Bleeding and recurrent VTE with apixaban vs warfarin as outpatient treatment: time-course and subgroup analyses

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Key Points

• This study extends research on effectiveness/safety of apixaban (vs warfarin) by comparing outcomes over time and within subgroups.

• Across all analyses, risks of outcomes were lower with apixaban (vs warfarin), consistent with previously published research.

In the phase 3 trial Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy, apixaban was noninferior to enoxaparin, overlapped and followed by warfarin, in the treatment of venous thromboembolism (VTE) with significantly less bleeding; in a real-world evaluation, risks for bleeding and recurrent VTE were lower with apixaban vs warfarin plus parenteral anticoagulant (PAC) bridge therapy. The present study extends this research by comparing outcomes over time and within selected subgroups. A retrospective observational cohort design and 4 US private health care claims databases were used. Study population included patients who initiated outpatient treatment with apixaban or warfarin (plus PAC bridge therapy) for VTE. Major bleeding, clinically relevant nonmajor (CRNM) bleeding, and recurrent VTE were compared during the 180-day follow-up period, at selected follow-up time points (days 21, 90, 180), and within subgroups (pulmonary embolism [PE] with or without deep vein thrombosis [DVT], DVT only, provoked VTE, unprovoked VTE) using multivariable shared frailty models. Study population consisted of 20,561 apixaban patients and 35,080 warfarin patients; baseline characteristics were comparable. Overall, at selected follow-up time points, and within the aforementioned subgroups, adjusted risks were lower among apixaban vs warfarin patients: major bleeding, by 27% to 39%, CRNM bleeding, by 17% to 28%, and recurrent VTE, by 25% to 39% (all P < .01). In this real-world study of VTE patients, risks of bleeding and recurrent VTE were lower among apixaban (vs warfarin) patients during the 180-day follow-up period, at selected follow-up time points, and within subgroups defined by index VTE episode.

Introduction

In the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial, the efficacy and safety of apixaban, a direct-acting non–vitamin K antagonist, was compared with enoxaparin, overlapped and followed by warfarin, in the treatment of acute symptomatic venous thromboembolism (VTE).1 Apixaban was found to be noninferior to enoxaparin, overlapped and followed by warfarin, in terms of recurrent symptomatic VTE or VTE-related death, and it was associated with significantly less major bleeding and clinically relevant nonmajor (CRNM) bleeding. Similar findings were reported for prespecified subgroup analyses in AMPLIFY.
including patients with pulmonary embolism with or without deep vein thrombosis (PE ± DVT) and patients with deep vein thrombosis (DVT) only, as well as in a post hoc evaluation of risks at prespecified time points during the 6-month follow-up period.1,2 However, evidence from randomized controlled clinical trials may not reflect clinical practice; patients and their treatment may vary substantially from those in the trial setting.

To address this evidence gap, a retrospective study using data from 4 US private health care claims databases was recently undertaken to evaluate the effectiveness and safety of apixaban compared with warfarin plus parenteral anticoagulant (PAC) bridging therapy for the outpatient treatment of VTE in clinical practice in the United States.3 In this real-world study of nearly 36,000 matched patients, the risks of major bleeding, CRNM bleeding, and recurrent VTE were reported to be significantly lower (by 20%-25%) among patients receiving apixaban vs warfarin, and these results were found to be robust when using alternative study designs and data sources. Although subject to the uncontrolled settings of clinical practice, these real-world findings from a broad population of VTE patients are generally consistent with, and supplement, those from the AMPLIFY trial.

Notwithstanding findings from analyses of the overall VTE population, the risks of bleeding and recurrent VTE may not be proportional over time, and such risks may also vary across subgroups defined on the basis of important characteristics (eg, PE ± DVT vs DVT only, provoked vs unprovoked VTE). For these reasons, a follow-up evaluation was undertaken to compare the time-course of outcomes between VTE patients receiving outpatient treatment with apixaban vs warfarin, as well as to compare outcomes between apixaban patients and warfarin patients within specific subgroups, using the same 4 United States private health care claims databases.

