

# BEA ET AL

## ELIQUIS VS XARELTO<sup>®</sup> (rivaroxaban) IN COMMERCIALY INSURED AND MEDICARE PATIENTS WITH VTE

### Oral Anticoagulation and Risk of Adverse Clinical Outcomes in Venous Thromboembolism

Study published in *JAMA*<sup>®</sup> *Internal Medicine*

**STUDY POPULATION ANALYZED: 41,819**

#### INDICATIONS

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

JAMA<sup>®</sup> is a registered trademark of the American Medical Association.

XARELTO<sup>®</sup> (rivaroxaban) is a registered trademark of Bayer Aktiengesellschaft.

Authors affiliated with Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA; Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts, USA; Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

DVT=deep vein thrombosis; JAMA=Journal of the American Medical Association; PE=pulmonary embolism; RCT=randomized clinical trial; RWD=real-world data; VTE=venous thromboembolism.

**AMPLIFY RCT SUMMARY**

Please see [page 2](#).

**AMPLIFY-EXT RCT SUMMARY**

Please see [page 3](#).

**RCT VS RWD**

Please see [page 4](#).

#### 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.

# AMPLIFY: A PIVOTAL, PHASE III, RANDOMIZED CLINICAL TRIAL OF PATIENTS WITH VTE<sup>2-4</sup>

The primary objective of AMPLIFY was to determine whether ELIQUIS was **noninferior** to enoxaparin/warfarin for the incidence of recurrent VTE\* or VTE-related death (primary efficacy endpoint) and major bleeding (primary safety endpoint).<sup>2,3</sup>

**AMPLIFY study design:** AMPLIFY was a double-blind study that randomized patients with VTE (N=5400) into 2 groups: those who received ELIQUIS 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months (n=2693); or standard of care at the time, enoxaparin 1 mg/kg subcutaneously twice daily for at least 5 days (until INR  $\geq 2$ ) followed by warfarin (orally) with a target INR range of 2.0–3.0 for 6 months (n=2707). Patients were assessed up to 6 months after randomization and 30 days after the end of the intended treatment period.<sup>2,3</sup>

**Select inclusion/exclusion criteria:** The study included patients aged  $\geq 18$  years with objectively confirmed, symptomatic proximal DVT and/or PE, with or without prior parenteral anticoagulation  $\leq 48$  hours. Patients were excluded if they: required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent; had cancer and  $\geq 6$  months of LMWH treatment planned; or had one or more of the following: life expectancy  $< 6$  months, creatinine clearance  $< 25$  mL/min, significant liver disease, mechanical heart valve, atrial fibrillation, or active bleeding.<sup>2,4</sup>

**Baseline characteristics:** Approximately 90% of patients in AMPLIFY had an unprovoked DVT or PE at baseline. 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.<sup>2</sup>

**Major bleeding was defined as clinically overt bleeding accompanied by  $\geq 1$  of the following:** A decrease in hemoglobin of  $\geq 2$  g/dL; a transfusion of  $\geq 2$  units of packed red blood cells; bleeding at  $\geq 1$  critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; or fatal bleeding.<sup>4</sup>

## In AMPLIFY, ELIQUIS demonstrated comparable efficacy and superiority in major bleeding events vs enoxaparin/warfarin.<sup>2</sup>

### Recurrent VTE\*/VTE-related death:

2.3% (n=59/2609) for ELIQUIS vs 2.7% (n=71/2635) for enoxaparin/warfarin

RR=0.84 (95% CI: 0.60–1.18);

P<0.0001 for noninferiority

RRR<sup>†</sup>=16%; ARR<sup>†</sup>=0.4%

### Major bleeding<sup>‡</sup>:

0.6% (n=15/2676) for ELIQUIS vs 1.8% (n=49/2689) for enoxaparin/warfarin

RR=0.31 (95% CI: 0.17–0.55);

P<0.0001

RRR<sup>†</sup>=69%; ARR<sup>†</sup>=1.2%

In AMPLIFY, the incidence of VTE-related death for ELIQUIS and enoxaparin/warfarin was 0.4% and 0.6% of patients, respectively. The most commonly observed adverse reactions in ELIQUIS-treated patients (incidence  $\geq 1\%$ ) were epistaxis, contusion, hematuria, menorrhagia, hematoma, hemoptysis, rectal hemorrhage, and gingival bleeding.

