ARISTOTLE: a phase 3, randomized, double-blind trial of patients with nonvalvular atrial fibrillation (NVAF)[1,2]

INDICATION

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

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.

Continue ›

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Granger CB, Alexander JH, McMurray JJ, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

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)

IN PATIENTS WITH NVAF

RANDOMIZED, DOUBLE-BLIND
N=18,201

Follow-up: median of ≈1.7 years

ELIQUIS
5 mg or 2.5 mg† twice daily
(≈95% received 5 mg twice daily)
n=9120

warfarin
(target INR 2.0–3.0)
n=9081

Superiority of ELIQUIS to warfarin was also examined for:
Primary efficacy endpoint: stroke/SE
Primary safety endpoint: major bleeding
Key secondary efficacy outcome: all-cause mortality

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 a $CHADS_2$ score, and prior VKA experience.

BASELINE CHARACTERISTICS +

$CHADS_2$ SCORE +

***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.

SELECTED IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Granger CB, Alexander JH, McMurray JJ, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. **3.** Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(suppl 11):981-992. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1107039/suppl_file/nejmoa1107039_protocol.pdf. Accessed November 10, 2021.

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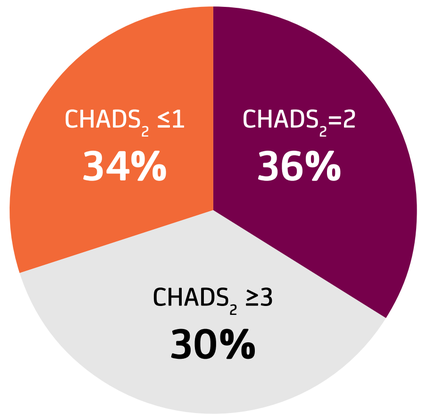
Baseline characteristics were well balanced across treatment arms[1,2]*

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.

*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.

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Granger CB, Alexander JH, McMurray JJ, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

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ARISTOTLE wa… …VAF[1-3]*

Primary objective

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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, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864-2870.

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In patients with NVAF,

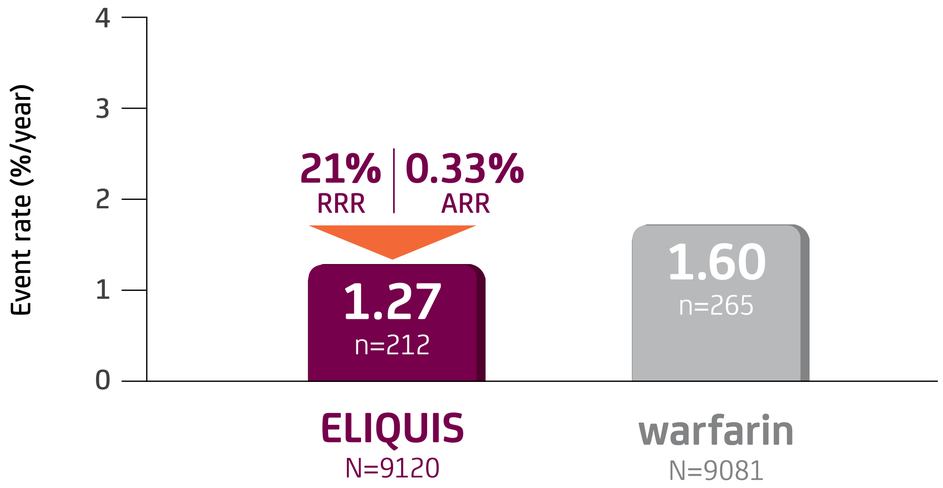
ONLY ELIQUIS demonstrated superiority in BOTH stroke/SE and major bleeding vs warfarin[1]

SUPERIOR

Risk reduction in stroke/SE

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

P=0.01



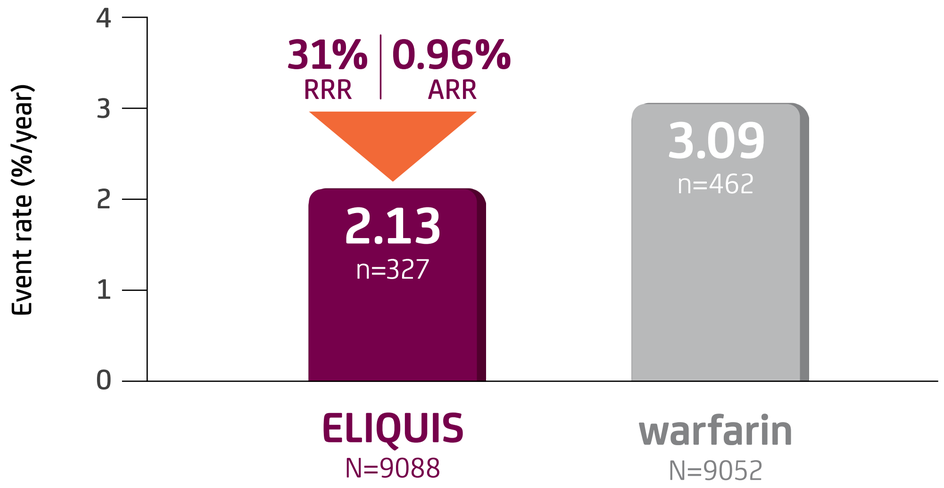
Primary efficacy endpoint

SUPERIOR

Based on fewer major bleeding events*

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

P<0.0001



Primary safety endpoint

SECONDARY EFFICACY 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 and ischemic strokes with hemorrhagic conversion compared with warfarin. Purely ischemic strokes 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.

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.

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In patients with NV

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- Increased Risk of Thr... the absence of adequ... transition from ELIQU... bleeding or completion...

