ARISTOTLE CLINICAL TRIAL CONTENT INSIDE

Real-world database analysis in Medicare patients with nonvalvular atrial fibrillation (NVAF)

Real-world observational, retrospective database analysis of the CMS database

CMS=Centers for Medicare and Medicaid Services.

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

(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.

Please see **Important Safety Information** throughout and Full Prescribing Information, including **Boxed WARNINGS**, or visit ELIQUIS.com.

Eliquis® (apixaban) tablets 5mg 2.5mg

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.

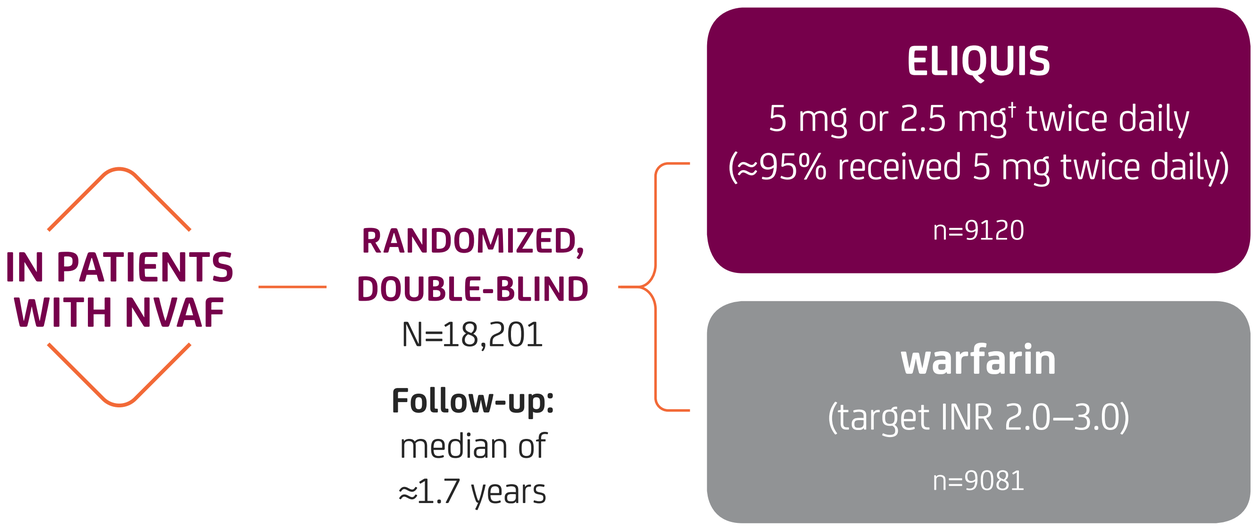
CONTRAINDICATIONS

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

ARISTOTLE was a pivotal, phase 3, 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

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, or retroperitoneal; and fatal bleeding.

Baseline characteristics: the 2 treatment groups were well balanced, including age, stroke risk as measured by $CHADS_2$ score, and prior VKA experience.

CHADS$_2$ SCORE +

BASELINE CHARACTERISTICS +

AVERROES STUDY DESIGN +

***Key inclusion criteria:** NVAF and ≥1 additional risk factors for stroke, including prior stroke or transient ischemic attack, prior SE, aged ≥75 years, arterial hypertension requiring treatment, diabetes mellitus, heart failure (New York Heart Association Class 2 or higher), or 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).

INR=international normalized ratio; LVEF=left ventricular ejection fraction; VKA=vitamin K antagonist.
†A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: aged ≥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.

References: 1. ELIQUIS® (apixaban). Package insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Granger CB, et al; for the ARISTOTLE Committees and Investigators. *N Engl J Med.* 2011;365(11):981-992. **3.** Protocol for: Granger CB, et al. *N Engl J Med.* 2011;365(11):981-992. doi:10.1056/NEJMoa1107039.

ARISTOTLE w… …VAF[1-3]*

Primary objective

Determine whethe…
risk of stroke (isch…

IN PATIENTS WITH NVAF

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…UDY DESIGN +

***Key inclusion criter…**
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Key exclusion criteri…
…at required anticoagulation (eg, a… …n and clopidogrel, and severe renal insufficiency (serum creatinine level of >2.5 mg/dL or calculated creatinine clearance of <25 mL/min).