Discontinuation due to bleeding events in AMPLIFY occurred in 0.7% vs 1.7% of patients treated with ELIQUIS and enoxaparin/warfarin, respectively.

## ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.<sup>2</sup>

\*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).<sup>3</sup>

<sup>†</sup>Statistical note: RRR was calculated as  $(1-RR) \times 100$ . ARR was calculated as the difference between the event rates and is expressed as percentage points.

<sup>‡</sup>Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.<sup>2</sup>

ARR=absolute risk reduction; CI=confidence interval; INR=International Normalized Ratio; LMWH=low-molecular-weight heparin; RR=relative risk; RRR=relative risk reduction.

## SELECTED IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

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

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

**Eliquis**<sup>®</sup>  
(apixaban) tablets 5mg  
2.5mg

## AMPLIFY-EXT: A PIVOTAL, PHASE III, RANDOMIZED CLINICAL TRIAL OF PATIENTS WITH VTE<sup>2,5,6</sup>

The objective of AMPLIFY-EXT was to compare the incidence of recurrent VTE<sup>\*</sup>/all-cause death (primary efficacy endpoint) and major bleeding (primary safety endpoint) for ELIQUIS and placebo in patients who had been treated for DVT and/or PE for 6–12 months with anticoagulant therapy without having a recurrent event, and for whom physicians were uncertain about continuing anticoagulant therapy.<sup>5</sup>

**AMPLIFY-EXT study design:** AMPLIFY-EXT was a double-blind study that randomized patients with VTE who had already received treatment for 6–12 months (N=1671) into 2 groups: those who received ELIQUIS 2.5 mg orally twice daily for 12 months (n=842), or placebo for 12 months (n=829) to simulate patients with DVT/PE who would have received no further treatment after completing initial therapy. Approximately one-third of patients participated in the AMPLIFY study prior to enrollment in AMPLIFY-EXT.<sup>2,5</sup>

**Select inclusion/exclusion criteria:** Adult patients were required to have objectively confirmed, symptomatic proximal DVT and/or PE, and were excluded if they had multiple episodes of unprovoked DVT or PE.<sup>2,6</sup>

**Baseline characteristics:** Approximately 92% of patients in AMPLIFY-EXT had an unprovoked DVT or PE at baseline. The 8% of patients with a provoked baseline event had one additional risk factor for recurrence.<sup>2</sup>

**Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following:** A decrease in hemoglobin of ≥2 g/dL; a transfusion of ≥2 units of packed red blood cells; bleeding at ≥1 critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; or fatal bleeding.<sup>6</sup>

**In AMPLIFY-EXT, ELIQUIS demonstrated superior efficacy and a similar rate of major bleeding events vs placebo.<sup>2</sup>**

**Recurrent VTE<sup>\*</sup>/all-cause death:**  
3.8% (n=32/840) for ELIQUIS vs 11.6%  
(n=96/829) for placebo  
**RR**=0.33 (95% CI: 0.22–0.48); **P**<0.0001  
**RRR**<sup>†</sup>=67%; **ARR**<sup>†</sup>=7.8%

**Major bleeding<sup>‡</sup>:**  
0.2% (n=2/840) for ELIQUIS vs 0.5%  
(n=4/826) for placebo  
**P**=NS

In AMPLIFY-EXT, the incidence of all-cause death for ELIQUIS and placebo was 2.6% and 4.0%, respectively. The most commonly observed adverse reactions in ELIQUIS-treated patients (incidence ≥1%) were epistaxis, hematuria, hematoma, contusion, and gingival bleeding.

Discontinuation due to bleeding events in AMPLIFY-EXT occurred in 1% vs 0.4% of patients treated with ELIQUIS and placebo, respectively.

**ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.<sup>2</sup>**

<sup>\*</sup>Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).<sup>5</sup>

<sup>†</sup>Statistical note: RRR was calculated as (1-RR)×100. ARR was calculated as the difference between the event rates and is expressed as percentage points.

<sup>‡</sup>Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.<sup>2</sup>

NS=nonsignificant.

