

ATHENS

CLINICAL IMPACT OF SWITCHING OR CONTINUATION OF APIXABAN OR RIVAROXABAN AMONG PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Published in *Journal of Clinical Medicine*

Outcomes observed in commercially insured and Medicare patients with NVAF in Optum[®] database (N=34,638)

INDICATION

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

Optum[®] is a registered trademark of Optum, Inc.
Sponsored by Pfizer Inc. and Bristol-Myers Squibb Co.

NVAF=nonvalvular atrial fibrillation; RCT=randomized clinical trial; RWD=real-world data.

ARISTOTLE RCT SUMMARY

Please see [page 2](#).

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.

ARISTOTLE: A PIVOTAL, PHASE III, RANDOMIZED CLINICAL TRIAL OF >18,000 PATIENTS WITH NVAF^{2-4*}

The primary objective of ARISTOTLE was to determine whether ELIQUIS[®] (apixaban) was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) or SE. The superiority of ELIQUIS to warfarin was also examined for stroke/SE (primary efficacy endpoint) and major bleeding (primary safety endpoint).

ARISTOTLE Study Design: ARISTOTLE was a double-blind study that randomized patients with NVAF (N=18,201) into two groups: those who received ELIQUIS 5 mg or 2.5 mg[†] twice daily (n=9120) or warfarin with a target INR range of 2.0–3.0 (n=9081). The median duration of follow-up was ≈1.7 years.^{2,3}

***Key inclusion criteria:** NVAF and ≥1 risk factors for stroke: prior stroke, TIA, or SE; ≥75 years of age; arterial hypertension requiring treatment; diabetes mellitus; heart failure ≥NYHA Class 2; and decreased LVEF ≤40%.

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 a critical site: intracranial[‡], intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; and fatal bleeding.

ELIQUIS demonstrated superiority in BOTH stroke/systemic embolism AND major bleeding vs warfarin

Stroke/SE: 1.27%/yr [n=212/9120] vs 1.60%/yr [n=265/9081]

HR=0.79 (95% CI: 0.66–0.95); **P**=0.01
RRR[§]= 21%; **ARR**[§]=0.33%/yr

Major bleeding^{||}: 2.13%/yr [n=327/9088] vs 3.09%/yr [n=462/9052]

HR=0.69 (95% CI: 0.60–0.80); **P**<0.0001
RRR[§]=31%; **ARR**[§]=0.96%/yr

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.

In another clinical trial (AVERROES—see study design on next page), ELIQUIS was associated with an increase in major bleeding compared with aspirin that was not statistically significant (1.4%/yr vs 0.92%/yr, HR=1.54 [95% CI: 0.96–2.45]; **P**=0.07).

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.

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.²

[†]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.

[‡]Intracranial bleeding included intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as intracranial major bleeding.

[§]Statistical note: RRR was calculated as (1-HR)×100. ARR was calculated as the difference between the event rates.

^{||}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; INR=International Normalized Ratio; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; RRR=relative risk reduction; SE=systemic embolism; TIA=transient ischemic attack.

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**.

Elquis
(apixaban) tablets 5mg/2.5mg

ARISTOTLE: A PIVOTAL, PHASE III, RANDOMIZED CLINICAL TRIAL OF >18,000 PATIENTS WITH NVAF^{2-4*} (CONTINUED)

AVERROES Study Design: A phase III, double-blind, randomized trial designed to compare the effects of ELIQUIS 5 mg or 2.5 mg[†] twice daily (n=2807) and aspirin (n=2791) (81 mg–324 mg once daily) on the risk of stroke and systemic embolism in 5598 patients with NVAF thought not to be candidates for warfarin therapy, and with ≥1 additional risk factor for stroke: prior stroke or TIA; ≥75 years of age; arterial hypertension (receiving treatment); diabetes mellitus (receiving treatment); heart failure (≥NYHA Class 2 at time of enrollment); LVEF ≤35%, or documented peripheral artery disease. Patients could not be receiving VKA therapy (e.g., warfarin), either because it had already been demonstrated or was expected to be unsuitable for them. The mean follow-up period was 1.1 years. The primary efficacy endpoint was stroke/SE and the primary safety endpoint was major bleeding.^{2,5}

*Key inclusion criteria: NVAF and ≥1 risk factors for stroke: prior stroke, TIA, or SE; ≥75 years of age; arterial hypertension requiring treatment; diabetes mellitus; heart failure ≥NYHA Class 2; and decreased LVEF ≤40%.

VKA=vitamin K antagonist.

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

SELECT CHARACTERISTICS OF RANDOMIZED CLINICAL TRIALS AND REAL-WORLD DATA

RANDOMIZED CLINICAL TRIALS⁶⁻⁸

- **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)



REAL-WORLD OBSERVATIONAL STUDIES⁷⁻⁹

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

OBJECTIVE: To assess stroke/SE and major bleeding outcomes¹:

- in patients with NVAf who started and continued ELIQUIS vs those who switched* to XARELTO® (rivaroxaban)
- in patients with NVAf who started and continued XARELTO vs those who switched* to ELIQUIS

METHODS OF ANALYSIS IN ATHENS¹

INDEX DRUG: ELIQUIS or XARELTO

INDEX DATE: For switchers, date of switch; for continuers, assigned index date[†]

DATA SOURCE: Optum® Clinformatics® Data Mart 2012-2022[‡]



Data source

- The Optum Clinformatics database contains medical and pharmacy data for individuals and dependents with commercial employer-sponsored insurance and individuals with Medicare insurance in the U.S.



Inclusion criteria

- Patients ≥18 years of age with a diagnosis of NVAf on or before the index anticoagulation date
 - Diagnoses were identified based on ICD-9 and ICD-10 codes (ICD-9: 427.31; ICD-10: I48.0, I48.1, I48.2, I48.91)
- The comparative analysis included only patients who started on ELIQUIS or XARELTO because they are the most commonly used DOACs
- Minimum 6 months of continuous enrollment prior to DOAC initiation date



Exclusion criteria

- Patients with valvular heart disease, venous thromboembolism, or transient AF in the 6 months prior to or on the DOAC initiation date
- Patients with any OAC prescription in the 6 months before DOAC initiation, or >1 OAC prescription claim on the DOAC initiation date
- Patients with hip or knee replacement surgery 6 weeks prior to or on the DOAC initiation date
- Patients who were pregnant at any time during the study period
- Patients with no follow-up information



Outcomes

- Outcomes below required hospitalization and were identified based on first listed diagnosis
 - Incidence of stroke/SE
 - Incidence of major bleeding
- Results shown are for the matched cohorts

CONTINUED ON NEXT PAGE

*Reasons for switching treatment were not captured or evaluated.

