Risk of hospitalised bleeding in comparisons of oral anticoagulant options for the primary treatment of venous thromboembolism

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Summary

Understanding of the comparative bleeding risks of oral anticoagulant (OAC) therapies for the primary treatment of venous thromboembolism (VTE) is limited. Therefore, among anticoagulant-naïve VTE patients, we conducted comparisons of apixaban, rivaroxaban and warfarin on the rate of hospitalised bleeding within 180 days of OAC initation. MarketScan databases for the time-period from 2011 to 2016 were used and, for each OAC comparison, new users were matched with up to five initiators of a different OAC. The final analysis included 83 985 VTE patients, who experienced 1944 hospitalised bleeding events. In multivariable-adjusted Cox regression models, rate of hospitalised bleeding was lower among new users of apixaban when compared to new users of rivaroxaban [hazard ratio (95% confidence interval) 0·58 (0·41–0·80)] or warfarin [0·68 (0·50–0·92)]. Overall, the hospitalised bleeding rate was similar when comparing new users of rivaroxaban to new users of warfarin [0·98 (0·68–1·11)], though there was some suggestion that rivaroxaban was associated with lower bleeding risk among younger individuals. Findings from this large real-world population concur with results from the randomised trial which found lower bleeding risk with apixaban *versus* warfarin and, for the first time, reveal a lower risk of bleeding in a comparison of apixaban *versus* rivaroxaban.

Keywords: venous thromboembolism, comparative effectiveness, oral anticoagulant, rivaroxaban, apixaban.

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), annually affects 10 million individuals globally (Raskob *et al*, 2014). Direct oral anticoagulants (DOACs), specifically dabigatran, rivaroxaban, apixaban and edoxaban (Schulman *et al*, 2009, 2014; Einstein Investigators, 2010; Einstein-PE Investigators, 2012, Agnelli *et al*, 2013; Buller *et al*, 2013) are now included – together with warfarin – as standards of care for VTE treatment in current guidelines (Kearon *et al*, 2016).

The first 3–6 months of anticoagulant treatment for VTE is generally viewed as active treatment of the initial thrombosis (primary treatment). In phase III randomised controlled trials (RCTs) of VTE primary treatment (Schulman *et al*, 2009, 2014; Einstein Investigators, 2010; Agnelli *et al*, 2013, Buller *et al*, 2013) the DOACs were each shown to be non-

inferior to warfarin in the prevention of recurrent VTE and VTE-related death. In addition, in meta-analyses of the phase III RCTs (van Es *et al*, 2014; Gómez-Outes *et al*, 2014) DOACs have had a lower risk of most bleeding complications when compared to warfarin. However, no randomised study has conducted comparisons between the DOACs and bleeding risk in the context of VTE treatment. Furthermore, despite the promising results from RCTs, whether DOACs are as effective and safe when used in the general VTE patient population as in clinical trials is unknown. Although RCTs are considered the gold standard for evaluating the efficacy of new drugs, they generally do not conduct direct comparisons of novel treatments, but instead compare novel treatments to established therapies, and have important limitations. They recruit selected (possibly nongeneralisable)

patients, their size usually does not allow for the detection of infrequent adverse effects or the evaluation of patient subgroups, and results might not reflect the effectiveness of a new treatment in usual practice (Basu, 2012; Kunz *et al*, 2012). For instance, concerns have been raised about use of DOACs among patients with kidney disease, because impaired renal function may lead to DOAC accumulation and increased bleeding risk (Lega *et al*, 2014). Compliance to DOACs in real-world settings may also be poorer than typically exhibited among RCT participants (Tsai *et al*, 2013; Shore *et al*, 2014, 2015; Garkina *et al*, 2016; Manzoor *et al*, 2017). Furthermore, no VTE RCTs have conducted comparisons between DOACs.

Using VTE patient data from a routine practice setting, we characterised the rate of major hospitalised bleeding events associated with use of apixaban, rivaroxaban and warfarin during the VTE primary treatment period. We also evaluated associations in subgroups of particular interest. Comparisons with dabigatran and edoxaban were not made, because these OACs were prescribed relatively infrequently in our study time-period, from 2011 to 2016.

