Journal of the American Heart Association

ORIGINAL RESEARCH

Increased Cardiovascular Risk With Lorlatinib in Patients With ALK-Mutated Lung Cancer: A Real-World Comparative Study

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BACKGROUND: The discovery of driver mutations has transformed advanced non–small cell lung cancer treatment, with ALK (anaplastic lymphoma kinase)–rearranged patients achieving longest overall survival. However, the risk of cancer therapy–related cardiovascular diseases (CTRCVDs) is underrecognized, particularly comparing second-generation ALK–tyrosine kinase inhibitors alectinib and brigatinib to the third-generation tyrosine kinase inhibitor lorlatinib, which offers the longest progression-free survival. We aimed to compare CTRCVDs risks among patients with lung cancer receiving ALK-tyrosine kinase inhibitor, assess incidence trends, and identify clinical risk factors associated with ALK-tyrosine kinase inhibitor-related CTRCVDs.

METHODS: This retrospective cohort study of 946 848 adults with lung cancer (2010–2024) using TriNetX compared CTRCVDs risk in ALK-mutated patients treated with lorlatinib versus brigatinib/alectinib. After excluding ROS1-mutated cases and 1:1 propensity score matching, 744 patients per group were analyzed. CTRCVDs, defined as myocardial infarction, stroke, arterial embolism, or heart failure, were evaluated with Kaplan–Meier analysis and Cox proportional hazards models over 2 years.

RESULTS: Lorlatinib treatment was associated with a significantly increased risk of CTRCVDs (hazard ratio [HR], 3.00 [95% CI, 1.65–5.45]; $P<0.001$). Incidence rose from 2.2% at 6 months to 6.6% at 3 years, versus 1.7% and 2.2% in the brigatinib/alectinib cohort. Multivariable analysis identified advanced age (HR, 1.02 [95% CI, 1.00–1.04]; $P=0.04$), atrial fibrillation/flutter history (HR, 2.39 [95% CI, 1.13–5.07]; $P=0.002$), and lorlatinib use (HR, 2.42 [95% CI, 1.57–3.72]; $P<0.001$) as independent predictors.

CONCLUSION: These findings underscore the importance of routine cardiovascular monitoring, particularly in older patients and those with atrial arrhythmias.

Key Words: *ALK* rearrangement ■ cancer therapy–related cardiovascular diseases ■ cardio-oncology ■ lorlatinib ■ non–small cell lung cancer

Lung cancer is among the most commonly diagnosed cancers and stands as the leading cause of cancer-related mortality globally.[1] Recent advancements in treatment, particularly the approval and use of targeted therapies, have contributed to reductions in lung cancer mortality. These therapies specifically target genetic changes in patients with non–small-cell lung cancer (NSCLC), including epidermal growth factor receptor

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This article was sent to Tochukwu M. Okwuosa, DO, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.043620

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Lorlatinib confers a markedly higher risk of therapy-related cardiovascular events (myocardial infarction, stroke, arterial embolism, heart failure) than alectinib or brigatinib in patients with lung cancer.

What Are the Clinical Implications?

- Conduct routine cardiac monitoring for all lorlatinib patients, irrespective of lipid status, with extra vigilance in older patients or those with atrial arrhythmias.
- Future research should define standardized monitoring protocols, evaluate cardioprotective strategies, and use cardiovascular risk profiles to guide ALK (anaplastic lymphoma kinase)- tyrosine kinase inhibitor selection.

Nonstandard Abbreviations and Acronyms

AEs	adverse events
CTRCVDs	cancer therapy-related cardiovascular diseases

mutations, *ALK* (anaplastic lymphoma kinase) fusions, *ROS1* fusions, and others like *BRAF*, *MET*, *RET*, *KRAS*, and *HER2* mutations.[2] The *ALK* gene fusion represents a distinct molecular subset of NSCLC, accounting for approximately 4% to 6% of lung adenocarcinomas.[3] Notably, patients with ALK-positive NSCLC have the longest overall survival rates, with the ALEX (A Study Comparing Alectinib With Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Participants) study reporting a median overall survival of 47.0 months for those treated with alectinib, the highest among targeted therapies for these mutations. In comparison, the FLAURA Phase III (AZD9291 Versus Gefitinib or Erlotinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer) trial found that osimertinib achieved a median overall survival of 38.6 months for epidermal growth factor receptor-mutant cases, whereas the PROFILE 1001 (A Study of Oral PF-02341066, A C-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, in Patients With Advanced Cancer) study indicated that crizotinib led to a lower median survival of 19.2 months for ROS1-positive NSCLC.[4]

According to the National Comprehensive Cancer Network guidelines, alectinib, brigatinib, and lorlatinib are the preferred options for first-line monotherapy in patients with metastatic NSCLC harboring *ALK* rearrangements.[5] Recently, Solomon et al published 5-year outcomes from their phase III CROWN (A Study of Lorlatinib Versus Crizotinib in First Line Treatment of Patients With ALK-Positive NSCLC) study, revealing that in patients with ALK-positive NSCLC treated with lorlatinib, the 5-year median progression-free survival (PFS) reached 60.2 months.[6] This significantly exceeds the median PFS reported for alectinib (34.8 months) and brigatinib (30.8 months).[7,8] However, beyond the well-known side effects of lorlatinib—including hypercholesterolemia and hypertriglyceridemia, both of which are recognized risk factors for atherosclerosis—its potential cardiac and vascular adverse effects have been largely overlooked.[9,10] In the lorlatinib group of the 5-year outcomes from the phase III CROWN study, 7% of patients (10/149) experienced grade 3 or higher cardiac and vascular adverse events (AEs), including 2 fatalities attributed to cardiac failure.[6] Due to the potential underreporting of symptoms in clinical trials, lorlatinib may be associated with a higher incidence of cardiac and vascular AEs in real-world settings.[11] Retrospective analysis of real-world data from the US Food and Drug Administration Adverse Events Reporting System examined cardiac disorders associated with ALK-tyrosine kinase inhibitors (TKIs), including lorlatinib, alectinib, brigatinib, and crizotinib. The findings revealed notable signals of cardiac disorders, particularly heart failure, associated only with crizotinib and lorlatinib. The study further highlighted cases of lorlatinib-induced cardiomyopathy.[12] Another study using the Food and Drug Administration Adverse Events Reporting System also identified lorlatinib-related AE signals, including heart failure, cerebral infarction, and cerebrovascular accidents.[13]

