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AMPLIFY →

A PIVOTAL, PHASE III, RANDOMIZED CLINICAL TRIAL IN PATIENTS WITH ACUTE SYMPTOMATIC DVT AND/OR PE[1-3]

JIN ET AL →

A REAL-WORLD, INDEPENDENTLY FUNDED, RETROSPECTIVE DATABASE ANALYSIS ASSESSING THE RISK OF RECURRENT VTE AND HEMORRHAGE IN COMMERCIALLY-INSURED AND MEDICARE ADVANTAGE PATIENTS WITH VTE IN CLINICAL PRACTICE[4]

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

INDICATIONS

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (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 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

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RANDOMIZED CLINICAL TRIALS[5-7]	VS	REAL-WORLD OBSERVATIONAL STUDIES[6-8]
Prospective design with **prespecified**, well-defined inclusion/exclusion criteria, outcomes, and endpoints		**Observational in nature** and use data from routine clinical practice
Patients are **randomly** assigned to treatment or comparator		Patients are **not randomized**
Randomized clinical trials are designed to show **causality** (ie, efficacy and safety data)		Can only evaluate **association** and therefore unable to determine causality

AMPLIFY: A RANDOMIZED, DOUBLE-BLIND, PHASE III NONINFERIORITY CLINICAL TRIAL[1-3]

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

PRIMARY EFFICACY ENDPOINT: **Recurrent VTE or VTE-related death**
PRIMARY SAFETY ENDPOINT: **Major bleeding**

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

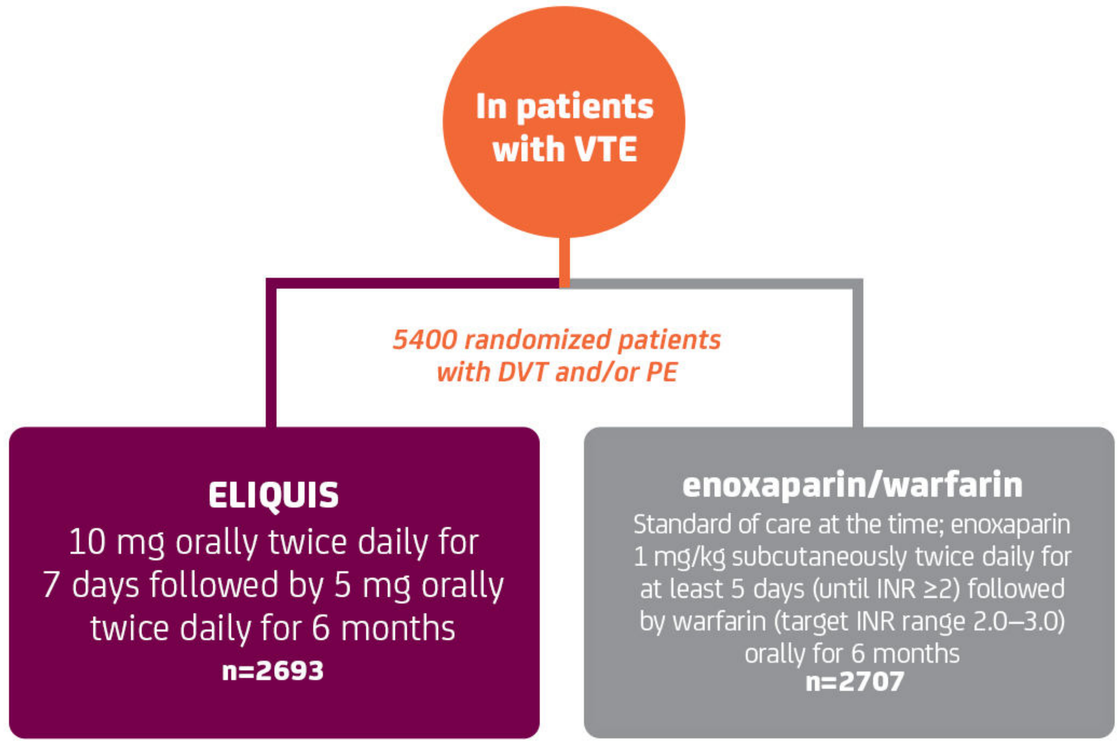
Select exclusion criteria:

- Patients who required:
  - Thrombectomy or
  - Insertion of a caval filter or
  - Use of a fibrinolytic agent
- Patients who had cancer and ≥6 months of LMWH treatment planned
- Patients with one or more of the following:
  - A life expectancy of <6 months
  - Creatinine clearance <25 mL/min
  - Significant liver disease
  - Mechanical heart 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).

