REAL-WORLD BLEEDING WITH IBRUTINIB IN B-CELL MALIGNANCIES

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ABSTRACT

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Ibrutinib is used to treat B-cell malignancies. Bleeding occurred in up to 50% of ibrutinib-treated clinical trial participants, but major bleeding was uncommon. However, trials excluded patients with certain risk factors and may underestimate major bleeding frequency in clinical practice. Furthermore, many ibrutinib-treated patients concomitantly use oral anticoagulants (OACs) to prevent thromboembolic events caused by comorbid conditions and ibrutinib-related atrial fibrillation. Thus, clinicians are confronted with the decision of concomitantly treating patients with ibrutinib and OACs without sufficient knowledge of the bleeding risk. We conducted two cohort studies in a commercially-insured population to estimate hazard ratios (HRs), using inverse probability of treatment weighting-adjusted Cox proportional hazards regression, for bleeding with ibrutinib vs. bendamustine-rituximab (BR). We also evaluated the performance of SuperLearner-high-dimensional propensity score (SL-hdPS), a novel approach that reduced propensity score overfitting and improved bias reduction vs. hdPS alone in simulation studies. In Aim 1, we assessed rates of major (resulting in hospitalization) and clinically-relevant (resulting in emergency department presentation or hospitalization) bleeding with ibrutinib versus BR in individuals not concomitantly treated with OACs. The major and clinically-relevant bleeding HRs for ibrutinib (vs. BR) were 1.61 (95% confidence interval: 0.67-3.84) and 2.66 (1.29-5.49), respectively. In Aim 2, we assessed rates of major, clinically-relevant, and provider-diagnosed (in any healthcare setting; specified post-hoc) bleeding with ibrutinib vs. BR in individuals concomitantly treated with OACs. Major and clinically-relevant bleeding HRs could not be estimated due to low event counts. The

provider-diagnosed bleeding HR for ibrutinib + OAC (vs. BR + OAC) was 2.70 (1.25-5.82). In Aim 3, we evaluated the performance of SL-hdPS compared to hdPS alone using the Aim 1 and 2 cohorts. SL-hdPS resulted in better covariate balance than hdPS alone in the Aim 1 cohort but resulted in overfitting and suboptimal covariate balance in the Aim 2 cohort. This work fills an important knowledge gap in ibrutinib-related bleeding which may inform ibrutinib's benefit-harm balance. It also provides support for the use of SL to help optimize covariate balance when using hdPS in certain small sample studies.

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CHAPTER 1 – INTRODUCTION

Ibrutinib in B-cell Malignancies

Ibrutinib, a Bruton's Tyrosine Kinase (BTK) inhibitor, is an orally-administered targeted therapy used to treat B-cell malignancies. Ibrutinib has revolutionized the treatment landscape for several cancers including chronic lymphocytic leukemia (CLL), a hematologic cancer characterized by the over-proliferation and accumulation of B-cells within the blood, bone marrow, lymph nodes, and spleen. CLL is the most prevalent leukemia in western countries, with an estimated 20,160 new cases and 4,410 deaths from CLL in 2022 in the US.[1,2] In pivotal clinical trials, ibrutinib demonstrated a 6.5 year progression-free survival (PFS) of 61% in untreated CLL compared to 9% with chlorambucil,[3] and also improved PFS in both treatment-naïve (E1912 and A041202 trials)[4,5] and previously-treated (HELIOS trial)[6,7] CLL compared to chemoimmunotherapy. Thus, ibrutinib is recommended in both first-line and relapsed/refractory CLL. It was reported that 44% of CLL patients enrolled in the informCLL registry received ibrutinib, making it the most commonly used CLL treatment in the era of novel targeted therapies.[8] The observed frequent use of ibrutinib demonstrates the agent's impact on modern CLL treatment. Additionally, ibrutinib produced high overall response rates in clinical trials for previously-treated mantle cell lymphoma (MCL) (67% with a 17.5-month median duration of response)[9] and previously-treated marginal zone lymphoma (MZL) (58% with a 27.6-month median duration of response),[10] supporting its use as a single-agent therapy option in relapsed/refractory MCL and MZL.

Bleeding in Ibrutinib-treated Patients

Although ibrutinib has a favorable safety profile compared to chemotherapy, bleeding occurs in ~50% of patients[11,12] due to ibrutinib's on-target BTK and potentially off-target (Tec) effects on collagen-induced platelet aggregation.[12-16] The high incidence of bleeding in pivotal studies resulted in the recognition of bleeding as an expected adverse effect of ibrutinib—an adverse effect not frequently observed with other cancer therapies. A meta-analysis of bleeding of any severity in ibrutinib clinical trials found a pooled incidence rate of 20.8 (95% confidence interval [95% CI]: 19.1-22.1) per 100 person-years, which is a 172% increase in risk compared to alternative treatments (relative risk [RR] 2.72, 1.62-6.58).[11] Although bleeding was common in clinical trials, major bleeding (typically defined as fatal, life-threatening, or transfusion-requiring) was relatively uncommon, with incidences ranging from 2-8%.[5,9,17-20] However, due to the exclusion of patients with comorbidities and other risk factors for bleeding, these findings may underestimate the frequency of major bleeding in real-world clinical practice.[21] Clinical trials excluded patients with inadequate kidney or liver function, gastrointestinal disease, an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 3, or concomitant use of certain medications (vitamin K antagonists, cytochrome P450 3A4/5 [CYP3A4/5] inhibitors, or proarrhythmogenic drugs).[5,17,22,23] These exclusions however are not considered contraindications to ibrutinib therapy[24] and subsequently do not dictate real-world treatment decisions. Such patients are likely to be more susceptible to ibrutinib-associated bleeding, which would result in a higher incidence of major bleeding. Few studies have measured the real-world incidence of ibrutinib-associated major bleeding, and no study has directly compared the real-world risk of major bleeding between ibrutinib and an alternative cancer therapy. Given the high clinical and economic costs of major bleeding,[12,25,26] characterizing ibrutinib's risk of major bleeding

in real-world settings may have significant implications on its benefit-harm balance in patients at high risk of bleeding.

Bleeding with Concomitant Ibrutinib and Oral Anticoagulants

Ibrutinib-treated patients are primarily older adults (median age of diagnosis: 70 years for CLL, 67 years for MCL, and 60 years for MZL),[2,27,28] thus many patients have multiple comorbidities. In fact, up to 69% of CLL patients have two or more comorbidities at the time of diagnosis.[29] Furthermore, ibrutinib is specifically recommended for patients ≥ 65 years of age or with significant comorbidities in CLL, and for elderly or infirm patients in MZL.[30,31] Thus, many patients beginning ibrutinib therapy may take oral anticoagulants (OACs), which have an associated bleeding risk (major bleeding incidence of 1 – 5%),[32] for indications such as deep vein thrombosis/pulmonary embolism prophylaxis or stroke prevention in the setting of pre-existing atrial fibrillation. Moreover, 4 – 16% of patients develop new-onset atrial fibrillation while taking ibrutinib,[33,34] further increasing the likelihood of concomitant treatment with ibrutinib and OACs. Although up to one-third of ibrutinib-treated patients may be co-exposed to OACs,[21] information on the bleeding risk in these patients are lacking.[12,35] Clinicians are therefore regularly confronted with the challenging decision of whether to use OACs in ibrutinib-treated patients or ibrutinib in OAC-treated patients without sufficient knowledge of the risk of bleeding associated with use of this combination. While bleeding events seem likely to be more frequent with ibrutinib and OACs taken together than either drug taken alone, this remains unconfirmed.[12,35] In fact, a study exploring OAC/antiplatelet use as a risk factor for major hemorrhage in ibrutinib-treated patients suggested that patients co-treated with ibrutinib and an OAC and/or antiplatelet have a similar risk of major hemorrhage compared to patients co-treated with an alternative therapy and an OAC and/or antiplatelet.[36] This

interpretation, however, was made by indirectly comparing the similarly increased major hemorrhage risk associated with OAC/antiplatelet use in both ibrutinib-treated patients (RR 1.9, 1.2-3.0) and comparator-treated patients (RR 2.4, 1.0-5.6). To more validly assess the risk of bleeding with concomitant use of ibrutinib and OACs, a study directly comparing bleeding in patients co-exposed to ibrutinib and OACs with patients co-exposed to an alternative treatment and OACs is needed. Addressing this knowledge gap is of major public health importance. Indeed, the U.S. Department of Health and Human Services specifically highlights the need for prevention of OAC-related adverse drug events in its National Action Plan for Adverse Drug Event Prevention.[37]

Using SuperLearner to Improve High-dimensional Propensity Score

Observational studies utilizing high dimensional healthcare data (e.g., administrative claims and electronic health records) are frequently conducted to assess the safety and effectiveness of medical treatments. These studies can provide valuable insight on the causal effects of treatments that are deemed unethical or infeasible to be studied in a randomized clinical trial.[38,39] However, observational studies are prone to confounding bias, as medications are prescribed selectively rather than at random.[40,41] The systematic differences in characteristics between those who do and do not receive a treatment can distort the true effect of the treatment exposure.[42] Statistical methods, such as propensity scores, are employed to minimize bias stemming from a multitude of measured potential confounders when estimating treatment effects using observational data.[41,43]

Propensity score methods aim to minimize the impact of confounding via the estimation of the predicted probability for receiving a treatment based on measured factors. Although these methods are effective in balancing measured baseline covariates

and subsequently reducing confounding bias,[44] they are not necessarily able to account for confounding by unmeasured factors, i.e., unmeasured confounding.[41] The development of data-adaptive approaches have aimed to address this issue. Specifically, the high-dimensional propensity score (hdPS) is a semi-automated propensity score method that exploits the vast number of covariates available in high dimensional healthcare databases which, in combination, are hypothesized to be a good overall proxy for unmeasured confounders in some settings.[45] This method empirically identifies covariates with the highest potential for confounding and includes them, along with pre-specified covariates, in the propensity score estimation. This approach is increasingly being used in pharmacoepidemiologic studies.[46-50]

Though the hdPS algorithm automatically identifies covariates and prioritizes them by potential for confounding, it does not specify the optimal number of empirically-identified covariates to include in the propensity score estimation. Including too few covariates may not account for the entirety of the present confounding. Conversely, including too many covariates may have drawbacks as well. Among these potential drawbacks include overfitting of the propensity score (i.e., first stage) model, an issue not well understood in the setting of propensity scores. Overfitting refers to a situation in which a model fits too closely to the particular data under study and subsequently may not fit alternative datasets.[51] It has been argued that overfitting is not a primary concern with propensity score estimation—as the goal of this method is not necessarily to be generalizable, but to remove imbalances in important baseline factors.[52] However, simulation studies found that the severe overfitting of propensity scores corresponds with increased bias and mean squared error (MSE), suggesting that the overly generous

inclusion of covariates in a propensity score may negatively impact its ability to adjust for confounding.[53]

A novel data-adaptive approach combining hdPS with SuperLearner (SL), an ensemble prediction model method that predicts based on a weighted combination of a variety of prediction models, was proposed to assist researchers with the optimal selection of empirically-identified variables for propensity score estimation.[53,54] In plasmode simulation studies (simulation studies in which elements of observed real-world data are incorporated to provide more realistic simulations),[55] the SL-hdPS approach was found to be generally more effective in reducing bias (25 – 34% more than hdPS in small sample scenarios in which severe overfitting is more likely) and MSE compared to hdPS alone. However, this method has not been used in real-world examples; the potential benefits observed in simulation studies have yet to be seen in the applied setting with parameters such as baseline covariate balance.

Specific Aims

The objective of this dissertation was to assess the rate of real-world bleeding with ibrutinib versus bendamustine-rituximab (BR), a widely-used alternative regimen in B-cell malignancies,[30,56] in individuals with and without concomitant use of OACs using a large nationally-represented commercial claims database. We also assessed the performance of a novel SL-hdPS approach in the applied small sample setting using the cohorts developed to address Aims 1 and 2. Specifically, we aimed to:

Aim 1: Measure the comparative rate of major bleeding and clinically-relevant bleeding in ibrutinib-treated versus BR-treated individuals not concomitantly exposed to an OAC.

Aim 2: Measure the comparative rate of major, clinically-relevant, and provider-diagnosed (specified post-hoc) bleeding in individuals concomitantly exposed to ibrutinib and an OAC versus individuals concomitantly exposed to BR and an OAC.

Aim 3: Evaluate the performance of SL-hdPS in comparison to hdPS alone, in terms of applied study parameters such as baseline covariate balance, in a small sample setting: the study of real-world bleeding with ibrutinib.

This work fills an important knowledge gap in ibrutinib's adverse event profile, potentially improving clinical decision-making for patients who may benefit from ibrutinib. It also elucidates the utility of a novel propensity score method in the applied study setting.

CHAPTER 2 – MAJOR BLEEDING WITH IBRUTINIB VERSUS BENDAMUSTINE-RITUXIMAB: A POPULATION-BASED COHORT STUDY

Introduction

Bleeding of any severity occurs in up to 50% of ibrutinib-treated patients,[11,12] due to ibrutinib's on-target BTK and potentially off-target (Tec) effects on collagen-induced platelet aggregation.[12-16] Major bleeding, however, was uncommonly observed in clinical trials, with incidences ranging from 2 – 8%.[5,9,17-20] Although major bleeding was uncommon in these studies, it may occur more frequently in clinical practice because of its use in patients who were excluded from clinical trials, including those with renal dysfunction and/or those taking concomitant warfarin with or without cytochrome P450 3A4/5 (CYP3A4/5) inhibitors.[5,17,18,22] Indeed, higher incidences of major bleeding (8 – 18%) have been reported in real-world populations compared to clinical trials.[21,57,58] Few studies have examined this topic however, and those that have did not directly compare the rate of major bleeding between ibrutinib-treated individuals and individuals treated with therapeutic alternatives. Furthermore, many of these studies were limited to a single institution. Thus, the comparative rate of major bleeding with ibrutinib vs. other CLL therapies in a population-based setting remains unknown.

Given ibrutinib's current widespread use and the life-threatening potential of major bleeding,[12] a more robust assessment of ibrutinib-related major bleeding may inform its benefit-risk profile, which is particularly important as second-generation BTK inhibitors (e.g., acalabrutinib and zanubrutinib) emerge. We therefore conducted a population-based cohort study to compare the real-world rate of major and clinically

relevant bleeding between ibrutinib and a therapeutic alternative in CLL, bendamustine-rituximab (BR).

Methods

Overview and data source

We conducted an incident-user, active comparator retrospective cohort study to compare incidence rates of major and clinically-relevant bleeding between ibrutinib- and BR-treated individuals diagnosed with CLL. We used 2013 – 2020 Optum Clinformatics de-identified commercial health insurance data, which includes >80 million commercially-insured and Medicare Advantage beneficiaries of a large US-based private health insurer. Optum Clinformatics includes demographic and enrollment information and inpatient, outpatient, and pharmacy claims (for drugs dispensed in the outpatient setting) for enrollees. It also includes laboratory results for a subset of individuals.

Defining the study population

We included individuals who were incident users of either ibrutinib, i.e., had a preceding 6-month baseline period devoid of ibrutinib dispensing, or BR, i.e., had a preceding 6-month baseline period devoid of bendamustine administration between November 1, 2013 and February 29, 2020. We allowed rituximab administrations during the baseline period, as rituximab may be used as part of other CLL regimens or for other medical conditions, but included it in the targeted CLL therapy covariate (see covariate ascertainment below). We included individuals who were diagnosed with CLL, defined as having at least two CLL diagnosis codes (International Classification of Diseases-9-Clinical Modification [ICD-9-CM] 204.1x or ICD-10-CM C91.1x), any position, any claim-type, ≥1 day apart preceding the index date (date of incident exposure to ibrutinib or BR). We excluded individuals with any of the following: 1) interruption in insurance plan

enrollment during the 6-month baseline period; 2) bendamustine administration within 28 days (the duration of one BR cycle) prior to the index date for ibrutinib-treated individuals or ibrutinib exposure within 7 days (the duration of ibrutinib's effect on platelets observed in *in vitro* studies)[13,15] prior to the index date for BR-treated individuals; or 3) co-exposure to an oral anticoagulant (warfarin, rivaroxaban, apixaban, dabigatran, or edoxaban) at the index date (Figure 1). We implemented the third criterion to compare findings from this study to those of our study investigating major bleeding in individuals co-exposed to ibrutinib and an oral anticoagulant (Chapter 3). We allowed bleeding events during the baseline period, but included baseline bleeding as a covariate in the propensity score estimation (see covariate ascertainment below). We included only the first observation meeting inclusion and exclusion criteria, per individual.

Follow-up began on the index date and continued until the first occurrence of: 1) an outcome (defined below); 2) a >7-day therapy gap for ibrutinib or >56-day gap between BR administrations (allowing for an up to 28-day delay in a treatment cycle); 3) a dispensing or administration of an alternative CLL therapy; 4) a dispensing of an oral anticoagulant; 5) insurance plan disenrollment; 6) the end of the dataset (February 29, 2020); or day 180 (to account for the differing treatment duration between ibrutinib and BR). We excluded non-outcome hospitalization time from follow-up to minimize immeasurable time bias.[59]

Exposure and covariate ascertainment

We used National Drug Codes to ascertain ibrutinib exposure from dispensings in the prescription claims. We used Healthcare Common Procedure Coding System codes and National Drug Codes to ascertain BR exposure from administrations in the inpatient and outpatient medical claims. We chose BR as the active comparator referent as it is a common CLL chemoimmunotherapy used in similar settings as ibrutinib.[60] We

considered but decided against a newer CLL therapy (e.g., idelalisib, acalabrutinib, and venetoclax) as the referent, given uncommon use of these agents during the study period. We considered an individual exposed to BR if they had a rituximab administration on the same day as or within 7 days before a bendamustine administration. This ensured the capture of individuals who received BR according to the typical administration schedule,[61] and those with slight variations.

Potential confounders were identified during the 6-month baseline period preceding the index date. Pre-specified variables included demographics, CLL complications (thrombocytopenia, lymphadenopathy, splenomegaly), CLL therapy use within the past 6 months (categorized as targeted therapy or chemotherapy), coexisting medical conditions and medication use associated with an increased risk of bleeding, and a claims-based frailty index[62] (Table 1). We also used the high-dimensional propensity score (hdPS) approach[45,52] to empirically identify additional covariates with a high potential for confounding—which are hypothesized to be proxies for unmeasured confounders. This approach ranks and selects potential confounders based on their empiric association with either the exposure or both the exposure and outcome, as described below.

Outcome ascertainment

The primary outcome was major bleeding, defined as bleeding resulting in inpatient hospitalization. We used a previously validated algorithm to identify outcomes, which demonstrated a positive predictive value of 89% in health insurance claims data using ICD-9-CM codes.[63] We identified outcomes in inpatient claims with a bleeding diagnosis code as the principal discharge diagnosis (indicative of reason for admission), or a bleeding diagnosis code as a secondary discharge diagnosis with a principal discharge diagnosis suggestive of a possible bleed (e.g., gastric ulcer) (Table 2). Bleeding events

due to major trauma, as identified by the algorithm, were excluded. The secondary outcome was clinically-relevant bleeding, which was a composite of bleeding events resulting in inpatient hospitalization (i.e., major bleeding) and those resulting in emergency department presentation.

Statistical analysis

We calculated descriptive statistics for baseline variables, crude incidence rates, and unadjusted association measures, the latter using Cox proportional hazards models. We utilized a semi-automated, data-adaptive hdPS approach to reduce the impact of confounders. First, we used the hdPS algorithm to empirically identify variables with high potential for confounding bias to be included in the propensity score model (Table 3). This entailed identifying the 200 most prevalent codes from each of 11 pre-specified data dimensions (e.g., diagnoses, procedures, dispensed drugs, and laboratory orders), ranking these codes by potential for bias via their association with the exposure, and then selecting the 200 top-ranked covariates for inclusion in the propensity score. We also used the hdPS algorithm to screen these selected covariates for instrumental variables and excluded them from the model, as instruments can cause bias in the propensity score estimation.[52] Second, we included these top empirically-identified covariates, along with demographic and clinical variables that were pre-specified, into a logistic regression model to calculate propensity scores—defined as an individual's predicted probability of receiving ibrutinib vs. BR. Third, we calculated the stabilized inverse probability of treatment weight (sIPTW) for each individual based on propensity scores. We used standardized differences to assess covariate balance in the unweighted and weighted cohorts, with an absolute standardized difference of < 0.1 as a threshold for adequate balance. Lastly, we estimated hazard ratios using Cox proportional hazards regression, weighted based on sIPTW, and used a robust variance

estimator to account for weighting. The model also adjusted for calendar year of cohort entry and any covariates that remained imbalanced after sIPTW. We assessed the proportional hazards assumption by including an interaction term of exposure by time since cohort entry in the model.

We calculated the E-value to assess the potential impact of unmeasured confounders.[64] The E-value provides the minimum strength of association, on the risk ratio scale, a potential confounder needs to have with both the exposure and outcome to move the outcome result effect estimate to a null value. We conducted numerous pre-specified sensitivity analyses (Table 4) for the primary outcome to assess the robustness of our findings and explored effect modification by use of medications that may affect the metabolism of ibrutinib or BR (e.g., CYP3A4 and CYP1A2 inhibitors). Analyses were conducted using SAS v9.4 (SAS Institute Inc.: Cary, NC). The University of Pennsylvania institutional review board deemed research using this dataset to be exempt from review.

Results

Baseline Characteristics

We identified 2,423 and 1,102 incident users of ibrutinib and BR, respectively (Figure 2). Individuals in the overall cohort were predominantly male (61.6%) and White (70.4%), with a median age of 72 years and a median frailty score of 0.135 (i.e., pre-frail category per frailty index).[62] Large proportions of individuals had baseline diagnoses of hypertension (59.2%), lymphadenopathy (42.4%), thrombocytopenia (25.9%), renal dysfunction (23.3%), and splenomegaly (22.0%). A small proportion of individuals had a bleeding event during the baseline period (3.6%). The majority of ibrutinib-treated individuals (88.1%) received an average daily dose of 420 mg at cohort entry (Table 5).

Unweighted baseline characteristics were generally similar between ibrutinib- and BR-treated individuals except for cohort entry year (≥ 2016: 81.8% in ibrutinib vs. 63.3% in BR), heparin use (7.1% in ibrutinib vs. 19.2% in BR), targeted CLL therapy use (12.0% in ibrutinib vs. 28.0% in BR), CYP2D6 inhibitor use (21.0% in ibrutinib vs. 35.6% in BR), and CYP2D6 inducer use (9.8% in ibrutinib vs. 25.3% in BR). All weighted pre-specified baseline characteristics that were included in the propensity score were well-balanced except for geographic region of residence (absolute standardized difference = 0.14) (Table 5 and 6).

Follow-up Time and Crude Outcome Incidence Rates

Among 687 person-years (p-y) of follow-up in ibrutinib-treated individuals (median follow-up of 95 days per user), we identified 21 major bleeding events (crude incidence rate: 3.1 per 100 p-y, 95% confidence interval [95% CI]: 2.0 – 4.7) (Table 7). Among 361 p-y of follow-up in BR-treated individuals (median follow-up of 137 days per user), we identified nine major bleeding events (crude incidence rate: 2.5 per 100 p-y, 95% CI: 1.3 – 4.8). Major bleeding events were predominantly gastrointestinal (47.6% and 66.7% of major bleeds in ibrutinib- and BR-treated individuals, respectively) (Table 8). We identified 40 and 15 clinically-relevant bleeding events in ibrutinib-treated individuals (crude incidence rate: 5.8 per 100 p-y, 95% CI: 4.3 – 7.9) and BR-treated individuals (crude incidence rate: 4.2 per 100 p-y, 95% CI: 2.5 – 6.8), respectively.

sIPTW-adjusted Findings

The propensity score included 198 covariates (29 pre-specified and 169 empirically selected by the hdPS algorithm) (Table 9 and Figure 3). Crude and sIPTW-adjusted hazard ratios (HR) are presented in Table 7 and Kaplan-Meier curves are presented in Figure 4. Ibrutinib (vs. BR) had an elevated, yet statistically compatible with the null, hazard of major bleeding (sIPTW-adjusted HR: 1.61, 95% CI: 0.67 – 3.84), and an

elevated and statistically significant hazard of clinically-relevant bleeding (sIPTW-adjusted HR: 2.66, 95% CI: 1.29 – 5.49). The E-value corresponding to the clinically-relevant bleeding effect estimate was 4.76 (E-value for the lower bound of the 95% CI: 1.90). This indicates that an unmeasured confounder, beyond the measured confounders included in the propensity score, would need a risk ratio association of 4.76 with both the exposure and outcome to move the clinically-relevant bleeding effect estimate to a null value of 1 (and a risk ratio association of 1.90 with both the exposure and outcome to move the lower bound of the 95% CI to a null value of 1). Results from sensitivity analyses were consistent with our primary findings; analyses showed an elevated, yet statistically compatible with the null, hazard of major bleeding with an HR ranging from 1.51 – 1.85 (Table 10). We did not identify effect modification by use of medications with potential for drug interactions (Table 11).

Discussion

This population-based cohort study compared the rates of real-world major and clinically-relevant bleeding in ibrutinib-treated individuals vs. individuals treated with chemoimmunotherapy. Ibrutinib had an elevated hazard of major bleeding compared to BR, although this finding was compatible with the null. Ibrutinib was associated with a 2.6-fold hazard of clinically-relevant bleeding compared to BR, suggesting a potential risk of clinically-relevant bleeding events in patients treated with ibrutinib in routine clinical practice.

The pathophysiology of ibrutinib-related bleeding is not fully understood.[12-15] Ibrutinib irreversibly inhibits BTK and Tec at clinically-relevant concentrations. This interferes with the interaction between glycoprotein VI and collagen, thus impairing platelet adhesion and aggregation.[13-16] Other mechanisms of ibrutinib-related bleeding,

such as the inhibition of C-type lectin-like receptor 2 and von Willebrand factor, have been proposed as well.[13,65]

The crude incidence rate of major bleeding among ibrutinib-treated individuals in our study (3.1 per 100 p-y, 95% CI: 2.0 – 4.7) is comparable to that found in meta-analyses of ibrutinib clinical trials,[11,36] which reported pooled incidence rates of major bleeding ranging from 2.8 – 3.9 per 100 p-y. Though prior real-world observational studies did not report incidence rates, their crude incidence proportions (8-18%)[21,57,58] were notably higher than that of our study (0.87%). Several reasons may have contributed to this difference. First, these studies reported longer median follow-up in ibrutinib-treated individuals (up to 405 days) than our study (95 days), thus including events that occurred in late periods of ibrutinib use. Second, our study population derived from Optum Clinformatics primarily comprises privately-insured, employed individuals across the US. These individuals may be less vulnerable to ibrutinib-related bleeding compared to other populations. This has been observed previously with medication-related bleeding; studies investigating gastrointestinal bleeds with oral anticoagulants in a Medicare population reported outcome incidence rates up to twice that reported in studies using Optum.[66-68] Third, our outcome definition differed from other studies. We defined major bleeding as a bleeding event resulting in inpatient hospitalization, yet previous studies[11,21,36,58] identified major bleeding according to the Common Terminology Criteria for Adverse Events[69] or the Medical Dictionary for Regulatory Activities,[70] which could have included bleeding events that arose during a hospitalization. Though bleeding events might have occurred during hospitalization in our study, they could have been attributable to causes other than ibrutinib (e.g., surgical complications). Last, we excluded individuals who were dispensed oral anticoagulants. It is unclear if ibrutinib increases the risk of major bleeding in individuals co-exposed to

oral anticoagulants compared to alternative therapies, though studies[21,36,71] have found an increased bleeding rate in ibrutinib-treated individuals with baseline anticoagulant use. Given the potential need to prescribe such medications in patients experiencing ibrutinib-related atrial fibrillation,[33,34] a study directly assessing the rate of major bleeding in individuals co-exposed to ibrutinib and oral anticoagulants is needed.

