AMPLIFY CLINICAL
TRIAL CONTENT INSIDE

Real-world pooled database analysis in Medicare Advantage and commercial patients with venous thromboembolism (VTE)

Real-world observational, retrospective database analysis of the Truven, IMS LifeLink PharMetrics, Optum, and Humana databases

INDICATION

ELIQUIS is indicated for the treatment of DVT and PE, and to reduce the risk of recurrent DVT and PE following initial therapy.

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

Please see **Important Safety Information** throughout and Full Prescribing Information, including **Boxed WARNINGS**, or visit ELIQUIS.com.

Eliquis® (apixaban) tablets 5mg 2.5mg

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of ELIQUIS and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

AMPLIFY was a randomized double-blind, phase 3 noninferiority clinical trial[1,2]

Primary objective:

To determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE* or VTE-related death

IN PATIENTS WITH DVT AND/OR PE

RANDOMIZED, DOUBLE-BLIND
N=5400

ELIQUIS
10 mg orally twice daily for 7 days followed by 5 mg orally twice daily for 6 months
n=2693

enoxaparin/warfarin
enoxaparin 1 mg/kg subcutaneously twice daily for at least 5 days (until INR ≥2) followed by warfarin (target INR range 2.0-3.0) orally for 6 months
n=2707

Select inclusion criteria: objectively confirmed, symptomatic proximal DVT and/or PE.

Select exclusion criteria: patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent; who had cancer and ≥6 months of low-molecular weight heparin treatment planned; and patients with a life expectancy of <6 months, creatinine clearance <25 mL/min, significant liver disease, mechanical valve, atrial fibrillation, or active bleeding.

Primary efficacy endpoint: recurrent VTE* or VTE-related death

Primary safety endpoint: major bleeding

- Approximately 90% of patients had an unprovoked DVT or PE at baseline, and 10% of patients with a provoked DVT or PE were required to have an additional ongoing risk factor, which included a previous episode of DVT or PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype[1]
- Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours)[1]

Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following[3]:

- Fatal bleeding
- Critical site bleeding (bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal)
- Hemoglobin decrease (a decrease in hemoglobin of 2 g/dL or more)
- Transfusion (a transfusion of 2 or more units of packed red blood cells)

BASELINE CHARACTERISTICS +

DVT=deep vein thrombosis; INR=international normalized ratio; PE=pulmonary embolism.
*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).

References: 1. ELIQUIS® (apixaban) Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, et al. *N Engl J Med.* 2013;368(8):699-708. **3.** Agnelli G, et al. *N Engl J Med.* 2013;369(9):799-808.

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BASELINE CHARACTERISTICS +

For the treatment of DVT/PE,

ELIQUIS® (apixaban) was studied across various patient subgroups[1]

Select clinical characteristics represented in AMPLIFY patient population[1]	ELIQUIS n=2691		enoxaparin/warfarin n=2704	
Extensive PE at baseline*	13.3%	n=357	12.1%	n=326
Weight ≥100 kg	19.4%	n=522	19.2%	n=518
Moderate renal impairment (CrCl >30 to ≤50 mL/min)	6.0%	n=161	5.5%	n=148
Severe renal impairment (CrCl ≤30 mL/min)	0.5%	n=14	0.6%	n=15
Previous VTE	17.2%	n=463	15.1%	n=409
Active cancer[2†‡]	3.3%	n=88	3.0%	n=81

†Baseline values taken from the journal publication Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost.* 2015;13:2187-2191.

CrCl=creatinine clearance.
*Pulmonary embolism was defined as extensive if there were 2 or more lobes involving 50% or more of the vasculature for each lobe.
‡Active cancer was defined as cancer diagnosed or treated within the past 6 months without the necessity for low-molecular-weight heparin treatment.

References: 1. Agnelli G, et al. *N Engl J Med.* 2013;369(9):799-808. **2.** Agnelli G, et al. *J Thromb Haemost.* 2015;13(12):2187-2191.