### 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.

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

**Eliquis**<sup>®</sup>  
(apixaban) tablets 5mg  
2.5mg

# SELECT CHARACTERISTICS OF RANDOMIZED CLINICAL TRIALS AND REAL-WORLD DATA

---

## RANDOMIZED CLINICAL TRIALS<sup>7-9</sup>

---



---

## REAL-WORLD OBSERVATIONAL STUDIES<sup>8-10</sup>

---

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

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

# STUDY OVERVIEW<sup>1</sup>

**OBJECTIVE:** To compare effectiveness and safety outcomes of select OACs among patients with VTE\*

**STUDY DESIGN:** Real-world, retrospective, observational, new-user cohort analysis

## Cohort Description

Patients covered by commercial or Medicare insurance from 3 US healthcare claims databases (CMS fee-for-service Medicare claims [2016–2020], Merative MarketScan<sup>®</sup> [2016–2022], and Optum<sup>®</sup> Clinformatics<sup>®</sup> Data Mart [2016–2024]), including:

- Adult patients aged  $\geq 18$  years ( $\geq 65$  years for Medicare) who initiated OACs within 30 days of a VTE hospitalization discharge\*<sup>†</sup>
- $\geq 12$  months of continuous insurance coverage
- Had not used any OAC<sup>‡</sup> or been hospitalized for VTE in the past year
- Initiated OAC between January 1, 2017, and the latest available in the data

**163,593 patients met the inclusion/exclusion criteria<sup>§</sup>**

Patients who met the inclusion criteria were propensity score matched to help balance baseline characteristics

ELIQUIS  
(n=20,947)

XARELTO  
(n=20,872)

## Assessed Outcomes

### Primary outcomes<sup>||</sup>

- Hospitalization for recurrent VTE, which included DVT or PE
- Hospitalization for major bleeding, which included intracranial, gastrointestinal, or other major bleeding events

**These outcomes were identified based on ICD-10 codes<sup>||, ||</sup>**

## BASELINE CHARACTERISTICS

Please see [page 6](#).

MarketScan<sup>®</sup> is a registered trademark of Merative U.S. LP.

\*New users of ELIQUIS, XARELTO, or warfarin. The date of OAC initiation was considered the cohort entry date. VTE was defined based on ICD-10 codes for DVT or PE as the primary discharge diagnosis.

<sup>†</sup>For patients with multiple VTE hospitalizations, the earliest event in the study period was selected.

<sup>‡</sup>Inclusive of apixaban, rivaroxaban, warfarin, edoxaban, or dabigatran.

<sup>§</sup>The published analysis includes a warfarin patient cohort, which has been excluded from this presentation.

<sup>||</sup>Hospitalizations for VTE or gastrointestinal bleeding were based on ICD-10 codes listed in the primary position. Hospitalizations for intracranial hemorrhage or other major bleeding were based on ICD-10 codes listed in any position.<sup>11</sup>

CMS=Centers of Medicare and Medicaid Services; ICD-10=International Classification of Diseases, Tenth Revision; OAC=oral anticoagulant.

## 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 for adults. Please visit [www.andexxa.com](http://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**.

**Eliquis**<sup>®</sup>  
(apixaban) tablets 5mg  
2.5mg

# BASELINE CHARACTERISTICS (POST-MATCHING)<sup>1</sup>

BEA ET AL: INDEPENDENTLY FUNDED  
Real-world data analysis 

	ELIQUIS (n=20,947)	XARELTO (n=20,872)
<b>DEMOGRAPHICS</b>		
Age, years, mean	72.1	72.0
Female	57.2%	57.5%
Male	42.8%	42.5%
<b>INDEX EVENT</b>		
Deep vein thrombosis	31.4%	30.9%
Pulmonary embolism	68.6%	69.1%
<b>COMORBIDITY SCORES</b>		
Combined comorbidity score, mean	4.7	4.7
Frailty score, mean	0.2	0.2
Modified HAS-BLED, mean	2.2	2.2
<b>BASELINE COMORBIDITIES</b>		
Acute myocardial infarction	6.7%	6.6%
Anemia	38.0%	38.0%
Any prior bleeding	29.5%	29.6%
Atrial fibrillation or flutter	16.4%	16.3%
Cancer, excluding nonmelanoma	19.5%	19.7%
Cerebrovascular disease	16.5%	16.6%
Chronic liver disease	11.4%	11.6%
Chronic kidney disease, stage 3	21.4%	21.1%
Chronic kidney disease, stage 4	1.9%	1.9%
Congestive heart failure	27.3%	27.3%
COVID-19*	1.2%	1.3%
Dementia	11.5%	11.6%
Diabetes	33.8%	33.8%
Fracture	8.7%	8.7%
Ischemic heart disease	37.1%	37.2%
Major surgery	8.0%	7.9%
Obstructive lung disorder	34.9%	35.4%
Peptic ulcer disease	3.1%	3.1%
Peripheral vascular disease	16.9%	16.9%
Valvular heart disease	27.9%	27.7%