Our adjusted primary outcome analysis found an elevated, yet consistent with the null, rate of major bleeding with ibrutinib compared to BR. It is likely that our study was underpowered due to the low number of outcomes; however, a lack of a difference in the rate of major bleeding between ibrutinib and BR cannot be excluded. Using Austin's method for obtaining the number needed to harm (NNH) from adjusted survival models,[72] we calculated an NNH of 252 for major bleeding. This indicates that, if our results are interpreted as causal, one additional individual would experience major bleeding for every 252 individuals who were treated with ibrutinib rather than BR. Caron et al. and Wang et al. also found increased pooled relative risks of major bleeding vs. comparator therapies in clinical trials ranging from 1.66 – 2.46.[11,73] Our adjusted secondary outcome analysis showed a positive association of ibrutinib (vs. BR) with clinically-relevant bleeding (i.e., bleeding resulting in inpatient admission or emergency department presentation). We calculated an NNH of 58 for clinically-relevant bleeding. Though prior studies did not examine a similarly-defined outcome, comparative rates of lower-severity bleeding were reported. Caron et al. and Wang et al. both observed a larger relative risk with all-severity bleeding in clinical trials (pooled relative risks ranging from 2.72 – 3.08)[11,73] than with major bleeding. Abdel-Qadir et al. conducted a population-based cohort study and observed a similar association with hospital-diagnosed bleeding in ibrutinib-exposed patients compared to chemotherapy-exposed patients (HR 2.58, 95% CI 1.76 – 3.78).[71] Overall, these findings support current

recommendations to consider ibrutinib's potential bleeding risk when assessing it as a treatment option.[12,35,74,75]

Our study has several strengths. It is the largest study to investigate major bleeding in individuals treated with ibrutinib in real-world practice. Our use of an incident-user design and BR as an active comparator reference helped to mitigate confounding and provided a clinically meaningful comparison. Additionally, we used hdPS—a semi-automated, data-adaptive approach—to further improve confounding adjustment. Last, we identified major bleeding using an algorithm that was validated and showed good PPV with ICD-9-CM codes in a similar claims database.[63]

Our study also has limitations. First, we were unable to obtain CLL characteristics like Rai staging and high-risk genomic features such as the presence of deletion 17p or immunoglobulin heavy-chain gene mutation. However, we included complications of CLL that may impact bleeding occurrence (e.g., thrombocytopenia) in the propensity score. Second, we used prescription dispensings to identify ibrutinib exposure, which may not directly reflect ingestion. To address this, we conducted a sensitivity analysis in which therapy gaps between prescriptions were modified. Third, due to a pre-existing concern of bleeding with ibrutinib, treated individuals may have been counseled by their provider on this potential adverse event. Thus, ibrutinib-treated individuals experiencing bleeding may have been more likely to present to the emergency department than BR-treated individuals, potentially leading to a bias away from the null in the secondary outcome. Finally, though we used a rigorous study design and adjustment method to address confounding, residual differences between ibrutinib- and BR-treated individuals may remain.

Ibrutinib is currently the most commonly used CLL therapy in the US. Our study found that, though the rate of major bleeding with ibrutinib in a real-world population was

comparable to clinical trial populations, an increased rate of clinically-relevant bleeding compared to BR is evident. As the use of 2nd-generation BTK inhibitors increases, clinicians will require information on the real-world risks with individual agents within the therapy class. This study will help serve as a benchmark for ibrutinib-related bleeding until a comparative post-market study among all available BTK inhibitors can be conducted.

This chapter is an edited version of a published paper: Dhopeshwarkar N, Yang W, Hennessy S, Rhodes JM, Cuker A, Leonard CE. Rate of major bleeding with ibrutinib versus bendamustine-rituximab in chronic lymphocytic leukemia: A population-based cohort study. *Am J Hematol.* 2022. doi: https://doi.org/10.1002/ajh.26632.

Table 1. Pre-specified baseline covariates.

Demographics	Age	
	Sex	
	Geographic region of residence	
	Race	
	Education level	
	Housing	
	Household income	
	Total net worth of beneficiary	
CLL complications	Thrombocytopenia	
	Lymphadenopathy	
	Splenomegaly	
Medical conditions	Hypertension	
	Renal dysfunction	
	Liver dysfunction	
	Stroke	
	Peptic ulcer	
	Bleeding*	
Concomitant medications	Medications associated with bleeding risk	Antiplatelets
		NSAIDs
		Heparin
	CLL therapy	Targeted therapy
		Chemotherapy
	Medications that can affect CYP metabolism[1]	CYP3A4 inhibitors
		CYP3A4 inducers
		CYP2D6 inhibitors
		CYP2D6 inducers
		CYP1A2 inhibitors
		CYP1A2 inducers
Measure of frailty	Claims-based frailty index[2]	

CLL = chronic lymphocytic leukemia; CYP = cytochrome P450; NSAID = nonsteroidal anti-inflammatory drug

See **Figure 1** for details on timing of covariate measurement

* Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim

1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.
2. Kim DH, et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7.

Table 2. Diagnosis codes used in outcome definition.

Bleed Site	ICD-9-CM Code	ICD-9-CM Code Description	ICD-10-CM Code*
Diagnosis Codes Indicating Bleeding†‡			
Gastrointestinal	531.0x, 531.2x, 531.4x, 531.6x	Gastric ulcer with hemorrhage	K25.0, K25.2, K25.4, K25.6
	532.0x, 532.2x, 532.4x, 532.6x	Duodenal ulcer with hemorrhage	K26.0, K26.2, K26.4, K26.6
	533.0x, 533.2x, 533.4x, 533.6x	Peptic ulcer with hemorrhage	K27.0, K27.2, K27.4, K27.6
	534.0x, 534.2x, 534.4x, 534.6x	Gastrojejunal ulcer with hemorrhage	K28.0, K28.2, K28.4, K28.6
	535.01, 535.11, 525.21, 535.31, 535.41, 535.51, 535.61	Gastritis, gastroduodenitis, or duodenitis with hemorrhage	K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91
	537.83	Angiodysplasia of stomach and duodenum with hemorrhage	K31.811
	456.0, 456.20	Esophageal varices with bleeding	I85.01, I85.11
	530.7, 530.21	Mallory-Weiss tear (gastroesophageal laceration-hemorrhage syndrome) or ulcer of esophagus with bleeding	K22.11, K22.6
	530.82	Esophageal hemorrhage	-
	578.0	Hematemesis	K92.0
	455.2, 455.5, 455.8	Hemorrhoids with other complication	-
	562.02, 562.03, 562.12, 562.13	Diverticulosis or diverticulitis with hemorrhage	K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93
	568.81	Hemoperitoneum	K66.1
	569.3	Hemorrhage of rectum and anus	K62.5

	569.85	Angiodysplasia of intestine with hemorrhage	K55.21
	578.1	Blood in stool	K92.1
	578.9	Hemorrhage of gastrointestinal tract, unspecified	K92.2
Genitourinary	593.81	Vascular disorders of kidney	N28.0
	599.7x	Hematuria	R31.0, R31.1, R31.21, R31.29, R31.9
	623.8	Other specified noninflammatory disorders of vagina	N89.8
	626.6	Metrorrhagia	N92.1
Cerebral	430	Subarachnoid hemorrhage	I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.2, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.6, I60.7, I60.8, I60.9
	431	Intracerebral hemorrhage	I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9
	432.0	Nontraumatic extradural hemorrhage	I62.1
	432.1	Subdural hemorrhage	I62.00, I62.01, I62.02, I62.03
	432.9	Unspecified intracranial hemorrhage	I62.9
Other	423.0	Hemopericardium	I31.2
	459.0	Hemorrhage, unspecified	R58
	568.81	Hemoperitoneum (nontraumatic)	K66.1
	719.1x	Hemarthrosis	M25.00, M25.011, M25.012, M25.019, M25.021

			, M25.022 , M25.029 , M25.031 , M25.032 , M25.039 , M25.041 , M25.042 , M25.049 , M25.051 , M25.052 , M25.059 , M25.061 , M25.062 , M25.069 , M25.071 , M25.072 , M25.073 , M25.074 , M25.075 , M25.076 , M25.08
	784.7	Epistaxis	R04.0
	784.8	Hemorrhage from throat	R04.1
	786.3x	Hemoptysis	R04.2, R04.81, R04.89, R04.9
Diagnosis Codes Suggestive of Possible Bleeding[§]			
Gastrointestinal	531.1x, 531.3x, 531.5x, 531.7x, 531.9x	Gastric ulcer without mention of hemorrhage	K25.1, K25.3, K25.5, K25.7, K25.9
	532.1x, 531.3x, 531.5x, 531.7x, 532.9x	Duodenal ulcer without mention of hemorrhage	K26.1, K26.3, K26.5, K26.7, K26.9

	533.1x, 533.3x, 533.5x, 533.7x, 533.9x	Peptic ulcer without mention of hemorrhage	K27.1, K27.3, K27.5, K27.7, K27.9
	534.1x, 534.3x, 534.5x, 534.7x, 534.9x	Gastrojejunal ulcer without mention of hemorrhage	K28.1, K28.3, K28.5, K28.7, K28.9
	535.00, 535.10, 535.20, 535.30, 535.40, 535.50, 535.60	Gastritis, gastroduodenitis, or duodenitis without mention of hemorrhage	K29.00, K29.20, K29.30, K29.40, K29.50, K29.60, K29.70, K29.80, K29.90
	562.00, 562.01, 562.10, 562.11	Diverticula or diverticulitis without mention of hemorrhage	K57.00, K57.10, K57.12, K57.20, K57.30, K57.32, K57.40, K57.50, K57.52, K57.80, K57.92
	455.0, 455.1, 455.3, 455.4, 455.6, 455.7, 455.9	Hemorrhoids	K64.0, K64.1, K64.2, K64.3, K64.4, K64.5, K64.8, K64.9
	530.1x	Esophagitis	K20.0, K20.8, K20.9, K21.0
	530.20	Ulcer of esophagus without bleeding	K22.10
Unspecified	285.1	Acute posthemorrhagic anemia‖	D62
	280.0	Anemia due to loss of blood‖	D50.0
	285.9	Anemia, unspecified‖	D64.9
	790.92	Abnormal coagulation profile‖	R79.1
	287.49, 287.5	Thrombocytopenia‖	D69.59, D69.6
Genitourinary	626.2	Excessive/frequent menstruation**	-

CM = clinical modification; ICD = International Classification of Diseases

* ICD-9-CM diagnoses were mapped to ICD-10-CM diagnoses using forward-backwards mapping with general equivalence maps[1]

† Outcomes were excluded if a major trauma code was recorded on the day prior to admission through the day after admission. See Cunningham et al.[2] for list of trauma codes

‡ Diagnosis code required to be the principal discharge diagnosis

§ Diagnosis code required to be the principal discharge diagnosis with either 1) a diagnosis code indicating bleeding as a secondary diagnosis or 2) a revenue code indicating a transfusion
‖ Diagnosis code required to be the principal discharge diagnosis with a diagnosis code indicating bleeding as a secondary diagnosis (a transfusion revenue code is not sufficient)
** Diagnosis code required to be the principal discharge diagnosis with a diagnosis code of either 1) anemia (ICD-9-CM: 280.0, 285.1, 285.9; ICD-10-CM: D50.0, D62, D64.9) 2), orthostasis (ICD-9-CM: 458.0; ICD-10-CM: I95.1), or 3) syncope (ICD-9-CM: 780.2; ICD-10-CM: R55) as a secondary diagnosis

1. Fung et al. Preparing for the ICD-10-CM transition: Automated methods for translating ICD codes in clinical phenotype definitions. *EGEMS (Wash DC).* 2016;4(1):1211.
2. Cunningham et al. An Automated Database Case Definition for Serious Bleeding Related to Oral Anticoagulant Use. *Pharmacoepidemiol Drug Saf*. 2011:20(6):560-566.

Table 3. High-dimensional propensity score specifications.

Data dimensions (*p*)	Inpatient[a] ICD-CM[*] diagnoses
	Inpatient[a] ICD-CM/PCS[*] procedures
	Inpatient[a] CPT/HCPCS procedures
	Laboratory[b] LOINC observations
	Outpatient[c] ICD-CM[*] diagnoses
	Outpatient[c] ICD-CM/PCS[*] procedures
	Outpatient[c] CPT/HCPCS procedures
	Other setting[d] ICD-CM[*] diagnoses
	Other setting[d] ICD-CM/PCS[*] procedures
	Other setting[d] CPT/HCPCS procedures
	Outpatient pharmacy dispensings[e]
Granularity of *p*	3 digits for ICD-9-CM diagnoses[*], 7 characters for LOINC observations, 2 digits for ICD-9-CM procedures[*], 5 digits for CPT, 5 characters for HCPCS, and medication active ingredient for outpatient pharmacy dispensings[†]
Empiric covariates identified (*n*), per *p*, ranked in descending order by prevalence	*n* = 200
Method of covariate ranking	Exposure-only: univariate association between covariate and exposure
Empiric covariates selected (*k*), across *p*, after ranking	*k* = 200
Zero-cell correction screening	No, zero-cell correction screening is not applicable to exposure-only method of covariate ranking

CM = Clinical Modification; CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD = International Classification of Diseases; LOINC = Logical Observation Identifiers Names and Codes; PCS = Procedure Coding System
a. Claims arising from Diagnosis, Procedure, and Medical tables with place of service = inpatient hospital
b. Claims arising from Laboratory table
c. Claims arising from Diagnosis, Procedure, and Medical tables with place of service other than inpatient hospital or facility listed in footnote d
d. Claims arising from Diagnosis, Procedure, and Medical tables with place of service = assisted living facility, group home, skilled nursing facility, nursing facility, custodial care facility, inpatient psychiatric facility, intermediate care facility, residential substance facility, psychiatric

residential treatment facility, comprehensive inpatient rehabilitation facility, or comprehensive outpatient rehabilitation facility
e. Claims arising from Prescription table

* ICD-10-CM diagnoses and procedures were mapped backwards to ICD-9-CM using general equivalence mapping[1]
† Defined using medication active ingredient from Cerner Multum (Cerner Corporation: Kansas City, MO) Lexicon

1. Fung et al. Preparing for the ICD-10-CM transition: Automated methods for translating ICD codes in clinical phenotype definitions. *EGEMS (Wash DC).* 2016;4(1):1211.

Table 4. Pre-specified sensitivity analyses.

Analysis	Rationale
Depleting days' supply of ibrutinib dispensings* during non-outcome hospitalizations and including non-outcome hospitalizations in follow-up time	Days of non-outcome hospitalization are subtracted from ibrutinib dispensings, as individuals may use their home supply of ibrutinib during the hospitalization stay, thereby minimizing exposure misclassification.
Increasing permissible therapy gap between ibrutinib dispensings from 7 to 14 days	Increases proportion of follow-up time contributed by periods of presumed nonadherence to ibrutinib, thereby minimizing premature censoring of follow-up among poor adherers.
Decreasing permissible therapy gap between bendamustine administrations from 56 to 42 days	Decreases proportion of follow-up time contributed by periods of presumed delays in therapy administration, thereby minimizing exposure misclassification.
Including non-facility inpatient claims in the primary outcome	Non-facility inpatient claims were excluded from the primary outcome in the primary analysis to minimize outcome misclassification, as these claims may include diagnoses recorded during the hospitalization which do not indicate the reason for hospitalization. This sensitivity analysis tests the opposite assumption.
Including inpatient claims with a CLL diagnosis code as the primary discharge diagnosis and a bleeding diagnosis code as a secondary discharge diagnosis in the primary outcome	Individuals with CLL may be given a primary discharge diagnosis of CLL on the inpatient claim even if bleeding resulted in the hospitalization. This sensitivity analysis includes these inpatient claims in the primary outcome, thereby minimizing outcome misclassification.
Competing risk analysis with disenrollment as competing event	Accounts for a possible competing risk of death that may preclude individuals from developing an outcome. Disenrollment was used as a proxy for death, as death dates were unavailable.

CLL = chronic lymphocytic leukemia

* In the primary analysis, days of hospitalization were added to the ibrutinib prescription claim's days' supply, as individuals may receive hospital supply of ibrutinib during their hospitalization stay

Table 5. Baseline characteristics of ibrutinib-treated and bendamustine-rituximab-treated individuals.

	Unweighted			Weighted
Characteristic, N (%)	**Ibrutinib N = 2,423**	**Bendamustine-Rituximab N = 1,102**	**Absolute Standardized Difference**	**Absolute Standardized Difference**
Average daily dose*†			N/A	N/A
<420 mg	241 (10.0)	-		
420 mg	2,135 (88.1)	-		
>420 mg	47 (1.9)	-		
Demographics				
Cohort entry year‡§			0.53	0.44
2013	12 (0.5)	38 (3.4)		
2014	208 (8.6)	203 (18.4)		
2015	221 (9.1)	163 (14.8)		
2016	356 (14.7)	166 (15.1)		
2017	423 (17.5)	195 (17.7)		
2018	522 (21.5)	197 (17.9)		
2019	603 (24.9)	122 (11.1)		
2020	78 (3.2)	18 (1.6)		
Age in years, median (IQR)	73 (66 – 80)	71 (65 – 77)	0.13	0.06
Sex			0.05	0.04
Female	945 (39.00)	407 (36.9)		
Male	1,477 (60.96)	695 (63.1)		
Unknown	1 (0.04)	0 (0.0)		
Geographic region of residence			0.25	0.14
East North Central	390 (16.1)	168 (15.2)		
East South Central	93 (3.8)	43 (3.9)		
Middle Atlantic	189 (7.8)	78 (7.1)		
Mountain	227 (9.4)	123 (11.2)		
New England	75 (3.1)	44 (4.0)		
Pacific	349 (14.4)	93 (8.4)		
South Atlantic	620 (25.6)	279 (25.3)		
West North Central	173 (7.1)	122 (11.1)		
West South Central	300 (12.4)	152 (13.8)		
Unknown	7 (0.3)	0 (0.0)		
Race/ethnicity			0.06	0.05
Asian	39 (1.6)	11 (1.0)		
Black	254 (10.5)	108 (9.8)		
Hispanic	157 (6.5)	68 (6.2)		
White	1,696 (70.0)	784 (71.1)		

Unknown	277 (11.4)	131 (11.9)		
Education level§			0.11	0.05
<12th Grade	9 (0.4)	1 (0.1)		
High school diploma	601 (24.8)	257 (23.3)		
<Bachelor degree	1 203 (49.6)	594 (53.9)		
Bachelor degree+	384 (15.9)	151 (13.7)		
Unknown	226 (9.3)	99 (9.0)		
Housing§			0.07	<0.01
Probable homeowner	1,717 (70.9)	816 (74.1)		
Probable renter	125 (5.1)	50 (4.5)		
Unknown	581 (24.0)	236 (21.4)		
Household income§			0.11	0.06
<$40K	545 (22.5)	215 (19.5)		
$40K-$49K	153 (6.3)	77 (7.0)		
$50K-$59K	197 (8.1)	88 (8.0)		
$60K-$74K	238 (9.8)	136 (12.3)		
$75K-$99K	348 (14.4)	174 (15.8)		
$100K+	529 (21.8)	236 (21.4)		
Unknown	413 (17.1)	176 (16.0)		
Total net worth of beneficiary§			0.16	0.05
<$25K	409 (16.9)	174 (15.8)		
$25K-$149K	367 (15.1)	191 (17.3)		
$150K-$249K	213 (8.8)	128 (11.6)		
$250K-$499K	402 (16.6)	138 (12.5)		
$500K+	624 (25.8)	297 (27.0)		
Unknown	408 (16.8)	174 (15.8)		
CLL complications, present in baseline period				
Thrombocytopenia	646 (26.7)	267 (24.2)	0.06	0.01
Lymphadenopathy	954 (39.4)	539 (48.9)	0.19	0.05
Splenomegaly	485 (20.0)	290 (26.3)	0.15	<0.01
Medical conditions, present in baseline period				
Hypertension	1,419 (58.6)	667 (60.5)	0.04	0.05
Renal dysfunction	565 (23.3)	258 (23.4)	<0.01	0.01
Liver dysfunction	374 (15.4)	204 (18.5)	0.08	<0.01
Stroke	114 (4.7)	66 (6.0)	0.06	0.02
Peptic ulcer	49 (2.0)	37 (3.4)	0.08	0.01
Bleeding‖	72 (3.0)	56 (5.1)	0.11	0.04

Medications dispensed in the 90 days prior to index date¶				
Antiplatelets	104 (4.3)	52 (4.7)	0.02	0.01
NSAIDs	172 (7.1)	75 (6.8)	0.01	0.02
Heparin	172 (7.1)	211 (19.2)	0.36	0.04
CLL therapy – targeted	290 (12.0)	308 (28.0)	0.41	0.05
CLL therapy – chemotherapy	144 (5.9)	35 (3.2)	0.13	0.07
CYP3A4 inhibitors**	124 (5.1)	42 (3.8)	0.06	0.02
CYP3A4 inducers**	53 (2.2)	14 (1.3)	0.07	0.03
CYP2D6 inhibitors**	509 (21.0)	392 (35.6)	0.33	0.06
CYP2D6 inducers**	238 (9.8)	279 (25.3)	0.42	<0.01
CYP1A2 inhibitors**	21 (0.9)	3 (0.3)	0.08	<0.01
CYP1A2 inducers**	334 (13.8)	177 (16.1)	0.06	0.04
Measure of frailty				
Claims-based frailty index, median (IQR)††	0.137 (0.110 – 0.172)	0.132 (0.108 – 0.164)	0.12	0.03

CLL = chronic lymphocytic leukemia; CYP = cytochrome P450; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug

* Average daily dose calculation: prescription quantity × capsule or tablet strength / prescription days' supply
† Bendamustine-rituximab dose was unavailable in Optum Clinformatics
‡ Covariate was not forced into propensity score, but included as a categorical variable in outcome model
§ Variable contains group-level information based on census data
‖ Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim
¶ Antimicrobial medications were examined within 14 (rather than 90) days prior to index date as these agents are typically prescribed for acute conditions
** Medications identified using the Drug Interactions Flockhart Table™[1]
†† Claims-based frailty index[2] categories: non-frail: <0.10; pre-frail: 0.10 – 0.19; mildly frail: 0.20 – 0.29; moderately frail: 0.30 – 0.39; severely frail: ≥0.40

1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.
2. Kim et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7.

Table 6. Baseline characteristics in the weighted population.

Characteristic, N (%)	Ibrutinib N = 2,373	Bendamustine-Rituximab N = 1,138	Absolute Standardized Difference
Demographics			
Cohort entry year*			0.44
2013	14 (0.6)	51 (4.5)	
2014	236 (10.0)	205 (18.0)	
2015	252 (10.6)	129 (11.4)	
2016	344 (14.5)	179 (15.7)	
2017	407 (17.1)	197 (17.3)	
2018	478 (20.2)	208 (18.2)	
2019	567 (23.9)	142 (12.4)	
2020	75 (3.2)	28 (2.5)	
Age in years, median (IQR)	72 (65 – 79)	71 (65 – 77)	0.06
Sex			0.04
Female	890 (37.5)	437 (38.4)	
Male	1,482 (62.5)	701 (61.6)	
Unknown	1 (0.0)	0 (0.0)	
Geographic region of residence			0.14
East North Central	395 (16.7)	223 (19.6)	
East South Central	92 (3.9)	33 (2.9)	
Middle Atlantic	181 (7.6)	87 (7.7)	
Mountain	236 (9.9)	106 (9.3)	
New England	81 (3.5)	49 (4.3)	
Pacific	299 (12.6)	121 (10.7)	
South Atlantic	603 (25.4)	302 (26.5)	
West North Central	192 (8.0)	95 (8.3)	
West South Central	287 (12.1)	122 (10.7)	
Unknown	7 (0.3)	0 (0.0)	
Race			0.05
Asian	34 (1.4)	10 (0.8)	
Black	241 (10.2)	121 (10.6)	
Hispanic	145 (6.1)	53 (4.7)	
White	1,689 (71.2)	824 (72.4)	
Unknown	264 (11.1)	130 (11.5)	
Education level†			0.05
<12th Grade	7 (0.3)	2 (0.2)	
High school diploma†	579 (24.4)	288 (25.3)	
<Bachelor degree	1,223 (51.5)	577 (50.7)	
Bachelor degree+	352 (14.9)	165 (14.5)	
Unknown	212 (8.9)	106 (9.3)	
Housing†			<0.01

Probable homeowner	1,718 (72.4)	824 (72.4)	
Probable renter	116 (4.9)	56 (4.9)	
Unknown	539 (22.7)	258 (22.7)	
Household income†			0.06
<$40K	498 (21.0)	259 (22.8)	
$40K-$49K	158 (6.7)	81 (7.1)	
$50K-$59K	188 (8.0)	80 (7.0)	
$60K-$74K	255 (10.7)	128 (11.2)	
$75K-$99K	364 (15.3)	167 (14.7)	
$100K+	523 (22.0)	248 (21.8)	
Unknown	387 (16.3)	175 (15.4)	
Total net worth of beneficiary†			0.05
<$25K	390 (16.4)	195 (17.2)	
$25K-$149K	369 (15.6)	186 (16.3)	
$150K-$249K	236 (9.9)	111 (9.8)	
$250K-$499K	383 (16.2)	195 (17.1)	
$500K+	613 (25.8)	278 (24.4)	
Unknown	382 (16.1)	173 (15.2)	
CLL complications, present in baseline period			
Thrombocytopenia	631 (26.6)	296 (26.0)	0.01
Lymphadenopathy	1,011 (42.6)	511 (44.9)	0.05
Splenomegaly	513 (21.6)	250 (22.0)	<0.01
Medical conditions, present in baseline period			
Hypertension	1,385 (58.4)	635 (55.8)	0.05
Renal dysfunction	551 (23.2)	259 (22.7)	0.01
Liver dysfunction	397 (16.7)	190 (16.7)	<0.01
Stroke	110 (4.6)	59 (5.2)	0.02
Peptic ulcer	57 (2.4)	25 (2.2)	0.01
Bleeding‡	90 (3.8)	35 (3.1)	0.04
Medications dispensed in the 90 days prior to index date§			
Antiplatelets	110 (4.7)	54 (4.8)	0.01
NSAIDs	170 (7.2)	88 (7.7)	0.02
Heparin	207 (8.7)	114 (10.0)	0.04
CLL therapy – targeted	378 (15.9)	202 (17.8)	0.05
CLL therapy – chemotherapy	125 (5.3)	78 (6.8)	0.07
CYP3A4 inhibitors‖	117 (4.9)	50 (4.4)	0.02
CYP3A4 inducers‖	46 (1.9)	27 (2.4)	0.03
CYP2D6 inhibitors‖	585 (24.7)	253 (22.2)	0.06
CYP2D6 inducers‖	331 (14.0)	159 (14.0)	<0.01
CYP1A2 inhibitors‖	17 (0.7)	8 (0.7)	<0.01
CYP1A2 inducers‖	337 (14.2)	179 (15.7)	0.04

Measure of frailty			
Claims-based frailty index, median (IQR)¶	0.136 (0.109 – 0.170)	0.136 (0.110 – 0.167)	0.03

CLL = chronic lymphocytic leukemia; CYP = cytochrome P450; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug

* Covariate was not forced into propensity score, but included as a categorical variable in outcome model
† Variable contains group-level information based on census data
‡ Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim
§ Antimicrobial medications were examined within 14 (rather than 90) days prior to index date as these agents are typically prescribed for acute conditions
‖ Medications identified using the Drug Interactions Flockhart Table™[1]
¶ Claims-based frailty index[2] categories: non-frail: <0.10; pre-frail: 0.10 – 0.19; mildly frail: 0.20 – 0.29; moderately frail: 0.30 – 0.39; severely frail: ≥0.40

1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.
2. Kim et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7.

Table 7. Rate of major bleeding and clinically-relevant bleeding in ibrutinib-treated compared to bendamustine-rituximab-treated individuals.