DVT=deep vein thrombosis; INR=international normalized ratio; PE=pulmonary embolism.
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For the treatment of DVT/PE,

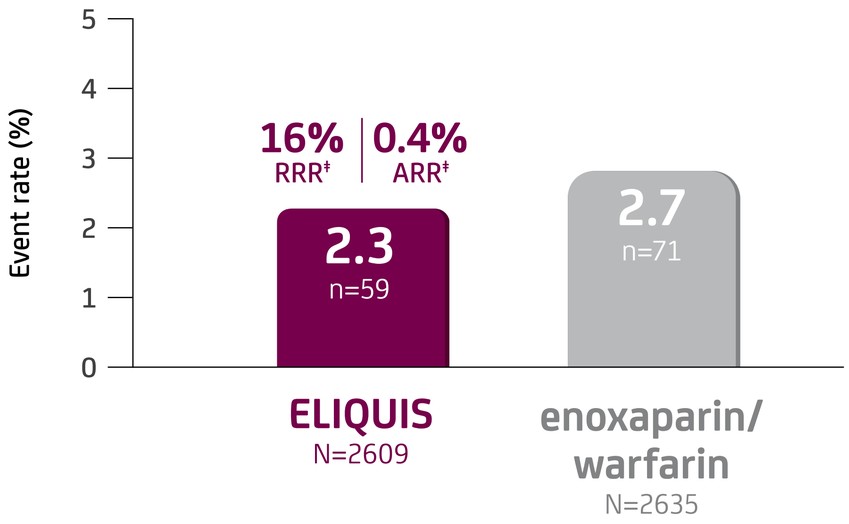
ELIQUIS demonstrated BOTH comparable efficacy AND superiority in major bleeding events vs enoxaparin/warfarin[1]

COMPARABLE

In VTE*/VTE-related death

RR=0.84 (95% CI: 0.60, 1.18)

P<0.0001 for noninferiority



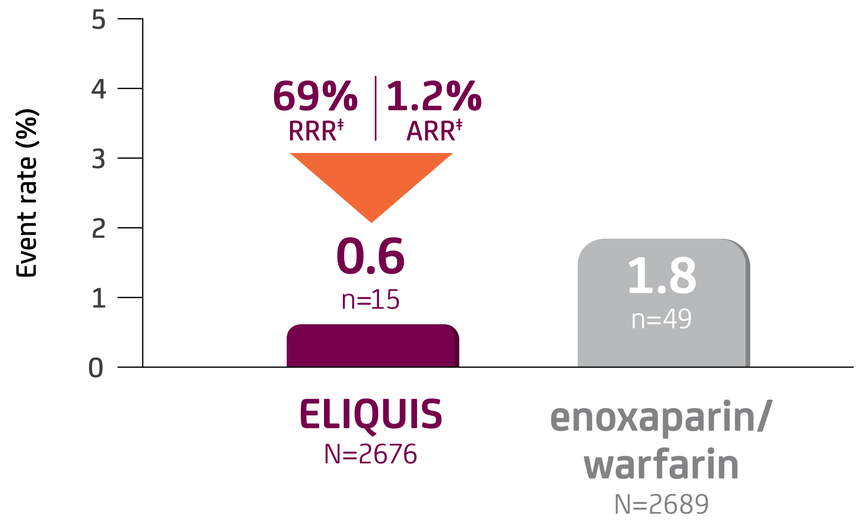
Primary efficacy endpoint

SUPERIOR

Major bleeding events†

RR=0.31 (95% CI: 0.17, 0.55)

P<0.0001



Primary safety endpoint

Consistent efficacy and rates of major bleeding across key patient subgroups[2]

- Renal impairment
- Age
- Weight
- Gender

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

The incidence of VTE-related death in AMPLIFY for ELIQUIS and warfarin was 0.4% and 0.6% of patients, respectively.†

- In AMPLIFY, discontinuation rate due to bleeding events: 0.7% with ELIQUIS vs 1.7% with enoxaparin/warfarin
- In AMPLIFY, the most commonly observed adverse reactions in patients treated with ELIQUIS (incidence ≥1%) were epistaxis, contusion, hematuria, menorrhagia, hematoma, hemoptysis, rectal hemorrhage, and gingival bleeding

ARR=absolute risk reduction; CI=confidence interval; HR=hazard ratio; RRR=relative risk reduction.
*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).
†Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.
‡RRR was calculated as (1-RR) x 100. ARR is calculated as the difference between the incidences and is expressed as percentage points.

