INDEPENDENTLY FUNDED, RETROSPECTIVE, OBSERVATIONAL, REAL-WORLD DATABASE ANALYSIS[1,2]

# SENTINEL* DATABASE ANALYSIS

## COMPARATIVE BLEEDING AND STROKE RISKS AMONG SELECT DOAC USERS WITH NONVALVULAR ATRIAL FIBRILLATION AGED <65 YEARS IN THE SENTINEL SYSTEM[1]

**Outcomes in 153,978 patients using ELIQUIS or XARELTO® (rivaroxaban).**

**Content herein should not be construed as an actual or implied endorsement by the FDA of any of the products discussed.**

### INDICATION

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

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

**1.** U.S. Food and Drug Administration. Modular program report: thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleeding, & major extracranial bleeding following apixaban and rivaroxaban use in patients aged 64 and younger with atrial fibrillation: an IPTW analysis, part **2.** Sentinel Initiative; request cder_mpl2p_wp044. August 21, 2024. Accessed October 3, 2024. https://www.sentinelinitiative.org/sites/default/files/documents/Sentinel_Report_cder_mpl2p_wp044.pdf

*FDA Sentinel is a national safety surveillance system for medical products that is primarily composed of aggregated electronic healthcare and administrative claims data.[2]

DOAC=direct oral anticoagulant; FDA=Food and Drug Administration; 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.**

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# ARISTOTLE: A PIVOTAL, PHASE III, RANDOMIZED CLINICAL TRIAL OF >18,000 PATIENTS WITH NVAF[3-5]*

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 2 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.[3,4]

*__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.[3]

**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 a prespecified subgroup analysis of patients <65 years**, incidence of stroke/SE was 1.0%/yr [n=51/2731] with ELIQUIS and 0.9%/yr [n=44/2740] with warfarin (HR=1.16 [95% CI: 0.77–1.73]) and incidence of major bleeding was 1.2%/yr [n=56/2723] with ELIQUIS and 1.5%/yr [n=72/2732] with warfarin (HR=0.78 [95% CI: 0.55–1.11]).¶

In another clinical trial (AVERROES), 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.[3]

†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)x100. 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.
¶The 95% CIs do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors.

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; VKA=vitamin K antagonist.

## SELECTED IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

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

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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[3,6,7]

**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.[3,6]

*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.

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

## RANDOMIZED CLINICAL TRIALS[8-10]

- **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[9-11]

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

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# STUDY OVERVIEW[1]

SENTINEL DATABASE ANALYSIS
Real-world data analysis

**OBJECTIVE: To compare major extracranial bleeding, GI bleeding, intracranial hemorrhage, and thromboembolic stroke outcomes in ELIQUIS or XARELTO users with NVAF aged <65 years**
**STUDY DESIGN: Real-world, retrospective, observational, new-user cohort analysis**[1,2]

## Cohort Description

**Patients from the FDA Sentinel System, including:**

- Patients aged 21–64 years with NVAF
- New, standard-dose DOAC prescription* between October 19, 2010 and February 28, 2022

153,978 patients met the inclusion/exclusion criteria

**Patients who met inclusion criteria were weighted with inverse probability treatment weighting (IPTW) to help balance baseline characteristics†**

| ELIQUIS (n=96,013) | XARELTO (n=57,965) |
|---|---|

## Assessed Outcomes‡

- Major extracranial bleeding
- GI bleeding
- Intracranial hemorrhage
- Thromboembolic stroke

**BASELINE CHARACTERISTICS**
Please see **page 6**.

*New users of standard-dose ELIQUIS or XARELTO with a diagnosis of NVAF within the 183 days prior to DOAC initiation.
†IPTW is a commonly used statistical method in real-world comparative studies to more closely approximate a randomized clinical trial and to help balance baseline characteristics in the absence of randomization.[12]
‡Outcomes were defined by their ICD-9-CM or ICD-10-CM codes as primary diagnosis from an inpatient encounter.
GI=gastrointestinal; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM=International Classification of Diseases, Tenth Revision, Clinical Modification.