	Ibrutinib	Bendamustine-Rituximab
Follow-up Time		
Follow-up, sum, in person-years	687	361
Follow-up, median per individual, in days	95	137
Outcomes during follow-up	**N**	
Major Bleeding	21	9
Clinically-relevant Bleeding	40	15
Measure of outcome occurrence	**Crude Incidence Rate, per 100 person-years (95% Confidence Interval)**	
Major Bleeding	3.1 (2.0 – 4.7)	2.5 (1.3 – 4.8)
Clinically-relevant Bleeding	5.8 (4.3 – 7.9)	4.2 (2.5 – 6.8)
Relative effect estimate for outcome	**Hazard Ratio (95% Confidence Interval)**	
Major Bleeding		
Unadjusted*	1.16 (0.53 – 2.54)	1.00 (reference)
Adjusted†‡	1.61 (0.67 – 3.84)	1.00 (reference)
Clinically-relevant Bleeding		
Unadjusted§	1.34 (0.74 – 2.43)	1.00 (reference)
Adjusted‖‡	2.66 (1.29 – 5.49)	1.00 (reference)

* Did not fail a test for non-proportional hazards (p = 0.42)
† Did not fail a test for non-proportional hazards (p = 0.23)
‡ Model weighted based on stabilized inverse probability of treatment weights and adjusted for cohort entry year and geographic region of residence
§ Did not fail a test for non-proportional hazards (p = 0.22)
‖ Did not fail a test for non-proportional hazards (p = 0.11)

Table 8. Site of bleed for major bleeding and clinically-relevant bleeding.

	Major Bleeding			Clinically-relevant Bleeding		
Site of Bleed, N (%)	**Ibrutinib**	**Bendamustine-Rituximab**	**Total**	**Ibrutinib**	**Bendamustine-Rituximab**	**Total**
Cerebral	4 (19.0)	2 (22.2)	6 (20.0)	4 (10.0)	2 (13.3)	6 (10.9)
Gastrointestinal	10 (47.6)	6 (66.7)	16 (53.4)	12 (30.0)	8 (53.3)	20 (36.4)
Genitourinary	3 (14.3)	0 (0.0)	3 (10.0)	8 (20.0)	1 (6.7)	9 (16.4)
Other*	3 (14.3)	1 (11.1)	4 (13.3)	15 (37.5)	4 (26.7)	19 (34.5)
Unspecified*	1 (4.8)	0 (0.0)	1 (3.3)	1 (2.5)	0 (0.0)	1 (1.8)
Total	21 (100.0)	9 (100.0)	30 (100.0)	40 (100.0)	15 (100.0)	55 (100.0)

* See **Table 2** for bleed types in Other and Unspecified sites of bleed

Table 9. List of empirically-identified covariates included in propensity score.

Dimension	Variable	Code	Code Description
Drug	D01V000Freq	Drug-specific NDCs	sulfamethoxazole-trimethoprim
Drug	D01V007Once	Drug-specific NDCs	acetaminophen-oxycodone
Drug	D01V010Freq	Drug-specific NDCs	montelukast
Drug	D01V010Spor	Drug-specific NDCs	montelukast
Drug	D01V011Spor	Drug-specific NDCs	levothyroxine
Drug	D01V012Freq	Drug-specific NDCs	mupirocin topical
Drug	D01V014Freq	Drug-specific NDCs	amoxicillin-clavulanate
Drug	D01V023Freq	Drug-specific NDCs	furosemide
Drug	D01V023Once	Drug-specific NDCs	furosemide
Drug	D01V023Spor	Drug-specific NDCs	furosemide
Drug	D01V029Freq	Drug-specific NDCs	trazodone
Drug	D01V049Once	Drug-specific NDCs	methylprednisolone
Drug	D01V059Freq	Drug-specific NDCs	glipizide
Drug	D01V078Freq	Drug-specific NDCs	pantoprazole
Drug	D01V078Spor	Drug-specific NDCs	pantoprazole
Drug	D01V084Freq	Drug-specific NDCs	acyclovir
Drug	D01V107Freq	Drug-specific NDCs	alprazolam
Drug	D01V112Spor	Drug-specific NDCs	citalopram
Drug	D01V114Freq	Drug-specific NDCs	tamsulosin
Drug	D01V126Freq	Drug-specific NDCs	potassium chloride
Drug	D01V126Once	Drug-specific NDCs	potassium chloride
Drug	D01V126Spor	Drug-specific NDCs	potassium chloride
Drug	D01V151Freq	Drug-specific NDCs	oxycodone
Drug	D01V151Once	Drug-specific NDCs	oxycodone
Drug	D01V151Spor	Drug-specific NDCs	oxycodone

Drug	D01V197Freq	Drug-specific NDCs	zolpidem
Drug	D01V197Spor	Drug-specific NDCs	zolpidem
Drug	D01_INT_UNIQ_Q1ServiceInt	-	Healthcare utilization intensity: # of unique drugs dispensed, 1st quartile
Inpatient ICD-9 Dx	D02V002Spor	429	Ill-defined descriptions and complications of heart disease
Inpatient ICD-9 Dx	D02V004Freq	427	Cardiac dysrhythmias
Inpatient ICD-9 Dx	D02V005Freq	486	Pneumonia, organism NOS
Inpatient ICD-9 Dx	D02V009Freq	244	Acquired hypothyroidism
Inpatient ICD-9 Dx	D02V013Freq	V45	Other postprocedural states
Inpatient ICD-9 Dx	D02V014Freq	789	Other symptoms involving abdomen and pelvis
Inpatient ICD-9 Dx	D02V015Spor	518	Other diseases of lung
Inpatient ICD-9 Dx	D02V029Freq	787	Symptoms involving digestive system
Inpatient ICD-9 Dx	D02V054Freq	V10	Personal history of malignant neoplasm
Inpatient ICD-9 Dx	D02V069Spor	202	Other malignant neoplasms of lymphoid and histiocytic tissue
Inpatient ICD-9 Dx	D02V077Freq	38	Septicemia
Inpatient ICD-9 Dx	D02V097Freq	799	Other ill-defined and unknown causes of morbidity and mortality
Inpatient ICD-9 Dx	D02V097Spor	799	Other ill-defined and unknown causes of morbidity and mortality
Inpatient ICD-9 Dx	D02V139Freq	491	Chronic bronchitis
Inpatient ICD-9 Dx	D02_INT_UNIQ_Q1ServiceInt	-	Healthcare utilization intensity: # of unique inpatient ICD-9 diagnoses, 1st quartile
Outpatient ICD-9 Dx	D03V000Freq	200	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue
Outpatient ICD-9 Dx	D03V000Once	200	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue
Outpatient ICD-9 Dx	D03V000Spor	200	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue
Outpatient ICD-9 Dx	D03V005Freq	491	Chronic bronchitis
Outpatient ICD-9 Dx	D03V005Once	491	Chronic bronchitis
Outpatient ICD-9 Dx	D03V005Spor	491	Chronic bronchitis

Outpatient ICD-9 Dx	D03V007Spor	496	Chr airway obstruct NEC
Outpatient ICD-9 Dx	D03V009Freq	781	Symptoms involving nervous and musculoskeletal systems
Outpatient ICD-9 Dx	D03V009Spor	781	Symptoms involving nervous and musculoskeletal systems
Outpatient ICD-9 Dx	D03V019Freq	427	Cardiac dysrhythmias
Outpatient ICD-9 Dx	D03V039Freq	284	Aplastic anemia and other bone marrow failure syndromes
Outpatient ICD-9 Dx	D03V039Once	284	Aplastic anemia and other bone marrow failure syndromes
Outpatient ICD-9 Dx	D03V039Spor	284	Aplastic anemia and other bone marrow failure syndromes
Outpatient ICD-9 Dx	D03V048Freq	300	Anxiety, dissociative and somatoform disorders
Outpatient ICD-9 Dx	D03V060Freq	275	Disorders of mineral metabolism
Outpatient ICD-9 Dx	D03V060Spor	275	Disorders of mineral metabolism
Outpatient ICD-9 Dx	D03V073Freq	202	Other malignant neoplasms of lymphoid and histiocytic tissue
Outpatient ICD-9 Dx	D03V073Once	202	Other malignant neoplasms of lymphoid and histiocytic tissue
Outpatient ICD-9 Dx	D03V073Spor	202	Other malignant neoplasms of lymphoid and histiocytic tissue
Outpatient ICD-9 Dx	D03V077Freq	486	Pneumonia, organism NOS
Outpatient ICD-9 Dx	D03V090Freq	562	Diverticula of intestine
Outpatient ICD-9 Dx	D03V102Freq	273	Disorders of plasma protein metabolism
Outpatient ICD-9 Dx	D03V106Freq	357	Inflammatory and toxic neuropathy
Outpatient ICD-9 Dx	D03V113Freq	794	Nonspecific abnormal results of function studies
Outpatient ICD-9 Dx	D03V116Freq	728	Disorders of muscle ligament and fascia
Outpatient ICD-9 Dx	D03V117Freq	V49	Other conditions influencing health status
Outpatient ICD-9 Dx	D03V132Spor	682	Other cellulitis and abscess
Outpatient ICD-9 Dx	D03V134Freq	211	Benign neoplasm of other parts of digestive system
Outpatient ICD-9 Dx	D03V140Once	279	Disorders involving the immune mechanism
Outpatient ICD-9 Dx	D03V142Freq	185	Malignant neoplasm of prostate
Outpatient ICD-9 Dx	D03V163Freq	461	Acute sinusitis
Outpatient ICD-9 Dx	D03V183Freq	V72	Special investigations and examinations

Outpatient ICD-9 Dx	D03V183Once	V72	Special investigations and examinations
Outpatient ICD-9 Dx	D03V188Freq	281	Other deficiency anemias
Outpatient ICD-9 Dx	D03V188Spor	281	Other deficiency anemias
Outpatient ICD-9 Dx	D03V216Freq	571	Chronic liver disease and cirrhosis
Outpatient ICD-9 Dx	D03V216Once	571	Chronic liver disease and cirrhosis
Outpatient ICD-9 Dx	D03V239Freq	573	Other disorders of liver
Outpatient ICD-9 Dx	D03V239Once	573	Other disorders of liver
Outpatient ICD-9 Dx	D03V296Freq	459	Other disorders of circulatory system
Outpatient ICD-9 Dx	D03V296Once	459	Other disorders of circulatory system
Other setting ICD-9 Dx	D04_INT_ALL_Q2ServiceInt	-	Healthcare utilization intensity: total # of other setting ICD-9 diagnoses, 2nd quartile
Other setting ICD-9 Dx	D04_INT_UNIQ_Q2ServiceInt	-	Healthcare utilization intensity: # of unique other setting ICD-9 diagnoses, 2nd quartile
Other setting ICD-9 Dx	D04_INT_UNIQ_Q4ServiceInt	-	Healthcare utilization intensity: # of unique other setting ICD-9 diagnoses, 4th quartile
Inpatient ICD-9 Px	D05V006Once	99	other nonoperative procedures
Inpatient CPT Px	D08V045Once	74177	Computed tomography, abdomen and pelvis
Inpatient CPT Px	D08V309Freq	88341	Immunohistochemistry or immunocytochemistry, per specimen
Inpatient CPT Px	D08V655Once	71045	Radiologic examination, chest
Outpatient CPT Px	D09V012Freq	96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
Outpatient CPT Px	D09V021Freq	88189	Flowcytometry/read, 16 & >
Outpatient CPT Px	D09V023Freq	88342	Immunohistochemistry
Outpatient CPT Px	D09V023Once	88342	Immunohistochemistry
Outpatient CPT Px	D09V023Spor	88342	Immunohistochemistry
Outpatient CPT Px	D09V033Once	86803	Hepatitis C ab test
Outpatient CPT Px	D09V050Freq	87186	Microbe susceptible, mic
Outpatient CPT Px	D09V061Once	J7050	Infusion, normal saline solution, 250 cc

Outpatient CPT Px	D09V074Freq	85610	Prothrombin time
Outpatient CPT Px	D09V074Once	85610	Prothrombin time
Outpatient CPT Px	D09V100Freq	97110	Therapeutic exercises
Outpatient CPT Px	D09V101Spor	36591	Draw blood off venous device
Outpatient CPT Px	D09V102Freq	96523	Irrigation drug delivery device
Outpatient CPT Px	D09V102Spor	96523	Irrigation drug delivery device
Outpatient CPT Px	D09V103Freq	97140	Manual therapy
Outpatient CPT Px	D09V116Spor	71010	Chest x-ray
Outpatient CPT Px	D09V138Freq	82947	Assay glucose, blood quant
Outpatient CPT Px	D09V138Once	82947	Assay glucose, blood quant
Outpatient CPT Px	D09V140Once	G0202	Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (cad) when performed
Outpatient CPT Px	D09V157Freq	88237	Tissue culture, bone marrow
Outpatient CPT Px	D09V160Freq	J2250	Injection, midazolam hydrochloride, per 1 mg
Outpatient CPT Px	D09V160Once	J2250	Injection, midazolam hydrochloride, per 1 mg
Outpatient CPT Px	D09V162Freq	J3010	Injection, fentanyl citrate, 0.1 mg
Outpatient CPT Px	D09V162Once	J3010	Injection, fentanyl citrate, 0.1 mg
Outpatient CPT Px	D09V172Freq	83735	Assay magnesium
Outpatient CPT Px	D09V177Freq	96361	Intravenous infusion, hydration
Outpatient CPT Px	D09V177Once	96361	Intravenous infusion, hydration
Outpatient CPT Px	D09V1802Freq	J2704	Injection, propofol, 10 mg
Outpatient CPT Px	D09V1802Once	J2704	Injection, propofol, 10 mg
Outpatient CPT Px	D09V1806Freq	88374	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe
Outpatient CPT Px	D09V197Freq	J2405	Injection, ondansetron hydrochloride, per 1 mg
Outpatient CPT Px	D09V197Once	J2405	Injection, ondansetron hydrochloride, per 1 mg
Outpatient	D09V199Freq	96374	Therapeutic, prophylactic, or diagnostic

CPT Px			injection (specify substance or drug)
Outpatient CPT Px	D09V221Freq	J3490	Drugs unclassified injection
Outpatient CPT Px	D09V221Once	J3490	Drugs unclassified injection
Outpatient CPT Px	D09V230Freq	84520	Assay urea nitrogen
Outpatient CPT Px	D09V2690Once	99152	Moderate (Conscious) Sedation
Outpatient CPT Px	D09V2803Spor	77067	Breast, Mammography
Outpatient CPT Px	D09V296Once	85060	Blood smear interpretation
Outpatient CPT Px	D09V307Once	88311	Decalcify tissue
Outpatient CPT Px	D09V309Once	85097	Bone marrow interpretation
Outpatient CPT Px	D09V311Spor	74176	Computed tomography, abdomen and pelvis
Outpatient CPT Px	D09V315Once	88313	Special stains
Outpatient CPT Px	D09V315Spor	88313	Special stains
Outpatient CPT Px	D09V316Freq	38221	Bone marrow biopsy
Outpatient CPT Px	D09V342Once	G0364	Bone marrow aspirate & biopsy
Outpatient CPT Px	D09V343Once	J7040	Infusion, normal saline solution, sterile
Outpatient CPT Px	D09V355Once	88262	Chromosome analysis, 15-20
Outpatient CPT Px	D09V380Once	74178	Computed tomography, abdomen and pelvis
Outpatient CPT Px	D09V380Spor	74178	Computed tomography, abdomen and pelvis
Outpatient CPT Px	D09V405Once	88264	Chromosome analysis, 20-25
Outpatient CPT Px	D09V406Freq	88280	Chromosome karyotype study
Outpatient CPT Px	D09V406Once	88280	Chromosome karyotype study
Outpatient CPT Px	D09V466Freq	82248	Bilirubin, direct
Outpatient CPT Px	D09V477Once	99202	Office/outpatient visit, new
Outpatient CPT Px	D09V495Spor	78815	Pet image w/CT, skull-thigh
Outpatient CPT Px	D09V560Once	38220	Bone marrow aspiration
Outpatient CPT Px	D09V641Once	77012	CT scan for needle biopsy
Outpatient	D09V641Spor	77012	CT scan for needle biopsy

CPT Px			
Outpatient CPT Px	D09V991Freq	3074F	Syst BP lt 130 mm hg
Outpatient CPT Px	D09V991Once	3074F	Syst BP lt 130 mm hg
Outpatient CPT Px	D09V992Freq	3078F	Diast BP < 80 mm hg
Outpatient CPT Px	D09V992Once	3078F	Diast BP < 80 mm hg
Other setting CPT Px	D10_INT_ALL_Q4ServiceInt	-	Healthcare utilization intensity: total # of other setting CPT procedures, 4th quartile
Other setting CPT Px	D10_INT_UNIQ_Q4ServiceInt	-	Healthcare utilization intensity: # of unique other setting CPT procedures, 4th quartile
Laboratory Tests	D11V019Spor	48642-3	Glomerular filtration rate/1.73 sq M predicted among non-blacks [Volume Rate/Area] in Serum or Plasma by Creatinine-based formula (MDRD)
Laboratory Tests	D11V054Freq	19139-5	Pathologist name
Laboratory Tests	D11V066Freq	32623-1	Platelet mean volume [Entitic volume] in Blood by Automated count
Laboratory Tests	D11V075Freq	2777-1	Phosphate [Mass/volume] in Serum or Plasma
Laboratory Tests	D11V077Once	11579-0	Thyrotropin [Units/volume] in Serum or Plasma by Detection limit <= 0.05 mIU/L
Laboratory Tests	D11V084Freq	3084-1	Urate [Mass/volume] in Serum or Plasma
Laboratory Tests	D11V100Freq	2276-4	Ferritin [Mass/volume] in Serum or Plasma
Laboratory Tests	D11V125Freq	737-7	Lymphocytes/100 leukocytes in Blood by Manual count
Laboratory Tests	D11V125Spor	737-7	Lymphocytes/100 leukocytes in Blood by Manual count
Laboratory Tests	D11V150Freq	23658-8	Other Antibiotic [Susceptibility]
Laboratory Tests	D11V183Freq	8251-1	Service comment
Laboratory Tests	D11V517Once	53115-2	Immature granulocytes [#/volume] in Blood by Automated count
Laboratory Tests	D11V518Once	71695-1	Immature granulocytes/100 leukocytes in Blood by Automated count
CPT = Current Procedural Terminology; Dx = Diagnosis; ICD = International Classification of Diseases; NDC = National Drug Code; Px = Procedure			

Table 10. Results from sensitivity analyses.

	Number of Major Bleeding Events	Hazard Ratio (95% Confidence Interval)*
Depleting days' supply of ibrutinib dispensings during non-outcome hospitalizations and including non-outcome hospitalizations in follow-up time	29	1.54 (0.64 – 3.72)
Increasing permissible therapy gap of ibrutinib dispensings from 7 to 14 days	31	1.67 (0.72 – 3.88)
Decreasing permissible therapy gap between bendamustine administrations from 56 to 42 days	30	1.51 (0.64 – 3.58)
Including non-facility inpatient claims in the primary outcome	65	1.85 (0.99 – 3.46)
Including inpatient claims with a CLL diagnosis code as the primary discharge diagnosis and a bleeding diagnosis code as a secondary discharge diagnosis in the primary outcome	42	1.75 (0.81 – 3.77)
Competing risk analysis with disenrollment as competing event	30	1.61 (0.67 – 3.84)

CLL = chronic lymphocytic leukemia

* Model weighted based on stabilized inverse probability of treatment weights and adjusted for cohort entry year and geographic region of residence

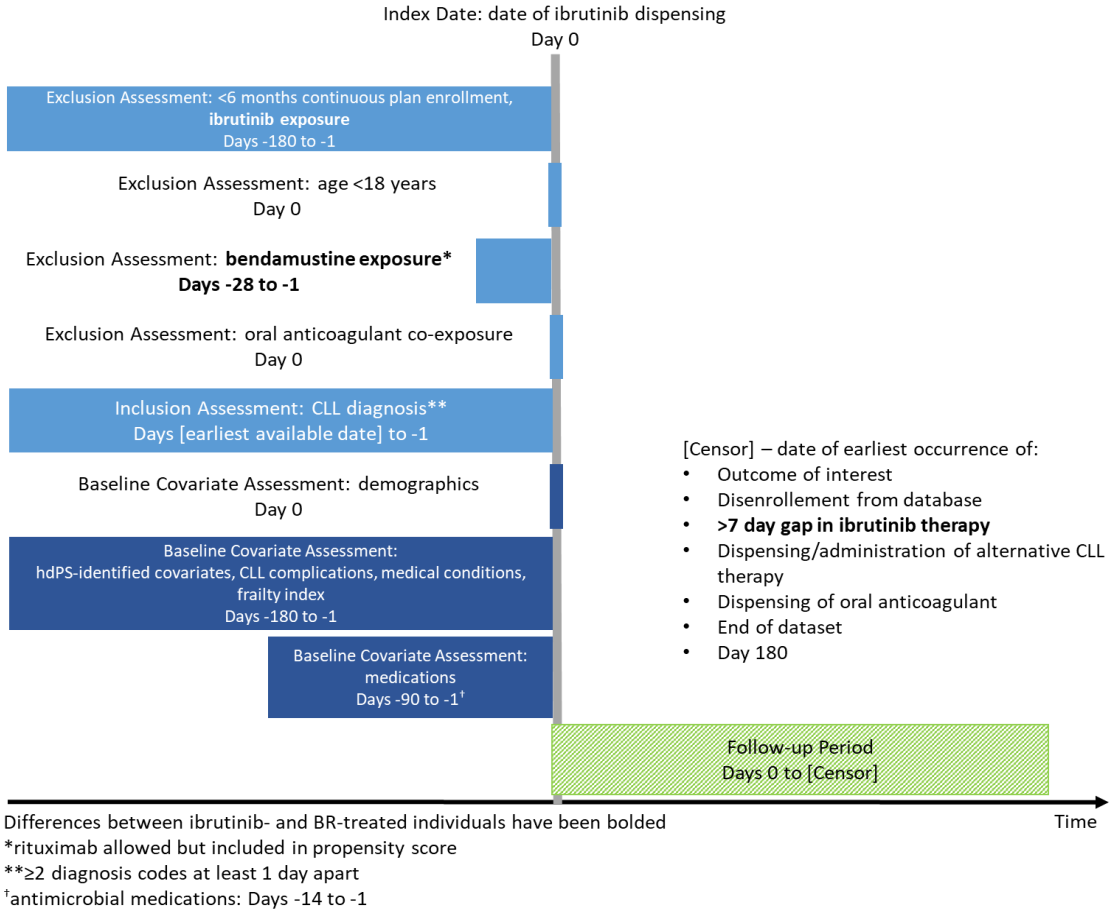
Table 11. Results from effect modification analyses.

	P-value	Hazard Ratio (95% Confidence Interval)
CYP3A4 inhibitors	0.68	Not displayed because p-value is not significant
CYP3A4 inducers	0.47	
CYP2D6 inhibitors	0.14	
CYP2D6 inducers	0.15	
CYP1A2 inhibitors	0.99	
CYP1A2 inducers	0.47	

CYP = cytochrome P450

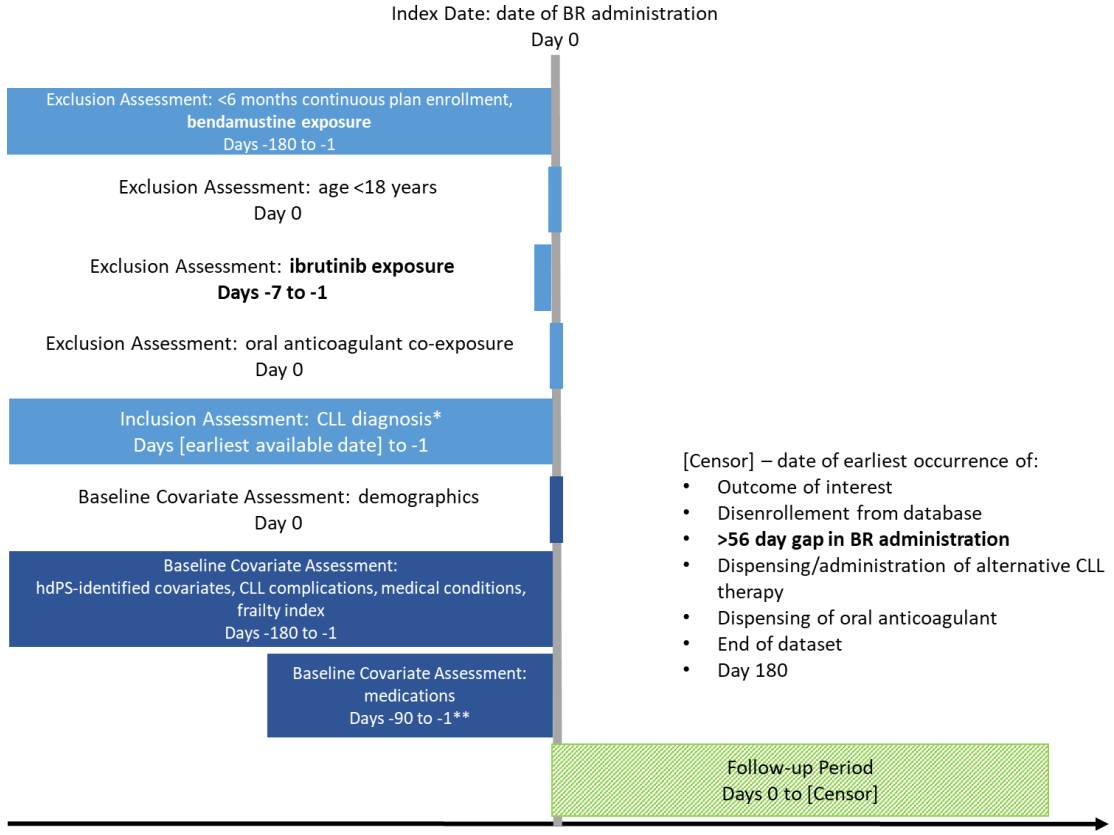
Figure 1. Study design depiction for A) ibrutinib-treated and B) bendamustine-rituximab-treated individuals.

A)



Differences between ibrutinib- and BR-treated individuals have been bolded
*rituximab allowed but included in propensity score
**≥2 diagnosis codes at least 1 day apart
†antimicrobial medications: Days -14 to -1

B)



Differences between ibrutinib- and BR-treated individuals have been bolded
*≥2 diagnosis codes at least 1 day apart
**antimicrobial medications: Days -14 to -1

Figure 2. Study cohort flowchart.

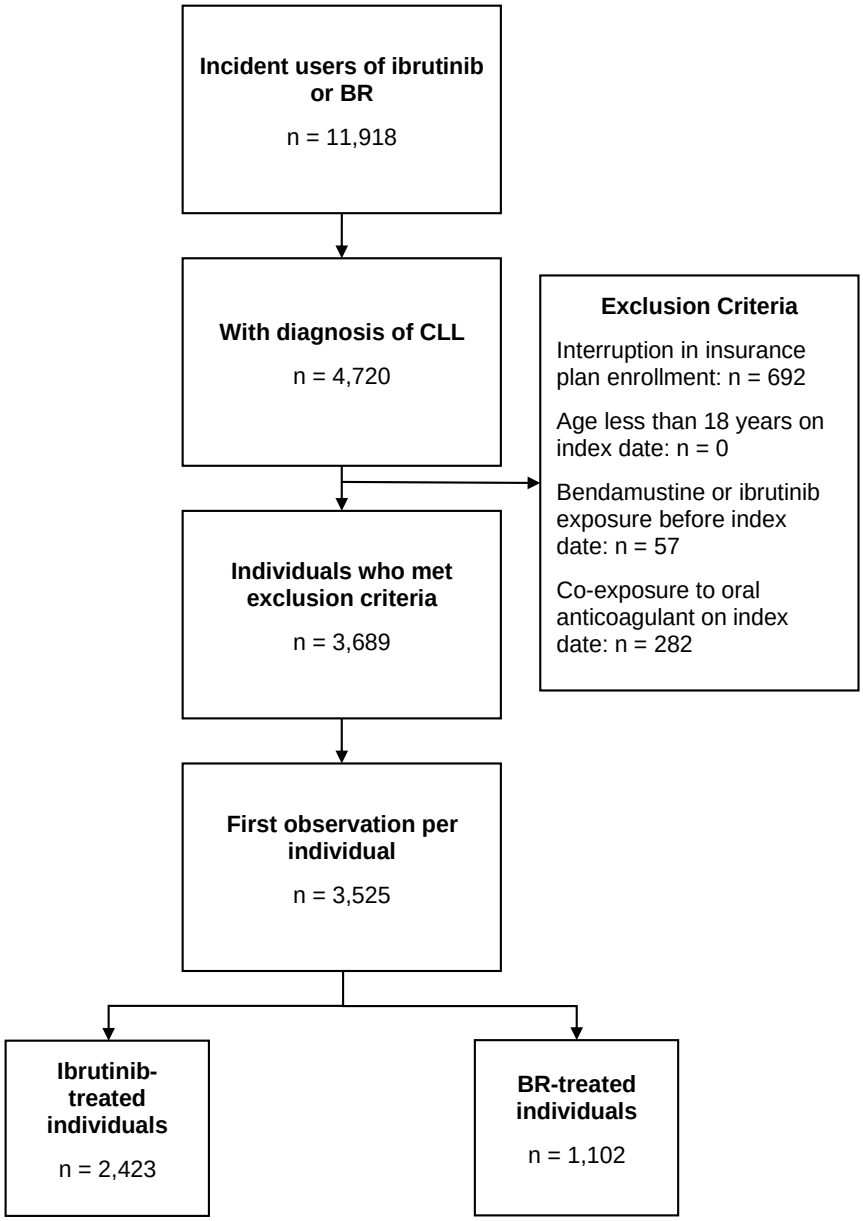


Figure 3. Propensity score distribution in unweighted population.

