RETROSPECTIVE, OBSERVATIONAL, REAL-WORLD DATABASE ANALYSIS

NVAF HOSPITAL READMISSIONS

COMPARISON OF STROKE-RELATED READMISSIONS AMONG HOSPITALIZED NONVALVULAR ATRIAL FIBRILLATION (NVAF) PATIENTS TREATED WITH ORAL ANTICOAGULANTS IN THE UNITED STATES (N=529,983)

Published in *Journal of Drug Assessment*[1]

INDICATION

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

ARISTOTLE RCT SUMMARY
Please see **page 2**.

RCT VS RWD
Please see **page 3**.

Sponsored by Pfizer Inc. and Bristol-Myers Squibb Company.
RCT=randomized clinical trial; RWD=real world data.

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 RCT SUMMARY

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 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.[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.

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]

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), 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)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.

ARR=absolute risk reduction; CI=confidence interval; HR=hazard ratio; INR=International Normalized Ratio; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; NVAF=nonvalvular atrial fibrillation; 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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SELECT CHARACTERISTICS OF RANDOMIZED CLINICAL TRIALS AND REAL-WORLD DATA

RANDOMIZED CLINICAL TRIALS[6-8]	VS	REAL-WORLD OBSERVATIONAL STUDIES[7-9]
Prospective design with **prespecified**, well-defined inclusion/exclusion criteria, outcomes, and endpoints		**Observational in nature** and use data from routine clinical practice
Patients are **randomly** assigned to treatment or comparator		Patients are **not randomized**
Randomized clinical trials are designed to show **causality** (ie, efficacy and safety data)		Can only evaluate **association** and therefore unable to determine causality

SELECTED IMPORTANT SAFETY INFORMATION

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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HOSPITAL READMISSIONS STUDY OVERVIEW[1]

HOSPITAL READMISSIONS
Real-world data anaysis

OBJECTIVE: To compare the risks of 1-month stroke and major bleeding–related readmissions among patients previously hospitalized for NVAF and treated with ELIQUIS, XARELTO®, or warfarin

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

Cohort Description

Patients from the Premier Hospital database including:

- Adult patients with a hospital discharge diagnosis code indicating a primary or secondary diagnosis of NVAF* between January 1, 2013 and September 30, 2017
- 1-year baseline prior to index hospitalization
- Treated with ELIQUIS, XARELTO, or warfarin during index hospitalization†
- **529,983 patients met the inclusion/exclusion criteria**

Propensity Score Matching (1:1)‡

ELIQUIS (n=59,747)	XARELTO (n=59,747)	ELIQUIS (n=69,765)	warfarin (n=69,765)

Assessed Outcomes

- Stroke-related hospital readmission
- Major bleeding–related§ hospital readmission

- Stroke-related hospital readmission
- Major bleeding–related§ hospital readmission

BASELINE CHARACTERISTICS
Please see **page 5**.

*Any discharge ICD-9/10 CM code indicating NVAF.
†The published analysis includes a PRADAXA® (dabigatran etexilate) patient cohort, which has been excluded from this presentation due to the low use of PRADAXA in the US.
‡Propensity score matching helped to ensure cohort groups were comparable based on their baseline characteristics.
§Major bleeding was identified by the first-listed ICD-9/10 CM code.
XARELTO® (rivaroxaban) is a registered trademark of Bayer Aktiengesellschaft.
PRADAXA® is a registered trademark of Boehringer Ingelheim Pharmaceuticals, Inc.

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

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.
- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

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SELECT BASELINE CHARACTERISTICS (POST-MATCHING)[1]