Major bleeding was defined as clinically overt bleeding accompanied by at least one of the following:

1. **Hemoglobin decrease**—A decrease in hemoglobin of ≥2 g/dL;
2. **Transfusion**—A transfusion of 2 or more units of packed red blood cells;
3. **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;
4. **Fatal bleeding**



*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).
INR=International Normalized Ratio; LMWH=low-molecular-weight heparin.

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]

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	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.
†Sum of qualifying diagnosis of PE only and PE with DVT.
‡Patients with CrCl <25 mL/min were excluded.
CrCl=creatinine clearance; SD=standard deviation.

SELECTED IMPORTANT SAFETY INFORMATION

- **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.

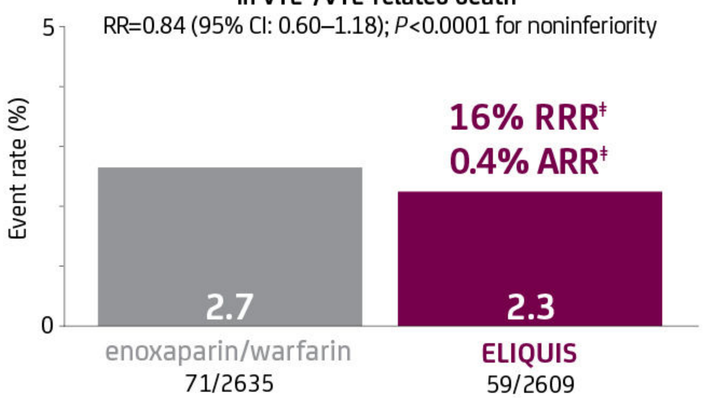
FOR THE TREATMENT OF DVT/PE,

IN AMPLIFY, ELIQUIS DEMONSTRATED BOTH COMPARABLE EFFICACY AND SUPERIORITY IN MAJOR BLEEDING EVENTS VS ENOXAPARIN/WARFARIN[1,2]

COMPARABLE

in VTE*/VTE-related death†

RR=0.84 (95% CI: 0.60–1.18); *P*<0.0001 for noninferiority

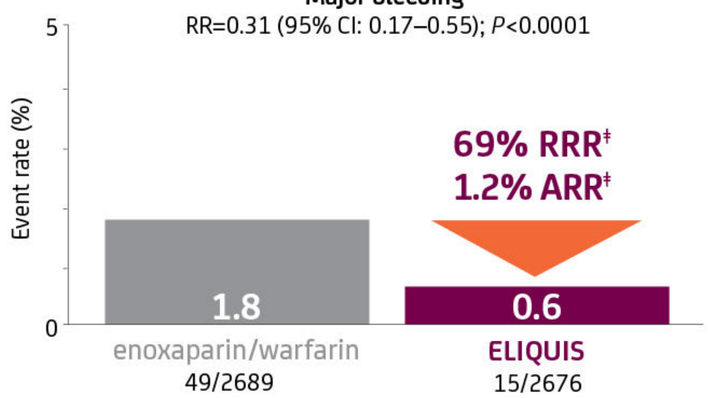


Primary Efficacy Endpoint

SUPERIOR

Major bleeding†

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



Primary Safety Endpoint

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

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[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).[2]
†Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.[1]
‡Statistical note: RRR was calculated as (1-RR)x100. ARR was calculated as the difference between the event rates and is expressed as percentage points.
ARR=absolute risk reduction; CI=confidence interval; RR=relative risk; RRR=relative risk reduction.

SELECTED IMPORTANT SAFETY INFORMATION

- **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.