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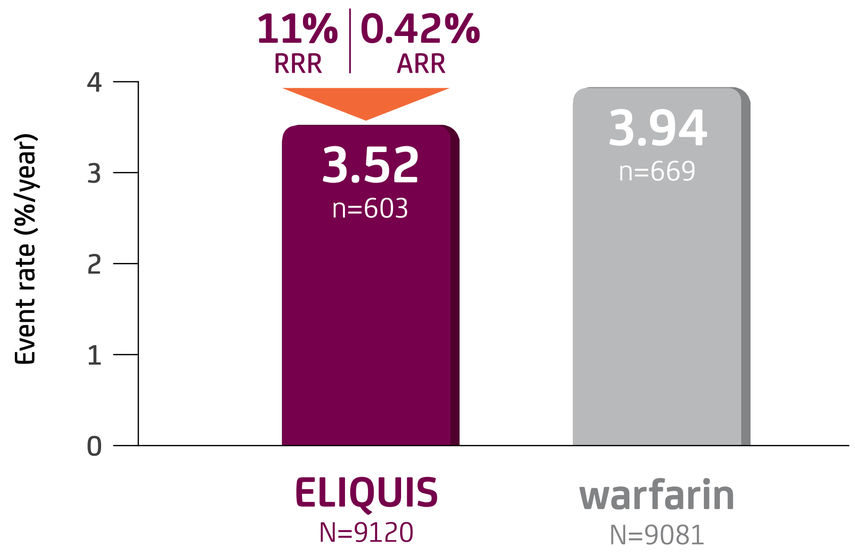
ELIQUIS® (apixaban) is the only anticoagulant that demonstrated a superior reduction in the risk of death vs warfarin[1,2]

SUPERIOR

Significant risk reduction in all-cause mortality

HR=0.89 (95% CI: 0.80, 0.998)

P=0.046



Secondary efficacy endpoint

- Cardiovascular deaths (1.80%/year vs 2.02%/year, HR=0.89 [95% CI: 0.76, 1.04]), particularly stroke deaths (0.42% vs 0.72%), were the greatest contributors to the reduction in all-cause mortality vs warfarin[2,3]
- The incidence of nonvascular mortality was similar in patients taking ELIQUIS to that in patients taking warfarin (1.14%/year vs 1.22%/year, HR=0.93 [95% CI: 0.77, 1.13])[2]

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.

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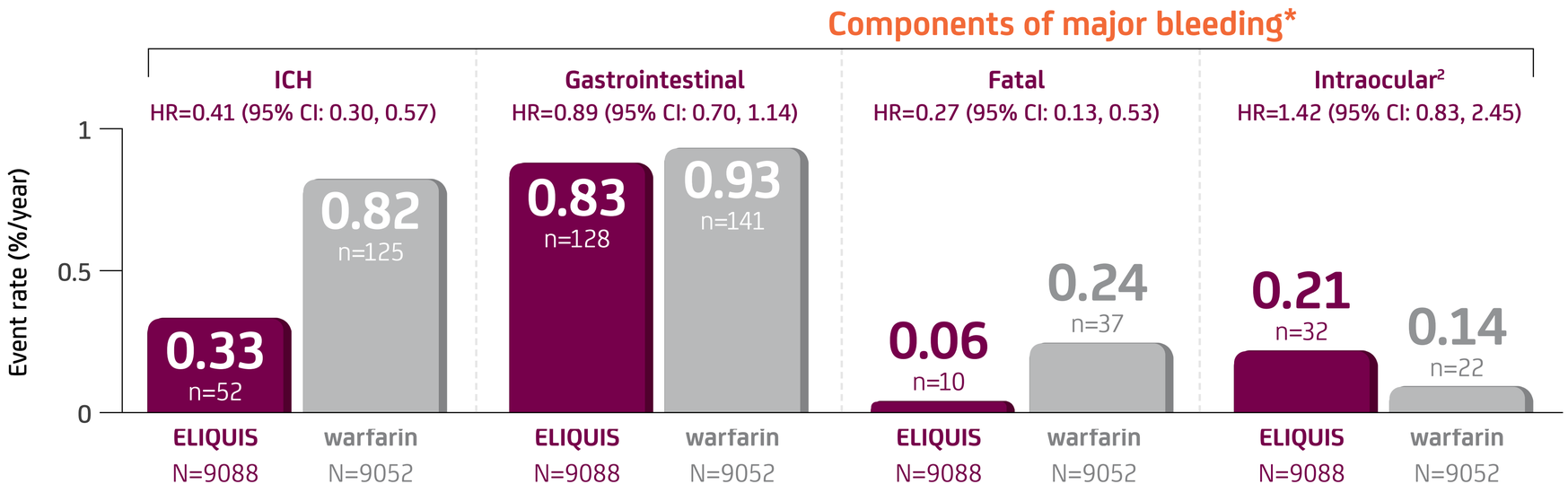
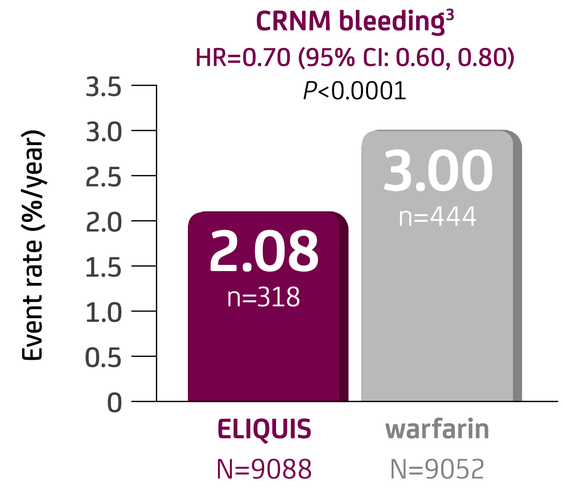
In patients with NVAF,

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





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

- 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% 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%/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[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.

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.

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, Alexander JH, McMurray JJ, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. **5.** Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(suppl 11):981-992. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1107039/suppl_file/nejmoa1107039_protocol.pdf. Accessed November 10, 2021.

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In patients with NVAF,

ELIQUIS demonstrated generally consistent results across most major subgroups[1]

In ARISTOTLE, results for the primary endpoints were generally consistent across most major subgroups, including:

Primary efficacy endpoint: stroke/SE

- Weight
- $CHADS_2$* score
- Prior warfarin use
- Level of renal impairment
- Geographic region
- Aspirin use at randomization

EFFICACY FOREST PLOT +

Primary safety endpoint: major bleeding

- Age
- Weight
- $CHADS_2$* score
- Prior warfarin use
- Geographic region
- Aspirin use at randomization

SAFETY FOREST PLOT +

Patients with diabetes who were treated with ELIQUIS bled more than patients without diabetes (3.0%/year vs 1.9%/year, respectively). Major bleeds were observed in patients treated with ELIQUIS and warfarin with diabetes at a rate of 3.0%/year and 3.1%/year, respectively.

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

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.