CONTINUED ON NEXT PAGE

**In the AMPLIFY registrational trial, patients with atrial fibrillation, atrial flutter, creatinine clearance <25 mL/min, significant liver disease, and use of fibrinolytic agents were excluded. In adults with NVAf, ELIQUIS is indicated to reduce the risk of stroke.<sup>2,4</sup>**

ELIQUIS: ELIQUIS is not recommended in patients with severe hepatic impairment.<sup>2</sup>

XARELTO: No clinical data are available for adult patients with severe hepatic impairment.<sup>12</sup>

Avoid use of XARELTO in patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased.<sup>12</sup>

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use with oral anticoagulants increases the risk of bleeding.<sup>2</sup>

\*Any COVID-19-related inpatient and outpatient diagnoses or medications (eg, nirmatrelvir/ritonavir, remdesivir, molnupiravir).

HAS-BLED=hypertension, abnormal renal and liver function, stroke, bleeding, labile International Normalized Ratio, elderly, drugs and alcohol; NSAID=nonsteroidal anti-inflammatory drug; NVAf=nonvalvular atrial fibrillation.

Please see Important Safety Information throughout and [click here](#) for U.S. Full Prescribing Information, including **Boxed WARNINGS**.

**Eliquis**  
(apixaban) tablets 5mg  
2.5mg

# BASELINE CHARACTERISTICS (POST-MATCHING)<sup>1</sup> (CONTINUED)

BEA ET AL: INDEPENDENTLY FUNDED  
Real-world data analysis 

	ELIQUIS (n=20,947)	XARELTO (n=20,872)
<b>BASELINE COMEDICATIONS</b>		
Angiotensin-converting enzyme inhibitors	30.2%	30.0%
Angiotensin II receptor blockers	21.9%	22.2%
Antiarrhythmic agents	2.8%	2.7%
Antiplatelet agents	9.6%	9.7%
Beta-blockers	42.4%	42.2%
Calcium channel blockers	24.5%	24.6%
COPD and asthma medications	24.4%	24.8%
Estrogen	3.5%	3.6%
Loop diuretics	24.8%	25.1%
Nonsteroidal anti-inflammatory drugs	22.8%	23.2%
Opioids	49.2%	49.5%
Potassium-sparing diuretics	5.4%	5.4%
Proton-pump inhibitors	35.3%	35.6%
Statins	48.3%	48.4%
Thiazide diuretics	13.2%	13.6%
<b>HEALTHCARE UTILIZATION</b>		
No. of hospitalizations, mean	1.1%	1.1%
No. of emergency department visits, mean	2.1%	2.0%
Cardiologist visit	77.8%	77.9%
Nephrologist visit	9.6%	9.7%

**In the AMPLIFY registrational trial, patients with atrial fibrillation, atrial flutter, creatinine clearance <25 mL/min, significant liver disease, and use of fibrinolytic agents were excluded. In adults with NVAf, ELIQUIS is indicated to reduce the risk of stroke.<sup>2,4</sup>**

ELIQUIS: ELIQUIS is not recommended in patients with severe hepatic impairment.<sup>2</sup>

XARELTO: No clinical data are available for adult patients with severe hepatic impairment.<sup>12</sup>

Avoid use of XARELTO in patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased.<sup>12</sup>

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use with oral anticoagulants increases the risk of bleeding.<sup>2</sup>

COPD=chronic obstructive pulmonary disease.

Please see Important Safety Information throughout and [click here](#) for U.S. Full Prescribing Information, including **Boxed WARNINGS**.