HOSPITAL READMISSIONS
Real-world data anaysis

	ELIQUIS (n=59,747)	XARELTO (n=59,747)	ELIQUIS (n=69,765)	warfarin (n=69,765)
AGE, YEARS (MEAN)*	72.8	72.7	76.0	76.0
SEX*				
Female	48.1%	48.1%	50.5%	50.7%
Male	51.9%	52.0%	49.5%	49.3%
RACE*				
White	84.7%	84.3%	84.4%	84.6%
Black	6.9%	7.2%	6.7%	6.6%
Other	8.4%	8.5%	9.0%	8.8%
COMORBIDITY SCORES (MEAN)				
CCI Score*	2.1	2.1	1.7	1.7
$CHADS_2$ Score	2.3	2.4	1.2	1.2
CHA_2DS_2- VASc Score*	3.8	3.8	1.6	1.6
HAS-BLED Score*	2.9	2.9	1.1	1.1
STROKE/BLEEDING HISTORY*				
Prior stroke	0.4%	0.4%	2.1%	2.0%
Stroke in index hospitalization	5.5%	5.7%	6.9%	7.0%
Prior bleeding	1.3%	1.3%	1.7%	1.8%
Bleeding in index hospitalization	6.1%	6.3%	7.5%	7.4%
HOSPITAL LOCATION				
Urban	86.8%	86.6%	85.9%	85.7%
Rural	13.3%	13.4%	14.1%	14.3%
HOSPITAL TEACHING STATUS				
Yes	37.6%	38.0%	38.4%	37.9%
No	62.4%	62.1%	61.6%	62.1%
HOSPITAL BEDS				
0-99	6.1%	6.1%	6.3%	6.5%
100-199	15.8%	15.7%	16.2%	16.1%
200-299	19.5%	19.4%	18.9%	19.3%
300-399	18.4%	18.1%	18.0%	18.1%
400-499	12.2%	12.6%	13.4%	13.5%
≥500	28.1%	28.1%	27.2%	26.6%
INDEX HOSPITAL LENGTH OF STAY,* DAYS (MEAN)	4.0	4.0	4.4	4.4

Each cohort was matched separately; therefore it is not appropriate to compare across cohorts.

*Variables used for PSM. Payer type was also used in PSM.

CCI=Charlson Comorbidity Index; $CHADS_2$ Score=congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke; CHA_2DS_2-VASc Score=congestive heart failure, age ≥75 years, diabetes mellitus, stroke, vascular disease; HAS-BLED=hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition; PSM=propensity score matching.

METHODS OF ANALYSIS[1]

STUDY DRUG: ELIQUIS, XARELTO, or warfarin
STUDY DURATION: January 1, 2012 through September 30, 2017
BASELINE PERIOD: 1 year prior to the index hospitalization* admission
DATA SOURCE: Premier Hospital database

Data source

- The Premier Hospital database is a nationally representative inpatient hospitalization records database capturing more than 45 million hospital discharges and ~20% of all hospital admissions from more than 700 acute care hospitals in the US

Inclusion criteria

- Patients aged ≥18 years with a hospital discharge diagnosis code indicating a primary or secondary diagnosis of NVAF
  - Diagnoses were identified based on ICD-9 and ICD-10 codes
- 1-year baseline period prior to index hospitalization
- Treatment with ELIQUIS, XARELTO, PRADAXA, or warfarin during index hospitalization*†

Exclusion criteria

- Patients with evidence of any of the following during the index hospitalization or within 12 months prior to the index date*: rheumatic mitral valvular heart disease or mitral valve stenosis, venous thromboembolism (deep vein thrombosis or pulmonary embolism), heart valve replacement/transplant, reversible AF (pericarditis, hyperthyroidism or thyrotoxicity, acute myocardial infarction, acute myocarditis), dialysis, kidney transplant, end-stage chronic kidney disease, or a pharmacy claim for SAVAYSA
- Patients with medical claims indicating a hip or knee surgery within 6 weeks prior to the index date
- Patients with a medical claim indicating pregnancy at any time during the study period
- Patients with >1 OAC prescription claim or death during the index hospitalization

METHODS CONTINUED ON NEXT PAGE

*The index hospitalization was defined as first NVAF hospitalization. The index date for evaluation of hospital readmissions was defined as the discharge date of the index hospitalization.
†The published analysis includes a PRADAXA patient cohort, which has been excluded from this presentation due to the low use of PRADAXA in the US.
SAVAYSA® (edoxaban) is a registered trademark of Daiichi Sankyo, Inc.

AF=atrial fibrillation; OAC=oral anticoagulant.