[†]Assigned index date was randomly assigned based on the distribution of the time from initial DOAC prescription date to the switch date from the switch cohort.

[‡]ELIQUIS and XARELTO were approved for stroke risk reduction in patients with NVAf in 2012 and 2011, respectively.^{10,11}

XARELTO® (rivaroxaban) is a registered trademark of Bayer Aktiengesellschaft.

Clinformatics® is a registered trademark of OptumInsight, Inc.

AF=atrial fibrillation; DOAC=direct oral anticoagulant; ICD=International Classification of Diseases; OAC=oral anticoagulant.

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.

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(apixaban) tablets 5mg
2.5mg

METHODS OF ANALYSIS IN ATHENS¹ (CONTINUED)

INDEX DRUG: ELIQUIS or XARELTO

INDEX DATE: For switchers, date of switch; for continuers, assigned index date*

DATA SOURCE: Optum® Clinformatics® Data Mart 2012-2022[†]



Statistical analyses

- PSM (1:5) was conducted between continuers and switchers based on their baseline characteristics, duration from their initial DOAC prescription to the index date, and major bleeding and stroke events between DOAC initiation and index date
 - Group 1: patients who started and continued ELIQUIS vs switched to XARELTO
 - Group 2: patients who started and continued XARELTO vs switched to ELIQUIS
- T-test, chi-squared test, or Fisher exact test was used where appropriate to compare baseline characteristics
- Risks of stroke/SE and major bleeding between the switcher and continuer groups were compared using a Cox proportional hazards model



Sensitivity analysis

- Sensitivity analysis was consistent with the main analysis:
 - Risks of stroke/SE and major bleeding were also studied in a selected cohort of patients who initiated treatment with standard dose of ELIQUIS and XARELTO



Follow-up period

- Patients were followed until an outcome of interest, DOAC discontinuation (across analyses, 30 days without evidence of anticoagulation of interest from the last supplied date of the last filled prescription; for continuers who reinitiated their initial DOAC within 90 days from the last day of the last filled prescription, end of treatment after re-initiation), switch to another OAC, the end of the study period, the end of continuous enrollment, or death, whichever occurred earlier
- The average duration of anticoagulation:
 - 313.9 days for patients who switched from ELIQUIS to XARELTO and 390.9 days for patients who continued on ELIQUIS
 - 377.9 days for patients who switched from XARELTO to ELIQUIS and 355.3 days for patients who continued on XARELTO

*Assigned index date was randomly assigned based on the distribution of the time from initial DOAC prescription date to the switch date from the switch cohort.

[†]ELIQUIS and XARELTO were approved for stroke risk reduction in patients with NVAF in 2012 and 2011, respectively.^{10,11}

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.

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Study design/definitions

- Due to the nature of retrospective, observational cohort studies, no causal relationships can be inferred, and only associations were assessed
- In contrast to clinical trials, outcomes were defined by using ICD-9 and ICD-10 diagnosis codes rather than clinical outcome adjudication
- There is no guarantee that patients were dosed according to the U.S. prescribing information for ELIQUIS and XARELTO. Medications were based on pharmacy fills and there was no way to determine if a patient took their medication as prescribed



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, such as geographic variation in the preferences of patients, physicians, and others. The risk of confounding is especially important for interpreting DOAC vs DOAC comparison—which is for hypothesis generation, given the lack of head-to-head clinical trials—and therefore results should be interpreted with caution^{1,12}



Data collection

- A major assumption of this study is that claims for prescribed oral anticoagulants are representative of actual patient utilization. It is possible that there are differences between prescribing and usage practices
- Dose reduction criteria for ELIQUIS and XARELTO could not be evaluated as serum creatinine/creatinine clearance and body weight data were unavailable
- Reasons for switching from ELIQUIS to XARELTO or from XARELTO to ELIQUIS were not captured or evaluated
- Sample size for the switch group is much smaller than the sample size for continuers
- The claims database lacked information on lab values such as serum creatinine clearance, preventing investigators from evaluating renal function. The severity and stages of renal dysfunction may not be completely balanced between switchers and continuers



Generalizability

- The study was restricted to patients covered by commercial employer-sponsored insurance or Medicare insurance, which therefore limits the generalizability of the findings

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

• Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary

Embolectomy: Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

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ATHENS: A RETROSPECTIVE, OBSERVATIONAL, REAL-WORLD DATABASE ANALYSIS¹

ATHENS
Real-world data analysis 

OBJECTIVE: To assess stroke/SE and major bleeding outcomes:

- in patients with NVAf who started and continued ELIQUIS vs those who switched* to XARELTO
- in patients with NVAf who started and continued XARELTO vs those who switched* to ELIQUIS

See **page 9** for patients who
STARTED ON ELIQUIS

N=167,868

See **page 15** for patients who
STARTED ON XARELTO

N=65,888

Guidance from section 2.4 of ELIQUIS Prescribing Information on switching to/from ELIQUIS²:

When switching from ELIQUIS to anticoagulants other than warfarin (oral or parenteral), discontinue ELIQUIS and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of ELIQUIS. **When switching from anticoagulants other than warfarin** (oral or parenteral) to ELIQUIS, discontinue the anticoagulant other than warfarin and begin taking ELIQUIS at the usual time of the next dose of the anticoagulant other than warfarin.

Guidance from section 2.3 of XARELTO Prescribing Information on switching to/from XARELTO¹³:

For adult patients **currently taking XARELTO and transitioning to an anticoagulant** with rapid onset, discontinue XARELTO and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next XARELTO dose would have been taken. For adult patients **currently receiving an anticoagulant other than warfarin**, start XARELTO 0 to 2 hours prior to the next scheduled administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant.

*Reasons for switching treatment were not captured or evaluated.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS):** Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive APS. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

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STUDY OVERVIEW FOR PATIENTS WHO STARTED ON ELIQUIS¹

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

Cohort Description

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

- Adult patients with diagnosis of AF on or before index anticoagulant start date
- ≥6 months of continuous enrollment prior to DOAC initiation date
- Started on ELIQUIS during the study identification period, between January 1, 2013 and December 31, 2021
- **167,868 patients who started on ELIQUIS met the inclusion/exclusion criteria**
 - 132,676 patients continued with ELIQUIS
 - 2901 patients switched to XARELTO. Reasons for switching treatment are unknown

Propensity Score Matching (1:5)*

ELIQUIS continuers[†]
(n=14,500)

ELIQUIS to XARELTO switchers[‡]
(n=2900)

Assessed Outcomes

- Incidence of stroke/SE
- Incidence of major bleeding

These outcomes required hospitalization and were identified based on first listed diagnosis.

