

Pr *Eliquis*[®]
apixaban

#1 DISPENSED NOAC IN CANADA AS PRESCRIBED BY:^{1*}

- ✓ Family Medicine/General Practitioners
- ✓ Cardiologists
- ✓ Neurologists
- ✓ Nephrologists
- ✓ Geriatricians
- ✓ Internal Medicine

A SUMMARY OF THE PIVOTAL TRIAL DATA

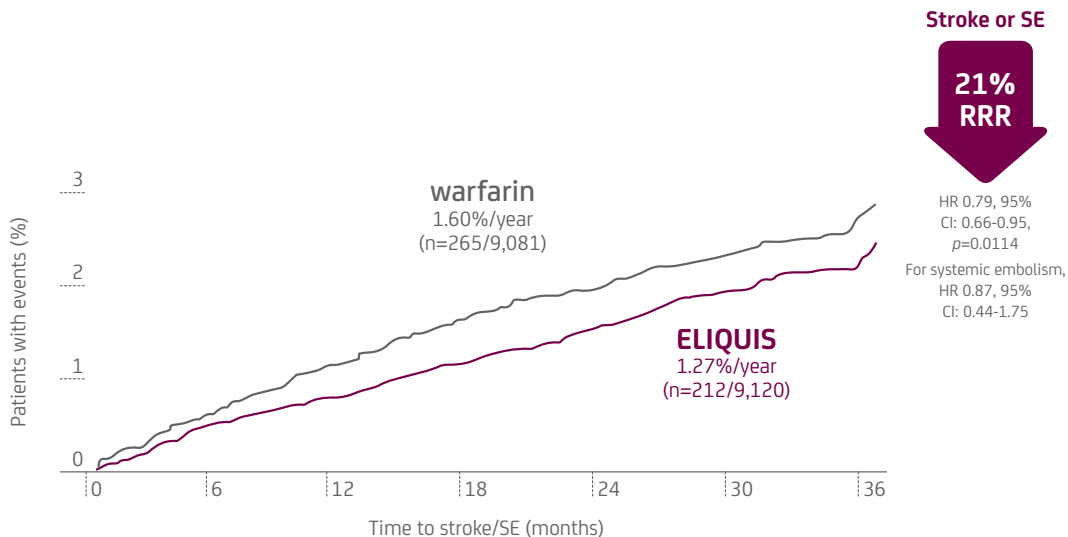
ELIQUIS: The only oral anticoagulant with both a randomized, controlled study vs. warfarin and a randomized, controlled study vs. ASA in patients with AF^{2*}

ELIQUIS is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery; the prevention of stroke and systemic embolism (SE) in patients with atrial fibrillation (AF); the treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.

NOAC = non-vitamin K antagonist oral anticoagulant

* Comparative clinical significance unknown.

In patients with atrial fibrillation, **ELIQUIS** was demonstrated to be **SUPERIOR** to **warfarin** for the primary efficacy endpoint of combined stroke and systemic embolism^{3*}