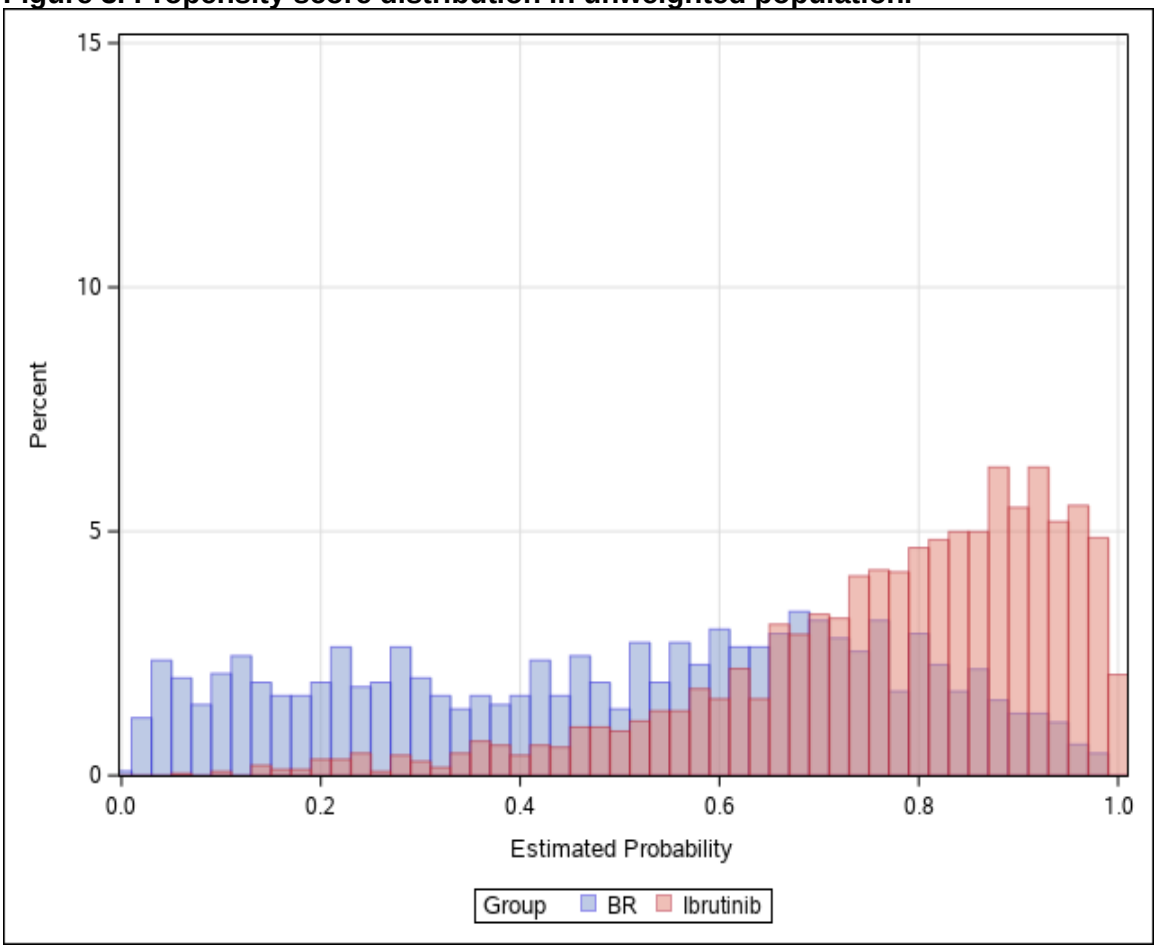
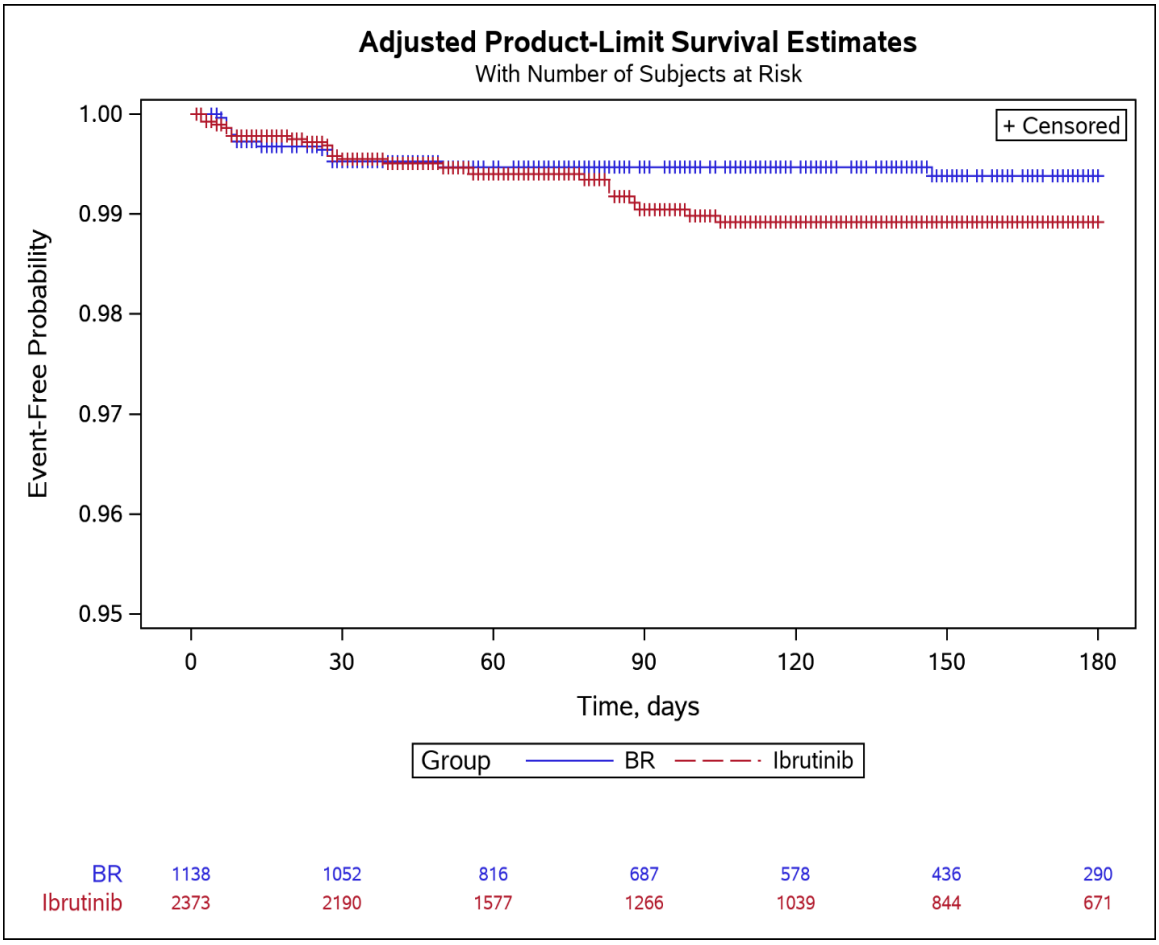
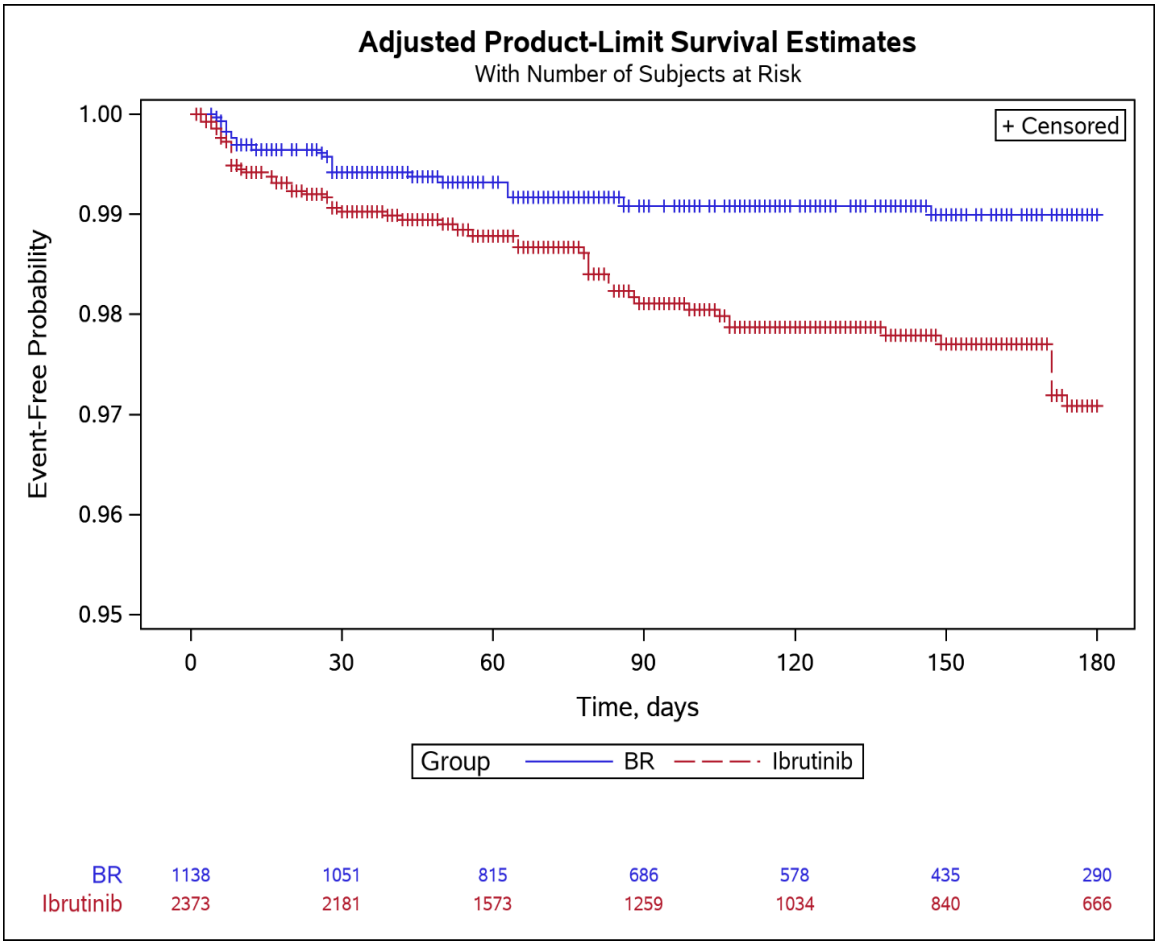


Figure 4. Kaplan-Meier curves for A) major bleeding and B) clinically-relevant bleeding, in the weighted population based on stabilized inverse probability of treatment weighting. The number of individuals remaining in the risk set at each time point is displayed below the graph legend. BR = bendamustine-rituximab.

A)



B)


Adjusted Product-Limit Survival Estimates
With Number of Subjects at Risk
+ Censored
Event-Free Probability
1.00
0.99
0.98
0.97
0.96
0.95
0
30
60
90
120
150
180
Time, days
Group
BR
Ibrutinib
BR 1138 1051 815 686 578 435 290
Ibrutinib 2373 2181 1573 1259 1034 840 666

CHAPTER 3 – BLEEDING WITH CONCOMITANT IBRUTINIB AND ORAL ANTICOAGULANT THERAPY: A POPULATION-BASED COHORT STUDY

Introduction

Given the older age and potential multimorbidity of the ibrutinib-treated population,[27-29,76] many patients have a clinical indication for an oral anticoagulant (OAC). Moreover, up to 16% of patients develop atrial fibrillation while on ibrutinib,[33,34] further increasing the likelihood of concomitant treatment with ibrutinib and OACs. Bleeding may be more frequent in patients concomitantly treated with OACs given their associated bleeding risk, though data on concomitant ibrutinib and OAC use are limited.[12] Clinicians are thus regularly confronted with the challenging decision to use ibrutinib in OAC-treated patients or OACs in ibrutinib-treated patients without sufficient knowledge of the bleeding risk with this combination. In fact, a study exploring OAC and/or antiplatelet use as a risk factor for major hemorrhage in ibrutinib-treated patients suggested that patients co-treated with ibrutinib and an OAC/antiplatelet have a similar risk of major hemorrhage compared to patients co-treated with an alternative therapy and an OAC/antiplatelet.[36] This interpretation, however, was made by indirectly comparing the similarly increased major hemorrhage risk associated with OAC and/or antiplatelet use in both ibrutinib-treated patients (RR 1.9, 95% CI: 1.2–3.0) and comparator-treated patients (RR 2.4, 95% CI:1.0–5.6). To more validly assess the risk of bleeding with concomitant use of ibrutinib and OACs, a study directly comparing the rate of bleeding in patients co-exposed to ibrutinib and OACs with patients co-exposed to an alternative treatment and OACs is needed. Elucidation of the rate of bleeding associated with this combination may inform ibrutinib's benefit-harm balance in this potentially high-risk subpopulation.

We therefore conducted a population-based cohort study to compare the real-world rate of major, clinically-relevant, and provider-diagnosed bleeding between concomitant ibrutinib + OAC treatment and concomitant BR + OAC treatment in individuals with CLL, MCL, or MZL. Additionally, to elucidate the magnitude of the difference in bleeding rates between individuals concomitantly treated with ibrutinib + OACs and individuals treated with ibrutinib alone, we compared findings to those detailed in Chapter 2,[77] which assessed the real-world rate of major and clinically-relevant bleeding with ibrutinib versus BR in patients not concomitantly using OACs.

Methods

Overview and data source

We conducted a retrospective cohort study to compare incidence rates of bleeding between individuals concomitantly treated with ibrutinib + an OAC and individuals treated with BR + an OAC. We used Optum Clinformatics de-identified commercial health insurance data, which includes over 80 million commercially-insured and Medicare Advantage beneficiaries of a large US-based private health insurer. Optum Clinformatics includes demographic and enrollment information, medical claims for inpatient and outpatient care, and pharmacy claims for drugs dispensed in the outpatient care setting.

Defining the study population

We included individuals with incident co-exposure to an OAC (warfarin, rivaroxaban, apixaban, dabigatran, or edoxaban) and either ibrutinib or BR between November 1, 2013 and February 29, 2020. Individuals entered the cohort by 1) initiating cancer therapy (ibrutinib or BR) during OAC therapy, i.e., cancer therapy-triggered cohort entry, 2) initiating an OAC during cancer therapy, i.e., OAC-triggered cohort entry, or 3)

initiating cancer therapy and an OAC on the same day, i.e., synchronous-triggered cohort entry (Figure 5). The date of incident co-exposure served as the index date, and individuals were required to have a preceding 6-month baseline period devoid of 1) ibrutinib dispensing (in ibrutinib users) or bendamustine administration (in BR users) for cancer therapy-triggered cohort entry individuals, 2) OAC dispensing for OAC-triggered cohort entry individuals, or 3) both for synchronous-triggered cohort entry individuals. We allowed rituximab administrations during the baseline period, as rituximab may be used as part of other cancer therapy regimens or for other medical conditions.

We included individuals who were diagnosed with CLL (ICD-9-CM 204.1x or ICD-10-CM C91.1x), MCL (ICD-9-CM 200.4x or ICD-10-CM C83.1x), or MZL (ICD-9-CM 200.3x or ICD-10-CM C88.4). For each cancer type, we required at least two any claim-type any-position diagnosis codes ≥1 day apart preceding the index date. We excluded individuals with: 1) interruption in insurance plan enrollment during the baseline period; 2) age <18 years on the index date; 3) bendamustine administration within 28 days (the duration of one BR cycle) prior to the index date for ibrutinib + OAC-treated individuals; or 4) ibrutinib dispensing within 7 days (the duration of ibrutinib's effect on platelets observed in *in vitro* studies)[13,15] prior to the index date for BR + OAC-treated individuals (Figure 6). We did not exclude individuals with a prior history of bleeding (i.e., a bleed during the baseline period), but rather included baseline bleeding in the propensity score (see covariate ascertainment below). We included only the first observation meeting inclusion and exclusion criteria, per individual.

Follow-up began on the index date and continued until the first occurrence of: 1) an outcome (defined below); 2) a >7-day therapy gap for ibrutinib or >56-day gap between BR administrations (allowing for an up to 28-day delay in a treatment cycle); 3) a >7-day therapy gap for the OAC; 4) a dispensing or administration of an alternative

anticancer therapy; 5) a dispensing of an alternative OAC; 6) insurance plan disenrollment; 7) the end of the dataset (February 29, 2020); or 8) day 180 (to account for the differing treatment duration between ibrutinib and BR).

Exposure and covariate ascertainment

We used National Drug Codes to ascertain ibrutinib and OAC exposure from dispensings in the prescription claims. We used Healthcare Common Procedure Coding System codes and National Drug Codes to ascertain BR exposure from administrations in the inpatient and outpatient medical claims. We chose BR as the active comparator referent as it is a chemoimmunotherapy used in similar settings as ibrutinib in CLL,[30] and is also used in MCL and MZL.[31] We considered but decided against newer therapies (e.g., acalabrutinib) as the referent, given uncommon use of these agents during the study period. We considered an individual exposed to BR if they had a rituximab administration on the same day as or within 7 days before a bendamustine administration. This ensured the capture of individuals who received BR according to the typical administration schedule, and those with slight variations.

Potential confounders, identified during the baseline period, included demographics, cancer complications (thrombocytopenia, lymphadenopathy, splenomegaly), cancer therapy use (categorized as targeted therapy or chemotherapy), coexisting medical conditions and medication use associated with an increased risk of bleeding, coexisting medical conditions treated with OACs, and a claims-based frailty index (Table 12).

Outcome ascertainment

The primary outcome was major bleeding, defined as a bleeding event resulting in inpatient hospitalization. We used a previously validated algorithm to identify outcomes, which demonstrated a positive predictive value of 89% in health insurance claims data

using ICD-9-CM codes.[63] We identified major bleeds in inpatient claims with a bleeding diagnosis code as the principal discharge diagnosis (indicative of reason for admission), or a bleeding diagnosis code as a secondary discharge diagnosis with a principal discharge diagnosis suggestive of a possible bleed (e.g., gastric ulcer) (Table 13). We also used the algorithm to identify and exclude bleeding events caused by major trauma. The secondary outcome was clinically-relevant bleeding, which was a composite of bleeding events resulting in inpatient hospitalization (i.e., major bleeding) and bleeding events resulting in emergency department presentation. We also assessed an outcome that was specified post-hoc due to the low number of primary and secondary outcomes and the sparsity of data on bleeding of any type in this patient population. This post-hoc outcome was provider-diagnosed bleeding, which was any bleed diagnosed by a healthcare provider. We identified post-hoc outcomes in any-setting claims (inpatient, outpatient, and other) with a bleeding diagnosis code in any claim position (i.e., we expanded the primary and secondary outcome definition to include all claim settings and claim positions).

Statistical analysis

We calculated descriptive statistics for baseline variables, crude incidence rates, and unadjusted association measures, the latter using Cox proportional hazards models. We utilized inverse probability of treatment weighting based on the propensity score to adjust for confounding. First, we included pre-specified demographic and clinical variables into a logistic regression model to calculate the propensity score—defined as an individual's predicted probability of concomitantly using ibrutinib + OAC vs. BR + OAC. Then, we calculated the stabilized inverse probability of treatment weight (sIPTW) based on the propensity score. We used standardized differences to assess covariate balance in the unweighted and weighted cohorts, with an absolute standardized

difference of <0.1 as a threshold for adequate balance. Lastly, we estimated hazard ratios (HRs) using Cox proportional hazards regression, weighted based on sIPTW, and used a robust variance estimator to account for weighting. The model also adjusted for calendar year of cohort entry and any covariates that remained imbalanced after sIPTW. We assessed the proportional hazards assumption by including an interaction term of exposure by time since cohort entry in the model.

Sensitivity and subgroup analyses

To assess the robustness of our findings, we conducted numerous sensitivity analyses including adjustment for cancer type, modification of therapy gaps for ibrutinib, BR, and OACs, and exclusion of individuals with bleeding during the baseline period (Table 14). We also calculated the E-value to assess the potential impact of unmeasured confounders.[64] The E-value provides the minimum strength of association, on the risk ratio scale, a potential confounder needs to have with both the exposure and outcome to move the outcome result effect estimate to a null value.

We conducted a pre-specified subgroup analysis by OAC type (direct oral anticoagulant [DOAC] vs. warfarin). In the DOAC subgroup analysis, we adjusted for DOAC dose intensity at cohort entry and included an additional censoring criterion during follow-up in which individuals were censored on the day of a DOAC dose intensity change (Table 15). We also explored effect modification by use of medications that may affect the metabolism of ibrutinib, BR, or OACs (e.g., CYP3A4, CYP1A2, P-glycoprotein inhibitors), and by exposure initiation order at cohort entry. Analyses were conducted using SAS v9.4 (SAS Institute Inc.: Cary, NC). The University of Pennsylvania institutional review board deemed research using this dataset to be exempt from review.

Results

Baseline characteristics

We identified 480 and 212 concomitant users of ibrutinib + OAC and BR + OAC, respectively (Figure 7). Individuals in the overall cohort were predominantly male (66.3%) and White (73.0%), with a median age of 77 years and a median frailty score of 0.170 (i.e., pre-frail category per frailty index; see Table 16 footnote for categories). Most individuals had CLL (77.9%). Large proportions of individuals had baseline diagnoses of hypertension (78.5%), atrial fibrillation (67.8%), renal dysfunction (35.5%), and thrombocytopenia (29.0%). A modest proportion of individuals had a bleeding event during the baseline period (8.1%). Most ibrutinib-treated individuals (74.4%) received an average daily dose of 420 mg at cohort entry (Table 16).

Among unweighted pre-specified baseline characteristics, there were differences between ibrutinib + OAC-treated and BR + OAC-treated individuals in CLL diagnosis (89.2% in ibrutinib + OAC vs. 52.4% in BR + OAC), cohort entry year (≥ 2016: 86.7% vs. 71.2%), median age (78 years vs. 73 years), geographic region (East North Central: 17.1% vs. 22.6%; South Atlantic: 28.1% vs. 18.9%), lymphadenopathy (31.5% vs. 55.7%), splenomegaly (12.1% vs. 24.5%), and heparin use (14.8% vs. 32.6%). After weighting, all baseline characteristics included in the propensity score were well-balanced except for household income (absolute standardized difference = 0.17) (Table 16, Table 17, and Figure 8).

Concomitant OAC use

The majority of ibrutinib + OAC-treated individuals (55.2%) entered the cohort by initiating an OAC while on ibrutinib, i.e., OAC-triggered cohort entry (Table 18), while the majority of BR + OAC-treated individuals (66.5%) entered the cohort by initiating BR while on an OAC, i.e., cancer therapy-triggered cohort entry. DOACs were used in 72.9% and 59.0% of ibrutinib + OAC-treated and BR + OAC-treated individuals,

respectively. A greater proportion of ibrutinib + OAC-treated individuals were on a low DOAC dose (23.1%) compared to BR + OAC-treated individuals (8.0%). Among ibrutinib + warfarin-treated individuals, 72% initiated ibrutinib while on warfarin.

Follow-up Time and Crude Outcome Incidence Rates

Among 72 p-y of follow-up in ibrutinib + OAC-treated individuals (median follow-up of 38 days per user), we identified nine major bleeding events (crude incidence rate: 12.5 per 100 p-y, 95% CI: 6.8 – 23.0) (Table 19). Among 39 p-y of follow-up in BR + OAC-treated individuals (median follow-up of 53 days per user), we identified no major bleeding events. Among ibrutinib + OAC-treated individuals, major bleeding events were predominantly gastrointestinal (n = 3) and cerebral (n = 3) (Table 20). We identified 19 and 3 clinically-relevant bleeding events in ibrutinib + OAC-treated individuals (crude incidence rate: 26.6 per 100 p-y, 95% CI: 18.1 – 39.1) and BR + OAC-treated individuals (crude incidence rate: 7.6 per 100 p-y, 95% CI: 2.5 – 22.3), respectively. Lastly, we identified 85 and 14 provider-diagnosed bleeding events in ibrutinib + OAC-treated individuals (crude incidence rate: 129.1 per 100 p-y, 95% CI: 105.9 – 157.4) and BR + OAC-treated individuals (crude incidence rate: 35.7 per 100 p-y, 95% CI: 21.4 – 59.8), respectively.

sIPTW-adjusted Findings

HRs for major and clinically-relevant bleeding could not be estimated due to the low number of events. Crude and sIPTW-adjusted HRs for provider-diagnosed bleeding are presented in Table 21, and the Kaplan-Meier curve is presented in Figure 9. Ibrutinib + OAC (vs. BR + OAC) had an elevated hazard of provider-diagnosed bleeding (sIPTW-adjusted HR: 2.70, 95% CI: 1.25 – 5.82). The E-value corresponding to the provider-diagnosed bleeding effect estimate was 4.84 (E-value for the lower bound of the 95% CI: 1.81). This indicates that an unmeasured confounder would need a risk ratio association

of 4.84 with both the exposure and outcome to move the provider-diagnosed bleeding effect estimate to a null value of 1 (and a risk ratio association of 1.81 with both the exposure and outcome to move the lower bound of the 95% CI to a null value of 1). Results from sensitivity analyses were generally consistent with our provider-diagnosed bleeding findings; analyses showed an elevated hazard of provider-diagnosed bleeding with an HR ranging from 2.28 – 2.97 (Table 22).

Subgroup analysis and effect modification

In the DOAC subgroup, the provider-diagnosed bleeding effect estimate for ibrutinib + OAC (vs. BR + OAC) was lower than that in the full cohort and statistically compatible with the null (sIPTW-adjusted HR: 1.91, 95% CI: 0.79 – 4.64). In the warfarin subgroup, the provider-diagnosed bleeding effect estimate for ibrutinib + OAC (vs. BR + OAC) was higher than that in the full cohort (sIPTW-adjusted HR: 7.33, 95% CI: 2.11 – 25.48). There was not evidence of effect modification by use of potentially-interacting medications or exposure initiation order at cohort entry (Table 23).

Discussion

In this population-based cohort study, rates of major, clinically-relevant, and provider-diagnosed bleeding in ibrutinib + OAC-treated individuals were 12.5, 26.6, and 129.1 per 100 p-y, respectively. While we were unable to estimate HRs for major and clinically-relevant bleeding, concomitant ibrutinib and OAC treatment was associated with a 2.7-fold hazard of provider-diagnosed bleeding compared to concomitant BR and OAC treatment. This association was notably higher, with a >7-fold hazard, among warfarin-treated individuals specifically. These findings suggest an increased bleeding rate with ibrutinib versus BR in patients concomitantly treated with OACs in the population-based setting. Though all individuals were exposed to a potential bleeding risk with OACs via

the disruption of coagulation through factor Xa, thrombin, or vitamin K inhibition, ibrutinib users were prone to an additional bleeding mechanism not typically observed with other cancer therapies: the impairment of platelet adhesion and aggregation through BTK inhibition[13].