Materials and methods
Study design and data sources
This study used a retrospective observational cohort design and data from 4 large integrated US private health care claims databases: the Truven Health Analytics’ MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases (the “MarketScan database”), the IMS LifeLink PharMetrics Plus Health Plan Claims Database (the “PharMetrics database”), the Optum Clinformatics Claims Database (the “Optum database”), and the Humana Medical, Lab, and Pharmacy Claims Database (the “Humana database”). ClinicalTrials.gov Identifier: NCT03521908). Patient-level data from the 4 databases spanned 1 March 2014 through 30 June 2017 and were pooled for analyses. Additional details on study methods and data sources, as well as the operational algorithms/codes that were used to define study variables, were published previously.3

Study population
The study population consisted of patients aged ≥18 years who, following a VTE event between 1 September 2014 (US Food and Drug Administration approval date for the use of apixaban in the treatment of VTE) and 30 June 2017 (end of study databases), received outpatient treatment with apixaban or warfarin. VTE was identified based on acute-care inpatient or outpatient (eg, emergency department, physician office) encounters with a diagnosis code for lower extremity DVT or pulmonary embolism (PE) in any position.
Table 1. Characteristics of patients receiving apixaban or warfarin as outpatient therapy for VTE

| Overall | Subgroups | Provoked Unprovoked | DVT only | PE ± DVT |
|---------|-----------|---------------------|----------|----------|
|         | Apixaban (n = 20,561) | Warfarin (n = 35,080) | Apixaban (n = 4,894) | Warfarin (n = 8,585) | Apixaban (n = 15,687) | Warfarin (n = 26,495) | Apixaban (n = 12,294) | Warfarin (n = 19,720) | Apixaban (n = 8,267) | Warfarin (n = 15,360) | P |
| Setting | Acute-care inpatient | 47.6 | 70.8 | <.001 | 47.3 | 71.4 | <.001 | 47.7 | 70.5 | <.001 | 29.3 | 55.8 | <.001 | 74.9 | 90.0 | <.001 |
|         | Ambulatory care | 52.4 | 29.2 | — | 52.7 | 28.6 | — | 52.3 | 29.5 | — | 70.7 | 44.2 | — | 25.1 | 10.0 | — |
| Diagnosis | PE ± DVT | 40.2 | 43.8 | <.001 | 36.4 | 40.7 | <.001 | 41.4 | 44.8 | <.001 | — | — | — | 100.0 | 100.0 | — |
|         | PE with DVT | 21.5 | 22.2 | .170 | 19.4 | 20.7 | .275 | 22.0 | 22.7 | .301 | — | — | — | 21.5 | 22.2 | .170 |
|         | PE without DVT | 78.5 | 77.8 | — | 80.6 | 79.3 | — | 78.0 | 77.3 | — | — | — | — | 78.5 | 77.8 |
|         | DVT only | 59.8 | 56.2 | — | 63.6 | 59.3 | — | 58.6 | 55.2 | — | 100.0 | 100.0 | — | — | — |
| Presumed etiology | Provoked | 23.8 | 24.5 | .075 | 100.0 | 100.0 | — | — | — | — | 25.3 | 25.8 | .335 | 21.5 | 22.7 | .031 |
|         | Unprovoked | 76.2 | 75.5 | — | — | — | — | 100.0 | 100.0 | — | 74.7 | 74.2 | — | 78.5 | 77.3 |
| Patient | Age, y | Mean (SD) | 60.2 (16.4) | 60.5 (16.5) | .065 | 57.6 (17.7) | 57.2 (17.7) | .260 | 61.1 (15.9) | 61.6 (15.9) | .002 | 60.2 (16.6) | 60.2 (16.7) | .958 | 60.3 (16.1) | 60.9 (16.2) | .008 |
|         | Median | 60 | 60 | — | 58 | 58 | — | 61 | 61 | — | 60 | 60 | — | 61 | 61 | — |
|         | Age, % | 18-49 y | 24.7 | 24.5 | <.001 | 31.7 | 32.5 | .223 | 22.5 | 22.0 | <.001 | 24.9 | 25.7 | <.001 | 24.5 | 23.0 | .001 |
|         | 50-64 y | 37.6 | 36.0 | — | 35.0 | 34.0 | — | 38.4 | 36.6 | — | 37.9 | 35.9 | — | 37.2 | 36.2 |
|         | 65-74 y | 17.6 | 18.2 | — | 15.0 | 15.9 | — | 18.4 | 19.0 | — | 17.3 | 17.2 | — | 18.0 | 19.6 |
|         | ≥75 y | 20.1 | 21.2 | — | 18.3 | 17.5 | — | 20.6 | 22.4 | — | 20.0 | 21.3 | — | 20.3 | 21.2 |
|         | Sex, % | Male | 51.5 | 50.9 | .192 | 36.5 | 38.2 | .050 | 56.2 | 55.0 | .036 | 52.5 | 52.5 | .448 | 49.9% | 48.9% | .114 |
|         | Female | 48.5 | 49.1 | — | 63.5 | 61.8 | — | 43.8 | 45.0 | — | 47.5 | 47.5 | — | 50.1% | 51.1% |
|         | Deyo-Charlson Comorbidity Index,22 mean (SD) | 1.0 (1.7) | 1.2 (1.8) | <.001 | 1.3 (1.9) | 1.4 (2.0) | .004 | 0.9 (1.6) | 1.1 (1.7) | <.001 | 1.1 (1.7) | 1.3 (1.9) | <.001 | 1.0 (1.6) | 1.1 (1.7) | <.001 |
CRNM bleeding was defined as an acute-care inpatient admission with a secondary diagnosis code or an ambulatory-care encounter with a diagnosis code (any position) for gastrointestinal bleeding or other noncritical care types/sites of bleeding. Events that met the definitions for major bleeding and CRNM bleeding were classified as major bleeding; CRNM bleeding events that followed major bleeding events were not considered in analyses of CRNM bleeding. Recurrent VTE was defined as an acute-care inpatient admission with a corresponding principal or first-listed diagnosis code that occurred 7 days after the index VTE encounter (service date, if outpatient VTE; discharge date, if inpatient VTE).