CHADS$_2$ score[1]

A CHADS$_2$ score was used to estimate stroke risk in patients with atrial fibrillation. It was calculated by adding up the applicable points below, with higher scores representing a greater risk for stroke.

CHADS$_2$ score

	Condition	Points
C	Congestive heart failure	1
H	Hypertension	1
A	Age (≥75)	1
D	Diabetes mellitus	1
S	History of stroke or transient ischemic attack	2
	Possible total:	**6 points**

Reference: 1. Gage BF, et al. *JAMA*. 2001;285(22):2864-2870.

INR=international normalized ratio; LVEF=left ventricular ejection fraction; VKA=vitamin K antagonist.
†A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: aged ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.
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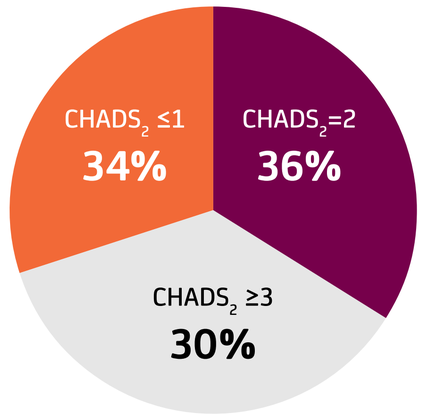
References: 1. ELIQUIS® (apixaban). Package insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Granger CB, et al; for the ARISTOTLE Committees and Investigators. *N Engl J Med*. 2011;365(11):981-992. **3.** Protocol for: Granger CB, et al. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039.

Baseline characteristics were well balanced across treatment arms[1,2]

ARISTOTLE	ELIQUIS n=9120	warfarin n=9081
Median age (years)	70	70
Mean $CHADS_2$* score	2.1±1.1	2.1±1.1
$CHADS_2$ ≤1	34% n=3100	34% n=3083
$CHADS_2$=2	36% n=3262	36% n=3254
$CHADS_2$ ≥3	30% n=2758	30% n=2744
Prior stroke, transient ischemic attack, or SE	19% n=1748	20% n=1790
Prior use of VKA (eg, warfarin) for >30 consecutive days	57% n=5208	57% n=5193

Distribution of $CHADS_2$ scores for the ELIQUIS® (apixaban) arm in ARISTOTLE



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

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

References: 1. ELIQUIS® (apixaban). Package insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Granger CB, et al; for the ARISTOTLE Committees and Investigators. *N Engl J Med*. 2011;365(11):981-992.

***Key inclu**
hypertensi

Key exclusi d
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).

INR=international normalized ratio; LVEF=left ventricular ejection fraction; VKA=vitamin K antagonist.
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AVERROES was a phase 3, randomized, double-blind trial vs aspirin in over 5500 patients with NVAF who were unsuitable for warfarin[1-3]

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 (SE) in patients with NVAF

IN PATIENTS WITH NVAF

RANDOMIZED, DOUBLE-BLIND
N=5598

Follow-up:
mean of
≈1.1 years

ELIQUIS® (apixaban)
5 mg or 2.5 mg† twice daily (≈94% received 5 mg twice daily)
n=2807

aspirin
81 mg to 324 mg orally once daily
n=2791

Primary efficacy endpoint: stroke/SE
Primary safety endpoint: major bleeding

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.

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.

$CHADS_2$ SCORE +

***Key inclusion criteria:** NVAF and ≥1 additional risk factors for stroke, which included prior stroke or transient ischemic attack, aged ≥75 years, arterial hypertension (receiving treatment), diabetes mellitus (receiving treatment), heart failure (New York Heart Association 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.

LVEF=left ventricular ejection fraction; VKA=vitamin K antagonist.
†A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: aged ≥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.

References: 1. ELIQUIS® (apixaban). Package insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Connolly SJ, et al; for the AVERROES Steering Committee and Investigators. *N Engl J Med.* 2011;364(9):806-817. **3.** Protocol for: Connolly SJ, et al. *N Engl J Med.* 2011;364(9):806-817. doi:10.1056/NEJMoa1007432.

