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ORIGINAL RESEARCH

Risk of Heart Failure Hospitalization in Patients Treated With Osimertinib

A Population-Based Retrospective Cohort Study

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ABSTRACT

BACKGROUND Osimertinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, is used to treat patients with epidermal growth factor receptor–mutant non–small-cell lung cancer. Although osimertinib has been linked to heart failure (HF), detailed risk estimates remain unclear.

OBJECTIVES The aim of this study was to examine the association between osimertinib use and HF hospitalization.

METHODS In this retrospective cohort study using a large-scale Japanese claims database, patients diagnosed with lung cancer between April 2008 and December 2021 who received cancer therapy were identified. Patients were categorized into osimertinib and control groups according to treatment received. The incidence of HF hospitalization during the treatment period was compared between the groups. Multivariable analyses were performed before and after propensity score matching.

RESULTS The osimertinib and control groups included 11,391 and 108,144 patients, respectively. Among the entire cohort, the median age was 70 years (Q1-Q3: 64-76 years), and the median follow-up duration was 173 days (Q1-Q3: 73-448 days). The incidence of HF hospitalization was 9.9 and 4.1 cases per 1,000 person-years in the osimertinib and control groups, respectively. In multivariable analysis, osimertinib was associated with a higher risk for HF hospitalization than control therapy (subdistribution HR: 2.56; 95% CI: 2.07-3.18; $P < 0.001$). This association remained significant after propensity score matching (subdistribution HR: 2.29; 95% CI: 1.62-3.24; $P < 0.001$).

CONCLUSIONS Osimertinib use was associated with an increased risk for HF hospitalization. Cardiac function should be closely monitored in patients receiving osimertinib. (JACC CardioOncol. 2025;7:738–748) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Advances in cancer therapy and supportive care have improved overall survival in patients with cancer in recent decades.[1] However, treatment-related complications, particularly cardiotoxicity, remain a major concern for cancer survivors.[2-5] Adverse cardiovascular events, including left ventricular dysfunction, heart failure (HF), ischemic heart disease, venous

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thromboembolism, arterial hypertension, arrhythmias, and valvular disease, are recognized complications of cancer therapy.[6,7]

Left ventricular dysfunction and HF have been well studied in patients treated with anthracyclines[8] or trastuzumab.[9] Moreover, tyrosine kinase inhibitors (TKIs) other than trastuzumab have also been linked to cardiac dysfunction.[10] A previous study revealed that severe cardiotoxicity, defined as left ventricular dysfunction with a left ventricular ejection fraction (LVEF) ≤ 40% or symptomatic HF, was associated with increased mortality in patients with cancer.[11] However, early detection and treatment of therapy-related cardiotoxicity may improve cardiac function.[12] Accordingly, identifying the risk level of left ventricular dysfunction or symptomatic HF related to cancer therapy is critical.

Osimertinib is an oral epidermal growth factor receptor (EGFR) TKI used to treat patients with EGFR-mutant non-small-cell lung cancer (NSCLC).[13] Compared with earlier generation EGFR TKIs[14,15] and cytotoxic chemotherapy,[16] osimertinib has demonstrated improved clinical outcomes in this population. Its common adverse effects include gastrointestinal symptoms and dermatologic toxicity.

Moreover, a study using the U.S. Food and Drug Administration Adverse Events Reporting System revealed that osimertinib was associated with cardiac adverse events, including QT interval prolongation, arrhythmias, and HF.[17] However, the association between osimertinib and HF remains controversial. Observed HF events may reflect osimertinib's prolonged treatment duration, owing to its clinical efficacy, or underlying characteristics of the treated population, such as older age and comorbidities including hypertension, ischemic heart disease, and arrhythmias.[18]

These uncertainties may stem from a lack of comparative studies that evaluate HF risk while adequately adjusting for baseline comorbidities. Therefore, we conducted this nationwide claims-based study in Japan to evaluate the association between osimertinib use and HF occurrence.

METHODS

DATA SOURCE. This retrospective cohort study was conducted using a large-scale claims database developed by Medical Data Vision (MDV). The MDV database includes inpatient and outpatient information on approximately 40 million patients, covering approximately 27% of acute care hospitals participating in Japan's Diagnosis Procedure Combination/Per Diem Payment System.

The database includes patient-level data such as sex, age, diagnoses, prescribed medications, procedures, primary and secondary resource-intensive conditions during hospitalization, and conditions that developed during hospitalization. The demographic and clinical characteristics of patients in the MDV database are broadly representative of the Japanese population, as reflected in national statistics.[19,20]

All patient data were deidentified by MDV prior to analysis; therefore, informed consent was not required. The study protocol, including exemption from the requirement to obtain informed consent, was reviewed and approved by the ethics committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and the Okayama University Hospital.

STUDY PATIENTS. Eligible patients were defined as follows: 1) patients with lung cancer, defined by International Classification of Diseases-10th Revision (ICD-10) code C34 (including various lung cancer subtypes), recorded in the MDV database between April 2008 and December 2021; 2) receipt of EGFR TKIs (including osimertinib), anaplastic lymphoma kinase (ALK) inhibitors, or cytotoxic chemotherapy, with study drugs listed in Supplemental Table 1; and 3) availability of data for ≥6 months prior to the date of first prescription of a study drug.

The index date was defined as the date of the first prescription of a study drug. Patients younger than 18 years on the index date were excluded from the cohort.