Methods

Study population

This retrospective cohort study utilised health claims data obtained from the MarketScan data warehouse (Truven Health Analytics, Inc., Ann Arbor, MI; Hansen, 2017) for the time-period from 1 January 2011 to 31 December 2016. We used data from both the MarketScan Commercial Database, which consists of employer and health plan sourced data, and the Medicare Supplemental database, which includes retirees with Medicare supplemental insurance paid for by employers. These databases contain detailed inpatient and outpatient medical claims that are linked to outpatient prescription drug claims and person-level enrollment information, are de-identified, compliant with the Health Insurance Portability and Accountability Act, and commercially available. As such, the University of Minnesota Institutional Review Board deemed this analysis exempt from review.

The present analysis includes individuals aged 18–99 years with incident VTE (DVT or PE), at least one prescription for OAC within the 31·5 days before or after their first VTE claim (note that hospital discharge dates are used) and ≥3 months of continuous enrollment prior to their first OAC prescription. VTE was defined as having at least one inpatient claim for VTE or 2 outpatient claims for VTE, 7–185 days apart, based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision (ICD-10-CM) codes. ICD-9-CM and ICD-10-CM codes to define VTE are provided in Table SI, and could occur in any position. The positive predictive value (PPV) was 91% in a recent validation study, which employed a definition similar to that used herein, inclusive of both

inpatient and outpatient encounters and additionally requiring treatment (Sanfilippo *et al*, 2015).

The initial sample included 472 757 VTE patients aged 18–99 years. The analytic sample was 367 886 once it was restricted to individuals ever prescribed an OAC between 1 January 2011 and 31 December 2016; 231 189 after requiring the first OAC prescription by ±31 days of the VTE date; and 173 779 after requiring ≥3 months of continuous enrollment before the first OAC prescription. These 173 779 were our eligible study population.

Anticoagulant use

Prescriptions for DOACs and warfarin were identified from outpatient pharmaceutical claims data, which includes information on the National Drug Code (NDC), the prescription fill date, and the number of days supplied. Validity of warfarin claims in administrative databases is excellent (sensitivity: 94%, PPV: 99%) (Garg *et al*, 2011). Validation studies of DOAC claims have not yet been conducted.

The analysis focused on 'new users' of OACs, meaning that the VTE patients did not have any prior exposure to OACs during the time period under observation. Patients were categorised according to the first OAC prescription filled, and remained in this initial category for the entire analysis, in order to mimic the intent-to-treat approach of a RCT (Hernán *et al*, 2008).

Identification of hospitalised bleeding events

Hospitalised bleeding events were identified based on hospitalisation discharge codes indicating intracranial haemorrhage, gastrointestinal bleeding and other major bleeding. Intracranial haemorrhage was defined by ICD-9-CM codes 430, 431 or 432 as the primary discharge diagnosis in an inpatient claim (Cunningham *et al*, 2011); the PPV of this definition is estimated to be >90% (Fang *et al*, 2011; Andrade *et al*, 2012). Gastrointestinal bleeding and other major bleeding events were defined using the algorithm determined by Cunningham *et al* (2011), which is based on inpatient claims as primary and secondary diagnoses, and presence of transfusion codes. The PPV for gastrointestinal bleeding is estimated to be 86% (Cunningham *et al*, 2011), and for other bleeding (including genitourinary bleeding, haemopericardium, haemoperitoneum, haemarthrosis, epistaxis, haemoptysis, haemorrhage from throat and unspecified haemorrhage) the PPV was similar (Cunningham *et al*, 2011). Crosswalks, with review for face validity, were used to translate ICD-9-CM codes to ICD-10-CM codes.