References: 1. ELIQUIS® (apixaban) Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, et al. *N Engl J Med.* 2013;369(9):799-808.

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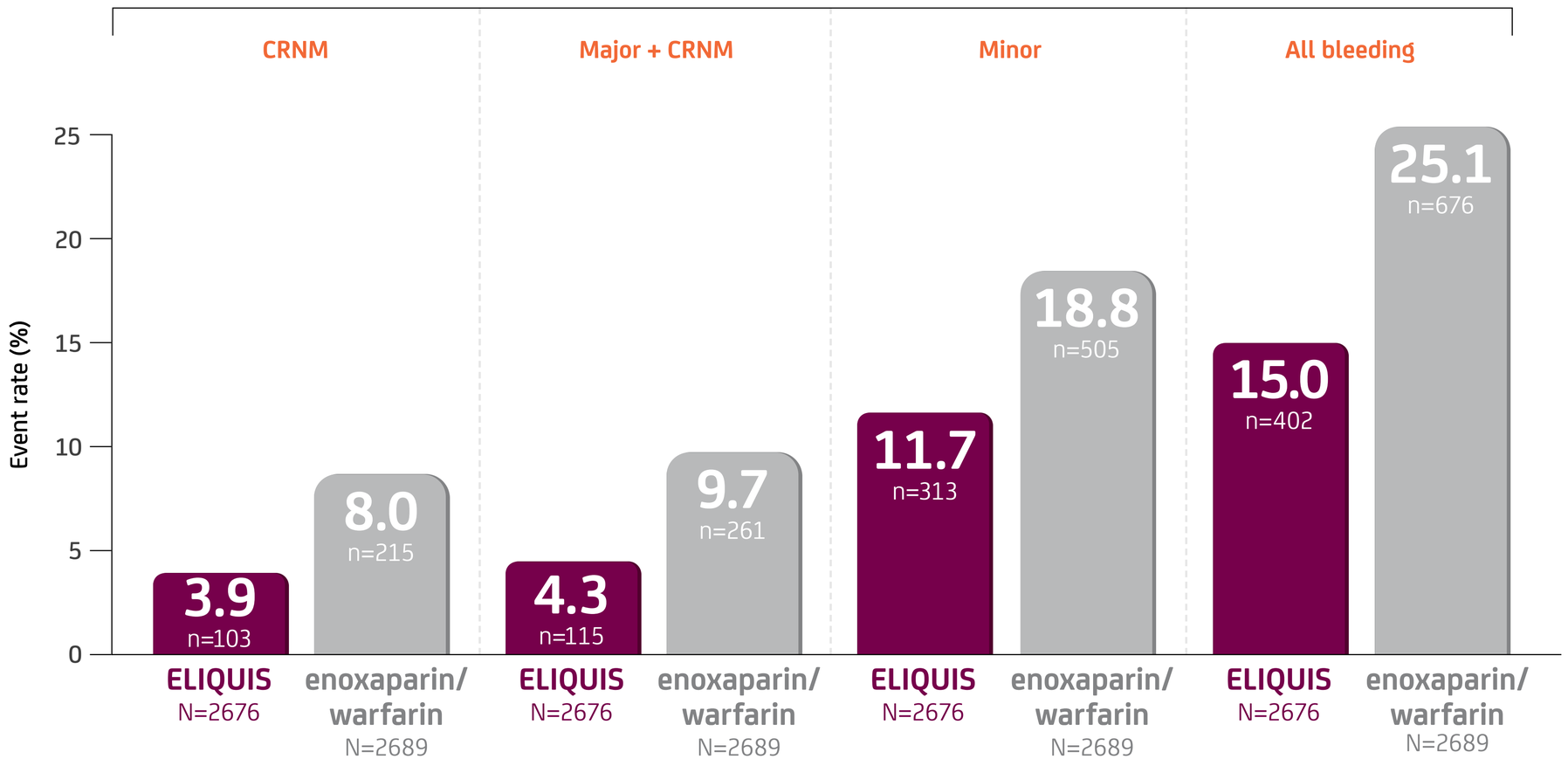
For the treatment of DVT/PE,