## 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.
- **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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# SELECT BASELINE CHARACTERISTICS (POST-MATCHING)[1]

SENTINEL DATABASE ANALYSIS
Real-world data analysis

| | ELIQUIS (N=96,013) | XARELTO (N=57,965) |
|---|---|---|
| | (INVERSE PROBABILITY TREATMENT–WEIGHTED) | |
| **AGE, YEARS (MEAN)** | 56.7 | 56.6 |
| 21–49 | 15.9% | 15.6% |
| 50–64 | 84.1% | 84.4% |
| **SEX** | | |
| Female | 28.1% | 28.0% |
| Male | 71.9% | 72.0% |
| **RACE** | | |
| White | 15.6% | 13.2% |
| Black | 2.8% | 2.3% |
| Unknown | 80.8% | 83.8% |
| Other | 0.4% | 0.4% |
| **COMORBIDITY SCORES** | | |
| $CHA_2DS_2$-VASc (mean) | 1.7 | 1.7 |
| HAS-BLED (mean) | 1.0 | 1.0 |
| **BASELINE COMORBIDITIES** | | |
| Diabetes | 28.4% | 27.8% |
| Hypercholesterolemia | 27.1% | 26.8% |
| Hypertension | 72.9% | 72.4% |
| Kidney failure (chronic) | 7.0% | 6.8% |
| Kidney failure (acute) | 7.8% | 7.7% |
| Obesity | 37.6% | 37.2% |
| Peptic ulcer disease | 0.4% | 0.3% |
| Nicotine dependency | 26.7% | 26.3% |
| Hospitalized AMI (past 0–30 days) | 2.3% | 2.2% |
| Hospitalized AMI (past 31–183 days) | 1.2% | 1.2% |
| Coronary revascularization | 8.7% | 8.5% |
| Hospitalized heart failure | 15.9% | 15.5% |
| Outpatient heart failure | 15.4% | 14.9% |
| Other ischemic heart disease | 27.7% | 27.2% |
| Hospitalized stroke (past 0–30 days) | 1.3% | 1.3% |
| Hospitalized stroke (past 31–183 days) | 0.8% | 0.8% |
| Transient ischemic attack | 3.2% | 3.2% |
| Other medical conditions (falls, fractures, syncope, walker use) | 26.1% | 25.9% |
| Cardioversion | 15.9% | 16.0% |
| Cardioablation | 4.4% | 4.5% |
| Hospitalized for bleeding | 0.4% | 0.4% |

CONTINUED ON NEXT PAGE

Note: Inverse probability treatment weighting (IPTW) is a statistical method used to help balance baseline patient characteristics between treatment groups.[1,12] This is not a complete list of baseline characteristics. Additional baseline characteristics were assessed with this analysis.

AMI=acute myocardial infarction; $CHA_2DS_2$-VASc=congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category; HAS-BLED=hypertension, abnormal renal and liver function, stroke, bleeding, labile International Normalized Ratio, elderly, drugs and alcohol.

# SELECT BASELINE CHARACTERISTICS (POST-MATCHING)[1] (CONTINUED)



| | ELIQUIS (N=96,013) | XARELTO (N=57,965) |
|---|---|---|
| | (INVERSE PROBABILITY TREATMENT–WEIGHTED) | |
| **MEDICATIONS** | 2.4% | 2.4% |
| Estrogen replacement | 2.7% | 2.6% |
| H2-antagonist | 16.2% | 16.1% |
| NSAIDs | 20.8% | 20.4% |
| Proton pump inhibitors | 8.7% | 8.5% |
| SSRI antidepressants | 12.3% | 12.1% |
| Insulin | 7.4% | 7.1% |
| Metformin (biguanide) | 17.3% | 17.0% |
| Sulfonylureas | 5.4% | 5.2% |
| Other diabetes medications | 8.3% | 8.1% |
| ACEI/ARB | 50.4% | 50.1% |
| Antiarrhythmics | 28.5% | 28.5% |
| Anticoagulant (injectable) | 11.6% | 11.6% |
| Antiplatelets | 12.1% | 12.0% |
| Beta-blockers | 71.3% | 71.1% |
| Calcium channel blockers | 35.2% | 35.0% |
| Digoxin | 5.9% | 5.8% |
| Diuretics (loop) | 18.7% | 18.1% |
| Diuretics (potassium sparing) | 8.2% | 8.1% |
| Diuretics (thiazide) | 20.3% | 20.2% |
| Nitrates | 5.5% | 5.4% |
| Statins | 44.2% | 43.7% |
| Fibrates | 3.9% | 3.8% |
| Amiodarone | 10.1% | 10.0% |
| Dronedarone | 2.5% | 2.6% |

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use with oral anticoagulants increases the risk of bleeding.[3]

Note: Inverse probability treatment weighting (IPTW) is a statistical method used to help balance baseline patient characteristics between treatment groups.[1,12] This is not a complete list of baseline characteristics. Additional baseline characteristics were assessed with this analysis.

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; H2=histamine type 2 receptor; NSAID=nonsteroidal anti-inflammatory drug; SSRI=selective serotonin reuptake inhibitor.