Assessment of pre-specified covariates

Information prior to the OAC initiation date (minimum 90 days) from all data sources in MarketScan (i.e.,

demographic data, inpatient, outpatient, and pharmacy claims) was used to derive pre-specified covariates. We identified 16 pre-specified comorbidies using validated algorithms (Quan *et al*, 2005; Cunningham *et al*, 2011) applied to the inpatient and outpatient data, and 8 different medication categories based on pharmacy prescription fills were used to identify usage of 8 different medication categories. These pre-specified covariates are listed in Table I, and the codes are listed in Table SII. ICD-9-CM comorbidity codes were translated to ICD-10-CM codes using cross-walks, with review of face-validity.

Statistical analysis

A total of 173 779 VTE patients met the inclusion criteria and were eligible for matching. Each new OAC user was matched with up to five initiators of the comparing OAC by age (±3 years), sex, time since database enrollment (±90 days) and drug initiation date (±90 days). Matching was done separately for each OAC comparison, using an automated greedy matching algorithm (Bergstralh, 2003). The matched dataset included 83 985 participants. The majority of unmatched participants were warfarin users (96·6%).

Table I. Characteristics* of venous thromboembolism patients by anticoagulant use, MarketScan databases, 2011–2016.

	New users		
	Warfarin (N = 46 217)	Apixaban (N = 6786)	Rivaroxaban (N = 30 982)
Age, years	58.4 ± 15.9	60.4 ± 16.2	56.4 ± 15.4
Female, %	50.1	50.3	49.2
Comorbidities,†%			
Hypertension	59.8	64.2	55.6
Diabetes	24.4	24.9	20.7
Myocardial infarction	7.8	8.5	5.5
Heart failure	14.9	17.1	10.7
Ischaemic stroke/TIA	13.7	10.2	10.3
Haemorrhagic stroke	2.3	5.9	1.7
Peripheral artery disease	14.7	15.3	11.7
Dementia	2.0	3.1	1.4
Chronic pulmonary disease	30.1	26.7	27.1
Renal disease	12.7	13.2	7.1
Liver disease	10.5	9.7	9.6
Malignancy	18.8	17.0	16.1
Metastatic cancer	6.5	5.9	5.8
Depression	19.3	19.6	17.8
Haematological disorders	17.8	13.7	13.9
Alcohol abuse	0.9	1.9	0.9
Medications, %			
Antiplatelets	6.8	7.0	5.1
ACE inhibitors	25.5	24.6	22.2
Angiotensin receptor blockers	15.0	17.1	14.5
Beta-blockers	27.9	30.2	23.9
Calcium channel blockers	20.5	21.5	17.5
Statins	34.1	34.8	30.6
Diabetes medications	7.5	7.0	5.5
SSRIs	29.7	29.8	28.6
Follow-up information			
Number of bleeding events	1266	74	604
Cumulative incidence	2.74%	1.09%	1.95%
Person-years	19 910	2480	12 984
Rate per 6 months‡	3.2%	1.5%	2.3%

ACE, angiotensin-converting enzyme; ICD, International Classification of Diseases; N, number; OAC, oral anticoagulant; SSRI, selective serotonin reuptake inhibitors; TIA, transient ischaemic attack.

*Values correspond to mean ± SD or percentage.

†ICD codes used to define these comorbidities are provided in Table SI.

‡The rate is calculated per 6 months of follow-up since the analysis was restricted to the primary treatment phase, which we defined as the first 6 months following OAC prescription. Rate per 6 months can be calculated as follows: [(N events/person-years)/2].

After matching, for each OAC comparison, a propensity score for exposure to the OAC was created via logistic regression, using comorbidities and medications determined *a priori* (Table I). Cox proportional hazards regression was used to estimate the association between OACs and risk of incident bleeding. Follow-up began at the date of the first OAC prescription filled. Person-time was accrued until incident hospitalised bleeding, health plan disenrollment, the end of study follow-up or 180 days, whichever came first. Cox models were adjusted for age (continuous), sex and the propensity score (continuous) for OAC exposure. Multiplicative interactions were evaluated between OAC use and sex, age (<65 years vs. ≥65 years), and kidney disease status (yes vs. no).

