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ARISTOTLE

A PIVOTAL, PHASE III, RANDOMIZED CLINICAL TRIAL IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION (NVAF)[1-3]

FRALICK ET AL

A REAL-WORLD, INDEPENDENTLY FUNDED, RETROSPECTIVE DATABASE ANALYSIS OF PATIENTS WITH NVAF IN CLINICAL PRACTICE[4]

INDICATION

ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).

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.

SELECT CHARACTERISTICS OF RANDOMIZED CLINICAL TRIALS AND REAL-WORLD DATA

RANDOMIZED CLINICAL TRIALS[5-7]

- **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)

VS

REAL-WORLD OBSERVATIONAL STUDIES[6,8,9]

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

ARISTOTLE: A PIVOTAL, PHASE III, RANDOMIZED CLINICAL TRIAL OF >18,000 PATIENTS WITH NVAF[1-3]*

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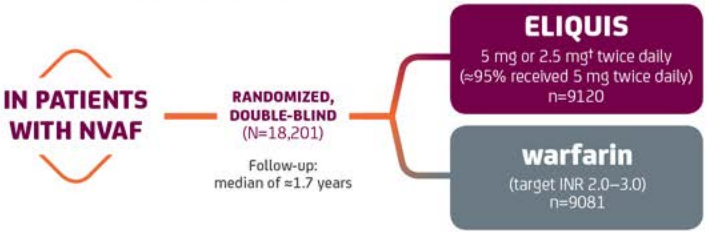
PRIMARY OBJECTIVE: Determine whether ELIQUIS was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) or systemic embolism (SE).

SUPERIORITY OF ELIQUIS TO WARFARIN WAS ALSO EXAMINED FOR:
PRIMARY EFFICACY ENDPOINT: Stroke/SE
PRIMARY SAFETY ENDPOINT: Major bleeding



***Key inclusion criteria:** NVAF and ≥1 risk factors for stroke: prior stroke, transient ischemic attack (TIA), or SE; ≥75 years of age; arterial hypertension requiring treatment; diabetes mellitus; heart failure ≥New York Heart Association (NYHA) Class 2; and decreased left ventricular ejection fraction (LVEF) ≤40%.

Key exclusion criteria: Atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation (eg, a prosthetic heart valve), stroke within the previous 7 days, a need for aspirin at a dose of >165 mg a day or for both aspirin and clopidogrel, and severe renal insufficiency (serum creatinine level of >2.5 mg/dL or calculated creatinine clearance of <25 mL/min).

Baseline characteristics: The 2 treatment groups were well balanced, including age, stroke risk ($CHADS_2$ score),[‡] and prior vitamin K antagonist (VKA) experience.

Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following: A decrease in hemoglobin of ≥2 g/dL[§]; transfusion of ≥2 units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial,[¶] intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; and fatal bleeding.

†A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.
‡Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.
§In AVERROES, a decrease in hemoglobin of ≥2 g/dL over a 24-hour period.
¶Intracranial bleeding included intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as intracranial major bleeding.
INR=international normalized ratio.

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.

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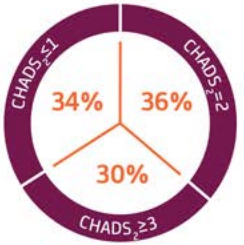
ARISTOTLE: BASELINE CHARACTERISTICS WERE WELL BALANCED ACROSS TREATMENT ARMS[1,2]*

ARISTOTLE	ELIQUIS n=9120	warfarin n=9081
Median age (yrs)	70	70
Mean $CHADS_2$ score†	2.1±1.1	2.1±1.1
$CHADS_2 \leq 1$	34% n=3100	34% n=3083
$CHADS_2 = 2$	36% n=3262	36% n=3254
$CHADS_2 \geq 3$	30% n=2758	30% n=2744
Prior stroke, TIA, or SE	19% n=1748	20% n=1790
Prior use of VKA (eg, warfarin) for >30 consecutive days	57% n=5208	57% n=5193
Heart failure or reduced LVEF	36% n=3235	35% n=3216
Hypertension requiring treatment	87% n=7962	88% n=7954
Aspirin use at time of randomization	31% n=2859	31% n=2773
Clopidogrel use at time of randomization	2% n=170	2% n=168
Renal function, creatinine clearance		
Normal (>80 mL/min)	41% n=3761	41% n=3757
Mild impairment (>50 to 80 mL/min)	42% n=3817	42% n=3770
Moderate impairment (>30 to 50 mL/min)	15% n=1365	15% n=1382
Severe impairment (≤30 mL/min)	2% n=137	2% n=133

Distribution of $CHADS_2$ scores for the ELIQUIS arm in ARISTOTLE



Mean percentage of time in therapeutic range (INR 2.0-3.0) was 62% for patients treated with warfarin.