ELIQUIS demonstrated fewer bleeding events across key secondary endpoints, including CRNM[1]*

Key secondary bleeding endpoints



- CRNM bleeding was defined as overt bleeding not meeting the criteria for major bleeding, but associated with at least 1 of the following[2]:
  - Medical intervention
  - Contact with an HCP
  - Interruption of the study drug
  - Discomfort or impairment in carrying out activities of daily life
- Minor bleeding was defined as all acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant nonmajor bleeding[2]

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

- **In AMPLIFY, the discontinuation rate due to bleeding events was 0.7% in ELIQUIS-treated patients compared with 1.7% in enoxaparin/warfarin-treated patients[1]**

CRNM=clinically relevant nonmajor; HCP=health care provider.
*Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

References: 1. ELIQUIS® (apixaban) Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, et al. *N Engl J Med.* 2013;369(9):799-808.

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SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.
- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.
- **Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS):** Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive APS. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

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Real-world pooled database analysis in Medicare Advantage and commercial patients with venous thromboembolism (VTE)

Real-world observational, retrospective database analysis of the Truven, IMS LifeLink PharMetrics, Optum, and Humana databases

Continue to Pooled database analysis

Analysis overview[1,2]

Objective

Evaluate the effectiveness and bleeding outcomes associated with ELIQUIS vs warfarin with parenteral anticoagulant (PAC) bridging therapy* in the outpatient treatment period of VTE

*Bridging therapies included low-molecular-weight heparin, heparin, and fondaparinux.

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

Analysis overview[1,2]

Objective

Study design

Data analysis

Population

Baseline characteristics

Considerations and limitations

Retrospective cohort database analysis of 4 pooled databases (from September 1, 2014, to June 30, 2017):

1. Truven Health Analytics' MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases
2. IMS LifeLink PharMetrics Plus Health Plan Claims Database
3. Optum Clinformatics Claims Database
4. Humana Medical, Lab, and Pharmacy Claims Database

Assessment of effectiveness and safety outcomes

Effectiveness outcome:

Recurrent VTE, defined as an acute-care inpatient admission with a corresponding principal or first-listed ICD-9-CM/ICD-10-CM diagnosis occurring >7 days after the index encounter. VTE-related death was not recorded in the observational retrospective claims analysis.

Safety outcomes:

- Major bleeding, defined as acute-care inpatient admission with a principal or first-listed ICD-9-CM/ICD-10-CM diagnosis code for gastrointestinal bleeding, intracranial hemorrhage, or other selected types of bleeding, or an ICD-9-CM/ICD-10-CM procedure code for the treatment of bleeding
- Clinically relevant nonmajor (CRNM) bleeding, defined as an acute-care inpatient admission with a secondary ICD-9-CM/ICD-10-CM diagnosis code or an ambulatory-care encounter with a diagnosis code for gastrointestinal bleeding or other noncritical care types/sites of bleeding

ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM=International Classification of Diseases, Tenth Revision, Clinical Modification.

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

Analysis overview[1,2]

Statistical methods were used to help control for baseline characteristics, analyze the data of this study, and assess the validity of the results

Methodology and statistical analyses

- **1:1 propensity score matching (PSM)** was used to balance demographics and clinical characteristics between ELIQUIS and warfarin
- Effectiveness and safety outcomes were measured using a shared frailty model (an extension of the Cox proportional hazards model that adjusts for correlation from matching)

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

Analysis overview[1,2]

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Additional methodology and statistical analysis information

1:1 propensity score matching: a statistical technique used to balance groups on baseline characteristics by assigning each subject in a group a propensity score (PS) based on the likelihood of treatment. This PS is most often derived from logistic regression. Subjects are then matched 1:1 across the groups such that the matched pair has similar PS values.[1]

Reference: 1. Brookhart MA, et al. *Circ Cardiovasc Qual Outcomes.* 2013;6(5):604-611.