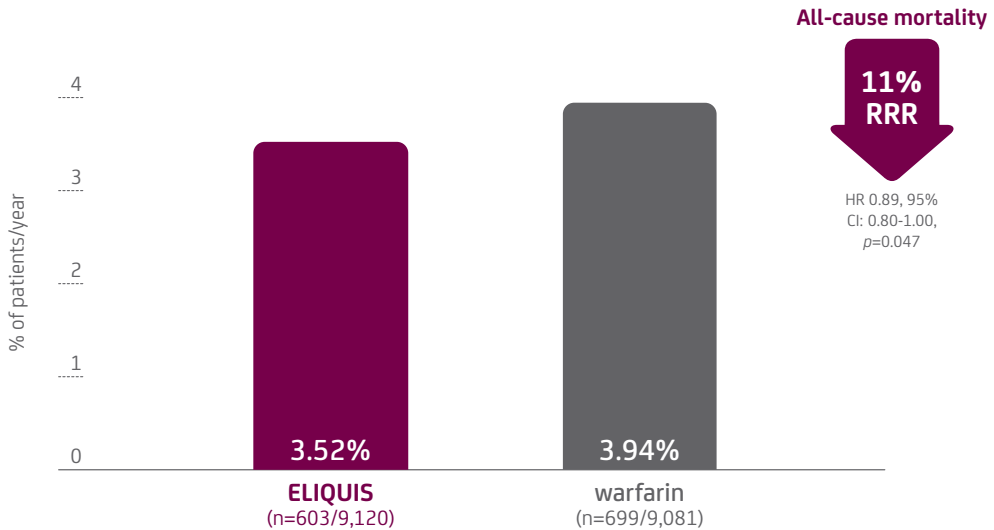
Adapted from Product Monograph³

Patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis, were excluded from the ARISTOTLE and AVERROES trials, and thus were not evaluated. These trial results do not apply to these patients, with or without atrial fibrillation.

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

* Randomized, double-blind, parallel-arm, non-inferiority trial in 18,201 patients with nonvalvular, persistent, paroxysmal, or permanent atrial fibrillation or atrial flutter and ≥ 1 of the following additional risk factors: prior stroke, transient ischemic attack or systemic embolism, age ≥ 75 years, arterial hypertension requiring treatment, diabetes mellitus, heart failure (NYHA Class ≥ 2), decreased left ventricular ejection fraction. Patients received apixaban 5 mg BID (n=9,120; 2.5 mg BID in a subset of patients with ≥ 2 of the following criteria: ≥ 80 years, body weight ≤ 60 kg, or a serum creatinine level ≥ 133 $\mu\text{mol/L}$) or warfarin (n=9,081) at a target INR range of 2.0-3.0 for a median of 90 weeks for apixaban and 88 weeks for warfarin. The median time in therapeutic range for subjects randomized to warfarin, excluding the first 7 days of the study and excluding warfarin interruptions, was 66%. The primary objective of the study was to determine if apixaban was non-inferior to warfarin for the prevention of total stroke (ischemic, hemorrhagic, or unspecified) and systemic embolism. Key study outcomes were assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial. The intention-to-treat (ITT) population was used for efficacy outcome testing, the on-treatment population for safety outcomes.³

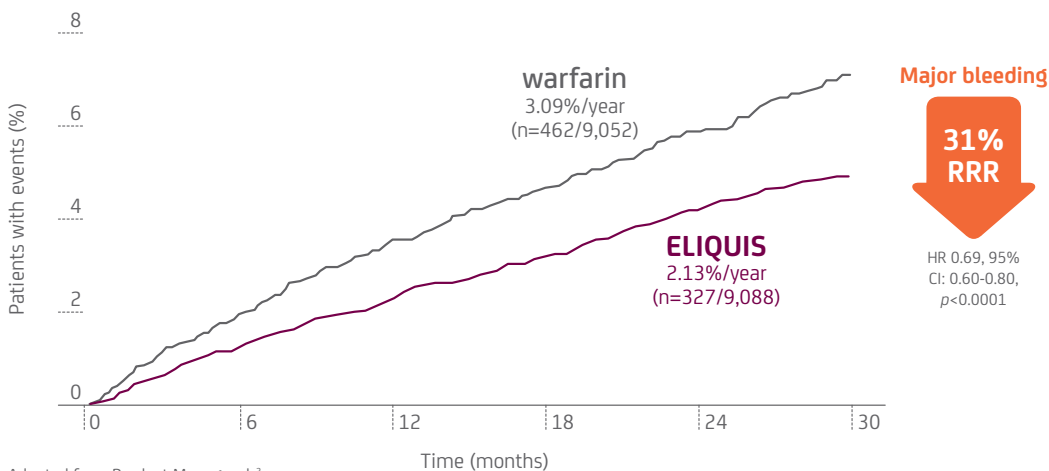
In patients with atrial fibrillation, **ELIQUIS** was demonstrated to be **SUPERIOR** to **warfarin** for the secondary endpoint of all-cause mortality^{3*}



Adapted from Product Monograph³

* ELIQUIS is not indicated to reduce all-cause mortality.

