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ARISTOTLE

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

RAY ET AL

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

INDICATION

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

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

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

SELECT CHARACTERISTICS OF RANDOMIZED CLINICAL TRIALS AND REAL-WORLD DATA

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RANDOMIZED CLINICAL TRIALS[5-7]

- **Prospective design** with **prespecified**, well-defined inclusion/exclusion criteria, outcomes, and endpoints
- Patients are **randomly** assigned to treatment or comparator
- Randomized clinical trials are designed to show **causality** (ie, efficacy and safety data)

VS

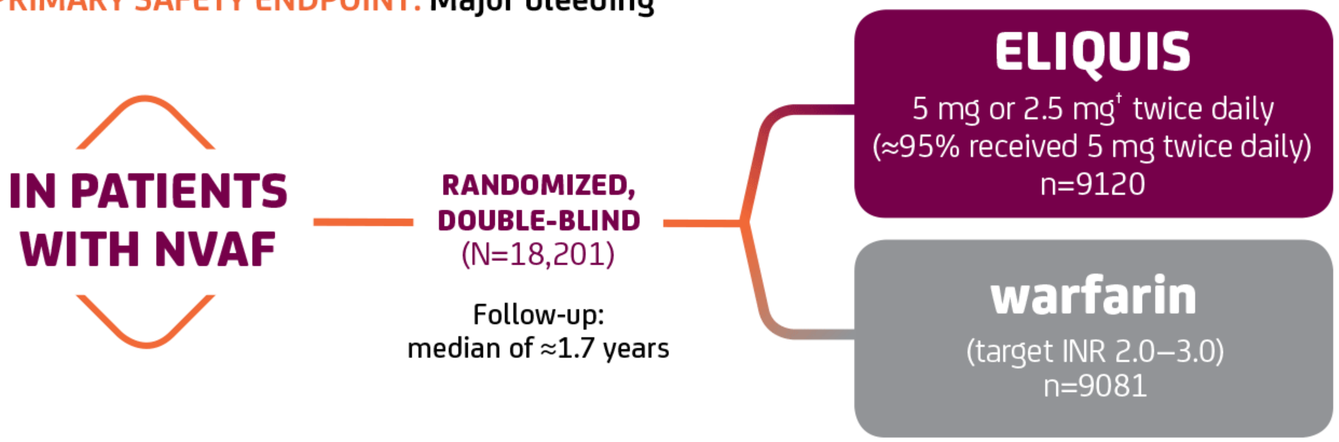
REAL-WORLD OBSERVATIONAL STUDIES[6,8,9]

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

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

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

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



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

INR=international normalized ratio; NVAF=nonvalvular atrial fibrillation; VKA=vitamin K antagonist.

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

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

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

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

SELECTED IMPORTANT SAFETY INFORMATION

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

WARNINGS AND PRECAUTIONS
- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

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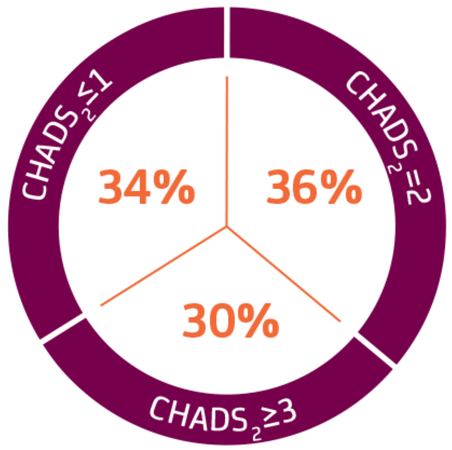
ARISTOTLE: BASELINE CHARACTERISTICS WERE WELL BALANCED ACROSS TREATMENT ARMS[1,2*]

ARISTOTLE	ELIQUIS n=9120	warfarin n=9081
Median age (yrs)	70	70
Mean $CHADS_2$ score†	2.1±1.1	2.1±1.1
$CHADS_2 \leq 1$	34% n=3100	34% n=3083
$CHADS_2 = 2$	36% n=3262	36% n=3254
$CHADS_2 \geq 3$	30% n=2758	30% n=2744
Prior stroke, TIA, or SE	19% n=1748	20% n=1790
Prior use of VKA (eg, warfarin) for >30 consecutive days	57% n=5208	57% n=5193
Heart failure or reduced LVEF	36% n=3235	35% n=3216
Hypertension requiring treatment	87% n=7962	88% n=7954

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



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

*This is not a complete list of baseline characteristics. Additional baseline characteristics were evaluated in this trial.
†Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.
TIA=transient ischemic attack.

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SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.

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

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

ARISTOTLE CONT'D	ELIQUIS n=9120	warfarin n=9081
Aspirin use at time of randomization	31% n=2859	31% n=2773
Clopidogrel use at time of randomization	2% n=170	2% n=168
Renal function, creatinine clearance		
Normal (>80 mL/min)	41% n=3761	41% n=3757
Mild impairment (>50 to 80 mL/min)	42% n=3817	42% n=3770
Moderate impairment (>30 to 50 mL/min)	15% n=1365	15% n=1382
Severe impairment (≤30 mL/min)	2% n=137	2% n=133

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

*This is not a complete list of baseline characteristics. Additional baseline characteristics were evaluated in this trial.
†Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.
TIA=transient ischemic attack.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
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  - 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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AVERROES: A PHASE III, RANDOMIZED, DOUBLE-BLIND TRIAL VS ASPIRIN IN OVER 5500 PATIENTS WITH NVAF WHO WERE UNSUITABLE FOR WARFARIN[1,10,11]

