ELIQUIS for the Treatment of DVT/PE

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

– Retrospective RWD Analysis of Patients Treated in the ED

DVT=deep vein thrombosis; ED=emergency department; PE=pulmonary embolism; RWD=real-world data.

INDICATION

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

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 clinical trials and real-world data

RANDOMIZED CLINICAL TRIALS[1-3]	vs	REAL-WORLD OBSERVATIONAL STUDIES[2,4]
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

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.
- **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.

Patients who have a DVT/PE

Risk of recurrence is highest in the first week following an initial DVT/PE and remains elevated through the fourth week[5]*

Approximately 4.5% of patients admitted for a DVT/PE are readmitted for a second DVT or PE, with almost half of readmissions occurring within the first 30 days[6†]

*A meta-analysis of 15 randomized controlled trials (N=27,237 patients) from 1992-2012 was conducted to evaluate the time course of recurrent DVT/PE over the first 3 months of treatment. Rates of recurrent DVT/PE remained elevated through the second, third, and fourth weeks. A statistically significant decrease in the incidence of recurrent DVT/PE was observed in week 2 compared to week 1, and week 5 compared to week 4 following initial DVT/PE event.[5]

†A retrospective observational cohort analysis of MarketScan database (Oct 2009-Apr 2013) identified 214,901 patients with a primary diagnosis of DVT or PE at hospital admission. The median time to hospital readmission due to DVT/PE was then assessed. This retrospective claims database analysis had several limitations, including potential for bias from missing data; therefore, the results may not be representative of national averages. Additionally, inadequate ICD-9-CM diagnostic code specificity may over/underestimate patient cohorts.[6]

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.

- **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: A phase III, double-blind, randomized clinical noninferiority trial[7-9]

Study objective: 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

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

Primary safety endpoint: Major bleeding†

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).
†See following page for definition of **major bleeding**.
INR=international normalized ratio; VTE=venous thromboembolism.

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.

AMPLIFY: A phase III, double-blind, randomized clinical noninferiority trial[7-9] (cont'd)

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

Select exclusion criteria:

- 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).

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

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

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.

AMPLIFY: Select patient characteristics[8,9]

	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]
SD=standard deviation.

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (cont'd)

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.

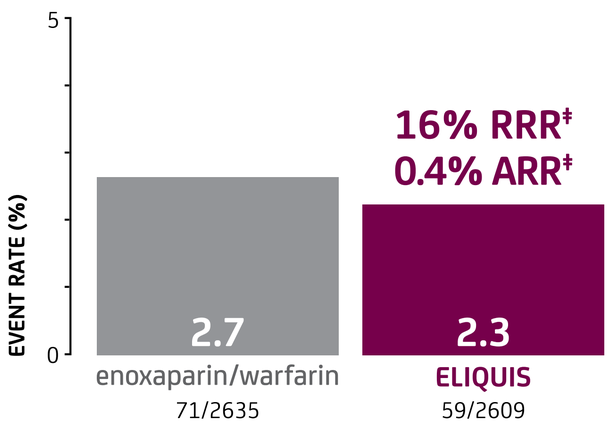
Eliquis® (apixaban) tablets 5mg 2.5mg

In AMPLIFY, ELIQUIS demonstrated BOTH comparable efficacy AND superiority in major bleeding events vs enoxaparin/warfarin[7]

COMPARABLE

in VTE*/VTE-related death

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

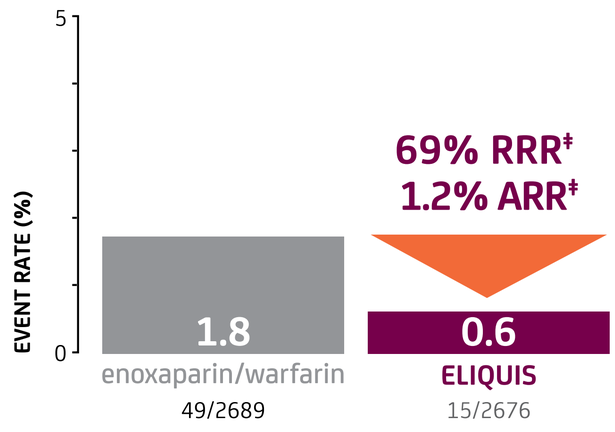


PRIMARY EFFICACY ENDPOINT

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.[7]