In patients with atrial fibrillation, **ELIQUIS** was demonstrated to be **SUPERIOR** to **warfarin** for the primary safety endpoint of major bleeding^{3,4*}



For every 1,000 patients with AF treated for 1.8 years, as compared to warfarin^{3,4}

Primary efficacy endpoint:
Combined stroke and systemic embolism

ELIQUIS prevented

6 more strokes

Primary safety endpoint:
Major bleeding

ELIQUIS had

15 fewer major bleeds

Secondary endpoint:
All-cause mortality

ELIQUIS had

8 fewer deaths

(3.52%/yr vs. 3.94%/yr, respectively; HR 0.89, 95% CI: 0.80-1.00, p=0.047)

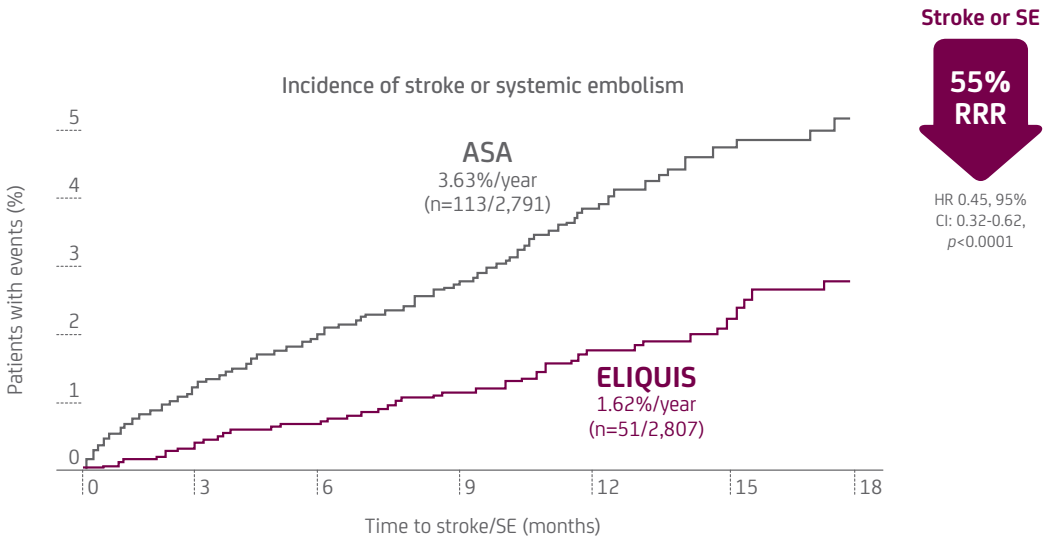
Adapted from Granger CB *et al.*⁴

As with all anticoagulants, ELIQUIS should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with ELIQUIS. The possibility of a hemorrhage should be considered in evaluating the condition of any anticoagulated patient. An unexplained fall in hemoglobin, hematocrit or blood pressure should lead to a search for a bleeding site. Patients should be advised of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Patients at high risk of bleeding should not be prescribed ELIQUIS. **Should severe bleeding occur, treatment with ELIQUIS must be discontinued and the source of bleeding investigated promptly.** Close clinical surveillance (i.e., looking for signs of bleeding or anemia) is recommended throughout the treatment period. This may include looking for obvious signs of bleeding, e.g., hematomas, epistaxis, or hypotension, testing for occult blood in the stool, checking serum hemoglobin for significant decrease, etc., especially if other factors/conditions that generally increase the risk of hemorrhage are also present.³

Bleeding of any type was observed at a rate of 18% per year in AF patients. Common adverse reactions with ELIQUIS were epistaxis (6.2%), contusion (5.0%), hematoma (2.6%), hematuria (3.7%), hemorrhage (including eye [2.3%], gastrointestinal [2.1%], rectal [1.6%] and other [1.7%]) and gingival bleeding (1.2%).³

* Major bleeding was defined as clinically overt bleeding accompanied by a decrease in the hemoglobin level of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red cells, occurring at a critical site, or resulting in death.⁴ Dataset includes events occurring on-treatment plus the following two days. Concomitant aspirin use with either ELIQUIS or warfarin increased the risk of major bleeding 1.5 to 2 times when compared with those patients not treated with concomitant aspirin. ELIQUIS should be used with caution in patients treated concomitantly with antiplatelet agents.³