*Propensity score matching ensured switcher and continuer groups were comparable based on their baseline characteristics, duration from their initial DOAC prescription to the index date, and major bleeding and stroke events between DOAC initiation and index date.

[†]Patients with at least 2 prescription claims for the initial DOAC and no evidence of switching as defined below.

[‡]Patients with at least one claim for a different DOAC within 30 days before discontinuing their initial DOAC to 90 days after discontinuing their initial DOAC.

SELECTED IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

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SELECT BASELINE CHARACTERISTICS (POST-MATCHING)¹

ATHENS
Real-world data analysis 

	ELIQUIS CONTINUERS (N=14,500)	ELIQUIS TO XARELTO SWITCHERS (N=2900)
AGE*, YEARS (MEAN)	75.0	74.8
18–54	2.8%	3.2%
55–64	10.0%	9.9%
65–74	31.9%	31.6%
75–79	20.9%	20.5%
≥80	34.3%	34.8%
SEX*		
Female	51.2%	50.9%
Male	48.8%	49.1%
COMORBIDITY SCORES (MEAN)		
CCI score*	2.6	2.7
CHA ₂ DS ₂ -VASc Score	4.0	4.1
HAS-BLED Score†	2.8	2.9
BASELINE COMORBIDITIES		
Any bleeding history*	15.6%	15.6%
Congestive heart failure*	27.7%	28.7%
Diabetes*	31.0%	32.5%
Hypertension*	85.0%	85.4%
Renal disease*	26.5%	27.1%
Liver disease*	5.2%	5.7%
Myocardial infarction*	11.1%	11.6%
Dyspepsia or stomach discomfort*	13.4%	13.9%
Peripheral vascular disease*	24.8%	26.4%
Transient ischemic attack*	13.5%	14.1%
Alcoholism*	2.9%	3.0%
Peripheral arterial disease*	12.9%	14.1%
Coronary artery disease*	38.9%	39.9%
Stroke/SE*	11.5%	12.2%
All-cause hospitalization	35.1%	38.6%
TIME TO INDEX DATE, IN DAYS*‡ (MEAN)	138.9	145.0
EVENT AFTER DOAC INITIATION BEFORE INDEX DATE		
Stroke/SE event after OAC initiation before index date*	1.5%	1.5%
Major bleeding event after OAC initiation before index date*	1.1%	1.1%
DOSAGE OF ELIQUIS AT INITIATION[§]		
Low dose	18.1%	16.0%
Standard dose	81.9%	84.0%
Unknown	0.0%	0.0%
FOLLOW-UP DURATION IN DAYS[¶] (MEAN)	390.9	313.9

*Variables used for PSM.

†Because the International Normalized Ratio value was not available in the database, a modified HAS-BLED score was calculated with a range of 0 to 8.

‡Date of DOAC switch or assigned index date.

§ELIQUIS low dose 2.5 mg, ELIQUIS standard dose 5 mg.

||Unknown indicates that the authors did not have enough information to assign dosage.

¶From the day after the index date to treatment end, death, enrollment end, study end.

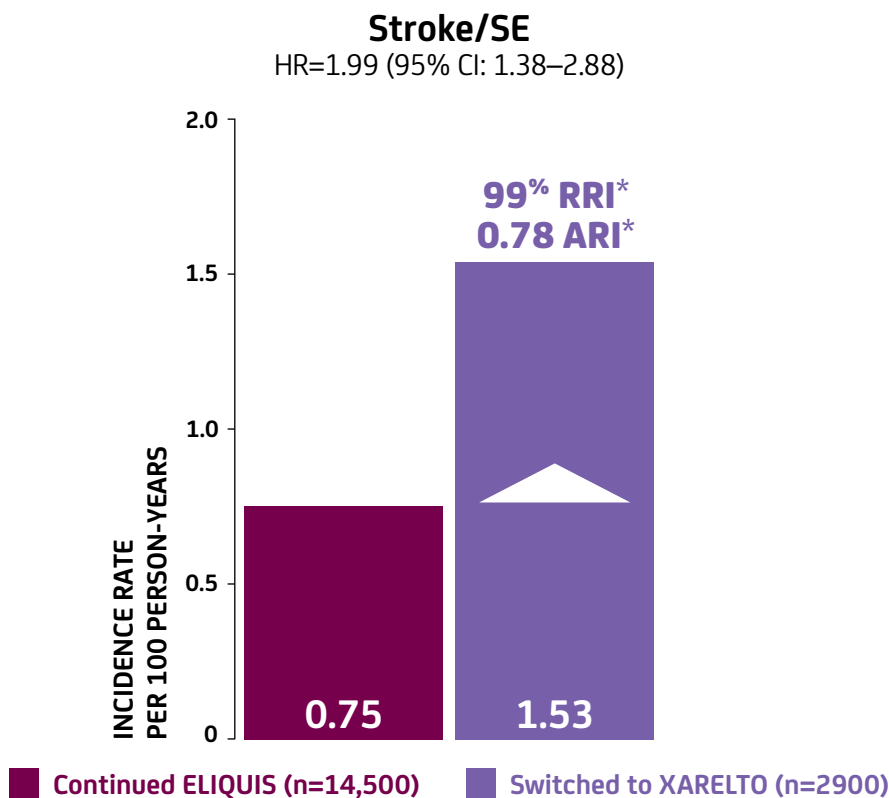
CCI=Charlson Comorbidity Index; CHA₂DS₂-VASc=congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74 years, sex; HAS-BLED=hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio, elderly, drugs/alcohol.

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

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OUTCOMES: STROKE/SYSTEMIC EMBOLISM IN PATIENTS WHO CONTINUED ON ELIQUIS VS THOSE WHO SWITCHED TO XARELTO¹

ATHENS
Real-world data analysis 



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.¹²

The definitions of outcomes, follow-up period, and the patient population in ARISTOTLE were different than in this analysis.^{1,2}

There are currently no results from clinical trials comparing ELIQUIS to XARELTO.^{14,15}

*Statistical note: RRI was calculated as (HR-1)×100. ARI represents the difference between the event rates and is expressed as per 100 person-years. ARI=absolute risk increase; RRI=relative risk increase.