The cumulative incidence of major bleeding (1.88%) among ibrutinib + OAC-treated individuals in our study was lower than that reported in other studies, which ranged from 13 – 16%.[58,78] This difference may be attributed to: 1) our use of a primarily privately-insured, employed population across the US, and thus a potentially less vulnerable population to medication-related bleeding compared to others,[66-68] 2) a difference in major bleeding definitions; other studies used the Common Terminology Criteria for Adverse Events,[69] which may have included bleeding events that arose during hospitalization, and 3) a shorter duration of follow-up (median of 38 days) for ibrutinib + OAC-treated individuals in our study compared to others (median of 13 months);[58] previous literature did not report incidence rates of major bleeding which would have accounted for this follow-up time difference. These potential reasons may have also contributed to the difference in cumulative incidence for broader-defined bleeding outcomes between studies: 17.7% for provider-diagnosed bleeding in our study vs. 53 – 73% for bleeding of any severity in other studies.[58,79]

Our adjusted post-hoc outcome analysis found an elevated rate of provider-diagnosed bleeding with concomitant ibrutinib + OAC therapy compared to concomitant BR + OAC therapy. We used Austin's method for attaining the number needed to harm (NNH) from adjusted survival models and calculated an NNH = 6 for provider-diagnosed bleeding. This indicates that, if our results are interpreted as causal, one additional OAC-treated individual would experience provider-diagnosed bleeding for every six OAC-treated individuals who were concomitantly treated with ibrutinib rather than BR. Our

subgroup analysis revealed a possible differential effect by OAC type, with a marked increase in the provider-diagnosed bleeding HR (7.33, 95% CI: 2.11 – 25.48) for the warfarin subgroup. This suggests that the rate of bleeding with ibrutinib and concomitant warfarin may be considerably higher than with concomitant DOACs. These data support previous recommendations to select a DOAC when anticoagulation is warranted, like the occurrence of ibrutinib-related atrial fibrillation,[12,75,80,81] based largely on several cases of serious bleeds in patients concomitantly treated with warfarin in an early-phase ibrutinib clinical trial.[9] Despite these previous cautions against using warfarin in ibrutinib-treated individuals, warfarin users accounted for 27% of the ibrutinib + OAC-treated group in our cohort—with 72% of ibrutinib + warfarin-treated individuals having been on warfarin before starting ibrutinib. It is unclear if these individuals had a specific clinical reason for not switching to a DOAC (e.g., presence of a contraindication or condition that DOACs are not approved for) or if switching was deemed unnecessary due to patient tolerability before ibrutinib initiation. Nonetheless, the notable increased rate of provider-diagnosed bleeding in the warfarin-treated subgroup provides epidemiologic support for the recommendation to use DOACs over warfarin when possible.

We compared incidence rates of major and clinically-relevant bleeding to our study described in Chapter 2 which, using the same data source and methods, investigated these outcomes in ibrutinib-treated individuals with CLL not concomitantly exposed to OACs.[77] Crude incidence rates for major and clinically-relevant bleeding were four times higher for ibrutinib + OAC-treated individuals in this study (major bleeding: 12.5 per 100 p-y; clinically-relevant bleeding: 26.6 per 100 p-y) compared to ibrutinib-treated individuals in the previous study (major bleeding: 3.1 per 100 p-y; clinically-relevant bleeding: 5.8 per 100 p-y). This suggests that, as expected, OACs increase bleeding risk in ibrutinib-treated patients. The notable increase in major and

clinically-relevant bleeding rates may have implications on the benefit-harm balance of initiating OAC therapy in patients on ibrutinib.

Our study has notable strengths. This study directly compared bleeding rates between individuals concomitantly exposed to ibrutinib and an OAC and individuals concomitantly exposed to an alternative cancer therapy and an OAC. Additionally, we identified major bleeding using an algorithm that was validated in a similar claims database and demonstrated an 89% PPV with ICD-9-CM codes.[63]

Our study has limitations. First, we were unable to obtain cancer characteristics (e.g., Rai staging for CLL, Lugano staging for MZL) and high-risk genetic features (e.g., deletion 17p or immunoglobulin heavy-chain gene mutation for CLL, TP53 mutation for MCL). However, we included cancer complications that may affect bleeding occurrence (e.g., thrombocytopenia) in the propensity score. Second, we used prescription dispensings to identify ibrutinib and OAC exposure, which may not directly reflect ingestion. We conducted sensitivity analyses in which therapy gaps were modified to address this. Third, individuals who initiated cancer therapy during OAC therapy may have had a lower risk of bleeding during follow-up compared to those who initiated OAC therapy during cancer therapy due to a possible depletion of susceptibles effect with OACs.[82] To account for this, we examined effect modification by exposure initiation order at cohort entry; however, our sample size limited our ability to detect such effect. Fourth, our provider-diagnosed bleeding post-hoc outcome was based on ICD-9 codes from a validated algorithm but was not validated itself. However, a prior study demonstrated that these codes generally had high sensitivity (93%) and specificity (88%) for identifying physician-diagnosed bleeds from discharge claims.[83] Last, though we adjusted for important confounders, differences from unmeasured confounders may remain.

Because of the multimorbidity of CLL, MCL, and MZL patients and the risk of new-onset atrial fibrillation with ibrutinib, clinicians frequently face the conundrum of concomitantly treating patients with ibrutinib and OACs. Our study found an increased rate of provider-diagnosed bleeding with ibrutinib + OACs compared to BR + OACs. The rate of bleeding may be considerably higher among warfarin-treated individuals; therefore, it may be prudent to consider a DOAC rather than warfarin when oral anticoagulation is needed for patients on ibrutinib therapy.

Table 12. Pre-specified baseline covariates.

Demographics	Age	
	Sex	
	Geographic region of residence	
	Race	
	Education level	
	Housing	
	Household income	
	Total net worth of beneficiary	
Cancer complications	Thrombocytopenia	
	Lymphadenopathy	
	Splenomegaly	
Medical conditions	Hypertension	
	Renal dysfunction	
	Liver dysfunction	
	Stroke	
	Peptic ulcer	
	Bleeding*	
	Atrial fibrillation	
	Deep vein thrombosis	
	Pulmonary embolism	
Concomitant medications	Medications associated with bleeding risk	Antiplatelets
		NSAIDs
		Heparin
	Anticancer therapy	Targeted therapy†
		Chemotherapy
	Medications that can affect CYP metabolism[1,2]	CYP3A4 inhibitors
		CYP3A4 inducers
		CYP2D6 inhibitors‡
		CYP2D6 inducers§
		CYP1A2 inhibitors
		CYP1A2 inducers
		P-gp inhibitors

		P-gp inducers
Measure of frailty	Claims-based frailty index[3]	

BR = bendamustine-rituximab; CYP = cytochrome P450; NSAID = nonsteroidal anti-inflammatory drug; P-gp = p-glycoprotein

See **Figure 6** for details on timing of covariate measurement

* Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim
† Rituximab was excluded from targeted anticancer therapy covariate as it is part of the BR regimen
‡ Diphenhydramine and hydroxyzine were excluded from CYP2D6 inhibitors covariate as they are used as pre-treatment medications for BR, thus are highly correlated to exposure status but are not confounders
§ Dexamethasone was excluded from CYP2D6 inducers covariate as it is used as a pre-treatment medication for BR, thus is highly correlated to exposure status but is not a confounder

1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.
2. Inhibitors and inducers of P-glycoprotein (P-gp) drug efflux pump (P-gp multidrug resistance transporter). UpToDate®. 2022.
3. Kim DH, et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7.

Table 13. Diagnosis codes used in outcome definition.

Bleed Site	ICD-9-CM Code	ICD-9-CM Code Description	ICD-10-CM Code*
Diagnosis Codes Indicating Bleeding†‡			
Gastrointestinal	531.0x, 531.2x, 531.4x, 531.6x	Gastric ulcer with hemorrhage	K25.0, K25.2, K25.4, K25.6
	532.0x, 532.2x, 532.4x, 532.6x	Duodenal ulcer with hemorrhage	K26.0, K26.2, K26.4, K26.6
	533.0x, 533.2x, 533.4x, 533.6x	Peptic ulcer with hemorrhage	K27.0, K27.2, K27.4, K27.6
	534.0x, 534.2x, 534.4x, 534.6x	Gastrojejunal ulcer with hemorrhage	K28.0, K28.2, K28.4, K28.6
	535.01, 535.11, 525.21, 535.31, 535.41, 535.51, 535.61	Gastritis, gastroduodenitis, or duodenitis with hemorrhage	K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91
	537.83	Angiodysplasia of stomach and duodenum with hemorrhage	K31.811
	456.0, 456.20	Esophageal varices with bleeding	I85.01, I85.11
	530.7, 530.21	Mallory-Weiss tear (gastroesophageal laceration-hemorrhage syndrome) or ulcer of esophagus with bleeding	K22.11, K22.6
	530.82	Esophageal hemorrhage	-
	578.0	Hematemesis	K92.0
	455.2, 455.5, 455.8	Hemorrhoids with other complication	-
	562.02, 562.03, 562.12, 562.13	Diverticulosis or diverticulitis with hemorrhage	K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81,

			K57.91, K57.93
	568.81	Hemoperitoneum	K66.1
	569.3	Hemorrhage of rectum and anus	K62.5
	569.85	Angiodysplasia of intestine with hemorrhage	K55.21
	578.1	Blood in stool	K92.1
	578.9	Hemorrhage of gastrointestinal tract, unspecified	K92.2
Genitourinary	593.81	Vascular disorders of kidney	N28.0
	599.7x	Hematuria	R31.0, R31.1, R31.21, R31.29, R31.9
	623.8	Other specified noninflammatory disorders of vagina	N89.8
	626.6	Metrorrhagia	N92.1
Cerebral	430	Subarachnoid hemorrhage	I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.2, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.6, I60.7, I60.8, I60.9
	431	Intracerebral hemorrhage	I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9
	432.0	Nontraumatic extradural hemorrhage	I62.1
	432.1	Subdural hemorrhage	I62.00, I62.01, I62.02, I62.03
	432.9	Unspecified intracranial hemorrhage	I62.9
Other	423.0	Hemopericardium	I31.2
	459.0	Hemorrhage, unspecified	R58

	568.81	Hemoperitoneum (nontraumatic)	K66.1
	719.1x	Hemarthrosis	M25.00, M25.011, M25.012, M25.019, M25.021, M25.022, M25.029, M25.031, M25.032, M25.039, M25.041, M25.042, M25.049, M25.051, M25.052, M25.059, M25.061, M25.062, M25.069, M25.071, M25.072, M25.073, M25.074, M25.075, M25.076, M25.08
	784.7	Epistaxis	R04.0
	784.8	Hemorrhage from throat	R04.1
	786.3x	Hemoptysis	R04.2, R04.81, R04.89, R04.9
Diagnosis Codes Suggestive of Possible Bleeding[§]			
Gastrointestinal	531.1x, 531.3x, 531.5x, 531.7x, 531.9x	Gastric ulcer without mention of hemorrhage	K25.1, K25.3, K25.5, K25.7, K25.9
	532.1x, 531.3x, 531.5x, 531.7x, 532.9x	Duodenal ulcer without mention of hemorrhage	K26.1, K26.3, K26.5, K26.7, K26.9
	533.1x, 533.3x, 533.5x, 533.7x, 533.9x	Peptic ulcer without mention of hemorrhage	K27.1, K27.3, K27.5, K27.7, K27.9
	534.1x, 534.3x, 534.5x,	Gastrojejunal ulcer without mention of hemorrhage	K28.1, K28.3, K28.5,

	534.7x, 534.9x		K28.7, K28.9
	535.00, 535.10, 535.20, 535.30, 535.40, 535.50, 535.60	Gastritis, gastroduodenitis, or duodenitis without mention of hemorrhage	K29.00, K29.20, K29.30, K29.40, K29.50, K29.60, K29.70, K29.80, K29.90
	562.00, 562.01, 562.10, 562.11	Diverticula or diverticulitis without mention of hemorrhage	K57.00, K57.10, K57.12, K57.20, K57.30, K57.32, K57.40, K57.50, K57.52, K57.80, K57.92
	455.0, 455.1, 455.3, 455.4, 455.6, 455.7, 455.9	Hemorrhoids	K64.0, K64.1, K64.2, K64.3, K64.4, K64.5, K64.8, K64.9
	530.1x	Esophagitis	K20.0, K20.8, K20.9, K21.0
	530.20	Ulcer of esophagus without bleeding	K22.10
Unspecified	285.1	Acute posthemorrhagic anemia‖	D62
	280.0	Anemia due to loss of blood‖	D50.0
	285.9	Anemia, unspecified‖	D64.9
	790.92	Abnormal coagulation profile‖	R79.1
	287.49, 287.5	Thrombocytopenia‖	D69.59, D69.6
Genitourinary	626.2	Excessive/frequent menstruation**	-

CM = clinical modification; ICD = International Classification of Diseases

* ICD-9-CM diagnoses were mapped to ICD-10-CM diagnoses using forward-backwards mapping with general equivalence maps[1]
† Outcomes were excluded if a major trauma code was recorded on the day prior to admission through the day after admission. See Cunningham et al.[2] for list of trauma codes
‡ Diagnosis code required to be the principal discharge diagnosis
§ Diagnosis code required to be the principal discharge diagnosis with either 1) a diagnosis code indicating bleeding as a secondary diagnosis or 2) a revenue code indicating a

transfusion
‖ Diagnosis code required to be the principal discharge diagnosis with a diagnosis code indicating bleeding as a secondary diagnosis (a transfusion revenue code is not sufficient)
** Diagnosis code required to be the principal discharge diagnosis with a diagnosis code of either 1) anemia (ICD-9-CM: 280.0, 285.1, 285.9; ICD-10-CM: D50.0, D62, D64.9) 2), orthostasis (ICD-9-CM: 458.0; ICD-10-CM: I95.1), or 3) syncope (ICD-9-CM: 780.2; ICD-10-CM: R55) as a secondary diagnosis

1. Fung et al. Preparing for the ICD-10-CM transition: Automated methods for translating ICD codes in clinical phenotype definitions. *EGEMS (Wash DC).* 2016;4(1):1211.
2. Cunningham et al. An Automated Database Case Definition for Serious Bleeding Related to Oral Anticoagulant Use. *Pharmacoepidemiol Drug Saf*. 2011:20(6):560-566.

Table 14. Pre-specified and post-hoc sensitivity analyses.

Type	Analysis	Rationale
Pre-specified	Depleting days' supply of ibrutinib dispensings* during non-outcome hospitalizations	Days of non-outcome hospitalization are subtracted from ibrutinib dispensings, as individuals may use their home supply of ibrutinib during the hospitalization stay, thereby minimizing exposure misclassification.
	Increasing permissible therapy gap between ibrutinib dispensings from 7 to 14 days	Increases proportion of follow-up time contributed by periods of presumed nonadherence to ibrutinib, thereby minimizing premature censoring of follow-up among poor adherers.
	Increasing permissible therapy gap between OAC dispensings from 7 to 14 days	Increases proportion of follow-up time contributed by periods of presumed nonadherence to the OAC, thereby minimizing premature censoring of follow-up among poor adherers.
	Decreasing permissible therapy gap between bendamustine administrations from 56 to 42 days	Decreases proportion of follow-up time contributed by periods of presumed delays in therapy administration, thereby minimizing exposure misclassification.
	Adjusting for cancer type (CLL, MCL, or MZL) in the Cox proportional hazards regression outcome model	Adjusts for cancer type as a covariate in the outcome model. Cancer type was not included in the propensity score in the primary analysis, as it may be an instrument which can cause bias in the propensity score estimation.
	Competing risk analysis with disenrollment as competing event	Accounts for a possible competing risk of death that may preclude individuals from developing an outcome. Disenrollment was used as a proxy for death, as death dates were unavailable.
Post-hoc	Excluding individuals with bleeding during the baseline period†	Individuals with bleeds diagnosed during the baseline period may

		experience ‘carry-forward coding’ in which outcomes experienced during follow-up represent historic bleeding events

CLL = chronic lymphocytic leukemia, MCL = mantle cell lymphoma, MZL = marginal zone lymphoma; OAC = oral anticoagulant

* In the primary analysis, days of hospitalization were added to the ibrutinib prescription claim’s days’ supply, as individuals may receive hospital supply of ibrutinib during their hospitalization stay

† Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim

Table 15. Direct oral anticoagulant dose categories used for dose intensity adjustment in subgroup analysis.

	Average Daily Dose*	
DOAC	**Low Intensity†**	**High Intensity‡**
Apixaban	≤ 5 mg	≥ 10 mg
Rivaroxaban	≤ 10 mg	≥ 15 mg
Dabigatran	≤ 220 mg	≥ 300 mg
Edoxaban	≤ 30 mg	≥ 60 mg

DOAC = direct oral anticoagulant

* Average Daily Dose = prescription quantity x capsule or tablet strength / prescription days' supply
† Low intensity includes doses indicated for deep vein thrombosis/pulmonary embolism prophylaxis and deep vein thrombosis/pulmonary embolism treatment in patients with renal dysfunction[1]
‡ High intensity includes doses indicated for deep vein thrombosis/pulmonary embolism treatment and stroke/pulmonary embolism prevention in patients with non-valvular atrial fibrillation[1]

1. Cuker et al. American Society of Hematology 2021 Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19. *Blood Adv.* 2021;5(3):872-888.

Table 16. Baseline characteristics of ibrutinib + OAC-treated and bendamustine-rituximab + OAC-treated individuals.

	Unweighted			Weighted
Characteristic, N (%)*	**Ibrutinib + OAC N = 480**	**Bendamustine-Rituximab + OAC N = 212**	**Absolute Standardized Difference**	**Absolute Standardized Difference**
Average daily ibrutinib dose†‡			N/A	N/A
<420 mg	85 (17.7)	N/A		
420 mg	357 (74.4)	N/A		
>420 mg	38 (7.9)	N/A		
Cancer type				
CLL	428 (89.2)	111 (52.4)	0.89	0.86
MCL	40 (8.3)	73 (34.4)		
MZL	12 (2.5)	28 (13.2)		
Demographics				
Cohort entry year§			0.53	0.52
2013	2 (0.4)	7 (3.2)		
2014	19 (4.0)	28 (13.2)		
2015	43 (9.0)	26 (12.3)		
2016	64 (13.3)	26 (12.3)		
2017	77 (16.0)	40 (18.9)		
2018	111 (23.1)	42 (19.8)		
2019	134 (27.9)	40 (18.9)		
2020	30 (6.3)	3 (1.4)		
Age in years, median (IQR)	78 (72 – 84)	73 (67 – 79)	0.51	0.04
Sex			0.06	0.04
Female	166 (34.6)	67 (31.6)		
Male	314 (65.4)	145 (68.4)		
US geographic region of residence			0.38	0.08
East North Central	82 (17.1)	48 (22.6)		
East South Central	10 (2.1)	7 (3.3)		
Middle Atlantic	32 (6.7)	11 (5.2)		
Mountain	53 (11.0)	33 (15.6)		
New England	15 (3.1)	12 (5.7)		
Pacific	64 (13.3)	15 (7.1)		
South Atlantic	135 (28.1)	40 (18.9)		
West North Central	31 (6.5)	12 (5.7)		
West South Central	57 (11.9)	33 (15.6)		

Unknown	1 (0.21)	1 (0.47)		
Race			0.12	0.07
Asian	8 (1.7)	2 (0.9)		
Black	41 (8.5)	15 (7.1)		
Hispanic	33 (6.9)	14 (6.6)		
White	345 (71.9)	160 (75.5)		
Unknown	53 (11.0)	21 (9.9)		
Education level‖			0.12	0.04
<12th Grade	2 (0.4)	0 (0.0)		
High school diploma	111 (23.1)	44 (20.7)		
<Bachelor degree	240 (50.0)	118 (55.7)		
Bachelor degree+	86 (17.9)	31 (14.6)		
Unknown	41 (8.6)	19 (9.0)		
Housing‖			0.07	0.05
Probable homeowner	349 (72.7)	157 (74.1)		
Probable renter	15 (3.1)	9 (4.3)		
Unknown	116 (24.2)	46 (21.7)		
Household income‖			0.07	0.17
<$40K	114 (23.7)	48 (22.6)		
$40K-$49K	30 (6.3)	13 (6.1)		
$50K-$59K	39 (8.1)	19 (9.0)		
$60K-$74K	45 (9.4)	19 (9.0)		
$75K-$99K	75 (15.6)	36 (17.0)		
$100K+	102 (21.3)	42 (19.8)		
Unknown	75 (15.6)	35 (16.5)		
Total net worth of beneficiary‖			0.05	0.09
<$25K	74 (15.4)	30 (14.1)		
$25K-$149K	75 (15.6)	36 (17.0)		
$150K-$249K	46 (9.6)	21 (9.9)		
$250K-$499K	72 (15.0)	32 (15.1)		
$500K+	138 (28.8)	58 (27.4)		
Unknown	75 (15.6)	35 (16.5)		
Cancer complications, present in baseline period				
Thrombocytopenia	149 (31.0)	52 (24.5)	0.15	0.02
Lymphadenopathy	151 (31.5)	118 (55.7)	0.50	0.01

Splenomegaly	58 (12.1)	52 (24.5)	0.33	0.01
Medical conditions, present in baseline period				
Hypertension	382 (79.6)	161 (75.9)	0.09	<0.01
Renal dysfunction	164 (34.2)	82 (38.7)	0.09	0.04
Liver dysfunction	78 (16.3)	43 (20.3)	0.10	0.02
Stroke	54 (11.3)	18 (8.5)	0.09	0.06
Peptic ulcer	9 (1.9)	7 (3.3)	0.09	0.06
Bleeding[¶]	39 (8.1)	17 (8.0)	0.004	0.07
Atrial fibrillation	333 (69.4)	136 (64.2)	0.11	0.03
Deep vein thrombosis	57 (11.9)	44 (20.8)	0.24	0.03
Pulmonary embolism	52 (10.8)	44 (20.8)	0.27	<0.01
Medications dispensed in the 90 days prior to index date[**]				
Antiplatelets	26 (5.4)	6 (2.8)	0.13	<0.01
NSAIDs	33 (6.9)	11 (5.2)	0.07	0.03
Heparin	71 (14.8)	69 (32.6)	0.43	0.01
Anticancer therapy – targeted[††]	16 (3.3)	6 (2.8)	0.03	0.04
Anticancer therapy - chemotherapy[††]	28 (5.8)	8 (3.8)	0.10	0.07
CYP3A4 inhibitors[‡‡]	64 (13.3)	38 (17.9)	0.13	0.02
CYP3A4 inducers[‡‡]	10 (2.1)	4 (1.9)	0.01	0.01
CYP2D6 inhibitors[‡‡]	49 (10.2)	27 (12.7)	0.08	0.01
CYP2D6 inducers[‡‡§§]	1 (0.2)	0 (0.0)	0.06	0.07
CYP1A2 inhibitors[‡‡]	20 (4.2)	16 (7.6)	0.14	<0.01
CYP1A2 inducers[‡‡]	88 (18.3)	37 (17.5)	0.02	0.09
P-gp inhibitors[‖‖]	87 (18.1)	39 (18.4)	0.007	0.06
P-gp inducers[‖‖]	4 (0.8)	1 (0.5)	0.04	0.02
Measure of frailty				
Claims-based frailty index, median (IQR)[¶¶]	0.173 (0.140 – 0.209)	0.161 (0.136 – 0.198)	0.17	0.01

CLL = chronic lymphocytic leukemia; CYP = cytochrome P450; IQR = interquartile range; MCL = mantle

cell lymphoma; MZL = marginal zone lymphoma; NSAID = nonsteroidal anti-inflammatory drug; OAC = oral anticoagulant; P-gp = p-glycoprotein

* Unless otherwise specified
† Average daily dose calculation: prescription quantity × capsule or tablet strength / prescription days' supply
‡ Bendamustine-rituximab dose was unavailable in Optum Clinformatics
§ Covariate was not forced into propensity score, but included as a categorical variable in outcome model
‖ Variable contains group-level information based on census data
¶ Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim
** Antimicrobial medications were examined within 14 (rather than 90) days prior to index date as these agents are typically prescribed for acute conditions
†† Anticancer therapy was examined within 180 days prior to index date
‡‡ Medications identified using the Drug Interactions Flockhart Table™[1]
§§ Variable not included in propensity score due to low cell counts
‖‖ Medications identified using UpToDate® list of P-gp inhibitors and inducers[2]
¶¶ Claims-based frailty index[3] categories: non-frail: <0.10; pre-frail: 0.10 – 0.19; mildly frail: 0.20 – 0.29; moderately frail: 0.30 – 0.39; severely frail: ≥0.40

1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.
2. Inhibitors and inducers of P-glycoprotein (P-gp) drug efflux pump (P-gp multidrug resistance transporter). UpToDate®. 2022.
3. Kim et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7.

Table 17. Baseline characteristics in the weighted population.

