



# Bristol-Myers Squibb and Pfizer Present Large Real-World Observational Analysis of the Effectiveness and Safety of Direct Oral Anticoagulants Compared to Warfarin in Patients with Non-Valvular Atrial Fibrillation

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In this U.S. Medicare database analysis, Eliquis® (apixaban) was associated with significantly lower risk of stroke or systemic embolism and lower rate of major bleeding compared to warfarin

Bristol-Myers Squibb Company (NYSE:BMJ) and Pfizer Inc. (NYSE:PFE) today announced findings from a real-world data analysis of the U.S. Medicare database comparing the risk of stroke or systemic embolism and rate of major bleeding among patients with non-valvular atrial fibrillation who were treated with direct oral anticoagulants versus warfarin. In the analysis, titled Effectiveness and Safety of Apixaban, Dabigatran, and Rivaroxaban Compared to Warfarin among Non-Valvular Atrial Fibrillation Patients in the U.S. Medicare Population, Eliquis® (apixaban) was associated with a significantly lower risk of stroke or systemic embolism and lower rate of major bleeding compared to warfarin.<sup>i</sup> These data, which supplement results from randomized trials, are being presented at the American College of Cardiology's (ACC) 66th Annual Scientific Session in Washington, D.C.

In this observational analysis, medical and pharmacy claims were evaluated from the U.S. Medicare fee-for-service database of non-valvular atrial fibrillation patients age 65 and older who were newly prescribed oral anticoagulation therapy between January 1, 2013, and December 31, 2014 (n=186,132, following inclusion and exclusion criteria). The analysis included 41,606 patients treated with Eliquis or warfarin (20,803 patients each in the Eliquis and warfarin cohorts), balanced according to select demographic and clinical characteristics. The matched Eliquis-warfarin cohorts, followed for a mean of 5.7 and 6.5 months, respectively, had a mean age of 78 years, a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 4.6 and 4.7, respectively, and a HAS-BLED score of 3.3. CHA<sub>2</sub>DS<sub>2</sub>-VASc score is a method for estimating stroke risk in patients with atrial fibrillation, and HAS-BLED score helps to estimate risk of major bleeding in patients with atrial fibrillation. Real-world data analyses cannot be used as stand-alone evidence to validate the efficacy and/or safety of a treatment. Observational real-world studies can only evaluate association and not causality.<sup>ii,iii</sup> Please see full methodology and additional limitations below.

“Studies such as this large U.S. Medicare database analysis supplement pivotal trials by broadening and deepening our scientific knowledge of how patients respond to direct oral anticoagulants in everyday clinical practice,” said Alpesh Amin, M.D., principal investigator and Professor of Medicine, University of California, Irvine. “Given the diversity of patients with non-valvular atrial fibrillation, analyses of real-world data provide further information that adds to data generated in randomized clinical trials.”

Eliquis, in this analysis, was associated with a significantly lower risk of stroke or systemic embolism (HR: 0.40, 95% CI: 0.31-0.53; p<0.0001) and lower rate of major bleeding (HR: 0.51, 95% CI: 0.44-0.58; p<0.0001) than patients treated with warfarin. The findings from the Eliquis-warfarin cohort complement the results of the randomized Phase 3 ARISTOTLE (Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.<sup>iv</sup> For data on other cohorts, please refer to the full abstract.

“The U.S. Medicare system currently covers more than 57 million Americans,<sup>v</sup> including over two million who have been treated with anticoagulants,” said Rory O’Connor, M.D., Chief Medical Officer, Pfizer Innovative Health. “Increasingly, real-world data analyses are being utilized to enhance the understanding of data associated with health interventions. With the advent of large, representative and anonymized datasets, such as records from the Centers for Medicare & Medicaid Services, we can provide additional information that clinicians can use in their treatment decisions.”

“The Bristol-Myers Squibb and Pfizer Alliance continues to invest heavily in research analyses that provide more information on care for patients with non-valvular atrial

fibrillation,” said Christoph Koenen, M.D., MBA, VP, Development Lead, Eliquis, Bristol-Myers Squibb. “Our real-world data program – ACROPOLIS™ – aims to generate evidence from routine clinical practice settings by analyzing patient databases around the world, including medical records, medical and pharmacy health insurance claims data and national health data systems.”

