Eliquis® (apixaban) tablets 5mg 2.5mg

ELIQUIS for the Treatment of DVT/PE

AMPLIFY: Phase III, Double-blind, Randomized Clinical Trial

A Real-World, Observational, Retrospective Database Analysis

Independently funded by the University of Pennsylvania

DVT=deep vein thrombosis; PE=pulmonary embolism.

INDICATION[1]

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, (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.

Please see additional Important Safety Information throughout and click here for U.S. Full Prescribing Information, including **Boxed WARNINGS**.

SELECT CHARACTERISTICS OF RANDOMIZED CLINICAL TRIALS AND REAL-WORLD DATA

RANDOMIZED CLINICAL TRIALS

- **Prospective design** with **prespecified**, well-defined inclusion/exclusion criteria, outcomes, and endpoints[4,5]
- Patients are **randomly** assigned to treatment or comparator[4,5]
- Randomized clinical trials are designed to show **causality** (ie, efficacy and safety data)[6]

VS

REAL-WORLD OBSERVATIONAL STUDIES

- **Observational in nature** and use data from routine clinical practice[5,7]
- Patients are **not randomized**[5,7]
- Can only evaluate **association** and therefore unable to determine causality[7]

AMPLIFY: A PHASE III, DOUBLE-BLIND, RANDOMIZED CLINICAL NONINFERIORITY TRIAL[2]

Study objective[1]:
To determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE* or VTE-related death.

5400 randomized patients with DVT and/or PE[1,8]

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

enoxaparin/warfarin
Standard of care at the time; 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

Primary efficacy endpoint: **Recurrent VTE* or VTE-related death[8]**

Primary safety endpoint: **Major bleeding[8]**

Select inclusion criteria: Objectively confirmed, symptomatic proximal DVT and/or PE.[8]

Select exclusion criteria[1,8]:
- Patients who required:
  - –Thrombectomy
  - –Insertion of a caval filter
  - –Use of a fibrinolytic agent
- Patients who had cancer and ≥6 months of low-molecular-weight heparin treatment planned
- Patients with:
  - –A life expectancy of <6 months
  - –Creatinine clearance <25 mL/min
  - –Significant liver disease
  - –Mechanical valve
  - –Atrial fibrillation
  - –Active bleeding

Baseline characteristics: Approximately 90% of patients had an unprovoked DVT or PE at baseline, and the 10% of patients with a provoked DVT/PE were required to have an additional ongoing risk factor, which included a previous episode of DVT/PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype. Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours).[1,8]

Major bleeding was defined as clinically overt bleeding accompanied by at least one of the following[2,8]:
- 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
- Transfusion—A transfusion of 2 or more units of packed red blood cells
- Hemoglobin decrease—A decrease in hemoglobin of 2 g/dL or more

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).[8]
DVT=deep vein thrombosis; INR=international normalized ratio; PE=pulmonary embolism; VTE=venous thromboembolism.

SELECTED IMPORTANT SAFETY INFORMATION

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

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.

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AMPLIFY: SELECT PATIENT BASELINE CHARACTERISTICS[2,8]

	ELIQUIS (n=2691)	ENOXAPARIN/WARFARIN (n=2704)
MEAN AGE, YEARS (SD)	57.2 (16.0)	56.7 (16.0)
MALE SEX, % (N)	58.3% (1569)	59.1% (1598)
QUALIFYING DIAGNOSIS, % (N)		
DVT	65.0% (1749)	65.9% (1783)
PE	34.6% (930)	33.5% (906)
PE only	25.2% (678)	25.2% (681)
PE with DVT	9.4% (252)	8.3% (225)
EXTENSIVE PE* AT BASELINE, % (N/TOTAL PE†)	38.4% (357/930)	36.0% (326/906)
RENAL IMPAIRMENT, % (N)		
Moderate (CrCl >30 to ≤50 mL/min)	6.0% (161)	5.5% (148)
Severe‡ (CrCl ≤30 mL/min)	0.5% (14)	0.6% (15)
PREVIOUS VTE, % (N)	17.2% (463)	15.1% (409)

*PE was defined as extensive if there were ≥2 lobes involving ≥50% of vasculature for each lobe.[8]
†Sum of qualifying diagnosis of PE only and PE with DVT.[8]
‡Patients with CrCl <25 mL/min were excluded.[8]
CrCl=creatinine clearance; DVT=deep vein thrombosis; PE=pulmonary embolism; SD=standard deviation; VTE=venous thromboembolism.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