Characteristic, N (%)*	Ibrutinib + OAC N = 498	Bendamustine-Rituximab + OAC N = 200	Absolute Standardized Difference
Cancer type			
CLL	442 (88.8)	109 (54.5)	0.86
MCL	43 (8.6)	56 (28.0)	
MZL	13 (2.6)	35 (17.5)	
Demographics			
Cohort entry year†			0.52
2013	8 (1.6)	6 (3.0)	
2014	19 (3.8)	29 (14.5)	
2015	51 (10.2)	26 (13.0)	
2016	75 (15.1)	21 (10.5)	
2017	72 (14.5)	41 (20.5)	
2018	105 (21.1)	38 (19.0)	
2019	138 (27.7)	37 (18.5)	
2020	30 (6.0)	2 (1.0)	
Age in years, median (IQR)	76 (69 – 83)	75 (69 – 81)	0.04
Sex			0.04
Female	162 (32.5)	62 (31.0)	
Male	336 (67.5)	138 (69.0)	
Geographic region of residence			0.08
East North Central	95 (19.1)	38 (19.0)	
East South Central	11 (2.2)	5 (2.5)	
Middle Atlantic	33 (6.6)	13 (6.5)	
Mountain	75 (15.1)	26 (13.0)	
New England	16 (3.2)	6 (3.0)	
Pacific	55 (11.0)	24 (12.0)	
South Atlantic	121 (24.3)	53 (26.5)	
West North Central	30 (6.0)	11 (5.5)	
West South Central	61 (12.3)	23 (11.5)	
Unknown	1 (0.20)	1 (0.5)	
Race			0.07
Asian	7 (1.4)	3 (1.5)	
Black	36 (7.2)	15 (7.5)	
Hispanic	33 (6.6)	13 (6.5)	
White	369 (74.1)	150 (75.0)	
Unknown	53 (10.7)	19 (9.5)	
Education level‡			0.04
<12th Grade	2 (0.4)	0 (0.0)	
High school diploma	108 (21.7)	44 (22.0)	
<Bachelor degree	263 (52.8)	105 (52.5)	
Bachelor degree+	81 (16.3)	34 (17.0)	

Unknown	44 (8.8)	17 (8.5)	
Housing‡			0.05
Probable homeowner	370 (74.3)	145 (72.5)	
Probable renter	18 (3.6)	7 (3.5)	
Unknown	110 (22.1)	48 (24.0)	
Household income‡			0.17
<$40K	115 (23.1)	48 (24.0)	
$40K-$49K	33 (6.6)	10 (5.0)	
$50K-$59K	41 (8.2)	17 (8.5)	
$60K-$74K	41 (8.2)	24 (12.0)	
$75K-$99K	90 (18.1)	32 (16.0)	
$100K+	103 (20.7)	42 (21.0)	
Unknown	75 (15.1)	27 (13.5)	
Total net worth of beneficiary‡			0.09
<$25K	74 (14.8)	29 (14.5)	
$25K-$149K	82 (16.5)	37 (18.5)	
$150K-$249K	45 (9.0)	19 (9.5)	
$250K-$499K	69 (13.9)	26 (13.0)	
$500K+	153 (30.7)	62 (31.0)	
Unknown	75 (15.1)	27 (13.5)	
Cancer complications, present in baseline period			
Thrombocytopenia	146 (29.3)	57 (28.5)	0.02
Lymphadenopathy	206 (41.4)	82 (41.0)	0.01
Splenomegaly	88 (17.7)	34 (17.0)	0.01
Medical conditions, present in baseline period			
Hypertension	382 (76.7)	154 (77.0)	<0.01
Renal dysfunction	180 (36.1)	69 (34.5)	0.04
Liver dysfunction	87 (17.5)	37 (18.5)	0.02
Stroke	50 (10.0)	17 (8.5)	0.06
Peptic ulcer	10 (2.0)	6 (3.0)	0.06
Bleeding§	38 (7.6)	11 (5.5)	0.07
Atrial fibrillation	332 (66.7)	137 (68.5)	0.03
Deep vein thrombosis	78 (15.7)	29 (14.5)	0.03
Pulmonary embolism	70 (14.1)	28 (14.0)	<0.01
Medications dispensed in the 90 days prior to index date‖			
Antiplatelets	22 (4.4)	9 (4.5)	<0.01
NSAIDs	29 (5.8)	10 (5.0)	0.03
Heparin	101 (20.2)	40 (20.0)	0.01
Anticancer therapy – targeted¶	14 (2.8)	4 (2.0)	0.04
Anticancer therapy -	25 (5.0)	7 (3.5)	0.07

chemotherapy¶			
CYP3A4 inhibitors**	71 (14.2)	30 (15.0)	0.02
CYP3A4 inducers**	10 (2.0)	4 (2.0)	0.01
CYP2D6 inhibitors**	50 (10.0)	20 (10.0)	0.01
CYP2D6 inducers**††	1 (0.2)	0 (0.0)	0.07
CYP1A2 inhibitors**	28 (5.6)	12 (6.0)	<0.01
CYP1A2 inducers**	85 (17.1)	41 (20.5)	0.09
P-gp inhibitors‡‡	98 (19.7)	44 (22.0)	0.06
P-gp inducers‡‡	3 (0.6)	1 (0.5)	0.02
Measure of frailty			
Claims-based frailty index, median (IQR)§§	0.169 (0.136 – 0.205)	0.169 (0.137 – 0.207)	0.01

CLL = chronic lymphocytic leukemia; CYP = cytochrome P450; IQR = interquartile range; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NSAID = nonsteroidal anti-inflammatory drug; OAC = oral anticoagulant; P-gp = p-glycoprotein

* Unless otherwise specified
Cancer type was formatted as a categorical variable with a category for each cancer
† Covariate was not forced into propensity score, but included as a categorical variable in outcome model
‡ Variable contains group-level information based on census data
§ Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim
‖ Antimicrobial medications were examined within 14 (rather than 90) days prior to index date as these agents are typically prescribed for acute conditions
¶ Anticancer therapy was examined within 180 days prior to index date
** Medications identified using the Drug Interactions Flockhart Table™[1]
†† Variable not included in propensity score due to low cell counts
‡‡ Medications identified using UpToDate® list of P-gp inhibitors and inducers[2]
§§ Claims-based frailty index[3] categories: non-frail: <0.10; pre-frail: 0.10 – 0.19; mildly frail: 0.20 – 0.29; moderately frail: 0.30 – 0.39; severely frail: ≥0.40

1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.
2. Inhibitors and inducers of P-glycoprotein (P-gp) drug efflux pump (P-gp multidrug resistance transporter). UpToDate®. 2022.
3. Kim et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7.

Table 18. Characteristics of OAC use in ibrutinib + OAC-treated and bendamustine-rituximab + OAC-treated individuals.

Characteristic, N (%)	**Ibrutinib + OAC N = 480**	**Bendamustine-Rituximab + OAC N = 212**
Initiation order at cohort entry		
Cancer therapy-triggered	215 (44.8)	141 (66.5)
OAC-triggered	265 (55.2)	69 (32.5)
Synchronous-triggered	0 (0.0)	2 (0.9)
OAC type		
DOAC	350 (72.9)	125 (59.0)
Warfarin	130 (27.1)	87 (41.0)
DOAC Subgroup	**Ibrutinib + OAC N = 350**	**Bendamustine-Rituximab + OAC N = 125**
DOAC agent		
Rivaroxaban	100 (28.6)	53 (42.4)
Apixaban	236 (67.4)	63 (50.4)
Dabigatran	14 (4.0)	9 (7.2)
Edoxaban	0 (0.0)	0 (0.0)
DOAC dose intensity at cohort entry*		
Low	81 (23.1)	10 (8.0)
High	269 (76.9)	115 (92.0)

DOAC = direct oral anticoagulant; OAC = oral anticoagulant

* See **Table 15** for DOAC dose intensity categories

Table 19. Follow-up time and crude outcome incidence rates.

	Ibrutinib + OAC	Bendamustine-Rituximab + OAC
Follow-up time		
Follow-up, sum, in person-years	72	39
Follow-up, median per individual, in days	38	53
Outcomes during follow-up	**N**	
Major Bleeding	9	0
Clinically-relevant Bleeding	19	3
Provider-diagnosed Bleeding	85	14
Measure of outcome occurrence	**Crude Incidence Rate, per 100 person-years (95% Confidence Interval)**	
Major Bleeding	12.5 (6.8 – 23.0)	0 (0 – 0)
Clinically-relevant Bleeding	26.6 (18.1 – 39.1)	7.6 (2.5 – 22.3)
Provider-diagnosed Bleeding	129.1 (105.9 – 157.4)	35.7 (21.4 – 59.8)
OAC = oral anticoagulant		

Table 20. Site of bleed for major, clinically-relevant, and provider-diagnosed bleeding.

	Major Bleeding			Clinically-relevant Bleeding			Provider-diagnosed Bleeding		
Site of Bleed, N (%)	**Ibrutinib + OAC**	**Bendamustine-Rituximab + OAC**	**Total**	**Ibrutinib + OAC**	**Bendamustine-Rituximab + OAC**	**Total**	**Ibrutinib + OAC**	**Bendamustine-Rituximab + OAC**	**Total**
Cerebral	3 (33.3)	0 (0.0)	3 (33.3)	4 (21.1)	0 (0.0)	4 (18.2)	4 (4.7)	0 (0.0)	4 (4.1)
Gastrointestinal	3 (33.4)	0 (0.0)	3 (33.4)	6 (31.5)	1 (33.3)	7 (31.8)	18 (21.2)	4 (28.6)	22 (22.2)
Genitourinary	1 (11.1)	0 (0.0)	1 (11.1)	4 (21.1)	2 (66.7)	6 (27.3)	27 (31.8)	8 (57.1)	35 (35.3)
Other*	1 (11.1)	0 (0.0)	1 (11.1)	4 (21.1)	0 (0.0)	4 (18.2)	31 (36.4)	0 (0.0)	31 (31.3)
Unspecified*	1 (11.1)	0 (0.0)	1 (11.1)	1 (5.2)	0 (0.0)	1 (4.5)	5 (5.9)	2 (14.3)	7 (7.1)
Total	9 (100.0)	0 (0.0)	9 (100.0)	19 (100.0)	3 (100.0)	22 (100.0)	85 (100.0)	14 (100.0)	99 (100.0)

OAC = oral anticoagulant

* See **Table 13** for bleed types in Other and Unspecified sites of bleed

Table 21. Adjusted outcome findings for primary and subgroup analyses.

	Ibrutinib + OAC	Bendamustine-Rituximab + OAC
Primary Analysis	**Hazard Ratio (95% Confidence Interval)**	
Major Bleeding*		
Unadjusted	-	-
Adjusted	-	-
Clinically-relevant Bleeding*		
Unadjusted	-	-
Adjusted	-	-
Provider-diagnosed Bleeding		
Unadjusted†	3.28 (1.86 – 5.77)	1.00 (reference)
Adjusted‡§	2.70 (1.25 – 5.82)	1.00 (reference)
Subgroup Analysis	**Hazard Ratio (95% Confidence Interval)**	
DOAC		
Provider-diagnosed Bleeding‖¶	1.91 (0.79 – 4.64)	1.00 (reference)
Warfarin		
Provider-diagnosed Bleeding‡**	7.33 (2.11 – 25.48)	1.00 (reference)

DOAC = direct oral anticoagulant; OAC = oral anticoagulant

* Unadjusted and adjusted hazard ratios could not be estimated due to low event counts
† Did not fail a test for non-proportional hazards (p = 0.99)
‡ Model weighted based on stabilized inverse probability of treatment weights and adjusted for cohort entry year and household income
§ Did not fail a test for non-proportional hazards (p = 0.63)
‖ Model weighted based on stabilized inverse probability of treatment weights and adjusted for cohort entry year, household income, and DOAC dose category at cohort entry. Individuals with a DOAC dose change during follow-up were censored on date of dose change
¶ Did not fail a test for non-proportional hazards (p = 0.76)
** Did not fail a test for non-proportional hazards (p = 0.32)

Table 22. Results from sensitivity analyses.

	Number of Provider-diagnosed Bleeding Events	Hazard Ratio (95% Confidence Interval)*
Depleting days' supply of ibrutinib dispensings during hospitalizations	99	2.75 (1.28 – 5.94)
Increasing permissible therapy gap of ibrutinib dispensings from 7 to 14 days	104	2.63 (1.22 – 5.67)
Decreasing permissible therapy gap between bendamustine administrations from 56 to 42 days	97	2.79 (1.26 – 6.20)
Increasing permissible therapy gap between OAC dispensings from 7 to 14 days	107	2.82 (1.39 – 5.69)
Adjusting for cancer type (CLL, MCL, or MZL) in the Cox proportional hazards regression outcome model	99	2.92 (1.39 – 6.15)
Competing risk analysis with disenrollment as competing event	99	2.70 (1.25 – 5.82)
Excluding individuals with bleeding during the baseline period	83	2.28 (1.03 – 5.03)

CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; OAC = oral anticoagulant

* Model weighted based on stabilized inverse probability of treatment weights and adjusted for cohort entry year and household income

Table 23. Results from effect modification analyses.

	P-value	Hazard Ratio (95% Confidence Interval)
CYP3A4 inhibitors	0.55	Not displayed because p-value is not significant
CYP3A4 inducers	<0.01	Not displayed because of unstable hazard ratio estimate*
CYP2D6 inhibitors	0.11	Not displayed because p-value is not significant
CYP2D6 inducers	-	Not displayed because interaction term could not be included in model†
CYP1A2 inhibitors	0.82	Not displayed because p-value is not significant
CYP1A2 inducers	0.23	
P-gp inhibitors	0.31	
P-gp inducers	0.58	
Exposure initiation order at cohort entry	0.60	

CYP = cytochrome P450; P-gp = p-glycoprotein

* There was only 1 outcome among the 14 individuals who had CYP3A4 inducer use during the baseline period, thus the hazard ratio estimate was unstable

† There was only 1 individual in the cohort who had CYP2D6 inhibitor use during the baseline period, thus the interaction term could not be included

Figure 5. Incident co-exposure definition for individuals with A) cancer therapy-triggered, B) OAC therapy-triggered, and C) synchronous-triggered cohort entry. For A) and C), the 6 months preceding the index date needed to be devoid of ibrutinib dispensing for ibrutinib + OAC-treated individuals and bendamustine for BR + OAC-treated individuals. BR = bendamustine-rituximab; OAC = oral anticoagulant.

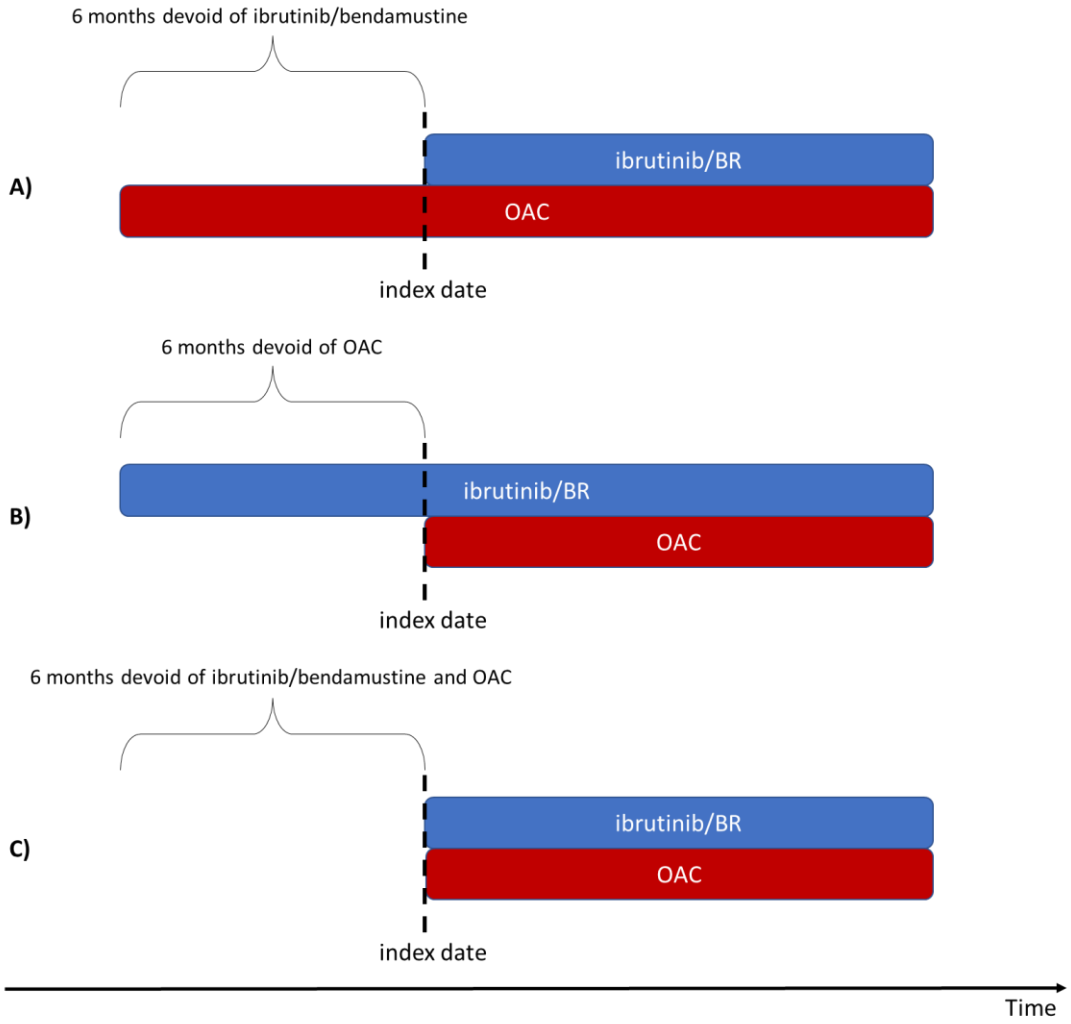
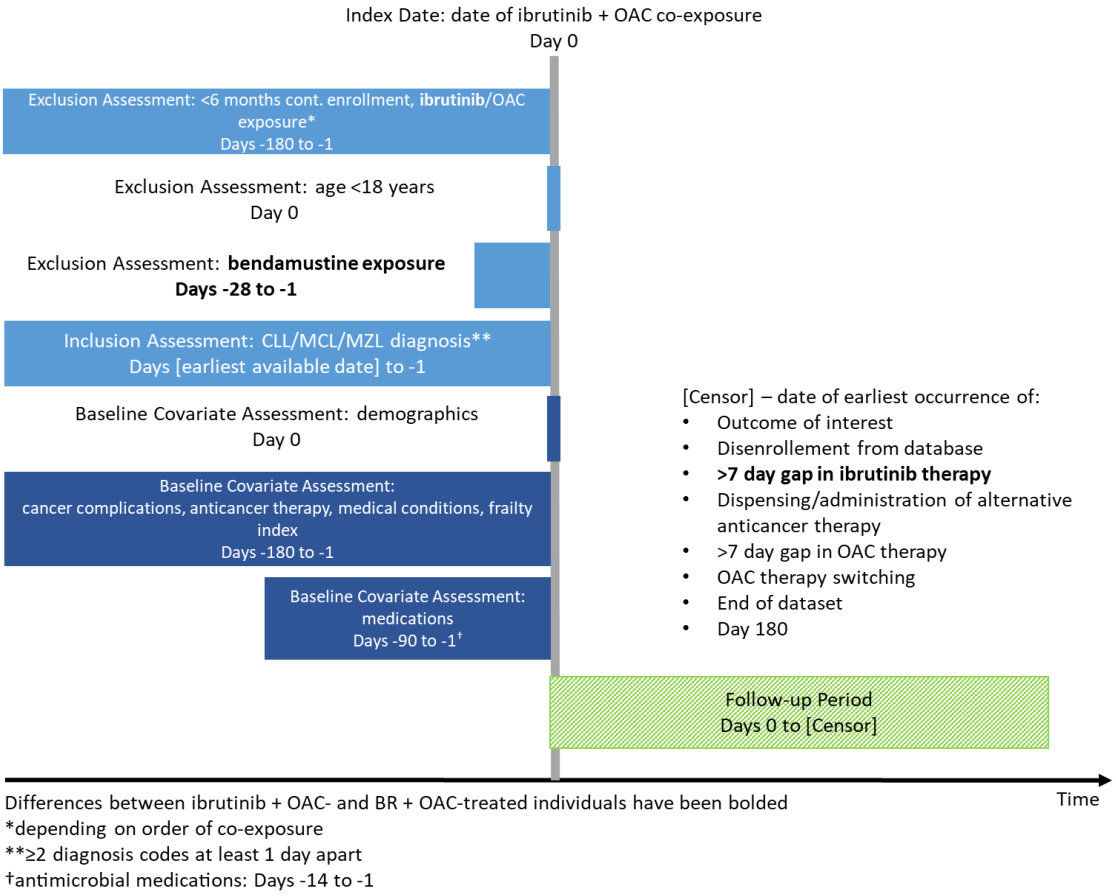


Figure 6. Study design depiction for A) ibrutinib + OAC-treated individuals and B) bendamustine-rituximab + OAC-treated individuals.

A)



Differences between ibrutinib + OAC- and BR + OAC-treated individuals have been bolded
*depending on order of co-exposure
**≥2 diagnosis codes at least 1 day apart
†antimicrobial medications: Days -14 to -1

B)

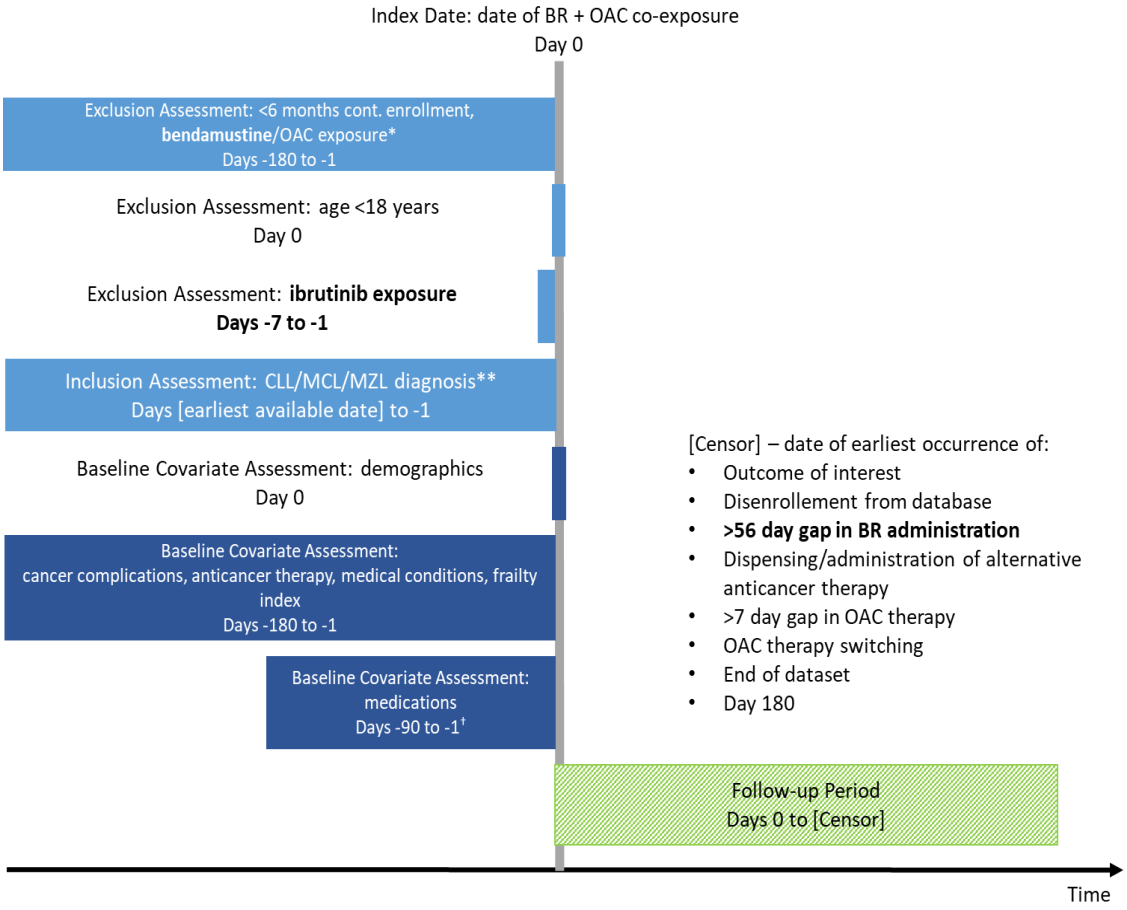

Index Date: date of BR + OAC co-exposure
Day 0
Exclusion Assessment: <6 months cont. enrollment, **bendamustine**/OAC exposure*
Days -180 to -1
Exclusion Assessment: age <18 years
Day 0
Exclusion Assessment: **ibrutinib exposure**
Days -7 to -1
Inclusion Assessment: CLL/MCL/MZL diagnosis**
Days [earliest available date] to -1
Baseline Covariate Assessment: demographics
Day 0
Baseline Covariate Assessment: cancer complications, anticancer therapy, medical conditions, frailty index
Days -180 to -1
Baseline Covariate Assessment: medications
Days -90 to -1†
[Censor] – date of earliest occurrence of:
• Outcome of interest
• Disenrollement from database
• **>56 day gap in BR administration**
• Dispensing/administration of alternative anticancer therapy
• >7 day gap in OAC therapy
• OAC therapy switching
• End of dataset
• Day 180
Follow-up Period
Days 0 to [Censor]
Time

Figure 7. Study cohort flowchart.

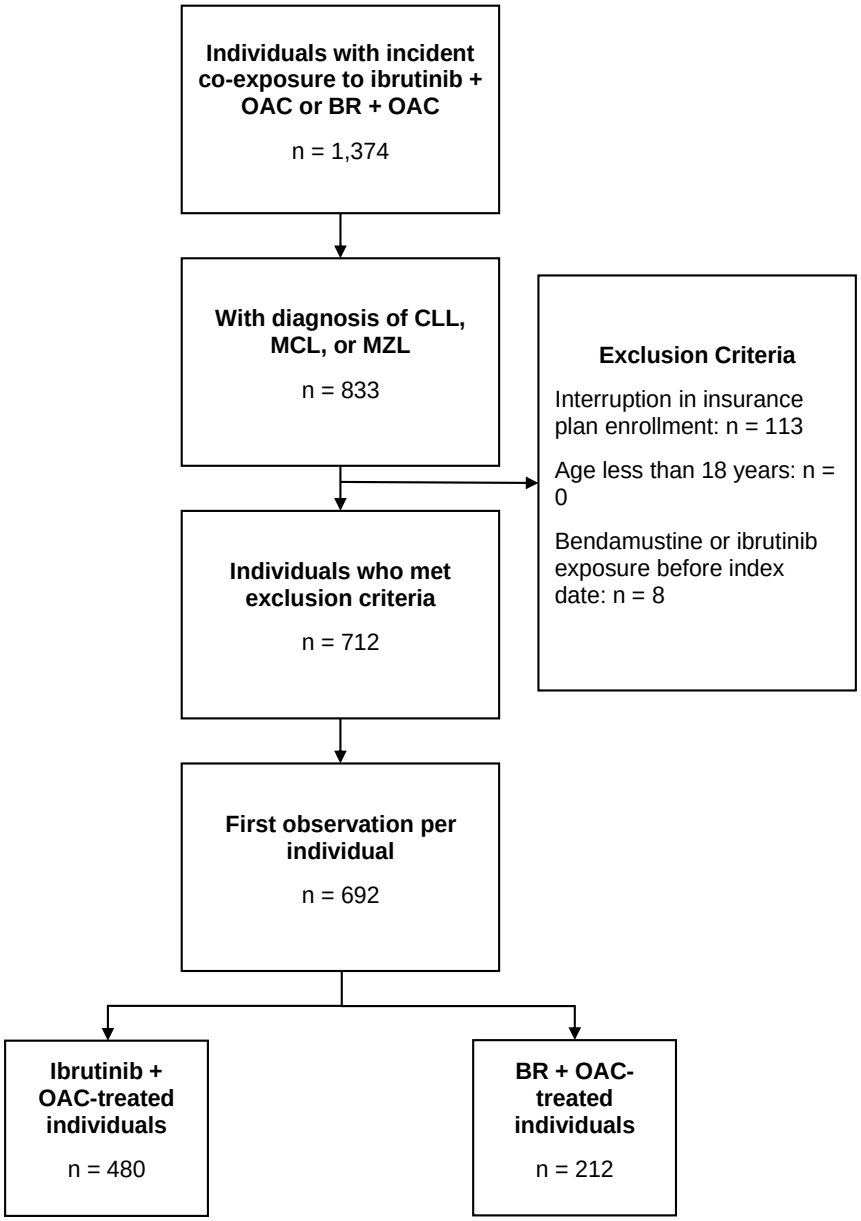


Figure 8. Propensity score distribution in unweighted population.