**Eliquis**  
(apixaban) tablets <sup>5mg</sup>/<sub>2.5mg</sub>

# METHODS OF ANALYSIS<sup>1</sup>

**STUDY DRUG\*:** ELIQUIS or XARELTO

**INDEX DATE:** Date of OAC initiation, occurring between January 1, 2017, and the latest available in the data

**BASELINE PERIOD:** 1 year prior to index date

**DATA SOURCES:** Fee-for-service Medicare claims database, collected by the Centers for Medicare & Medicaid Services (2016–2020); Merative MarketScan (2016–2022); Optum’s De-identified Clinformatics Data Mart database (2016–2024)



## Data source

- The 3 US healthcare claims databases (Medicare, MarketScan, and Clinformatics) include information on enrollment, demographics, inpatient and outpatient diagnoses and procedures, billed laboratory tests, claims for filled prescription medications, and information on all-cause mortality



## Inclusion criteria

- Patients aged  $\geq 18$  years ( $\geq 65$  years for Medicare) who were prescribed an OAC within 30 days of inpatient discharge with a VTE diagnosis<sup>†</sup>
  - Treatment groups were assigned based on the first OAC filled after discharge from VTE hospitalization
  - Diagnoses were identified based on ICD-10 codes for DVT or PE as the primary discharge diagnosis
- Minimum 12 months of continuous insurance coverage



## Exclusion criteria

- End-stage kidney disease, hospitalization for VTE in the past year, hospice or palliative care in the year prior to the index VTE event, prior use of OACs in the year prior to the index date, or initiation of multiple OACs on the index date



## Outcomes

- The primary outcomes below required hospitalization<sup>1,11</sup>:
  - Recurrent VTE, including DVT or PE, based on ICD-10 codes in primary position
  - Gastrointestinal bleeding, based on ICD-10 codes in primary position, and intracranial or other major bleeding events, based on ICD-10 codes in any position
- Results shown are for the matched cohorts

**Definitions for treatment phase (3 months) and extended phase (>3 months) in this study differ from AMPLIFY, in which patients were treated with ELIQUIS for 6 months, and AMPLIFY-EXT, in which the extended phase was after 6 months of treatment.**<sup>1,3,5</sup>

CONTINUED ON NEXT PAGE

\*The published analysis includes a warfarin patient cohort, which has been excluded from this presentation.

<sup>†</sup>For patients with multiple VTE hospitalizations, the earliest event in the study period was selected.

ICD-10 CODES  
Please see [page 10](#).

## 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.

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

**Eliquis**<sup>®</sup>  
(apixaban) tablets 5mg  
2.5mg

# METHODS OF ANALYSIS<sup>1</sup> (CONTINUED)



## Statistical analyses

- PSM was used to help balance baseline characteristics between treatment groups using covariates known or suspected to be risk factors for the effectiveness and safety outcomes and exposures
- Covariates were assessed during the 365 days before and including OAC initiation date and included patient demographics, index VTE event, prior bleeding history, select comorbidities, prescription medications, comorbidity scores, and prior healthcare utilization



## Sensitivity analyses

- The sensitivity analyses below were consistent with the primary analysis:
  - Following patients from the day after OAC initiation until the first occurrence of outcome, loss of health insurance coverage, death, end of available data, or 365 days after OAC initiation
  - Requiring all diagnostic codes for major bleeding to be in the primary position for discharge
  - Modification of continuous exposure definition to extend the allowable gap between OAC dispensings from 14 to 30 days
  - Exclusion of patients who had an outpatient VTE diagnosis in any position during the baseline period



## Follow-up period

- Patients were followed from the day after OAC initiation until the first occurrence of outcome, treatment discontinuation (continuous exposure allowed for gaps of up to 14 days), switching to a different OAC, loss of health insurance coverage, death, or end of available data
- The median duration of follow-up was<sup>11</sup>:
  - 173 days for XARELTO patients (IQR, 62–369 days) and 182 days for ELIQUIS patients (IQR, 72–375 days) for recurrent VTE
  - 172 days for XARELTO patients (IQR, 61–367 days) and 183 days for ELIQUIS patients (IQR, 72–375 days) for major bleeding

**Definitions for treatment phase (3 months) and extended phase (>3 months) in this study differ from AMPLIFY, in which patients were treated with ELIQUIS for 6 months, and AMPLIFY-EXT, in which the extended phase was after 6 months of treatment.<sup>1,3,5</sup>**

IQR=interquartile range; PSM=propensity score matching.

## 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.
- **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 additional Important Safety Information throughout and [click here](#) for U.S. Full Prescribing Information, including **Boxed WARNINGS**.