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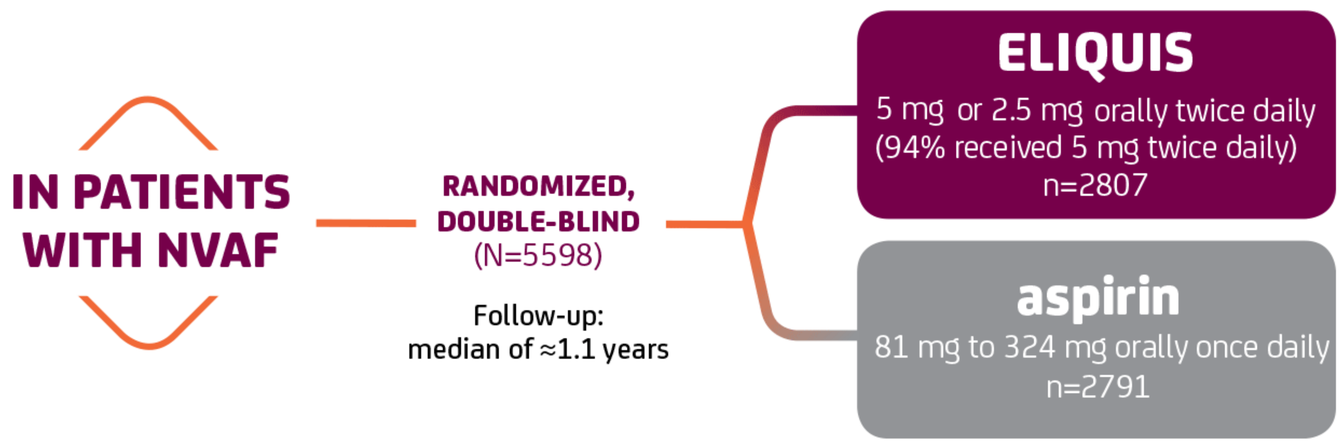
This trial included 5598 patients with NVAF thought not to be candidates for warfarin therapy with 1 or more additional risk factors for stroke.*

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



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

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

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

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

†A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.
‡Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.
§Intracranial bleeding included intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as intracranial major bleeding.
LVEF=left ventricular ejection fraction; NVAF=nonvalvular atrial fibrillation; NYHA=New York Heart Association; VKA=vitamin K antagonist.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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

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

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

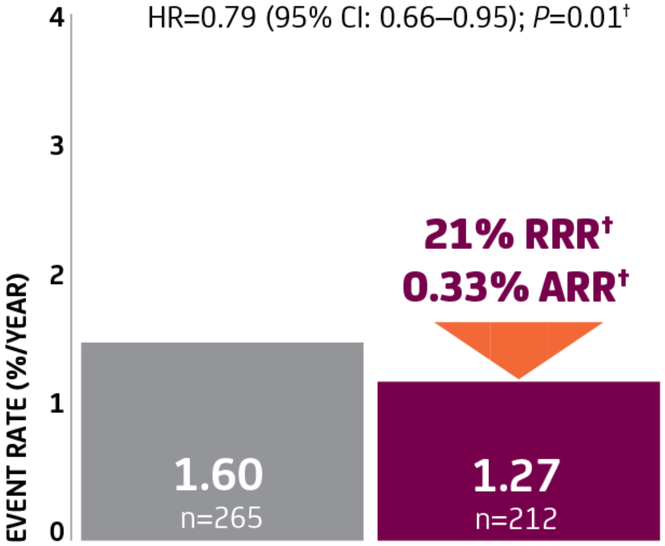
FOR PATIENTS WITH NVAF

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

SUPERIOR

RISK REDUCTION IN STROKE/SE

HR=0.79 (95% CI: 0.66–0.95); *P*=0.01†

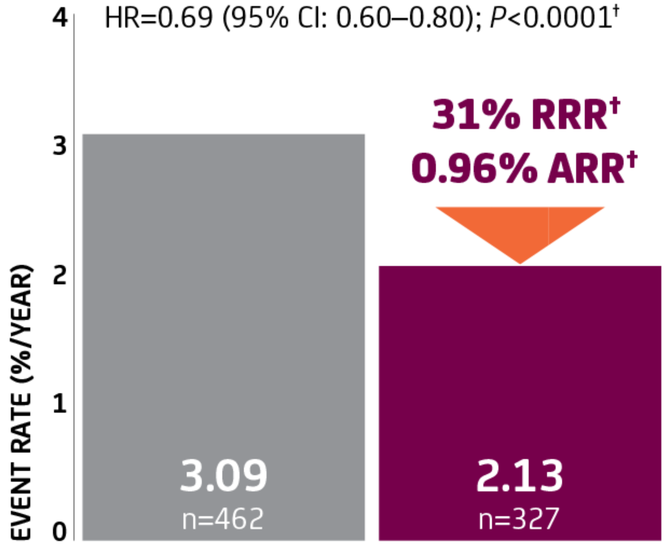


PRIMARY EFFICACY ENDPOINT

SUPERIOR

BASED ON FEWER MAJOR BLEEDING EVENTS*

HR=0.69 (95% CI: 0.60–0.80); *P*<0.0001†



PRIMARY SAFETY ENDPOINT

*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.
†Statistical note: RRR was calculated as (1-HR)x100. ARR was calculated as the difference between the event rates.
ARR=absolute risk reduction; CI=confidence interval; HR=hazard ratio; NVAF=nonvalvular atrial fibrillation; RRR=relative risk reduction.