Patients with cancer exhibit a persistently elevated risk of cardiovascular mortality compared with the general population, from diagnosis through survivorship. This reflects a shared dysregulation of immune, genetic, metabolic, hormonal, and microbial pathways that together perturb cellular aging, proliferation, metabolism, and injury.[14] In the first year after diagnosis, patients with lung cancer experience the highest proportion of deaths attributable to fatal heart disease among all populations with cancer, and this elevated risk persists across all follow-up intervals, with the standardized mortality ratio for fatal heart disease remaining between 4 and 5 even beyond 10 years post diagnosis.[15] Moreover, for individuals diagnosed with lung cancer, cardiovascular disease represents a major competing cause of mortality.[16] Prolongation of PFS in patients with ALK-rearranged tumors effectively transforms what was once a terminal diagnosis into a chronic condition,[17] underscoring the importance of

characterizing lorlatinib's cardiovascular effects and identifying its associated risk factors.

Although the 5-year results from the phase III CROWN trial demonstrated that lorlatinib did not result in a higher incidence of cardiovascular events compared with crizotinib, even among patients with preexisting hyperlipidemia,[6] real-world evidence suggests a potentially increased cardiovascular risk associated with lorlatinib.[12,13] Conflicting data between clinical trials and real-world studies regarding the cardiovascular safety of lorlatinib warrant further investigation. Its superior PFS often results in prolonged exposure, which may increase the risk of cardiovascular toxicities. We conducted this study to evaluate lorlatinib-associated cardiovascular AEs in a real-world setting. Given the low prevalence of ALK-positive cases, large-scale registry and database studies are required to adequately address these questions. Therefore, we conducted a retrospective cohort study that is unprecedented in evaluating cardiovascular events and their accumulation in ALK-positive patients with NSCLC treated with lorlatinib versus those treated with alectinib or brigatinib, with adjustments for baseline cardiovascular risk factors. This study aims to clarify the cardiovascular risks of lorlatinib.

METHODS

Transparency and Data Availability Statement

The data used in this study were obtained from the TriNetX Research Network. Access to TriNetX data requires institutional membership and a data-sharing agreement with TriNetX. Data sets are accessed through queries performed on the TriNetX platform. The analytic methods and study materials used to conduct this research are available upon reasonable written request to the corresponding author for purposes of reproducing the results or replicating the procedures.

Data Source

We conducted a retrospective observational cohort study using the TriNetX global research network database, which provides access to anonymized patient-level data, including demographics, diagnoses, medical procedures, medications, laboratory results, and genomic information. The TriNetX platform aggregates data from electronic health records of >164 million patients across >130 health care organizations in countries such as the United States, Australia, the United Kingdom, Spain, Germany, India, Japan, and Taiwan. These organizations include hospitals, primary care practices, and specialty clinics, with contributions from both insured and uninsured patient populations. To date, >1000 peer-reviewed studies using TriNetX data have been published in PubMed-indexed journals. The platform complies with the Health Insurance Portability and Accountability Act and ensures patient privacy through robust de-identification protocols. Because this study relied on a fully anonymized research database, it qualified for exemption from institutional review board approval and the requirement for written informed consent.

Study Population and Design

This retrospective cohort study included data from January 1, 2010, to October 31, 2024. Patients with lung cancer (*International Classification of Diseases, Tenth Revision* [*ICD-10*]: C34) aged >18 years were identified using the *ICD-10*, RxNorm codes, and curated electronic health record data. In earlier years, certain countries continued to use *ICD, Ninth Revision* (*ICD-9*) coding systems; within the TriNetX platform, these codes are systematically mapped to their corresponding *ICD-10-Clinical Modification* (*CM*) concepts based on general equivalence mappings plus custom algorithms and curation to transform data to ensure standardized data representation across institutions. Patients were categorized into 2 cohorts: the lorlatinib cohort (Cohort 1; RxNorm: 2103164), and the brigatinib or alectinib cohort (Cohort 2; brigatinib: RxNorm: 1921217; alectinib: RxNorm: 1727455). Because the clinical trials showed clinical activity for patients harboring *ROS1* mutation,[18,19] we excluded patients with *ROS1* mutation in the lorlatinib cohort. We also excluded patients receiving lorlatinib treatment in the brigatinib and alectinib cohort, because lorlatinib can be used as a second- or third-line treatment option for ALK-positive metastatic NSCLC after acquiring resistance to brigatinib and alectinib.[20] The index date was defined as the initiation date of lorlatinib, brigatinib, or alectinib. Detailed cohort definitions are available in Table S1, and the modeling framework for cohort selection, propensity score matching, and outcome analysis is illustrated in Figure S1. This study adhered to Strengthening the Reporting of Observational Studies in Epidemiology guidelines to ensure comprehensive and transparent reporting of observational research.

Study End Point

The primary outcomes, assessed over a defined 2-year follow-up period, included cancer therapy–related cardiovascular diseases (CTRCVDs), namely myocardial infarction (ICD-10: I21, I22), stroke (ICD-10: I63), arterial embolism (*ICD-10*: I74), and heart failure (*ICD-10*: I42, I50, or left ventricular ejection fraction ≤50% coded as RxNorm FINDING: 2003). Patients with a documented history of these events within 1 day before the index date were excluded. Secondary outcomes included

the individual components of CTRCVD (heart failure and stroke). Detailed outcome definitions are provided in Table S1. Hyperlipidemia was assessed as a positive control, and urinary tract disorders and conjunctival diseases served as falsification outcomes. To evaluate the temporal risk of CTRCVDs among patients receiving lorlatinib, we calculated the incidence rates of CTRCVDs and hyperlipidemia at 6 months, 1 year, 2 years, and 3 years after initiating therapy, comparing patients treated with lorlatinib to those treated with brigatinib or alectinib.