In sensitivity analyses, we adjusted for empirically-defined high-dimensional propensity scores (HDPS) (Schneeweiss *et al*, 2009) instead of the propensity scores created using the pre-specfied comorbidities and medications. We have detailed our MarketScan HDPS approach previously (Lutsey *et al*, 2018). Separate high-dimensional propensity scores were calculated for each of the three comparisons, and for the periods before and after ICD-10 adoption (1 October 2015). To estimate one effect over these two study periods, an indicator variable for ICD-9 or ICD-10 study period was included in the model. There was no evidence of multiplicative interactions in the association between OACs and bleeding risk by ICD-9 or ICD-10 study period.

Additional sensitivity analyses were also conducted (i) to correspond to a 3-month primary treatment period, by ending follow-up 90 days after the OAC initiation date, (ii) stratifying according to whether the initial VTE event was managed on an inpatient or outpatient basis, and (iii) requiring ≥6 months of continuous enrollment before the first OAC prescription (≥3 months was used for the primary analysis). All statistical analyses were performed with SAS v 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the 83 985 matched VTE patients, according to initial filled OAC prescription, are provided in Table I. Mean age (standard deviation) of these VTE patients was 57·9 (15·8) years and 50% were female. The final number matched in each OAC category was: warfarin 46 217 patients; apixaban 6786 patients; rivaroxaban 30 982 patients. Overall, the distribution of covariates was relatively similar across OAC options, though rivaroxaban users tended to have fewer comorbid conditions. VTE events were initially managed in an inpatient setting for 61% of the sample.

A total of 1944 hospitalised bleeding events occurred during the first 180 days after OAC initiation; 74 occurred among apixaban users, 604 among rivaroxaban users and 1266 among warfarin users. The cumulative incidence of hospitalised bleeding was 1·1% among apixaban users, 2·0% among rivaroxaban users and 2·7% among warfarin users (Table I).

The rate of hospitalised bleeding was lower among apixaban users, as compared to rivaroxaban users [hazard ratio (HR) (95% confidence interval (CI)): 0·58 (0·41, 0·80)] (Table II). Results were similar across subgroups defined according to sex, age (<65 years vs. ≥65 years) and prevalent kidney disease (Fig 1). Findings were also similar in analyses that limited follow-up to 90 days (Table III). Likewise, apixaban was associated with lower hospitalised bleeding risk than rivaroxaban in a number of sensitivity analyses, including adjusting for the empirically-derived HDPS, restricting to VTE cases initially managed as inpatients, and when requiring 6 months of continuous enrollment prior to anticoagulant initiation (Tables SIII–SV).

In comparisons of apixaban *versus* warfarin, apixaban was associated with lower risk of hospitalised bleeding after both 180 days of follow-up [HR (95% CI): 0·68 (0·50, 0·92); Table II] and 90 days of follow-up (Table III). Although not statistically significant on the multiplicative scale, there was some evidence that this association was stronger among men than women ($P_{interaction}$ = 0·10), and among VTE patients aged <65 years than ≥65 years ($P_{interaction}$ = 0·06; Fig 1). When adjusting for HDPS instead of the *a priori* propensity score, the association was attenuated [HR 95% CI: 0·84 (0·60, 1·18); Table SIII]. Results were similar to the main findings in additional sensitivity analyses restricting to VTE

Table II. Adjusted hazard ratios (95% CIs)* for hospitalised bleeding within 180 days comparing new users of specific oral anticoagulants among patients with venous thromboembolism, MarketScan databases, 2011–2016.

Apixaban *versus* Rivaroxaban	Rivaroxaban	Apixaban
Number matched	14 751	6638
Number of bleeding events	170	49
Person-years	5824	2432
HR (95% CI)	1 (reference)	0·58 (0·41, 0·80)

Apixaban *versus* Warfarin	Warfarin	Apixaban
Number matched	13 595	6441
Number of bleeding events	191	52
Person-years	5548	3055
HR (95% CI)	1 (reference)	0·68 (0·50, 0·92)

Rivaroxaban *versus* Warfarin	Warfarin	Rivaroxaban
Number matched	46 154	28 010
Number of bleeding events	719	367
Person-years	19 886	11 962
HR (95% CI)	1 (reference)	0·98 (0·86, 1·11)

CI, confidence interval; HR, hazard ratio.