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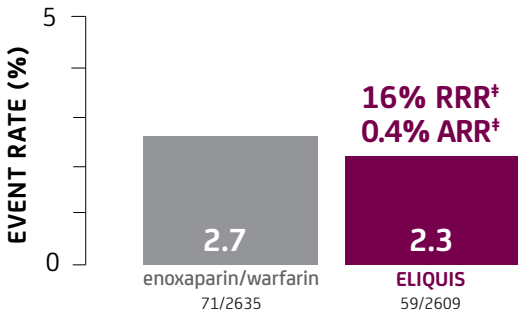
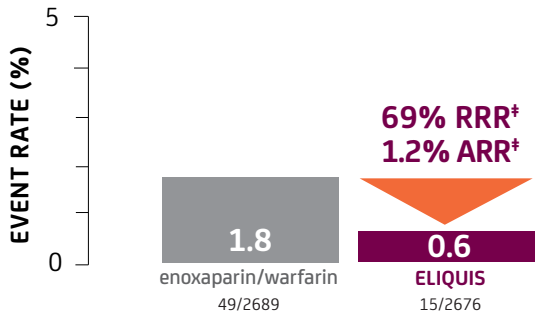
IN AMPLIFY, ELIQUIS DEMONSTRATED BOTH COMPARABLE EFFICACY AND SUPERIORITY IN MAJOR BLEEDING EVENTS VS ENOXAPARIN/WARFARIN[1]

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†
RR=0.31 (95% CI: 0.17–0.55); *P*<0.0001



PRIMARY SAFETY ENDPOINT

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[1]

The incidence of VTE-related death in AMPLIFY for ELIQUIS and enoxaparin/warfarin was 0.4% and 0.6% of patients, respectively.[1]

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

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).[8]
†Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.[1]
‡RRR was calculated as (1-RR) x 100. ARR is calculated as the difference between the incidences and is expressed as percentage points.
ARR=absolute risk reduction; CI=confidence interval; DVT=deep vein thrombosis; PE=pulmonary embolism; RR=relative risk; RRR=relative risk reduction; VTE=venous thromboembolism.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

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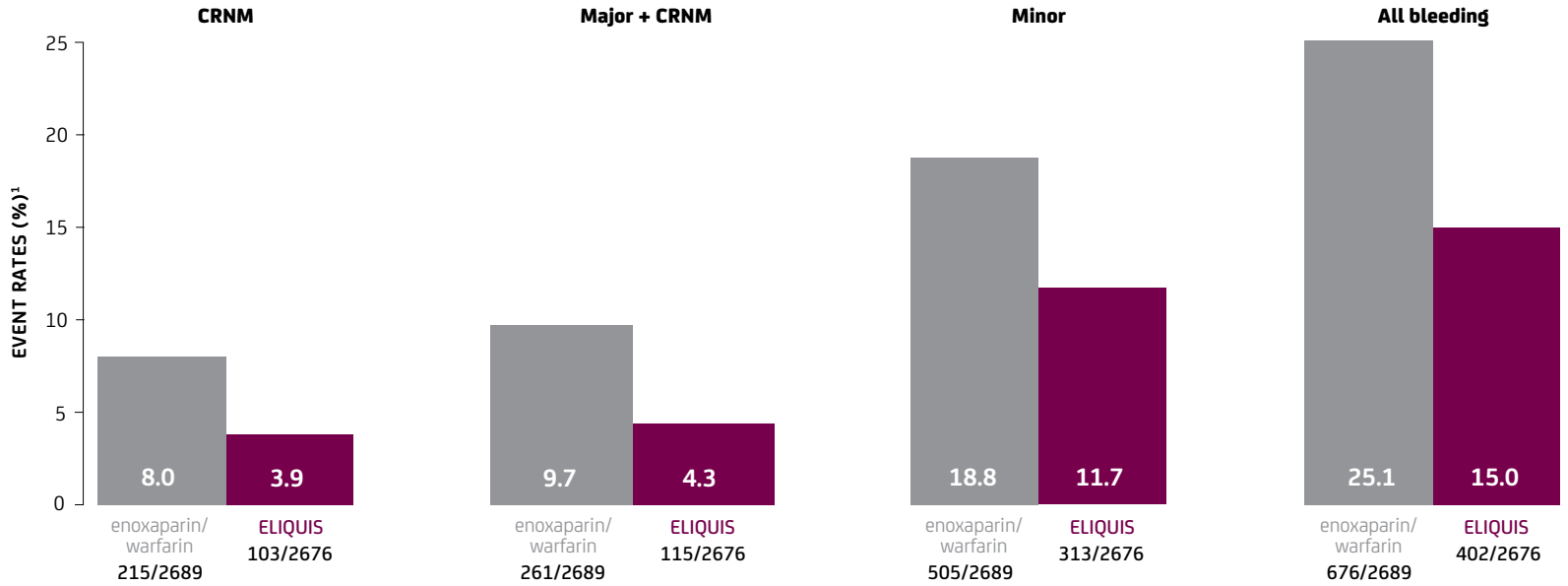
IN AMPLIFY, ELIQUIS DEMONSTRATED FEWER BLEEDING EVENTS ACROSS KEY SECONDARY ENDPOINTS, INCLUDING CRNM BLEEDING*[1]