*This is not a complete list of baseline characteristics. Additional baseline characteristics were evaluated in this trial.

†Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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

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

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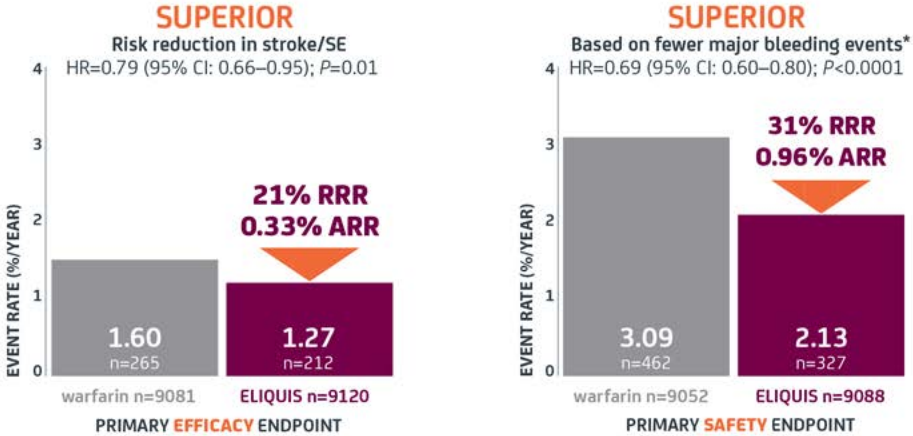
FOR PATIENTS WITH NVAF

ARISTOTLE: ELIQUIS DEMONSTRATED SUPERIORITY IN BOTH STROKE/SE AND MAJOR BLEEDING VS WARFARIN[1]



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

- Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke (0.24%/yr [n=40/9120] ELIQUIS vs 0.47%/yr [n=78/9081] warfarin, HR=0.51 [95% CI: 0.35–0.75]) and ischemic strokes with hemorrhagic conversion (0.07%/yr [n=12/9120] ELIQUIS vs 0.12%/yr [n=20/9081] warfarin, HR=0.60 [95% CI: 0.29–1.23]) compared to warfarin. Purely ischemic strokes (0.83%/yr [n=140/9120] ELIQUIS vs 0.82%/yr [n=136/9081] warfarin, HR=1.02 [95% CI: 0.81–1.29]) occurred with similar rates on both drugs[1]
- In another clinical trial (AVERROES), ELIQUIS was associated with an increase in major bleeding compared with aspirin that was not statistically significant (1.41%/yr vs 0.92%/yr, HR=1.54 [95% CI: 0.96–2.45]; *P*=0.07)[1]
- The most common reason for treatment discontinuation in both ARISTOTLE and AVERROES was bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively[1]

*Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period). Bleeding events in each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints.
ARR=absolute risk reduction; CI=confidence interval; HR=hazard ratio; RRR=relative risk reduction.

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FOR PATIENTS WITH NVAF

ARISTOTLE: ELIQUIS DEMONSTRATED LOWER RATES IN SELECT BLEEDING OUTCOMES VS WARFARIN[1,10,11]

COMPONENTS OF MAJOR BLEEDING*

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

- In another clinical trial (AVERROES), ELIQUIS was associated with an increase in major bleeding compared with aspirin that was not statistically significant (1.41%/yr vs 0.92%/yr, HR=1.54 [95% CI: 0.96–2.45]; *P*=0.07)[1]
- The most common reason for treatment discontinuation in both ARISTOTLE and AVERROES was bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively[1]

Components of ICH and fatal bleeding

- There were significantly fewer ICH events vs warfarin. Hemorrhagic stroke†: 0.24%/yr (n=38/9088) vs 0.49%/yr (n=74/9052), HR=0.51 (95% CI: 0.34–0.75); other ICH: 0.10%/yr (n=15/9088) vs 0.34%/yr (n=51/9052), HR=0.29 (95% CI: 0.16–0.51)[1]
- There were significantly fewer fatal bleeding events vs warfarin. Intracranial: 0.03%/yr (n=4/9088) vs 0.20%/yr (n=30/9052), HR=0.13 (95% CI: 0.05–0.37); nonintracranial: 0.04%/yr (n=6/9088) vs 0.05%/yr (n=7/9052), HR=0.84 (95% CI: 0.28–2.15)[1]

CRNM was defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to[2,3]:

1. Hospital admission; 2. Physician-guided medical or surgical treatment for bleeding; or 3. A change in antithrombotic therapy

*Bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

†On-treatment analysis based on the safety population, compared with intent-to-treat analysis presented in efficacy population.