AMPLIFY: COMPONENTS OF MAJOR BLEEDING[2]*

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	enoxaparin/warfarin (n=2689)	ELIQUIS (n=2676)
FATAL BLEEDING,† % (n)	0.1% (2)	<0.1% (1)
NONFATAL MAJOR BLEEDING AT A CRITICAL SITE, % (n)	0.5% (14)	0.1% (4)
• Intracranial	0.2% (6)	0.1% (3)
• Retroperitoneal	0.1% (3)	<0.1% (1)
• Intrathoracic	<0.1% (1)	0%
• Intraocular	0.1% (2)	0%
• Intraarticular	0.1% (2)	0%
OTHER NONFATAL MAJOR BLEEDING,‡ % (n)	1.2% (33)	0.4% (10)

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

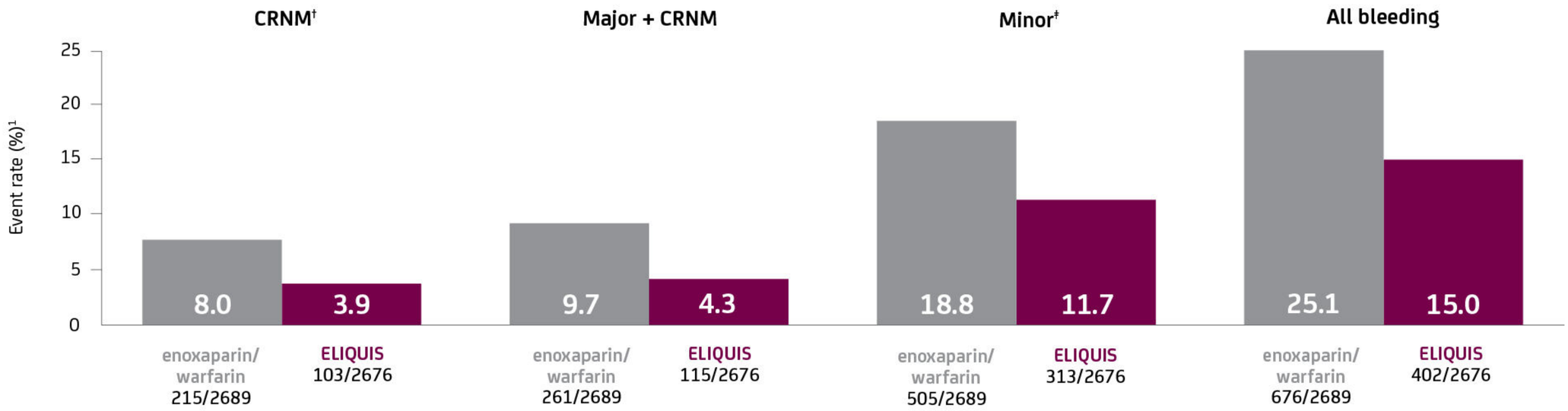
In AMPLIFY, the discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in the enoxaparin/warfarin-treated patients.[1]

*For patients who had more than one event, only the first event was counted.
†Death from gastrointestinal bleeding occurred in one patient in each group, and death from intramuscular bleeding in one patient in the conventional-therapy group.
‡Other nonfatal major bleeding events included gastrointestinal bleeding, intramuscular bleeding, epistaxis, urogenital bleeding, and subcutaneous hematoma.

SELECTED IMPORTANT SAFETY INFORMATION

- **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.

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]

*Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.[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.[2]
‡Minor bleeding was defined as all acute clinically overt bleeding events not meeting the criteria for either major bleeding or CRNM bleeding.[3]
CRNM=clinically relevant non-major.

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.

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INDEPENDENTLY FUNDED, RETROSPECTIVE, OBSERVATIONAL, REAL-WORLD DATABASE ANALYSIS[4]

JIN ET AL

THE LARGEST STUDY COMPARING EFFECTIVENESS AND SAFETY OF ELIQUIS VS XARELTO® (rivaroxaban) FOR COMMERCIALLY INSURED AND MEDICARE ADVANTAGE PATIENTS WITH DVT/PE

Independently funded by Stanford University

TOTAL STUDY POPULATION ANALYZED: 41,830

Published in *Thrombosis Research*

Study evaluating hemorrhage and recurrent venous thromboembolism in patients with VTE prescribed ELIQUIS and XARELTO

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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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STUDY OVERVIEW[4]

JIN ET AL: INDEPENDENTLY FUNDED
Real-world data analysis

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OBJECTIVE: To assess the risk of recurrent VTE and hemorrhage in patients with VTE treated with ELIQUIS or XARELTO.