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[1]

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

CRNM bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with at least 1 of the following: medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life.[8]

Minor bleeding was defined as all acute clinically overt bleeding events not meeting the criteria for either major bleeding or CRNM bleeding.[2]

*Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.[1]

CRNM=clinically relevant nonmajor.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

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Eliquis® (apixaban) tablets 5mg 2.5mg

FOR THE TREATMENT OF DVT/PE

INDEPENDENTLY FUNDED,
RETROSPECTIVE COHORT,
REAL-WORLD DATABASE ANALYSIS[3]

Published in the *Annals of Internal Medicine*®

Risk for Recurrent Venous Thromboembolism and Bleeding With ELIQUIS Compared With XARELTO® (rivaroxaban): An Analysis of Real-World Data[3]

Independently funded by the University of Pennsylvania.[3]

TOTAL STUDY POPULATION: 37,236 VTE PATIENTS[3]

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DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

ADVERSE REACTIONS

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

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STUDY DESIGN AND OBJECTIVE

Includes patients covered by commercial healthcare plans[3]

Adult new users* of XARELTO or ELIQUIS within 30 days of a VTE hospitalization (N=49,900)[3]

XARELTO (n=21,613) | **ELIQUIS (n=28,287)**

1:1 PROPENSITY SCORE MATCHING (PSM)

XARELTO (n=18,618)

Propensity score matching was used to reduce differences in baseline characteristics between both groups.[3]

ELIQUIS (n=18,618)

OBJECTIVE[3]

The objective of this real-world, retrospective analysis was to compare effectiveness and safety of ELIQUIS to XARELTO for newly prescribed patients with VTE.

PRIMARY EFFECTIVENESS OUTCOME[3]

Composite: Recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE).

PRIMARY SAFETY OUTCOME[3]

Composite: Gastrointestinal (GI) bleeding or intracranial bleeding.†

COMPONENTS OF COMPOSITE OUTCOMES[3]

DVT, PE, GI bleeding,† intracranial bleeding.†

*New user was defined as patients without use of apixaban or rivaroxaban during the 12-month look-back period.[3]
†Did not consider bleeding events documented in the outpatient setting, but rather focused on bleeding resulting in hospitalization.[3]
VTE=venous thromboembolism.

SELECT BASELINE CHARACTERISTICS[3]

	ELIQUIS (n=18,618)	XARELTO (n=18,618)
	AFTER 1:1 PROPENSITY SCORE MATCHING	
AGE, YEARS (MEAN)	67.4	67.5
SEX		
Male	47.5%	47.4%
Female	52.5%	52.5%
VTE TYPE*		
Provoked VTE	42.2%	42.2%
Unprovoked VTE	56.5%	56.5%
BASELINE COMORBIDITIES		
Anemia	15.1%	15.0%
Angina	2.3%	2.3%
Cancer	21.4%	22.4%
Chronic kidney disease	30.5%	31.0%
Coronary artery disease	1.2%	1.2%
Diabetes	29.5%	29.4%

Baseline characteristics were assessed up to 12 months before the cohort entry date.[3]

This is not a complete list of baseline characteristics. Additional baseline characteristics were assessed with this analysis.[3]

All baseline characteristics were well balanced after PSM (standardized difference <0.1).[3]

*Users were classified based on incident VTE type into 2 groups: VTE provoked by transient risk factors (for example, trauma, pregnancy, postpartum, surgery), and VTE that was either provoked by chronic risk factors (for example, cancer) or unprovoked.[3]
PSM=propensity score matching; VTE=venous thromboembolism.