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

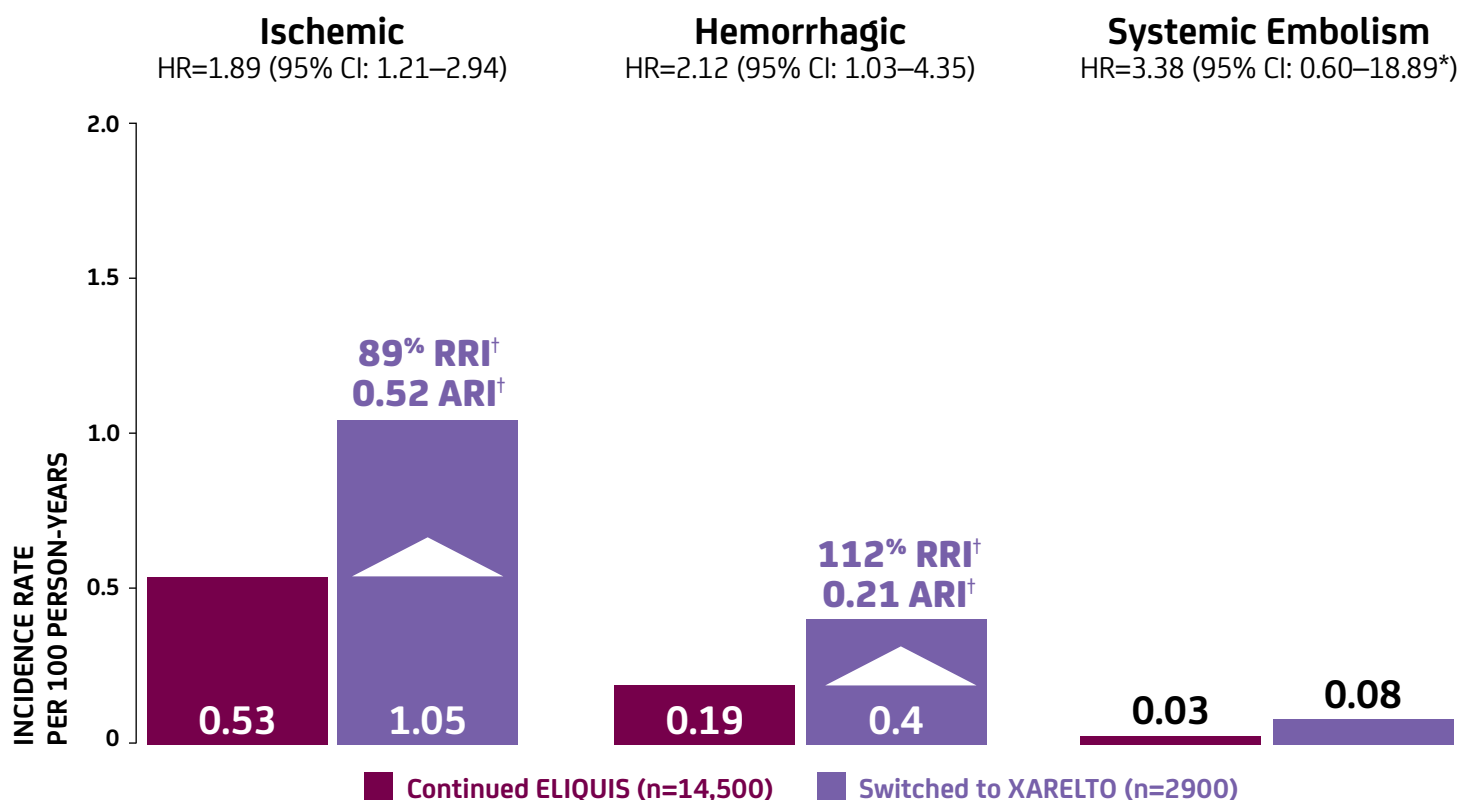
Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

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COMPONENTS OF STROKE/SYSTEMIC EMBOLISM IN PATIENTS WHO CONTINUED ON ELIQUIS VS THOSE WHO SWITCHED TO XARELTO¹

ATHENS
Real-world data analysis 



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The definitions of outcomes, follow-up period, and the patient population in ARISTOTLE were different than in this analysis.^{1,2}

There are currently no results from clinical trials comparing ELIQUIS to XARELTO.^{14,15}

*CI was truncated.

[†]Statistical note: RRI was calculated as (HR-1)x100. ARI represents the difference between the event rates and is expressed as per 100 person-years.

SELECTED IMPORTANT SAFETY INFORMATION

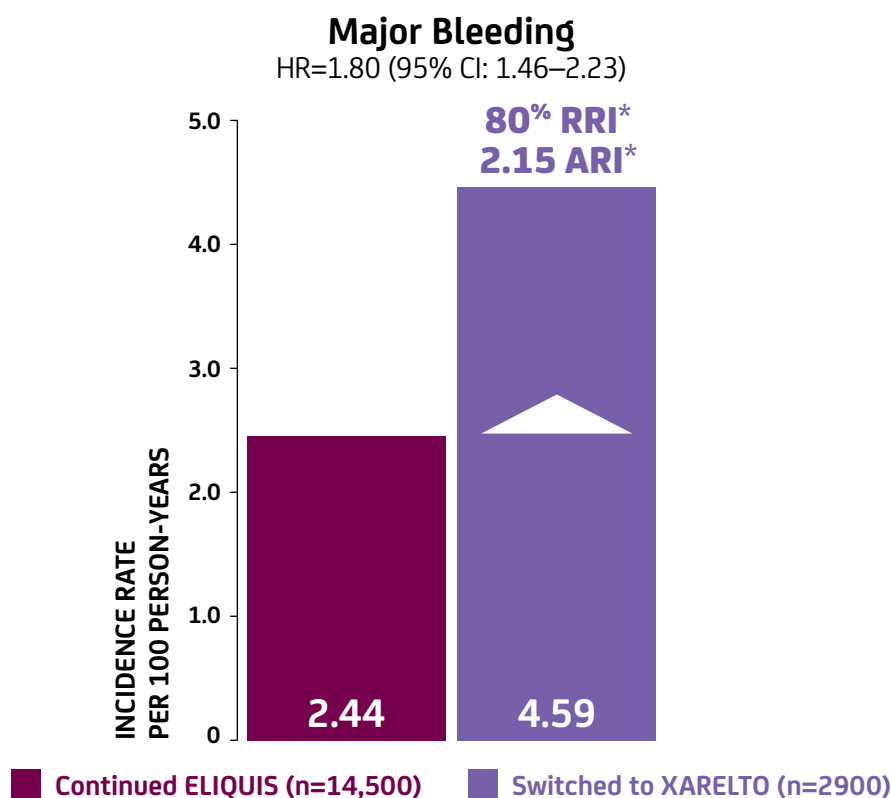
DRUG INTERACTIONS (cont'd)

- **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.