Statistical Analysis

All statistical analyses were conducted using the TriNetX platform, with statistical significance defined as a 2-sided $P<0.05$. We performed 1:1 propensity score matching using greedy nearest-neighbor matching without replacement (caliper of 0.10 SD) to balance cardiovascular risk factors between the lorlatinib cohort and the brigatinib or alectinib cohort. Matching was based on 23 variables associated with cardiovascular risk, all measured 1 day before the initiation of ALK-TKI therapy. These variables encompassed demographic characteristics (age, sex, and race or ethnicity, including White, Hispanic or Latino, and Asian), cardiovascular comorbidities (such as hypertension, diabetes, hyperlipidemia, atrial fibrillation and flutter, overweight or obesity, acute kidney failure and chronic kidney disease, and nicotine dependence), the use of cardiovascular medications (including statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and antiarrhythmic agents), and body mass index. Laboratory measurements included hemoglobin A1c, low-density lipoprotein (LDL) cholesterol, and triglycerides. Additionally, health care use variables—namely emergency department visits, inpatient hospital admissions, and observation care services—were included to account for baseline health care engagement. These variables were selected based on their established relevance to cardiovascular outcomes and potential to act as confounders, thereby enhancing the comparability between treatment groups and the internal validity of the study. Baseline characteristics were assessed using standardized mean differences (SMDs); all variables exhibited SMDs below 0.1, reflecting good balance between the cohorts. Following matching, we compare the two matched cohorts and examined the primary (CTRCVD), secondary (heart failure, stroke), and falsification outcome (urinary tract disorder, conjunctival disease) by estimating hazard ratios (HRs) with 95% CIs from univariate Cox proportional hazards models in R's survival package. We confirmed that the proportional hazards assumption was satisfied for all outcomes by applying the generalized Schoenfeld residuals test using the cox.zph function. Survival analyses for each outcome were conducted using Kaplan–Meier curves, with statistical differences being assessed with log-rank tests. Additionally, sensitivity analyses were conducted by using E values for the observed HRs to evaluate the robustness of the observed associations to unmeasured confounding, a metric recommended for observational studies. A higher E value suggests that a stronger unmeasured confounder would be required to negate the observed associations between exposure and outcomes.[21] Additionally, to predict CTRCVD risk, we constructed a multivariable Cox proportional hazards model. Covariates included in the model were selected based on clinical relevance and prior literature, comprising demographic factors (eg, age, sex, race, ethnicity), cardiovascular comorbidities (eg, hypertension, diabetes, dyslipidemia, etc), and cancer treatment modality. Kaplan–Meier curves and histograms were generated using Python (version 3.10; Python Software Foundation) and GraphPad Prism (version 8.0.2; GraphPad Software, Inc., San Diego, CA).

RESULTS

Study Population and Baseline Characteristics

Between January 1, 2010, and October 31, 2024, a total of 946 848 patients with lung cancer were identified. After excluding those with *ROS1* mutations and a documented history of myocardial infarction, stroke, arterial embolism, or heart failure, 798 patients who received lorlatinib and 1581 patients who received brigatinib or alectinib were included in the analysis before matching (Figure 1). After propensity score matching, 744 individuals remained in each group, and all covariates were well balanced with SMDs <0.1 (Figure S2). We collected 23 variables related to cardiovascular disease that could potentially act as confounders. These included demographic characteristics (age, sex, race, and ethnicity), cardiovascular comorbidities (such as diabetes, hypertension, and others), cardiovascular medications (including statins, angiotensin-converting enzyme inhibitors, and others), laboratory parameters (hemoglobin A1c, body mass index, low-density lipoprotein cholesterol, and triglycerides), and health care use measures (emergency department visits, inpatient hospital admissions, and observation care services). All variables were reported both before and after propensity score matching, as detailed in Table. Following matching, the mean age of participants was 57 years, while 56% were women and the majority were White. The median follow-up duration was 16 months.

Comparison of CTRCVDs Between Lorlatinib and Brigatinib or Alectinib

The incidence of CTRCVDs was significantly higher in patients receiving lorlatinib compared with those

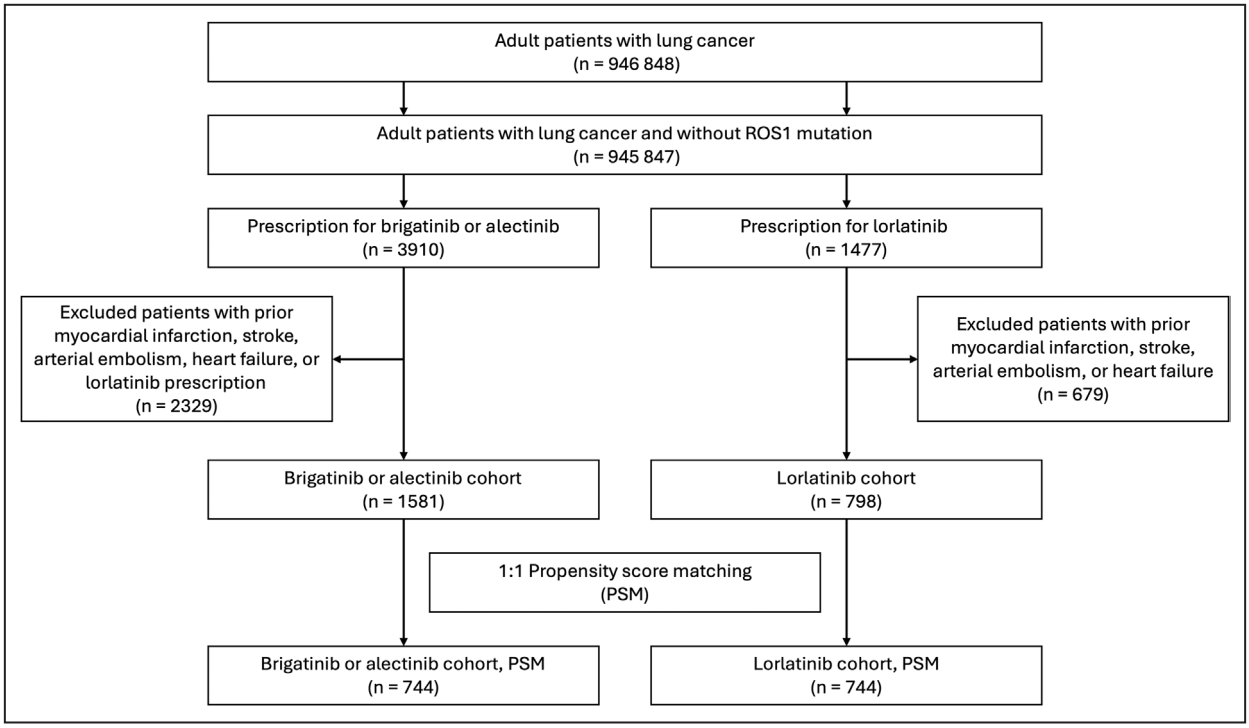

Figure 1. Study inclusion and exclusion flow diagram.

treated with brigatinib or alectinib (39 [5.2%] versus 15 [2.0%]; HR, 3.00; 95% CI, 1.65–5.45; *P*<0.001) (Figure 2). Kaplan–Meier analysis further revealed a substantially higher cumulative incidence of CTRCVDs in the lorlatinib group, with a statistically significant difference identified using the log-rank test (*P*<0.001) (Figure 3). The median time to cardiovascular events was 8.7 months in the lorlatinib group and 8.6 months in the alectinib or brigatinib group.