DEFINITION OF THE PRIMARY OUTCOME. The primary outcome of the present study was hospitalization for HF or a diagnosis of HF during hospitalization, collectively defined as HF hospitalization (HFH). Previous studies using claims databases have shown that defining HF on the basis of ICD-10 codes in combination with relevant medications yields higher diagnostic accuracy than using ICD-10 codes alone.[21,22]

Accordingly, HFH in this study was defined as follows[23]: 1) the presence of ICD-10 code I50.0, I50.1, I50.9, or I11.0 (excluding suspected diagnosis) recorded as the cause of hospitalization, primary diagnosis, highest or second highest resource-

ABBREVIATIONS AND ACRONYMS

ALK = anaplastic lymphoma kinase

EGFR = epidermal growth factor receptor

GLS = global longitudinal strain

HER2 = human epidermal growth factor receptor 2

HF = heart failure

HFH = heart failure hospitalization

ICD-10 = International Classification of Diseases-10th Revision

LVEF = left ventricular ejection fraction

MDV = Medical Data Vision

NSCLC = non-small-cell lung cancer

SGLT2 = sodium-glucose cotransporter 2

sHR = subdistribution HR

SMD = standardized mean difference

TKI = tyrosine kinase inhibitor

consuming condition, or a condition that developed during hospitalization; and 2) the administration of intravenous furosemide, vasodilators (nitroglycerin, isosorbide nitrate, carperitide, and nicorandil), or inotropic agents (dobutamine, dopamine, noradrenaline, milrinone, and olprinone) within 2 days of the HF diagnosis.

We considered HFH events to be associated with study drug exposure if they occurred from 7 days after the index date through 30 days after the final prescription. This definition was based on a prior study reporting that HF events were observed beginning 7 days after the initiation of osimertinib therapy.[18] Extending follow-up beyond 30 days after discontinuation would have reduced the ability to attribute HFH events to a specific study drug.

HF-RELATED COMORBIDITIES AND MEDICATIONS. We investigated HF-related comorbidities and medications on the index date. Comorbidities included history of HF, arterial hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, atrial fibrillation or other arrhythmias, cardiomyopathy, valvular heart disease, chronic kidney disease, and chronic obstructive pulmonary disease. These conditions were defined using ICD-10 codes (Supplemental Table 2).

Guideline-directed medical therapy—including beta blockers, renin-angiotensin-aldosterone system inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors—is recommended for HF, particularly in patients with reduced LVEFs, as these therapies have been shown to improve clinical outcomes.[24,25] Therefore, HF-related medications were defined as beta-blockers (carvedilol or bisoprolol), angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, SGLT2 inhibitors, and oral diuretic agents (loop diuretic agents or tolvaptan).

STATISTICAL ANALYSIS. Patients were categorized into osimertinib and control groups according to the cancer treatment received. The control group included patients treated with EGFR TKIs other than osimertinib, ALK inhibitors, or cytotoxic chemotherapy.

Follow-up began on the index date and continued until the earliest of the following: HFH event, treatment switch to different drug class (eg, from EGFR TKI to ALK inhibitor or cytotoxic chemotherapy), 30 days after the final prescription of the study drug, or death. Patients with fewer than 7 days of follow-up from the index date were excluded, as HFH events were considered related to study drug exposure only if they occurred at least 7 days after treatment initiation.

Baseline characteristics on the index date are expressed as count (percentage) or median (Q1-Q3) and were analyzed using the chi-square test (or the Fisher exact test when expected cell counts were <5) for categorical variables and the Mann-Whitney U test for continuous variables. Death was regarded as a competing risk for the primary outcome; therefore, we analyzed HFH using Gray's test and the Fine-Gray model. The results are presented as the cumulative incidence with 95% CI and subdistribution hazard ratio (sHR) with 95% CI. Model assumptions were confirmed using Schoenfeld residuals. Covariates included in the Fine-Gray model were sex, age, osimertinib use, history of HF, hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, atrial fibrillation, other arrhythmias, chronic kidney disease, and chronic obstructive pulmonary disease. We selected 65 years of age as the cutoff for analyses on the basis of clinical guidelines in cardio-oncology, which identify age $\geq$65 years as a risk factor for developing HF during treatment with various chemotherapies.[7] Matching was not considered in the model.

Osimertinib has been approved for the treatment of patients with NSCLC in Japan since May 2016 and as a first-line therapy since August 2018. Given the inclusion of relatively recent cases in the osimertinib group and the potential impact of evolving cancer therapies over the study period, we performed Fine-Gray analysis stratified by treatment period (before or after 2016), line of cancer treatment, and history of radiotherapy (defined by procedure codes M000 or M001, which may include treatments other than chest irradiation).

For the analysis restricted to the osimertinib group, which evaluated HFH risk factors, cancer treatment line, and history of radiotherapy were added as covariates, excluding osimertinib use. Additionally, we evaluated differences in primary outcomes between the osimertinib and other EGFR TKI groups using the Fine-Gray model, as this analysis was focused solely on patients with NSCLC harboring EGFR mutations.

Given the variety of factors that contribute to HF, propensity score matching was performed to adjust for differences in patient characteristics between the osimertinib and control groups. The propensity score was calculated using logistic regression, with the following variables included: age, sex, HF-related medications, and medical history at the index date. Patients were matched using the nearest neighbor approach within a caliper width of 0.2.