CRNM=clinically relevant nonmajor; ICH=intracranial hemorrhage.

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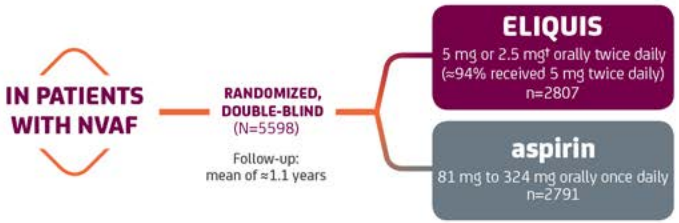
AVERROES: A PHASE III, RANDOMIZED, DOUBLE-BLIND TRIAL VS ASPIRIN IN OVER 5500 PATIENTS WITH NVAF WHO WERE UNSUITABLE FOR WARFARIN[1,12,13]

*This trial included 5598 patients with NVAF thought not to be candidates for warfarin therapy with 1 or more additional risk factors for stroke**

PRIMARY OBJECTIVE: Determine how ELIQUIS 5 mg twice daily (2.5 mg twice daily† in selected patients) compared with aspirin (81 mg to 324 mg once daily) in reducing the risk of stroke or SE in patients with NVAF.

PRIMARY EFFICACY ENDPOINT: Stroke/SE
PRIMARY SAFETY ENDPOINT: Major bleeding



***Key inclusion criteria:** NVAF and ≥1 additional risk factors for stroke, which included prior stroke or TIA, age ≥75 years, arterial hypertension (receiving treatment), diabetes mellitus (receiving treatment), heart failure (NYHA Class 2 or higher at the time of enrollment), LVEF ≤35%, or documented peripheral artery disease. Patients could not be receiving VKA therapy (eg, warfarin), either because it had already been demonstrated to be unsuitable for them or because it was expected to be unsuitable.

Baseline characteristics: The 2 treatment groups were well balanced with respect to baseline characteristics, including age, stroke risk at entry as measured by $CHADS_2$ score,‡ and prior use of a VKA within 30 days before screening.

Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following: A decrease in hemoglobin of ≥2 g/dL over 24 hours; transfusion of ≥2 units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial,§ intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; and fatal bleeding.

†A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.
‡Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.
§Intracranial bleeding included intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as intracranial major bleeding.

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.

ADVERSE REACTIONS

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

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INDEPENDENTLY FUNDED,
RETROSPECTIVE, OBSERVATIONAL,
REAL-WORLD DATABASE ANALYSIS

FRALICK ET AL

Published in the *Annals of Internal Medicine*®[4]

Effectiveness and Safety of ELIQUIS Compared With XARELTO® (rivaroxaban) for Patients With Nonvalvular Atrial Fibrillation in Routine Practice: A Cohort Study

Independently funded by internal resources in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital®.[4]

TOTAL STUDY POPULATION: 78,702 NVAF PATIENTS[4]

SELECTED IMPORTANT SAFETY INFORMATION

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

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.

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STUDY DESIGN AND OBJECTIVES[4]

Includes patients covered by commercial or Medicare Advantage healthcare plans

Adults with NVAF, newly prescribed ELIQUIS standard dose (5 mg BID) or XARELTO standard dose (20 mg QD) (N=99,878)*

XARELTO (n=40,706) | **ELIQUIS (n=59,172)**

1:1 PROPENSITY SCORE MATCHING (PSM)

XARELTO (rivaroxaban) **(n=39,351)**

1:1 PSM was intended to help balance demographics and clinical characteristics between cohorts to adjust for confounding[4]

For details on 1:1 PSM limitations, including potential residual confounders, please see page 13

ELIQUIS (apixaban) **(n=39,351)**

OBJECTIVE

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

PRIMARY EFFECTIVENESS OUTCOME

Composite of ischemic stroke (IS) or systemic embolism (SE)

PRIMARY SAFETY OUTCOME

Composite of gastrointestinal (GI) bleeding or intracranial hemorrhage (ICH)

The primary effectiveness and safety outcomes were based on ICD-9 and ICD-10 codes, required hospitalization, and were based only on the primary diagnosis code.