**Eliquis**<sup>®</sup>  
(apixaban) tablets 5mg  
2.5mg

Diagnosis codes used for VTE in the study inclusion criteria included the following categories:

	ICD-10 Codes	Care Setting, Position
<b>DEEP VEIN THROMBOSIS</b>	I80.x, I81, I82.0, I82.1, I82.21x, I82.22x, I82.29x, I82.3, I82.40x, I82.41x, I82.42x, I82.43x, I82.44x, I82.45x, I82.46x, I82.49x, I82.4Yx, I82.4Zx, I82.50x, I82.51x, I82.53x, I82.54x, I82.55x, I82.56x, I82.59x, I82.5Yx, I82.5Zx, I82.60x, I82.62x, I82.70x, I82.72x, I82.A1x, I82.A2x, I82.B1x, I82.B2x, I82.C1x, I82.C2x, I82.89x, I82.9x	Inpatient, Primary
<b>PULMONARY EMBOLISM</b>	I26.x	Inpatient, Primary

Diagnosis and procedure codes used for VTE or major bleeding in the study outcomes included the following categories:

	ICD-10 Codes	Care Setting, Position
<b>DEEP VEIN THROMBOSIS</b>	I80.x, I81, I82.0, I82.1, I82.210, I82.220, I82.290, I82.3, I82.40x, I82.41x, I82.42x, I82.43x, I82.44x, I82.45x, I82.46x, I82.49x, I82.4Yx, I82.4Zx, I82.60x, I82.62x, I82.A1x, I82.A2x, I82.B1x, I82.C1x, I82.890, I82.90	Inpatient, Primary
<b>PULMONARY EMBOLISM</b>	I26.x	Inpatient, Primary
<b>GASTROINTESTINAL BLEED</b>	I85.01, I85.11, K20.81, K20.91, K22.11, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.x1, K31.811, K31.82, K55.21, K57.x1, K57.x3, K62.5, K92.0, K92.1, K92.2, OW3P0ZZ, OW3P3ZZ, OW3P4ZZ, OW3P7ZZ	Inpatient, Primary
<b>INTRACRANIAL HEMORRHAGE</b>	I60.x, I61.x, I62.x (except I62.03), S06.4XxA, S06.5XxA, S06.6XxA	Inpatient, Any
<b>OTHER MAJOR BLEEDING</b>	I31.2, R58, R31.0, R31.9, M25.00, M25.01x - M25.07x, R04.x (except R04.81)	Inpatient, Any



## Study design/definitions

- Due to the nature of retrospective, observational, cohort studies, no causal relationships can be inferred, and only statistical associations were assessed
- In contrast to clinical trials, outcomes were defined using ICD-10 diagnosis codes rather than outcome adjudication<sup>11</sup>
- Follow-up period included all available follow-up for patients; this is inclusive of the treatment phase and the extended treatment phase. There is no guarantee that patients were dosed according to the US prescribing information for ELIQUIS and XARELTO
- The presence of a claim for a filled prescription did not indicate whether the medication was consumed or taken as prescribed
- Definitions of treatment phase (3 months), extended phase (>3 months), and continuous treatment exposure (<14 days) differ from AMPLIFY and AMPLIFY-EXT<sup>1,3,5</sup>
- New users were defined as patients who had not received any OAC in the previous 12 months. Patients may have received OAC treatment prior to that period



## Bias/Confounding

- In order to reduce the effect of potential selection bias, propensity score matching was conducted; however, residual confounding is possible due to unmeasured factors and patient characteristics not captured in administrative claims databases, such as socioeconomic status, differences in insurance coverage, body mass index, laboratory results, cancer-related variables (ie, stages, location, specific cancer treatments), or over-the-counter medication use. The risk of confounding is especially important for interpreting DOAC vs DOAC comparison—which is for hypothesis generation—and therefore results should be interpreted with caution
- Comorbidity and comedication covariates were evaluated up to one year prior to the index date. Differences in the duration of comorbidities and exposure to comedications in relation to the index date may have influenced outcomes differently
- Imbalances in the cause of censoring may bias the results

CONTINUED ON NEXT PAGE

DOAC=direct oral anticoagulant; ICD=International Classification of Diseases.