## Methodology

In addition to the apixaban cohort, this analysis of the U.S. Medicare database included cohorts comparing two other direct oral anticoagulants (rivaroxaban and dabigatran) separately with warfarin. The analysis was conducted in patients age 65 and older with non-valvular atrial fibrillation who had not received an oral anticoagulant for at least one year. Patients had to have continuous health plan enrollment with medical and pharmacy benefits for at least 12 months pre-index date. Patients with evidence of valvular heart disease, transient atrial fibrillation, venous thromboembolism, valve replacement or surgery or indication of pregnancy 12 months prior to the index date were excluded.

This analysis was designed according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for comparative effectiveness research, which include recommendations for research question development, transparency of analytical plans and control of confounding factors.<sup>vi,vii,viii</sup> One-to-one propensity score matching methodology (PSM) was applied in the analysis to balance select demographic and clinical characteristics. Cox proportional hazards models were used to estimate the hazard ratio (HR) of stroke/systemic embolism and major bleeding using primary ICD-9 codes of inpatient claims.

## Limitations of Real-World Data Analyses and of the U.S. Medicare Database Analysis

Real-world data have the potential to supplement randomized clinical trial data by providing additional information about how a medicine performs in routine medical practice. Real-world data analyses have several limitations. For example, the source and type of data used may limit the generalizability of the results and of the endpoints. It is important to note that there are no head-to-head clinical trials comparing direct oral anticoagulants.

In the U.S. Medicare database analysis, laboratory results and time in therapeutic range information were not available. Diagnoses were identified through ICD-9 codes, and drug prescriptions were identified through prescription claims. PSM methodology was used to mimic randomization by balancing pre-defined demographic and clinical characteristics at baseline for both treatment cohorts. As an observational study using PSM, unobserved

cofounders (e.g., laboratory values and patient preferences) may exist for which the analysis did not control. As with any real-world data analysis, missing values, coding errors and lack of clinical accuracy may have introduced bias.

Due to these limitations, real-world data analyses cannot be used as stand-alone evidence to validate the efficacy and/or safety of a treatment. Observational real-world studies can only evaluate association and not causality.<sup>ii,iii</sup>

## 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 for multiple indications in the U.S. based on efficacy and safety data from seven Phase 3 clinical trials. Eliquis is a prescription medicine indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAf); 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; for the treatment of DVT and PE; and to reduce the risk of recurrent DVT and PE, following initial therapy.

## ELIQUIS 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. 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. **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours. Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients. **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients. **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of

patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

## ADVERSE REACTIONS

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

## TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

## DRUG INTERACTIONS

**Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) 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 strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS 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 and other thromboembolic events. **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 ACROPOLIS™

ACROPOLIS™ (Apixaban ExperienCe Through Real-WOrld POpuLatlon Studies) is the Eliquis (apixaban) global real-world data program designed to generate additional evidence from routine clinical practice settings to further inform healthcare decision makers, including healthcare providers and payers. The ACROPOLIS program will include retrospective, outcomes-based analyses from over 10 databases around the world, including medical records, medical and pharmacy health insurance claims data, and national health data systems.

Analyses of real-world data allow for a broader understanding of patient outcomes associated with Eliquis outside of the clinical trial setting, as well as insight into other measures of healthcare delivery, such as hospitalization and costs.

#### About ARISTOTLE

ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboemboLic Events in Atrial Fibrillation) 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 the Bristol-Myers Squibb/Pfizer Collaboration

In 2007, Pfizer and Bristol-Myers Squibb entered into a worldwide collaboration to develop and commercialize apixaban, 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 about Bristol-Myers Squibb, visit us at [BMS.com](http://BMS.com) or follow us on LinkedIn, Twitter, YouTube and Facebook.

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, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at [www.pfizer.com](http://www.pfizer.com). In addition, to learn more, please visit us on [www.pfizer.com](http://www.pfizer.com) and follow us on Twitter at @Pfizer and @PfizerNews, LinkedIn, YouTube and like us on Facebook at [Facebook.com/Pfizer](https://www.facebook.com/Pfizer).

#### Bristol-Myers Squibb Forward-Looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2016, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

#### Pfizer Disclosure Notice

The information contained in this release is as of March 17, 2017. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of



new information or future events or developments.

This release contains forward-looking information about Eliquis (apixaban), including its potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including, without limitation, the ability to meet anticipated clinical trial commencement and completion dates as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of Eliquis; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the SEC and available at [www.sec.gov](http://www.sec.gov) and [www.pfizer.com](http://www.pfizer.com).

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