In patients with NVAF,

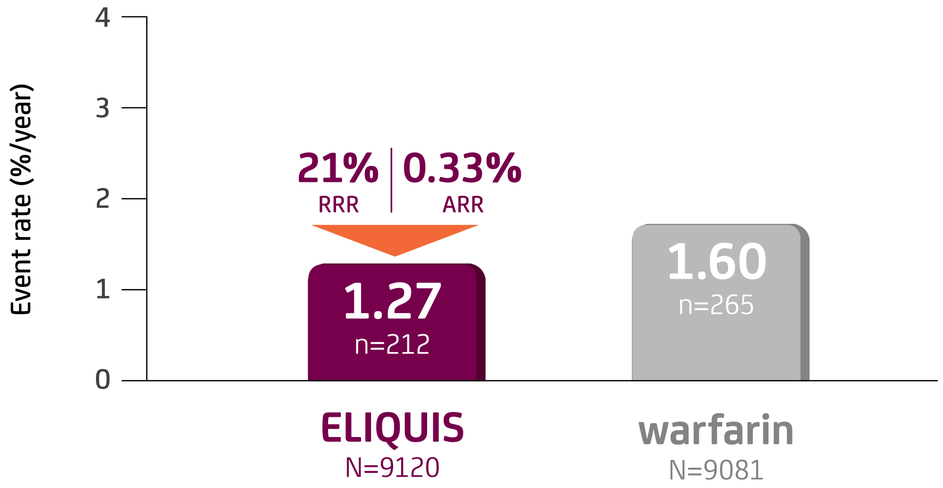
ELIQUIS demonstrated superiority in BOTH stroke/SE and major bleeding vs warfarin[1]

SUPERIOR

Risk reduction in stroke/SE

HR=0.79 (95% CI: 0.66, 0.95)

P=0.01



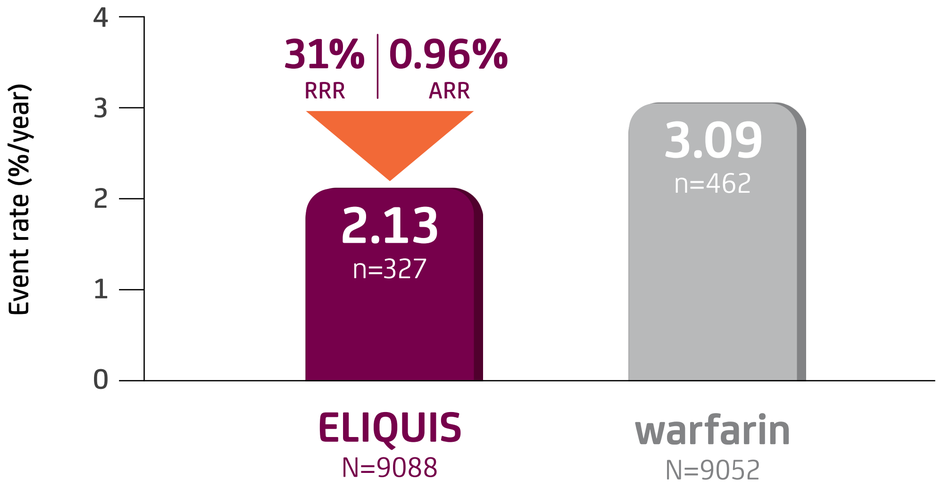
Primary efficacy endpoint

SUPERIOR

Based on fewer major bleeding events*

HR=0.69 (95% CI: 0.60, 0.80)

P<0.0001



Primary safety endpoint

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

- Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke (0.24%/year [n=40/9120] ELIQUIS vs 0.47%/year [n=78/9081] warfarin, HR=0.51 [95% CI: 0.35, 0.75]) and ischemic strokes with hemorrhagic conversion (0.07%/year [n=12/9120] ELIQUIS vs 0.12%/year [n=20/9081] warfarin, HR=0.60 [95% CI: 0.29, 1.23]) compared with warfarin. Purely ischemic strokes (0.83%/year [n=140/9120] ELIQUIS vs 0.82%/year [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%/year vs 0.92%/year, 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]

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

Reference: 1. ELIQUIS® (apixaban). Package insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY.