**Patient characteristics**

Patient characteristics were ascertained based on information available during the 6-month period ending on the date of the first receipt of index therapy and included age, sex, comorbidity profile, selected surgeries, and outpatient pharmacotherapy. Characteristics of the index VTE encounter, including VTE care setting (acute-care inpatient vs ambulatory care only), VTE diagnosis (PE ± DVT vs DVT only), and presumed VTE etiology (provoked vs unprovoked), were also ascertained.

**Statistical analyses**

Risks of major bleeding, CRNM bleeding, and recurrent VTE were compared between patients who received apixaban vs warfarin using shared frailty models (an extension of the Cox proportional hazards model that adjusts for intracluster [ie, intradatabase] correlation), with adjustment of estimated hazard ratios (HRs) for systematic differences between treatment groups in their baseline characteristics. Patients who did not experience the outcome of interest were censored as of the end of their follow-up period, as defined above. Patients who experienced a major bleeding event at any time during their follow-up period were excluded from analyses of CRNM bleeding events. Baseline characteristics were selected for inclusion in multivariate models using a stepwise selection method (variable entry/retention criterion; P < .10). The presence of multicollinearity and hazards assumptions were evaluated using published methods. Analyses were conducted (1) considering all patients in the study population and using all available follow-up, (2) considering only patients remaining "at risk" as of selected time points (ie, days 21, 90, and 180) and truncating follow-up at those time points, and (3) considering subgroups defined on index VTE diagnosis and presumed VTE etiology. Missing data were not imputed; only observed data were used in characterizing study variables. All statistical tests were 2 sided and were performed at a significance level of α = 0.05.

**Results**

**Patient characteristics**

Approximately 1.4 million adult patients had a diagnosis of VTE between September 2014 and June 2017; among these patients, 285 042 (21%) had ≥1 filled prescription for apixaban (n = 48 239) or warfarin (n = 236 803) during the 30-day period following their
Among the 285,042 patients, 55,641 patients (apixaban, n = 20,561; warfarin, n = 35,080) met all remaining selection criteria and were included in the study population. Apixaban patients and warfarin patients were comparable in terms of age (mean [standard deviation; SD]: 60 [16] vs 61 [17] years), sex (male: 52% vs 51%), index VTE diagnosis (DVT only: 60% vs 56%); comorbidity profiles, surgical history, and use of outpatient pharmacotherapy were also largely comparable (Table 1). A higher percentage of warfarin patients required hospitalization for their qualifying VTE encounter (71% vs 48% for apixaban). Characteristics of apixaban patients and warfarin patients within subgroups defined on their index VTE diagnosis and presumed index VTE etiology were largely comparable to the overall population of apixaban patients and warfarin patients, respectively, with a few exceptions (eg, VTE care setting, sex). A complete reporting of all baseline characteristics for the overall study population and subgroups of interest is available in supplemental Tables 2 and 3.