*Analyses matched on age, sex and time since database enrollment, and adjusted for age, sex, and a comorbidity score (created using prevalence of 16 common diagnoses and 8 medications).
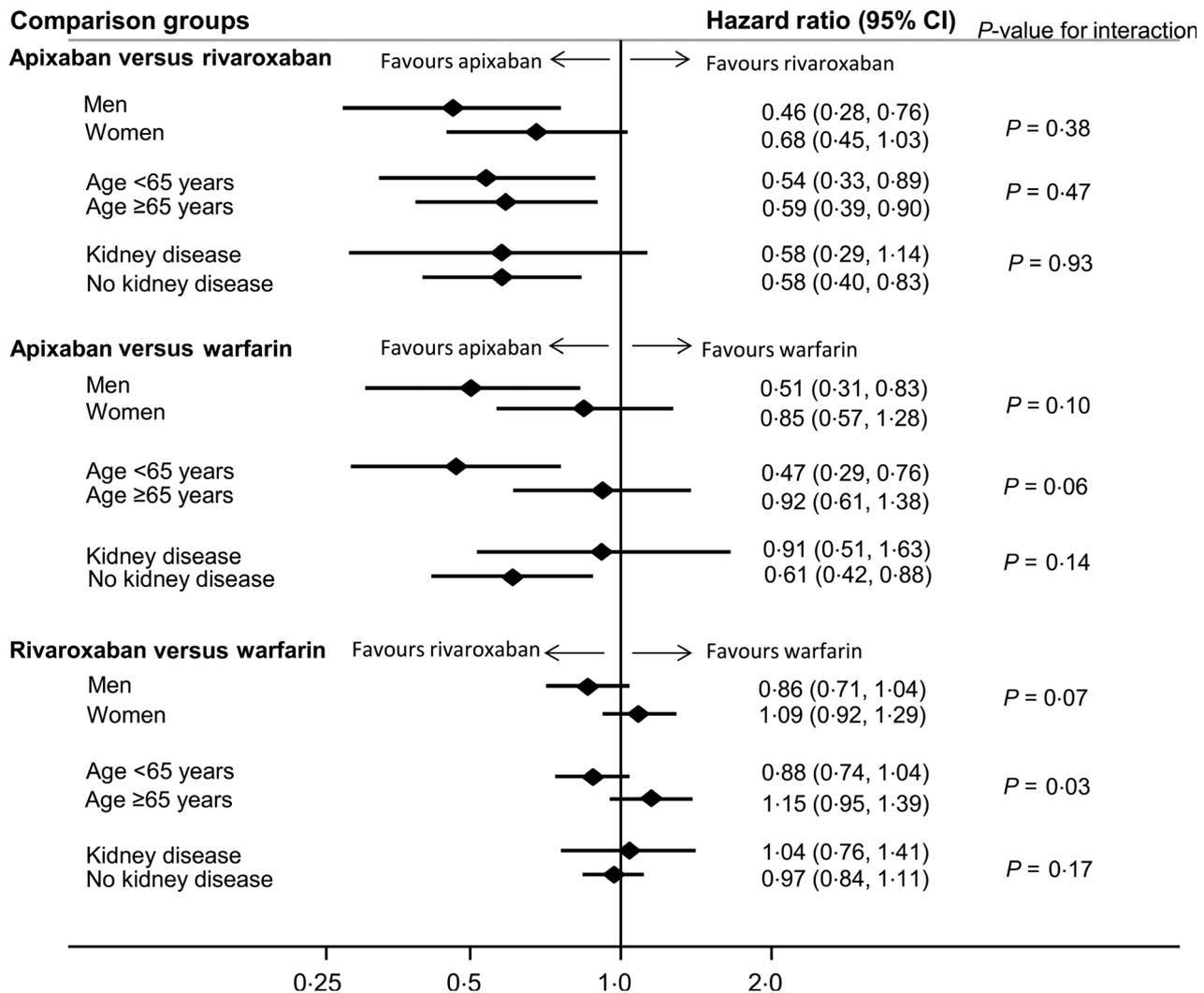
Fig 1. Adjusted hazard ratios (95% CIs)* of incident hospitalised bleeding within 180 days, according to initial oral anticoagulant therapy for the treatment of patients with venous thromboembolism, stratified by subgroups of interest. *Analyses matched on age, sex and time since database enrollment, and adjusted for age, sex, and a comorbidity score (created using prevalence of 16 common diagnoses and 8 medications). The diamonds represent hazard ratios and the horizontal lines represent CIs. CI, confidence interval.