STUDY DESIGN: Real-world, retrospective, observational cohort analysis.

Cohort Description[4,9]

Patients from an Optum® Clinformatics® Data Mart Database covered by commercial or Medicare Advantage healthcare plans, including:

- Adult patients with prior diagnosis of either DVT or PE on or before index anticoagulant start date
- ≥6 months of continuous pre-DVT/PE diagnosis follow up
- Prescribed ELIQUIS or XARELTO within 14 days of diagnosis

34,201 ELIQUIS patients and 46,007 XARELTO patients met the inclusion/exclusion criteria.

Patients who met inclusion criteria were cohort matched*

ELIQUIS (n=15,776)

XARELTO (n=26,054)

Outcomes with ELIQUIS or XARELTO were assessed

Primary outcomes†

- Recurrent VTE
- Intracranial hemorrhage (ICH)
- Non-intracranial hemorrhage (non-ICH)

These outcomes required hospitalization and were identified based on ICD-9 or -10 codes.

*Cohort matching was used to account for imbalances in baseline characteristics between the two groups.
†The comparative analysis used a competing risk model that accounted for death as a competing risk factor that precluded hospitalization for the outcomes of interest.

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.

Please see Important Safety Information throughout and click here for U.S. FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**.

BASELINE CHARACTERISTICS (POST-MATCHING)[4]

JIN ET AL: INDEPENDENTLY FUNDED
Real-world data analysis

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	ELIQUIS (n=15,776)	XARELTO (n=26,054)
AGE (MEAN, SD)	65.6, 15.4	65.5, 15.4
RACE		
Asian	0.6%	0.6%
Black	9.4%	9.4%
Hispanic	4.9%	4.9%
Unknown	9.8%	9.8%
White	75.3%	75.3%
SEX		
Female	56.1%	56.1%
Male	43.9%	43.9%
NO PRIOR PE	50.4%	50.4%
PRIOR PRESCRIPTION ANTIPLATELET MEDICATION*	2.6%	2.6%
CCI (MEAN, SD)†	1.13, 2.0	1.13, 2.0
MEDICARE	60.5%	60.5%

CONTINUED ON NEXT PAGE

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

†As described in Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries.[10]
CCI=Charlson Comorbidity Index; SD=standard deviation.

BASELINE CHARACTERISTICS (POST-MATCHING)[4] (CONTINUED)

JIN ET AL: INDEPENDENTLY FUNDED
Real-world data analysis

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	ELIQUIS (n=15,776)	XARELTO (n=26,054)
INDIVIDUAL COMORBIDITIES		
Hypertension (complicated)	11.1%	11.1%
Hypertension (uncomplicated)	52.6%	52.6%
Type 2 diabetes	22.9%	22.9%
Heart failure	9.3%	9.3%
Vascular disease	9.8%	9.8%
Pulmonary disease	20.4%	20.4%
Renal disease	10.4%	10.4%
Liver disease	3.2%	3.2%
Obesity	38.2%	38.2%
Tobacco use	29.7%	29.7%
Cerebrovascular disease	4.0%	4.0%
Malignancy (except skin)	10.6%	10.6%
Metastatic cancer	3.9%	3.9%
Low body weight	0.6%	0.6%

METHODS OF ANALYSIS[4]

INDEX DRUG: ELIQUIS or XARELTO
INDEX DATE: First known ELIQUIS or XARELTO prescription
DATA SOURCE: Optum® Clinformatics® Data Mart 2003—2019*

Data source
- The Optum Clinformatics database includes diagnosis, procedure, and pharmaceutical claims data derived from a database of administrative health claims for members of commercial and Medicare Advantage health plans
- Linked mortality data from Social Security Death File to account for death as a competing risk