To evaluate balance between groups before and after matching, standardized mean differences (SMDs) were calculated. An SMD <0.1 was considered indicative of balance. For sensitivity analysis, propensity score matching was performed between the osimertinib and EGFR TKI groups, and the difference in HFH risk between the groups was assessed using the Fine-Gray model.

Statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University),[26] a graphical user interface for R version 4.3.1 (R Foundation for Statistical Computing). Statistical significance was set at a 2-sided *P* value <0.05 for all analyses.

RESULTS

PATIENT CHARACTERISTICS. A total of 11,391 and 108,144 eligible patients were included in the osimertinib and control groups, respectively. The control group comprised 13,685 patients who received EGFR TKIs other than osimertinib, 2,431 patients who received ALK inhibitors, and 92,028 patients who received cytotoxic chemotherapy (Supplemental Table 3).

The median age of the entire cohort was 70 years (Q1-Q3: 64-76 years); in the osimertinib and control groups, the median ages were 73 years (Q1-Q3: 66-79 years) and 70 years (Q1-Q3: 64-76 years), respectively. The median follow-up period for the entire cohort was 173 days (Q1-Q3: 73-448 days); in the osimertinib and control groups, the median follow-up periods were 264 days (Q1-Q3: 86-545 days) and 165 days (Q1-Q3: 72-436 days), respectively. Patient characteristics for each group are shown in **Table 1**. The follow-up period was significantly longer in the osimertinib group compared with the control group ($P < 0.001$). Although most patient background characteristics differed only slightly between groups, the differences were statistically significant. Notably, the percentage of female patients differed substantially between groups, with a higher proportion of women in the osimertinib group. Moreover, the osimertinib group had a lower percentage of patients with chronic obstructive pulmonary disease compared with the control group. The number of patients with histories of HF at baseline was 1,488 (13.1%) in the osimertinib group and 15,722 (14.5%) in the control group.

INCIDENCE OF HFH. Across the entire cohort, 504 HFH events were recorded. The median time from the index date to HFH was 155 days (Q1-Q3: 64-393 days). The incidence of HFH was 9.9 cases per 1,000 person-years in the osimertinib group and 4.1 cases per 1,000 person-years in the control group. The cumulative incidence of HFH was significantly higher in the osimertinib group than in the control group (5.2% at 5 years [95% CI: 2.1%-10.5%] vs 1.4% at 5 years [95% CI: 1.1%-1.6%]; $P < 0.001$) (**Figure 1**).

Within the control group, HFH incidence was similar across drug classes, including EGFR TKIs other than osimertinib (Supplemental Figure 1). The median time to HFH did not significantly differ between the osimertinib and control groups (183 days [Q1-Q3: 45-339.5 days] vs 151 days [Q1-Q3: 69-409.75 days]; $P = 0.12$). However, most HF events in the osimertinib group occurred relatively early during treatment.[17,18]

To explore early risk, we reanalyzed HFH incidence within 180 days of the index date, consistent

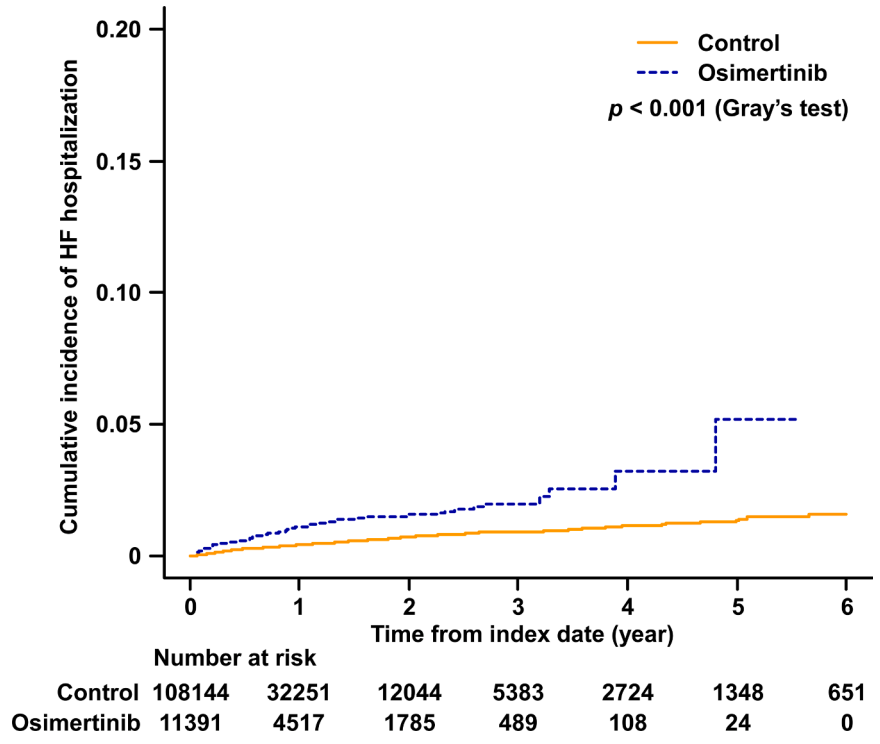
TABLE 1 Baseline Patient Characteristics at the Index Date