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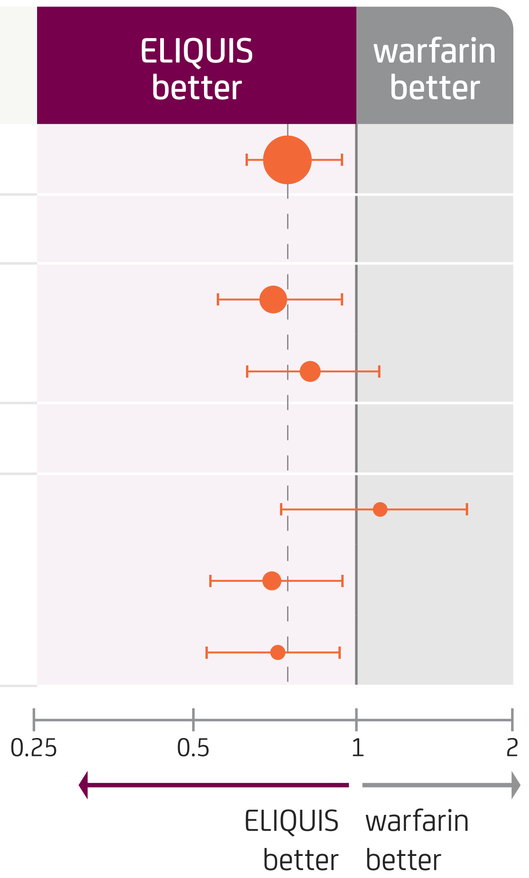
EFFICACY

In patients with NVAF,

Stroke/SE hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
All patients	212/9120 (1.3)	265/9081 (1.6)	0.79 (0.66, 0.95)
Prior warfarin/VKA status			
Experienced (57%)	102/5208 (1.1)	138/5193 (1.5)	0.73 (0.57, 0.95)
Naïve (43%)	110/3912 (1.5)	127/3888 (1.8)	0.86 (0.66, 1.11)
Age			
<65 years (30%)	51/2731 (1.0)	44/2740 (0.9)	1.16 (0.77, 1.73)
≥65 to <75 years (39%)	82/3539 (1.3)	112/3513 (1.7)	0.72 (0.54, 0.96)
≥75 years (31%)	79/2850 (1.6)	109/2828 (2.2)	0.71 (0.53, 0.95)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

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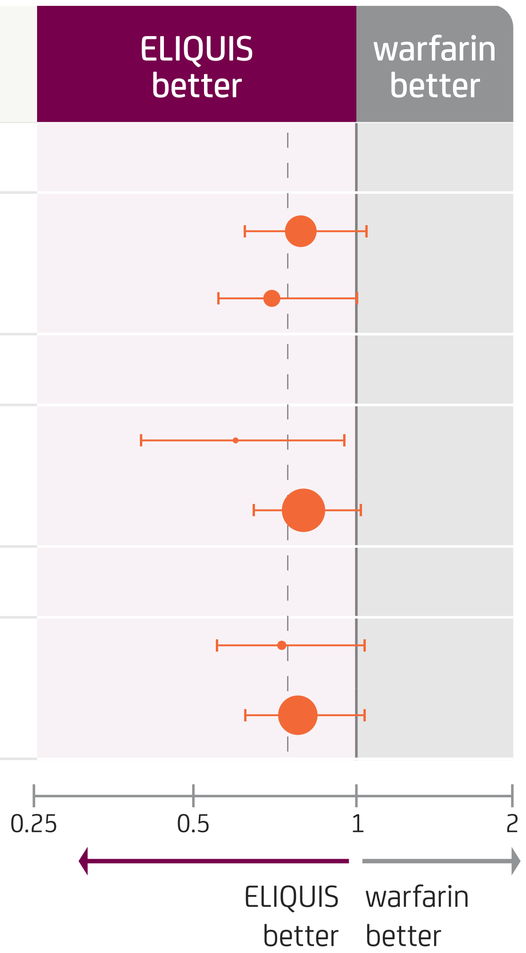
EFFICACY

In patients with NVAF,

Stroke/SE hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
Sex			
Male (65%)	132/5886 (1.2)	160/5899 (1.5)	0.82 (0.65, 1.04)
Female (35%)	80/3234 (1.3)	105/3182 (1.8)	0.74 (0.56, 1.00)
Weight			
≤60 kg (11%)	34/1018 (2.0)	52/967 (3.2)	0.63 (0.41, 0.97)
>60 kg (89%)	177/8070 (1.2)	212/8084 (1.4)	0.83 (0.68, 1.01)
Prior stroke or transient ischemic attack			
Yes (19%)	73/1694 (2.5)	98/1742 (3.2)	0.76 (0.56, 1.03)
No (81%)	139/7426 (1.0)	167/7339 (1.2)	0.82 (0.65, 1.03)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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.

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Data on file: APIX 032. Bristol-Myers Squibb Company, Princeton, NJ.

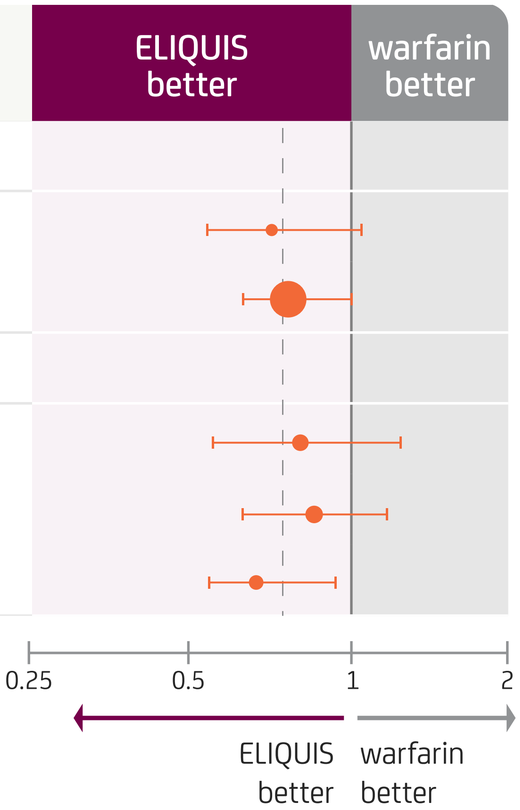
EFFICACY

In patients with NVAF,

Stroke/SE hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
Diabetes mellitus			
Yes (25%)	57/2284 (1.4)	75/2263 (1.9)	0.75 (0.53, 1.05)
No (75%)	155/6836 (1.2)	190/6818 (1.5)	0.81 (0.65, 1.00)
$CHADS_2$ score			
≤1 (34%)	44/3100 (0.7)	51/3083 (0.9)	0.85 (0.57, 1.27)
2 (36%)	74/3262 (1.2)	82/3254 (1.4)	0.90 (0.66, 1.23)
≥3 (30%)	94/2758 (2.0)	132/2744 (2.8)	0.70 (0.54, 0.91)