SELECTED IMPORTANT SAFETY INFORMATION

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.

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SELECT BASELINE CHARACTERISTICS[3] (cont'd)

	ELIQUIS (n=18,618)	XARELTO (n=18,618)
BASELINE COMORBIDITIES (cont'd)		
End-stage renal disease	**1.5%**	**0.4%**
Heart failure	**19.4%**	**19.5%**
Hemophilia	**0.2%**	**0.2%**
Hypertension	**68.7%**	**69.0%**
Stroke	**19.4%**	**17.5%**
Transient ischemic attack	**14.7%**	**14.5%**
Ulcer	**6.8%**	**6.9%**
BASELINE MEDICATIONS†		
Antiplatelet	**12.6%**	**12.6%**
NSAIDs	**21.2%**	**21.1%**
Proton-pump inhibitors	**29.0%**	**29.1%**

Baseline characteristics were assessed up to 12 months before the cohort entry date.[3]

This is not a complete list of baseline characteristics. Additional baseline characteristics were assessed with this analysis.[3]

All baseline characteristics were well balanced after PSM (standardized difference <0.1).[3]

†Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use with oral anticoagulants increases the risk of bleeding.[1]

NSAID=nonsteroidal anti-inflammatory drug.

SELECTED IMPORTANT SAFETY INFORMATION

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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METHODS OF ANALYSIS[3]

Study date: 01/01/2015–06/30/2020
Index drug: ELIQUIS or XARELTO
Index date: Date of first prescription of ELIQUIS or XARELTO
Baseline period: 12 months prior to index date
Data source: Optum® Clinformatics®

DATA SOURCE

- Optum® Clinformatics® database captured commercial data in the United States. It included deidentified individual-level data on enrollment, patient demographics, outpatient claims, inpatient claims, prescription drug claims, and laboratory data for a subset of patients

INCLUSION CRITERIA

- Patients with VTE were identified by inpatient claims using International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) codes (415.1, 453.8, 453.2, 451.2, 451.9, 453.1, 453.9, I82.4, I82.9, I26.0, I26.9, 451.19, 451.81, 451.83, 451.89, 451.11) in the primary or principal position between 1/1/2015 and 6/30/2020
- Patients ≥18 years who initiated treatment with ELIQUIS or XARELTO within 30 days of diagnosis
- "New user" was defined as the absence of prior use of any anticoagulants during baseline period

EXCLUSION CRITERIA

- Less than 12 months of continuous enrollment before cohort entry
- History of prior dispensing of any anticoagulant during the baseline period
- History of DVT or PE during the baseline period (before index VTE diagnosis)

NOTE: Patients with mechanical heart valve were not excluded from this study. This was a small subset of patients (0.5%). The use of ELIQUIS or XARELTO is not recommended in patients with prosthetic heart valves.[1,3,9]

OUTCOMES

- Composite effectiveness endpoint of recurrent DVT or PE with hospitalization, based on ICD codes in principal position
- Composite safety endpoint of GI or intracranial bleeding with hospitalization, based on ICD codes in principal position
  - Bleeding other than GI or intracranial were not included
- Components of the composite endpoints were also analyzed separately

STATISTICAL ANALYSIS

- 1:1 PSM was employed to balance baseline characteristics between the ELIQUIS and XARELTO arms
- Cox proportional hazard models were used after PSM to estimate the HRs and 95% CIs for the outcomes. The model was adjusted for the calendar year
- **Sensitivity analyses were consistent with the primary analysis and included:**
  - Used IPTW average treatment effects (ATE) and average treatment effects on the treated (ATT) as methods of adjustment instead of matching. The IPTW method balances the characteristics of the two cohorts, while preserving the full sample size that met the inclusion criteria of the study[3]
  - Increased the gap between contiguous refills from 7 days to 15 days and 30 days
  - Symmetrically trimmed the tails of PS to remove extreme observations
  - Included VTE events occurring in the outpatient setting in the outcome definition
  - Examined the incidence of prostate cancer and breast cancer as negative control outcomes

FOLLOW-UP PERIOD

- Follow-up period began on cohort entry date and continued until the end of the study period (June 30, 2020), the occurrence of a study outcome of interest, discontinuation of the index medication, start of a comparator, or end of health plan enrollment for more than 30 days
- Median follow-up was 102 days for new ELIQUIS users and 105 days for new XARELTO users

ATE=average treatment effects; ATT=average treatment effects on the treated; CI=confidence interval; DVT=deep vein thrombosis; GI=gastrointestinal; HR=hazard ratio; IPTW=inverse probability of treatment weighting; PE=pulmonary embolism; PS=propensity score; PSM=propensity score matching; VTE=venous thromboembolism.