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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METHODS OF ANALYSIS[1] (CONTINUED)

STUDY DRUG: ELIQUIS, XARELTO, or warfarin
STUDY DURATION: January 1, 2012 through September 30, 2017
BASELINE PERIOD: 1 year prior to the index hospitalization* admission
DATA SOURCE: Premier Hospital database

Outcomes

- Hospital readmission with a primary discharge diagnosis of:
  - Stroke, including ischemic stroke, hemorrhagic stroke, and systemic embolism
  - Major bleeding, including gastrointestinal bleeding, intracranial bleeding, and other types of major bleeding
- Results are shown for matched cohorts

Follow-up period

- The overall study period included a follow-up period for observation of readmission within 1 month of hospital discharge

Statistical analyses

- PSM (1:1) was used to control for baseline characteristics between cohorts
  - PSM baseline covariates included age, sex, race, payer type, CCI, CHA_2DS_2-VASc score, HAS-BLED score, index bleed, prior bleed, index stroke, prior stroke, index hospital length of stay, and index hospitalization cost
- ANOVA or χ^2 tests were used where appropriate to compare baseline characteristics
- Logistic regression analyses were conducted to further evaluate the potential impact of ELIQUIS vs XARELTO or ELIQUIS vs warfarin on the risk of major bleeding–related and stroke-related readmissions within 1 month of hospital discharge

Sensitivity analyses

- Sensitivity analyses were generally consistent with the main analysis and included:
  - Stroke-related hospital readmissions within 1 month of discharge of initial hospitalization when hemorrhagic strokes were not included in stroke events
  - Comparisons of 3-month readmissions rates, associated length of stay, and costs of all-cause, major bleeding–related, and stroke-related readmissions between ELIQUIS and each of the other OAC cohorts

*The index hospitalization was defined as first NVAF hospitalization. The index date for evaluation of hospital readmissions was defined as the discharge date of the index hospitalization.
†The published analysis includes a PRADAXA patient cohort, which has been excluded from this presentation due to the low use of PRADAXA in the US.

ANOVA=analysis of variance.

LIMITATIONS OF ANALYSIS[1]

Study design/definitions

- Due to the nature of retrospective, observational cohort studies, no causal relationships 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 rather than clinical outcome adjudication
- There is no guarantee that patients were dosed according to the US prescribing information for ELIQUIS, XARELTO, or warfarin

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 use of over-the-counter medications (e.g., aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs]). The risk of confounding is especially important for interpreting ELIQUIS vs XARELTO comparisons—which are for hypothesis generation, given the lack of head-to-head clinical trials—and therefore results should be interpreted with caution

Data collection

- Limitations associated with retrospective data analyses, such as missing variables and miscoded or missing data, are possible
- 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
- Only readmissions to the same hospital or hospital system within the Premier network could be identified in the database. This may have led to an underestimation of the actual readmission rates
- Major bleeding–related and stroke-related readmissions were evaluated by the primary hospital discharge diagnoses for the readmissions, which may or may not have fully captured the entire cause of readmissions
- As with all studies relying on administrative billing information, there may have been inaccuracies from hospital billing and coding errors, as well as missing data

Generalizability

- This study was restricted to patients admitted at hospitals within the Premier Hospital database, which therefore limits the generalizability of the findings