## SELECTED IMPORTANT SAFETY INFORMATION

### ADVERSE REACTIONS

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

### 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.

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

*Eliquis*<sup>®</sup>  
(apixaban) tablets 5mg  
2.5mg

# LIMITATIONS OF ANALYSIS<sup>1</sup> (CONTINUED)



## Data collection

- Limitations associated with retrospective data analyses, such as missing baseline variables and miscoded or missing data, are possible. Supplements, over-the-counter medications, and inpatient medications are not captured in the healthcare claims databases included in this study
- Exposure misclassification is possible because there is no information about adherence
- Outcome misclassification is possible because study outcomes were based on ICD codes<sup>1,11</sup>
  - Although sensitivity analyses yielded similar results, not all hospitalizations with a bleeding diagnosis may have been due to major bleeding
- Overall follow-up duration was not reported (median follow-up was reported only after censoring for either VTE or major bleeding)<sup>11</sup>



## Generalizability

- This study was restricted to adults covered by commercial, commercial/Medicare Advantage, or Medicare insurance, which therefore limits the generalizability of the findings<sup>1,11</sup>
- Study population included inpatient VTE cases only, which may limit generalizability of the results to outpatient populations

## 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*

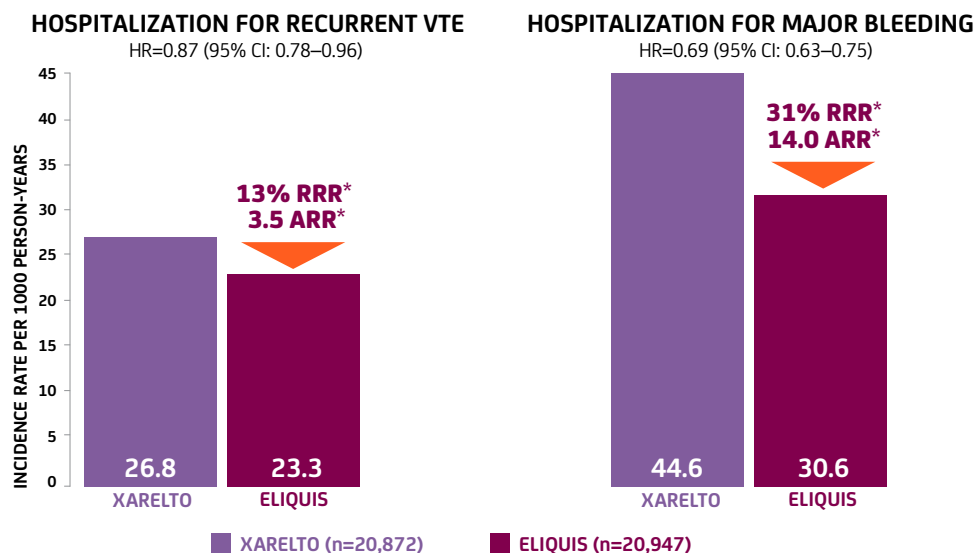
Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

- **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.

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

**Eliquis**<sup>®</sup>  
(apixaban) tablets 5mg  
2.5mg

# HOSPITALIZATIONS FOR RECURRENT VTE AND MAJOR BLEEDING IN PATIENTS TREATED WITH ELIQUIS VS XARELTO<sup>1</sup>



**In this real-world analysis, ELIQUIS was associated with relative risk reductions of 13% and 31% in hospitalizations for recurrent VTE and major bleeding, respectively, compared to XARELTO.**

## ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.<sup>2</sup>

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.<sup>13</sup>

The definitions of outcomes, treatment period, follow-up period, and the patient population in AMPLIFY or AMPLIFY-EXT were different than in this analysis.<sup>1,2</sup>

Other studies (including RCT and RWD analyses) in adult patients comparing ELIQUIS with other DOACs, which may have used different methods, populations, and outcome definitions, have shown different findings.<sup>14-22</sup>

\*Statistical note: RRR was calculated as (1-HR)x100. ARR represents the difference between the event rates and is expressed as per 1000 person-years. ARR=absolute risk reduction; CI=confidence interval; HR=hazard ratio; RRR=relative risk reduction.

## 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 additional Important Safety Information throughout and [click here](#) for U.S. Full Prescribing Information, including **Boxed WARNINGS**.