ADDITIONAL OUTCOMES

IS, SE, GI bleeding, ICH, other bleeding†

*Lower doses of either medication were not included, and it was assumed that dosing was twice daily for ELIQUIS and once daily for XARELTO on the basis of their product labeling.
"Newly prescribed" was defined as those without a prescription for apixaban, rivaroxaban, dabigatran, or edoxaban in the preceding 180 days of the analysis.
†Other bleeding was bleeding that was neither GI nor ICH bleeding, including, but not limited to, intraocular, genitourinary, and joint bleeding.
ICD=International Classification of Diseases.

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SELECT BASELINE CHARACTERISTICS[4]

	ELIQUIS (n=39,351)	XARELTO (n=39,351)
	AFTER 1:1 PROPENSITY SCORE MATCHING	
AGE, YEARS (MEAN)	69.4	69.3
SEX		
Male	60.3%	60.4%
Female	39.7%	39.6%
BASELINE COMORBIDITY		
$CHADS_2$ score		
0	12.7%	12.5%
1	42.4%	43.1%
≥2	44.9%	44.5%
Hypertension	80.0%	80.0%
Hyperlipidemia	63.4%	63.5%
IS or TIA	9.3%	9.2%
ICH	0.6%	0.6%
Heart failure	21.6%	21.6%
Ischemic heart disease	38.9%	38.8%

Baseline characteristics were assessed up to 180 days before the index date unless otherwise specified.[4]

This is not a complete list of baseline characteristics. Additional baseline characteristics were assessed with this analysis.[4]

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (cont'd)

- **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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SELECT BASELINE CHARACTERISTICS[4] (cont'd)

	ELIQUIS (n=39,351)	XARELTO (n=39,351)
	AFTER 1:1 PROPENSITY SCORE MATCHING	
BASELINE COMORBIDITY (cont'd)		
Chronic kidney disease (stage 3 or 4)	6.2%	6.4%
History of bleeding		
GI	2.9%	2.9%
Other	6.4%	6.4%
Liver disease	0.7%	0.7%
Smoking	20.5%	20.5%
Obesity or overweight	28.5%	28.5%
MEDICATIONS		
Antiplatelets	9.7%	9.6%
Warfarin		
90–180 days before index date	13.0%	13.0%
31–89 days before index date	13.0%	13.0%
1–30 days before index date	12.0%	12.1%

Baseline characteristics were assessed up to 180 days before the index date unless otherwise specified.[4]

This is not a complete list of baseline characteristics. Additional baseline characteristics were assessed with this analysis.[4]

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

SELECTED IMPORTANT SAFETY INFORMATION

PREGNANCY

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

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

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

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METHODS OF ANALYSIS[4]

Patients were identified between: 12/28/2012–01/01/2019
Index drug: Use of 5 mg ELIQUIS or 20 mg XARELTO*
Index date: Date of dispensing of ELIQUIS or XARELTO
Baseline period: 180 days prior to index date
Data source: Optum® Clinformatics®

INCLUSION CRITERIA

- Most patients within Optum® Clinformatics® were covered by employer-sponsored insurance, with approximately 10% of patients receiving healthcare coverage through Medicare Advantage plans
- Patients with atrial fibrillation or atrial flutter were identified by using ICD-9 and ICD-10 codes (ICD-9: 427.31, 427.32; ICD-10: I48.x)
- Persons older than 18 years who received a diagnosis of atrial fibrillation or atrial flutter and filled a new prescription for 5 mg ELIQUIS or 20 mg XARELTO between December 28, 2012 and January 1, 2019
- "Newly prescribed" was defined as those without a prescription for apixaban, rivaroxaban, dabigatran, or edoxaban in the preceding 180 days of the analysis
- **Lower dosages of either medication were not included**

EXCLUSION CRITERIA

- Patients with any of the following characteristics in the 180 days before cohort entry were excluded: insufficient database enrollment (ie, <180 days), stage 5 chronic kidney disease requiring dialysis, cancer, valvular heart disease, venous thromboembolism, hip surgery, or knee surgery