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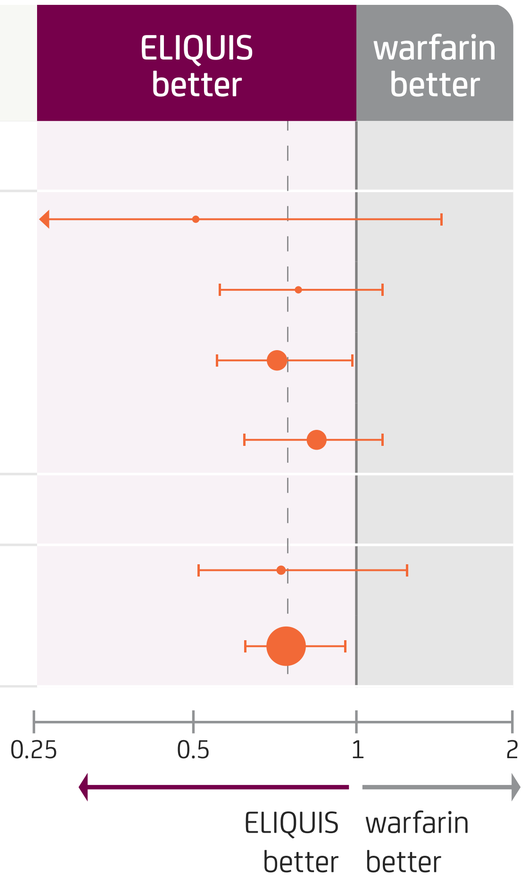
EFFICACY

In patients with NVAF,

Stroke/SE hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
Creatinine clearance			
<30 mL/min (1%)	6/137 (2.8)	10/133 (5.1)	0.55 (0.20, 1.53)
30–50 mL/min (15%)	48/1365 (2.0)	59/1382 (2.5)	0.83 (0.57, 1.21)
>50–80 mL/min (42%)	87/3817 (1.2)	116/3770 (1.7)	0.74 (0.56, 0.97)
>80 mL/min (41%)	70/3761 (1.0)	79/3757 (1.1)	0.88 (0.64, 1.21)
Geographic region			
US (19%)	31/1720 (0.9)	39/1697 (1.2)	0.79 (0.50, 1.27)
Non-US (81%)	181/7400 (1.3)	226/7384 (1.7)	0.79 (0.65, 0.96)



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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.

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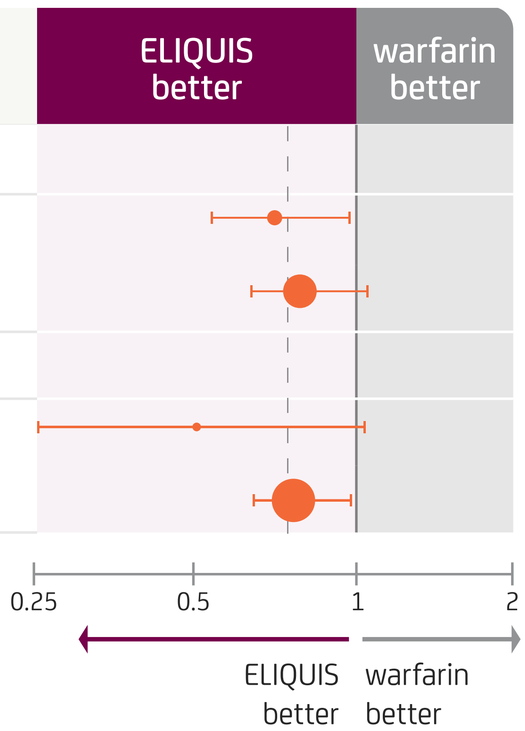
EFFICACY

In patients with NVAF,

Stroke/SE hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
Aspirin at randomization			
Yes (31%)	70/2859 (1.3)	94/2773 (1.9)	0.72 (0.53, 0.98)
No (69%)	142/6261 (1.2)	171/6308 (1.5)	0.83 (0.67, 1.04)
ELIQUIS dose			
2.5 mg BID (5%)	12/428 (1.7)	22/403 (3.3)	0.50 (0.25, 1.02)
5.0 mg BID (95%)	200/8692 (1.3)	243/8678 (1.5)	0.82 (0.68, 0.98)



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SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

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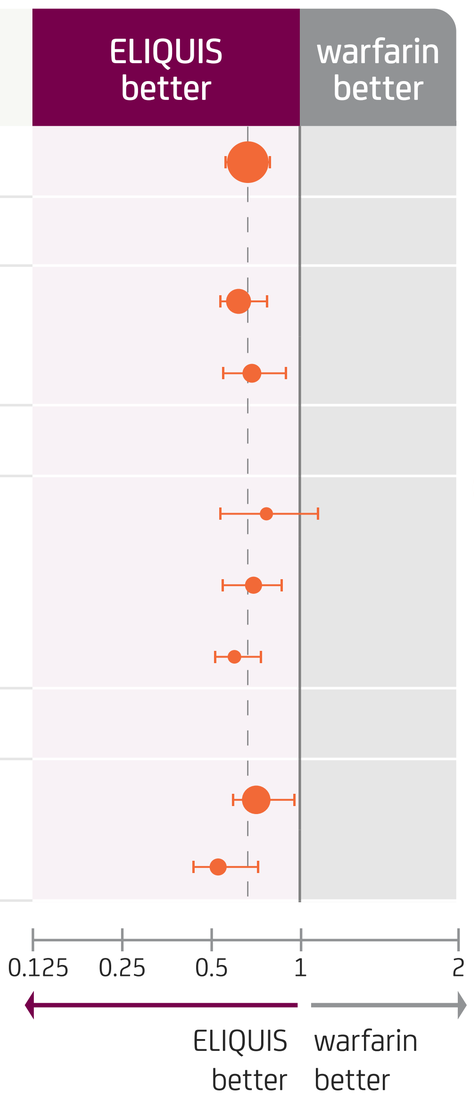
SAFETY

