CARDIOVASCULAR CAUSE-OF-DEATH TRENDS IN CHRONIC LYMPHOCYTIC LEUKEMIA IN THE BTK-INHIBITOR ERA: A POPULATION-BASED COMPETING RISK ANALYSIS (SEER 2005 - 2022)

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the United States and predominantly affects older adults, a population already at increased risk for cardiovascular disease. The introduction of **Bruton tyrosine kinase inhibitors (BTKi)** has transformed CLL treatment and significantly improved disease control and survival. However, BTK inhibitors are associated with important **cardiovascular toxicities**, particularly atrial fibrillation and hypertension, raising concerns about their potential impact on cardiovascular mortality. As survival improves and patients live longer with CLL, **non-malignant causes of death, including cardiovascular disease, may represent an increasingly important component of overall mortality.** The population-level impact of the BTKi era on cardiovascular cause-of-death in CLL remains unclear.

AIM

To evaluate **temporal trends in cardiovascular mortality among patients with chronic lymphocytic leukemia (CLL)** before and after the introduction of Bruton tyrosine kinase inhibitors (BTKi), using **population-based competing-risk analysis** to determine whether the BTKi era was associated with changes in cardiovascular cause-of-death.

METHOD

STUDY DESIGN AND DATA SOURCE

Population-based retrospective cohort study using the **Surveillance, Epidemiology, and End Results (SEER) database (2005–2022)**.

Patients with **CLL/SLL (ICD-O-3: 9823/3)** were identified.

STUDY POPULATION

60,994 patients with CLL/SLL were included.

- **Pre-BTKi era: 2005 – 2013 (n=25,316)**
- **BTKi era: 2014 – 2022 (n=35,678)**

OUTCOMES

PRIMARY OUTCOME: Cardiovascular cause-of-death based on SEER cause-of-death recoding.

COMPETING EVENT: CLL-specific death

STATISTICAL ANALYSIS

Cumulative incidence functions (CIFs) were used to estimate the probability of cardiovascular death in the presence of competing risks.

Gray's test was used to compare cumulative incidence between eras.

Fine-Gray competing-risk regression was performed to estimate subdistribution hazard ratios (SHRs) with 95% confidence intervals.

Multivariable models were adjusted for **age, sex, race/ethnicity, chemotherapy receipt, marital status, income quintile, and rural–urban classification**.

Era × sex and **era × race/ethnicity** interactions were assessed.

Statistical significance was defined as **$p < 0.05$**.

RESULTS

- **60,994 CLL/SLL patients** were included; 58.2% were male and 80.9% were Non-Hispanic White.
- **Overall survival improved** in the BTKi era, with 12-month OS increasing from **89.9% to 92.7%** (HR 0.856; p<0.0001).
- **CLL-specific mortality declined** significantly in the BTKi era (SHR 0.624; p<0.0001).
- The proportion of cardiovascular deaths remained **stable** (23.1% vs. 23.4%; p=0.649), while 60-month cumulative cardiovascular mortality **decreased from 7.3% to 6.1%** (Gray's $p=1.9\times10^{-9}$).
- After adjustment, the BTKi era was associated with a **22.8% lower cardiovascular mortality hazard** (SHR 0.772; 95% CI 0.726–0.821; p<0.0001).
- **Non-Hispanic Black patients** had higher CV mortality (SHR 1.327), while patients aged **≥85 years** had a **13.3-fold higher risk** compared with those aged 50–64 years (both p<0.0001).
- No significant **era × sex** or **era × race/ethnicity** interactions were observed.

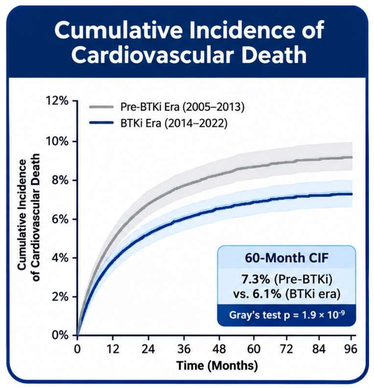

FIGURE 1: The cumulative incidence of cardiovascular death was consistently lower in the BTKi era compared with the pre-BTKi era. At 60 months, cardiovascular mortality was **6.1% vs. 7.3%**, respectively (Gray's test $p=1.9\times10^{-9}$).ve

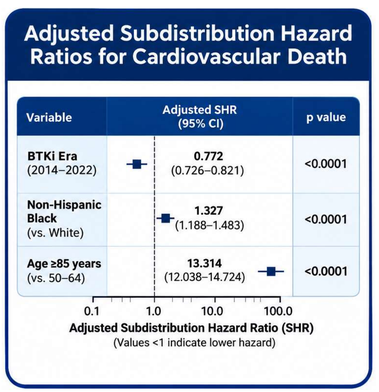

FIGURE 2: After multivariable adjustment, the BTKi era was associated with a **22.8% lower cardiovascular mortality hazard** (SHR 0.772). Higher risk was observed among **Non-Hispanic Black patients** and those aged **≥85 years**.

CONCLUSION

Patients with chronic lymphocytic leukemia (CLL) experience a substantial cardiovascular mortality burden, with temporal trends suggesting an evolving impact of cardiovascular disease on long-term outcomes. These findings highlight the importance of **early cardiovascular risk assessment, prevention, and ongoing monitoring** in patients with CLL. Integrating cardiovascular care into CLL survivorship strategies may help reduce competing mortality and improve long-term outcomes.