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

OUTCOMES: MAJOR BLEEDING IN PATIENTS WHO CONTINUED ON ELIQUIS VS THOSE WHO SWITCHED TO XARELTO¹



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.²

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.¹²

The definitions of outcomes, follow-up period, and the patient population in ARISTOTLE were different than in this analysis.^{1,2}

There are currently no results from clinical trials comparing ELIQUIS to XARELTO.^{14,15}

*Statistical note: RRI was calculated as (HR-1)x100. ARI represents the difference between the event rates and is expressed as per 100 person-years.

SELECTED IMPORTANT SAFETY INFORMATION

PREGNANCY

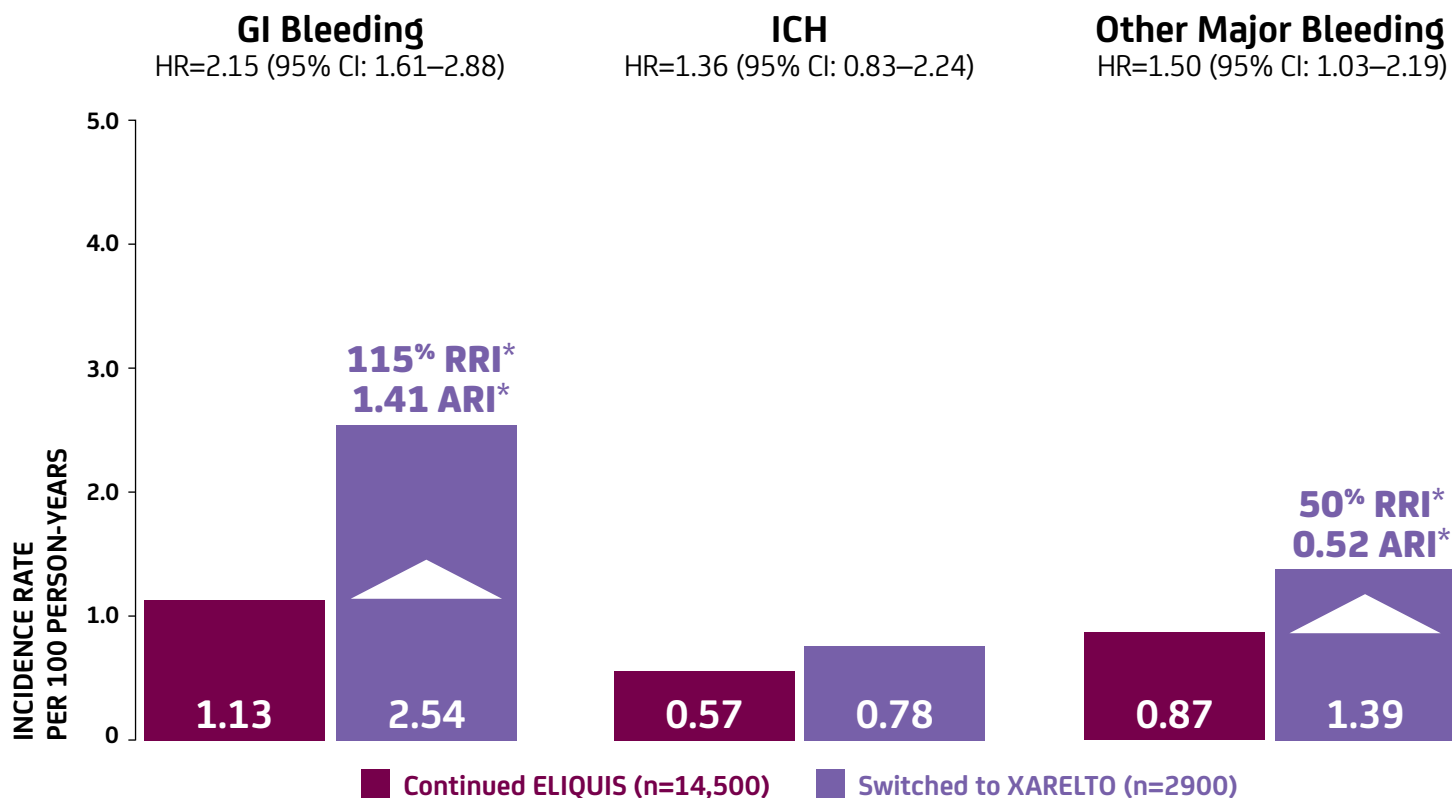
- The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.
 - Labor or delivery:*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

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COMPONENTS OF MAJOR BLEEDING IN PATIENTS WHO CONTINUED ON ELIQUIS VS THOSE WHO SWITCHED TO XARELTO¹

ATHENS
Real-world data analysis 



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*Statistical note: RRI was calculated as (HR-1)x100. ARI represents the difference between the event rates and is expressed as per 100 person-years.
GI=gastrointestinal; ICH=intracranial hemorrhage.

SELECTED IMPORTANT SAFETY INFORMATION

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

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

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STUDY OVERVIEW FOR PATIENTS WHO STARTED ON XARELTO¹

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

Cohort Description

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

- Adult patients with diagnosis of AF on or before index anticoagulant start date
- ≥6 months of continuous enrollment prior to DOAC initiation date
- Started on XARELTO during the study identification period, between January 1, 2013 and December 31, 2021
- **65,888 patients who started on XARELTO met the inclusion/exclusion criteria**
 - 45,654 patients continued with XARELTO
 - 2877 patients switched to ELIQUIS. Reasons for switching treatment are unknown

Propensity Score Matching (1:5)*

XARELTO continuers[†]
(n=14,365)

XARELTO to ELIQUIS switchers[‡]
(n=2873)

Assessed Outcomes

- Incidence of stroke/SE
- Incidence of major bleeding

These outcomes required hospitalization and were identified based on first listed diagnosis.

*Propensity score matching ensured switcher and continuer groups were comparable based on their baseline characteristics, duration from their initial DOAC prescription to the index date, and major bleeding and stroke events between DOAC initiation and index date.