Prediction of CTRCVD Risk in Patients Treated With ALK-TKIs

A multivariable Cox proportional hazards model was conducted to predict the risk of CTRCVD. Patients who had an advanced age (HR, 1.02; 95% CI, 1.00–1.04; *P*=0.04), had a history of atrial fibrillation or flutter (HR, 2.39; 95% CI, 1.13–5.07; *P*=0.02), and were treated with lorlatinib (HR, 2.42; 95% CI, 1.57–3.72; *P*<0.01) exhibited a significantly higher risk of developing CTRCVD (Figure 4).

Subgroup Analysis of CTRCVDs and Positive-Control Comparison Between Lorlatinib and Brigatinib/Alectinib, and Exploratory Analysis Among Patients Without Hyperlipidemia

Patients treated with lorlatinib exhibited a significantly higher incidence of heart failure (HR, 2.73; 95% CI, 1.26–5.93; *P*=0.008), stroke (HR, 4.87; 95% CI, 1.63–14.49; *P*=0.002), and hyperlipidemia (used as a positive control; HR, 5.22; 95% CI, 4.14–6.59; *P*<0.001) compared with those receiving brigatinib or alectinib (Figure 2). Kaplan–Meier analyses confirmed significant differences between treatment groups (Figure 5A, heart failure; Figure 5B, stroke; Figure 5C, hyperlipidemia).

To evaluate the potential contribution of factors other than hyperlipidemia to cardiac and vascular-related adverse effects, a subgroup analysis was conducted among patients without hyperlipidemia. In this subgroup, the incidence of CTRCVDs remained significantly higher in the lorlatinib group compared with the brigatinib and alectinib groups (Figure 5D; log-rank test, *P*=0.002). In addition, each specific cardiovascular outcome was reported, with cardiomyopathy excluded from the definition of heart failure (Table S2). Treatment with lorlatinib remained significantly associated with an increased risk of heart failure and stroke.

Falsification Outcomes and Sensitivity Analysis

To enhance the robustness of our findings and mitigate potential biases, we performed a falsification analysis by examining unrelated conditions, such as urinary tract disorders and conjunctival diseases. These conditions demonstrated no significant event rates (Table S3). Despite collecting over 20 variables and performing propensity score matching, the potential influence of unmeasured confounders on our results cannot be entirely

Table. Baseline Characteristics of the Study Cohort Before and After Propensity Score Matching Between Lorlatinib and Brigatinib or Alectinib Treatment

Characteristics	Patients, no. (%)					
	Before propensity score matching			After propensity score matching		
	Lorlatinib (No.=768)	Brigatinib or alectinib (No.=1516)	SMD	Lorlatinib (No.=744)	Brigatinib or alectinib (No.=744)	SMD
Demographics						
Age, y, mean±SD	56.8±12.8	59.4±13.1	0.20	57.1±12.6	56.7±13.2	0.03
Female sex	433 (56.4)	833 (54.9)	0.03	419 (56.3)	413 (55.5)	0.02
White race	402 (52.3)	837 (55.2)	0.06	391 (52.6)	407 (54.7)	0.04
Hispanic or Latino ethnicity	33 (4.3)	79 (5.2)	0.04	33 (4.4)	36 (4.8)	0.04
Asian race	117 (15.2)	196 (12.9)	0.07	116 (15.6)	106 (14.2)	0.02
Comorbidities						
Hypertension	186 (24.2)	423 (27.9)	0.08	183 (24.6)	186 (25.0)	0.01
Diabetes	73 (9.5)	146 (9.6)	<0.01	71 (9.5)	61 (8.2)	0.05
Hyperlipidemia	195 (25.4)	358 (23.6)	0.04	180 (24.2)	173 (23.3)	0.02
Atrial fibrillation and flutter	27 (3.5)	55 (3.6)	<0.01	27 (3.6)	26 (3.5)	0.01
Overweight and obesity	50 (6.5)	111 (7.3)	0.03	48 (6.5)	52 (7.0)	0.02
Acute kidney failure and chronic kidney disease	84 (10.9)	140 (9.2)	0.06	80 (10.8)	75 (10.1)	0.02
Nicotine dependence	39 (5.1)	85 (5.6)	0.02	39 (5.2)	38 (5.1)	0.01
Cardiovascular medications						
Statin	209 (27.2)	330 (21.8)	0.13	192 (25.8)	180 (24.2)	0.04
Angiotensin-converting enzyme inhibitor	71 (9.2)	136 (9.0)	0.01	69 (9.2)	61 (8.2)	0.04
Angiotensin receptor blocker	88 (11.5)	183 (12.1)	0.02	87 (11.7)	73 (9.8)	0.06
Beta blockers	146 (19.0)	336 (22.2)	0.08	144 (19.4)	143 (19.2)	<0.01
Antiarrhythmic drugs	331 (43.1)	638 (42.1)	0.02	319 (42.9)	313 (42.1)	0.02
Laboratory tests						
Hemoglobin A1c ≥7%	30 (3.9)	56 (3.7)	0.01	30 (4.0)	23 (3.1)	0.05
Low-density lipoprotein cholesterol ≥130 mg/dL	102 (13.3)	153 (10.1)	0.10	87 (11.7)	85 (11.4)	0.01
Triglycerides ≥150 mg/dL	111 (14.5)	132 (8.7)	0.18	90 (12.1)	95 (12.8)	0.02
Body mass index, kg/m^2, mean±SD	26.6±5.7	26.5±5.7	<0.01	26.6±5.7	26.8±6.0	0.04
Health care use						
Emergency department services	161 (21.0)	308 (20.3)	0.02	154 (20.7)	159 (21.4)	0.02
Hospital inpatient and observation care services	111 (14.5)	261 (17.2)	0.08	110 (14.8)	104 (14.0)	0.02

Values are mean±SD or n (%). SMD indicates standardized mean difference.

excluded. To address this, we conducted sensitivity analyses using E values for both primary and secondary outcomes. A higher E value indicates that a substantially stronger unmeasured confounder would be needed to nullify the observed association between exposure and outcome. Our findings revealed high E values, suggesting that the influence of unmeasured confounding is likely minimal (Figure 2).