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

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

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.
- **Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS):** Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive APS. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

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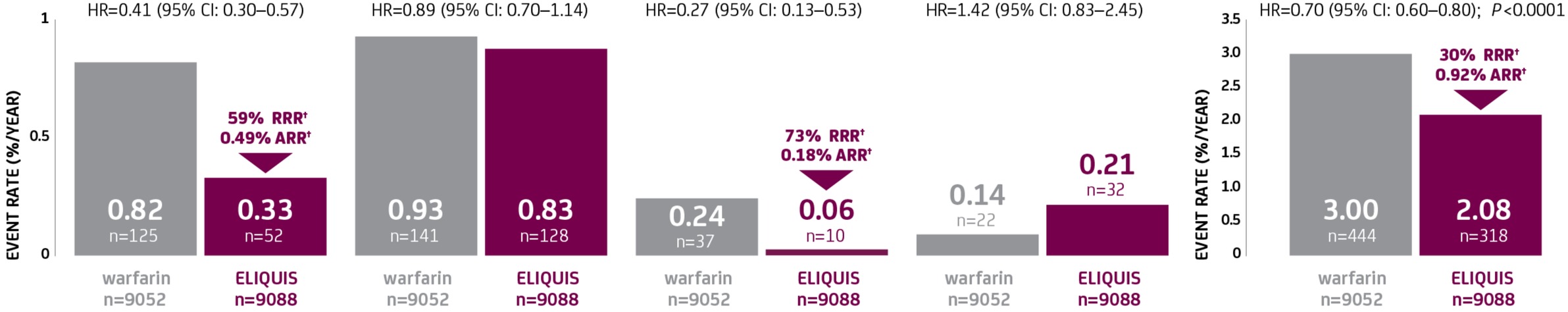
FOR PATIENTS WITH NVAF

ARISTOTLE: ELIQUIS DEMONSTRATED LOWER RATES IN SELECT BLEEDING OUTCOMES VS WARFARIN[1,12,13]

COMPONENTS OF MAJOR BLEEDING*



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

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

Components of ICH and fatal bleeding

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

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

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

*Bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
†Statistical note: RRR was calculated as (1-HR)x100. ARR was calculated as the difference between the event rates.
‡On-treatment analysis based on the safety population, compared with intent-to-treat analysis presented in efficacy population.
CRNM=clinically relevant nonmajor; ICH=intracranial hemorrhage.

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INDEPENDENTLY FUNDED BY THE NHLBI
RETROSPECTIVE, OBSERVATIONAL REAL-WORLD DATABASE ANALYSIS[4]

RAY ET AL

THE LARGEST STUDY COMPARING ELIQUIS VS XARELTO IN MEDICARE BENEFICIARIES WITH NVAF (N=581,451)

Association of ELIQUIS vs XARELTO® (rivaroxaban) with Major Ischemic or Hemorrhagic Events in Patients with NVAF

Published in the *Journal of the American Medical Association (JAMA)*

NHLBI=National Heart, Lung, and Blood Institute; NVAF=nonvalvular atrial fibrillation.

Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation- Ray, WA, et al., *JAMA.* 2021;326(23):2395-2404.

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.

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

STUDY OVERVIEW[4]

OBJECTIVE: To compare major ischemic and hemorrhagic outcomes in patients with atrial fibrillation treated with ELIQUIS or XARELTO

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

Records of 2,078,642 Medicare beneficiaries with fee-for-service (Parts A and B) and prescription drug coverage (Part D) who had an ELIQUIS or XARELTO prescription filled between January 1, 2013 and November 30, 2018 were screened. 581,451 patients met the inclusion criteria and were included in the analysis

Patients who met inclusion criteria were weighted with IPTW to balance baseline characteristics†

Outcomes with ELIQUIS or XARELTO‡ were assessed

INCLUSION CRITERIA

- Adults (≥65 years) with nonvalvular atrial fibrillation
- Newly* prescribed ELIQUIS (5 mg BID or 2.5 mg BID) or XARELTO (20 mg QD or 15 mg QD)

ELIQUIS (n=353,879)

XARELTO (n=227,572)

PRIMARY OUTCOME

- Composite of major ischemic events (ischemic stroke and systemic embolism) or major hemorrhagic events (hemorrhagic stroke, other intracranial bleeding, and fatal non-intracranial bleeding)

SECONDARY OUTCOMES§

- Nonfatal non-intracranial bleeding (gastrointestinal, other, or unspecified)

*Newly prescribed was defined as those without a prescription for ELIQUIS or XARELTO in the preceding year of the analysis.
†IPTW is a commonly used statistical method in real-world comparative studies to more closely approximate a randomized clinical trial and to balance baseline characteristics in the absence of randomization.[14]
‡Outcomes were identified from hospital primary discharge diagnosis codes.
§Additional secondary outcomes not shown here included total mortality, which included fatal ischemic or hemorrhagic events (death within 30 days of event onset) and other deaths during follow-up.
BID=twice a day; IPTW=inverse probability treatment weighting; QD=once a day.

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.

SELECT BASELINE CHARACTERISTICS[4]

	ELIQUIS (n=353,879)	XARELTO (n=227,572)
	(INVERSE PROBABILITY TREATMENT-WEIGHTED)	
AGE, YEARS (MEAN)	77	77
USE OF REDUCED DOSE ANTICOAGULANT	23.1%	23.2%
SEX, MALE/FEMALE	50%/50%	50%/50%
RACE, WHITE	92.4%	92.4%
BASELINE COMORBIDITIES/MEDICAL HISTORY (PAST YEAR)		
CHA_2DS_2-VASc score (mean)	4.3	4.3
Hypertension	90.3%	90.3%
Diabetes	34.9%	34.8%
Heart failure	29.8%	29.8%
Ischemic stroke, systemic embolism, intracranial bleeding	9.2%	9.3%
Acute kidney failure	9.3%	9.3%
Transient ischemic attack	6.5%	6.6%
Myocardial infarction	6.3%	6.3%
Bleeding at gastrointestinal or other sites	15.1%	15.1%

Inverse probability treatment weighting is a statistical method used to balance baseline patient characteristics between treatment groups.