**Eliquis**<sup>®</sup>  
(apixaban) tablets 5mg  
2.5mg

## REFERENCES

1. Bea S, Iyer GS, Kim DH, et al. Oral anticoagulation and risk of adverse clinical outcomes in venous thromboembolism. *JAMA Intern Med.* 2025;185(7):837-846. doi:10.1001/jamainternmed.2025.1109
2. Eliquis [package insert]. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY.
3. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. doi:10.1056/NEJMoa1302507
4. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808, Protocol. doi:10.1056/NEJMoa1302507
5. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708. doi:10.1056/NEJMoa1207541
6. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708, Protocol. doi:10.1056/NEJMoa1207541
7. Stanley K. Design of randomized controlled trials. *Circulation.* 2007;115(9):1164-1169. doi:10.1161/CIRCULATIONAHA.105.594945
8. Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. *JACC Cardiovasc Interv.* 2008;1(3):211-217. doi:10.1016/j.jcin.2008.01.008
9. Kovesdy CP, Kalantar-Zadeh K. Observational studies versus randomized controlled trials: avenues to causal inference in nephrology. *Adv Chronic Kidney Dis.* 2012;19(1):11-18. doi:10.1053/j.ackd.2011.09.004
10. Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health.* 2007;10(5):326-335. doi:10.1111/j.1524-4733.2007.00186.x
11. Bea S, Iyer GS, Kim DH, et al. Oral anticoagulation and risk of adverse clinical outcomes in venous thromboembolism. *JAMA Intern Med.* 2025;185(7):837-846, Supplement. doi:10.1001/jamainternmed.2025.1109
12. Xarelto [package insert]. Janssen Pharmaceuticals, Inc., Titusville, NJ.
13. Silverman SL. From randomized controlled trials to observational studies. *Am J Med.* 2009;122(2):114-120. doi:10.1016/j.amjmed.2008.09.030
14. Dawwas GK, Leonard CE, Lewis JD, Cuker A. Risk for recurrent venous thromboembolism and bleeding with apixaban compared with rivaroxaban: an analysis of real-world data. *Ann Intern Med.* 2022;175(1):20-28. doi:10.7326/M21-0717
15. Jin MC, Sussman ES, Feng AY, et al. Hemorrhage risk of direct oral anticoagulants in real-world venous thromboembolism patients. *Thromb Res.* 2021;204:126-133. doi:10.1016/j.thromres.2021.06.015
16. Aryal MR, Gosain R, Donato A, et al. Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world. *Blood Adv.* 2019;3(15):2381-2387. doi:10.1182/bloodadvances.2019000572
17. Mantha S, Ansell J. Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. *J Thromb Thrombolysis.* 2015;39(2):155-165. doi:10.1007/s11239-014-1102-5
18. Sindet-Pedersen C, Staerk L, Pallisgaard JL, et al. Safety and effectiveness of rivaroxaban and apixaban in patients with venous thromboembolism: a nationwide study. *Eur Heart J Cardiovasc Pharmacother.* 2018;4(4):220-227. doi:10.1093/ehjcvp/pyy021
19. Cohen AT, Hamilton M, Mitchell SA, et al. Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: systematic review and network meta-analysis. *PLoS One.* 2015;10(12):e0144856. doi:10.1371/journal.pone.0144856
20. Lutsey PL, Zakai NA, MacLehose RF, et al. Risk of hospitalised bleeding in comparisons of oral anticoagulant options for the primary treatment of venous thromboembolism. *Br J Haematol.* 2019;185(5):903-911. doi:10.1111/bjh.15857
21. Bott-Kitslaar DM, McBane RD, Casanegra AI, et al. Apixaban and rivaroxaban in patients with acute venous thromboembolism. *Mayo Clin Proc.* 2019;94(7):1242-1252. doi:10.1016/j.mayocp.2018.09.022
22. Howe Z, Naville-Cook C, Cole D. Bleeding rates of veterans taking apixaban or rivaroxaban for atrial fibrillation or venous thromboembolism. *J Thromb Thrombolysis.* 2019;47(2):280-286. doi:10.1007/s11239-018-1770-7

[Click here to learn more about ELIQUIS.](#)

Please see Important Safety Information throughout and [click here](#) for U.S. Full Prescribing Information, including **Boxed WARNINGS**.



Bristol Myers Squibb®



ELIQUIS® and the ELIQUIS logo are trademarks of Bristol-Myers Squibb Company.

All other trademarks are property of their respective companies.

© 2025 Bristol-Myers Squibb Company. 432-US-2500361 10/25

**Eliquis**  
(apixaban) tablets 5mg  
2.5mg