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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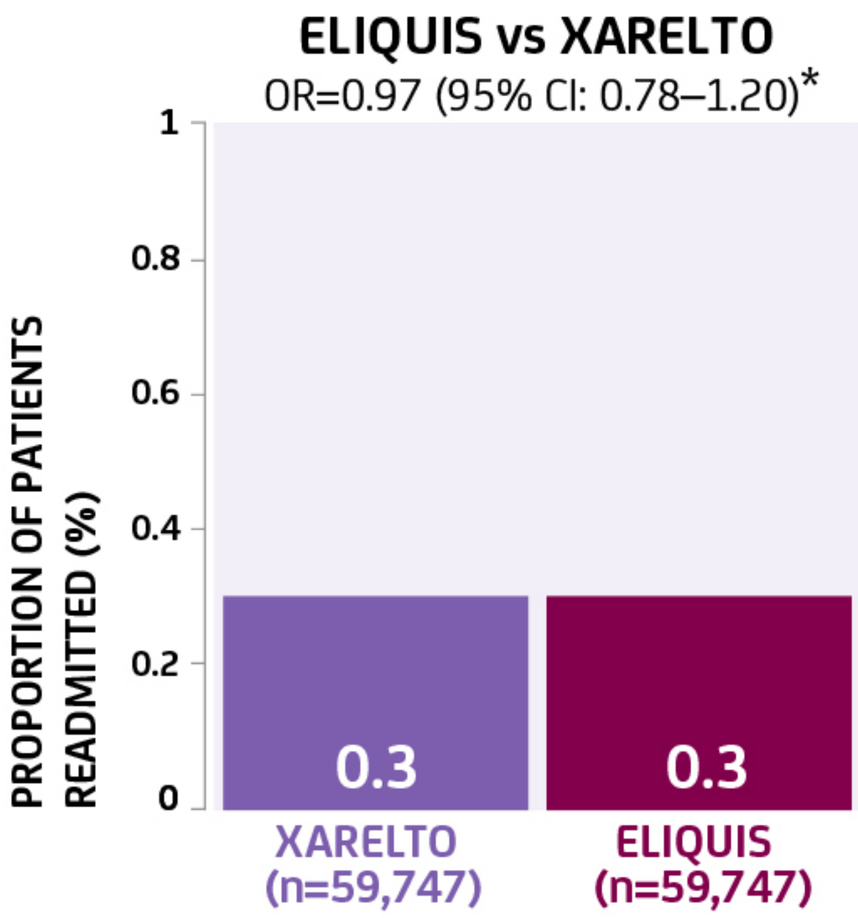
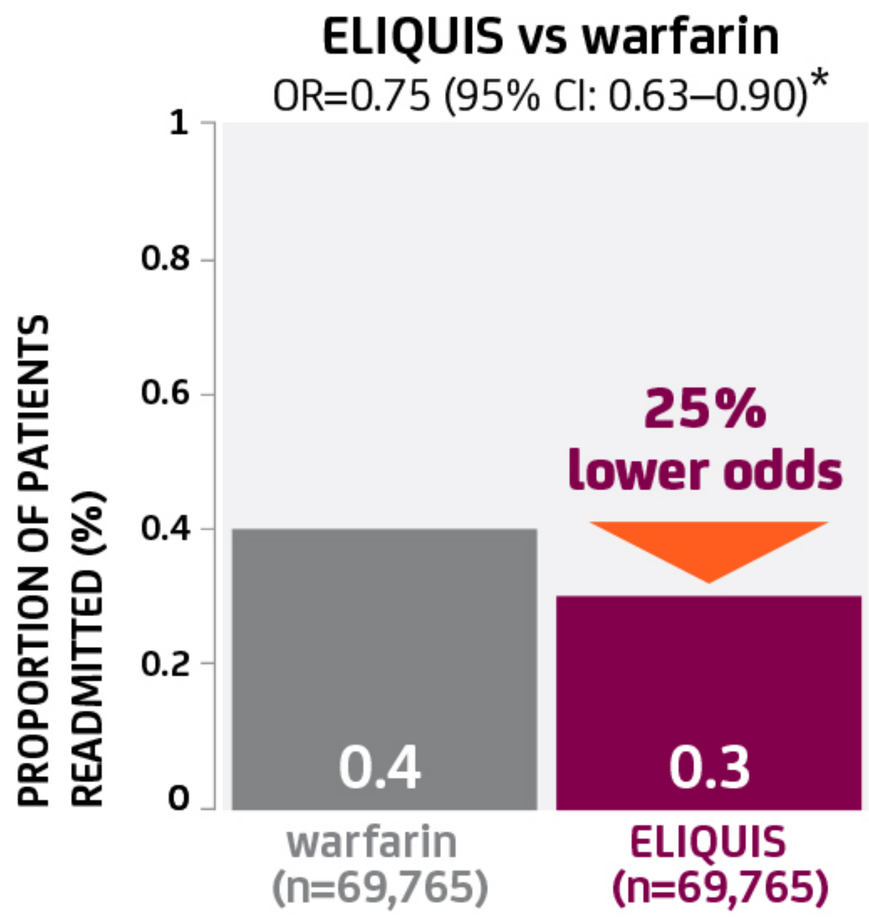
STROKE–RELATED READMISSION RATES WITHIN 1 MONTH OF DISCHARGE (MATCHED POPULATIONS)[1]

HOSPITAL READMISSIONS
Real-world data anaysis





Each cohort was matched separately; therefore it is not appropriate to compare across cohorts.