The incidence of VTE-related death in AMPLIFY for ELIQUIS and enoxaparin/warfarin was 0.4% and 0.6% of patients, respectively.[7†]

- Discontinuation rate due to bleeding events: 0.7% in ELIQUIS-treated patients vs 1.7% with enoxaparin/warfarin[7]
- 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[7]

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).

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

‡RRR was calculated as (1-RR) x 100. ARR is calculated as the difference between the incidences and is expressed as percentage points.

ARR=absolute risk reduction; CI=confidence interval; RR=relative risk; RRR=relative risk reduction.

SELECTED IMPORTANT SAFETY INFORMATION

PREGNANCY

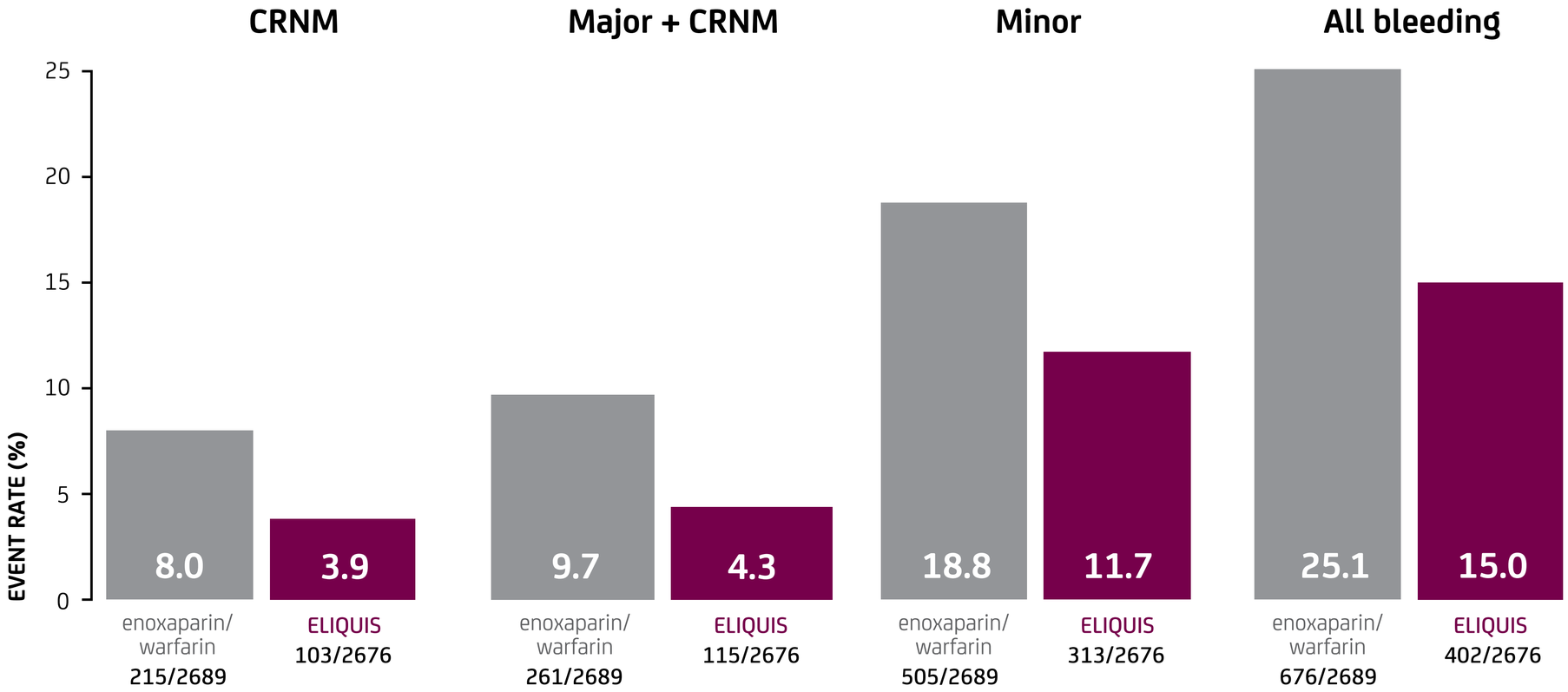
- The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.
  - *Labor or 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.

