course a retrospective review. We have some level of standardization in that all patients were evaluated with the same next-generation sequencing analysis, but it will be prudent to eventually gain larger multi-institution pooled analyses to further validate these molecular characteristics and specifically their effect on prognosis and outcomes.

Our study successfully depicts the molecular similarities between t-MN and t-ALL and observed mutational profiles including the propensity for *TP53m* to represent a significant proportion of these cases and to possibly drive poorer outcomes. We will need larger studies to further validate these findings and to build on understanding the genetic interactions and milieu of t-ALL. We will additionally need to evaluate the outcomes with *TP53m* directed therapies in these patients harboring *TP53m* allowing for more tailored treatment choices beyond chemotherapy to improve disease and survival outcomes. Future studies would perhaps evaluate the association between clonal hematopoiesis after exposure to cytotoxic therapy and the emergence of t-ALL, given their shared genomic alterations. This may lead to understanding the predilection of disease and correlations with these specific molecular subtypes of t-ALL.

## CONFLICT OF INTEREST

The authors report no relevant conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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# Apixaban has superior effectiveness and safety compared to rivaroxaban in patients with commercial healthcare coverage: A population-based analysis in response to CVS 2022 formulary changes

To the Editor:

CVS Caremark, part of CVS Health, announced the exclusion of apixaban (Eliquis®) from the CVS 2022 Caremark Preferred Drug List contracted with some insurers. Warfarin and rivaroxaban are listed as

**TABLE 1** Risk of recurrent venous thromboembolism (VTE) and bleeding comparing apixaban and rivaroxaban among VTE patients with commercial healthcare coverage, excluding patients with dual Medicare enrollment, overall, and by age group

| Primary analysis | Apixaban | | | | Rivaroxaban | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Outcome | *N* | Events, n | PYs follow-up, *n* | Incidence rate per 100 PYs | *N* | Events, n | PYs of follow-up, n | Incidence rate per 100 PYs | Adjusted marginal HR (95% CI) |
| | | Apixaban | | | | Rivaroxaban | | | |
| Recurrent VTE | 15 453 | 387 | 4365 | 8.9 | 15 453 | 478 | 4251 | 11.2 | 0.78 (0.69, 0.90) |
| DVT | | 369 | 4368 | 8.4 | | 445 | 4257 | 10.5 | 0.84 (0.73, 0.97) |
| PE | | 18 | 4322 | 0.4 | | 33 | 4426 | 0.7 | 0.56 (0.31, 1.01) |
| Bleeding | 15 453 | 333 | 4390 | 7.6 | 15 453 | 459 | 4278 | 10.7 | 0.70 (0.61, 0.80) |
| Intracranial | | 6 | 4323 | 0.1 | | 6 | 4426 | 0.1 | 0.79 (0.24, 2.57) |
| GI | | 327 | 4323 | 7.0 | | 423 | 4426 | 9.6 | 0.66 (0.57, 0.76) |

| Subgroup analysis | | | | | | |
|---|---|---|---|---|---|---|
| Examination of effect modification by age | N apixaban | N rivaroxaban | aHR for recurrent VTE with apixaban compared to rivaroxaban (95% CI) | *p*-value for interaction | aHR for bleeding events with apixaban compared to rivaroxaban (95% CI) | *p*-value for interaction |
| <65 years | 5867 | 5867 | 0.78 (0.62, 0.98) | .64 | 0.77 (0.56, 1.06) | .20 |
| ≥ 65 years | 9351 | 9351 | 0.76 (0.64, 0.90) | | 0.59 (0.50, 0.70) | |

*Note*: Results from Cox proportional hazard models after PS 1:1 matching without replacement using a caliper of 0.1 of the standard deviation of the logit of PS.

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; PE, pulmonary embolism; PYs, person-years; VTE, venous thromboembolism.

preferred alternatives. Apixaban is a direct oral anticoagulant (DOAC) indicated for the prevention and treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). One factor that may have influenced the exclusion of apixaban from CVS formulary coverage was the limited evidence comparing apixaban to other DOACs specifically in younger patients with commercial healthcare coverage. Recently, researchers showed a lower rate of thromboembolic and bleeding events with apixaban compared to rivaroxaban.[1,2] However, these studies focused on Medicare beneficiaries 65 years or older[2] or included commercially insured adults with dual enrollment in Medicare.[1] To address this policy-relevant gap in evidence, we examined the effectiveness and safety of apixaban compared to rivaroxaban in a new-user cohort of VTE patients with commercial healthcare coverage, excluding patients with dual Medicare enrollment, overall, and stratified by age group.

We used commercial data from Optum's deidentified Clinformatics® Data Mart Database, which captures the healthcare experience of a privately insured population in the United States. The administrative database includes deidentified individual-level data on enrollment, patient demographics, outpatient claims, inpatient claims, prescription drug claims, and laboratory data for a subset of beneficiaries. Studies using the Optum Clinformatics Data Mart Database are categorized as exempt from Institutional Review Board approval at the University of Pennsylvania.