	Osimertinib (n = 11,391)	Control (n = 108,144)	*P* Value
Female	7,200 (63.2)	34,300 (31.7)	<0.001
Age, y	73 (66-79)	70 (64-76)	<0.001
Age group			
<55 y	843 (7.4)	8,320 (7.7)	
55-64 y	1,555 (13.7)	19,702 (18.2)	
65-74 y	4,137 (36.3)	47,720 (44.1)	
≥75 y	4,856 (42.6)	32,402 (30.0)	
Follow-up, d	264 (86-545)	165 (72-436)	<0.001
History of heart failure	1,488 (13.1)	15,722 (14.5)	<0.001
Hypertension	4,930 (43.3)	44,808 (41.4)	<0.001
Diabetes mellitus	2,674 (23.5)	31,201 (28.9)	<0.001
Dyslipidemia	2,589 (22.7)	23,887 (22.1)	0.12
Ischemic heart disease	1,056 (9.3)	13,247 (12.2)	<0.001
AF	662 (5.8)	6,862 (6.3)	0.027
Arrhythmia other than AF	761 (6.7)	6,995 (6.5)	0.39
Valvular heart disease	488 (4.3)	4,986 (4.6)	0.12
Cardiomyopathy	39 (0.3)	524 (0.5)	0.042
Chronic kidney disease	396 (3.5)	3,932 (3.6)	0.40
COPD	542 (4.8)	12,594 (11.6)	<0.001
Beta-blocker use	605 (5.3)	6,230 (5.8)	0.052
ACEI and ARB use	1,755 (15.4)	14,634 (13.5)	<0.001
ARNI use	3 (0.03)	7 (0.006)	0.062
MRA use	214 (1.9)	1,836 (1.7)	0.17
SGLT2 inhibitor use	131 (1.2)	2,958 (2.7)	<0.001
Oral diuretic agent use	573 (5.0)	4,959 (4.6)	0.034
Line of cancer treatment			
First-line	7,264 (63.8)	99,741 (92.2)	<0.001
Second-line or later	4,127 (36.2)	8,403 (7.8)	<0.001
Previous radiotherapy	2,083 (18.3)	20,392 (18.9)	0.14

Values are n (%) or median (Q1-Q3). A 2-sided *P* value of <0.05 was considered to indicate statistical significance.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; COPD = chronic obstructive pulmonary disease; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium glucose cotransporter 2.

FIGURE 1 Cumulative Incidence of HF Hospitalization During Lung Cancer Therapy



Cumulative incidence of heart failure (HF) hospitalization in patients treated with osimertinib (dashed line) vs those receiving other therapies (solid line). The difference between groups was evaluated using Gray's test.

with the cohort's median follow-up duration. In this analysis, the median time to HFH was significantly shorter in the osimertinib group than in the control group (44.5 days [Q1-Q3: 21-72 days] vs 76 days [Q1-Q3: 42-118 days]; $P < 0.001$).

Given that patient characteristics may influence HFH risk, we first examined baseline associations between background variables and HFH occurrence (Supplemental Table 4). Hypertension and ischemic heart disease were more common in patients who experienced HFH. We then performed multivariable analysis to evaluate the independent association between these factors and HFH incidence. Osimertinib use remained associated with higher risk for HFH than other therapies (sHR: 2.56; 95% CI: 2.07-3.18; $P < 0.001$) (**Table 2**). Compared with the use of other EGFR TKIs, osimertinib use remained significantly associated with increased HFH incidence (sHR: 3.19; 95% CI: 2.28-4.45; $P < 0.001$).

In subgroup analysis stratified by treatment period, line of cancer treatment, and history of radiotherapy, osimertinib use was consistently associated with higher HFH incidence (Supplemental Figure 2).

ANALYSES OF HFH INCIDENCE USING PROPENSITY SCORE MATCHING. We performed propensity score matching to compare the incidence of HFH between the osimertinib and control groups. After matching, the SMDs for all covariates were less than or near the conventional threshold of 0.1, indicating generally well-balanced patient characteristics between groups (**Table 3**).

In the matched cohort, multivariable analysis showed that osimertinib use was associated with a significantly higher incidence of HFH compared with other therapies (sHR: 2.29; 95% CI: 1.62-3.24; $P < 0.001$) (**Table 4**). Among patients who experienced HFH events, the median number of echocardiograms performed did not differ between the osimertinib and control groups (1 [Q1-Q3: 0-1] vs 1 [Q1-Q3: 0-1]; $P = 0.82$).

In the sensitivity analysis comparing the osimertinib and other EGFR TKI groups, 10,732 patients remained after propensity score matching. The SMD

for all covariates was again <0.1, indicating good balance (Supplemental Table 5). In this matched population, osimertinib use was associated with an increased incidence of HFH (sHR: 2.65; 95% CI: 1.84-3.83; $P < 0.001$).

CLINICAL FACTORS ASSOCIATED WITH HFH. To evaluate risk factors for HFH during osimertinib therapy, we performed 2 analyses: 1) a subgroup analysis after propensity score matching; and 2) an analysis restricted to patients treated with osimertinib prior to matching. In the subgroup analysis, osimertinib use was associated with a higher incidence of HFH in most subgroups (Figure 2). However, no significant association was observed in patients <65 years of age.

In multivariable analyses restricted to patients receiving osimertinib, older age, history of HF, atrial fibrillation, hypertension, and chronic kidney disease were each associated with an increased risk for HFH (Table 5).