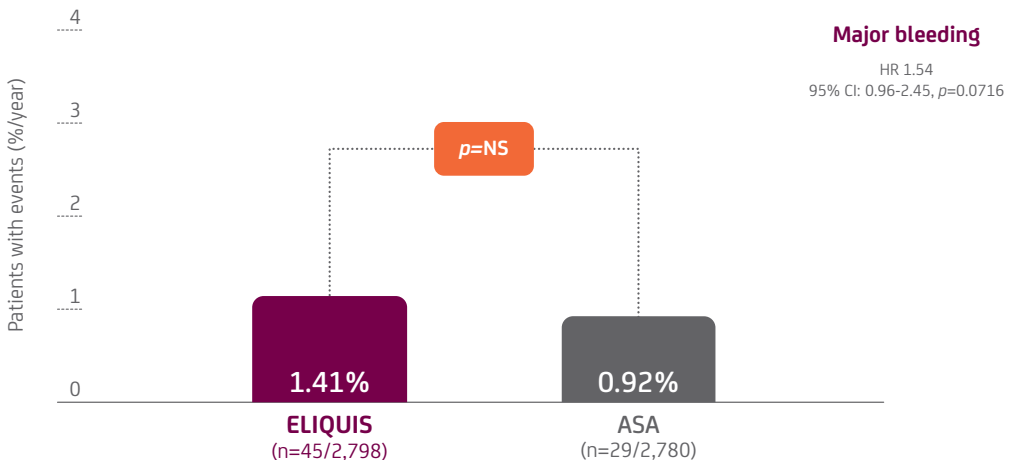
In patients with atrial fibrillation, **ELIQUIS** was demonstrated to be **SUPERIOR to ASA** for the primary efficacy endpoint of combined stroke and systemic embolism^{3*}



Adapted from Product Monograph³

* Randomized, double-blind, parallel-arm, multinational trial in 5,599 patients with nonvalvular, persistent, paroxysmal, or permanent AF or atrial flutter and one or more of the following additional risk factors: prior stroke, transient ischemic attack; age ≥75 years; arterial hypertension requiring treatment; diabetes mellitus; heart failure (NYHA class ≥2); decreased left ventricular ejection fraction; documented peripheral arterial disease. Patients received apixaban 5 mg BID (2.5 mg BID in a subset of patients with ≥2 of the following criteria: ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥133 μmol/L) or ASA 81 to 324 mg once daily for a median of 58 weeks for apixaban, and 59 weeks for ASA. The primary objective of the study was to determine if apixaban was superior to ASA (81 to 324 mg QD) in the prevention of stroke or systemic embolism. VKA therapy had been tried but discontinued in 40% of patients prior to enrollment. Common reasons for unsuitability for VKA therapy included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), CHADS₂ score = 1 and physician did not recommend VKA (21.3%), patient could not be relied on to adhere to VKA medication instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%). AVERROES was stopped early upon the recommendation of the trial's independent Data Monitoring Committee which found that a pre-defined interim analysis revealed clear evidence of apixaban providing a clinically important reduction in stroke/SE and acceptable safety profile.³

In patients with atrial fibrillation, **ELIQUIS** demonstrated the following non-statistically significant result for the primary safety endpoint of major bleeding vs. **ASA**^{3*}