Inclusion criteria
- Patients at least 18 years of age with a diagnosis of DVT or PE on or before the index anticoagulation start date
  - –Diagnoses were identified based on ICD-9 and ICD-10 codes (ICD-9: 415.1x, 453.4x, 453.5x; ICD-10: I26.x, I82.4x, I82.5x)[9]
- Patients who were prescribed oral anticoagulants within 14 days of receiving a diagnosis of DVT or PE. Although warfarin, ELIQUIS, XARELTO, PRADAXA, and SAVAYSA were initially identified for descriptive reporting of treatment patterns, the comparative analysis included only ELIQUIS and XARELTO due to higher prevalence of use over time
- Minimum 6 months of continuous pre-DVT/PE diagnosis follow-up

Exclusion criteria
- Patients with a prior diagnosis of atrial fibrillation, intracranial hemorrhage, or an unruptured intracranial aneurysm

Outcomes
- Outcomes below required hospitalization and were identified based on ICD-9 and -10 codes
- Results shown are for the matched cohorts
- **Primary Outcomes**
  - –Recurrent VTE, based on ICD codes in principal position
  - –Hemorrhage, intracranial and non-intracranial, based on ICD codes
- **Other Outcomes**
  - –Recurrent VTE and hemorrhage by route of hospital admission (emergency department or non-emergency department) were evaluated, but are not presented here

CONTINUED ON NEXT PAGE

*ELIQUIS and XARELTO were approved for the treatment of DVT and PE and to reduce the risk of recurrent DVT and PE following initial therapy in 2014 and 2012, respectively.[11,12]
Pradaxa® (dabigatran etexilate) is a registered trademark of Boehringer Ingelheim International GmbH.
Savaysa® (edoxaban) is a registered trademark of Daiichi Sankyo, Inc.
ICD=International Classification of Diseases.

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.

METHODS OF ANALYSIS[4] (CONTINUED)

INDEX DRUG: ELIQUIS or XARELTO
INDEX DATE: First known ELIQUIS or XARELTO prescription
DATA SOURCE: Optum® Clinformatics® Data Mart 2003—2019*

Statistical analyses

- To account for imbalances in baseline characteristics among treatment groups, a statistical method called coarsened exact matching was used
  - –This method creates similar subgroups (or strata) based on covariates in the treatment groups[9]
  - –The subgroups are weighted by the subgroup size in the analysis[9]
- Event rates were calculated as the total number of events divided by the cumulative years of continuous follow-up in patients on anticoagulation
- Univariable comparisons were conducted using the Kaplan-Meier method and the multivariable Cox proportional-hazards model to evaluate the independent contributions of covariates to risk
- To more accurately estimate risk during anticoagulation, death was considered a competing risk that precluded patients from hospitalization for recurrent VTE or hemorrhage. Given the comorbidity burden frequently observed among patients with VTE, it is possible that death due to unrelated causes may lead to a biased estimation of recurrent VTE and hemorrhage risk. After matching, the Fine-Gray statistical model was used to account for death as a competing risk[4,9]
- Sensitivity analyses:
  - –The risk of recurrent VTE and hemorrhage was assessed in the first 3 weeks of anticoagulation, which did not identify a difference in event rate on a week-to-week basis
  - –Analyses excluding events during the first 3 weeks of anticoagulation were generally consistent with the main analyses

Follow-up period

- Patients were followed until end of enrollment, death, outcome event, or discontinuation of anticoagulation (switch to a different oral anticoagulation or 14 days without evidence of anticoagulation)
- The average duration of anticoagulation:
  - –140.2 days for ELIQUIS
  - –140.9 days for XARELTO

*ELIQUIS and XARELTO were approved for the treatment of DVT and PE and to reduce the risk of recurrent DVT and PE following initial therapy in 2014 and 2012, respectively.[11,12]

SELECTED IMPORTANT SAFETY INFORMATION

- **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.