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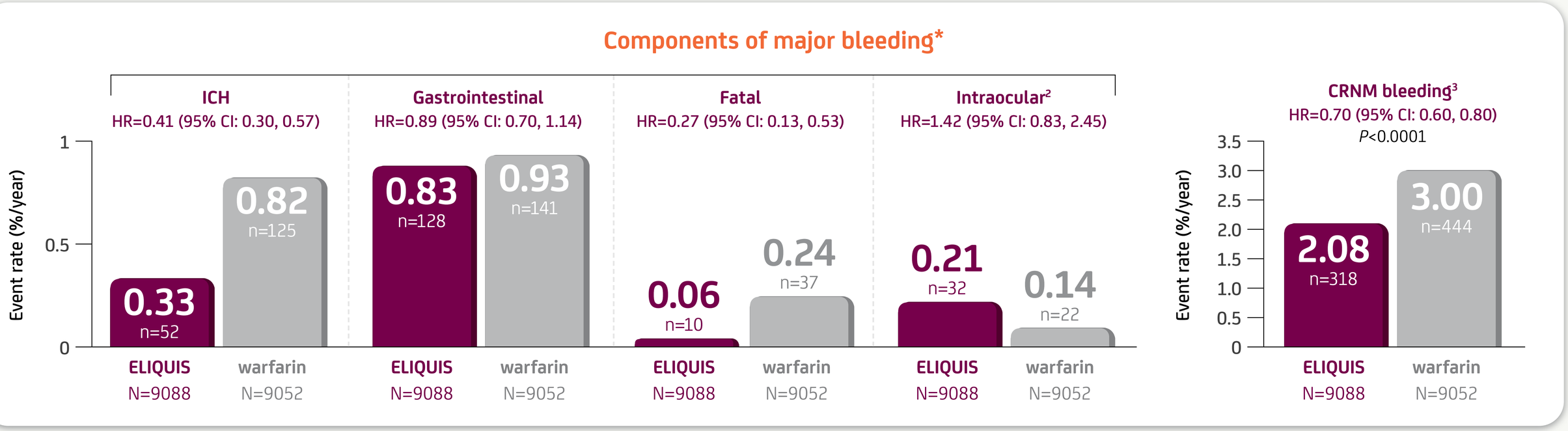
In patients with NVAF,

ELIQUIS demonstrated lower rates in select bleeding outcomes vs warfarin[1-3]*



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- 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% of patients treated with ELIQUIS and aspirin, respectively[1]

Components of ICH and fatal bleeding

- There were significantly fewer ICH events vs warfarin. Hemorrhagic stroke†: 0.24%/year (n=38/9088) vs 0.49%/year (n=74/9052), HR=0.51 (95% CI: 0.34, 0.75); other ICH: 0.10%/year (n=15/9088) vs 0.34%/year (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%/year (n=4/9088) vs 0.20%/year (n=30/9052), HR=0.13 (95% CI: 0.05, 0.37); nonintracranial: 0.04%/year (n=6/9088) vs 0.05%/year (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[4,5]:

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

CRNM=clinically relevant nonmajor; ICH=intracranial hemorrhage.
*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.
†On-treatment analysis based on the safety population, compared with intent-to-treat analysis presented in the efficacy population.

References: 1. ELIQUIS® (apixaban). Package insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Data on file: APIX 060. Bristol-Myers Squibb Company, Princeton, NJ. **3.** Data on file: APIX 063. Bristol-Myers Squibb Company, Princeton, NJ. **4.** Granger CB, et al; for the ARISTOTLE Committees and Investigators. *N Engl J Med*. 2011;365(11):981-992. **5.** Protocol for: Granger CB, et al. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039.

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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.
- **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.

Please see **Important Safety Information** throughout and Full **Prescribing Information**, including **Boxed WARNINGS**, or visit **ELIQUIS.com**.

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Real-world database analysis in Medicare patients with nonvalvular atrial fibrillation (NVAF)

Real-world observational, retrospective database analysis of the CMS database

Analysis overview[1]

Objective

Evaluate stroke/systemic embolism (SE) and major bleeding outcomes associated with each of the 3 direct oral anticoagulants (DOACs) as compared with warfarin among oral anticoagulant (OAC) treatment-naïve patients with NVAF, identified in claims data from CMS*

*Only results from the ELIQUIS vs warfarin cohort are discussed in this section.

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

Analysis overview[1]

Objective

Study design

Data analysis

Population

Baseline characteristics

Considerations and limitations

Retrospective cohort database analysis of CMS health care claims from the largest US database (from January 1, 2013, to December 31, 2014) of patients aged ≥65 with NVAF

This study evaluated 3 DOACs vs warfarin in propensity score-matched cohorts. **Only results from the ELIQUIS vs warfarin cohort are discussed in this section.**

Assessment of effectiveness and safety outcomes

Primary effectiveness outcome:
Stroke or SE, identified by ICD-9-CM codes in the primary discharge diagnosis in the inpatient setting.