Adapted from Product Monograph³

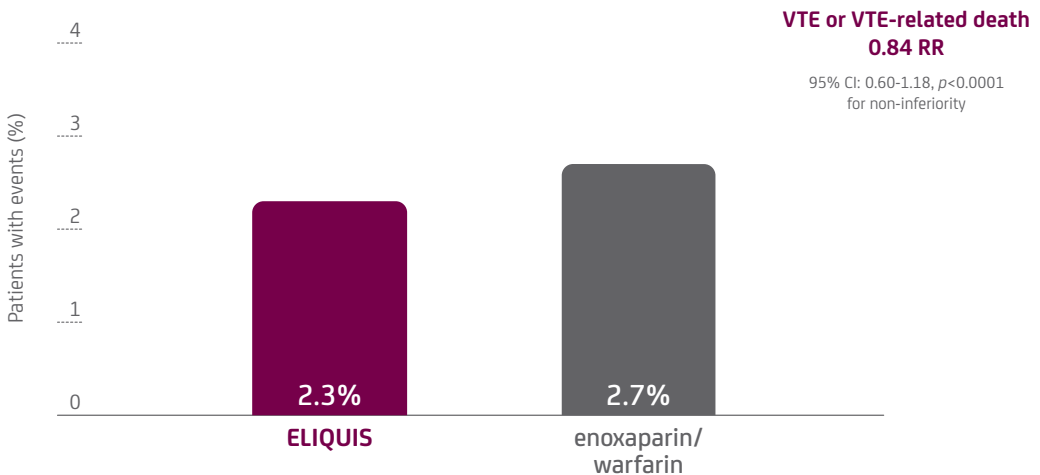
Other bleeding results included:³

- Major + CRNM bleeding:[†] 4.46%/year vs. 3.24%/year for ASA; HR 1.38, 95% CI: 1.07-1.78, $p=0.0144$
- All bleeding: 10.85%/year vs. 8.32%/year for ASA; HR 1.30, 95% CI: 1.10-1.53, $p=0.0017$

* Dataset includes events occurring on-treatment, plus the following two days for patients that did not enter the open-label extension. Major bleeding defined as clinically overt bleeding accompanied by ≥ 1 of the following: a decrease in the hemoglobin level of ≥ 2 g/dL over a 24-hour period, transfusion of ≥ 2 units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding.^{3,5}

† Clinically relevant non-major (CRNM) = clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy. Dataset includes events occurring on-treatment, plus the following two days for patients that did not enter the open-label extension.³

In patients with DVT and/or PE, **ELIQUIS** was demonstrated to be **NON-INFERIOR** to **enoxaparin/warfarin** for the primary combined endpoint of recurrent symptomatic VTE (non-fatal DVT or PE) or VTE-related death^{3*}

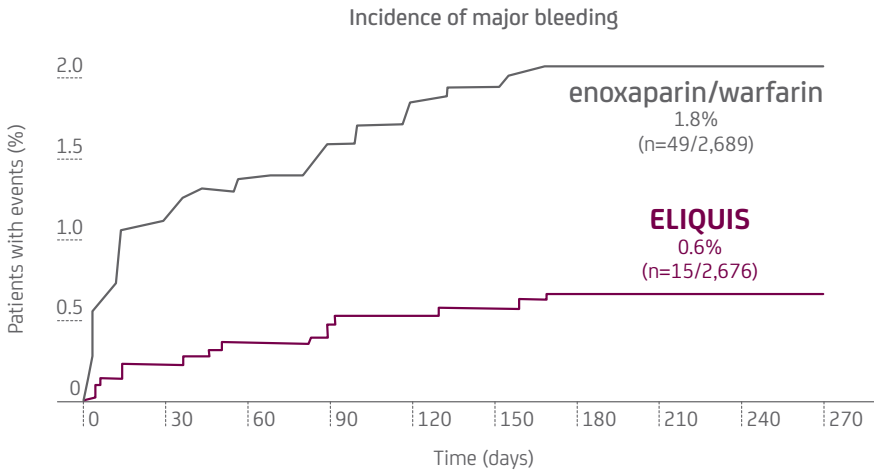


Adapted from Product Monograph³

RR = relative risk

* Randomized, parallel-group, double-blind multinational trial in 5,395 patients with symptomatic proximal DVT and/or symptomatic PE. Patients were randomized to apixaban 10 mg BID for 7 days followed by 5 mg BID for 6 months, or enoxaparin 1 mg/kg BID subcutaneously for ≥ 5 days (until INR ≥ 2) and warfarin (target INR range 2.0-3.0) orally for 6 months. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9. The primary study objective was to determine if apixaban was non-inferior to enoxaparin/warfarin therapy in the combined endpoint of adjudicated recurrent symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE-related death over 6 months of therapy. The key study outcomes were pre-specified and tested in a sequential, hierarchical manner to preserve overall type I error (false-positive) at $\leq 5\%$. Apixaban was tested compared to enoxaparin/warfarin for: (1) non-inferiority on the composite endpoint of VTE/VTE-related death, (2) superiority on major bleeding, (3) superiority on the composite endpoint of VTE/VTE-related death, and (4) superiority on the composite of major/CRNM bleeding.³

In patients with DVT and/or PE, **ELIQUIS** demonstrated **STATISTICAL SUPERIORITY** to **enoxaparin/warfarin** for the primary safety endpoint of major bleeding^{3,6*}