In patients with NVAF,

Major bleeding hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
All patients	327/9088 (2.1)	462/9052 (3.1)	0.69 (0.60, 0.80)
Prior warfarin/VKA status			
Experienced (57%)	185/5196 (2.1)	274/5180 (3.2)	0.66 (0.55, 0.80)
Naïve (43%)	142/3892 (2.2)	188/3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 years (30%)	56/2732 (1.2)	72/2732 (1.5)	0.78 (0.55, 1.11)
≥65 to <75 years (39%)	120/3529 (2.0)	166/3501 (2.8)	0.71 (0.56, 0.89)
≥75 years (31%)	151/2836 (3.3)	224/2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225/5868 (2.3)	294/5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102/3220 (1.9)	168/3173 (3.3)	0.58 (0.45, 0.74)



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

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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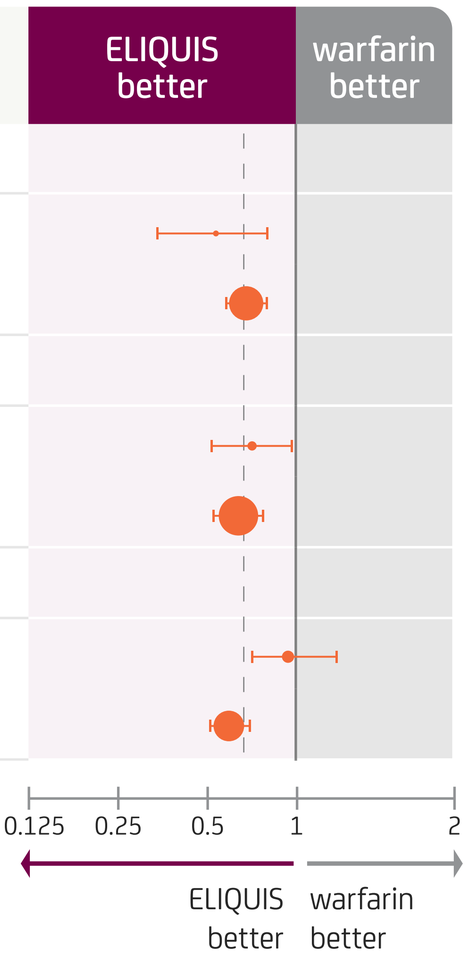
SAFETY

In patients with NVAF,

Major bleeding hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
Weight			
≤60 kg (11%)	36/1013 (2.3)	62/965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290/8043 (2.1)	398/8059 (3.0)	0.72 (0.62, 0.83)
Prior stroke or transient ischemic attack			
Yes (19%)	77/1687 (2.8)	106/1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250/7401 (2.0)	356/7317 (2.9)	0.68 (0.58, 0.80)
Diabetes mellitus			
Yes (25%)	112/2276 (3.0)	114/2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215/6812 (1.9)	348/6802 (3.1)	0.60 (0.51, 0.71)



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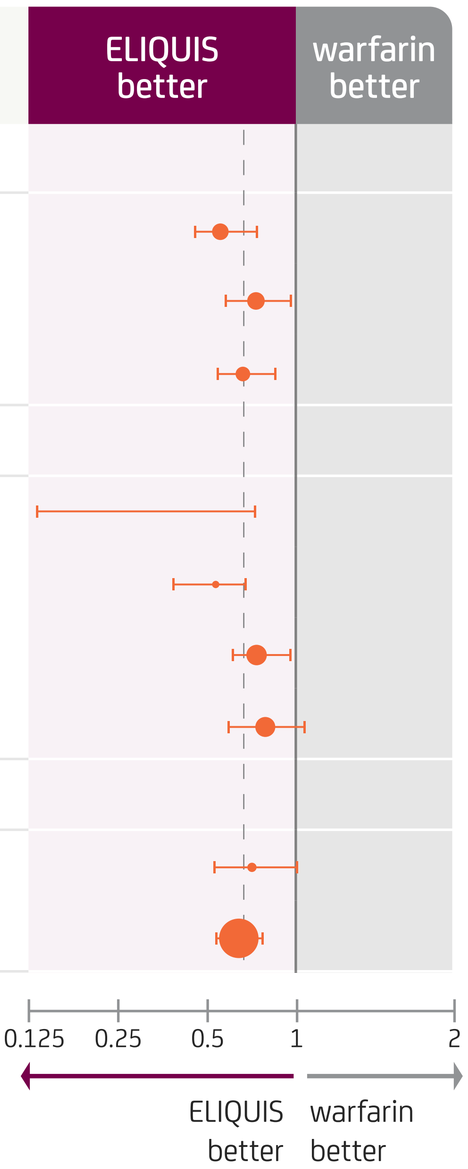
SAFETY

In patients with NVAF,

Major bleeding hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
$CHADS_2$ score			
≤1 (34%)	76/3093 (1.4)	126/3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125/3246 (2.3)	163/3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126/2749 (2.9)	173/2730 (4.1)	0.70 (0.56, 0.88)
Creatinine clearance			
<30 mL/min (1%)	7/136 (3.7)	19/132 (11.9)	0.32 (0.13, 0.78)
30–50 mL/min (15%)	66/1357 (3.2)	123/1380 (6.0)	0.53 (0.39, 0.71)
>50–80 mL/min (42%)	157/3807 (2.5)	199/3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96/3750 (1.5)	119/3746 (1.8)	0.79 (0.61, 1.04)
Geographic region			
US (19%)	83/1716 (2.8)	109/1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244/7372 (2.0)	353/7359 (2.9)	0.68 (0.57, 0.80)



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

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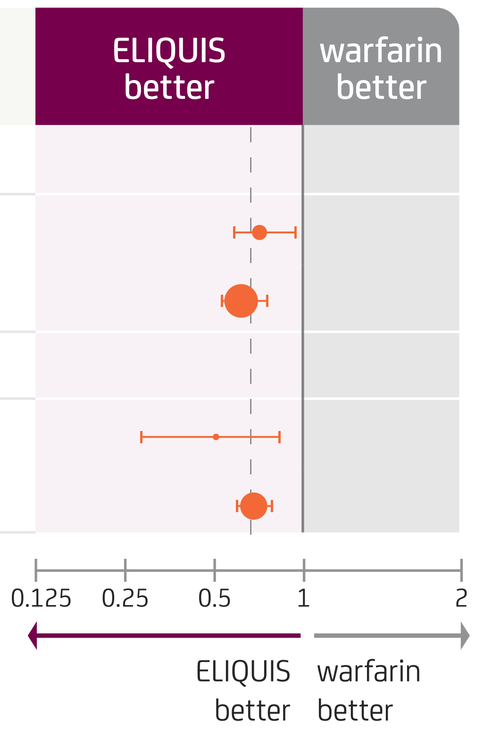
SAFETY