Temporal Incidence Rates of CTRCVDs and Hyperlipidemia

We examined the incidence rates of CTRCVDs and hyperlipidemia at 6 months, 1 year, 2 years, and 3 years following treatment with lorlatinib, and compared these rates with those in patients treated with brigatinib or alectinib. As anticipated, the incidence of hyperlipidemia was significantly higher in the lorlatinib group compared with the brigatinib and alectinib groups as early as 6 months after treatment initiation. The incidence of CTRCVDs in the lorlatinib cohort markedly increased over time, rising from 2.2% at 6 months to 6.6% at 3 years. In contrast, the incidence of CTRCVDs in the brigatinib or alectinib group remained lower, at 1.7% at 6 months and 2.2% at 3 years. Additionally, the incidence of CTRCVDs increased progressively over time, with a more pronounced rise observed in the lorlatinib cohort (Figure 6).

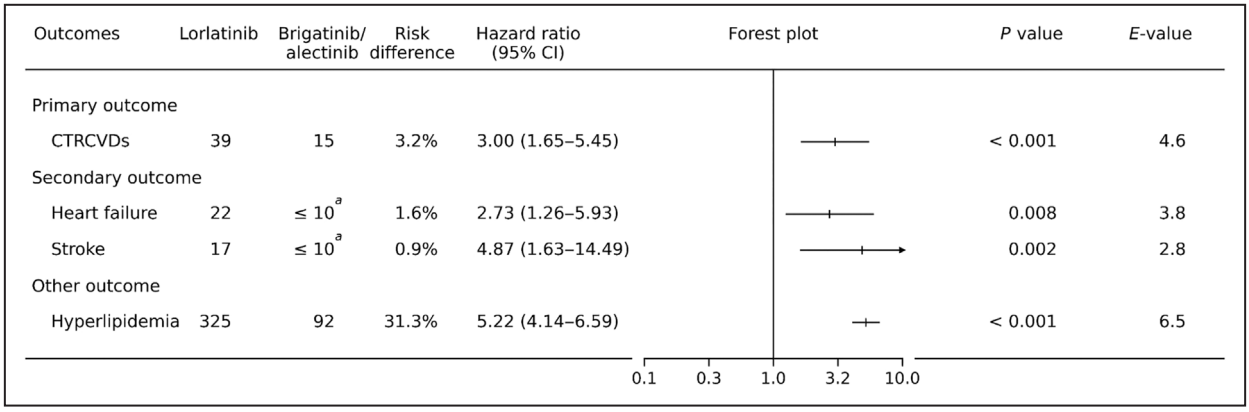

Figure 2. Comparison of outcomes between lorlatinib and brigatinib or alectinib treatment in relation to cancer therapy–related cardiovascular diseases.
Hazard ratios are presented with 95% CIs. Statistical significance was defined as a *P* value <0.05. CTRCVD indicates cancer therapy–related cardiovascular disease.

DISCUSSION

Lorlatinib has achieved the longest median PFS reported to date in first-line ALK inhibitor trials,[6] and its significant efficacy has also been demonstrated in real-world settings.[22] However, the distinctive adverse effects associated with lorlatinib—including hypertriglyceridemia, hypercholesterolemia, weight gain, and neurocognitive events—remain a substantial concern for both health care professionals and patients.[23] Hyperlipidemia, a well-established risk factor for atherosclerosis,[24] has been linked to an increased risk of stroke, cardiovascular disease, and mortality.[25,26] Consequently, there is a critical need to consider the potential for atherosclerosis-related cardiac and vascular AEs in patients undergoing treatment with lorlatinib.

In the CROWN study, approximately 30% of patients in the lorlatinib group experienced cardiac and vascular AEs of any grade, with 7% reporting grade 3 or higher events. Notably, 3 fatalities were attributed to pulmonary embolism, cardiac failure, and acute cardiac failure.[6] Another study conducted in Chinese patients using lorlatinib reported similar findings, with 26.6% of patients experiencing any-grade cardiovascular AEs and 6.4% experiencing grade 3 or higher cardiovascular AEs.[27] Our study corroborates prior concerns by demonstrating that patients treated with lorlatinib exhibited a significantly higher incidence of both cardiac and vascular AEs, including myocardial infarction, stroke, arterial embolism, and heart failure, compared with those receiving alectinib or brigatinib (HR, 3.00; 95% CI, 1.65–5.45; *P*<0.001). Notably, the incidence of these cardiac and vascular AEs in the lorlatinib group progressively increased over time, rising from 2.2% at 6 months to 6.6% at 3 years, compared with 1.7% at 6 months and 2.2% at 3 years in the brigatinib or alectinib group. To minimize the impact of confounding factors, we applied propensity score matching to achieve balanced baseline cardiovascular risk profiles between the groups. Additionally, sensitivity analyses using E values were performed to assess the potential influence of unmeasured confounders, demonstrating that the observed associations are robust even in the presence of hypothetical confounding, thereby further strengthening the validity of our findings. These findings underscore the critical importance of routine monitoring for both cardiac and vascular complications such as heart failure or stroke in patients receiving lorlatinib. The progressive increase in the incidence of these AEs over time highlights the need for vigilant and surveillance to ensure timely identification and management of these potentially serious complications.

Discrepancies in the reported incidence of AEs between clinical trials and real-world studies are well-documented. These differences are not solely attributable to the exclusion of high-risk populations from clinical trials but are also influenced by underreporting or incomplete reporting of treatment-related AEs. Clinical trials often fail to report all-cause AEs comprehensively, or they use variable incidence thresholds, resulting in selective documentation of specific events.[11,28] For instance, in the case of cardiotoxicity associated with the third-generation epidermal growth factor receptor TKI osimertinib, real-world studies have revealed that the incidence and severity of osimertinib-induced cardiotoxicity are higher than those initially reported in clinical trials.[29–31] These findings highlight the critical role of real-world studies in uncovering the true burden of drug-induced AEs and ensuring more comprehensive risk assessments.