Major bleeding

**69%
RRR**

RR 0.3
95% CI: 0.17-0.55,
 $p < 0.0001$

Adapted from Agnelli G *et al.*⁶

Adverse reactions related to bleeding occurred in 15.6% of ELIQUIS-treated patients vs. 24.6% of enoxaparin/warfarin-treated patients in AMPLIFY. Common adverse reactions with ELIQUIS were epistaxis (2.9%), contusion (1.8%), hematuria (1.7%), menorrhagia (1.4%), hematoma (1.3%), hemoptysis (1.2%), gingival bleeding (1.0%) and rectal hemorrhage (1.0%).³

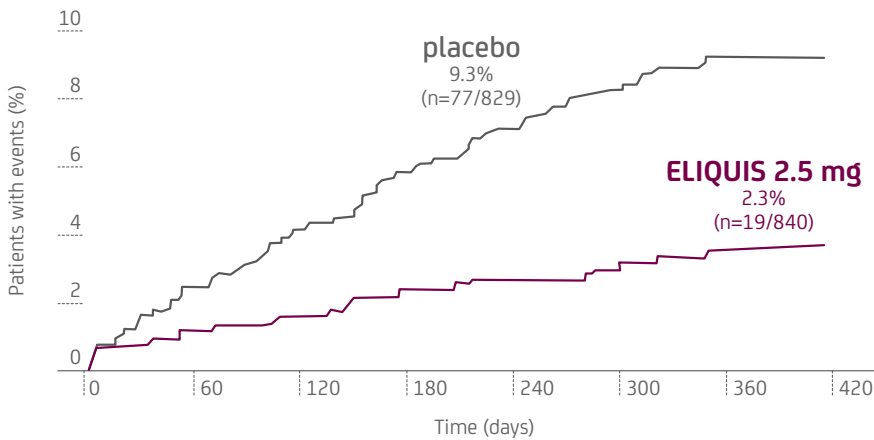
* Major bleeding was defined as bleeding that was overt and associated with a decrease in the hemoglobin level of ≥ 2 g/dL, required the transfusion of ≥ 2 units of blood, occurred into a critical site, or contributed to death.⁶

ELIQUIS was demonstrated to be **SUPERIOR** to **placebo** for the primary efficacy endpoint of the prevention of combined recurrent symptomatic VTE or all-cause death^{3,6*}

Symptomatic VTE or all-cause death

**76%
RRR**

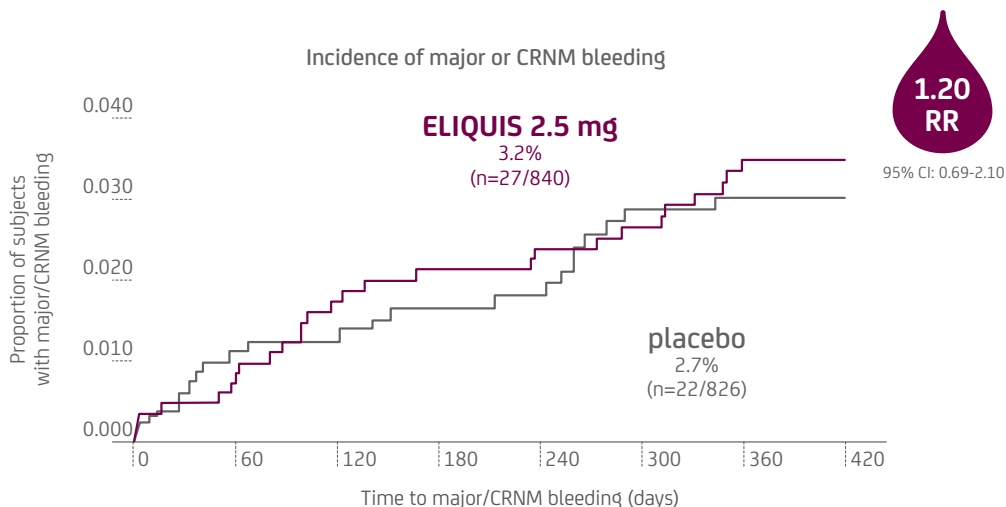
RR 0.24
95% CI: 0.15-0.40,
 $p < 0.0001$
for superiority