CONTINUED ON NEXT PAGE

SELECT BASELINE CHARACTERISTICS[4]

	ELIQUIS (n=353,879)	XARELTO (n=227,572)
	(INVERSE PROBABILITY TREATMENT-WEIGHTED)	
BASELINE COMORBIDITIES/MEDICAL HISTORY (PAST YEAR) CONT'D		
Kidney disease, stage 3 or unspecified chronic	16.3%	16.3%
Chronic obstructive pulmonary disease	22.3%	22.3%
Smoking or other tobacco use[15]	30.9%	30.9%
MEDICATIONS		
Diltiazem or verapamil	21.2%	21.2%
Amiodarone	11.4%	11.4%
Beta-blockers[15]	77.3%	77.3%
Statins[15]	62.4%	62.3%
P2Y12 inhibitors or other antiplatelet drugs	16.0%	16.0%
Nonsteroidal anti-inflammatory drugs (NSAIDs)	16.7%	16.7%

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

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

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METHODS OF ANALYSIS[4]

Study drug: ELIQUIS (5 mg/2.5 mg) or XARELTO (20 mg/15 mg)

Study duration: January 1, 2013 to November 30, 2018

Baseline period: One year prior to study enrollment

Data source: Centers for Medicare and Medicaid Services Chronic Condition Data Warehouse

MEDICARE DATA

- US Medicare Master Beneficiary Summary File, which includes: enrollment status, deaths for beneficiaries
- Claim files for medical care services (pharmacy, hospital, outpatient, and nursing homes)

INCLUSION CRITERIA

- Patients aged ≥65 years with fee-for-service (Parts A and B) and prescription drug (Part D) Medicare coverage with a filled ELIQUIS or XARELTO prescription for atrial fibrillation between January 1, 2013 and November 30, 2018
- Complete demographic information and have filled a prescription for either ELIQUIS or XARELTO for atrial fibrillation
  - Included patients on both standard and reduced dose
  - Included patients newly prescribed, defined as those without a prescription in the preceding year
- Continuous enrollment in Medicare and at least one outpatient visit and one filled prescription (other than the study anticoagulant) during the year before cohort entry
- Diagnosis of atrial fibrillation/flutter in the 90 days before cohort entry (based on ICD-9: 427.31, 427.32; ICD-10: I48.x)[15]

EXCLUSION CRITERIA

- Patients with any of the following characteristics were excluded: enrollment in Medicare part C, terminal illness, long-term care residence (except <30 days following inpatient stay), mitral valve stenosis, severe chronic kidney disease (stage 4, 5, or end-stage), conditions that can cause reversible atrial fibrillation (eg, thyrotoxicosis), patients with mechanical heart valves (except bioprosthetic heart valve), oral anticoagulant use in the one year before cohort entry, stroke or bleeding-related hospitalization in the past 30 days

NOTE: A subset of patients with bioprosthetic heart valve replacement (2.8% of total cohort) were included in the primary study population.[15] Exclusion of these patients in a sensitivity analysis showed results consistent with those from the primary study population. The use of ELIQUIS or XARELTO is not recommended in patients with prosthetic heart valves.

OUTCOMES

- **Primary outcome**: composite of major ischemic or hemorrhagic events
  - Major ischemic events: ischemic stroke, systemic embolism
  - Major hemorrhagic events: hemorrhagic stroke, other intracranial bleeding, fatal non-intracranial bleeding (death within 30 days of bleeding onset)
- **Secondary outcomes**: nonfatal non-intracranial bleeding and total mortality*
  - Nonfatal non-intracranial bleeding: gastrointestinal (GI) bleeding, other or unspecified bleeding
- Strokes and bleeding events were identified from hospital principal discharge diagnosis codes and fatal extracranial bleeding was defined as death within 30 days of bleeding event

STATISTICAL ANALYSES

- Inverse probability treatment weighting (IPTW) was determined by calculating a propensity score (ie, probability of XARELTO use) and was used to balance baseline characteristics between the cohorts
  - IPTW adjustment controlled for 208 covariates potentially associated with both outcomes and anticoagulant choice such as demographic characteristics, cardiovascular conditions, and risk factors for bleeding
- Hazard ratios (HRs) were calculated using the IPT-weighted proportional hazards regression
- Adjusted relative risk of the outcomes was estimated with HRs

*Additional secondary outcomes not shown here included total mortality, which included fatal ischemic or hemorrhagic events (death within 30 days of event onset) and other deaths during follow-up.

CONTINUED ON NEXT PAGE

METHODS OF ANALYSIS CONT'D[4]

SENSITIVITY ANALYSES

- Sensitivity analyses were generally consistent with the main analysis and included:
  - Exclusion of patients with heart valve replacement, unspecified or stage 3 chronic kidney disease, or extreme propensity scores
  - Follow-up limited to one year following cohort entry
  - Maximum allowed gap in anticoagulant days of supply was decreased from 30 days to 7 days
  - Broadened stroke definition to identify strokes in the primary and secondary hospital discharge diagnoses
  - Other analyses included propensity score matching (PSM) and estimation of HRs from a proportional hazards regression with all of the study covariates

FOLLOW-UP PERIOD

- Patients were followed for up to 4 years, beginning the day after filling the initial oral anticoagulant prescription. Follow-up ended with the following events: treatment discontinuation; switch to another anticoagulant or to another dose; development of stage 4, 5, or end-stage chronic kidney disease; the last study day or 4 years after anticoagulant initiation; loss of enrollment; occurrence of any study outcome; or death
- During the study period, the median (interquartile range; IQR) follow-up was 174 (62–397) days:
  - 176 (64–392) days for ELIQUIS
  - 171 (59–407) days for XARELTO