Eliquis® (apixaban) tablets 5mg 2.5mg

In AMPLIFY, ELIQUIS demonstrated fewer bleeding events across key secondary endpoints, including CRNM bleeding[7]*



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[7]

- In AMPLIFY, the discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared with 1.7% in the enoxaparin/warfarin-treated patients[7]

*Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.[7]
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.[9]
CRNM=clinically relevant nonmajor.

SELECTED IMPORTANT SAFETY INFORMATION

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.

Retrospective Real-World Data Analysis of Patients Treated With ELIQUIS or Warfarin for VTE in the ED: Hospital Readmissions (Inpatient or ED)

Published in the peer-reviewed journal *Hospital Practice*

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.

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

Objectives and methods of analysis[10]

Objectives: To evaluate the following in patients with VTE treated with ELIQUIS or warfarin in the ED, with or without inpatient care following the ED encounter:

- VTE or major bleeding-related hospital readmissions* (inpatient or ED) during the 1-month period following the initial hospitalization or ED encounter

This analysis included outcomes that are not presented here.

Index event:	Index date:	Baseline period:
First VTE ED visit	ED or hospital discharge date after the index event	12 months prior to index event

Study design

Retrospective observational study of the Premier Hospital database health care claims (from August 1, 2014, through May 31, 2018) for patients with VTE who were treated with ELIQUIS or warfarin in the ED, with or without inpatient care following the ED encounter.

The Premier® Hospital database is a hospital drug utilization database in the United States. It contains complete billing and coding history for more than 8 million hospital admissions per year (more than 25% of all inpatient admissions annually in the United States) and >765 million outpatient visits (ie, ED, ambulatory surgery centers, alternate sites of care for primary diagnosis) since 2012.

Statistical analysis

- Multivariate logistic regression analysis was used to compare the likelihood of 1-month hospital readmission (ED or inpatient) in patients initially treated in the ED with ELIQUIS compared to warfarin, after adjusting for differences in patient characteristics

Specific characteristics adjusted for:

- Age, gender, race, payer type, Charlson Comorbidities Index score group, prior VTE diagnosis in the baseline period, prior bleeding diagnosis in the baseline period, index event VTE type, and hospital characteristics (geographic region, urban/rural location, teaching status, and bed size)

Subgroup analyses

Subgroup analyses of the adjusted outcomes of major bleeding-related and VTE-related 30-day readmissions were additionally conducted for study subpopulations that included:

- Patients with an index ED visit only without inpatient admission
- ED patients admitted to the inpatient setting

*Major bleeding-related and VTE-related readmissions were defined as readmissions with a corresponding primary discharge ICD-9/ICD-10 diagnosis code.

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

Premier® is a registered trademark of Premier Healthcare Alliance.

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.

Study population[10]

Inclusion criteria

- Patients aged ≥18 with an ED visit with a primary discharge diagnosis code of VTE
- Primary discharge diagnosis of VTE identified by

  ICD-9-CM or ICD-10-CM codes from the Premier Hospital database from August 1, 2014, through May 31, 2018
  - The ICD-9-CM and ICD-10-CM codes used for the diagnosis of VTE included the following main categories[11]:
    - PE and infarction (except due to sepsis)
    - Phlebitis and thrombophlebitis of deep veins of lower extremities
    - Other acute venous embolism and thrombosis of deep vessels of lower extremities
  - There were patients included in the study who had codes other than the above, for phlebitis and thrombophlebitis or other venous embolism or thrombosis that involved[11]:
    - Superficial vessels
    - Vessels of the upper extremities or of other sites
- Patients who received ELIQUIS or warfarin for the treatment of VTE during ED encounter
  - Patients treated with warfarin were additionally required to have received ≥1 injectable anticoagulant, including LMWH, UFH, or fondaparinux, during ED visits
  - Patients treated with ELIQUIS included those with or without injectable anticoagulant usage