- Effectiveness and safety outcomes were measured using a shared frailty model (an extension of the Cox proportional hazards model that adjusts for correlation from matching)

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

Analysis overview[1,2]

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Considerations and limitations

Statistical methods were used to help control for baseline characteristics, analyze the data of this study, and assess the validity of the results

Sensitivity analyses

- **Sensitivity analyses** were performed to assess the validity and robustness of the data. Results from analyses based on each of the 4 databases separately and those from sensitivity analyses employing alternative methods for confounding adjustment were largely similar to the main analysis

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

Analysis overview[1,2]

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Additional sensitivity analysis information

Sensitivity analyses: secondary analyses performed by modifying certain assumptions to test the robustness of the results and to assess the extent to which results may be due to unobserved confounding.[1]

Reference: 1. Delaney JAC, Seeger JD. *Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide.* Rockville, MD: Agency for Healthcare Research and Quality (US); 2013.

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

Analysis overview[1,2]

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Considerations and limitations

Inclusion criteria

- ☑ Aged ≥18 years
- ☑ Encounter in the acute-care inpatient setting or outpatient setting with ICD-9-CM/ICD-10-CM diagnosis codes for lower extremity DVT or PE in any position from September 1, 2014, through June 30, 2017 (index encounter) *i*
- ☑ ≥1 pharmacy claim for ELIQUIS or warfarin with PAC bridge therapy† during the 30-day period following the index encounter

Exclusion criteria

- ☒ Outpatient warfarin patients with no evidence of PAC bridge therapy† within +/-14 days of the first receipt of warfarin or who received PAC bridge therapy† beyond the 14 days
- ☒ <6 months enrollment prior to index VTE encounter
- ☒ Evidence of VTE, atrial fibrillation/flutter, and major bleeding or CRNM in the 6-month prior to index VTE encounter
- ☒ Evidence of inferior vena cava filter or pregnancy at any time during the study period
- ☒ Evidence of malignancy (other than nonmelanoma skin cancer) during 90-day period preceding index therapy

Baseline period
6 months prior to index therapy*

Index therapy* and propensity score matching

Variable follow-up period‡

N=35,756

ELIQUIS n=17,878 vs warfarin n=17,878

After propensity score matching, mean follow-up duration was 143 days for ELIQUIS and 152 days for warfarin

Patients were followed for a maximum of 6 months.

DVT=deep vein thrombosis; PE=pulmonary embolism.
*Index therapy was defined as the date of the first prescription of ELIQUIS or warfarin.
†Bridging therapies included low-molecular-weight heparin, heparin, and fondaparinux.
‡Patients were followed from index date until the earliest of the following: end of 6-month (180-day) period, date of health plan disenrollment, date of death (in hospital), date of index therapy discontinuation, date of switch to another oral anticoagulant, date of initiation of PAC (new episode), or end of study period (June 30, 2017).

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

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Identification of VTE

ICD code categories[1]

The ICD-9-CM and ICD-10-CM codes used for the diagnosis of VTE included the following main categories:

- PE and infarction (except due to sepsis)
- Phlebitis and thrombophlebitis of deep veins of lower extremities
- Other acute venous embolism and thrombosis of deep vessels of lower extremities

Patients in the study had codes other than the above, for phlebitis and thrombophlebitis or other venous embolism or thrombosis that involved:

- Superficial vessels
- Vessels of the upper extremities or of other sites
- Those that were chronic in nature

Reference: 1. Weycker D, et al. *J Thromb Haemost.* 2018;118(11)(suppl):1951-1961.

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☒ Evidence of malignancy (other than nonmelanoma skin cancer) during 90-day period preceding index therapy

ELIQUIS n=17,878 vs warfarin n=17,878

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Analysis overview[1,2]