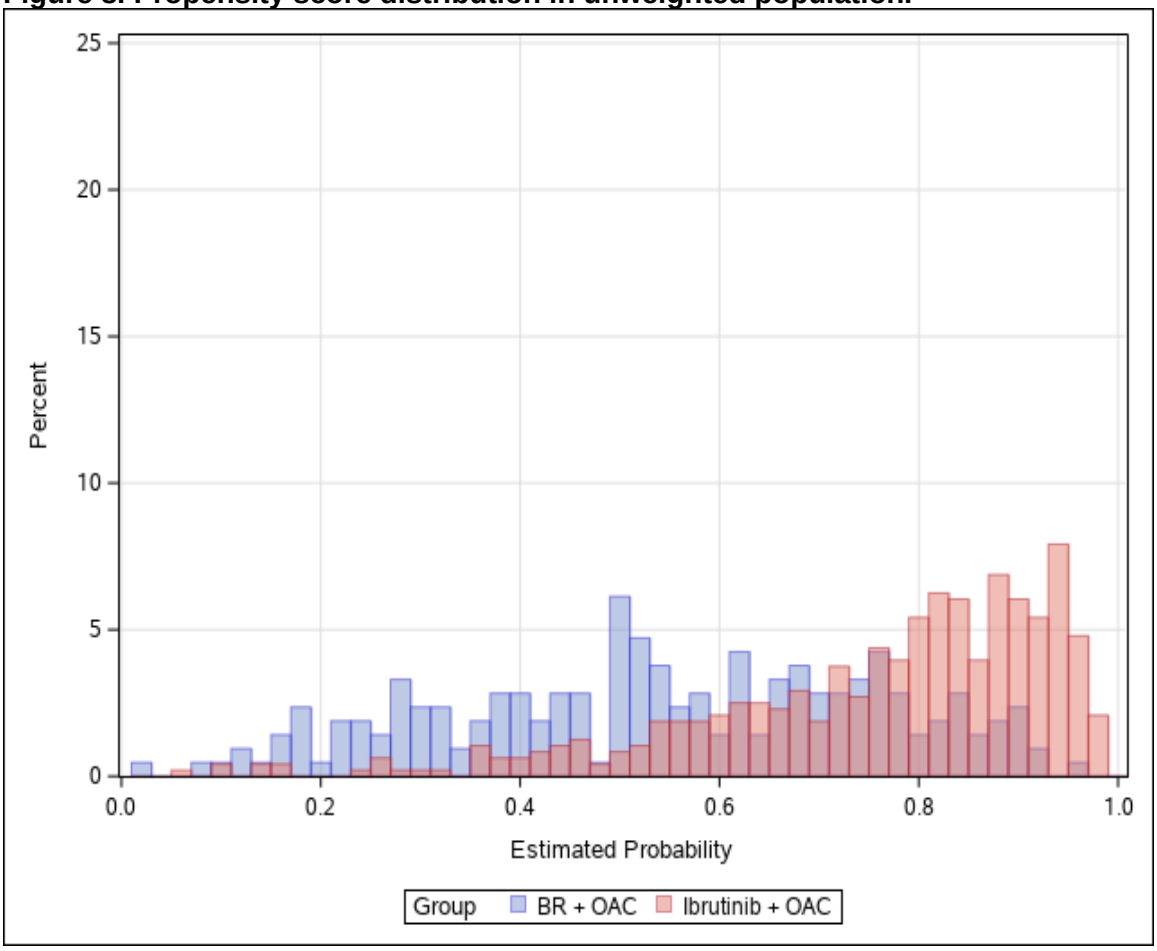
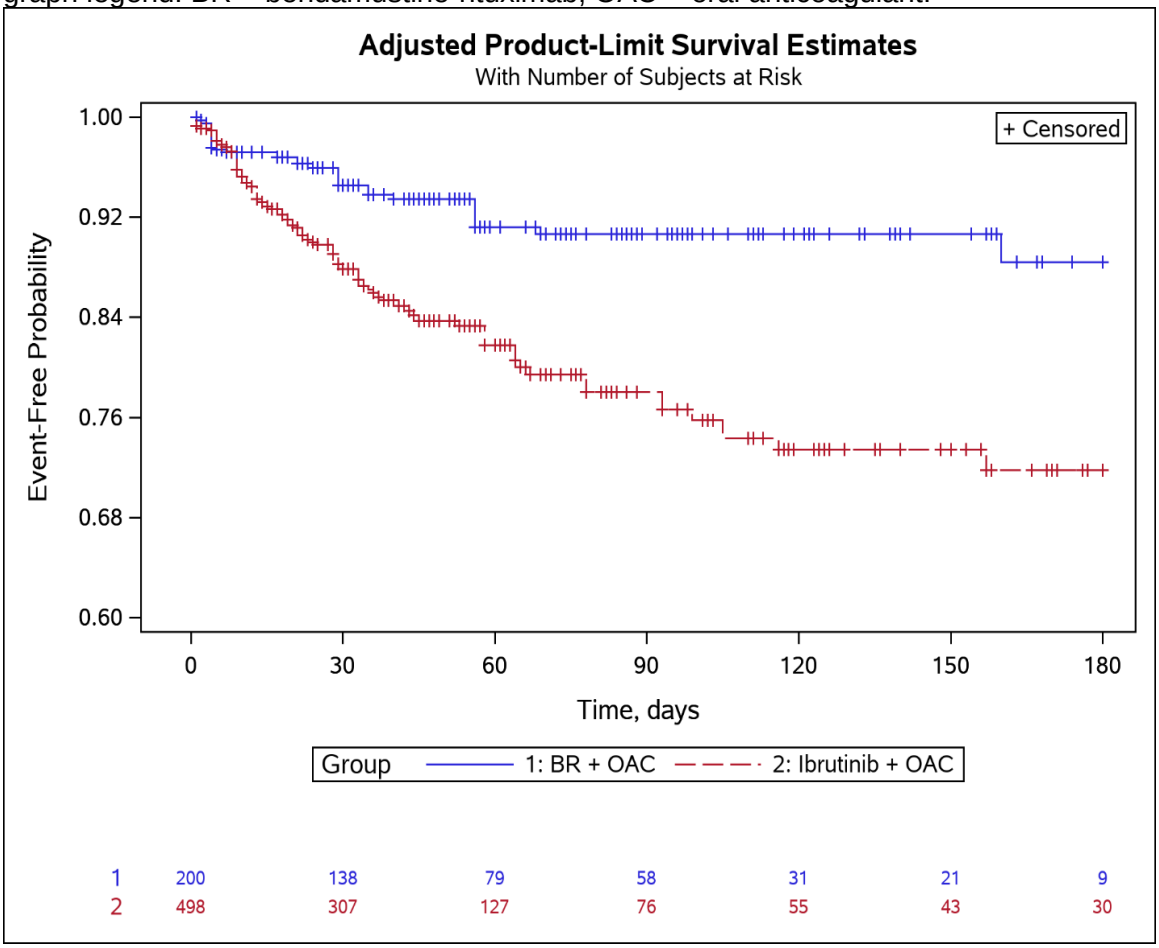


Figure 9. Kaplan-Meier curve for provider-diagnosed bleeding in the weighted population based on stabilized inverse probability of treatment weighting. The number of individuals remaining in the risk set at each time point is displayed below the graph legend. BR = bendamustine-rituximab; OAC = oral anticoagulant.



CHAPTER 4 – COMBINING SUPERLEARNER WITH HIGH-DIMENSIONAL PROPENSITY SCORE: A REAL-WORLD APPLICATION

Introduction

High-dimensional propensity score (hdPS) is a semi-automated propensity score method that empirically identifies covariates with the highest potential for confounding and includes them, along with pre-specified covariates, in the propensity score estimation. Though hdPS automatically identifies covariates and prioritizes them, it does not specify the optimal number of empirically-identified covariates to include in the propensity score. Including too few covariates may not account for the entirety of the present confounding. Conversely, including too many covariates may result in overfitting of the propensity score model. Though it has been argued in the past that overfitting is not an important concern with propensity score estimation,[52] simulation studies found that severe overfitting of propensity scores corresponds with increased bias and decreased precision in the effect estimate.[53]

Wyss et al.[53] proposed a novel data-adaptive approach combining hdPS with SuperLearner (SL)[54] to assist researchers with the optimal selection of empirically-identified variables for propensity score estimation. In plasmode simulation studies (simulation studies in which elements of observed real-world data are incorporated to provide more realistic simulations), this SL-hdPS approach was generally found to be more effective in reducing bias compared to hdPS alone (25 – 34% compared to hdPS in small sample scenarios in which severe overfitting is more likely) and increased precision as well. However, these potential benefits have yet to be seen in the applied setting. We aimed to examine the performance of SL-hdPS in comparison to hdPS

alone, with ‘applied study’ assessment parameters, such as baseline covariate balance among pre-specified and empirically-identified covariates and treatment effect estimate precision, using two real-world cohorts used to assess the comparative rate of bleeding with ibrutinib vs. bendamustine-rituximab (BR). Given the frequent occurrence of bleeding with ibrutinib in clinical trials,[11,12] ibrutinib may be selectively prescribed for individuals who have a low baseline risk of bleeding. This potential confounding concern makes this research question an apt example for assessing SL-hdPS.

Methods

Overview and data source

We compared the performance of SL-hdPS with several hdPS models, each with a different number of empirically-identified covariates, using two cohorts: 1) a cohort of individuals treated with ibrutinib or BR and 2) a cohort of individuals concomitantly treated with ibrutinib + an oral anticoagulant (OAC) or BR + an OAC. These cohorts were derived from Optum Clinformatics de-identified commercial health insurance data from 2013 – 2020. Optum Clinformatics consists of >80 million commercially-insured and Medicare Advantage beneficiaries of a large US-based private health insurer, and includes demographic and enrollment information and inpatient, outpatient, and pharmacy claims (for drugs dispensed in the outpatient setting) for enrollees. It also includes laboratory results for a subset of individuals.

Study cohorts

Cohort 1 included individuals with incident use of either ibrutinib or BR between November 1, 2013 and February 29, 2020. Individuals were included if they were diagnosed with chronic lymphocytic leukemia (CLL) and excluded if they were co-exposed to an OAC. Pre-specified covariates were ascertained during a six-month

baseline period preceding the index date and included demographics, coexisting medical conditions, anticancer therapy use, medication use associated with an increased risk of bleeding, and a claims-based frailty index.[62] The outcomes of interest were major bleeding and clinically-relevant bleeding. Major bleeding was defined as bleeding resulting in hospitalization and was identified using an algorithm previously validated in health insurance claims data.[63] Clinically-relevant bleeding was a composite of bleeding events resulting in hospitalization and those resulting in emergency department presentation. More details on defining the cohort, covariate ascertainment, and outcome definitions can be found in the methods section of Chapter 2.

Cohort 2 included individuals with incident co-exposure (i.e., concomitant use) of either ibrutinib + an OAC or BR + an OAC between November 1, 2013 and February 29, 2020. Individuals were included if they were diagnosed with CLL, mantle cell lymphoma (MCL), or marginal zone lymphoma (MZL). Pre-specified covariates ascertained during a six-month baseline period preceding the index date included those specified in Cohort 1 as well as five additional covariates related to OAC use. The outcome of interest was provider-diagnosed bleeding, i.e., any bleed diagnosed by a healthcare provider. Outcomes were identified in any-setting claims with a bleeding diagnosis code in any claim position. More details on defining the cohort, covariate ascertainment, and outcome definitions can be found in the methods section of Chapter 3.

High-dimensional propensity score

The hdPS method has been described in detail by Schneeweiss et al.[45] Briefly, this approach uses logistic regression to estimate the propensity for exposure based on pre-specified and empirically-identified covariates. To empirically identify covariates with the highest potential for confounding, we first selected the 200 most prevalent International Classification of Diseases (ICD) diagnoses, Current Procedural Terminology (CPT) and

Healthcare Common Procedure Coding System (HCPCS) codes, prescription active ingredient codes, and laboratory Logical Observation Identifiers Names and Codes (LOINCs) in each of three care settings (inpatient, outpatient, and all other settings). Then, these covariates were ranked by potential for confounding according to their univariate association with ibrutinib exposure. Last, the top *k* ranked covariates (*k* specified by the user; see below), along with pre-specified covariates were included in a logistic regression model to estimate the propensity score. A stabilized inverse probability weight (IPTW) was then calculated for each individual based on their propensity score.

SL-hdPS

SL is an ensemble approach that combines multiple prediction algorithms into a single ensemble algorithm.[54] SL uses V-fold cross-validation to generate weights for each of the prediction algorithms included in the ensemble based on the minimization of a loss function. Loss functions, such as negative log-likelihood, are used to measure a model's predictive accuracy. SL then returns a weighted prediction based on all included prediction algorithms, thus allowing researchers to bypass the need to select a single prediction model from the wide variety of models available. SL can be used to optimize hdPS with respect to the number of empirically-identified covariates included in the propensity score model.[53] Several hdPS models with a different number of empirically-identified covariates (i.e., *k* is varied among models) can be incorporated into SL to generate a weighted prediction, i.e., the estimated propensity score. Theoretically, this SL-hdPS approach can avoid issues with an hdPS candidate model incorporated in the ensemble that includes too few (thus, not accounting for all factors associated with the exposure) or too many covariates (thus, running the risk of overfitting) since these issues

may result in lower candidate model performance during cross-validation, and thus a lower weight for the model in the final ensemble prediction.

For each cohort, we specified six separate hdPS candidate models to be incorporated into SL. Each was a logistic regression model that included the same pre-specified covariates and a different number of empirically-identified covariates. Before specifying hdPS candidate models, we screened empirically-identified covariates for instrumental variables[52] and excluded them, yielding a total of 413 empirically-identified covariates for Cohort 1 and 200 empirically-identified covariates for Cohort 2. The total number of empirically-identified covariates included in candidate models for Cohort 2 was lower than that for Cohort 1 because of the smaller sample size. The candidate models for Cohort 1 included 25, 100, 200, 300, 400, and 413 empirically-identified covariates; all models also included 29 pre-specified covariates. The candidate models for Cohort 2 included 0 (only pre-specified covariates), 25, 50, 100, 150, and 200 empirically-identified covariates; all models also included 33 pre-specified covariates. We then ran SL, which included the six candidate models, using a negative log-likelihood loss function and V = 10 folds[84] to estimate the propensity score. IPTW was then calculated for each individual based on their propensity score.

Parameters of interest

We assessed several parameters of interest to compare the performance between SL-hdPS and the candidate hdPS models that were incorporated in SL. We compared propensity score distributions and the distribution of IPTW weights to assess for signals of propensity score overfitting, specifically examining magnitude of propensity score non-overlap and distribution of IPTW weights. We compared the balance in the pre-specified covariates (29 for Cohort 1 and 33 for Cohort 2) and full set of empirically-identified covariates (413 for Cohort 1 and 200 for Cohort 2) between approaches to assess the

ability to adjust for confounding in the applied setting where the true outcome effect estimate is unknown. We calculated absolute standardized differences (ASDs) for covariates and considered an ASD <0.10 as adequately balanced.[85] We also assessed balance at a stricter threshold of <0.05 to further elucidate the magnitude of covariate balance. We summarized covariate balance for each model by calculating the number of covariates that were balanced at both thresholds. Last, we estimated hazard ratios (HRs) and natural log hazard ratios (Ln[HRs]) with 95% confidence intervals (95% CIs) using Cox proportional hazards regression to compare treatment effect estimate precision between models.

Results

Study cohort characteristics

Cohort 1 included 2,423 and 1,102 incident users of ibrutinib and BR, respectively. Individuals were predominantly male (61.6%) and White (70.4%), with a median age of 72 years and a median frailty score of 0.135 (i.e., pre-frail category per frailty index). Cohort 2 included 480 and 212 concomitant users of ibrutinib + an OAC and BR + an OAC. Individuals were predominantly male (66.3%) and White (73.0%), with a median age of 77 years and a median frailty score of 0.170 (i.e., pre-frail category per frailty index). More details on the baseline characteristics of both cohorts can be found in Chapters 2 and 3.

Super learner cross-validation

The cross-validated negative log-likelihood and weight coefficients for candidate models in the SL ensemble for Cohorts 1 and 2 are presented in Tables 24 and 25.

Propensity score and IPTW distributions

For Cohort 1, there was a higher degree of non-overlap in the propensity score distribution and higher frequency of extreme propensity scores (i.e., a propensity score close to 0 or 1) as more empirically-identified covariates were added to the hdPS model (Figure 10). Candidate model 6 (29 pre-specified and 413 empirically-identified covariates) resulted in >5% of individuals with a propensity score close to 1 (i.e., almost 100% predicted probability of receiving ibrutinib), while candidate model 1 (29 pre-specified and 25 empirically-identified covariates) resulted in <1% of individuals with a propensity score close to 1. SL-hdPS resulted in less non-overlap compared to the candidate models with a higher number of covariates (Figure 11). A similar pattern was found in the distribution of weights after IPTW calculation. Among candidate models, the hdPS models with the most covariates had larger extreme weights (maximum weight: 51.29 in candidate model 5 and 48.77 in candidate model 6) (Table 26). SL-hdPS did not result in as extreme weights (maximum weight: 9.04) compared to all included candidate models.

Figures 12 and 13 display the propensity score distributions for the candidate models and SL-hdPS model for Cohort 2. Most candidate models displayed signs of severe overfitting with the percentage of individuals with a propensity score close to 1 or 0 exceeding 25%. Although SL-hdPS had a slightly reduced degree of non-overlap, the model still displayed signs of severe overfitting. After IPTW calculation, most candidate models had extreme weights exceeding 100 (Table 27). Extreme weights of candidate models 5 and 6 exceeded 1,000.

Covariate balance

Table 28 displays the covariate balance for the unweighted population and the weighted population based on candidate models and SL-hdPS for Cohort 1. In the unweighted population, 72.2% and 21.3% of all covariates were balanced at the ASD <0.10 and

ASD <0.05 thresholds, respectively. Among the six candidate models, candidate model 3 (29 pre-specified and 200 empirically-identified covariates) balanced the most variables at both thresholds (95.5% at ASD <0.10 and 72.2% at ASD <0.05). Including more than 200 empirically-identified covariates in hdPS seemed to slightly compromise covariate balance at both thresholds; candidate model 6 balanced 92.5% and 63.3% of covariates at ASD <0.10 and ASD <0.05, respectively. SL-hdPS performed better than all candidate models that were included in the ensemble; 96.8% and 74.7% of covariates were balanced at ASD <0.10 and ASD <0.05, respectively.

For Cohort 2, candidate model 6 balanced the most covariates among candidate models at both ASD thresholds (79.0% and 60.1% at ASD <0.10 and ASD <0.05, respectively). SL-hdPS balanced fewer covariates than all candidate models; 37.3% and 6.9% at ASD <0.10 and <0.05, respectively (Table 29).

Effect estimate precision

For Cohort 1, SL-hdPS produced effect estimates for major and clinically-relevant bleeding with confidence intervals that were generally narrower than those produced by the individual candidate models (Table 30). Effect estimates for Cohort 2 are not reported because of the suboptimal performance of candidate models and SL-hdPS, as described above.

Discussion

We found that, in certain scenarios, combining SL with hdPS can help researchers select the number of empirically-identified covariates to include in the hdPS model that results in maximized covariate balance—especially in a small-sample setting which may limit the number of covariates able to be included in the propensity score. In the Cohort 1 example, SL-hdPS slightly outperformed the best-performing candidate hdPS model by

balancing more covariates among the pre-specified and empirically-identified covariates. In Cohort 2 however, SL-hdPS resulted in an overfit propensity score model with suboptimal covariate balance compared to the individual candidate models.

Among candidate models for Cohort 1, candidate model 3 (29 pre-specified and 200 empirically-identified covariates) achieved the best balance in total covariates at both ASD thresholds. This may suggest that the candidate models with fewer covariates (candidate models 1 and 2) excluded important confounding variables and the candidate models with more covariates (candidate models 4, 5, and 6) resulted in overfitting that began to compromise the ability to balance all the covariates included. Overfitting of models with a large number of covariates may be further seen from the magnitude of non-overlap in propensity score distributions and the extreme IPTW weights. Wyss et al. found a similar pattern in plasmode simulation studies: including more than 100 covariates in the hdPS logistic regression model tended to increase the bias in estimated treatment effects among several scenarios (e.g., reduced sample size, rare outcome, reduced treatment prevalence, etc.), which was apparent with the hdPS model including 500 covariates (up to a 30% difference in the percentage of bias removed compared to the hdPS model with 100 covariates).[53] These findings in both the empiric and simulated settings suggest that propensity score models can be sensitive to the number of variables included.

In Cohort 1, SL-hdPS performed slightly better than the best performing candidate model in terms of maximizing covariate balance at both ASD thresholds. This was also found in plasmode simulation studies; SL-hdPS maximized treatment effect bias reduction in several scenarios compared to the individual hdPS models included in the ensemble.[53] The observed performance of SL-hdPS in the applied and simulated propensity score settings is consistent with SL's performance in the predictive outcome

modeling setting, which was shown to be slightly better than the best candidate predictive model included in terms of minimizing the cross-validated loss function (e.g., negative log-likelihood, mean squared error) and maximizing predictive accuracy.[54,86,87] This consistency in performance shows that SL-hdPS may be useful in estimating the propensity score in situations where incorporating hundreds of empirically-identified covariates may result in severe model overfitting, like studies with small samples. Furthermore, SL-hdPS may improve effect estimate precision as shown by Wyss et al.[53] and possibly in our applied Cohort 1—though the varied effect estimates among models makes interpretation challenging.

In contrasting to the Cohort 1 scenario, SL-hdPS did not perform well in Cohort 2. The SL-hdPS model showed signs of severe overfitting in the propensity score distribution and resulted in fewer balanced covariates compared to all of the candidate models included in the ensemble. Given the sample size of 692 individuals, this may have been caused by the inclusion of too many variables, and thus overfitting of, most candidate models—since SL's performance relies on the performance of the models included during V-fold cross validation. Though we reduced the maximum number of empirically-identified covariates (200 in Cohort 2 vs. 413 in Cohort 1), an additional variable screening or dimension reducing procedure may be useful for preventing overfitting among candidate models and improving the performance of SL. For example, shrinkage via least absolute shrinkage and selection operator (LASSO) or ridge regression or dimension reduction via principal component analysis[88-93] could be applied to candidate hdPS models before inclusion in the SL ensemble.

The strength of this study is that it evaluated the performance of SL-hdPS in the applied setting; SL-hdPS has only been demonstrated in the simulated setting previously. The limitation is that since we evaluated the performance of the approach in

addressing a novel research question, the true treatment effect estimate is unknown. However, like other applied studies, we measured covariate balance to assess the approach's ability to address confounding. Though we measured the balance in empirically-identified covariates, which are hypothesized to be a proxy for unmeasured confounders,[45] we could not directly the measure the magnitude of unmeasured confounding. Last, we evaluated the performance of SL-hdPS in two real-world cohorts; the results may not be generalizable to all studies as the potential benefit of the approach may vary based on an individual study's characteristics (e.g., sample size and amount of confounding present).

Although hdPS can be a useful approach that leverages the vast amount of data in electronic healthcare databases to reduce confounding, it may pose challenges with propensity score overfitting, especially in studies with small sample sizes. SL can assist researchers in optimizing the hdPS model, resulting in less overfitting, maximized covariate balance, and possibly improved effect estimate precision. However, additional covariate screening or dimension reduction may be necessary in studies with exceptionally small sample sizes before implementing SL-hdPS. Future research should also explore the incorporation of models other than logistic regression (e.g., random forest, neural networks, and classification and regression trees) in SL for improved model flexibility and potentially better hdPS performance.

Table 24. Cross-validation of candidate models included in SuperLearner ensemble for Cohort 1.

Candidate Model	Negative Log-Likelihood*	Weight Coefficient
Candidate Model 1	0.57	0.34
Candidate Model 2	0.56	0.30
Candidate Model 3	0.57	0.12
Candidate Model 4	0.60	0.20
Candidate Model 5	0.66	0.04
Candidate Model 6	0.66	0.00

* Based on 10-fold cross validation

Candidate Model 1: 29 pre-specified + 25 empirically-identified covariates
Candidate Model 2: 29 pre-specified + 100 empirically-identified covariates
Candidate Model 3: 29 pre-specified + 200 empirically-identified covariates
Candidate Model 4: 29 pre-specified + 300 empirically-identified covariates
Candidate Model 5: 29 pre-specified + 400 empirically-identified covariates
Candidate Model 6: 29 pre-specified + 413 empirically-identified covariates

Table 25. Cross-validation of candidate models included in SuperLearner ensemble for Cohort 2.

Candidate Model	Negative Log-Likelihood*	Weight Coefficient
Candidate Model 1	0.64	0.40
Candidate Model 2	0.95	0.16
Candidate Model 3	1.51	0.22
Candidate Model 4	3.96	0.00
Candidate Model 5	6.95	0.10
Candidate Model 6	9.44	0.12

* Based on 10-fold cross validation

Candidate Model 1: 33 pre-specified covariates
Candidate Model 2: 33 pre-specified + 25 empirically-identified covariates
Candidate Model 3: 33 pre-specified + 50 empirically-identified covariates
Candidate Model 4: 33 pre-specified + 100 empirically-identified covariates
Candidate Model 5: 33 pre-specified + 150 empirically-identified covariates
Candidate Model 6: 33 pre-specified + 200 empirically-identified covariates

Table 26. Inverse probability treatment weights for Cohort 1.

Model	Minimum	Maximum	50th Percentile	75th Percentile	90th Percentile	95th Percentile	99th Percentile
Candidate Model 1	0.33	5.91	0.90	1.06	1.44	1.82	3.07
Candidate Model 2	0.32	14.92	0.85	1.03	1.44	1.98	4.26
Candidate Model 3	0.31	17.80	0.82	1.01	1.48	1.99	4.23
Candidate Model 4	0.31	32.19	0.79	0.98	1.47	1.97	4.98
Candidate Model 5	0.31	51.29	0.77	0.97	1.43	2.04	5.60
Candidate Model 6	0.31	48.77	0.77	0.96	1.45	2.00	5.65
SL-hdPS	0.32	9.04	0.84	1.00	1.34	1.75	2.97

SL-hdPS = SuperLearner-high-dimensional propensity score

Candidate Model 1: 29 pre-specified + 25 empirically-identified covariates
Candidate Model 2: 29 pre-specified + 100 empirically-identified covariates
Candidate Model 3: 29 pre-specified + 200 empirically-identified covariates
Candidate Model 4: 29 pre-specified + 300 empirically-identified covariates
Candidate Model 5: 29 pre-specified + 400 empirically-identified covariates
Candidate Model 6: 29 pre-specified + 413 empirically-identified covariates

Table 27. Inverse probability treatment weights for Cohort 2.

Model	Minimum	Maximum	50th Percentile	75th Percentile	90th Percentile	95th Percentile	99th Percentile
Candidate Model 1	0.31	10.16	0.84	1.05	1.43	1.94	4.40
Candidate Model 2	0.31	201.23	0.76	0.95	1.31	1.74	4.41
Candidate Model 3	0.31	173.05	0.71	0.82	1.16	1.84	5.10
Candidate Model 4	0.31	358.69	0.70	0.75	1.00	1.53	5.13
Candidate Model 5	0.31	1806.46	0.69	0.69	0.77	0.89	2.21
Candidate Model 6	0.31	9.2×10^{14}	0.69	0.69	0.70	0.75	0.87
SL-hdPS	0.31	19.94	0.72	0.75	0.84	1.11	3.05

SL-hdPS = SuperLearner-high-dimensional propensity score

Candidate Model 1: 33 pre-specified covariates
Candidate Model 2: 33 pre-specified + 25 empirically-identified covariates
Candidate Model 3: 33 pre-specified + 50 empirically-identified covariates
Candidate Model 4: 33 pre-specified + 100 empirically-identified covariates
Candidate Model 5: 33 pre-specified + 150 empirically-identified covariates
Candidate Model 6: 33 pre-specified + 200 empirically-identified covariates

Table 28. Covariate balance in Cohort 1.

Model	Covariates Balanced at ASD Threshold (%)	
	ASD <0.10	ASD <0.05
Pre-specified + empirically-identified covariates*		
Unweighted	319 (72.2)	94 (21.3)
Candidate Model 1	394 (89.1)	250 (56.6)
Candidate Model 2	411 (93.0)	301 (68.1)
Candidate Model 3	422 (95.5)	319 (72.2)
Candidate Model 4	411 (93.0)	266 (60.2)
Candidate Model 5	415 (93.9)	278 (62.9)
Candidate Model 6	409 (92.5)	280 (63.3)
SL-hdPS	428 (96.8)	330 (74.7)
Pre-specified covariates only†		
Unweighted	16 (55.2)	5 (17.2)
Candidate Model 1	28 (96.6)	27 (93.1)
Candidate Model 2	28 (96.6)	22 (75.9)
Candidate Model 3	28 (96.6)	22 (75.9)
Candidate Model 4	25 (86.2)	15 (51.7)
Candidate Model 5	25 (86.2)	12 (41.3)
Candidate Model 6	25 (86.2)	13 (44.8)
SL-hdPS	28 (96.6)	26 (89.7)
Empirically-identified covariates only‡		
Unweighted	303 (73.4)	89 (21.5)
Candidate Model 1	366 (88.6)	223 (54.0)
Candidate Model 2	383 (92.7)	279 (67.6)
Candidate Model 3	394 (95.4)	297 (71.9)
Candidate Model 4	386 (93.5)	251 (60.8)
Candidate Model 5	390 (94.4)	266 (64.4)
Candidate Model 6	384 (93.0)	267 (64.6)
SL-hdPS	400 (96.9)	304 (73.6)

ASD = absolute standardized difference; SL-hdPS = SuperLearner-high-dimensional propensity score

* Percentage out of 442 total covariates (29 pre-specified and 413 empirically-identified)
† Percentage out of 29 pre-specified covariates
‡ Percentage out of 413 empirically-identified covariates

Candidate Model 1: 29 pre-specified + 25 empirically-identified covariates
Candidate Model 2: 29 pre-specified + 100 empirically-identified covariates
Candidate Model 3: 29 pre-specified + 200 empirically-identified covariates
Candidate Model 4: 29 pre-specified + 300 empirically-identified covariates
Candidate Model 5: 29 pre-specified + 400 empirically-identified covariates
Candidate Model 6: 29 pre-specified + 413 empirically-identified covariates

Table 29. Covariate balance in Cohort 2.