LIMITATIONS OF ANALYSIS[4]

Study design/definitions

- Due to the nature of retrospective, observational cohort studies, no causal relationships could be inferred, and only statistical associations were assessed[1,3]
- In contrast to clinical trials, outcomes were defined by using ICD-9 and ICD-10 diagnosis codes rather than clinical outcome adjudication[2,4]
- There is no guarantee that patients were dosed according to the US prescribing information for ELIQUIS and XARELTO

Bias/Confounding

- In order to reduce the effect of potential selection bias, multivariate modeling and cohort matching was conducted; however, bias from unobserved characteristics may persist (residual confounding)
- Evaluations using healthcare claims databases have limitations and may be biased due to systematic and unobserved differences in patients receiving ELIQUIS or XARELTO, physician prescribing habits, health plans, length of enrollment, and/or clinical practices. Such differences may be based on variations in market availability and, hence, differing indexing periods for ELIQUIS or XARELTO. This limitation is especially important for interpreting DOAC vs DOAC comparisons, which are for generating a hypothesis given the lack of head-to-head clinical trials; therefore, results should be interpreted with caution[4,13]
- The Social Security Death File in the Optum® Clinformatics® database may underestimate mortality rates. A more complete accounting of death could affect HRs. Random differences can not be excluded[4,14,15]

Data collection

- Limitations associated with retrospective data analyses, such as missing variables and miscoded or missing data, are possible
- Over-the-counter and inpatient medications are not captured in Optum Clinformatics, therefore, aspirin and heparin use were not assessed
- A major assumption of this study is that claims for prescribed oral anticoagulants are representative of actual patient utilization. It is possible that there are differences between prescribing and usage practices
- Mortality misclassification is possible: reported mortality available via linking with Social Security Death File conducted by Optum did not include cause of death, so death from DVT, PE, or anticoagulation cannot be differentiated from other causes of death. Additional deaths are possible as mortality captured in the database is only evidence of recorded death[14]
- Laboratory data unavailable for the vast majority of cohort

Generalizability

- The study was restricted to patients covered by UnitedHealth Group and only ~25% of Medicare Advantage enrollees, which therefore limits the generalizability of the findings

DOAC=direct oral anticoagulant.

SELECTED IMPORTANT SAFETY INFORMATION

- **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.

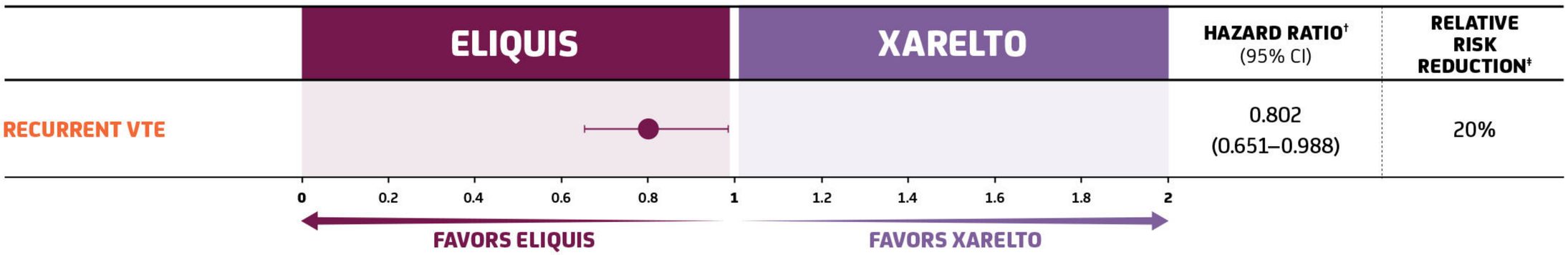
  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

PRIMARY OUTCOME

RECURRENT VTE FOR ELIQUIS AND XARELTO[4]*

JIN ET AL: INDEPENDENTLY FUNDED
Real-world data analysis

Eliquis® (apixaban) tablets 5mg 2.5mg



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.[13]

- 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[4,16-23]

The definitions of hemorrhage, recurrent VTE, follow-up period, and the patient population in AMPLIFY were different than in this analysis.[2,4]

Unlike in AMPLIFY, no enoxaparin/warfarin comparator arm was included in this analysis.[2,4]

There are currently no results from ELIQUIS vs XARELTO head-to-head clinical trials.[24]

*After cohort matching and a Fine-Gray statistical model accounting for death as a competing risk.
†Hazard ratios shown are derived from the Fine-Gray statistical model.
‡Statistical note: relative risk reduction was calculated as (1-HR)x100 and is shown where the 95% CI did not include 1.
CI=confidence interval.

SELECTED IMPORTANT SAFETY INFORMATION

- **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.