Use of index and other therapies

For apixaban patients, overall and across subgroups, the mean duration of follow-up ranged from 149 to 152 days, the mean number of filled outpatient prescriptions ranged from 4.0 to 4.5, and the mean number of therapy days ranged from 108 to 121; >90% of prescriptions were for the 5 mg tablet (supplemental Tables 4 and 5). For warfarin patients, mean duration of follow-up ranged from 142 to 143 days, the mean number of filled outpatient prescriptions ranged from 4.0 to 4.5, and the mean number of therapy days ranged from 108 to 121; 90% of prescriptions were for the 5 mg tablet (supplemental Tables 4 and 5). For CRNM bleeding, adjusted HRs for apixaban (vs warfarin) were: 0.77 (95% CI, 0.72-0.82) on an overall basis; 0.72 (95% CI, 0.65-0.81) at day 21, 0.75 (95% CI, 0.69-0.81) at day 90, and 0.70 (95% CI, 0.67-0.74) at day 180; and ranged from 0.70 (95% CI, 0.67-0.74) to 0.73 (95% CI, 0.69-0.79) across subgroups. For recurrent VTE, adjusted HRs for apixaban (vs warfarin) were: 0.75 (95% CI, 0.70-0.81) on an overall basis; 0.61 (95% CI, 0.50-0.73) at day 90, and 0.67 (95% CI, 0.62-0.72) at day 180; and ranged from 0.65 (95% CI, 0.60-0.70) to 0.70 (95% CI, 0.65-0.75) across subgroups of interest (ie, PE ± DVT only, provoked vs unprovoked VTE).
Discussion

Findings from the AMPLIFY clinical trial demonstrated the efficacy and safety of apixaban (vs enoxaparin overlapped and followed by warfarin) for the treatment of acute symptomatic VTE, and these findings were supplemented by a post hoc time-course analysis and prespecified subgroup analyses.1,2 Findings from a recent real-world retrospective observational study provided evidence on the effectiveness and safety of apixaban (vs warfarin plus PAC bridge therapy) for the outpatient treatment of VTE in US clinical practice.3 The findings from the present study supplement the evidence base for apixaban, providing additional real-world comparative data on the risks of bleeding and recurrent VTE at selected time points following therapy initiation, as well as within subgroups defined on important characteristics of the index VTE encounter.

In the AMPLIFY trial, apixaban was noninferior to enoxaparin, overlapped and followed by warfarin, in terms of recurrent symptomatic VTE or VTE-related death (relative risk [RR], 0.84; 95% CI, 0.60-1.18), with significantly less bleeding (major bleeding: RR, 0.44; 95% CI, 0.36-0.55; CRNM bleeding: RR, 0.48; 95% CI, 0.38-0.60).1 In subgroup analyses focusing on subjects with PE ± DVT and DVT only, the RRs of recurrent VTE/VTE-related death (PE ± DVT: RR, 0.90; 95% CI, 0.50-1.61; DVT only: RR, 0.83; 95% CI, 0.54-1.26) and major bleeding (PE ± DVT: RR, 0.16; 95% CI, 0.05-0.45; DVT only: RR, 0.47; 95% CI, 0.23-0.95) were similar to those based on the overall trial population.1 In the post hoc time-course analysis of outcomes at day 7, day 21, and day 90 of follow-up, RRs of recurrent VTE/VTE-related death ranged from 0.79 (95% CI, 0.43-1.46) to 0.83 (95% CI, 0.51-1.36) among subjects with documented outcome status on these days, and RRs of major bleeding ranged from 0.19 (95% CI, 0.06-0.45) to 0.29 (95% CI, 0.15-0.57) during study treatment among subjects with documented outcome status on these days.2 Notwithstanding differences in study designs and study populations, results from the present study are, in general, consistent with those from the AMPLIFY trial and suggest a better effectiveness and safety profile for apixaban vs warfarin in US clinical practice, among all such patients, during the initial and later periods of treatment, as well as within important subgroups.

Although the present study included data on nearly 56,000 VTE patients receiving outpatient treatment with apixaban or warfarin, analyses described herein are subject to the inherent limitations of retrospective observational studies using health care claims databases. Study results may be biased because of systematic differences in unobserved variables between apixaban patients and warfarin patients. For example, detailed information on inpatient drug utilization is not available in the study databases; thus, initial management of qualifying VTE events requiring inpatient care cannot be fully characterized. Differences in physician-level, practice-level, and plan-level prescribing and treatment patterns may also confound study results. Although information on drug dose and drug supply is available from outpatient pharmacy claims, we cannot determine from such data whether the dispensed drug was actually taken, when it was taken, or how much was taken. Because