LIMITATIONS OF ANALYSIS[4]

STUDY DESIGN/DEFINITIONS

- Due to the nature of retrospective, observational cohort studies, no causal relations could be inferred, and only statistical associations were assessed
- In contrast to clinical trials, outcomes were defined by using ICD-9 and ICD-10 diagnosis codes, and without outcome adjudication[15]
- The presence of a claim for a filled prescription does not indicate whether the medication was consumed or taken as prescribed
- There is no guarantee that patients were dosed according to the US prescribing information for ELIQUIS and XARELTO

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

DATA COLLECTION

- Exposure misclassification is possible since 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
- 30.4% of ELIQUIS patients and 33.4% of XARELTO patients discontinued treatment by the median 174 day of follow up

GENERALIZABILITY

- The study was restricted to Medicare beneficiaries in the US who were 65 years or older with both fee-for-service coverage (Parts A and B) and enrollment in the Part D program for prescription medications, which therefore limited the generalizability of the findings

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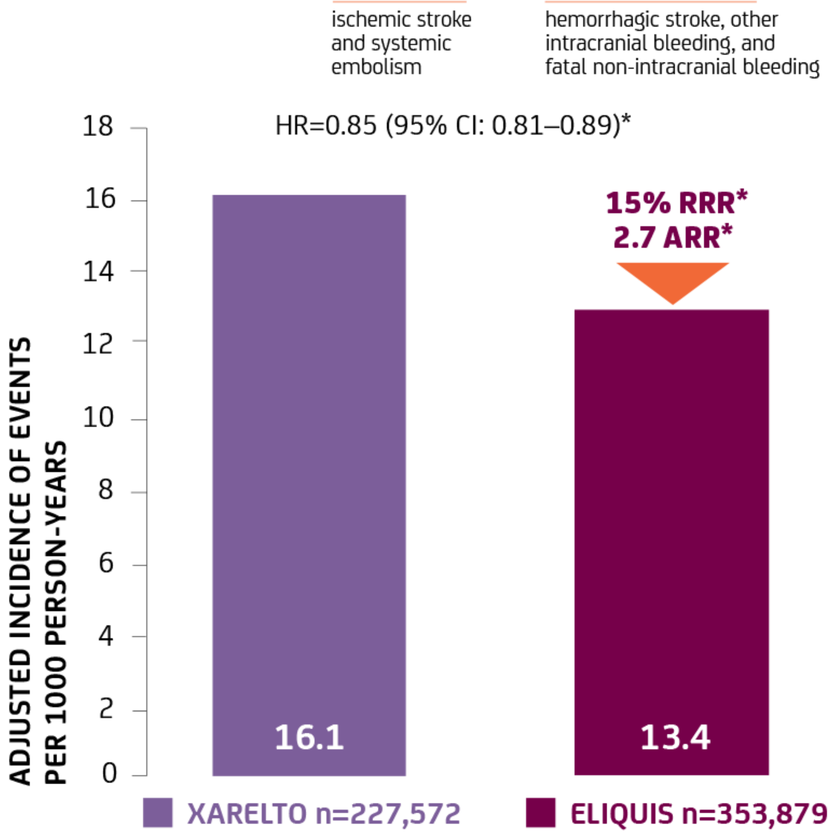
PRIMARY OUTCOME

INCIDENCE OF MAJOR ISCHEMIC AND HEMORRHAGIC EVENTS[4]

COMPOSITE OF MAJOR ISCHEMIC AND HEMORRHAGIC EVENTS



Retrospective, observational analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables; causality cannot be established in observational analyses.[9]

- Other real-world data analyses comparing ELIQUIS with other DOACs, using various data sources, time periods, study methodologies, and outcome definitions—showing different findings—have also been published[16-20]

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

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

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

*Statistical note: HRs were presented as XARELTO vs ELIQUIS in the original publication and were inverted in the figure on the left 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.
ARR=absolute risk reduction; CI=confidence interval; DOAC=direct oral anticoagulant; HR=hazard ratio; RRR=relative risk reduction.

