

# In A Subanalysis, The Benefits Of Eliquis® (apixaban) Vs. Warfarin In Reducing The Risk Of Stroke In Patients With Nonvalvular Atrial Fibrillation Were Consistent, Regardless Of Blood Pressure Control 1

Thursday, March 27, 2014 - 04:14am

Blood Pressure Control Key Factor in Stroke Risk

[Bristol-Myers Squibb Company](#) (NYSE: BMY) and [Pfizer Inc.](#) (NYSE: PFE) today announced the results of a pre-specified subanalysis of the Phase 3 ARISTOTLE trial that assessed the effect of blood pressure control on outcomes as well as the treatment effect of *Eliquis* (apixaban) compared to warfarin according to blood pressure control.<sup>1</sup> The results showed that poor blood pressure control was associated with a substantially higher risk of stroke or systemic embolism, independent of *Eliquis* or warfarin treatment. However, this subanalysis found consistent results for *Eliquis* versus warfarin in reducing the risk of stroke, regardless of blood pressure control.<sup>1</sup> These data will be presented Saturday, March 29, at the American College of Cardiology's (ACC) 63rd Annual Scientific Session in Washington, D.C.

“High blood pressure is a risk factor for stroke in patients with atrial fibrillation. In this analysis, poorly controlled blood pressure at any time during the trial increased the risk of stroke by approximately 50 percent. The results for apixaban compared to warfarin in reducing the risk of stroke were consistent regardless of blood pressure,” said study lead author Meena Rao, MD, MPH, Duke Clinical Research Institute at Duke University Medical Center. “These data highlight the critical importance of blood pressure control in addition to anticoagulation in helping to lower the risk of stroke in patients with atrial fibrillation.”

In ARISTOTLE, a total of 15,916 (87.5 percent) patients had a history of hypertension requiring treatment. During the trial, 50 percent of patients had poorly controlled hypertension (defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg) at some point. Poorly controlled hypertension during the course of the trial was associated with a significant 53 percent increase in the risk of stroke or systemic embolism. *Eliquis* was consistent in reducing the risk of stroke or systemic embolism versus warfarin in patients with and without poor blood pressure control during the trial (p for interaction = 0.97).<sup>1</sup>

In this subanalysis, the effect of *Eliquis* in reducing the risk of stroke and systemic embolism versus warfarin was consistent with the main results of the ARISTOTLE trial. Further, the effect of *Eliquis* in reducing the risk of stroke and systemic embolism versus warfarin was also consistent with the results of the ARISTOTLE trial in previously published subanalyses of other comorbidities, including congestive heart failure, advanced age, renal

impairment and prior stroke.

A total of 11 Bristol-Myers Squibb/Pfizer alliance-sponsored abstracts, including this ARISTOTLE subanalysis, were accepted for presentation at the American College of Cardiology's 63rd Annual Scientific Session.

## **INDICATION**

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

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

## **IMPORTANT SAFETY INFORMATION**

### **WARNINGS: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA**

**(A) Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.**

**(B) When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids, or Factor Xa inhibitors for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.**

**The risk of these events may be increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.**

**Monitor patients for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary. Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis**

## **CONTRAINDICATIONS**

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

## **WARNINGS AND PRECAUTIONS**

- **Increased Risk of Stroke with Discontinuation of ELIQUIS in Patients with Nonvalvular Atrial Fibrillation:** Discontinuing 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 patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, 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 anti-platelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs. Patients should be made aware of signs or symptoms of blood loss and instructed to immediately report to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
- There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations.
- **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.

## ADVERSE REACTIONS

The most common and most serious adverse reactions reported with ELIQUIS (apixaban) 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

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. For patients receiving 5 mg twice daily, the dose of ELIQUIS should be decreased when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke.
- **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 CATEGORY B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

**Please see full Prescribing Information, including BOXED WARNINGS and Medication Guide, available at [www.bms.com](http://www.bms.com).**

### **About ARISTOTLE**

The ARISTOTLE study was designed to evaluate the efficacy and safety of *Eliquis* versus warfarin for the prevention of stroke or systemic embolism. In ARISTOTLE, 18,201 patients were randomized (9,120 patients to *Eliquis* and 9,081 to warfarin). ARISTOTLE was an active-controlled, randomized, double-blind, multi-national trial in patients with nonvalvular atrial fibrillation or atrial flutter, and at least one additional risk factor for stroke. Patients were randomized to treatment with *Eliquis* 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, representing 4.7 percent of all patients) or warfarin (target INR range 2.0-3.0), and followed for a median of 1.8 years.

### **About Atrial Fibrillation**

Atrial fibrillation is the most common cardiac arrhythmia (irregular heartbeat). It is estimated that approximately 5.8 million Americans and six million individuals in Europe have atrial fibrillation. The lifetime risk of developing atrial fibrillation is estimated to be approximately 25 percent for individuals 40 years of age or older. One of the most serious medical concerns for individuals with atrial fibrillation is the increased risk of stroke, which is five times higher in people with atrial fibrillation than those without atrial fibrillation. In fact, 15 percent of all strokes are attributable to atrial fibrillation in the U.S. Additionally, strokes due to atrial fibrillation are more burdensome than strokes due to other causes. Atrial fibrillation-related strokes are more severe than other strokes, with an associated 30-day mortality of 24 percent and a 50 percent likelihood of death within one year in patients who are not treated with an antithrombotic.

### **About *Eliquis*®**

*Eliquis* (apixaban) is an oral selective Factor Xa inhibitor. By inhibiting Factor Xa, a key blood clotting protein, *Eliquis* decreases thrombin generation and blood clot formation. *Eliquis* is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery.

### **About the Bristol-Myers Squibb/Pfizer Collaboration**

In 2007, Pfizer and Bristol-Myers Squibb entered into a worldwide collaboration to develop and commercialize *Eliquis*, an oral anticoagulant discovered by Bristol-Myers Squibb. This global alliance combines Bristol-Myers Squibb's long-standing strengths in cardiovascular drug development and commercialization with Pfizer's global scale and expertise in this field.

### **About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit <http://www.bms.com> or follow us on Twitter at <http://twitter.com/bmsnews>.

**About Pfizer Inc.: Working together for a healthier world™**

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, Pfizer has worked to make a difference for all who rely on us. To learn more, please visit us at [www.pfizer.com](http://www.pfizer.com).

<sup>1</sup> Rao M, et al. Poorly Controlled Blood Pressure is Independently Associated with a 50% Higher Risk of Stroke or Systemic Embolism in Patients with Atrial Fibrillation. Poster presented at: American College of Cardiology 2014 Scientific Session; March 29, 2014; Washington, DC.

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