STATISTICAL ANALYSIS

- 1:1 PSM was employed to balance demographics and clinical characteristics between the ELIQUIS and XARELTO cohorts
- Cox proportional hazard models were used after propensity score matching to estimate the incidence rate, HR, and 95% CI for the primary outcome
- **Sensitivity analyses were consistent with the main analysis and included:**
  - A predefined analysis, in which:
    - The censoring criteria of drug discontinuation or switching was removed and all patients were followed for up to 365 days unless they reached the end of the study period, disenrolled, experienced a study outcome, or died
    - Analyses were performed with Aetion Evidence Platform, versions 3.11 and 3.4.2
  - Post hoc analyses, which included:
    - Stratification of patients by deciles of propensity scores (PS)
    - Symmetrically removing patients with PS below the 2.5th percentile and above the 97.5th percentile of the overall PS distribution
    - Creation of a composite outcome, including stroke, SE, GI bleeding, or ICH, which was analyzed using 1:1 PSM

FOLLOW-UP PERIOD

- Follow-up began the day after cohort entry and continued until the end of the study period (January 1, 2019), the end of continuous health plan enrollment, the occurrence of a study outcome, discontinuation of the initial medication, a switch to the comparator, or death. A medication was considered discontinued if 30 days had elapsed after the last prescription's supply expired and the prescription was not refilled
- Mean follow-up was 288 days (SD=298.0) for new ELIQUIS users and 291 days (SD=324.0) for new XARELTO users

*It was assumed that dosing was twice daily for ELIQUIS and once daily for XARELTO on the basis of their product labeling.
SD=standard deviation.

LIMITATIONS OF ANALYSIS

STUDY DESIGN/DEFINITIONS[4,6,9,14]

- Due to the nature of retrospective, observational cohort studies, no causal relations could be inferred and only statistical associations were assessed
- In contrast to clinical trials, outcomes were defined by using ICD-9 and ICD-10 diagnosis codes, and without outcome adjudication
- The presence of a claim for a filled prescription does not indicate whether the medication was consumed or taken as prescribed
- There is no guarantee that patients were dosed according to the US prescribing information for ELIQUIS and XARELTO
- Unmeasured confounding factors were not balanced
- Time-varying confounders that might affect a patient's risk of either stroke or bleeding were not accounted for
- The study was not adjusted for provider types, such as emergency medicine physicians and nurse practitioners, or the setting in which the patient was seen for the index prescription (for example, inpatient hospitalization, emergency department, or outpatient clinic). This might result in unmeasured confounding

BIAS/CONFOUNDING[4]

- Although cohorts were propensity-score matched, potential residual confounders exist, which were not available in the dataset. This limitation is especially important for interpreting DOAC vs DOAC comparison, which are for hypothesis generation, given the lack of head-to-head trials, and therefore results should be interpreted with caution

DATA COLLECTION[4,9]

- The database lacked information on other relevant baseline characteristics (including race, socioeconomic status, echocardiographic findings, and duration of atrial fibrillation)
- The study lacked information on over-the-counter prescriptions, such as aspirin, and laboratory values were not included in PSM matching due to missing data
- With observational studies based on information contained in healthcare databases, validation of data and coding through medical chart review may not be possible

GENERALIZABILITY[4]

- Results may not be generalizable to the overall NVAF population in the US because the study did not include uninsured patients and patients solely covered by other public health insurance plans

FOLLOW-UP[4]

- The study had a shorter follow-up relative to the clinical trials of DOACs

DOAC=direct oral anticoagulant.

SELECTED IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

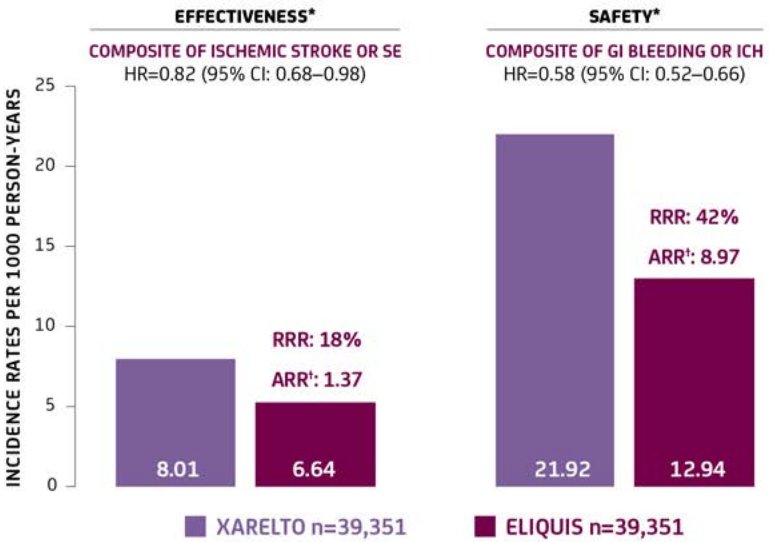
WARNINGS AND PRECAUTIONS

- **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.