LIMITATIONS OF ANALYSIS

STUDY DESIGN/DEFINITION

- Due to the nature of retrospective, observational cohort studies, no causal relations could be inferred, and only statistical associations were assessed[10]
- In contrast to clinical trials, outcomes were defined by using ICD-9 and ICD-10 diagnosis codes rather than outcome adjudication[3,5]
- The presence of a claim for a filled prescription does not indicate whether the medication was consumed or taken as prescribed by the US prescribing information

BIAS/CONFOUNDING[3,7,11]

- Although cohorts were PS-matched, residual confounding is possible due to unmeasured factors such as lack of information available on body mass index, lifestyle variables, or over-the-counter medications such as aspirin. This limitation is especially important for interpreting direct oral anticoagulant (DOAC) vs DOAC comparison, which are for hypothesis generation, given the lack of head-to-head trials, and therefore results should be interpreted with caution

DATA COLLECTION[3]

- Exposure misclassification is possible because some patients may have overstocked medications and taken longer times to pick up their next prescription from an outpatient pharmacy
- Outcome misclassification is possible because of the diagnostic codes that were used for billing purposes
- Only severe outcomes resulting in hospitalization were included and not those presenting in the outpatient setting
- There was a lack of information on adherence
- Death data was not available
- Laboratory values were not available for all patients

GENERALIZABILITY[3]

- The cohort was restricted to commercially insured patients with VTE, which limited the generalizability to other populations. Because propensity score matching resulted in the loss of participants, the estimated effect may not generalize to the unmatched population. However, study results were consistent when using other statistical methods of adjustment IPTW

FOLLOW-UP

- Relatively short follow-up: median follow-up was 102 days for new ELIQUIS users and 105 days for new XARELTO users[1,3]
- The study had a shorter follow-up relative to the clinical trials of DOACs[3]

ICD-9=International Classification of Diseases, Ninth Revision; ICD-10=International Classification of Diseases, Tenth Revision; IPTW=inverse probability of treatment weighting; PS=propensity score; VTE=venous thromboembolism.

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.

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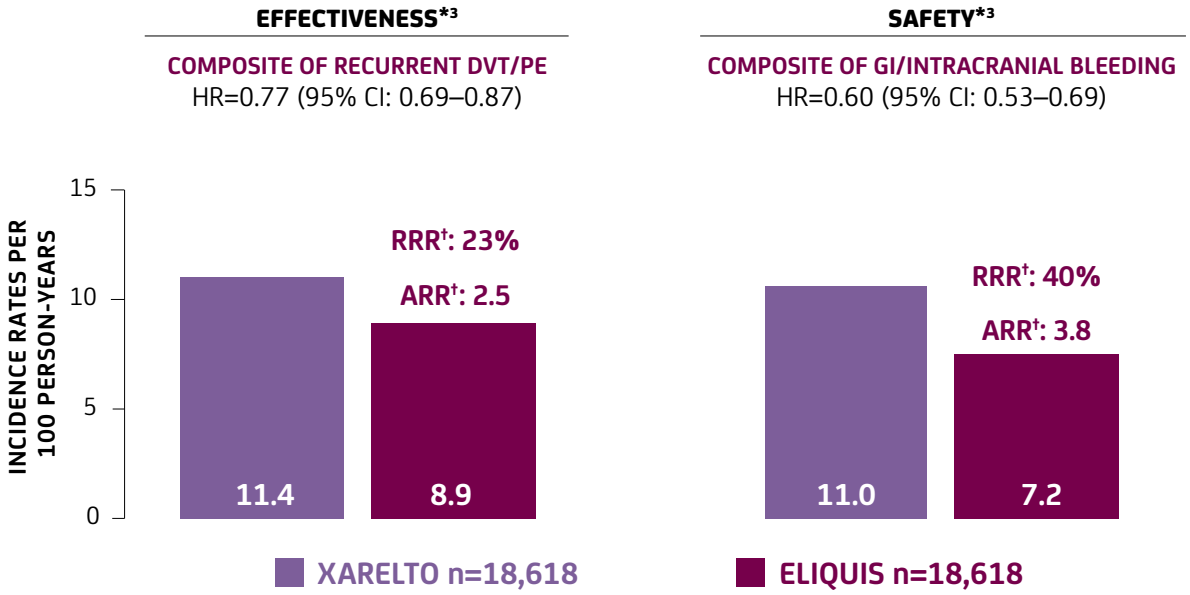
INCIDENCE OF RECURRENT VTE AND BLEEDING