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Select baseline characteristics	ELIQUIS n=17,878	warfarin n=17,878	Standard difference
Age, mean (SD)	60.0 (16.0)	60.0 (16.0)	0.0000
Gender, female, n (%)	8595 (48.1%)	8599 (48.1%)	0.0004
Charlson Comorbidity Index, mean (SD)	1.1 (1.7)	1.0 (1.7)	0.0001
Recent surgery (major), n (%)	1794 (10.0%)	1765 (9.9%)	0.0054
Index encounter VTE type, n (%)			
PE (with or without DVT)	7322 (41.0%)	7322 (41.0%)	0.0000
PE with DVT	1655 (9.3%)	1635 (9.1%)	0.0039
PE without DVT	5667 (31.7%)	5687 (31.8%)	0.0024
DVT only	10,556 (59.0%)	10,556 (59.0%)	0.0000
Unprovoked*	13,809 (77.2%)	13,809 (77.2%)	0.0000
Select medical history, n (%)			
Congestive heart failure	1,934 (10.8%)	1,873 (10.5%)	0.0111
Diabetes	4,342 (24.3%)	4,213 (23.6%)	0.0169
Hypertension	9,799 (54.8%)	9,467 (53.0%)	0.0373
Peripheral vascular disease	2,037 (11.4%)	2,052 (11.5%)	0.0026
Renal disease	2,388 (13.4%)	2,401 (13.4%)	0.0021
Coronary artery disease	3,464 (19.4%)	3,247 (18.2%)	0.0311
Bleeding	277 (1.5%)	263 (1.5%)	0.0064
Index encounter setting			
Acute care inpatient	9683 (54.2%)	9683 (54.2%)	0.0000
Ambulatory care	8195 (45.8%)	8195 (45.8%)	0.0000

CCI=Charlson Comorbidity Index; DVT=deep vein thrombosis; PE=pulmonary embolism; SD=standard deviation.
*Unprovoked VTE was defined as the absence of an event that was preceded (within 3 months) by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for medical or surgical reasons.

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

Analysis overview[1,2]

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Considerations and limitations

Study considerations and limitations

- Due to the nature of **observational cohort studies, no causal relations** could be inferred and only associations were assessed. Diagnoses were identified using **ICD-9-CM and ICD-10-CM codes**, which differ from those in the clinical trials
- The **study definitions** for VTE and bleeding events **have not been formally validated**; thus, their accuracy is unknown
- There is a **potential for underreporting** recurrent events
- The presence of a claim for a filled prescription does not indicate whether the medication was consumed or taken as prescribed
- **Evaluations using health care claims databases** inherently have limitations and may be biased due to systematic and unobserved differences in patients receiving ELIQUIS or warfarin, HCP prescribing habits, health plans, and clinical practices
  - Observed and unobserved heterogeneity may exist across 4 data sources
- Although the health plans contributing data to the 4 databases are different, the possibility exists that a patient may be insured by multiple plans, and thus included in more than 1 database
- **Some patients may be misclassified** in terms of their comorbidity profile and pre-index medical histories due to inaccuracies in algorithms/variables capturing acute and chronic conditions and histories that are incomplete
- There could be imprecision in characterizing the VTE as provoked or unprovoked
- Claims data lack laboratory results (ie, international normalized ratio values) and accuracy in the medical information
- Additionally, data on inpatient drug utilization are not available in the study databases, and thus it is **not possible to fully characterize the initial management of VTE** requiring inpatient care
- Mortality data is incomplete
- Because the study population included patient medical and drug benefits from private US health plans, **the study population may not be generalizable** to those with public health insurance, the uninsured, or other segments of the US population. Generalizability of findings should be limited to the study population in the United States
- Compared with clinical trials, the follow-up period for each cohort in this analysis may also have been shorter, which may impact the results
- This study was funded by Pfizer Inc. and Bristol-Myers Squibb Company

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961.

SELECTED IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- Combined P-gp and Strong CYP3A4 Inhibitors: Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.
  Clarithromycin
  Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.
- Combined P-gp and Strong CYP3A4 Inducers: Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.
- Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