# METHODS OF ANALYSIS[1]



**STUDY DRUG:** ELIQUIS or XARELTO
**STUDY DURATION:** October 19, 2010 to February 28, 2022
**BASELINE PERIOD:** 183 days (approximately 6 months)
**DATA SOURCE:** FDA Sentinel System

## Data source

- FDA Sentinel is a national safety surveillance system for medical products, capturing healthcare and administrative claims data[1,2]
- Five Sentinel data partners contributed to the analysis (4 nationally representative commercial insurance plans and 1 state Medicaid partner)[1,13]
- Data presented here are based on a report of an FDA analysis (August 21, 2024), not a final peer-reviewed publication, and do not reflect labeling decisions for any product.

## Inclusion criteria*

- New users of standard-dose ELIQUIS or XARELTO aged 21–64 years with a diagnosis of NVAF within the 183 days prior to DOAC initiation
- Continuous enrollment, allowing for gaps in coverage of ≤45 days, was required for at least 183 days prior to index exposure

## Exclusion criteria*

- Dialysis, kidney replacement, deep vein thrombosis, pulmonary embolism, joint replacement, mitral stenosis, valve replacement or repair, other oral anticoagulant dispensing, or institutional stay encounter (index date only)

## Outcomes

- Major extracranial bleeding
- GI bleeding
- Intracranial hemorrhage
- Thromboembolic stroke

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*Inclusion and exclusion criteria were defined using NDCs, ICD-9-CM, ICD-10-CM, ICD-10-PCS, and CPT-4 codes.

CPT-4=Current Procedural Terminology, Fourth Edition; ICD-10-PCS=International Classification of Diseases, Tenth Revision, Procedure Coding System; NDCs=National Drug Codes.

## 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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# METHODS OF ANALYSIS[1] (CONTINUED)



### Statistical analyses

- Inverse probability treatment weighting (IPTW) was determined by calculating a propensity score and was used to help balance baseline characteristics between the cohorts
- Baseline covariates included demographic factors, medical conditions and medication use, stroke and bleeding risk scores, and health care utilization
- HRs and 95% CIs were estimated for each outcome using Cox proportional hazards regression
- Adjusted relative risk of the outcomes was estimated with HRs

### Follow-up period

- Patients were followed from the day after initial DOAC exposure until an outcome of interest, end of DOAC exposure (exposure episodes <3 days apart were considered part of a continuous treatment period), end of study period, disenrollment, end of available data, an exclusion criteria event (comparator drug dispensing; alternate dose of index drug; warfarin, dabigatran, or edoxaban dispensing; kidney transplant; dialysis; or institutional stay encounter), or death, whichever occurred earlier

## SELECTED IMPORTANT SAFETY INFORMATION

### DRUG INTERACTIONS

- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.

  *Clarithromycin*

  Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.
- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

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# LIMITATIONS OF ANALYSIS[1]



### Study design/definitions

- Due to the nature of retrospective, observational cohort studies, no causal relationships can be inferred, and only statistical associations were assessed
- In contrast to clinical trials, outcomes were defined using ICD-9-CM and ICD-10-CM diagnosis codes and without outcome adjudication
- Algorithms used to define exposures, outcomes, inclusion and exclusion criteria, and covariates are imperfect and may be misclassified
- The presence of a claim for a filled prescription did not indicate whether the medication was consumed or taken as prescribed
- Statistical power may have been affected by the smaller numbers of bleeding and stroke outcomes in DOAC users aged <65 years (compared to previous studies in older adults)[1,4,14]
- Data presented are based on a study report, not a peer-reviewed publication; as such, results are subject to change and should be interpreted with caution
- Study details are limited, including exact data sources and statistical methods, which impacts interpretation of study design, results, strengths, and limitations

### Bias/confounding

- 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 trials—and therefore results should be interpreted with caution[1,14,15]

### Data collection

- Exposure misclassification is possible because there was no information about adherence
- Outcome misclassification is possible because the study outcomes were based on ICD codes
- Study outcomes did not include ischemic or hemorrhagic events without hospitalization, unless they resulted in death

### Generalizability

- The study was restricted to US patients in the FDA Sentinel System who were aged 64 years and younger, and new users of standard-dose DOACs, which therefore limits generalizability of the findings[1,2]
- The study only included new users of standard-dose DOACs and did not account for patients switching from other DOACs or treated with alternative doses; these factors may impact future results