patients managed in-hospital and requiring 6 months of continuous enrollment (Tables SIV and SV).

Bleeding risk was similar in analyses comparing rivaroxaban to warfarin. In the primary analysis, with 180 days of follow-up, the HR (95% CI) was 0·98 (0·86, 1·11). Results were similar when follow-up was restricted to 90 days (Table III), and in all sensitivity analyses (Tables SIII–SV). However, there was a significant multiplicative interaction ($P = 0.03$), whereby rivaroxaban was associated with lower bleeding risk among VTE patients <65 years [HR 95% CI: 0·88 (0·74, 1·04)] but not among those older than ≥65 years [HR 95% CI: 1·15 (0·95, 1·39)] (Fig 1). Though not significant, there was also some suggestion that rivaroxaban may be more protective than warfarin in men *versus* women ($P_{interaction} = 0.07$).

Discussion

In this real-world population of 83 985 patients prescribed OACs for the primary treatment of VTE, subsequent risk of hospitalised bleeding was lower among apixaban users than among rivaroxaban or warfarin users. Overall, bleeding risk was similar when comparing rivaroxaban *versus* warfarin. The present findings provide clinically relevant information about OACs and hospitalised bleeding risk in VTE patients by (i) providing a comparison of apixaban *versus* rivaroxaban, (ii) reporting bleeding risk for apixaban *versus* warfarin in a usual practice patient sample and (iii) demonstrating that, among those with known kidney disease, bleeding risk was generally similar among DOAC and warfarin users.

Table III. Adjusted hazard ratios (95% CIs)* for hospitalised bleeding within 90 days comparing new users of specific oral anticoagulants among patients with venous thromboembolism, MarketScan databases, 2011–2016.

Apixaban *versus* Rivaroxaban	Rivaroxaban	Apixaban
Number matched	14 751	6638
Number of bleeding events	132	38
Person-years	3280	1421
HR (95% CI)	1 (reference)	0·59 (0·41, 0·85)

Apixaban *versus* Warfarin	Warfarin	Apixaban
Number matched	13 595	6441
Number of bleeding events	131	39
Person-years	2405	1394
HR (95% CI)	1 (reference)	0·69 (0·48, 0·99)

Rivaroxaban *versus* Warfarin	Warfarin	Rivaroxaban
N matched	46 154	28 010
Number matched	490	283
Number of bleeding events	10 650	6447
HR (95% CI)	1 (reference)	1·09 (0·94, 1·26)

CI, confidence interval; HR, hazard ratio.
*Analyses matched on age, sex and time since database enrollment, and adjusted for age, sex, and a comorbidity score (created using prevalence of 16 common diagnoses and 8 medications).

Comparison of apixaban *versus* rivaroxaban

Our observation that apixaban was associated with the lowest risk of hospitalised bleeding is consistent with the known pharmokinetics of the anticoagulants as well as observations in other populations. Apixaban is dosed twice daily throughout treatment, *versus* once daily for rivaroxaban starting on day 22 of treatment. This is despite rivaroxaban having a shorter half-life than apixaban (Mueck *et al*, 2014). To achieve equivalence to warfarin (Einstein Investigators, 2010, Agnelli *et al*, 2013) the peak anticoagulant effect of rivaroxaban could be higher than apixaban to accommodate the once daily dosing (Salem *et al*, 2015). Other evidence that bleeding risk may be greater with rivaroxaban than apixaban comes from two network meta-analysis of phase III RCTs, which provided indirect evidence of higher major bleeding risk for rivaroxaban *versus* apixaban, though precision was poor (Mantha & Ansell, 2015; Sterne *et al*, 2017), an observational study that did not restrict to the 6-month primary treatment period (Dawwas *et al*, 2019), comparisons conducted in the context of atrial fibrillation (Norby & Alonso, 2017), and the observation of increased menstrual bleeding with rivaroxaban *versus* apixaban (Myers & Webster, 2016).