In patients with NVAF,

Major bleeding hazard ratios by baseline characteristics in ARISTOTLE[1,2]

n of events/N of patients (% per year)

Subgroup	ELIQUIS® (apixaban)	warfarin	Hazard ratio (95% CI)
Aspirin at randomization			
Yes (31%)	129/2846 (2.7)	164/2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198/6242 (1.9)	298/6290 (2.8)	0.66 (0.55, 0.79)
ELIQUIS dose			
2.5 mg BID (5%)	20/424 (3.3)	37/402 (6.7)	0.50 (0.29, 0.86)
5.0 mg BID (95%)	307/8664 (2.1)	425/8650 (3.0)	0.71 (0.61, 0.82)



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

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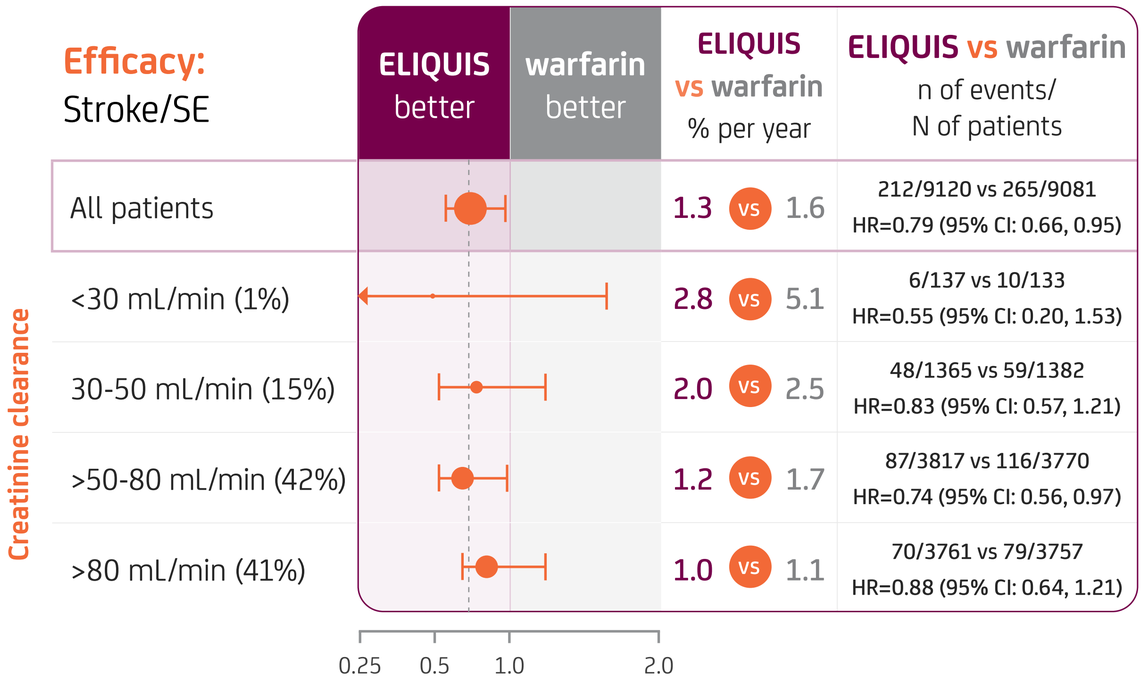
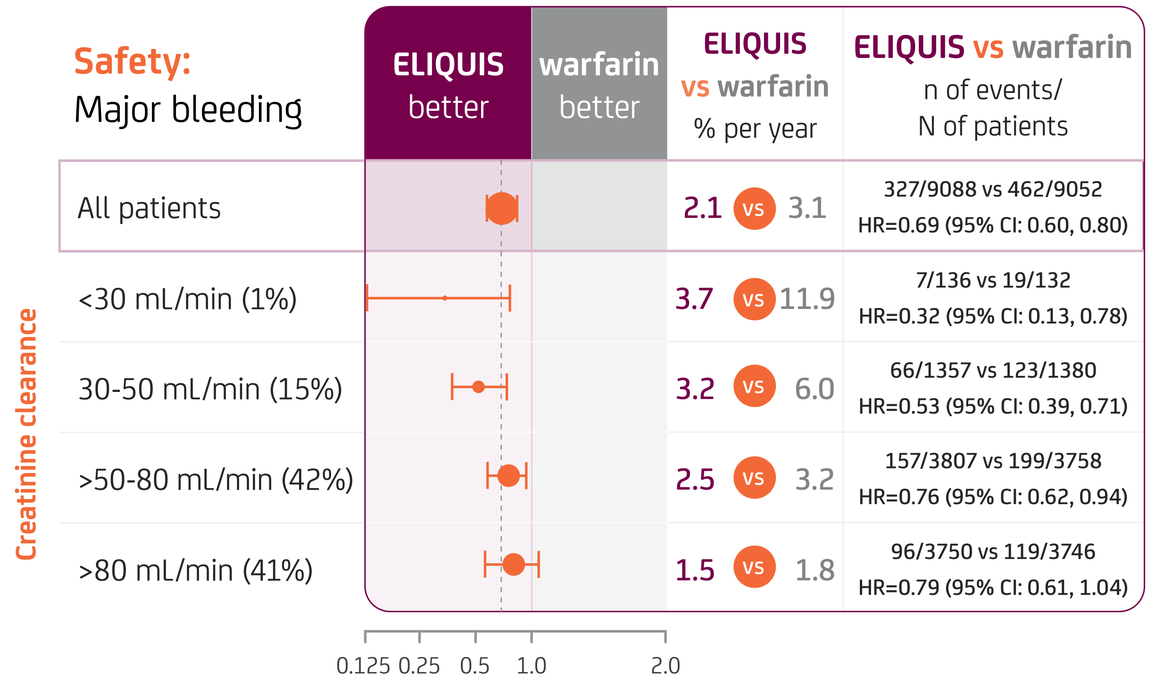
In patients with NVAF,

There was generally consistent efficacy and major bleeding events across levels of renal function in ARISTOTLE[1,2]

RESULTS FROM A PRESPECIFIED SUBGROUP ANALYSIS*





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

- Patients with a serum creatinine level of >2.5 mg/dL or calculated creatinine clearance of <25 mL/min were excluded from the ARISTOTLE trial[2]
- In the ARISTOTLE trial, 5319 patients in the ELIQUIS arm had various levels of renal impairment[2]

Note: The figures above present effects in one of various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted. The size of the dot for point estimate (hazard ratio) represents the number of patients across each level of renal function.