Primary safety outcome:
Major bleeding identified by ICD-9-CM codes in the primary discharge diagnosis in the inpatient setting.

Note: The data included in this presentation represent an updated analysis of the real-world analysis of the CMS database. For the previously published analysis, the underlying raw data received by the authors were missing partial information on a significant proportion of patients who would have otherwise met all the eligibility criteria. The analysis has been redone by adding back the patients inadvertently excluded. The updated analysis has been submitted to the journal *Current Medical Research and Opinion*.

ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification.

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

Analysis overview[1]

Objective

Study design

Data analysis

Population

Baseline characteristics

Considerations and limitations

Statistical methods were used to help control for baseline characteristics, analyze the data of this study, and assess the validity of the results

Methodology and statistical analyses

- Effectiveness and safety outcomes were measured independently
- **1:1 propensity score matching** was used to balance demographics and clinical characteristics between ELIQUIS and warfarin
- **Cox proportional hazards models** were used to compare the risk of stroke/SE and major bleeding in the propensity score matching cohorts

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

Analysis overview[1]

Objec

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Data

Population

Baseline characteristics

Considerations and limitations

Additional methodology and statistical analysis information

1:1 propensity score matching: a statistical technique used to balance groups on baseline characteristics by assigning each subject in a group a propensity score (PS) based on the likelihood of treatment. This PS is most often derived from logistic regression. Subjects are then matched 1:1 across the groups such that the matched pair has similar PS values.[1]

Cox proportional hazards regression models: a regression method that uses time-to-event data to generate hazard ratios by analyzing the association between a specified event and 1 or more predictor variables.[2,3]

References: 1. Brookhart MA, et al. *Circ Cardiovasc Qual Outcomes.* 2013;6(5):604-611. **2.** White SE. *Basic & Clinical Biostatistics.* 5th ed. McGraw-Hill Education; 2020. **3.** StatsDirect. Accessed January 12, 2021. https://www.statsdirect.com/help/Default.htm#survival_ analysis/cox_regression.htm.

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

Analysis overview[1]

Statistical methods were used to help control for baseline characteristics, analyze the data of this study, and assess the validity of the results

Sensitivity analyses

- **Sensitivity analyses** were performed to ensure the robustness of the results in the main analysis. The results of the sensitivity analyses were consistent with those of the main analysis

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

Analysis overview[1]

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Population

Baseline characteristics

Considerations and limitations

Additional sensitivity analysis information

Sensitivity analyses: secondary analyses performed by modifying certain assumptions to test the robustness of the results and to assess the extent to which results may be due to unobserved confounding.[1]

Reference: 1. Delaney JAC, Seeger JD. *Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide.* Rockville, MD: Agency for Healthcare Research and Quality (US); 2013.

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

Analysis overview[1]

Objective

Study design

Data analysis

Population

Baseline characteristics

Considerations and limitations

Inclusion criteria

- ☑ Aged ≥65 years
- ☑ ≥1 medical claim for atrial fibrillation (AF) (ICD-9-CM: 427.31) during the baseline period
- ☑ ≥1 pharmacy claim for an OAC from January 1, 2013, through December 31, 2014
- ☑ Continuous medical (Part A and Part B) and pharmacy (Part D) enrollment for 12 months prior to the index date* (baseline period)

Exclusion criteria

- ☒ Valvular heart disease
- ☒ Heart valve replacement or surgery
- ☒ Venous thromboembolism
- ☒ Transient AF (pericarditis, hyperthyroidism, thyrotoxicity)
- ☒ Indication of pregnancy during the entire study
- ☒ Pharmacy claim for an OAC during the baseline period
- ☒ >1 OAC claim on the index date*

Baseline period
12 months prior to index date*

Index date* and propensity score matching

Variable follow-up period†

N=77,480

ELIQUIS n=38,740 vs warfarin n=38,740

After propensity score matching, mean follow-up duration was ≈0.40 years and ≈0.50 years for ELIQUIS and warfarin, respectively.