TABLE 2 Multivariable Analysis of Risk Factors for Heart Failure Hospitalization

	Reference	Adjusted sHR (95% CI)	*P* Value
Female	Male	1.03 (0.85-1.25)	0.74
Age ≥65 y	Age <65 y	1.91 (1.46-2.51)	<0.001
Osimertinib use	Other therapy	2.56 (2.07-3.18)	<0.001
History of heart failure	No history of heart failure	2.84 (2.30-3.51)	<0.001
Hypertension	No hypertension	1.27 (1.04-1.55)	0.019
Dyslipidemia	No dyslipidemia	1.06 (0.86-1.30)	0.58
Diabetes mellitus	No diabetes mellitus	1.04 (0.85-1.27)	0.69
Ischemic heart disease	No ischemic heart disease	1.70 (1.36-2.12)	<0.001
AF	No AF	2.80 (2.21-3.54)	<0.001
Arrhythmias other than AF	No arrhythmias other than AF	0.82 (0.61-1.10)	0.18
Chronic kidney disease	No chronic kidney disease	1.84 (1.37-2.48)	<0.001
COPD	No COPD	1.35 (1.06-1.73)	0.017

A 2-sided *P* value of <0.05 was considered to indicate statistical significance.
sHR = subdistribution HR; other abbreviations as in Table 1.

DISCUSSION

This study demonstrated that osimertinib therapy was associated with a higher incidence of HFH compared with other therapies, including other EGFR TKIs, ALK inhibitors, and cytotoxic chemotherapy (Central Illustration). This association remained significant after propensity score matching. Additionally, older age, a history of HF, hypertension, atrial fibrillation, and chronic kidney disease were identified as risk factors for HFH during osimertinib therapy.

To our knowledge, this is the largest study to date comparing HFH events between patients receiving osimertinib and those receiving other cancer therapies. We believe these findings provide valuable evidence to guide the management of adverse cardiac events associated with osimertinib use. Strengths of the study include the large sample size, the availability of detailed comorbidity data, and the use of multiple analytical approaches to reduce potential confounding when evaluating the association between osimertinib and the clinically meaningful outcome of HFH.

A previous study using the Food and Drug Administration Adverse Events Reporting System database reported an association between osimertinib and increased risk for HF; however, that analysis lacked information on patient characteristics associated with HF occurrence.[17] In contrast, a study of 2 randomized trials showed no apparent causal relationship between osimertinib and HF, suggesting that observed HF events may have been attributable to pre-existing cardiac risk factors.[18] However, the number of HF cases in that study was insufficient to allow adjustment for baseline characteristics. More

TABLE 3 Patient Characteristics After Propensity Score Matching

	Osimertinib (n = 11,390)	Control (n = 11,390)	*P* Value	SMD
Female	7,199 (63.2)	7,212 (63.3)	0.87	0.002
Age, y	73 (66-79)	73 (66-79)	0.55	0.012
Age group				0.015
<55 y	843 (7.4)	807 (7.1)		
55-64 y	1,555 (13.7)	1,531 (13.4)		
65-74 y	4,137 (36.3)	4,142 (36.4)		
≥75 y	4,855 (42.6)	4,910 (43.1)		
Follow-up, d	264 (86-545)	172 (72-455)	<0.001	0.096
History of heart failure	1,487 (13.1)	1,524 (13.4)	0.48	0.01
Hypertension	4,929 (43.3)	4,938 (43.4)	0.92	0.002
Diabetes mellitus	2,674 (23.5)	2,700 (23.7)	0.70	0.005
Dyslipidemia	2,588 (22.7)	2,636 (23.1)	0.46	0.01
Ischemic heart disease	1,056 (9.3)	1,060 (9.3)	0.95	0.001
AF	662 (5.8)	692 (6.1)	0.42	0.011
Arrhythmia without AF	761 (6.7)	822 (7.2)	0.12	0.021
Valvular heart disease	488 (4.3)	506 (4.4)	0.58	0.008
Cardiomyopathy	39 (0.3)	39 (0.3)	1.00	<0.001
Chronic kidney disease	395 (3.5)	424 (3.7)	0.32	0.014
COPD	542 (4.8)	579 (5.1)	0.27	0.015
Beta blocker users	604 (5.3)	601 (5.3)	0.95	0.001
ACEI and ARB users	1,755 (15.4)	1,734 (15.2)	0.71	0.005
ARNI users	2 (0.02)	0 (0)	0.50	0.019
MRA users	214 (1.9)	211 (1.9)	0.92	0.002
SGLT2 inhibitor users	131 (1.2)	139 (1.2)	0.67	0.006
Oral diuretic agent users	572 (5.0)	582 (5.1)	0.79	0.004

Values are n (%) or median (Q1-Q3). A 2-sided *P* value of <0.05 was considered to indicate statistical significance.
SMD = standardized mean difference; other abbreviations as in Table 1.