Retrospective, observational 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.[5,7,11]

- Other real-world data analyses comparing ELIQUIS with other DOACs, using various data sources, time periods, study methodologies, and outcome definitions—showing different findings—have also been published[12-20]

The definitions of recurrent VTE, bleeding, follow-up period, and the patient population in AMPLIFY were different than in this analysis.[1,3]

Unlike in AMPLIFY, no enoxaparin/warfarin comparator arm was included in this analysis.[3,8]

There are currently no results from ELIQUIS vs XARELTO head-to-head clinical trials.[3,21]

†RRR was calculated as (1-HR) x 100. ARR was calculated as the difference between the incidence rates and is expressed per 100 person-years.[3]

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[1]

*Outcomes were based on ICD-9 and ICD-10 codes listed in the primary position in the inpatient discharge claims.[3]
Sensitivity analysis that used IPTW ATE instead of PSM for adjustment yielded similar results (ELIQUIS vs XARELTO): Recurrent VTE: HR=0.80 (95% CI: 0.72–0.89); Bleeding events: HR=0.60 (95% CI: 0.54–0.67).[3]
ARR=absolute risk reduction; ATE=average treatment effects; CI=confidence interval; DOAC=direct oral anticoagulant; DVT=deep vein thrombosis; GI=gastrointestinal; HR=hazard ratio; ICD-9=International Classification of Diseases, Ninth Revision; ICD-10=International Classification of Diseases, Tenth Revision; IPTW=inverse probability of treatment weighting; PE=pulmonary embolism; PSM=propensity score matching; RRR=relative risk reduction; VTE=venous thromboembolism.

SELECTED IMPORTANT SAFETY INFORMATION

LACTATION

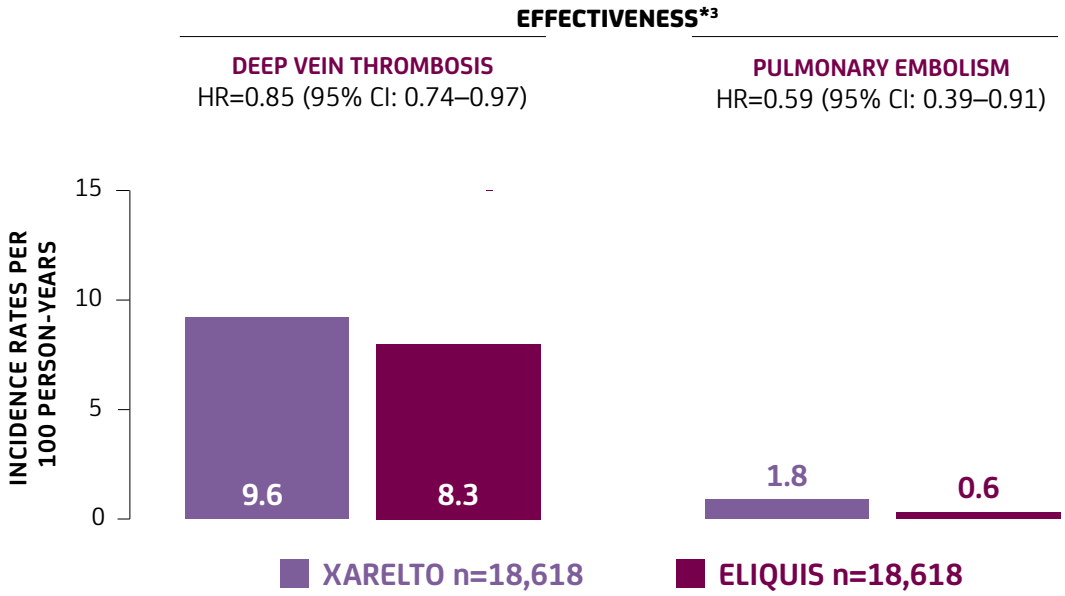
- Breastfeeding is not recommended during treatment with ELIQUIS.