*In a prespecified secondary analysis of ARISTOTLE, the outcome of the trial was evaluated in relation to renal function.

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.

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Granger CB, Alexander JH, McMurray JJ, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

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

Eliquis® (apixaban) tablets 5mg 2.5mg

AVERROES: a phase 3, randomized, double-blind trial vs aspirin in patients with nonvalvular atrial fibrillation (NVAF) who were unsuitable for warfarin[1,2]

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.

Continue ›

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Connolly SJ, Eikelboom J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817.

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

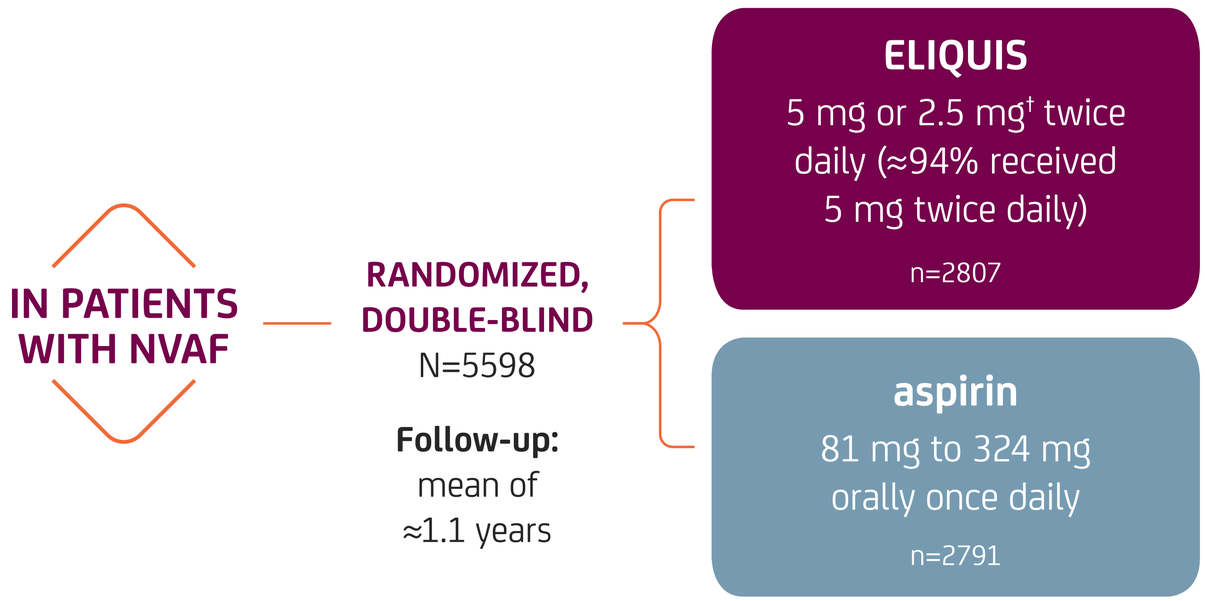
Eliquis® (apixaban) tablets 5mg 2.5mg

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



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 a $CHADS_2$ score, and prior use of a VKA within 30 days before screening.

BASELINE CHARACTERISTICS +

COMMON REASONS FOR WARFARIN UNSUITABILITY +

$CHADS_2$ 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.

SELECTED IMPORTANT SAFETY INFORMATION: ADVERSE REACTIONS

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

References: 1. ELIQUIS® (apixaban) Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Connolly SJ, Eikelboom J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817. **3.** Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(suppl 11):981-992. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1107039/suppl_file/nejmoa1107039_protocol.pdf. Accessed November 11, 2021.

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

Eliquis® (apixaban) tablets 5mg 2.5mg

Studied in AVERROES, a phase 3, randomized, double-blind trial vs aspirin in over 5500 patients with NVAF who were unsuitable for warfarin[1-3]

Baseline patient characteristics*

The 2 treatment arms were well balanced with respect to baseline characteristics[2]	ELIQUIS® (apixaban) n=2808		aspirin n=2791	
Mean age, years	70±9		70±10	
Mean $CHADS_2$† score	2.0±1.1		2.1±1.1	
$CHADS_2$ ≤1	36%	n=1004	37%	n=1022
$CHADS_2$=2	37%	n=1045	34%	n=954
$CHADS_2$ ≥3	27%	n=758	29%	n=812
Prior stroke or transient ischemic attack	14%	n=390	13%	n=374
Use of VKA (eg, warfarin) within 30 days before screening	14%	n=401	15%	n=426

± values are means ± SDs.
*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.

Medication doses of aspirin for patients in the aspirin arm of study[2]

Aspirin dose received at baseline	Number of patients (%) n=2791
81 mg	1786 (64%)
162 mg	750 (27%)
243 mg	60 (2%)
324 mg	184 (7%)
Data not available	11 (<1%)

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Connolly SJ, Eikelboom J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817. **3.** Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(suppl 11):981-992. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1107039/suppl_file/nejmoa1107039_protocol.pdf. Accessed November 11, 2021.

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.

SELECTED IMPORTANT SAFETY INFORMATION: ADVERSE REACTIONS

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

References: 1. ELIQUIS® (apixaban) Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Connolly SJ, Eikelboom J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817. **3.** Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(suppl 11):981-992. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1107039/suppl_file/nejmoa1107039_protocol.pdf. Accessed November 11, 2021.

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AVERROES wa
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This trial included 55

Primary objective

Determine how ELI
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Common reasons for warfarin unsuitability in the AVERROES clinical trial[1]

Reason for unsuitability of therapy*	ELIQUIS® (apixaban) n=2808	aspirin n=2791
Unable/unlikely to obtain INRs at requested intervals	1196 (43%)	1191 (43%)
Patient refused warfarin	1053 (38%)	1039 (37%)
$CHADS_2$† score of 1 and HCP did not recommend VKA (eg, warfarin)	590 (21%)	605 (22%)
Assessment that INR could not be maintained in therapeutic range	465 (17%)	468 (17%)
Patient could not be relied on to adhere to VKA (eg, warfarin) instruction	437 (16%)	405 (15%)
Expected difficulty in contacting patient in case of urgent dose change	322 (11%)	331 (12%)

HCP=health care provider; INRs=international normalized ratios.
*Reasons listed here were reported by 10% of patients or more; reasons reported by less than 10% of patients are not included in this table.
†Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.