TABLE 4 Multivariable Analysis of Risk Factors for Heart Failure Hospitalization After Propensity Score Matching

	Reference	Adjusted sHR (95% CI)	*P* Value
Female	Male	0.96 (0.70-1.34)	0.82
Age ≥65 y	Age <65 y	3.74 (1.84-7.61)	<0.001
Osimertinib use	Other therapy	2.29 (1.62-3.24)	<0.001
History of heart failure	No history of heart failure	2.88 (2.01-4.10)	<0.001
Hypertension	No hypertension	1.51 (1.07-2.14)	0.021
Dyslipidemia	No dyslipidemia	1.11 (0.77-1.59)	0.58
Diabetes mellitus	No diabetes mellitus	0.92 (0.64-1.32)	0.64
Ischemic heart disease	No ischemic heart disease	1.21 (0.78-1.88)	0.39
AF	No AF	3.36 (2.25-5.02)	<0.001
Arrhythmias other than AF	No arrhythmias other than AF	0.80 (0.46-1.39)	0.43
Chronic kidney disease	No chronic kidney disease	1.57 (0.89-2.76)	0.12
COPD	No COPD	0.84 (0.41-1.71)	0.62

A 2-sided *P* value of <0.05 was considered to indicate statistical significance.
Abbreviations as in Tables 1 and 2.

recently, a retrospective study investigated the incidence, risk factors, and outcomes of osimertinib-related cardiotoxicity, but it did not evaluate HF incidence among patients receiving osimertinib compared with other cancer therapies.[27]

To address these limitations, we compared the number of HFH events during osimertinib therapy with those occurring during other therapies using multivariable analysis, subgroup analyses stratified by type of cancer treatment, and propensity score matching adjusted for sex, age, HF-related medications, and HF-related comorbidities. Although a causal relationship could not be established because of the retrospective nature of the study, our findings support the possibility that osimertinib may contribute to HF risk.

A previous study in Japan reported an incidence of 4.9% for osimertinib-related cardiac adverse events, including a 2.4% incidence of HF with reduced LVEF.[28] Furthermore, 2 randomized controlled trials—FLAURA (AZD9291 Versus Gefitinib or Erlotinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer) and AURA3 (AZD9291 [Osimertinib] Versus Platinum-Based Doublet-Chemotherapy in Locally Advanced or Metastatic Non-Small Cell Lung Cancer)—reported that cardiac dysfunction, defined as reduced LVEF, occurred in 3.1% and 5.5% of patients treated with osimertinib, respectively.[18] In our study, the incidence of HFH events was 114 of 11,391 patients (1.0%) in the osimertinib group, a rate that was relatively lower than those reported in prior studies.

We believe that this difference is attributable to differences in HF definitions. In our study, HF was defined as hospitalization for HF or a diagnosis of HF during admission; therefore, outpatients with HF and asymptomatic patients with left ventricular dysfunction were not included. The reported incidence of cardiac failure in the FLAURA and AURA3 trials was 0.7% and 1.1%, respectively,[18] which is comparable with the incidence observed in our study. Given that our definition of HFH required treatment with diuretic agents, vasodilators, or inotropes within 2 days of diagnosis, we speculate that most HFH events were symptomatic.

As many patients with EGFR-mutant NSCLC receive osimertinib as first-line treatment,[29] we believe that HF associated with osimertinib, although infrequent, remains clinically meaningful.

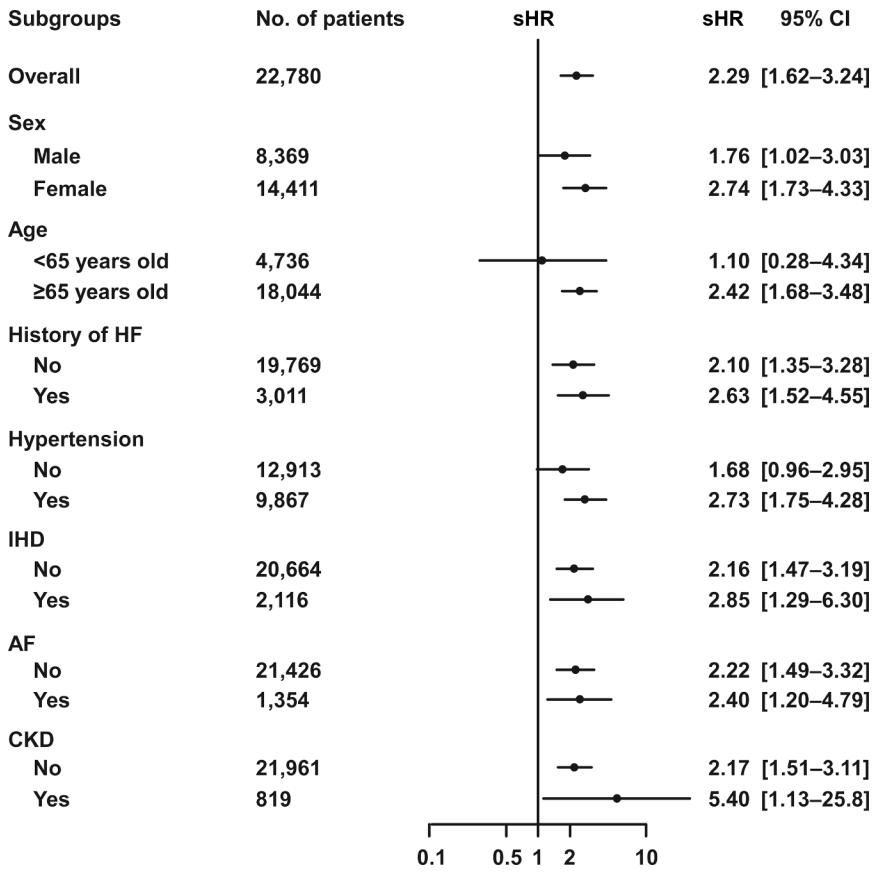
The mechanisms underlying osimertinib-induced cardiotoxicity are not fully understood. In our study, the incidence of HFH was higher among patients treated with osimertinib than among those treated with other EGFR TKIs, suggesting that EGFR alone may not account for cardiac dysfunction. A prior study reported that osimertinib inhibits human epidermal growth factor receptor 2 (HER2) in vitro.[13] This raises the possibility that HER2 inhibition may contribute to osimertinib-induced cardiotoxicity, as trastuzumab, a HER2-targeted monoclonal antibody, is known to cause HF.[9]