[†]Patients with at least 2 prescription claims for the initial DOAC and no evidence of switching as defined below.

[‡]Patients with at least one claim for a different DOAC within 30 days before discontinuing their initial DOAC to 90 days after discontinuing their initial DOAC.

SELECTED IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

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SELECT BASELINE CHARACTERISTICS (POST-MATCHING)¹

ATHENS
Real-world data analysis 

	XARELTO CONTINUERS (N=14,365)	XARELTO TO ELIQUIS SWITCHERS (N=2873)
AGE*, YEARS (MEAN)	74.1	74.1
18–54	3.8%	3.9%
55–64	10.8%	11.5%
65–74	32.9%	31.3%
75–79	21.4%	21.6%
≥80	31.1%	31.8%
SEX*		
Female	48.5%	47.9%
Male	51.5%	52.1%
COMORBIDITY SCORES (MEAN)		
CCI score*	2.8	2.9
CHA ₂ DS ₂ -VASc Score	4.0	4.1
HAS-BLED Score†	3.0	3.0
BASELINE COMORBIDITIES		
Any bleeding history*	27.8%	28.2%
Congestive heart failure*	33.5%	34.0%
Diabetes*	32.4%	33.1%
Hypertension*	87.0%	87.1%
Renal disease*	30.9%	31.3%
Liver disease*	6.1%	6.4%
Myocardial infarction*	12.1%	12.6%
Dyspepsia or stomach discomfort*	11.8%	12.0%
Peripheral vascular disease*	25.2%	25.4%
Transient ischemic attack*	11.7%	12.9%
Alcoholism*	2.5%	2.7%
Peripheral arterial disease*	13.2%	13.2%
Coronary artery disease*	40.2%	41.1%
Stroke/SE*	9.4%	10.9%
All-cause hospitalization	34.7%	41.6%
TIME TO INDEX DATE, IN DAYS*‡ (MEAN)	213.9	221.5
EVENT AFTER DOAC INITIATION BEFORE INDEX DATE		
Stroke/SE event after OAC initiation before index date*	0.7%	2.3%
Major bleeding event after OAC initiation before index date*	3.1%	5.4%
DOSAGE OF XARELTO AT INITIATION[§]		
Low dose	23.4%	23.6%
Standard dose	75.0%	74.2%
Unknown	1.7%	2.2%
FOLLOW-UP DURATION IN DAYS[¶] (MEAN)	355.3	377.9

*Variables used for PSM.

†Because the International Normalized Ratio value was not available in the database, a modified HAS-BLED score was calculated with a range of 0 to 8.

‡Date of DOAC switch or assigned index date.

§XARELTO low dose 10 mg (this is not an FDA-approved dose for stroke risk reduction in NVAf and represented 6.58% of patients in this analysis) or 15 mg; XARELTO standard dose 20 mg.^{1,16}

||Unknown indicates that the authors did not have enough information to assign dosage.

¶From the day after the index date to treatment end, death, enrollment end, study end.

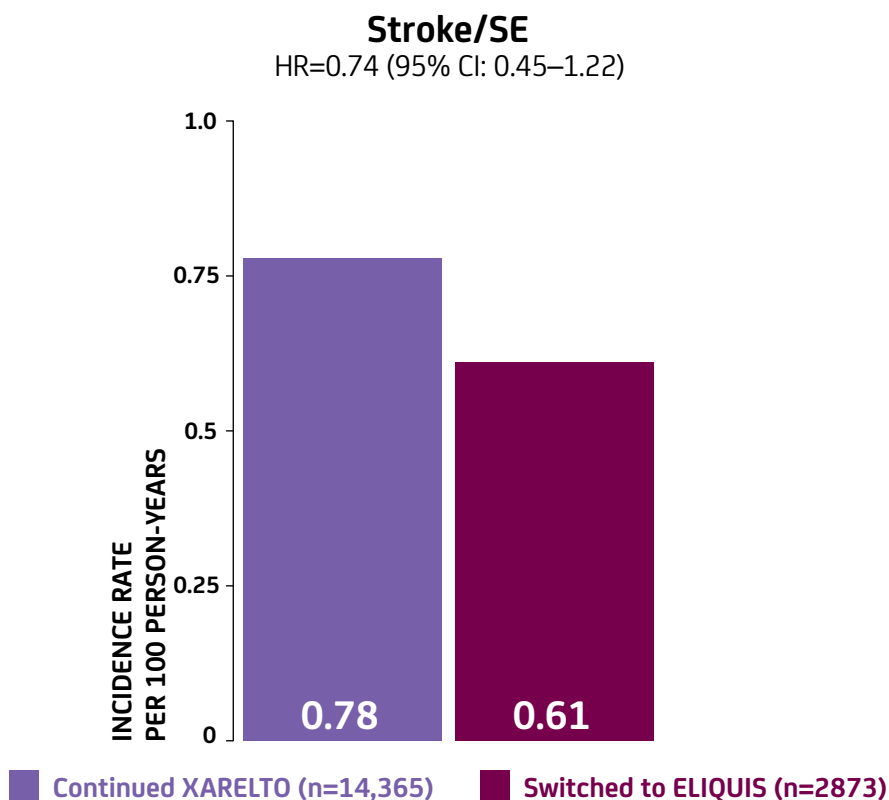
CCI=Charlson Comorbidity Index; CHA₂DS₂-VASc=congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74 years, sex; HAS-BLED=hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio, elderly, drugs/alcohol.

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click here for U.S. Full Prescribing Information, including **Boxed WARNINGS**.