Our study found that patients receiving lorlatinib have an increased risk of developing cardiovascular diseases, particularly heart failure and stroke. However, current cardio-oncology guidelines only recommend baseline

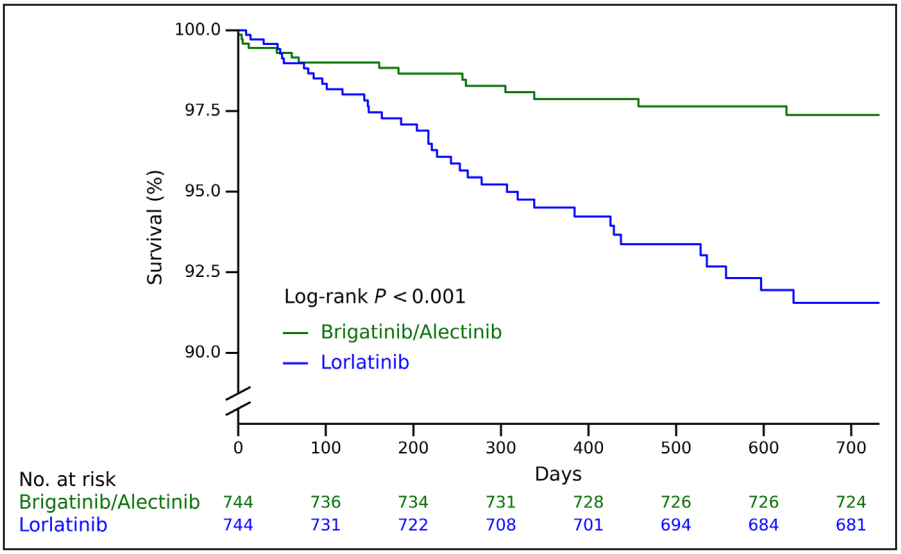

Figure 3. Kaplan–Meier curve for cancer therapy–related cardiovascular disease-free survival over time among patients treated with lorlatinib versus brigatinib or alectinib (log-rank test, *P*<0.001).

and periodic (every 3–6 months) monitoring of cholesterol profiles.[32] We propose stratifying patients into high- and low-risk categories. Based on our multivariable analysis, patients with ALK-mutated lung cancer who are of advanced age, have a history of atrial fibrillation or flutter, or have received lorlatinib are classified as high risk. The intensity and frequency of surveillance should then be tailored accordingly. Based on the recommendations of the European Society of Cardiology guidelines and relevant literature,[32,33] the use of osimertinib warrants cardiac echocardiography every 3 months. Therefore, we recommend that high-risk patients with ALK-mutated lung cancer should undergo echocardiographic evaluation, including assessment of global longitudinal strain (GLS), at baseline and subsequently every 3 to 6 months. In addition, management should emphasize targeted pharmacologic control of weight, lipid levels, and blood pressure. For instance, low-density lipoprotein cholesterol should be maintained at ≤100 mg/dL, with consideration of high-intensity statins or combination therapy with ezetimibe or PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors if the target is not achieved. Further research is warranted to address these recommendations. Until dedicated evidence becomes available, clinicians may consider following established cardiovascular prevention guidelines as a pragmatic alternative.[34–36]

The mechanisms behind lorlatinib-associated cardiac and vascular AEs are not well understood, with most hypotheses regarding ALK inhibitor-related cardiovascular effects derived from crizotinib, the first TKI shown to benefit patients with ALK-rearranged advanced non–small-cell lung cancer at 2010.[37] Lorlatinib demonstrated antitumor activity in patients with previously treated ALK- or ROS1-positive NSCLC only after its introduction in 2017.[38] Although the ROS1 tyrosine kinase receptor shares substantial homology with ALK,[39] alectinib does not significantly inhibit ROS1 activity.[40] Some studies suggest lorlatinib may have cardiovascular toxicity similar to crizotinib,[12] potentially due to their combined inhibition of ALK and ROS1, which may activate overlapping molecular pathways and increase cardiotoxicity risk. Crizotinib directly affects cardiac function by inhibiting hyperpolarization-activated cyclic nucleotide-gated channel 4 in mouse sinoatrial node cells[41] and has been linked to increased reactive oxygen species production, caspase activation, cholesterol accumulation, altered cardiac rhythm, and ion channel blockade in human cardiomyocytes.[42] Additionally, inhibition of autophagy, observed in various heart diseases, may also contribute to cardiotoxicity, as crizotinib has been shown to block autophagy through impaired autophagosome-lysosome fusion, leading to mitochondrial damage and cardiomyocyte death.[43] Crizotinib has also been linked to reductions in free testosterone levels,[44] which may elevate cardiovascular disease risk.[45] Finally, drug concentration and drug–drug interactions are critical factors contributing to cardiovascular risk, as patients experiencing grade 3 or higher AEs have shown significantly elevated serum lorlatinib levels.[46] Lorlatinib is primarily metabolized by cytochrome P450 enzymes,[47] whereas alectinib exhibits a lower affinity for these enzymes,[48] reducing the likelihood of drug interactions. The pharmacokinetics of lorlatinib may be affected by concomitant medications, potentially increasing AE risks.[49]