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.

Please see additional Important Safety Information throughout and click here for U.S. Full Prescribing Information, including **Boxed WARNINGS**.

COMPONENTS OF COMPOSITE: INCIDENCE OF RECURRENT DVT AND RECURRENT PE



Retrospective, observational 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.[5,7,11]

- Other real-world data analyses comparing ELIQUIS with other DOACs, using various data sources, time periods, study methodologies, and outcome definitions—showing different findings—have also been published[12-20]

The definitions of recurrent VTE, bleeding, follow-up period, and the patient population in AMPLIFY were different than in this analysis.[1,3]

Unlike in AMPLIFY, no enoxaparin/warfarin comparator arm was included in this analysis.[3,8]

There are currently no results from ELIQUIS vs XARELTO head-to-head clinical trials.[3,21]

*Outcomes are based on first VTE event and based on ICD-9 and ICD-10 codes listed in the primary position in the inpatient discharge claims.[3]
CI=confidence interval; DOAC=direct oral anticoagulant; DVT=deep vein thrombosis; HR=hazard ratio; ICD-9=International Classification of Diseases, Ninth Revision; ICD-10=International Classification of Diseases, Tenth Revision; PE=pulmonary embolism; VTE=venous thromboembolism.

SELECTED IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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.

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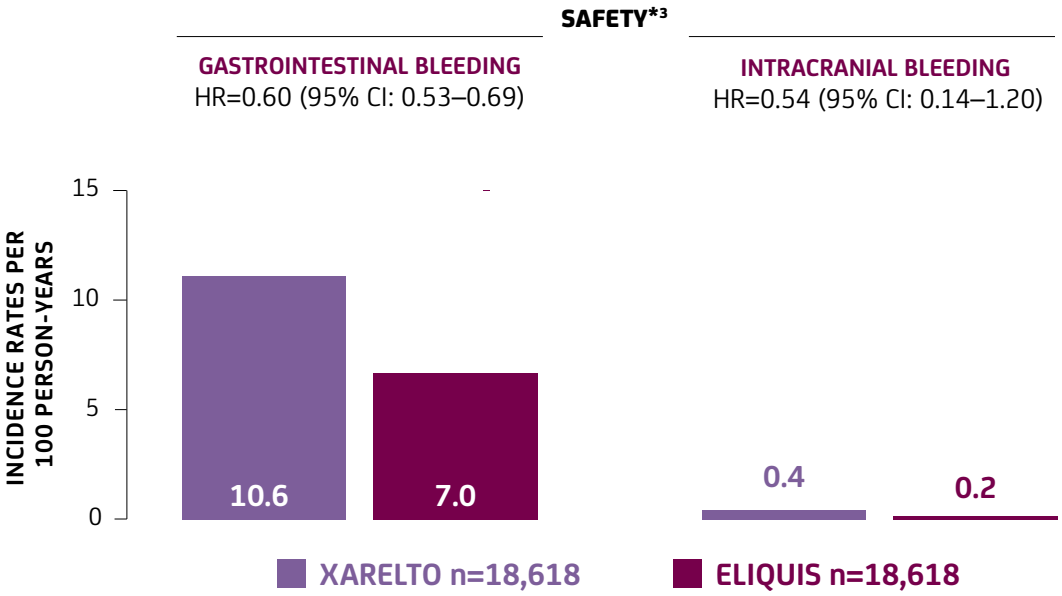
COMPONENTS OF COMPOSITE: INCIDENCE OF GI AND INTRACRANIAL BLEEDING



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Unlike in AMPLIFY, no enoxaparin/warfarin comparator arm was included in this analysis.[3,8]

There are currently no results from ELIQUIS vs XARELTO head-to-head clinical trials.[3,21]

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[1]

*Outcomes are based on first bleeding event and based on ICD-9 and ICD-10 codes listed in the primary position in the inpatient discharge claims.[3]

CI=confidence interval; DOAC=direct oral anticoagulant; GI=gastrointestinal; HR=hazard ratio; ICD-9=International Classification of Diseases, Ninth Revision; ICD-10=International Classification of Diseases, Tenth Revision; VTE=venous thromboembolism.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

Please see additional Important Safety Information throughout and click here for U.S. Full Prescribing Information, including **Boxed WARNINGS**.

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