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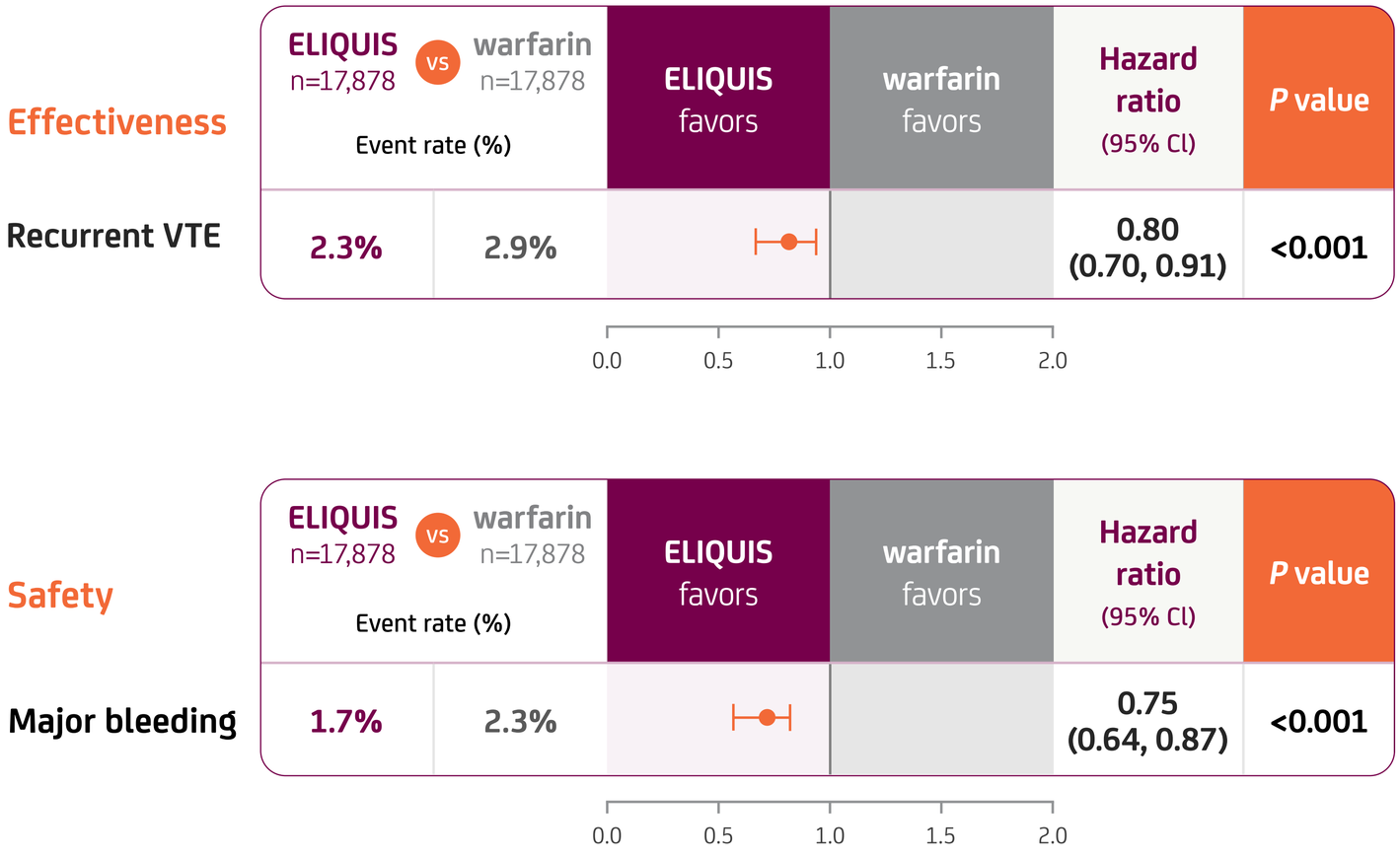
In a retrospective cohort database analysis of patients with VTE,

ELIQUIS was associated with lower rates of recurrent VTE and major bleeding vs warfarin[1,2]



Observational retrospective analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables; causality cannot be established in observational analyses.

In AMPLIFY, the efficacy event rate for ELIQUIS was not superior to warfarin[3]

- The definitions of recurrent VTE, major bleeding, the follow-up period, and the patient population in AMPLIFY were different than in this analysis. AMPLIFY included "VTE-related death" in the efficacy analysis, which could not be measured in an observational claims analysis[3]

Another real-world data analysis comparing ELIQUIS with warfarin used different data sources, time periods, and study methodology, and showed differing results.[4]

The *P* value is the probability that the size of the differences observed between treatments would occur due to chance alone. In an observational study, confounding may also contribute to the results.