Exclusion criteria

During index event:

- Patients who received treatment with both ELIQUIS and warfarin
- Patients treated with a DOAC other than ELIQUIS, such as XARELTO, PRADAXA, or SAVAYSA
- Patients transferred from other facilities or died during the index events

12 months prior to index event or during index event:

- Primary or secondary diagnosis code for atrial fibrillation/atrial flutter, or pregnancy
- Records of inferior vena cava filter usage

Xarelto® (rivaroxaban) is a registered trademark of Bayer Aktiengesellschaft. Pradaxa® (dabigatran etexilate) is a registered trademark of Boehringer Ingelheim Pharma GmbH & Co KG. Savaysa® (edoxaban) is a registered trademark of Daiichi Sankyo, Inc.
DOAC=direct oral anticoagulant; LMWH=low-molecular-weight heparin; UFH=unfractionated heparin.

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.

Select patient characteristics[10]*

	ELIQUIS n=12,174	WARFARIN n=27,767
DEMOGRAPHICS		
Age, mean (SD)	59.7 (17.0)	59.3 (17.2)
Gender, female, n (%)	6139 (50.4)	13,752 (49.5)
CHARLSON COMORBIDITY INDEX, MEAN (SD)	1.0 (1.8)	1.3 (2.0)
COMORBIDITIES AT INITIAL VTE ED EVENT, N (%)		
Hypertension	5340 (43.9)	14,068 (50.7)
Diabetes	2015 (16.6)	5552 (20.0)
Peripheral vascular disease	1333 (11.0)	3967 (14.3)
Coronary artery disease	1167 (9.6)	3451 (12.4)
PRIOR VTE DIAGNOSIS IN THE BASELINE PERIOD, N (%)	1215 (10.0)	3270 (11.8)
PRIOR ANY BLEEDING DIAGNOSIS IN THE BASELINE PERIOD, N (%)	165 (1.4)	460 (1.7)
PRIMARY DIAGNOSIS VTE TYPE, N (%)		
DVT	8809 (72.4)	15,966 (57.5)
PE	3365 (27.6)	11,801 (42.5)