We conducted a new-user active comparator cohort study. The study design, methods, and outcomes definitions are described in our recent study.[1] We included patients ≥18 years, who had ≥1 prescription of apixaban or rivaroxaban dispensed within 30 days of VTE diagnosis, and 12 months of continuous enrollment in medical and pharmacy benefits prior to treatment initiation (i.e., lookback period). To create a cohort of commercially insured patients, we excluded patients with dual enrollment (i.e., use of both commercial and Medicare insurance). We excluded patients with a prescription for any anticoagulant (i.e., dabigatran, edoxaban, and warfarin) during the lookback period and those who had diagnosis of PE or DVT prior to their index VTE. The primary effectiveness outcome was recurrent VTE, a composite of DVT and PE. The primary safety outcome was a composite of gastrointestinal (GI) and intracranial bleeding. Follow-up began on treatment initiation and ended at the earliest occurrence of an outcome of interest, treatment discontinuation, initiation of the comparator, disenrollment from the health plan, or end of the study period. We used propensity score matching to adjust for potential differences in baseline demographics and disease risk factors between new-users of apixaban and rivaroxaban. After propensity score 1:1 matching, we estimated marginal hazard ratios (HRs) and corresponding 95% CI via Cox proportional-hazards regression using a robust variance estimator while adjusting for calendar year. We assessed the potential for effect modification by age group (<65 years and ≥65 years). We performed matching again within each of the selected subgroups. We conducted all analyses using SAS v9.4 (SAS Institute Inc.: Cary, NC).

The analysis included 42 143 patients with VTE with commercial healthcare coverage who were new-users of apixaban or rivaroxaban (Table A1). In the matched cohort ($n$ = 15 453 for apixaban and $n$ = 15 453 for rivaroxaban), the mean age was 67 years. Approximately, 39% of patients were younger than 65 years ($n$ = 6049 for apixaban and $n$ = 5952 for rivaroxaban). Covariates were well-balanced after matching including male sex (48% vs. 48%), anemia (13% vs. 13%), chronic lung disease (31% vs. 31%), diabetes (28% vs. 28%), and peripheral vascular disease (20% vs. 20%). In the propensity score-matched cohort of VTE patients, the incidence rate of VTE per 100 person-years of follow-up was 8.9 among apixaban users and 11.2 among rivaroxaban users. After propensity-score matching, use of apixaban (vs. rivaroxaban) was associated with a lower rate of recurrent VTE (adjusted HR, 0.78 [95% CI, 0.69 to 0.90]) (Table 1). The results for the individual effectiveness outcome were similar for DVT (HR, 0.84 [95% CI, 0.73 to 0.97]) and PE (HR, 0.56 [95% CI, 0.31 to 1.01]). The incidence rate of GI and intracranial bleeding per 100 person-years of follow-up was 7.6 among apixaban users and 10.7 among rivaroxaban users. After propensity-score matching, use of apixaban (vs. rivaroxaban) was associated with a lower rate of GI and intracranial bleeding (HR, 0.70 [95% CI, 0.61 to 0.80]) (Table 1). The results were similar for GI bleeding (HR, 0.66 [95% CI, 0.57 to 0.76]) and intracranial bleeding (HR, 0.79 [95% CI, 0.24 to 2.57]). We did not find evidence of effect modification by age among users of apixaban (vs. rivaroxaban) for recurrent VTE ($p$-value for interaction = 0.64) or bleeding ($p$-value for interaction = 0.20) (Table 1).

In this large, propensity score-matched cohort of commercially insured patients with VTE, we found that apixaban use was associated with a lower rate of recurrent VTE, intracranial bleeding, and GI bleeding compared with rivaroxaban; results did not vary with age. Our results confirm and extend recent findings from observational studies.[1,2] Specifically, our findings suggest that benefits associated with apixaban use to treat VTE are (a) realized by patients with commercial insurance coverage and are not limited to those with Medicare coverage and (b) extend across age groups including those younger than 65 years.

Use of DOACs is guideline-recommended over warfarin therapy given their improved safety-efficacy profile and ease of use.[3,4] There are clinical situations in which rivaroxaban may be the most appropriate DOAC (e.g., patients who cannot reliably take twice-daily medications). However, based on the results of our analysis, there is compelling evidence favoring apixaban as compared to rivaroxaban in commercially insured patients with VTE. It is critical that insurance formulary coverage decisions follow the best available evidence and prioritize easy access to treatments with the highest degree of efficacy and safety. Formulary coverage decisions that are not evidence-based may have unintended consequences including inferior outcomes and increased overall healthcare costs.

## CONFLICT OF INTEREST

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## DATA AVAILABILITY STATEMENT

The data used for this study are not publicly available. Statistical codes are available upon request from the corresponding author. Protocol and ICD codes used in the current analysis can be found in our previously published work (PMID: 34871048).