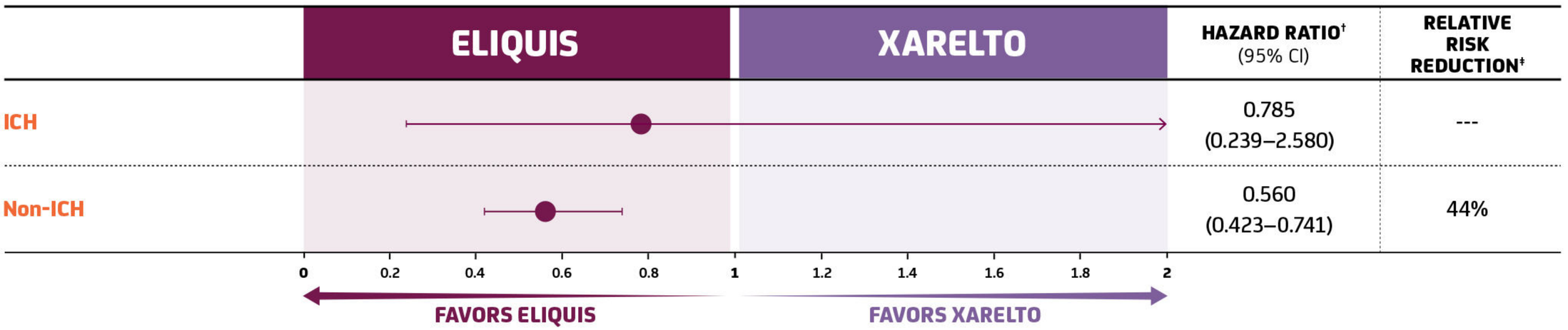
Please see Important Safety Information throughout and click here for U.S. FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**.

PRIMARY OUTCOME

INTRACRANIAL AND NON-INTRACRANIAL HEMORRHAGE FOR ELIQUIS AND XARELTO[4]*

JIN ET AL: INDEPENDENTLY FUNDED
Real-world data analysis

Eliquis® (apixaban) tablets 5mg 2.5mg



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

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.[13]

- 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[4,16-23]

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*After cohort matching and a Fine-Gray statistical model accounting for death as a competing risk.
†Hazard ratios shown are derived from the Fine-Gray statistical model.
‡Statistical note: relative risk reduction was calculated as (1-HR)x100 and is shown where the 95% CI did not include 1.
ICH=intracranial hemorrhage; non-ICH=non-intracranial hemorrhage.

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.

FOR PATIENTS WITH VTE

SUMMARY OF JIN ET AL: INDEPENDENTLY FUNDED
Real-world data analysis

Eliquis® (apixaban) tablets 5mg 2.5mg

PRIMARY OUTCOMES FROM A REAL-WORLD DATABASE ANALYSIS OF COMMERCIALLY-INSURED AND MEDICARE ADVANTAGE PATIENTS[4]

The largest study comparing effectiveness and safety of ELIQUIS vs XARELTO for commercially insured and Medicare Advantage patients with DVT/PE

This retrospective, observational real-world database analysis was independently funded by Stanford University. This analysis included 41,830 patients with DVT or PE who initiated treatment with ELIQUIS or XARELTO and met study inclusion and exclusion criteria.

Real-world effectiveness and safety outcomes for ELIQUIS vs XARELTO*

Recurrent VTE
HR=0.802
[95% CI: 0.651–0.988]†
20% relative risk reduction‡

Intracranial hemorrhage
HR=0.785
[95% CI: 0.239–2.580]†

Non-intracranial hemorrhage
HR=0.560
[95% CI: 0.423–0.741]†
44% relative risk reduction‡

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

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.[13]

The definitions of hemorrhage, recurrent VTE, follow-up period, and the patient population in AMPLIFY were different than in this analysis.[2,4]

There are currently no results from ELIQUIS vs XARELTO head-to-head clinical trials.[24]

*After cohort matching and a Fine-Gray statistical model accounting for death as a competing risk.
†Hazard ratios shown are derived from the Fine-Gray statistical model.
‡Statistical note: relative risk reduction was calculated as (1-HR)x100 and is shown where the 95% CI did not include 1.

LIMITATIONS

Please click here to review study limitations.

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 Important Safety Information throughout and click here for U.S. FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**.

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