoxicity comes from several complementary sources. Randomized clinical trials provide systematically collected safety information but may underestimate risk in patients with substantial baseline cardiovascular disease. Post-marketing pharmacovigilance expands detection of rare or unexpected events but cannot establish incidence with certainty because of reporting bias and incomplete denominators. Real-world cohort studies and case series bridge these approaches by describing patients treated in routine practice, although they are susceptible to confounding. [8-14,21]

Across the osimertinib development program, reductions in LVEF and heart failure events have been reported, prompting increased awareness of cardiac surveillance. Comparative analyses have also suggested that the cardiac adverse-event profile of osimertinib may differ from that of earlier EGFR-TKIs. Pharmacovigilance analyses have generated safety signals for heart failure, cardiomyopathy, QT prolongation, and atrial arrhythmias, supporting the need for continued monitoring after regulatory approval. [9,21]

Interpretation of these data requires caution. A reported adverse event does not automatically prove causation, and differences in ascertainment methods can substantially influence event rates. Nevertheless, consistency across clinical trials, spontaneous reports, and real-world observations strengthens the clinical signal. The most important practical conclusion is not that every patient requires intensive cardiac testing, but that surveillance should be proportional to baseline risk and evolving clinical findings.

Evidence source	Strength	Limitation	Contribution
Randomized clinical trials	Systematic data collection and comparator arms	Selected populations and limited power for rare events	Estimates of recognized cardiac adverse events

Post-marketing pharmacovigilance	Large populations and rare-signal detection	Reporting bias; no reliable denominator	Detection of unexpected or uncommon toxicity patterns
Real-world cohorts	Reflect routine clinical practice	Confounding and heterogeneous monitoring	Risk characterization in broader populations
Case reports/ series	Detailed temporal and clinical characterization	Cannot estimate incidence	Recognition of severe or reversible cardiomyopathy

Risk Factors for Cardiotoxicity

Risk assessment should begin before Osimertinib is prescribed. Advanced age, established heart failure, coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease, and prior exposure to cardiotoxic cancer therapy may increase vulnerability. Baseline abnormalities in LVEF or ECG parameters should prompt careful evaluation but do not automatically preclude therapy. The anticipated oncological benefit and availability of alternatives must be considered.

Medication-related factors are particularly relevant for QT prolongation. Patients may simultaneously receive antiemetics, antibiotics, antifungals, psychotropic drugs, antiarrhythmics, or other medicines capable of prolonging the QT interval. Electrolyte disturbances caused by vomiting, diarrhea, diuretics, or poor nutritional intake can further increase risk. A structured medication reconciliation should therefore be part of baseline and follow-up assessment. [17,22,27,28]

Risk factor	Potential consequence	Practical approach
Pre-existing heart failure or reduced LVEF	Greater susceptibility to decompensation	Baseline echocardiography and cardiology input
Coronary artery disease / hypertension	Reduced myocardial reserve	Optimize cardiovascular therapy
Older age / multimorbidity	Higher competing cardiovascular risk	Individualized surveillance
Prior cardiotoxic treatment	Cumulative myocardial injury	Document previous exposure and baseline function
QT-prolonging drugs	Additive repolarization risk	Medication review and substitution where feasible
Hypokalemia/ hypomagnesemia	Increased arrhythmia risk	Correct and monitor electrolytes

Diagnosis and Cardiac Monitoring

A practical monitoring strategy should be risk-adapted rather than uniform for every patient. Baseline assessment should include a focused cardiovascular history, examination, review of medications, blood pressure measurement, and 12-lead ECG. Echocardiography is particularly valuable in patients with pre-existing cardiovascular disease, symptoms, prior cardiotoxic exposure, or other significant risk factors. Biomarkers such as natriuretic peptides and cardiac troponin may be useful in selected patients, although their optimal routine use in osimertinib therapy remains uncertain. [27,30-34]

During treatment, clinicians should actively inquire about new dyspnea, edema, palpitations, syncope, chest discomfort, unexplained fatigue, and reduced exercise tolerance. Repeat ECGs are appropriate in patients with baseline QTc prolongation, concomitant QT-prolonging medications, electrolyte disturbances, or symptoms suggestive of arrhythmia. Echocardiography should be repeated when

symptoms develop or when baseline risk is high. Cardiac magnetic resonance imaging may help clarify unexplained ventricular dysfunction and distinguish ischemic, inflammatory, or nonischemic patterns when clinically indicated.

Baseline cardiovascular risk assessment
↓
ECG ± echocardiography ± biomarkers in selected/high-risk patients
↓
Periodic clinical review and ECG monitoring
↓
Investigate new symptoms or significant QTc/LVEF changes
↓
Cardio-oncology consultation
↓
Individualized treatment modification

Figure 2. Suggested Monitoring Pathway

Management of Osimertinib-Associated Cardiotoxicity

Management depends on the type and severity of toxicity. New symptomatic heart failure requires prompt evaluation to confirm ventricular dysfunction, identify reversible causes, and initiate evidence-based heart failure therapy. Depending on severity and oncological circumstances, temporary interruption of osimertinib may be appropriate. Decisions regarding permanent discontinuation or rechallenge should be multidisciplinary and individualized.