Apixaban and rivaroxaban *versus* warfarin

Hospitalised bleeding risk was lower among VTE patients using apixaban than among warfarin users. This is consistent

with results from the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) Phase III randomised controlled trial (Agnelli *et al*, 2013), which reported 6-month major bleeding in 0·6% of patients in the apixaban group and 1·8% of patients in the warfarin group, and a relative risk of 0·31 (95% CI: 0·17–0·55) when comparing apixaban to warfarin. Our results from a real-world population of VTE patients complement those from AMPLIFY. In the present analysis of MarketScan data, 1·1% of participants prescribed apixaban and 2·7% of participants prescribed warfarin had hospitalised bleeding in the primary treatment period, resulting in a HR (95% CI) of 0·68 (0·50–0·92). VTE patients included in the present analysis may be more representative of all VTE patients than those included in AMPLIFY, given that AMPLIFY excluded individuals with low haemoglobin concentrations, platelet counts or serum creatinine, whereas the MarketScan data included all enrollees in health plans reporting to MarketScan. The MarketScan findings also have greater precision than those of AMPLIFY because only 15 major bleeding events were reported in the apixaban group in AMPLIFY, whereas the MarketScan data identified 74 events among VTE patients prescribed apixaban. Together, these findings strongly suggest that apixaban is preferential to warfarin in terms of bleeding risk.

In contrast, overall there was no difference between rivaroxaban and warfarin in relation to risk of hospitalised bleeding in the present analysis [HR (95% CI): 0·98 (0·86–0·92)]. There was, however, suggestive evidence that rivaroxaban may be advantageous among VTE patients <65 years. The efficacy of rivaroxaban *versus* warfarin was evaluated in non-inferiority trials of DVT (EINSTEIN-DVT) (Einstein Investigators, 2010) and PE (EINSTEIN-PE) (Einstein-Pe Investigators, 2012) patients, respectively. Among DVT patients, risk of first major or clinically relevant nonmajor bleeding was similar [HR (95% CI): 0·97 (0·76, 1·22)] though there was some suggestion that rivaroxaban may be beneficial when looking only at major bleeding events [HR (95% CI): 0·65 (0·33, 1·30)]. Similarly, in EINSTEIN PE the HR (95% CI) for major or clinically relevant nonmajor bleeding was 0·90 (0·76, 1·07), while for major bleeding it was 0·49 (0·31, 0·79) (Einstein-Pe Investigators, 2012). Cumulative incidences for major bleeding in the rivaroxaban group in EINSTEIN-DVT (Einstein Investigators, 2010), EINSTEIN-PE (Einstein-Pe Investigators, 2012) and MarketScan were 0·8%, 1·1% and 2·0%, respectively while in the warfarin group they were 1·2%, 2·2% and 2·7%, respectively. The EINSTEIN trials both had numerous exclusion criteria, yielding patient populations that were probably healthier than individuals included in the present MarketScan analysis.

This report also provides novel information about the comparative effectiveness of individual OACs in key VTE patient subgroups, namely according to sex, age category and known kidney disease. Overall, findings from the primary analyses were robust across these subgroups. However, both

rivaroxaban and apixaban appeared to perform better among younger than older VTE patients, relative to warfarin. This observation is not entirely surprising; bleeding profile is known to vary by age, with risk and antithrombotic drug-related bleeding increasing with advancing age (Patti *et al*, 2017).