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

SELECTED IMPORTANT SAFETY INFORMATION

PREGNANCY

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

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

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

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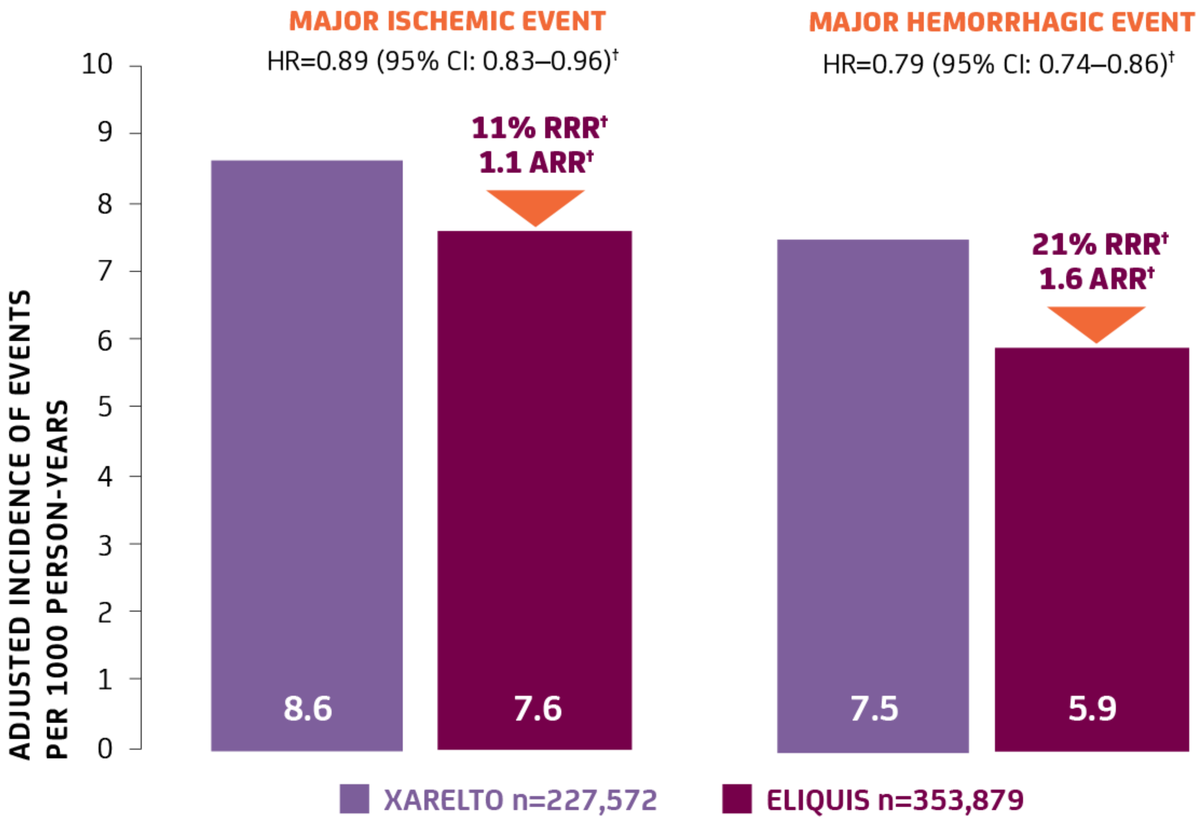
COMPONENTS OF PRIMARY OUTCOME

INCIDENCE OF MAJOR ISCHEMIC AND HEMORRHAGIC EVENTS[4]*



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*Ischemic events include ischemic stroke and systemic embolism. Hemorrhagic events include hemorrhagic stroke, other intracranial bleeding, and fatal non-intracranial bleeding.

†Statistical note: HRs were presented as XARELTO vs ELIQUIS in the original publication and were inverted in the figure on the left 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.

ARR=absolute risk reduction; CI=confidence interval; DOAC=direct oral anticoagulant; HR=hazard ratio; RRR=relative risk reduction.

SELECTED IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

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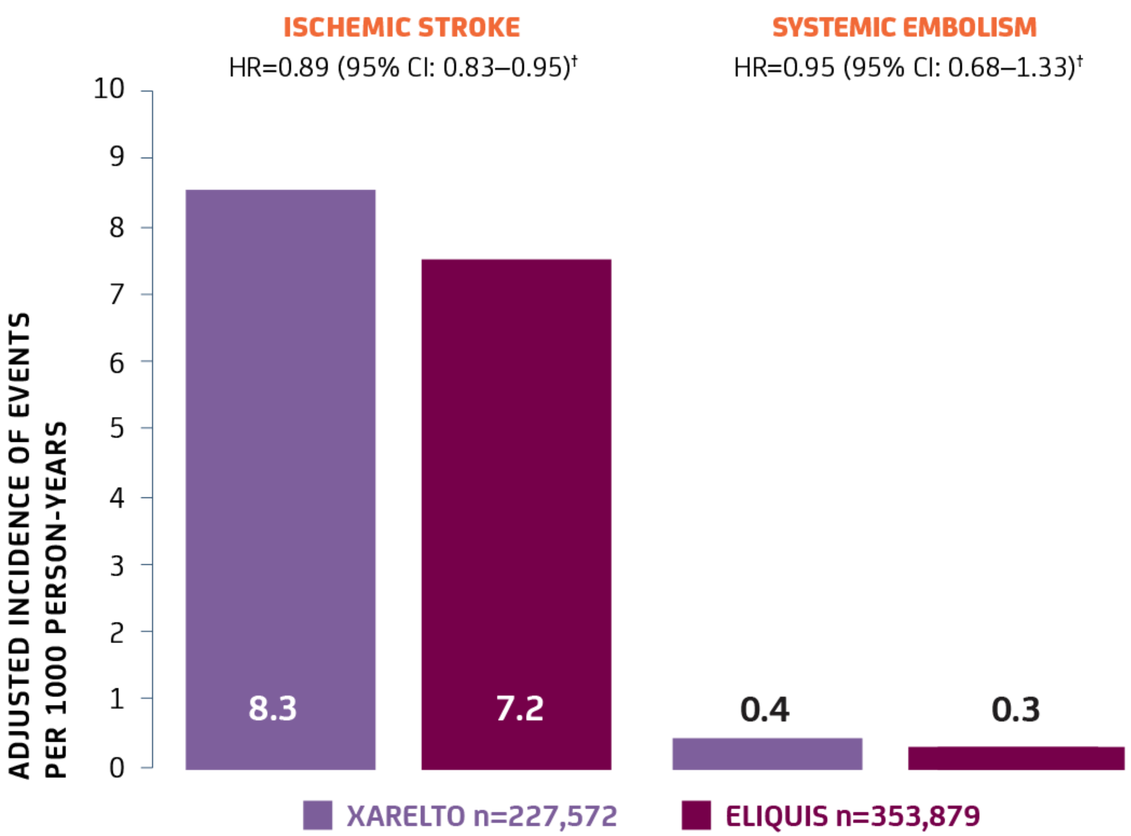
PRIMARY OUTCOME

COMPONENTS OF MAJOR ISCHEMIC EVENTS[4]*



*Ischemic events include ischemic stroke and systemic embolism.
†Statistical note: HRs were presented as XARELTO vs ELIQUIS in the original publication and were inverted in the figure above as ELIQUIS vs XARELTO.
CI=confidence interval; DOAC=direct oral anticoagulant; HR=hazard ratio.