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OUTCOMES: STROKE/SYSTEMIC EMBOLISM IN PATIENTS WHO CONTINUED ON XARELTO VS THOSE WHO SWITCHED TO ELIQUIS¹

ATHENS
Real-world data analysis 



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.¹²

The definitions of outcomes, follow-up period, and the patient population in ARISTOTLE were different than in this analysis.^{1,2}

There are currently no results from clinical trials comparing ELIQUIS to XARELTO.^{14,15}

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

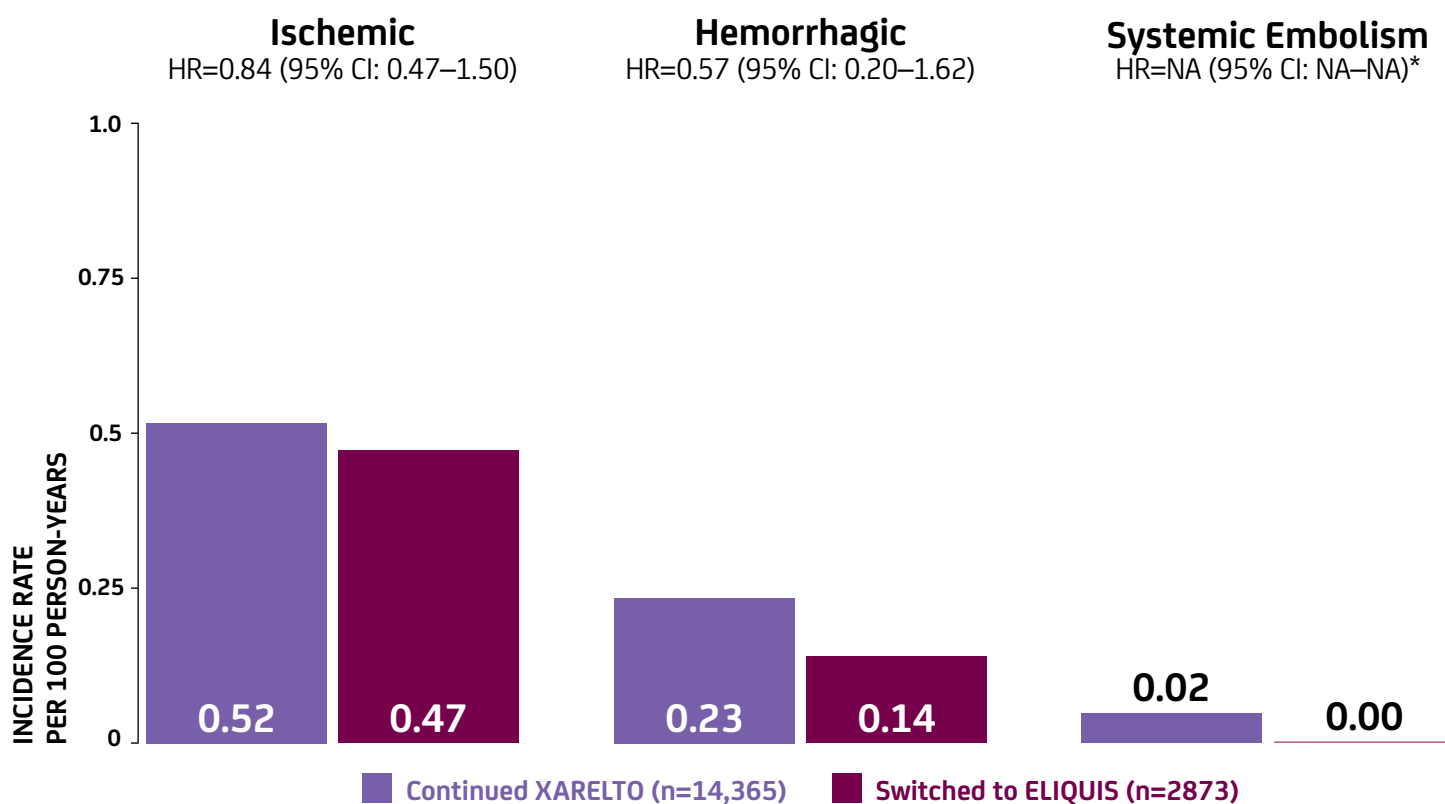
Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

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2.5mg

COMPONENTS OF STROKE/SYSTEMIC EMBOLISM IN PATIENTS WHO CONTINUED ON XARELTO VS THOSE WHO SWITCHED TO ELIQUIS¹

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*Proper HR and CI were not obtained due to one group with 0 events.
NA=not applicable.

SELECTED IMPORTANT SAFETY INFORMATION

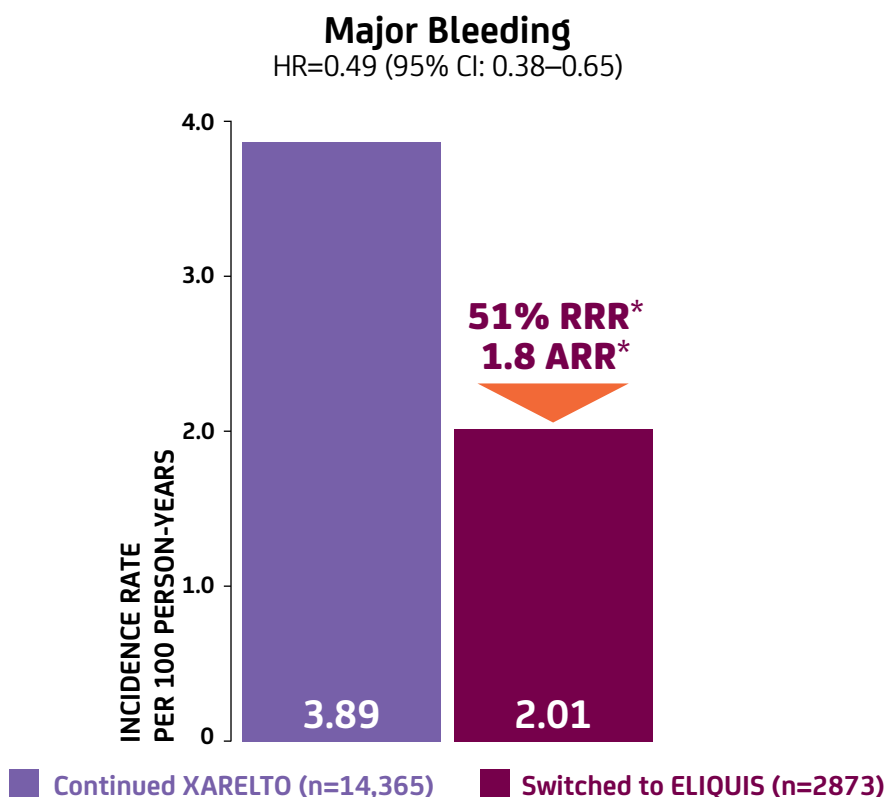
DRUG INTERACTIONS (cont'd)

- **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.
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OUTCOMES: MAJOR BLEEDING IN PATIENTS WHO CONTINUED ON XARELTO VS THOSE WHO SWITCHED TO ELIQUIS¹



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.²

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*Statistical note: RRR was calculated as $(1 - \text{HR}) \times 100$. ARR represents the difference between the event rates and is expressed as per 100 person-years.