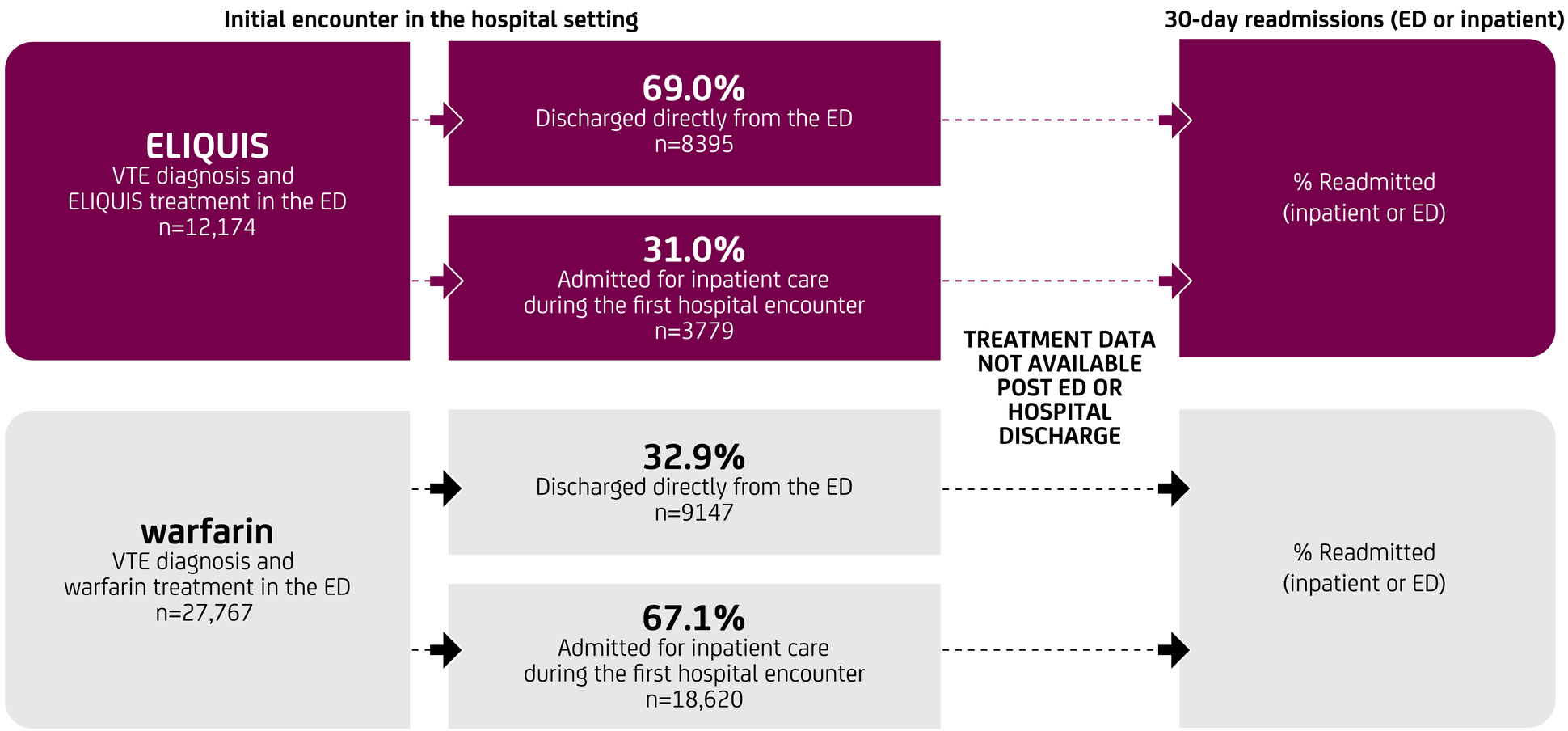
*Patient demographics and clinical characteristics were evaluated during the index event; prior VTE and any bleeding diagnoses were measured during the 12-month baseline period.

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.

Patient flow in the 2 study cohorts[10]



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.

Study considerations and select limitations[10]

- Due to the nature of **retrospective observational studies, no causal relationship** between the OAC treatment and outcomes could be concluded
- Premier Hospital database **did not include data about outpatient use of OACs or other medications** post hospital visit (including post ED direct discharge)
- **Findings may not have been generalizable** to the entire US population of patients with VTE in a hospital setting
- Administrative hospital data collected for purposes other than research and analysis are **subject to inherent limitations due to constraints of diagnostic codes, potential coding errors, and missing data**
- Because this study was based on claims data and because patients were not randomized to treatments, despite adjustment for **observed confounding factors**, an imbalance of unobserved variables between treatment arms could have resulted in residual confounding
- Only **readmissions** to the **same hospital or hospital system within the Premier network** could have been identified in the database. **This may have led to an underestimation of the readmission rates**
- In this analysis, VTE-related readmissions were defined as hospital readmissions (including subsequent ED visits or inpatient admissions), with the corresponding primary discharge ICD-9/ICD-10 diagnosis codes. These VTE-related readmissions may not all have been VTE recurrences
- VTE or bleeding-related deaths were not assessed in this analysis
- The duration and dosage of an injectable anticoagulant required for study inclusion for patients treated with warfarin or allowed for patients treated with ELIQUIS were not recorded in the database or assessed
- Utilization of outpatient routine monitoring among patients who were treated with warfarin was not evaluated in this analysis
- This analysis was funded by Pfizer Inc. and Bristol Myers Squibb. Some of the authors of the publication have received compensation from or have an affiliation with Pfizer Inc. and/or Bristol Myers Squibb

OAC=oral anticoagulant.