SEE MAJOR ISCHEMIC EVENTS DATA | SEE MAJOR HEMORRHAGIC EVENTS DATA

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

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

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.

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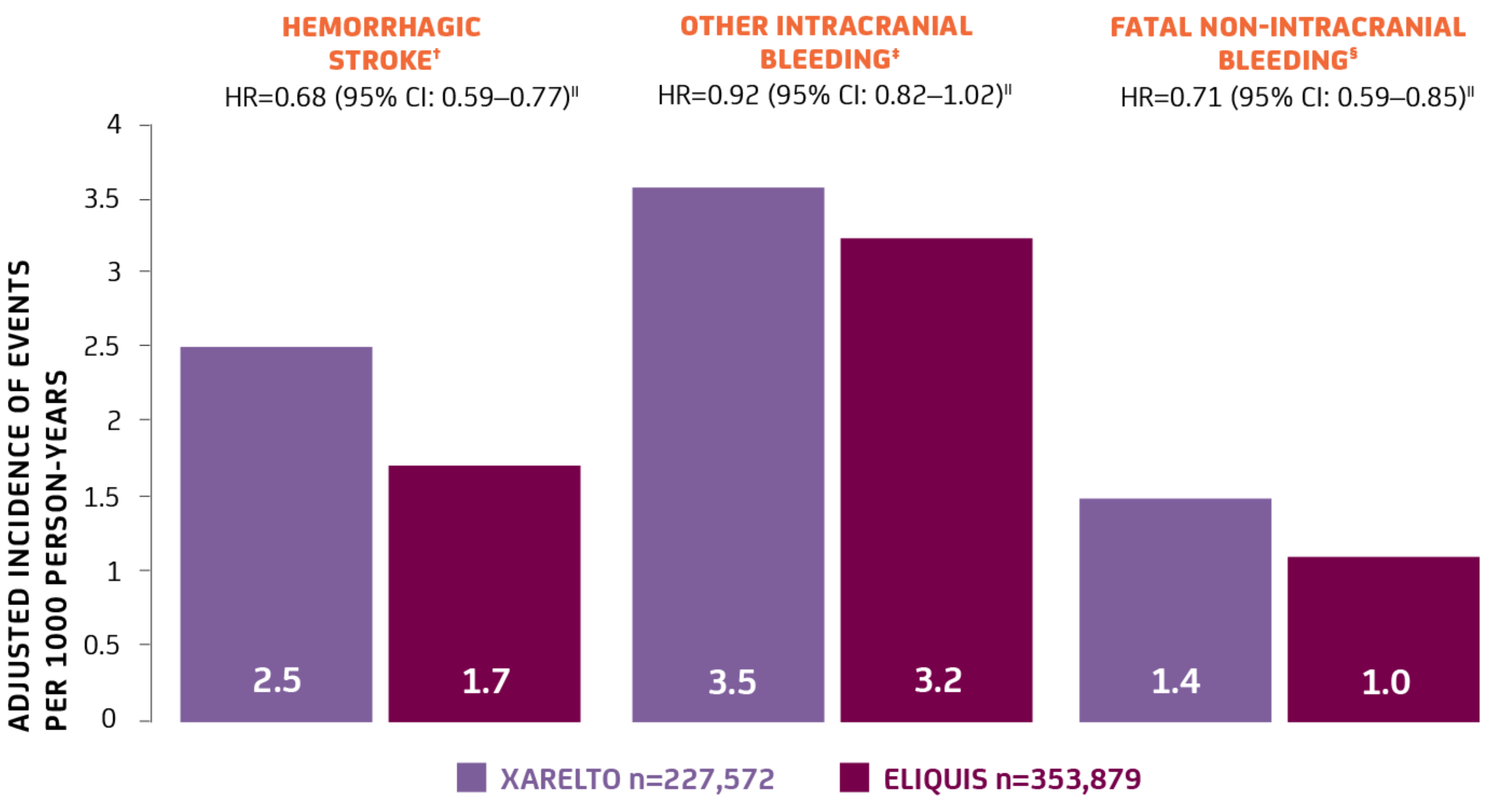
PRIMARY OUTCOME

COMPONENTS OF MAJOR HEMORRHAGIC EVENTS[4]*



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

*Hemorrhagic events include hemorrhagic stroke, other intracranial bleeding, and fatal non-intracranial bleeding.
†Hemorrhagic stroke was defined as either a subarachnoid or intracerebral hemorrhage.
‡Other intracranial bleeding included traumatic intracranial hemorrhages (except those indicating open wounds) to capture fall-related events.
§Fatal non-intracranial bleeding was considered as death within 30 days of bleeding onset.
‖Statistical note: HRs were presented as XARELTO vs ELIQUIS in the original publication and were inverted in the figure above as ELIQUIS vs XARELTO.
CI=confidence interval; DOAC=direct oral anticoagulant; HR=hazard ratio.