However, we believe that HER2 inhibition alone does not explain osimertinib-related cardiotoxicity, as other EGFR TKIs also inhibit HER2.[30,31] Osimertinib has been shown to induce cardiac injury in vitro and in vivo and can disrupt oxidative phosphorylation in cardiomyocytes, leading to mitochondrial dysfunction.[32,33] In contrast, SGLT2 inhibitors improve mitochondrial function, including oxidative phosphorylation.[34] Therefore, SGLT2 inhibitors may help mitigate osimertinib-related cardiotoxicity by counteracting mitochondrial disruption.

Further research is needed to clarify the mechanisms of osimertinib-induced HF and to evaluate the potential protective effects of SGLT2 inhibitors.

STUDY LIMITATIONS. First, as a retrospective analysis using the MDV claims database, this study lacked detailed clinical information, including echocardiographic parameters such as LVEF and global longitudinal strain (GLS), which are critical for the early

FIGURE 2 Risk of Osimertinib-Associated HF Hospitalization in Each Subgroup



Fine-Gray analysis was used to evaluate the risk for heart failure (HF) hospitalization across subgroups stratified by clinical characteristics after propensity score matching. AF = atrial fibrillation; CKD = chronic kidney disease; IHD = ischemic heart disease; sHR = subdistribution hazard ratio.

detection of cancer therapy-related cardiotoxicity. As a result, we could not assess baseline LVEF or GLS, their changes during treatment, or their association with HF occurrence.

Additionally, the severity of comorbid conditions could not be determined. Although multiple analyses were conducted to minimize bias, the absence of key clinical variables such as LVEF, GLS, and comorbidity severity introduces the possibility that differences in these factors between groups may have influenced the findings.

Moreover, data on cancer stage and metastasis were not available. However, in Japan, osimertinib was approved only for patients with unresectable or relapsed NSCLC until October 2022; thus, most patients receiving osimertinib likely had advanced-stage disease. Given that osimertinib was associated with an increased risk for HFH compared with other EGFR TKIs used for the same indication, the lack of cancer stage data may have had limited impact on the

TABLE 5 Multivariable Analysis of Risk Factors for Heart Failure Hospitalization in the Osimertinib Group

	Reference	Adjusted sHR (95% CI)	*P* Value
Female	Male	1.11 (0.75-1.63)	0.61
Age ≥65 y	Age <65 y	4.99 (1.81-13.7)	0.002
History of heart failure	No history of heart failure	2.86 (1.90-4.31)	<0.001
Hypertension	No hypertension	1.75 (1.14-2.67)	0.010
Dyslipidemia	No dyslipidemia	1.01 (0.66-1.53)	0.98
Diabetes mellitus	No diabetes mellitus	0.89 (0.58-1.37)	0.59
Ischemic heart disease	No ischemic heart disease	1.32 (0.81-2.17)	0.27
AF	No AF	3.40 (2.19-5.29)	<0.001
Arrhythmias other than AF	No arrhythmias other than AF	0.74 (0.38-1.43)	0.37
Chronic kidney disease	No chronic kidney disease	1.91 (1.04-3.52)	0.039
COPD	No COPD	0.78 (0.32-1.89)	0.58
Second-line or later treatment	First-line treatment	0.73 (0.49-1.08)	0.12
Radiotherapy prior to osimertinib use	No radiotherapy prior to osimertinib use	0.84 (0.48-1.46)	0.54

A 2-sided *P* value of <0.05 was considered to indicate statistical significance.
Abbreviations as in Tables 1 and 2.