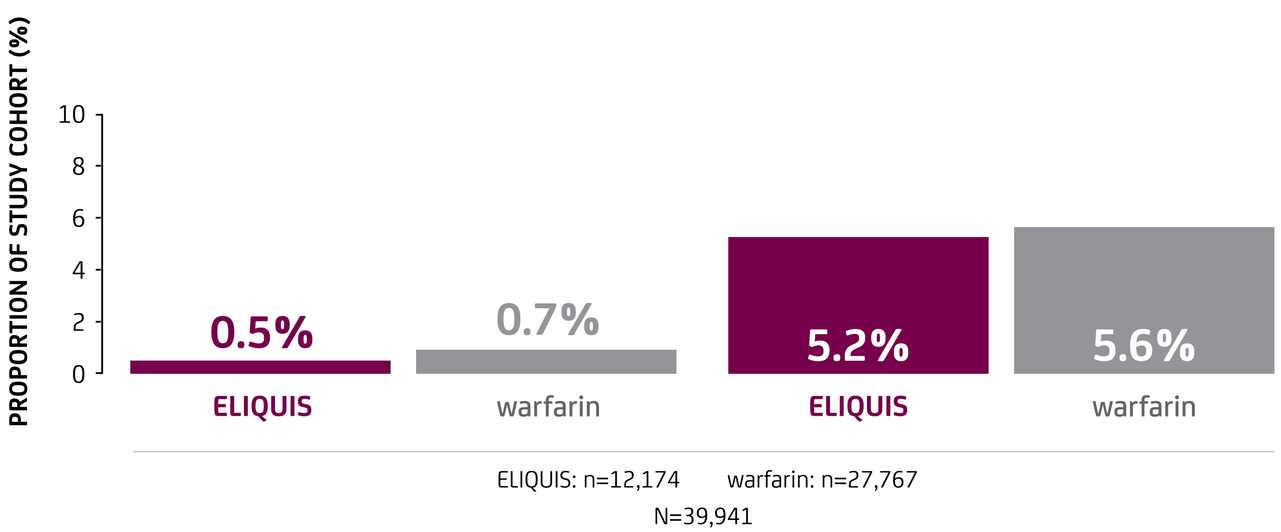
SELECTED IMPORTANT SAFETY INFORMATION

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.

Rate of hospital readmissions (inpatient or ED) in patients treated for initial VTE in the ED*† with ELIQUIS or warfarin[10]

30-DAY RATE OF READMISSION‡§



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[7]

Observational retrospective analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables; causality cannot be established in observational analyses.[12]

The general study design, including the definitions of VTE and bleeding-related outcomes, the follow-up period, and the patient population in AMPLIFY were different than in this analysis. AMPLIFY included "VTE-related death" in the efficacy analysis, which could not be evaluated in this analysis.[8,10]

*Major bleeding-related and VTE-related readmissions were defined as readmissions with a corresponding primary discharge ICD-9/ICD-10 diagnosis code.
†With or without inpatient care following the initial ED encounter.
‡Readmission rates are unadjusted.
§Readmission included ED visits and inpatient admissions.
¶ORs have been adjusted for confounding factors.
OR=odds ratio.

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (cont'd)

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.