Model	Covariates Balanced at ASD Threshold (%)	
	ASD <0.10	ASD <0.05
Pre-specified + empirically-identified covariates*		
Unweighted	46 (19.7)	7 (3.0)
Candidate Model 1	97 (41.6)	35 (15.0)
Candidate Model 2	118 (50.6)	83 (35.6)
Candidate Model 3	117 (50.2)	87 (37.3)
Candidate Model 4	124 (53.2)	113 (48.5)
Candidate Model 5	111 (47.6)	62 (26.6)
Candidate Model 6	184 (79.0)	140 (60.1)
SL-hdPS	87 (37.3)	16 (6.9)
Pre-specified covariates only†		
Unweighted	17 (51.5)	7 (21.2)
Candidate Model 1	32 (89.1)	23 (56.6)
Candidate Model 2	2 (6.1)	1 (3.0)
Candidate Model 3	4 (12.1)	1 (3.0)
Candidate Model 4	2 (6.1)	0 (0.0)
Candidate Model 5	1 (3.0)	0 (0.0)
Candidate Model 6	6 (18.2)	3 (9.1)
SL-hdPS	17 (51.5)	8 (24.2)
Empirically-identified covariates only‡		
Unweighted	29 (14.5)	0 (0.0)
Candidate Model 1	65 (32.5)	12 (6.0)
Candidate Model 2	116 (58.0)	82 (41.0)
Candidate Model 3	113 (56.5)	86 (43.0)
Candidate Model 4	122 (61.0)	113 (56.5)
Candidate Model 5	110 (55.0)	62 (31.0)
Candidate Model 6	178 (89.0)	137 (68.5)
SL-hdPS	70 (35.0)	8 (4.0)

ASD = absolute standardized difference; SL-hdPS = SuperLearner-high-dimensional propensity score

* Percentage out of 233 total covariates (33 pre-specified and 200 empirically-identified)
† Percentage out of 33 pre-specified covariates
‡ Percentage out of 200 empirically-identified covariates

Candidate Model 1: 33 pre-specified covariates
Candidate Model 2: 33 pre-specified + 25 empirically-identified covariates
Candidate Model 3: 33 pre-specified + 50 empirically-identified covariates
Candidate Model 4: 33 pre-specified + 100 empirically-identified covariates
Candidate Model 5: 33 pre-specified + 150 empirically-identified covariates
Candidate Model 6: 33 pre-specified + 200 empirically-identified covariates

Table 30. Treatment effect estimates for Cohort 1.

Model	Hazard Ratio (95% Confidence Interval)	Ln[Hazard Ratio (95% Confidence Interval)]	95% Confidence Interval Width*
Major Bleeding			
Candidate Model 1	1.13 (0.46 – 2.77)	0.12 (-0.77 – 1.02)	1.79
Candidate Model 2	1.41 (0.60 – 3.32)	0.34 (-0.51 – 1.20)	1.71
Candidate Model 3	1.70 (0.69 – 4.12)	0.53 (-0.37 – 1.42)	1.79
Candidate Model 4	1.62 (0.67 – 3.92)	0.48 (-0.40 – 1.37)	1.77
Candidate Model 5	1.93 (0.81 – 4.60)	0.66 (-0.21 – 1.53)	1.74
Candidate Model 6	1.90 (0.78 – 4.58)	0.64 (-0.25 – 1.52)	1.77
SL-hdPS	1.41 (0.60 – 3.32)	0.34 (-0.51 – 1.20)	1.71
Clinically-relevant Bleeding			
Candidate Model 1	1.63 (0.81 – 3.29)	0.49 (-0.21 – 1.19)	1.40
Candidate Model 2	2.15 (1.04 – 4.45)	0.77 (0.04 – 1.49)	1.45
Candidate Model 3	2.48 (1.22 – 5.02)	0.91 (0.20 – 1.61)	1.41
Candidate Model 4	2.43 (1.17 – 5.04)	0.89 (0.16 – 1.62)	1.46
Candidate Model 5	2.82 (1.44 – 5.55)	1.04 (0.36 – 1.71)	1.35
Candidate Model 6	2.77 (1.40 – 5.48)	1.02 (0.34 – 1.70)	1.36
SL-hdPS	2.06 (1.04 – 4.09)	0.72 (0.04 – 1.41)	1.37

SL-hdPS = SuperLearner-high-dimensional propensity score

* Based on Ln[Hazard Ratio (95% Confidence Interval)]

Candidate Model 1: pre-specified + 25 empirically-identified covariates
Candidate Model 2: pre-specified + 100 empirically-identified covariates
Candidate Model 3: pre-specified + 200 empirically-identified covariates
Candidate Model 4: pre-specified + 300 empirically-identified covariates
Candidate Model 5: pre-specified + 400 empirically-identified covariates
Candidate Model 6: pre-specified + 413 empirically-identified covariates

Figure 10. Propensity score distribution for candidate models in Cohort 1. Models included 29 pre-specified and A) 25 B) 100 C) 200 D) 300 E) 400 F) 413 empirically-identified covariates.

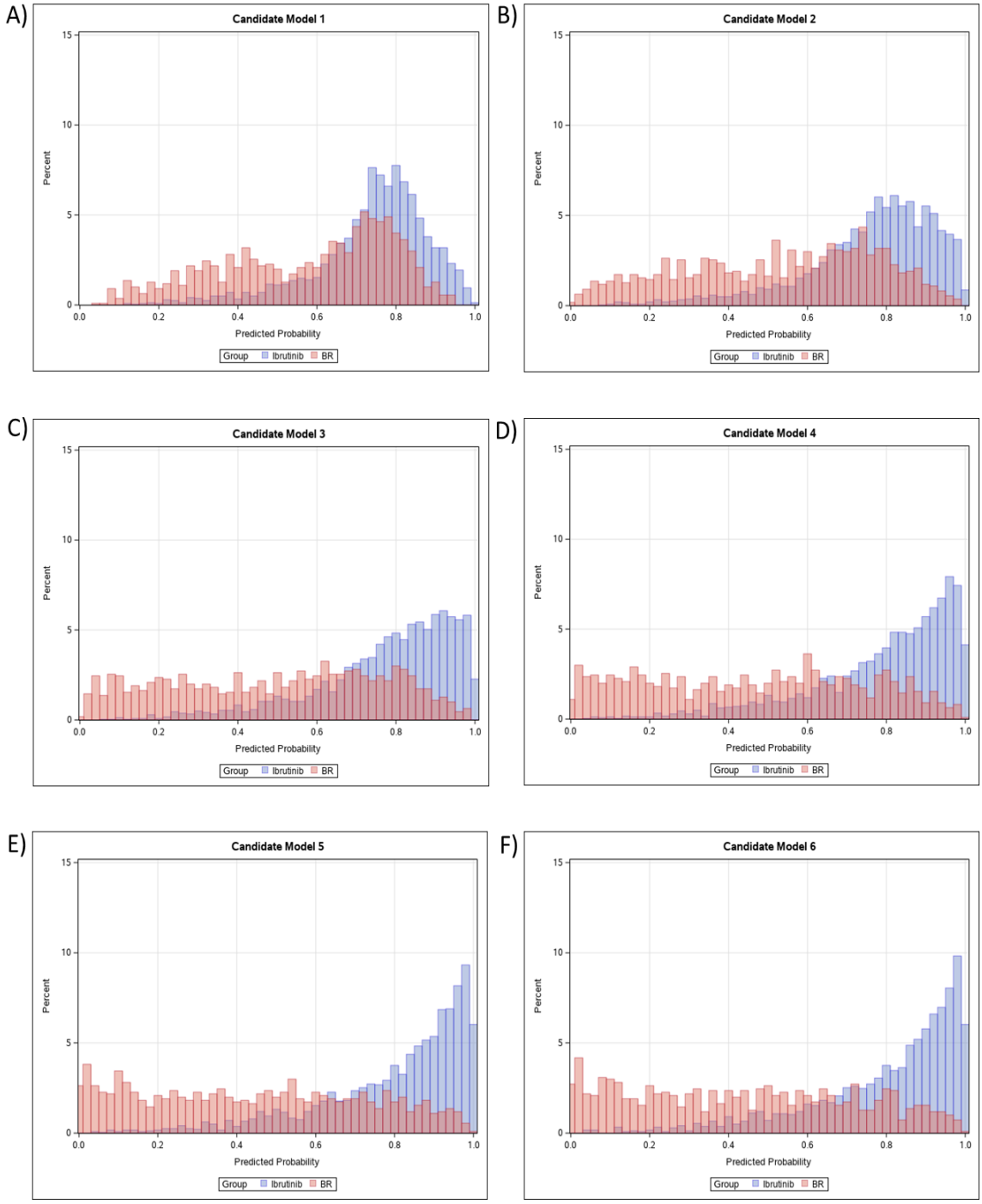


Figure 11. Propensity score distribution for SL-hdPS in Cohort 1.

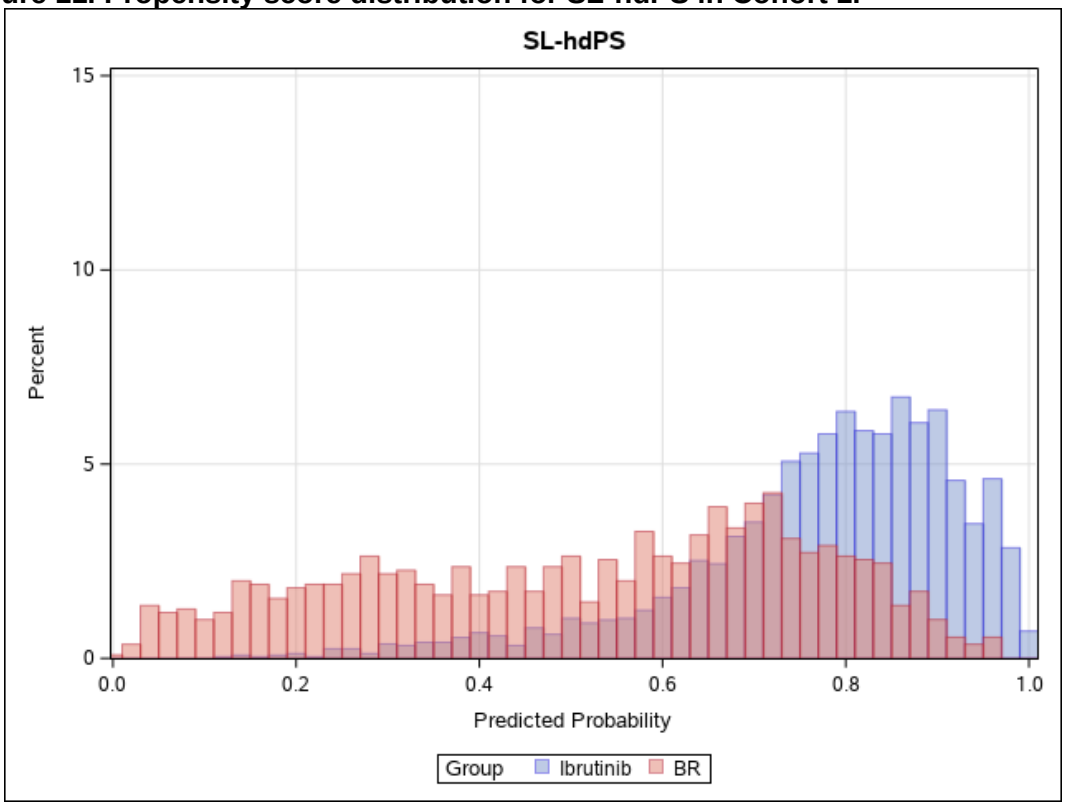


Figure 12. Propensity score distribution for candidate models in Cohort 2. Models included 33 pre-specified and A) 0 B) 25 C) 50 D) 100 E) 150 F) 200 empirically-identified covariates.

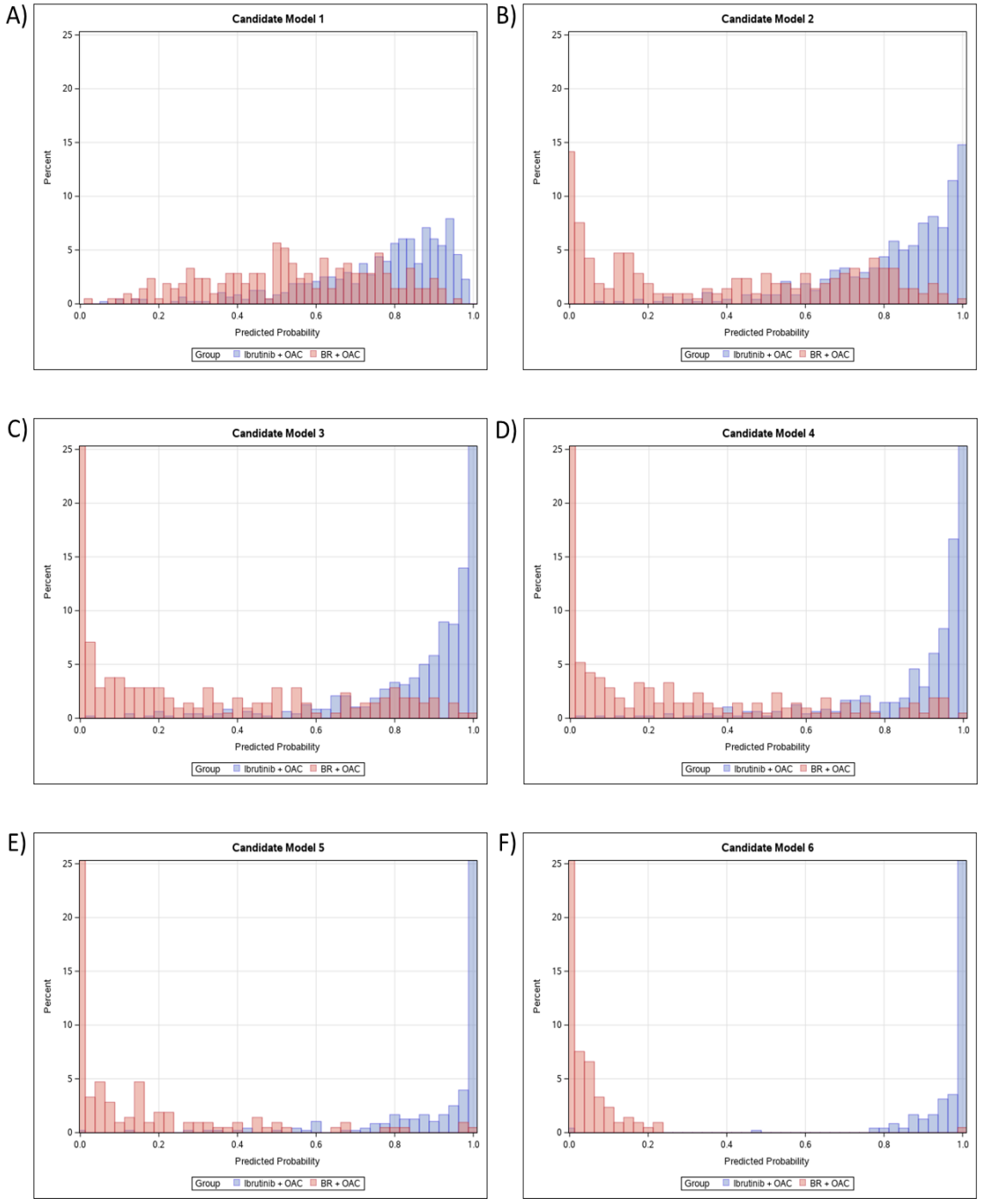
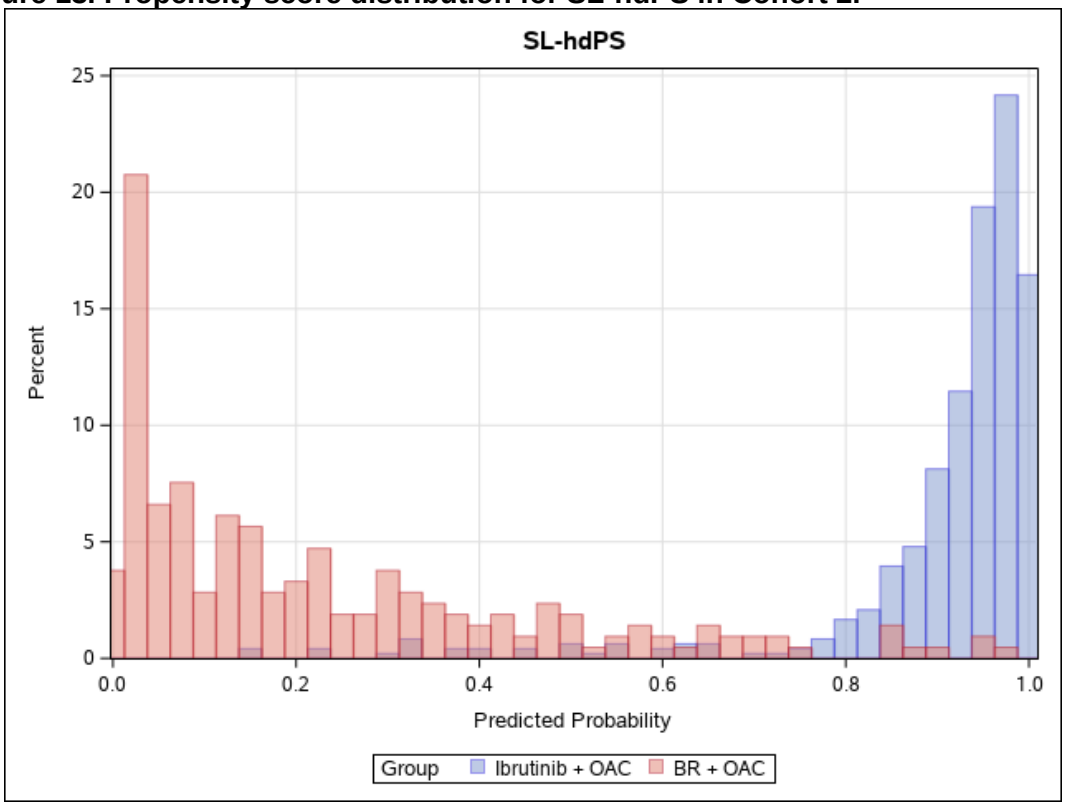


Figure 13. Propensity score distribution for SL-hdPS in Cohort 2.



CHAPTER 5 – SUMMARY AND FUTURE DIRECTIONS

Summary

In this dissertation, we assessed rates of bleeding with ibrutinib versus BR in real-world populations of individuals not concomitantly exposed to OACs and individuals concomitantly exposed to OACs. We also evaluated the performance of a novel SL-hdPS approach in comparison to hdPS alone in the applied small sample setting using the cohorts described in Chapters 2 and 3.

In Chapter 2, we conducted an incident-user, active comparator retrospective cohort study to compare incidence rates of major and clinically-relevant bleeding between ibrutinib-treated and BR-treated individuals diagnosed with CLL. We found that the rate of major bleeding with ibrutinib (3.1 per 100 p-y, 95% CI: 2.0 – 4.7) in a real-world population was similar to the rate of major bleeding reported in clinical trial populations.[11,36] Our adjusted major bleeding outcome analysis found an elevated, yet consistent with the null, rate of major bleeding with ibrutinib compared to BR (sIPTW-adjusted HR: 1.61, 95% CI: 0.67 – 3.84). Given the wide 95% CI which is consistent with the null, a lack of a difference cannot be excluded. We found an elevated and statistically-significant rate of clinically-relevant bleeding with ibrutinib compared to BR (sIPTW-adjusted HR: 2.66, 95% CI: 1.29 – 5.49).

In Chapter 3, we conducted a retrospective cohort study to compare incidence rates of major, clinically-relevant, and provider-diagnosed bleeding between ibrutinib + OAC-treated and BR + OAC-treated individuals diagnosed with CLL, MCL, or MZL. Although we were unable to estimate HRs for major and clinically-relevant bleeding

because of low event counts, our post-hoc outcome analysis found an elevated rate of provider-diagnosed bleeding with ibrutinib + OAC compared to BR + OAC (sIPTW-adjusted HR 2.70, 95% CI 1.25 – 5.82). A pre-specified subgroup analysis revealed a possible differential effect by OAC type, with a notably higher provider-diagnosed bleeding HR (7.33, 95% CI 2.11 – 25.48) among warfarin-treated individuals. Finally, we found that crude incidence rates of major and clinically-relevant bleeding were four times as high in individuals treated with ibrutinib + OAC compared to individuals treated with ibrutinib alone in Chapter 2.

In investigating the aims described in Chapters 2 and 3, we provided results that fill an important knowledge gap in ibrutinib-related bleeding in patients not concomitantly treated with OACs and patients concomitantly treated with OACs. We chose to analyze these populations separately because of the multimorbidity of (and thus presence of medical conditions treated with OACs in) and frequent occurrence of new-onset atrial fibrillation in ibrutinib-treated patients. Therefore, evidence on ibrutinib-related bleeding in the separate populations may inform a benefit-harm balance with ibrutinib versus other therapies that is tailored to these two types of patients. Additionally, analyzing a patient population concomitantly treated with OACs allowed for a secondary analysis that explored a possible differential bleeding effect by type of OAC, which may help inform OAC choice when oral anticoagulation is necessary for a patient on ibrutinib. Overall, we hope that findings from these studies are useful in better tailoring cancer therapy to reduce harm in patients with B-cell malignancies.

In Chapter 4, we compared the performance of SL-hdPS with hdPS alone in the applied setting using the cohorts described in Chapters 2 and 3. In Cohort 1 (users of ibrutinib or BR; described in Chapter 2), we found that including more than 200 empirically-identified covariates resulted in overfitting of the propensity score model and

fewer covariates balanced at ASD thresholds of <0.10 and 0.05. SL-hdPS seemed to reduce overfitting and maximized covariate balance compared to the separate hdPS candidate models included in the ensemble. In Cohort 2 (users of ibrutinib + OAC or BR + OAC; described in Chapter 3), which had a smaller sample size than Cohort 1, SL-hdPS showed signs of severe overfitting and produced fewer balanced covariates compared to the candidate models included in the ensemble. These findings in the applied setting combined with prior findings in the simulated setting[53] suggest that SL can assist researchers in avoiding overfitting issues with hdPS, resulting in optimal covariate balance. However, additional covariate screening or dimension reduction may be needed before implementing SL-hdPS for studies with small sample sizes.

Historically, hdPS has been used in studies of chronic diseases with large sample sizes (10,000 – 600,000 patients),[45,50,94-96] which likely did not have issues with severe propensity score overfitting. However, as the conduct of real-world evidence research increases in the oncology therapeutic area,[97-100] in which disease prevalence is generally lower than of more common chronic diseases, researchers choosing to use hdPS may encounter propensity score overfitting issues more frequently. Thus, methods to improve the performance of hdPS in studies with smaller sample sizes are needed. We found that combining SL with hdPS can help researchers prevent propensity score overfitting and improve covariate balance among pre-specified and empirically-identified covariates in the setting of a small sample size (3,525 individuals). We hope that this work contributes to the variety of semi-automated methods used to improve the quality of real-world evidence research in the oncology field and spurs further research on the challenges faced when implementing hdPS in studies with exceptionally small sample sizes, as we encountered in Cohort 2 (692 individuals).

Future Directions

The results presented in Chapters 2 and 3 of this dissertation provide valuable information about real-world bleeding with ibrutinib, a first-in-class BTK inhibitor. In Chapter 2, we compared rates of bleeding with ibrutinib versus BR, a chemoimmunotherapeutic regimen commonly used in CLL. However, the use of other therapies may become more common in the future. In the last several years, acalabrutinib and zanubrutinib, second-generation BTK inhibitors, have been approved for use in certain B-cell malignancies. Specifically, acalabrutinib is indicated for both first-line and relapsed/refractory CLL[30] and relapsed/refractory MCL, and zanubrutinib is indicated for relapsed/refractory MCL and relapsed/refractory MZL.[31] Mechanistically, these agents bind more selectively to cysteine 481 in the kinase domain[101] and are expected to have fewer 'off-target' effects compared to ibrutinib, potentially resulting in fewer adverse effects. In fact, recently published data from a head-to-head clinical trial of previously-treated CLL patients showed acalabrutinib to be noninferior to ibrutinib in terms of median PFS—with fewer bleeding events and a comparable number of major bleeding events.[102] Additionally, an interim analysis of a clinical trial comparing zanubrutinib with ibrutinib found zanubrutinib to be superior to ibrutinib in terms of overall response rate, with fewer major bleeding events.[103] As use of these agents begins to increase and the use of chemoimmuntherapeutic regimens decreases, studies will be needed to directly compare real-world rates of bleeding with ibrutinib versus newer BTK inhibitors to determine if comparative bleeding rates differ from clinical trials. In the study described in Chapter 2, we considered using acalabrutinib as the comparator, but the sample size of second-generation BTK inhibitor users is currently limited in databases like Optum Clinformatics. Conducting such a study once uptake of these agents rises

would provide a clinically informative comparison moving forward, which may help clinicians in selecting a therapy among BTK inhibitors.

In Chapter 3, we compared bleeding rates with concomitant ibrutinib and OAC use versus concomitant BR and OAC use. As previously mentioned, a future study using concomitant second-generation BTK inhibitor and OAC use as the comparison group would provide a clinical contrast that may be more relevant to future CLL, MCL, and MZL treatment strategies. Additionally, we conducted a secondary analysis in subgroups of DOAC users and warfarin users and found that the rate of provider-diagnosed bleeding may be markedly higher with concomitant ibrutinib and warfarin treatment; a study investigating bleeding rates among individual OACs (rather than DOACs vs. warfarin) in ibrutinib-treated patients may further help clinicians with choice of OAC if anticoagulation is necessary for a patient on ibrutinib therapy.

As previously mentioned, the mechanism of ibrutinib-related bleeding stems from unique antiplatelet effects through glycoprotein VI inhibition. A population-based study investigating the rates of thrombotic events in ibrutinib and other BTK inhibitors compared to alternative therapies may yield interesting findings—especially in individuals who require anticoagulation therapy. However, literature has suggested low rates of thrombotic events with ibrutinib;[104] thus, this there may be challenges in detecting a difference in effect. In addition to antiplatelet effects, ibrutinib may be associated with other cardiovascular toxicities including atrial fibrillation, hypertension, sudden cardiac arrest/ventricular arrhythmias, and heart failure. Prior literature has reported on ibrutinib-related atrial fibrillation[34] and hypertension,[105] but data on sudden cardiac death/ventricular arrhythmias and heart failure are limited.[106] Studies examining these outcomes using methods similar to those described in this dissertation may be useful in filling this knowledge gap.

In Chapter 4, we assessed the performance of SL-hdPS using two real-world cohorts. As mentioned in the limitations, the benefit of the approach may vary depending on study characteristics, namely sample size. Since SL-hdPS aims to prevent overfitting of the hdPS model, it may have the most benefit in studies with a small sample size. Future studies should assess the utility of the approach in the applied setting with larger sample sizes, as the benefit in such scenarios is unclear. We found that SL-hdPS did not perform well using Cohort 2, which included only 692 individuals. For studies with small sample sizes, it may be worthwhile to explore the application of additional covariate screening (e.g., LASSO or ridge regression) or dimension reduction (principal component analysis) procedures to candidate hdPS models prior to inclusion into SL.[92] However, it is worth noting that the large number of covariates identified by hdPS is hypothesized to be a proxy for overall health status, and therefore for unmeasured potential confounders.[45] If only a handful of empirically-identified covariates are included in SL after covariate selection procedures are applied, then this hypothesis may no longer apply. Finally, all of the candidate models that were included in SL were logistic regression models. SL has the benefit of not only including multiple models with a different number of covariates, but also different types of models. It has generally been recommended to be generous with the number and types of models included in the SL ensemble for increased flexibility.[54] For example, machine learning algorithms like classification and regression trees, random forest, and neural networks can be included in the ensemble in addition to logistic regression. Studies that explored machine learning techniques for propensity score estimation have shown promising results,[107,108] thus inclusion of such models in the SL-hdPS ensemble may improve performance.

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