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.[10]

The definitions of stroke and major bleeding, follow-up period, and the patient population in ARISTOTLE were different than in these analyses.[1,2]

There are currently no results from DOAC vs DOAC head-to-head clinical trials.[11,12]

*Statistical note: ORs are based on regression analysis. They were presented as competitor vs ELIQUIS in the original publication and were inverted in the figures as ELIQUIS vs competitor. Difference in odds was calculated as (1-OR)x100.

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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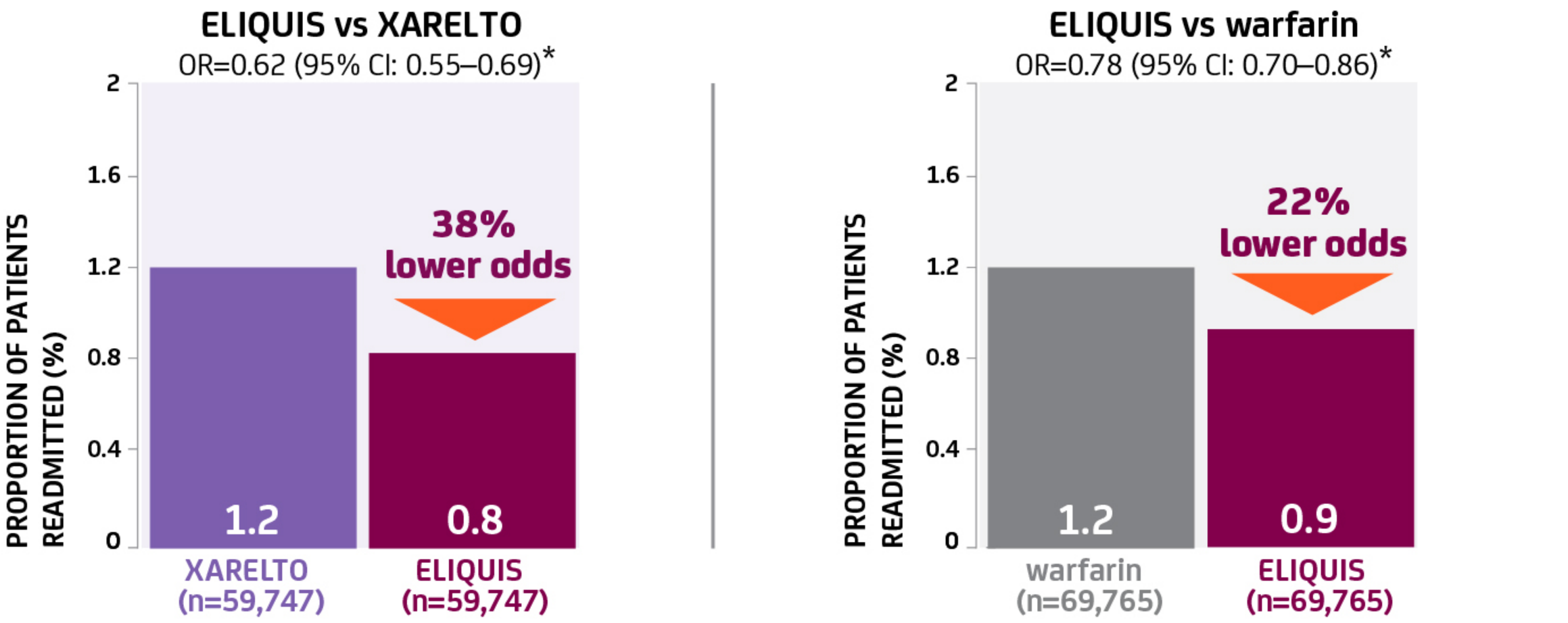
MAJOR BLEEDING–RELATED READMISSION RATES WITHIN 1 MONTH OF DISCHARGE (MATCHED POPULATIONS)[1]

HOSPITAL READMISSIONS
Real-world data anaysis



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.[10]

The definitions of stroke and major bleeding, follow-up period, and the patient population in ARISTOTLE were different than in these analyses.[1,2]

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Each cohort was matched separately; therefore it is not appropriate to compare across cohorts.

*Statistical note: ORs are based on regression analysis. They were presented as competitor vs ELIQUIS in the original publication and were inverted in the figures as ELIQUIS vs competitor. Difference in odds was calculated as (1-OR)x100.

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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