## 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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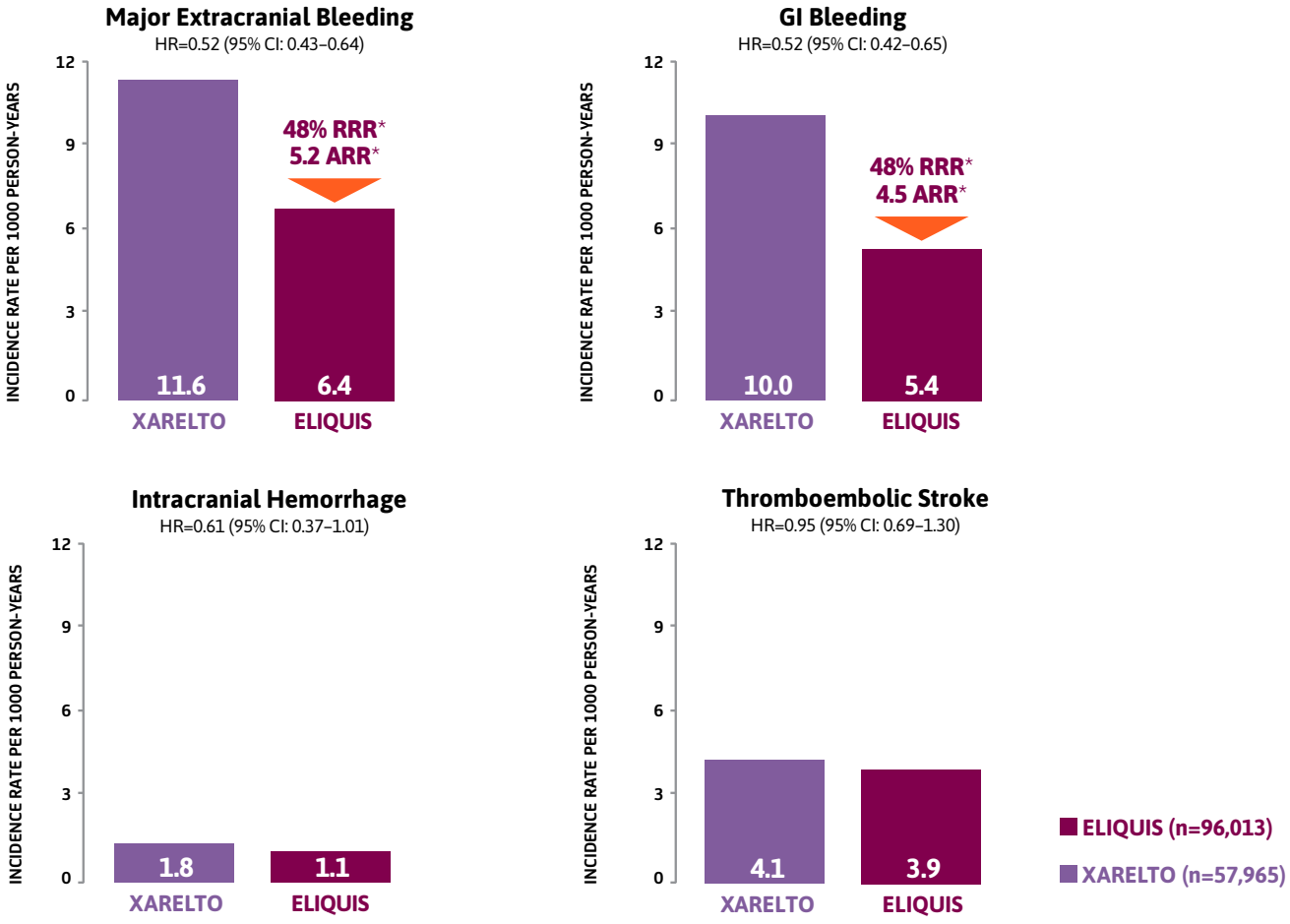
# INCIDENCE OF BLEEDING- & STROKE-RELATED OUTCOMES IN PATIENTS AGED <65 YEARS[1]

SENTINEL DATABASE ANALYSIS
Real-world data analysis




*Statistical note: HRs were presented as XARELTO vs ELIQUIS in the original report and were inverted in the figures above as ELIQUIS vs XARELTO. RRR was calculated as (1-HR)x100. ARR represents the difference between the event rates and is expressed as per 1000 person-years. Incidence rates for each cohort have been rounded to 1 decimal place in the figures above.

## ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[3]

**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.[16]**

The definitions of outcomes, follow-up period, and the patient population in ARISTOTLE were different than in this analysis.[1,3]

**There are currently no results from DOAC vs DOAC head-to-head clinical trials.[14,15]**

ARR=absolute risk reduction; RRR=relative risk reduction.

## 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.

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

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