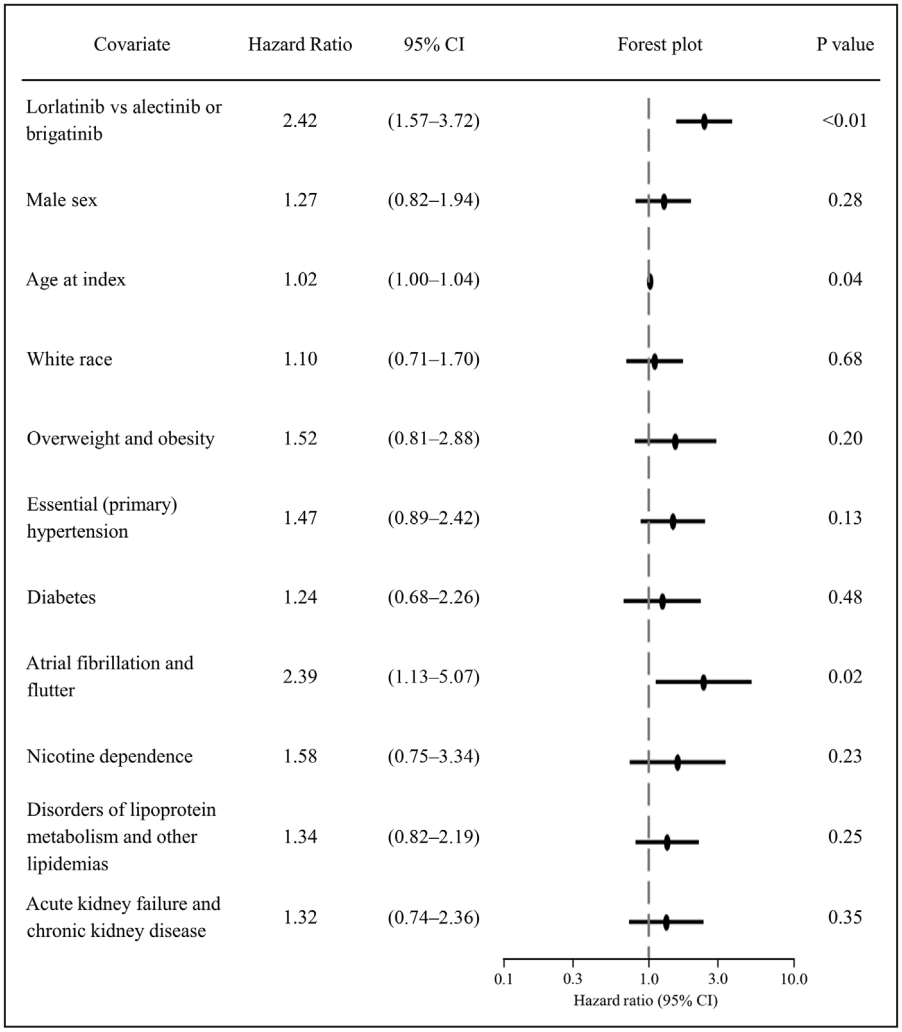

Figure 4. Multivariable Cox proportional hazards model predicting cancer therapy–related cardiovascular diseases.

Strengths and Limitations

The strengths of this study include its large sample size, particularly given that *ALK* mutations account for only ≈4% of NSCLC cases. Additionally, this study incorporates data from multiple health care organizations within large medical systems, representing diverse regions and ethnic groups. This is the first study to compare both cardiac and vascular adverse effects (including stroke, heart failure, myocardial infarction, and arterial embolism) associated with lorlatinib to those observed with brigatinib or alectinib. The study demonstrates a significantly higher incidence of these cardiac and vascular adverse effects in the lorlatinib group and presented the median time to AE onset to support more vigilant and timely monitoring by clinicians at appropriate points of treatment. Additionally, we tracked the incidence of cardiac and vascular adverse effects associated with lorlatinib and found that the incidence of these adverse effects increased with longer use of lorlatinib. More important, we found that advanced age, a history of atrial fibrillation or flutter, and treatment with lorlatinib were independently associated with the development of CTRCVD.

A limitation of this study is its reliance on data and analyses derived from the TriNetX aggregate electronic health record database, which inherently restricts the investigation of variables and analyses not included in the database. To account for the potential impact of unmeasured variables, we calculated E values to demonstrate that no plausible unmeasured confounders would significantly alter the study's conclusions. A second limitation of this study is the inability to ascertain the line of therapy or any dosage adjustments for patients receiving ALK TKIs, which is inherent to the design of the database. Nevertheless, these factors are expected to affect both cohorts equally, minimizing their potential