SAVAYSA® (edoxaban) was not available at the time of evaluation.
*Index date was defined as the date of the first OAC prescription fill. Index drug was defined as the first OAC prescription fill.
†Patients were followed from index date until the earliest of the following: OAC prescription discontinuation date, switch to an OAC other than the index drug, death, interruption in continuous enrollment, or end of the study period (December 31, 2014), whichever occurred earlier.

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

Analysis overview[1]

Objective

Study design

Data analysis

Population

Baseline characteristics

Considerations and limitations

Select baseline characteristics after PSM

	ELIQUIS n=38,740	warfarin n=38,740
Age, mean (SD)	78.3 (7.4)	78.2 (7.3)
Gender, female, n (%)	20,375 (52.6%)	20,561 (53.1%)
$CHADS_2$, mean (SD)	2.7 (1.4)	2.7 (1.4)
CHA_2DS_2-VASc, mean (SD)	4.6 (1.7)	4.6 (1.7)
HAS-BLED,* mean (SD)	3.2 (1.2)	3.3 (1.2)
Charlson Comorbidity Index, mean (SD)	2.7 (2.6)	2.8 (2.6)
Select medical history, n (%)		
Congestive heart failure	11,277 (29.1%)	11,545 (29.8%)
Diabetes	13,850 (35.8%)	14,007 (36.2%)
Hypertension	34,117 (88.1%)	34,357 (88.7%)
Peripheral vascular disease	21,370 (55.2%)	21,683 (56.0%)
Renal disease	9158 (23.6%)	9344 (24.1%)
Myocardial infarction	4895 (12.6%)	4979 (12.9%)
Transient ischemic attack	3032 (7.8%)	3117 (8.0%)
Coronary artery disease	18,572 (47.9%)	18,876 (48.7%)
Prior bleed	7914 (20.4%)	8065 (20.8%)
Prior stroke	4742 (12.2%)	4928 (12.7%)

After 1:1 propensity score matching, there were 38,740 ELIQUIS-warfarin matched pairs, with a mean age of 78 years, mean Charlson Comorbidity Index scores of 2.7 and 2.8, and mean CHA_2DS_2-VASc scores of 4.6 for patients taking ELIQUIS and warfarin, respectively.

PSM=propensity score matching; SD=standard deviation.
*Select HAS-BLED score risk factors were derived from ICD-9/Common Procedural Terminology codes, except labile international normalized ratio not captured in data source.

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

$CHADS_2$ and CHA_2DS_2-VASc scores

$CHADS_2$ and CHA_2DS_2-VASc scores were used to estimate stroke risk in patients with atrial fibrillation. They were calculated by adding the applicable points below, with higher scores representing a greater risk for stroke.

$CHADS_2$ score[1]

Condition		Points
C	Congestive heart failure	1
H	Hypertension	1
A	Age (≥75)	1
D	Diabetes mellitus	1
S	History of stroke or transient ischemic attack	2
	Possible total:	**6 points**

CHA_2DS_2-VASc score[2]

Condition		Points
C	Congestive heart failure/left ventricular dysfunction	1
H	Hypertension	1
A	Age (≥75)	2
D	Diabetes mellitus	1
S	History of stroke/transient ischemic attack, thromboembolism	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	Age (65-74)	1
Sc	Sex category (female)	1
	Possible total:	**9 points**

References: 1. Gage BF, et al. *JAMA*. 2001;285(22):2864-2870. **2.** Lip GY, et al. *Chest*. 2010;137(2):263-272.

After 1:1 propensity score matching, there were 38,740 ELIQUIS-warfarin matched pairs, with a mean age of 78 years, mean Charlson Comorbidity Index scores of 2.7 and 2.8, and mean CHA_2DS_2-VASc scores of 4.6 for patients taking ELIQUIS and warfarin, respectively.

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Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

HAS-BLED score[1]

A HAS-BLED score was used to estimate major bleeding risk in patients with atrial fibrillation. The scoring system was calculated using the algorithm below.

HAS-BLED score		
Condition		**Points**
H	Hypertension	1
A	Abnormal renal and liver function	1 or 2 (1 point each)
S	Stroke	1
B	Bleeding history or predisposition	1
L	Labile international normalized ratio	1
E	Elderly	1 point for age 65 or older
D	Drugs or alcohol	1 or 2 (1 point each)
	Possible total:	**9 points**

Reference: 1. Pisters R, et al. *Chest*. 2010;138(5):1093-1100.