SELECTED IMPORTANT SAFETY INFORMATION PREGNANCY

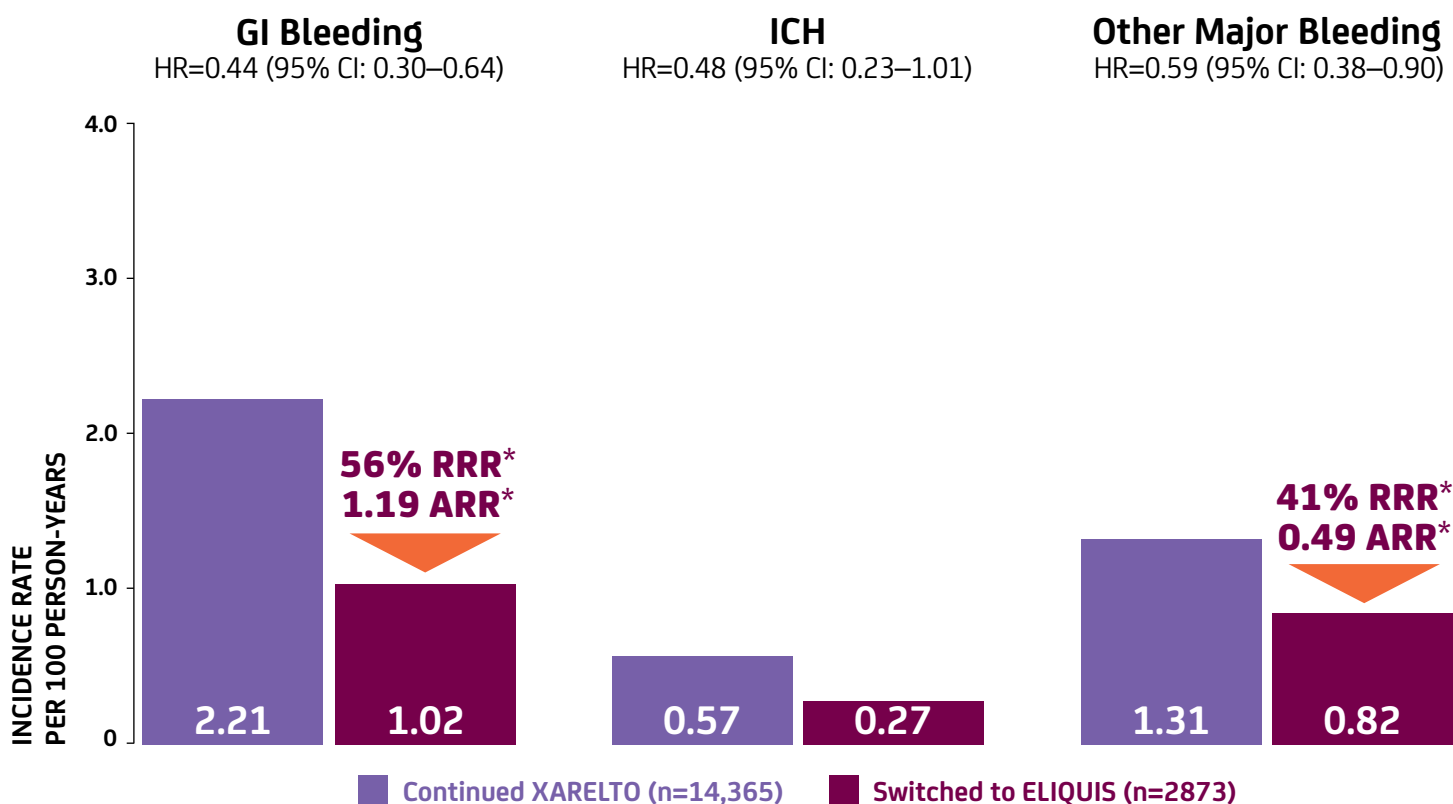
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COMPONENTS OF MAJOR BLEEDING IN PATIENTS WHO CONTINUED ON XARELTO VS THOSE WHO SWITCHED TO ELIQUIS¹

ATHENS
Real-world data analysis 



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GI=gastrointestinal; ICH=intracranial hemorrhage.

SELECTED IMPORTANT SAFETY INFORMATION

LACTATION

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- 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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OUTCOMES FROM A REAL-WORLD ANALYSIS OF COMMERCIALY INSURED AND MEDICARE PATIENTS¹

Summary of ATHENS
Real-world data analysis 

The first retrospective, observational real-world database analysis of patients in the U.S. with NVAF who started treatment with ELIQUIS and continued or switched to XARELTO between January 2013 and December 2021 and met study inclusion and exclusion criteria.

Real-world effectiveness and safety outcomes for patients who continued ELIQUIS vs those who switched to XARELTO

STROKE/SE

Continued **ELIQUIS** (n=14,500): 0.75/100 PYs
Switched to **XARELTO** (n=2900): 1.53/100 PYs
HR=1.99 (95% CI: 1.38–2.88)
RRI=99%; **ARI**=0.78

MAJOR BLEEDING

Continued **ELIQUIS** (n= 14,500): 2.44/100 PYs
Switched to **XARELTO** (n= 2900): 4.59/100 PYs
HR=1.80 (95% CI: 1.46–2.23)
RRI=80%; **ARI**=2.15

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.²

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.^{1,2}

The definitions of outcomes, follow-up period, and the patient population in ARISTOTLE were different than in this analysis.^{1,2}

There are currently no results from clinical trials comparing ELIQUIS to XARELTO.^{14,15}

PY=person-years.

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.

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OUTCOMES FROM A REAL-WORLD ANALYSIS OF COMMERCIALY INSURED AND MEDICARE PATIENTS¹

Summary of ATHENS
Real-world data analysis 

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Real-world effectiveness and safety outcomes for patients who continued XARELTO vs those who switched to ELIQUIS

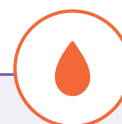
STROKE/SE

Continued **XARELTO** (n=14,365): 0.78/100 PYs
Switched to **ELIQUIS** (n=2873): 0.61/100 PYs
HR=0.74 (95% CI: 0.45–1.22)



MAJOR BLEEDING

Continued **XARELTO** (n=14,365): 3.89/100 PYs
Switched to **ELIQUIS** (n=2873): 2.01/100 PYs
HR=0.49 (95% CI: 0.38–0.65)
RRR=51%; ARR=1.8



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.²

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PY=person-years.

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

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