Reference: 1. Connolly SJ, Eikelboom J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817.

***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.

SELECTED IMPORTANT SAFETY INFORMATION: ADVERSE REACTIONS

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

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AVERROES wa
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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, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864-2870.

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.

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In patients with NVAF,

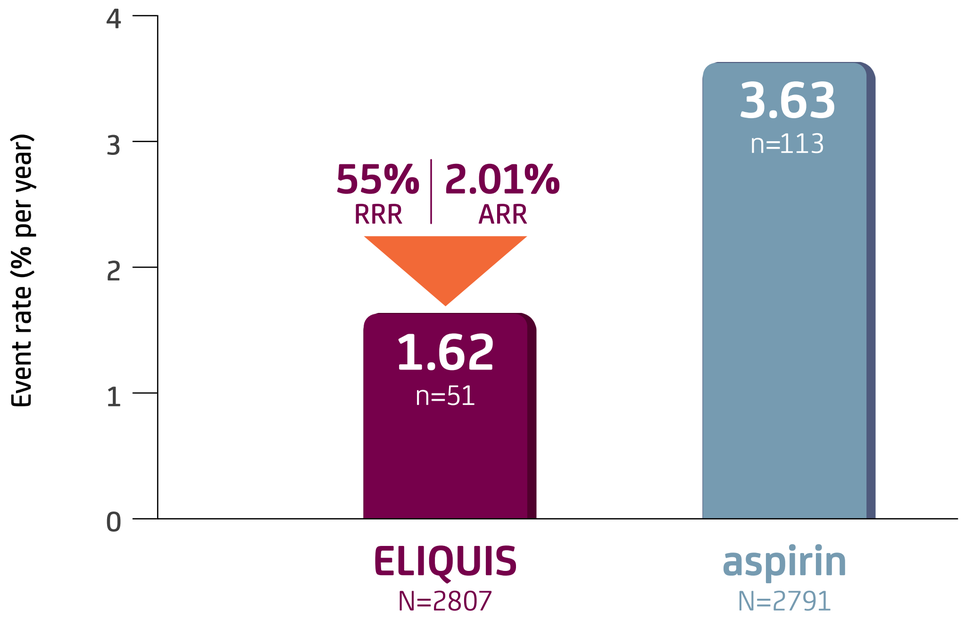
Results vs aspirin from the AVERROES clinical trial[1]

PRIMARY EFFICACY OUTCOME: ELIQUIS WAS SUPERIOR TO ASPIRIN IN REDUCING THE RISK OF STROKE AND SE

SUPERIOR

Risk reduction in stroke/SE vs aspirin

HR=0.45 (95% CI: 0.32, 0.62)
P<0.0001



Primary efficacy endpoint

AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke/SE for patients taking ELIQUIS compared with patients taking aspirin

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

SELECTED IMPORTANT SAFETY INFORMATION: 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.

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,

Results vs aspirin from the AVERROES clinical trial[1]

PRIMARY SAFETY OUTCOME: RATES OF MAJOR BLEEDING EVENTS vs ASPIRIN

No statistical difference in major bleeding events

	ELIQUIS n=2798 n (%/year)	aspirin n=2780 n (%/year)	Hazard ratio (95% CI)	*P* value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

- In AVERROES, ELIQUIS was associated with an increase in bleeding compared with aspirin that was not statistically significant
- The most common reason for treatment discontinuation in both studies was bleeding-related adverse reactions:
  - In ARISTOTLE, this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively
  - In AVERROES, this occurred in 1.5% and 1.3% of patients treated with ELIQUIS and aspirin, respectively

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

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

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.

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

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From selected double-blind, randomized, phase 3 trials

Summary of primary efficacy and safety endpoints[1,2]

		PROVEN EFFICACY Primary **efficacy** endpoint	MAJOR BLEEDING EVENTS Primary **safety** endpoint
In patients with NVAF	**ARISTOTLE** **ELIQUIS** vs warfarin	**SUPERIOR** **RISK REDUCTION IN STROKE/SE** 1.27%/year (212/9120) with ELIQUIS vs 1.60%/year (265/9081) with warfarin HR=0.79 (95% CI: 0.66, 0.95) *P*=0.01 21% RRR, 0.33%/year ARR	**SUPERIOR** **BASED ON FEWER MAJOR BLEEDING EVENTS*** 2.13%/year (327/9088) with ELIQUIS vs 3.09%/year (462/9052) with warfarin HR=0.69 (95% CI: 0.60, 0.80) *P*<0.0001 31% RRR, 0.96%/year ARR
	AVERROES† **ELIQUIS** vs aspirin	**SUPERIOR** **RISK REDUCTION IN STROKE/SE** 1.62%/year (51/2807) with ELIQUIS vs 3.63%/year (113/2791) with aspirin HR=0.45 (95% CI: 0.32, 0.62) *P*<0.0001 55% RRR, 2.01%/year ARR	**NO STATISTICAL DIFFERENCE** **IN MAJOR BLEEDING EVENTS*** 1.41%/year (45/2798) with ELIQUIS vs 0.92%/year (29/2780) with aspirin HR=1.54 (95% CI: 0.96, 2.45) *P*=0.07 (NS)

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

- In ARISTOTLE, superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared with warfarin. Purely ischemic strokes occurred with similar rates on both drugs
- In 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)
- The most common reason for treatment discontinuation in 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

Major bleeding was defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL,‡ a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site (intracranial,§ intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal), or bleeding with fatal outcome.

*Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. In ARISTOTLE, bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
†AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke and SE for ELIQUIS compared with aspirin.
‡In AVERROES, a decrease in hemoglobin of 2 g/dL or more over a 24-hour period.[2]
§In ARISTOTLE, intracranial bleed included intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

SELECTED IMPORTANT SAFETY INFORMATION: DRUG INTERACTIONS (cont'd)

- **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.

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Connolly SJ, Eikelboom J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364(9):806-817.

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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)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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

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

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IMPORTANT SAFETY INFORMATION (cont'd)

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.

ADVERSE REACTIONS

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TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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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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- 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.

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.

(continued on next page)

IMPORTANT SAFETY INFORMATION (cont'd)

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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