CRNM BLEEDING OUTCOMES +

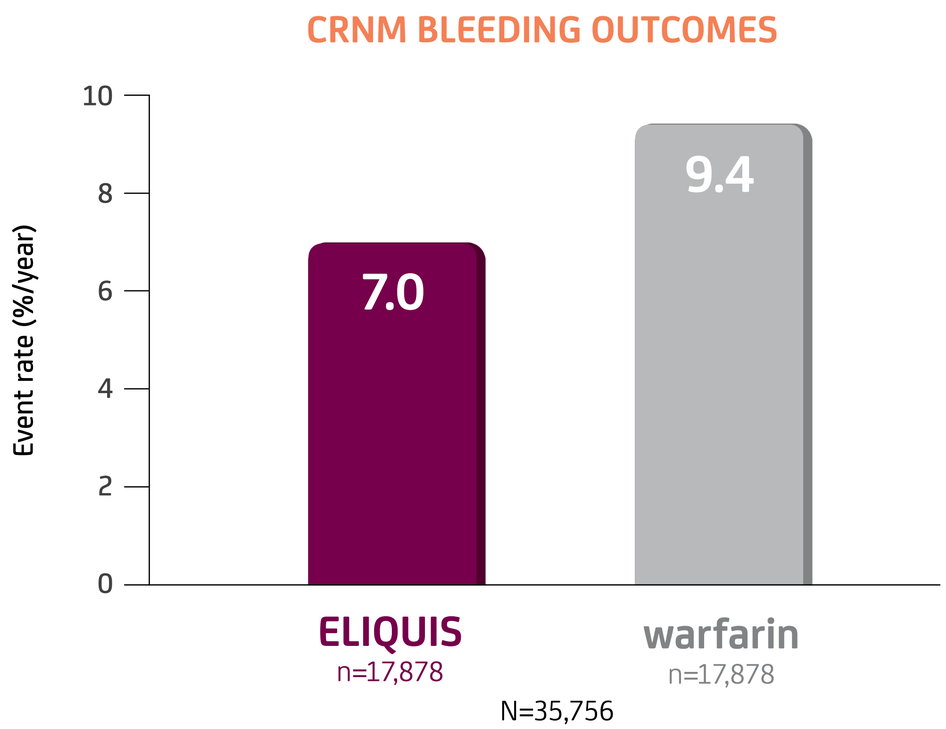
ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

CI=confidence interval.

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961. **3.** ELIQUIS Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **4.** Hlavacek P, et al. *Circ Cardiovasc Qual Outcomes*. https://doi.org/10.1161/hcq.12.suppl_1.138. Accessed May 17, 2019.

In a retrospective cohort database analysis of patients with VTE,

ELIQUIS was associated with lower rates in CRNM* bleeding vs warfarin[1,2]



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

Observational retrospective analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables; causality can not be established in observational analyses.

- The definitions of CRNM bleeding, the follow-up period, and the patient population in AMPLIFY were different than in this analysis.[3]
- In the main analysis, after 1:1 propensity score matching, the ELIQUIS and warfarin cohorts had a mean age of 60.0 years, a mean Deyo-Charlson Comorbidity Index of 1.1 and 1.0, respectively, and 59% presented with DVT only.[1,2]

*CRNM bleeding was defined as an acute-care inpatient admission with a secondary diagnosis code or an ambulatory-care encounter with a diagnosis code for GI bleeding or other noncritical care types/sites of bleeding. CRNM bleeding events that followed major bleeding events were not considered in analysis of CRNM bleeding.

References: 1. Weycker D, et al. *J Thromb Haemost.* 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961. **3.** ELIQUIS Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY.

CI=confide

References: 1. Weycker D, et al. *J Thromb Haemost*. 2018;118(11):1951-1961. **2.** Weycker D, et al. *J Thromb Haemost*. 2018;118(11)(suppl):1951-1961. **3.** ELIQUIS Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **4.** Hlavacek P, et al. *Circ Cardiovasc Qual Outcomes*. https://doi.org/10.1161/hcq.12.suppl_1.138. Accessed May 17, 2019.

SELECTED IMPORTANT SAFETY INFORMATION

PREGNANCY

- The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.
    - *Labor or delivery*: ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

- Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including ELIQUIS should be assessed in these patients and those with abnormal uterine bleeding.

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Weycker D, Li X, Wygant GD, et al. Effectiveness and safety of apixaban versus warfarin as outpatient treatment of venous thromboembolism in U.S. clinical practice. *J Thromb Haemost.* 2018;118(11):(suppl):1951-1961.

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