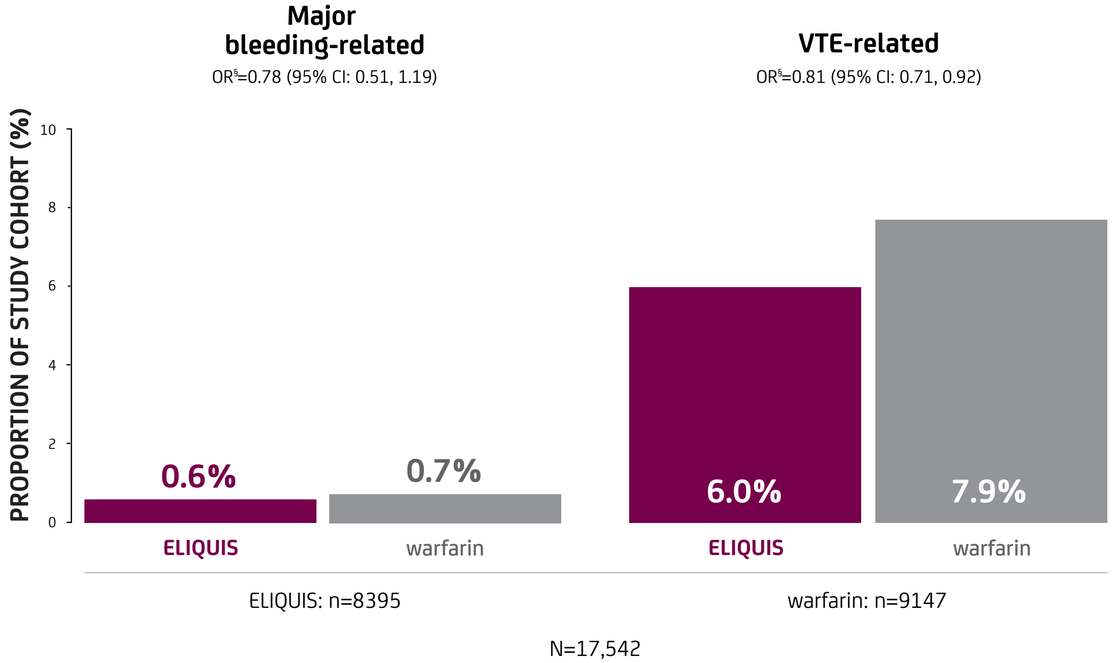
- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.
- **Anticoagulants and Antiplatelet Agents:** Coadministration 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.

ED only: Rate of hospital readmissions (inpatient or ED) in patients treated for initial VTE in the ED* with ELIQUIS or warfarin[10,11]

Subgroup analysis of patients with an initial VTE ED visit only

Subgroup analysis 1

30-DAY RATE OF READMISSION†‡ IN PATIENTS WITH AN INITIAL VTE ED VISIT ONLY



*With or without inpatient care following the initial ED encounter.
†Readmission rates are unadjusted.
‡Readmission included ED visits and inpatient admissions.
§ORs have been adjusted for confounding factors.

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[7]

Observational retrospective analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables; causality cannot be established in observational analyses.[12]

The general study design, including the definitions of VTE and bleeding-related outcomes, the follow-up period, and the patient population in AMPLIFY were different than in this analysis. AMPLIFY included "VTE-related death" in the efficacy analysis, which could not be evaluated in this analysis.[8,10]