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

Eliquis® (apixaban) tablets 5mg 2.5mg

INCIDENCE OF ISCHEMIC STROKE/SYSTEMIC EMBOLISM AND MAJOR BLEEDING[4]



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.[9]

- 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[14-17]

The definitions of outcomes, follow-up period, and the patient population in ARISTOTLE were different than in this analysis.[1,4]

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

There are currently no results from ELIQUIS vs XARELTO head-to-head clinical trials.[4]

*Outcomes were based on ICD-9 and ICD-10 codes, required hospitalization, and were based only on the primary diagnosis code.

†ARR was per 1000 person-years.

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

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

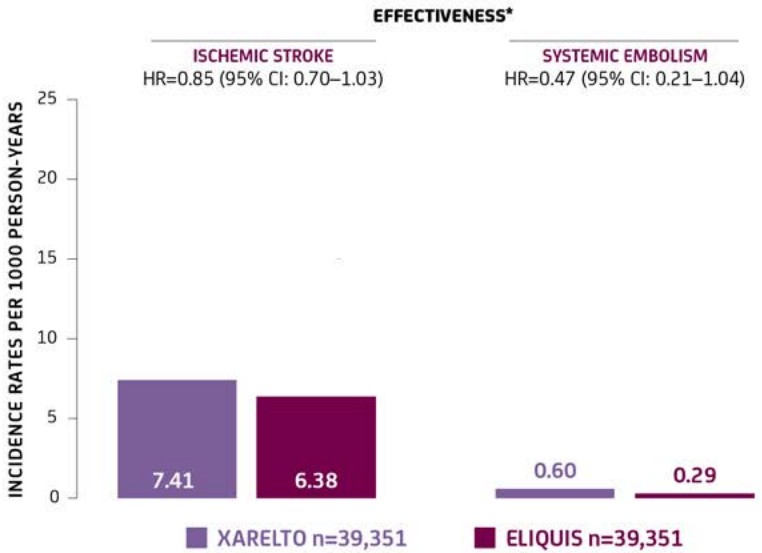
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

  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**.

ADDITIONAL OUTCOMES: INCIDENCE OF ISCHEMIC STROKE AND SYSTEMIC EMBOLISM[4]



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There are currently no results from ELIQUIS vs XARELTO head-to-head clinical trials.[4]

*Outcomes were based on ICD-9 and ICD-10 codes, required hospitalization, and were based only on the primary diagnosis code.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

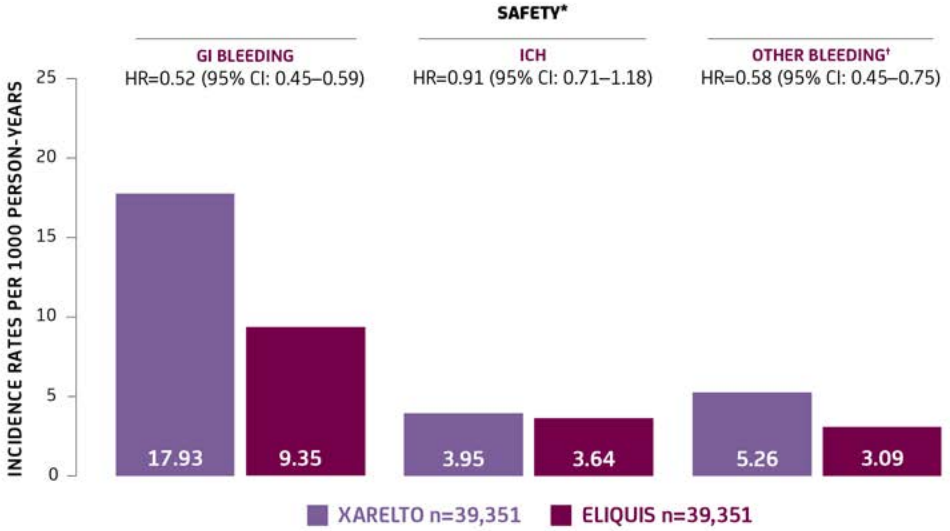
- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS 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.

ADVERSE REACTIONS

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

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

INCIDENCE OF ADDITIONAL BLEEDING OUTCOMES[4]



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

*Outcomes were based on ICD-9 and ICD-10 codes, required hospitalization, and were based only on the primary diagnosis code.
†Other bleeding was bleeding that was neither GI nor ICH bleeding, including, but not limited to, intraocular, genitourinary, and joint bleeding.

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