| Subgroup | No. Patients | No. Events | % Evented | Risk per 100 PY | HR | 95% CI | P |
|----------|--------------|------------|-----------|----------------|----|--------|---|
| All Patients |            |            |           |                |    |        |   |
| Apixaban | 20,561       | 440        | 2.1%      | 5.5            | 0.72 | 0.65 - 0.81 | <.001 |
| Warfarin  | 35,080       | 1,218      | 3.5%      | 8.4            | --  | --     | -- |
| Time-Course Patients |            |            |           |                |    |        |   |
| Follow-Up = 21 Days |            |            |           |                |    |        |   |
| Apixaban | 19,686       | 118        | 0.6%      | 10.4           | 0.61 | 0.49 - 0.75 | <.001 |
| Warfarin  | 33,895       | 392        | 1.2%      | 20.1           | --  | --     | -- |
| Follow-Up = 90 Days |            |            |           |                |    |        |   |
| Apixaban | 16,022       | 237        | 1.5%      | 6.0            | 0.65 | 0.56 - 0.75 | <.001 |
| Warfarin  | 28,973       | 773        | 2.7%      | 10.8           | --  | --     | -- |
| Follow-Up = 180 Days |            |            |           |                |    |        |   |
| Apixaban | 12,496       | 247        | 2.0%      | 4.0            | 0.67 | 0.58 - 0.77 | <.001 |
| Warfarin  | 24,716       | 875        | 3.5%      | 7.2            | --  | --     | -- |

CI: confidence interval; DVT: deep vein thrombosis; HR: hazard ratio; PE: pulmonary embolism; PY: patient-year; VTE: venous thromboembolism

Figure 3. Adjusted HRs for recurrent VTE.
laboratory test results are not available in the study data sources, it was not possible to evaluate the quality of anticoagulation therapy with warfarin (eg, time in therapeutic range) or the relationship between warfarin dose management and study outcomes. Study data sources do not include complete mortality information; thus, death was not treated as a competing risk, which might have inflated the estimated risks of the outcomes of interest. However, we believe that any such bias is small and does not disproportionately impact one treatment group vs the other.6

Algorithms used for identifying study outcomes (ie, major bleeding, CRNM bleeding, and recurrent VTE) have not been formally validated; thus, their accuracy is unknown. We note that our definition of major bleeding was based on the one set forth by the International Society on Thrombosis and Haemostasis, which has been used in several large clinical trials and has also been used in previous studies.3,7-19 Our definition of recurrent VTE has also been used in previous studies,3,16-19 and our definition of CRNM bleeding events included those that did not qualify as major bleeding and those that did not involve International Society on Thrombosis and Haemostasis–defined critical care sites.3,20 Because of the high probability that hospitalizations with a principal/first-listed diagnosis of VTE that occurred within 7 days of an index encounter are not recurrent VTE events, such events were excluded from consideration. Because the study databases do not include detailed clinical information, index VTE diagnosis (PE ± DVT vs DVT only) and presumed index VTE etiology were based on recorded diagnosis, procedure, and/or drug codes; the veracity of these algorithms is unknown. In addition, given the fact that complete data capture for variables indicating the presence of acute and chronic conditions is impossible, because results of physical examinations and laboratory testing are not available in claims data, as well as the fact that histories may be left truncated, some patients’ comorbidity profiles may be misclassified.

Health plans that contribute claims and enrollment information to the study databases used in these analyses are different, but the possibility exists that a patient may be insured by >1 plan at a given time (eg, due to secondary insurance) and, thus, may be included in >1 plan (and database) at the same time. The extent of such overlap is believed to be low.21 A patient may also be included in >1 database, albeit during different time periods (eg, if they changed residences or insurance plans during the study period). Finally, because the study population consisted of patients who received health insurance from private US health plans, the study results may not be generalizable to all patients treated in clinical practice across the United States, including those with public health insurance (eg, Medicare, Medicaid), the uninsured, and those residing outside of the United States.

In conclusion, in this large real-world retrospective observational study of VTE patients receiving outpatient treatment with apixaban or warfarin, the risks of major bleeding, CRNM bleeding, and recurrent VTE were significantly and consistently lower among apixaban patients during the maximum 180-day follow-up period, at selected time points during the follow-up period, and within subgroups defined on the basis of index VTE diagnosis and presumed index VTE etiology. Additional research evaluating the comparative effectiveness and safety of apixaban and warfarin in other countries and in other populations (eg, Medicare) is warranted.

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Authorship

Conflict-of-interest disclosures: M.A., A.H., and D.W. are employed by PAI. G.D.W., L.R., and J.D.G. are employed by, and own stock in, BMS. T.L., X.L., and J.M. are employed by, and own stock in, Pfizer Inc. A.T.C. receives consultancies and honoraria from AbbVie, Aspen, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Boston Scientific, CSL Behring, Daiichi-Sankyo, Johnson and Johnson, Leo Pharma, ONO, Pfizer, and Portola.

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