Strengths and limitations

The present analysis has numerous strengths. First, the sample size of OAC users was large, resulting in a relatively large number of hospitalised bleeding events, and the ability to conduct analyses restricted to key patient subgroups (e.g., those with known kidney disease). Second, we conducted comparisons between DOACs, thus providing information useful for clinical decision-making. Third, we evaluated these associations in the context of routine clinical practice. As such, our findings may be less prone to problems of external validity than RCTs, which may not be generalisable across all patient and provider profiles, nor representative of routine clinical practice.

This analysis also has important limitations. Foremost is the possibility of uncontrolled confounding. Of particular concern is the possibility that prescription patterns differed by VTE patient health, for instance, with more ill patients having a greater likelihood of being prescribed a certain OAC (e.g., warfarin), and also having greater bleeding risk. While risk factors for bleeding might impact choice of warfarin *versus* the DOACs, the choice between DOACs, which are all newer therapies, should be less likely to be based on patient conditions – there is no theoretical reason why providers would select apixaban *versus* rivaroxaban based on patient charcteristics. Nonetheless, we attempted to control for confounding through matching on initial patient characteristics, and adjusting (separately) for an *a priori*-defined propensity score, and an empirically derived HDPS that utilised the wealth of information available in the MarketScan databases. The HDPS approach has been shown to be effective at controlling for confounding (Schneeweiss *et al*, 2009). Misclassification is another concern, as with all analyses of administrative data. However, the algorithms for VTE, hospitalised bleeding and warfarin prescription fills all have high PPVs. The PPV for DOAC prescription fills has not yet been quantified, but may be similar to warfarin. As a final limitation, edoxaban and dabigatran were not included in the present analysis, as there were too few users of these OACs to make meaningful comparisons. Despite the noteworthy limitations of administrative data, when used with rigorous analytic methods, these data can provide timely answers about the comparative effectiveness of different treatment strategies (Parks & Redberg, 2017; Corrigan-Curay *et al*, 2018).

Conclusions

In the present analysis of a real-world insured patient population in the United States, risk of hospitalised bleeding in the VTE primary treatment phase was lower among users of apixaban *versus* users of rivaroxaban or warfarin. These findings were generally consistent across patient subgroups of sex, age and known kidney disease. Given that none of the phase III RCTs showed benefit for DOACs over warfarin for the outcomes of VTE recurrence and mortality, safety concerns, such as bleeding risk, and convenience, such as once or twice daily dosing, will probably drive anticoagulant choice. Of course, patients themselves may have different preferences for anticoagulant choice, such as ease of reversibility and the ability to measure levels (Kearon *et al*, 2016) which should be addressed when providers treat VTE.

Acknowledgements

Conflicts of interest

No conflicts of interest exist.

Authors' contributions

P. L. Lutsey, N. A. Zakai, R. F. MacLehose and A. Alonso designed the study. P. L. Lutsey, F. L. Norby, R. F. Walker, R. F. MacLehose, N. S. Roetker and A. Alonso were engaged with various aspects of data analysis. P. L. Lutsey drafted the manuscript. All authors aided in interpretation of findings, critically reviewed the manuscript and approved the submitted verison.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. ICD-9-CM and ICD-10 CM diagnosis codes for VTE.

Table SII. ICD-9-CM codes used to define pre-defined comorbidities.*

Table SIII. High dimensional propensity score-adjusted hazard ratios (95% confidence intervals)* for hospitalized bleeding within 180 days comparing new users of specific oral anticoagulants among patients with venous thromboembolism, MarketScan databases, 2011–2016.

Table SIV. Adjusted hazard ratios (95% confidence intervals)* for hospitalized bleeding within 180 days comparing new users of specific oral anticoagulants among patients with venous thromboembolism who were initially managed as inpatients, MarketScan databases, 2011–2016.

Table SV. Adjusted hazard ratios (95% confidence intervals)* for hospitalized bleeding within 180 days comparing new users of specific oral anticoagulants among patients with venous thromboembolism, and requiring 6-months of continuous enrollment prior to anticoagulant initiation, MarketScan databases, 2011–2016.

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