Adapted from Product Monograph³

* Patients were randomized to treatment with apixaban 2.5 mg BID, apixaban 5 mg BID, or placebo for 12 months after completing 6 to 12 months of initial anticoagulant treatment. The recommended dose for the continued prevention of recurrent DVT and PE is 2.5 mg BID. Approximately one third of patients participated in the AMPLIFY study prior to enrolment in the AMPLIFY-EXT study. The primary objective of the study was to determine if apixaban was superior to placebo in the combined endpoint of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or all-cause death.³

ELIQUIS was shown **NOT** to be **STATISTICALLY SIGNIFICANTLY DIFFERENT** to **placebo** for the secondary safety endpoint of major bleeding/CRNM bleeding^{3*}



In patients with symptomatic DVT or PE who have undergone ≥6 months of anticoagulant therapy

The number of patients who would need to be treated with apixaban 2.5 mg (for 1 year) to:

Prevent 1 episode of recurrent VTE (fatal or non-fatal) ▶ **14**

Prevent 1 episode of recurrent VTE or VTE-related death (secondary endpoint): ▶ **14**

Patients with events: 1.7% for ELIQUIS 2.5 mg vs. 8.8% for placebo, RR 0.19 (95% CI: 0.11-0.33, p<0.0001)

Adapted from Agnelli G et al.⁷

Adverse reactions related to bleeding occurred in 13.3% of ELIQUIS-treated patients vs. 8.7% of placebo-treated patients in AMPLIFY-EXT. Common adverse reactions with ELIQUIS in AMPLIFY-EXT were epistaxis (2.5%), hematuria (1.7%), contusion (1.6%), hematoma (1.6%), gingival bleeding (1.3%) and menorrhagia (1.0%).³

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Clinical use:

Safety and efficacy not established in pediatric patients (<18 years); therefore, Health Canada has not authorized an indication for pediatric use.

Contraindications:

- Clinically significant active bleeding, including gastrointestinal bleeding
- Lesions or conditions at increased risk of clinically significant bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Concomitant systemic treatment with strong inhibitors of **both** CYP3A4 and P-glycoprotein
- Concomitant treatment with any other anticoagulant including unfractionated heparin, except at doses used to maintain a patent central venous or arterial catheter, low molecular weight heparins, such as enoxaparin and dalteparin, heparin derivatives, such as fondaparinux, and oral anticoagulants, such as warfarin, dabigatran, rivaroxaban, except under circumstances of switching therapy to or from apixaban

Most serious warnings and precautions:

- **Bleeding:** if severe, discontinue
- **Peri-operative spinal/epidural anesthesia, lumbar puncture:** increased risk of hematoma
- **INR monitoring:** not a valid measure to assess anticoagulant activity of ELIQUIS
- **Premature discontinuation:** increases risk of thrombotic events

Other relevant warnings and precautions:

- Caution when used with drugs that affect hemostasis
- Not recommended in patients with prosthetic heart valves or with hemodynamically significant rheumatic heart disease, especially mitral stenosis
- Avoid use with strong inducers of both CYP3A4 and P-gp
- Caution in patients with mild or moderate hepatic impairment (not recommended if severe) or elevated liver enzymes
- Caution in patients ≥ 75 years in the treatment of DVT and PE and prevention of recurrent DVT and PE
- Pre-operative/post-operative considerations
- Not recommended as an alternative to unfractionated heparin for the treatment of VTE in patients with pulmonary embolism who are hemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy
- Not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (APS)
- Renal impairment: not recommended if creatinine clearance < 15 mL/min or dialysis; dosing adjustments may be required; renal function should be monitored
- Not recommended in pregnant or nursing women
- Hip fracture surgery patients

For more information:

Please consult the Product Monograph at https://www.bms.com/assets/bms/ca/documents/productmonograph/ELIQUIS_EN_PM.pdf or <https://www.pfizer.ca/pm/en/eliquis.pdf> for important information relating to adverse reactions, drug interactions and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling 1-866-463-6267.

References: 1. IQVIA, Compuscript, June 2020. 2. Data on file. BMS Medical letter, dated October 18, 2018. 3. ELIQUIS Product Monograph. Pfizer Canada ULC and Bristol-Myers Squibb Canada Co. 4. Granger CB *et al.*; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92. 5. Connolly SJ *et al.*; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364:806-17. 6. Agnelli G *et al.*; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799-808. 7. Agnelli G *et al.*; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;368:699-708.

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