Prior stroke 4742 (12.2%) 4928 (12.7%)

After 1:1 propensity score matching, there were 38,740 ELIQUIS-warfarin matched pairs, with a mean age of 78 years, mean Charlson Comorbidity Index scores of 2.7 and 2.8, and mean CHA_2DS_2-VASc scores of 4.6 for patients taking ELIQUIS and warfarin, respectively.

PSM=propensity score matching; SD=standard deviation.
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Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

Analysis overview[1]

Objective

Study design

Data analysis

Population

Baseline characteristics

Considerations and limitations

Study considerations and limitations

- In **retrospective claims database analyses**, clinical events could not be adjudicated based on clinical criteria used in pivotal randomized controlled trials
- Due to the nature of **observational cohort studies, no causal relations** could be inferred and only associations were assessed. Diagnoses were identified using ICD-9-CM codes, which is different from the clinical trials
- Although cohorts were propensity score matched, **potential residual confounders exist**, which were not available in the dataset
  - Claims for over-the-counter aspirin use and warfarin dose adjustment were not available in the database
- **Generalizability of findings may be limited** to the study population (ie, elderly, treatment-naïve OAC patients) in the United States
- The **follow-up period was not uniform**, which may have introduced bias into the results. Compared with clinical trials, the follow-up period for each cohort in this analysis was also shorter, which may have impacted the results
- **ICD-9-CM codes**, which were used to define baseline comorbidities and outcomes, were subject to limitations inherent in **potential coding errors and missing data**
- Claims data lacked laboratory results (ie, INR values) and accuracy in the medical information
- The presence of a claim for a filled prescription did not indicate whether the medication was consumed or taken as prescribed
- OAC drug prescription(s) or other comorbid conditions were not evaluated prior to the 12-month baseline period
- This study was funded by Pfizer Inc. and Bristol-Myers Squibb Company

INR=international normalized ratio.

Reference: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ.

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.

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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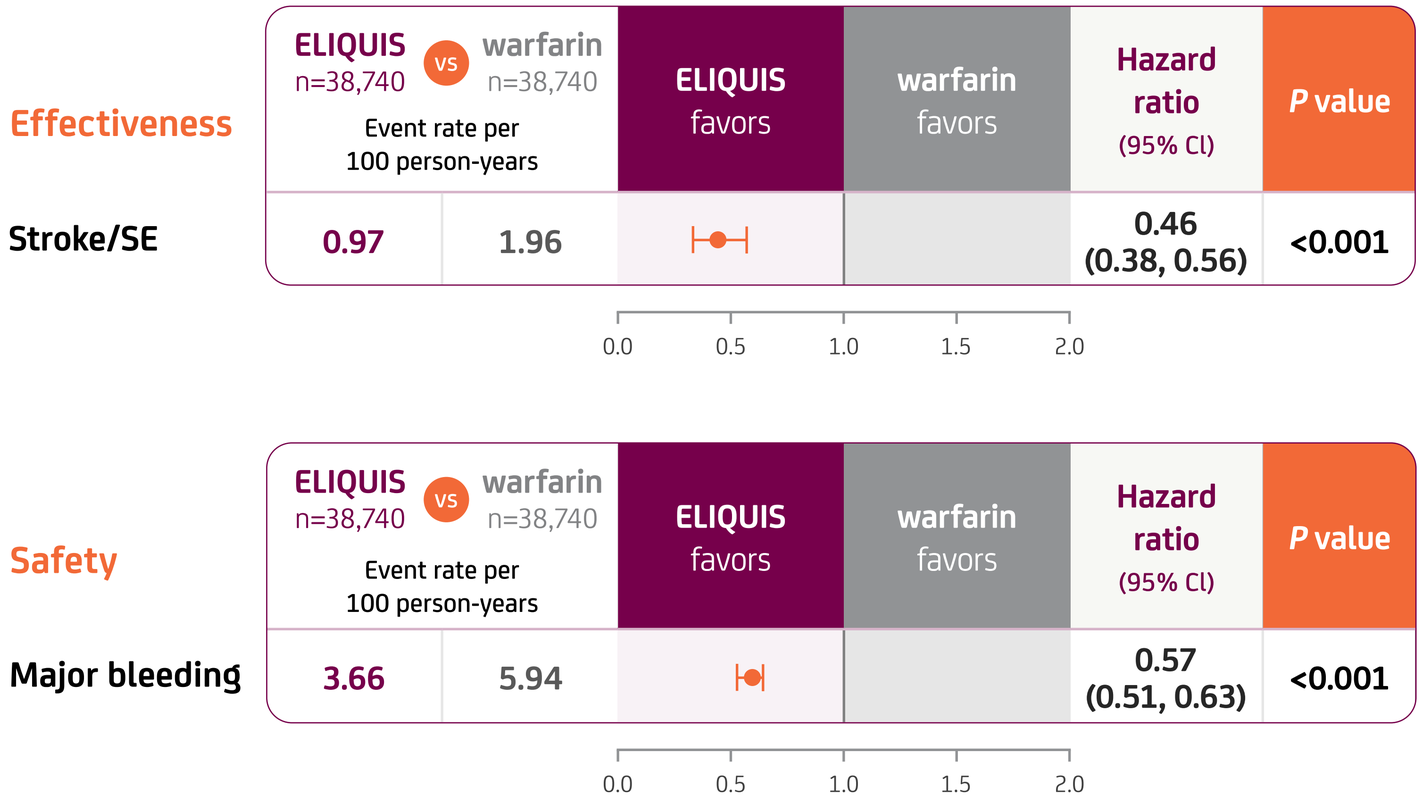
In a retrospective cohort database analysis of patients with NVAF,