SEE MAJOR ISCHEMIC EVENTS DATA | SEE MAJOR HEMORRHAGIC EVENTS DATA

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

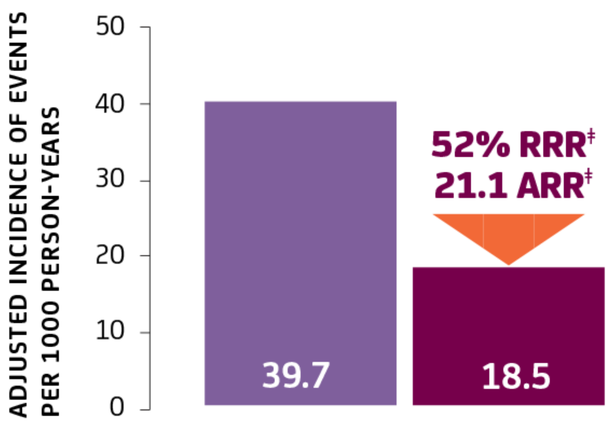
There are currently no results from ELIQUIS vs XARELTO head-to-head clinical trials.[4]

SECONDARY OUTCOME

INCIDENCE OF NONFATAL NON-INTRACRANIAL BLEEDING AND ITS COMPONENTS[4]

NONFATAL NON-INTRACRANIAL BLEEDING*

HR=0.48 (95% CI: 0.47–0.50)‡



XARELTO n=227,572 ELIQUIS n=353,879

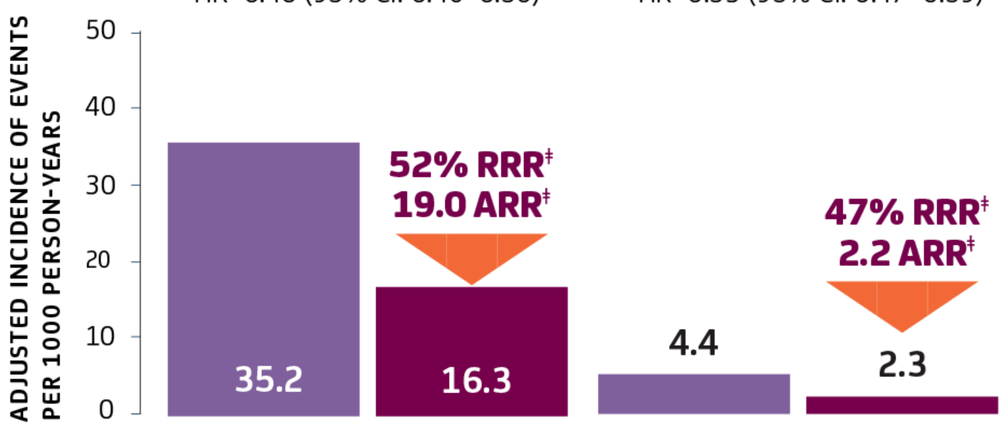
COMPONENTS OF NONFATAL NON-INTRACRANIAL BLEEDING*

GI BLEEDING†

HR=0.48 (95% CI: 0.46–0.50)‡

OTHER BLEEDING

HR=0.53 (95% CI: 0.47–0.59)‡



XARELTO n=227,572 ELIQUIS n=353,879

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

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

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

*Non-intracranial bleeding included gastrointestinal, other, or unspecified bleeding.
†GI bleeding included gastroduodenal, esophageal, upper (unspecified and other), lower, and unspecified bleeding.
‡Statistical note: HRs were presented as XARELTO vs ELIQUIS in the original publication and were inverted in the figure above as ELIQUIS vs XARELTO and RRR was calculated as (1-HR)x100. ARR represents the difference between the event rates and is expressed as per 1000 person-years.
ARR=absolute risk reduction; CI=confidence interval; DOAC=direct oral anticoagulant; GI=gastrointestinal; HR=hazard ratio; RRR=relative risk reduction.

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FOR PATIENTS WITH NVAF

OUTCOMES FROM A REAL-WORLD ANALYSIS OF A MEDICARE DATABASE[4]

THE LARGEST MEDICARE COHORT TO DATE COMPARING ELIQUIS WITH XARELTO

A retrospective, observational real-world database analysis independently funded by the NHLBI included 581,451 Medicare patients ≥65 years old with NVAF who initiated treatment with ELIQUIS (5 mg BID or 2.5 mg BID) or XARELTO (20 mg QD or 15 mg QD) between January 2013 and November 2018 and met study inclusion and exclusion criteria.

REAL-WORLD EFFECTIVENESS AND SAFETY OUTCOMES FOR ELIQUIS VS XARELTO

PRIMARY OUTCOME AND COMPONENTS

Composite of major ischemic or hemorrhagic events
13.4 vs 16.1 events per 1000 PYs
HR=0.85 [95% CI: 0.81–0.89]
ARR=2.7
15% relative risk reduction

Major ischemic events (stroke and systemic embolism)
7.6 vs 8.6 events per 1000 PYs
HR=0.89 [95% CI: 0.83–0.96]
ARR=1.1
11% relative risk reduction

Major hemorrhagic events (hemorrhagic stroke, intracranial bleeding, and fatal non-intracranial bleeding)
5.9 vs 7.5 events per 1000 PYs
HR=0.79 [95% CI: 0.74–0.86]
ARR=1.6
21% relative risk reduction

SECONDARY OUTCOMES AND COMPONENTS*

Nonfatal non-intracranial bleeding (GI and other)
18.5 vs 39.7 events per 1000 PYs
HR=0.48 [95% CI: 0.47–0.50]
ARR=21.1
52% relative risk reduction

GI bleeding
16.3 vs 35.2 events per 1000 PYs
HR=0.48 [95% CI: 0.46–0.50]
ARR=19.0
52% relative risk reduction

Other bleeding events
2.3 vs 4.4 events per 1000 PYs
HR=0.53 [95% CI: 0.47–0.59]
ARR=2.2
47% relative risk reduction

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

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

*Total mortality, an additional secondary outcome, is not shown.
ARR=absolute risk reduction; BID=twice a day; CI=confidence interval; DOAC=direct oral anticoagulant; GI=gastrointestinal; HR=hazard ratio; NHLBI=National Heart, Lung, and Blood Institute; NVAF=nonvalvular atrial fibrillation; PY=person-years; QD=once a day.

OTHER LIMITATIONS

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

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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

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

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

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