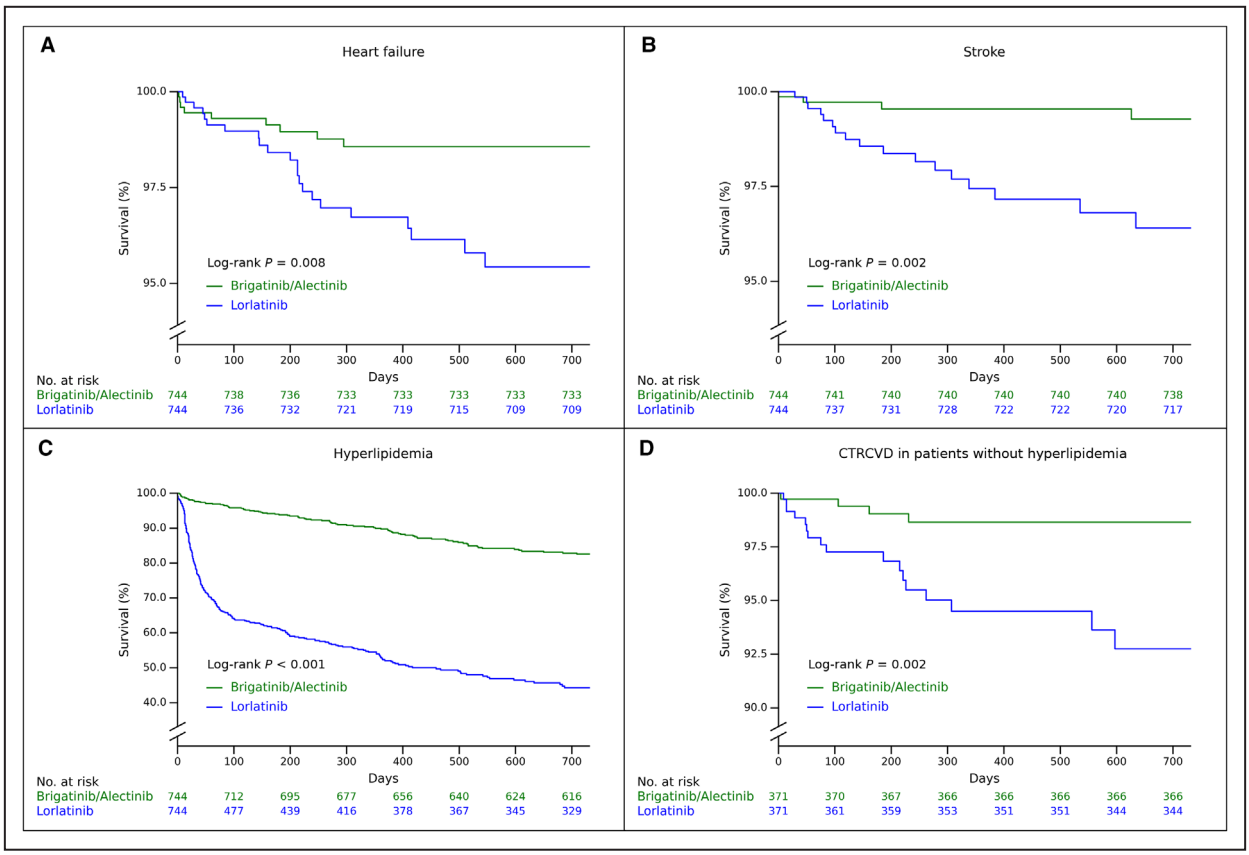

Figure 5. Kaplan–Meier curves for the cumulative incidence of specific cardiovascular events among patients treated with lorlatinib versus brigatinib or alectinib.
A, Heart failure (log-rank test, *P*=0.008); **B**, Stroke (log-rank test, *P*=0.002); **C**, Hyperlipidemia (log-rank test, *P*<0.001); **D**, Cancer therapy–related cardiovascular diseases among patients without hyperlipidemia (log-rank test, *P*=0.002). CTRCVD indicates cancer therapy–related cardiovascular disease.

impact on the comparative findings. In addition, our study did not reveal baseline systolic function. However, all enrolled patients were required to have preserved cardiac function at baseline, as those with a history of heart failure, known cardiomyopathy, or a left ventricular ejection fraction <50% were excluded. Finally, the

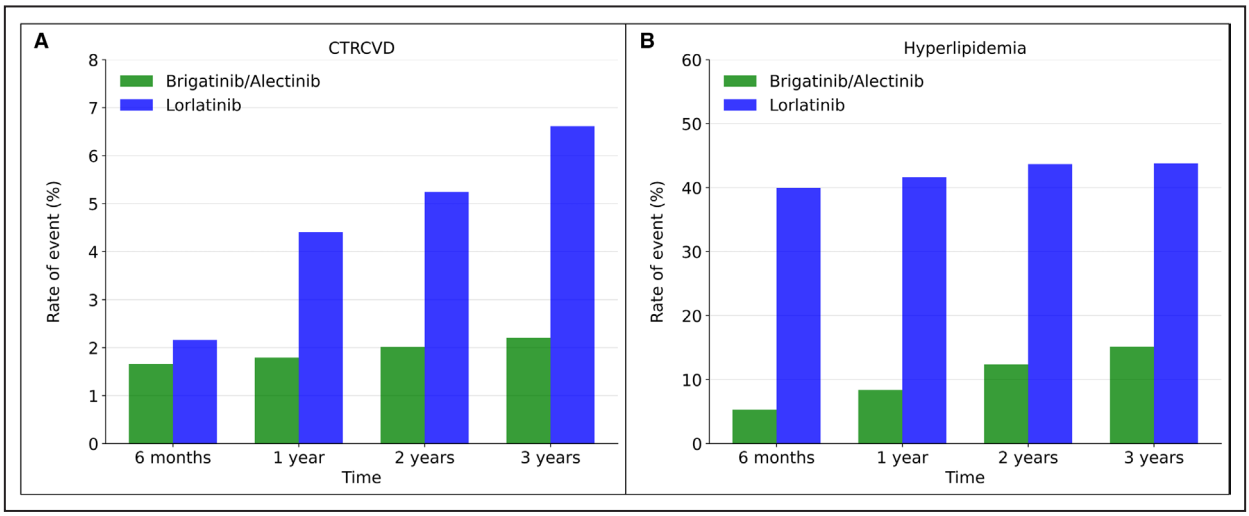

Figure 6. Rates of cancer therapy–related cardiovascular diseases and hyperlipidemia among patients treated with lorlatinib versus brigatinib or alectinib.
A, Rates of cancer therapy–related cardiovascular diseases (CTRCVD) at 6 months, 1 year, 2 years, and 3 years; **B**, Rates of hyperlipidemia at 6 months, 1 year, 2 years, and 3 years. CTRCVD indicates cancer therapy–related cardiovascular disease.

precise timing of hyperlipidemia and cardiac or vascular AEs in individual patients could not be determined, limiting our ability to establish a causal relationship between hyperlipidemia and cardiac or vascular AEs. However, our subgroup analysis demonstrated that even in patients without hyperlipidemia, the incidence of cardiac and vascular AEs remained significantly higher. These findings suggest that mechanisms beyond hyperlipidemia may contribute to lorlatinib-associated cardiac and vascular AEs, underscoring the need for further research to elucidate these pathways.

CONCLUSIONS

As ALK-TKIs extend progression-free survival in ALK-mutant lung cancer, potentially turning it into a chronic condition,[50] managing life-threatening side effects becomes crucial. Our study highlights that lorlatinib is associated with a higher incidence of cardiac and vascular AEs compared with alectinib or brigatinib, with these events increasing over time. Although lorlatinib remains the ALK inhibitor associated with the longest PFS in patients with ALK-positive NSCLC, our intent is not to discourage its use but rather to underscore the importance of vigilant cardiovascular monitoring by clinicians, particularly for older patients or those with a history of atrial fibrillation or flutter, in order to improve outcomes.

ARTICLE INFORMATION

Received May 15, 2025; accepted November 14, 2025.

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Acknowledgments

Concept and design: All authors. Acquisition, analysis, or interpretation of data: Chien-Yu Lin, Chin-Wei Kuo, Po-Lan Su, I.-Lin Tsai, Ting-Hui Liu, Chien-Chung Lin, Sheng-Hsiang Lin. Drafting of the article: Chien-Yu Lin. Critical revision of the article for important intellectual content and supervision: Chien-Chung Lin, Sheng-Hsiang Lin. Statistical analysis: Chien-Yu Lin, Sheng-Hsiang Lin. Obtained funding: Chien-Chung Lin. Administrative, technical, or material support: Jen Yang, Chien-Chung Lin, Sheng-Hsiang Lin.

Sources of Funding

National Science and Technology Council of Taiwan 110-2314-B-006-098-MY3, 113-2314-B-006-107-MY3.

Disclosures

Dr Chien-Chung Lin reported receiving personal fees from AstraZeneca, F. Hoffmann-La Roche AG, Boehringer Ingelheim, Pfizer Inc., Merck Sharp & Dohme, Chugai Pharmaceutical Co. Ltd., Amgen Inc., and Daiichi Sankyo Company Limited as payment or honoraria for lectures, presentations, speaking, and consulting outside the submitted work. No other disclosures were reported.

Supplemental Material

Tables S1–S3
Figures S1 and S2

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