ELIQUIS was associated with a reduced risk of stroke/SE and lower rates of major bleeding events vs warfarin[1]



The *P* value is the probability that the size of the differences observed between treatments would occur due to chance alone. In an observational study, confounding may also contribute to the results.

Observational retrospective analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables. Causality cannot be established in observational analyses.[1-3]

- The definitions of stroke and major bleeding, follow-up period, and the patient population in ARISTOTLE were different than in this analysis[1,4,5]
- In the main analysis, after 1:1 propensity score matching, the ELIQUIS and warfarin cohorts had a mean age of 78 years, mean CHA_2DS_2-VASc scores of 4.6, mean Charlson Comorbidity Index scores of 2.7 and 2.8, and a mean follow-up duration of ≈0.40 years and ≈0.50 years for patients taking ELIQUIS and warfarin, respectively[1]

SELECT MAJOR BLEEDING OUTCOMES +

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

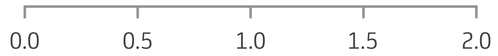
ARR=absolute risk ratio; CI=confidence interval; HR=hazard ratio; RRR=relative risk ratio.

References: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ. **2.** Garrison LP, et al. *Value Health*. 2007;10(5):326-335. **3.** Silverman SL. *Am J Med*. 2009;122(2):114-120. **4.** ELIQUIS® (apixaban). Package insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **5.** Granger CB, et al. *N Engl J Med.* 2011;365(11):981-992.

In a retrospective cohort database analysis of patients with NVAF,

ELIQUIS® (apixaban) was associated with lower rates in select bleeding outcomes vs warfarin[1]

Select Major Bleeding Outcomes	ELIQUIS n=38,740 vs warfarin n=38,740 Event rate per 100 person-years		ELIQUIS favors	warfarin favors	Hazard ratio (95% CI)	*P* value
Gastrointestinal bleeding	1.84	2.80			0.60 (0.52, 0.70)	<0.001
Intracranial bleeding	0.36	0.95			0.36 (0.26, 0.48)	<0.001



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

Observational retrospective 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.

- The definitions of stroke and major bleeding, follow-up period, and the patient population in ARISTOTLE were different than in this analysis[1-3]
- In the main analysis, after 1:1 propensity score matching, the ELIQUIS and warfarin cohorts had a mean age of 78 years, mean CHA_2DS_2-VASc scores of 4.6, mean Charlson Comorbidity Index scores of 2.7 and 2.8, and a mean follow-up duration of ≈0.40 years and ≈0.50 years for patients taking ELIQUIS or warfarin, respectively[1]

References: 1. Data on file: PubD# 00053110. Bristol-Myers Squibb, Princeton, NJ. **2.** ELIQUIS® (apixaban). Package insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **3.** Granger CB, et al. *N Engl J Med.* 2011;365(11):981-992.

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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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