For QT prolongation, the first steps include confirmation with repeat ECG, correction of potassium and magnesium abnormalities, review of interacting medications, and assessment for bradyarrhythmia or congenital susceptibility. Marked or persistent QTc prolongation requires closer monitoring and may necessitate treatment interruption according to product-specific prescribing guidance and clinical judgment. Patients with syncope, sustained ventricular arrhythmia, or hemodynamic instability require urgent specialist management. [7,17,19,22,27]

When cardiac function improves after interruption and appropriate cardiovascular treatment, rechallenge may be considered in carefully selected patients if the expected cancer benefit is substantial and no equally effective alternative is available. Such decisions should include documented shared decision-making and intensified surveillance. Rechallenge should not be viewed as routine; evidence remains limited and recurrence risk is uncertain.

Clinical problem	Immediate evaluation	General management principle
Asymptomatic LVEF decline	Repeat imaging; assess alternative causes	Cardiology review and individualized continuation/interruption
Symptomatic heart failure	Echo, ECG, biomarkers and cause assessment	Initiate guideline-directed HF therapy; consider interruption
QTc prolongation	Repeat ECG, electrolytes, medication review	Correct reversible factors; increase surveillance
Serious arrhythmia	Urgent rhythm assessment	Emergency management and multidisciplinary treatment decision
Recovered cardiac function	Reassess oncological benefit and risk	Selective rechallenge only with close monitoring

CHALLENGES AND KNOWLEDGE GAPS

Several uncertainties limit the development of standardized recommendations. First, the true

incidence of clinically important cardiotoxicity remains difficult to determine because studies use different definitions and monitoring schedules. Second, asymptomatic LVEF changes may be missed when echocardiography is performed only after symptoms develop. Third, the predictive value of biomarkers in this setting is not established. Finally, evidence regarding the safety of dose modification and rechallenge after recovery remains largely observational.

Another challenge is attribution. Patients with NSCLC frequently have smoking-related cardiovascular disease and may receive multiple anticancer therapies. Dyspnea and fatigue are nonspecific. Consequently, a temporal association with osimertinib should trigger investigation rather than automatic assignment of causality. Standardized cardio-oncology definitions and prospective adjudication will improve the quality of future evidence. [21,27,29,35]

FUTURE DIRECTIONS

Future research should move beyond passive recognition of adverse events toward prospective cardiovascular phenotyping. Clinical trials should incorporate standardized baseline risk assessment, longitudinal ECG and imaging strategies in selected populations, and prespecified definitions of cancer therapy-related cardiac dysfunction. Integration of electronic health records and pharmacovigilance databases may enable earlier signal detection and identification of high-risk phenotypes.

Artificial intelligence and advanced analytics may support risk prediction by integrating demographic factors, comorbidities, ECG features, laboratory values, imaging data, concomitant medications, and longitudinal treatment exposure. However, predictive models must be externally validated and should complement—not replace—clinical judgment. [27,29,35]

Mechanistic research is equally important. Better understanding of HER2-related effects, mitochondrial injury, oxidative stress, and ion-channel interactions could identify biomarkers of susceptibility and inform cardioprotective interventions. The ultimate goal is precision cardio-oncology: maintaining the survival benefits of targeted cancer therapy while tailoring cardiovascular surveillance to the patient most likely to benefit.

Clinical risk factors + molecular susceptibility + ECG/imaging/biomarkers + real-world pharmacovigilance

↓

Predictive risk stratification

↓

Personalized monitoring

↓

Early intervention

↓

Safer continuation of effective osimertinib therapy

Figure 3. Future Direction Toward Precision Cardio-Oncology

CONCLUSION

Osimertinib represents a major advance in the treatment of EGFR-mutated NSCLC, but its expanding use has highlighted an important cardiovascular safety signal. The spectrum of reported toxicity includes asymptomatic LVEF decline, cardiomyopathy, heart failure, QT prolongation, and arrhythmias. Available evidence suggests that these events are uncommon but potentially clinically significant and, in some patients, may improve with early recognition, treatment interruption, and appropriate cardiovascular management. [8-20]

The pathogenesis is likely multifactorial and remains incompletely characterized. A practical response should therefore focus on risk stratification, baseline cardiovascular assessment in appropriate patients, awareness of symptoms and ECG changes during treatment, correction of reversible risk factors, and early collaboration between oncology and cardiology teams. Uniform intensive monitoring for all patients is unlikely to be necessary; a personalized approach based on baseline cardiovascular risk and evolving clinical status is more rational.

As survival improves, cardiovascular safety will become an increasingly important determinant of treatment quality. Prospective studies, standardized definitions, mechanistic research, and real-world data are needed to refine surveillance and management. The central challenge is to ensure that the heart is not overlooked while targeted therapy successfully controls the cancer. Through proactive cardio-oncology care, the benefits of osimertinib can be preserved while reducing preventable cardiovascular harm.

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