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

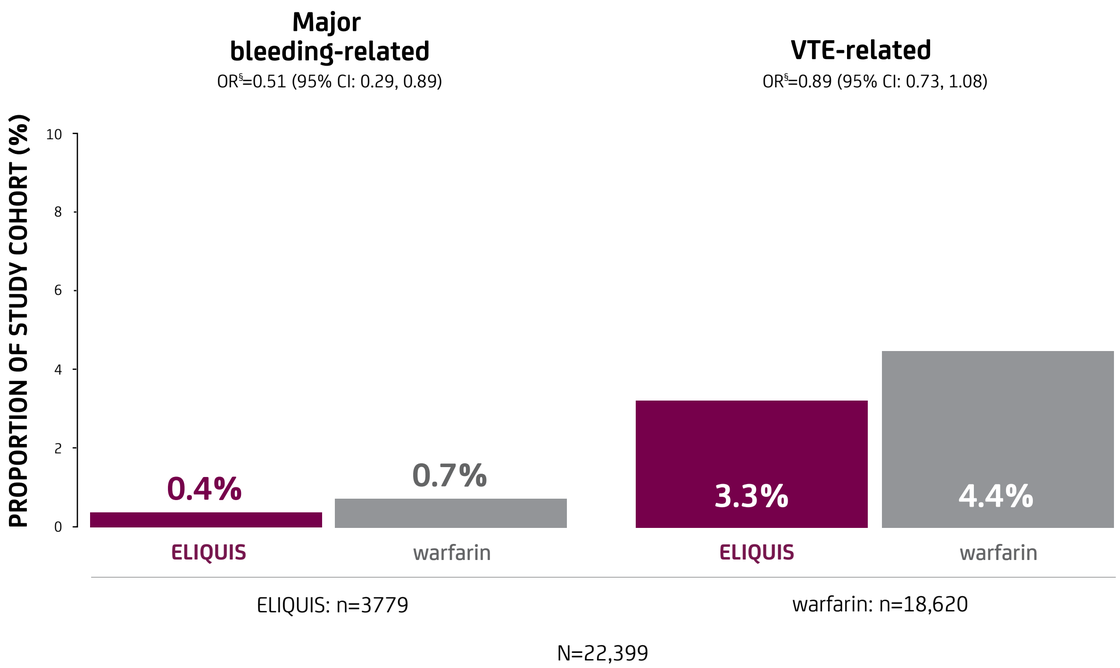
- Breastfeeding is not recommended during treatment with ELIQUIS.

ED + inpatient: Rate of hospital readmissions (inpatient or ED) in patients treated for initial VTE in the ED* with ELIQUIS or warfarin[10,11]

Subgroup analysis of patients with an initial VTE ED visit who were admitted to the inpatient setting

Subgroup analysis 2

30-DAY RATE OF READMISSION†‡ IN PATIENTS ADMITTED TO THE INPATIENT SETTING AFTER AN ED VISIT



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[7]

Observational retrospective analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables; causality cannot be established in observational analyses.[12]

The general study design, including the definitions of VTE and bleeding-related outcomes, the follow-up period, and the patient population in AMPLIFY were different than in this analysis. AMPLIFY included "VTE-related death" in the efficacy analysis, which could not be evaluated in this analysis.[8,10]

*With or without inpatient care following the initial ED encounter.
†Readmission rates are unadjusted.
‡Readmission included ED visits and inpatient admissions.
§ORs have been adjusted for confounding factors.

SELECTED IMPORTANT SAFETY INFORMATION

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.

References

1. Stanley K. Design of randomized controlled trials. *Circulation*. 2007;115(9):1164-1169.
2. Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. *JACC Cardiovasc Interv*. 2008;1(3):211-217.
3. 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.
4. 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.
5. Limone BL, Hernandez AV, Michalak D, Bookhart BK, Coleman CI. Timing of recurrent venous thromboembolism early after the index event: a meta-analysis of randomized controlled trials. *Thromb Res*. 2013;132(4):420 -426.
6. Nutescu EA, Crivera C, Schein JR, Bookhart BK. Incidence of hospital readmission in patients diagnosed with DVT and PE: clinical burden of recurrent events. *Int J Clin Pract*. 2015;69(3):321-327.
7. ELIQUIS [package insert]. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY.
8. Agnelli G, Buller HR, Cohen A, et al; for AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.
9. Agnelli G, Buller HR, Cohen A, et al; for AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9)(suppl appendix):799-808. doi:10.1056/NEJMoal302507.
10. Deitelzweig S, Hlavacek P, Mardekian J, et al. Comparison of inpatient admission rates of patients treated with apixaban vs warfarin for venous thromboembolism in the emergency department. *Hosp Pract*. 2020;48(1):41-48.
11. Deitelzweig S, Hlavacek P, Mardekian J, et al. Comparison of inpatient admission rates of patients treated with apixaban vs warfarin for venous thromboembolism in the emergency department. *Hosp Pract*. 2020;48(1)(suppl appendix):41-48. doi:10.1080/21548331.2020.1718925.
12. Silverman SL. From randomized controlled trials to observational studies. *Am J Med*. 2009;122(2):114-120.

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

Bristol Myers Squibb™ | Pfizer