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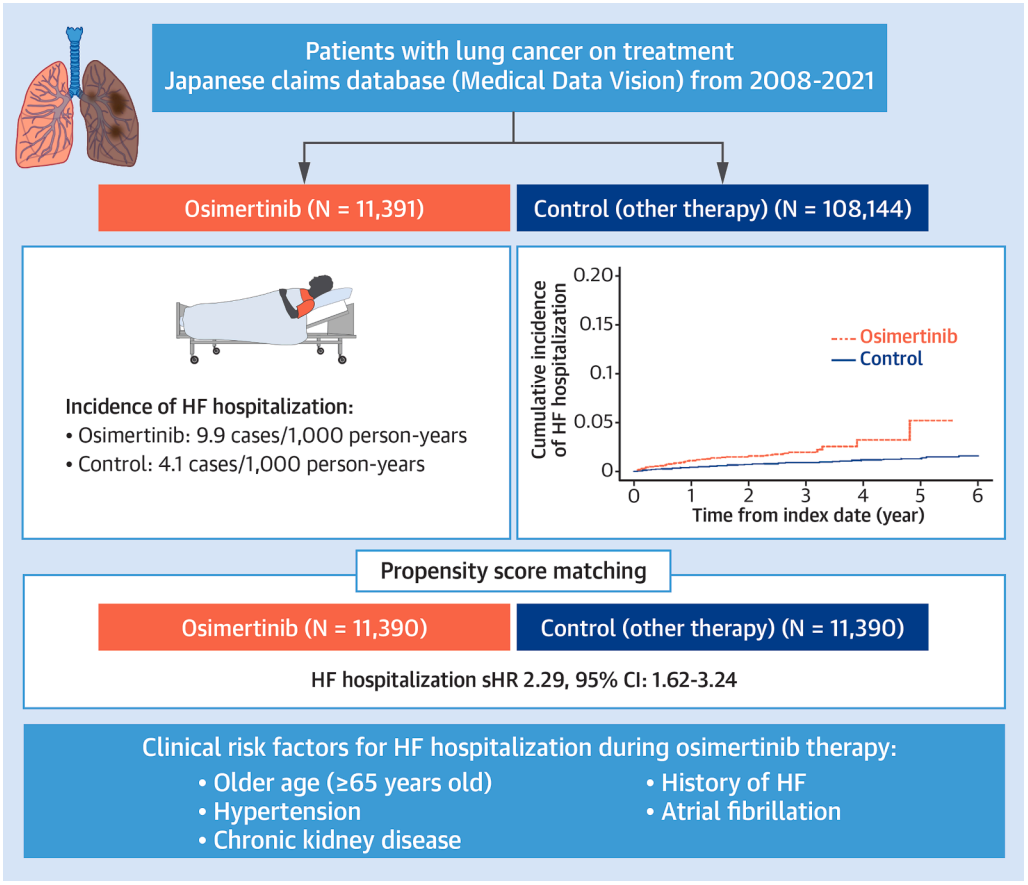
CENTRAL ILLUSTRATION **Retrospective Cohort Study Evaluating the Association Between Osimertinib Therapy and HF Hospitalization**



Tatebe Y, et al. JACC CardioOncol. 2025;7(6):738-748.

Multivariable analyses adjusted for heart failure (HF)–related comorbidities showed that osimertinib was associated with a higher incidence of HF hospitalization in patients with lung cancer compared with control therapies, including other epidermal growth factor receptor tyrosine kinase inhibitors, anaplastic lymphoma kinase inhibitors, and cytotoxic chemotherapy. Older age, history of HF, hypertension, atrial fibrillation, and chronic kidney disease may represent risk factors for HF hospitalization during osimertinib treatment.
sHR = subdistribution HR.

comparison between osimertinib and other EGFR-TKIs.

Second, because the definition of HF in this study relied on ICD-10 codes and concomitant medication rather than detailed patient-level clinical data, some HF cases, particularly asymptomatic or outpatient cases, may have been missed. However, prior studies have validated claims-based definitions of HF,[21,22] and the HF incidence rates observed in this study were consistent with those reported in previous clinical trials.[18]

Third, we could not determine whether all HFH events were directly attributable to osimertinib. Notably, the time to HFH was shorter in the osimertinib group only when limited to events occurring within 180 days of the index date, suggesting that HFH beyond this window may have been influenced by other factors. Nevertheless, we identified multiple risk factors for HFH during osimertinib therapy. In line with our findings, a recent study reported that a history of HF, atrial fibrillation, and older age were associated with increased risk for osimertinib-

induced cardiotoxicity.[27] However, these associations should be confirmed in prospective studies, as we could not establish a direct link between HFH events and osimertinib exposure.

Fourth, because the MDV database is not a closed system, HFH events that occurred outside of participating acute care hospitals may have been missed. Fifth, it is unclear whether the observed association between osimertinib and HF applies to patients with other cancer subtypes, as osimertinib was used exclusively to treat EGFR-mutated NSCLC in this cohort.

Finally, we did not assess overall survival among patients who developed HF during osimertinib treatment; therefore, the impact of osimertinib-associated HF on clinical outcomes remains uncertain. However, a recent retrospective study reported that osimertinib-induced cardiotoxicity was associated with poor prognosis in patients with NSCLC.[27] Given that acute HF is linked to increased mortality[35] and can disrupt cancer therapy, the clinical consequences of HF during cancer treatment are likely significant. Despite these limitations, the observed association between osimertinib use and increased HFH risk underscores the need for further investigation and routine cardiac monitoring in clinical practice.

CONCLUSIONS

In this large population-based study, osimertinib therapy was associated with a higher incidence of HFH compared with other therapies. Although the mechanisms and prevention strategies for osimertinib-associated cardiotoxicity remain unclear, our findings suggest that patients receiving osimertinib—particularly those who are older or have histories of HF, hypertension, atrial fibrillation, or chronic kidney disease—should undergo close cardiac monitoring.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with lung cancer, osimertinib therapy was associated with a higher incidence of HFH than other therapies, even after adjustment for HF-related comorbidities. Compared with other EGFR TKIs, osimertinib use was also associated with increased HFH incidence.

TRANSLATIONAL OUTLOOK: The mechanisms and prevention strategies for osimertinib-associated cardiotoxicity remain unclear. Further research is needed to identify underlying mechanisms and develop effective preventive approaches.

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KEY WORDS adverse events, cardiotoxicity, epidermal growth factor receptor tyrosine kinase inhibitor, heart failure, lung cancer, pharmacotherapy, propensity score matching

APPENDIX For supplemental tables and figures, please see the online version of this paper.