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# Prediction of outcomes in chronic lymphocytic leukemia patients treated with ibrutinib: Validation of current prognostic models and development of a simplified three-factor model

To the Editor:

The current shift in the treatment paradigm from chemoimmunotherapy (CIT) to targeted therapy complicates outcome prediction in chronic lymphocytic leukemia (CLL).[1] Existing prognostic markers have assumed new meanings in this treatment transition, while others have become less relevant or even obsolete.[2–4] Likewise, prognostic models developed during the CIT era, namely the CLL International Prognostic Index (CLL-IPI), and Barcelona-Brno (B-B) score, have lost part of their predictive power in the era of targeted therapy.[5–7]

Nowadays, ibrutinib, the first-in-class Bruton kinase (BTK) inhibitor, may claim the most extensive use in clinical practice compared to other targeted agents.[8] However, the magnitude of improvement in progression-free survival (PFS) with ibrutinib depends on the patient subgroup.[3,4,9,10] As a result, clinicians need reliable tools to predict outcomes in this homogeneously treated patient subset.

Two prognostic models originating from pooled analyses of randomized clinical trials of ibrutinib, idelalisib, or venetoclax have recently been developed to predict the prognosis of patients treated with new drugs in the upfront or relapsed/refractory setting.[11,12] These four-factor models share standard variables, such as serum $\beta_2$-microglobulin and lactate dehydrogenase (LDH). Moreover, the model by Soumerai et al.[11] (formally indicated as the BALL score: $\beta_2$_microglobulin, Anemia, LDH, time from the Last therapy) is complemented by hemoglobin concentration and time from the start of last therapy, whereas the model by Ahn et al.[12,13] (formally indicated as CLL4 model) is complemented by prior treatment and *TP53* status.

These prognostic models provide a "globally applicable" approach for clinical use in patients treated with targeted agents; however, a comparative performance analysis possibly extended to models generated in the CIT era is lacking.

We analyzed a national multicenter patient cohort consisting of 338 CLL patients treated at 16 Italian hematological institutions outside the context of clinical trials between February 2013 and February 2019 with ibrutinib-based treatment. Of note, none of these patients had previously received venetoclax, idelalisib or other novel agents prior to ibrutinib. In this patient cohort, we assessed the reliability of four well-known prognostic CLL models (the CLL-IPI, B-B, BALL, and CLL4 scores) to predict patient clinical outcomes. Relevant endpoints, such as PFS and overall survival (OS) rates, were analyzed in terms of discriminatory power (such as c-Harrell), and relative goodness of fit was assessed using Akaike information criteria ([AIC] lower is better). PFS was defined as the time from ibrutinib starting to disease progression or death for any cause. Ibrutinib-related lymphocytosis was not considered progressive disease (PD) if in the setting of improvement in other disease parameters. Finally, a multivariate analysis allowed the identification of prognostically independent factors potentially useful for building a simplified three-factor model.

The median age of patients was 69 years (range 32–88), and 62% were males. A cumulative illness rating scale (CIRS) score >6 (range 0–16) was present in 57.4% of patients. Two-hundred and seventy (79.8%) patients had been previously treated (median number of prior therapies 2; range, 1–9) while 68 (20.1%) were treatment-naive. According to the baseline characteristics, 173 (51.1%) patients were in Rai stage III–IV, 148 (43.8%) had LDH values greater than upper normal limit (UNL) and 119 (35.2%) had $\beta_2$-miroglobulin values >5 mg/L. High-risk CLL was distributed over several defined features: (i) 11q deletion in 16.9% of patients, (ii) *TP53* aberrations in 50.3%, and (iii) unmutated immunoglobulin heavy chain (*IGHV*) gene status in 72.5%. Finally, early progression of disease (POD), defined as the time from the start of last therapy <24 months, was recorded in 228 (67.5%) patients (Table S1).

After a median follow-up of 36 months (range 4–85), 80 patients (23.6%) died, while 115 (34.0%) patients had a PFS event. One-hundred and fifty-one (44.6%) patients discontinued treatment. The most common reasons for ibrutinib discontinuation were PD (72/151, 47.6%), and adverse events (59/151, 39.0%). PD was evidenced as Richter's transformation (RT) in 17 patients (5.0%). In 26 patients (17.2%), the cause of ibrutinib discontinuation was related to death.

The 3-year PFS and OS were 70.7% (95% confidence interval [CI]: 65.6%–75.8%) and 78.1% (95% CI: 72.8%–83.4%), respectively. Risk scores developed in patients treated with targeted agents (CLL4 score and BALL) were applied to our cohort of patients and succeeded in predicting OS (Figure 1A,B; $p < .0001$ for both) and PFS (Figure 1C,D; $p < .0001$ for both). However, risk scores developed in patients treated