Clinical Trial Data Can Be Supplemented by Real-world Evidence: An Example for an Oral Anticoagulant in Patients With Nonvalvular Atrial Fibrillation at Risk of Stroke

This article was developed in conjunction with and paid for by Bristol Myers Squibb and Pfizer.

BACKGROUND

Atrial fibrillation (AF) is the most common form of heart arrhythmia.[1] In 2022, approximately 9 million people in the United States are projected to have AF.[2] This number is expected to increase to approximately 12.1 million in 2030.[2] AF is associated with a near 5-fold increase in the risk of stroke and is often accompanied by cardiac comorbidities such as ischemic heart disease and congestive heart failure (CHF).[3,4] The majority of patients with AF are diagnosed with nonvalvular atrial fibrillation (NVAF), which excludes moderate-severe mitral valve stenosis and mechanical heart valve, among others.[5,6]

Although various medications are prescribed to help reduce the risk of stroke in those diagnosed with NVAF, this piece will focus on the efficacy and safety of one of the direct oral anticoagulants (DOACs). Currently, 4 DOACs have been approved in the United States (2010-2015) for various indications, including to reduce the risk of stroke and systemic embolism (SE) in patients with NVAF.[7-10] ELIQUIS® (apixaban)

INDICATION

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

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.

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is 1 of these 4 agents and was approved in the United States in 2012 to reduce the risk of stroke and SE in patients with NVAF.[7] This piece will show one example of how real-world evidence (RWE) may provide additional information about the effectiveness and safety associated with a product, in addition to randomized clinical trial (RCT) information. We will review the ARISTOLE pivotal clinical trial data for ELIQUIS and one observational retrospective real-world pooled analysis that evaluated the effectiveness and safety of ELIQUIS in the real world. Additionally, this piece will provide some background on real world evidence in general, as well as potential uses to help inform clinical and formulary decisions.

ARISTOTLE TRIAL: ELIQUIS (APIXABAN) VERSUS WARFARIN

ARISTOTLE was a pivotal phase 3, double-blind, randomized trial of 18,201 patients with NVAF, comparing ELIQUIS versus warfarin.[7,11] The primary efficacy endpoint was to determine whether ELIQUIS was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) and SE, while the primary safety endpoint was major bleeding events. The key secondary objectives were to determine whether ELIQUIS was superior to warfarin with respect to the primary outcome and to the rates of major bleeding and death from any cause.[11] Major bleeding was defined as clinically overt bleeding accompanied by at least 1 of the following: (1) a decrease in hemoglobin of at least 2 g/dL; (2) transfusion of at least 2 units of packed red blood cells; (3) bleeding that occurred in at least 1 of the following critical sites: intracranial[a], intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or (4) fatal bleeding.[7]

Key inclusion criteria consisted of NVAF and at least 1 risk factor for stroke: prior stroke, transient ischemic attack, or SE; age greater than or equal to 75 years; arterial hypertension requiring treatment; diabetes mellitus; heart failure greater than or equal to New York Heart Association Class 2; and decreased left ventricular ejection fraction less than or equal to 40%.[7,11] Key exclusion criteria consisted of AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF that required anticoagulation (e.g., a prosthetic heart valve), stroke within the previous 7 days, a need for aspirin at a dose of greater than 165 mg a day or for both aspirin and clopidogrel, and severe renal insufficiency (serum creatinine level of greater than 2.5 mg/dL or calculated creatinine clearance of less than 25 mL/min).[11] Subjects were randomized to receive either ELIQUIS at a dose of 5 mg or 2.5 mg twice daily (approximately 95% received 5 mg twice daily; n = 9120) or warfarin (target international normalized ratio, 2.0-3.0; n = 9081).[7,11] A dose of 2.5 mg twice daily of ELIQUIS was assigned to patients with at least 2 of the following characteristics: age at least 80 years, body weight less than or equal to 60 kg, or serum creatinine at least 1.5 mg/dL. Median follow-up was about 1.7 years.[7] The baseline characteristics of the 2 treatment groups were well balanced, including age, stroke risk based on $CHADS_2$ score,[b] and prior vitamin K antagonist (VKA) experience.[11]

Efficacy and Safety Data

In patients with NVAF, ELIQUIS demonstrated superiority in both stroke/SE and major bleeding versus warfarin (**FIGURE 1**).[7] The primary efficacy endpoint of stroke/SE demonstrated a significantly lower event rate for ELIQUIS versus warfarin: 1.27%/yr versus 1.60%/yr (HR = 0.79; 95% CI, 0.66-0.95; $P = 0.01$). The primary safety endpoint of major bleeding events demonstrated a significantly lower event rate for ELIQUIS versus warfarin: 2.13%/yr versus 3.09%/yr (HR = 0.69; 95% CI, 0.60-0.80; $P < 0.0001$).[7] Please note, ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

[a]Intracranial bleeding included intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as intracranial major bleeding.

[b]Scale from 0 to 6 to estimate stroke risk, with higher scores predicting greater risk.

IMPORTANT SAFETY INFORMATION (*continued*)

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.

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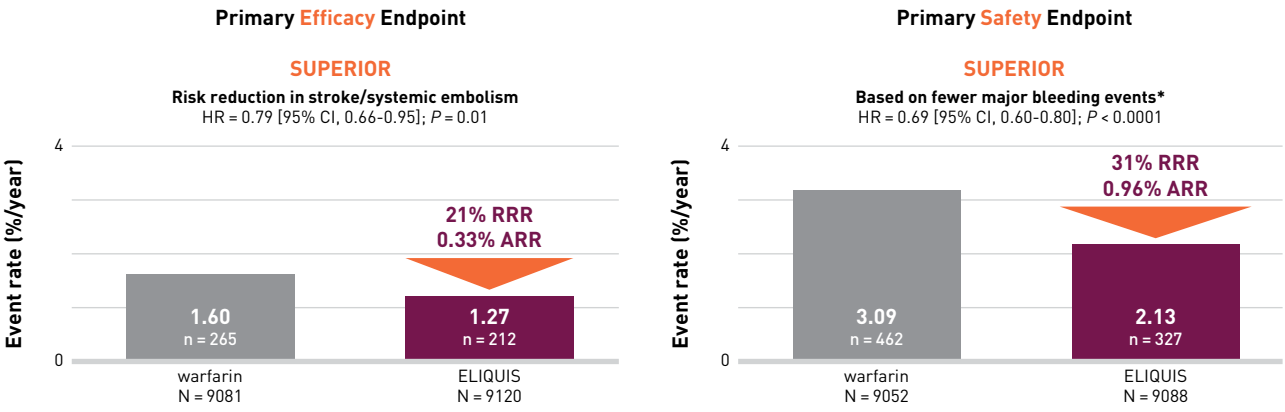
FIGURE 1. ARISTOTLE: Primary Efficacy and Safety Endpoints[7]



ELIQUIS (apixaban) increases the risk of bleeding and can cause serious, potentially fatal, bleeding

- Superiority to warfarin was primarily attributed to a reduction in hemorrhagic stroke (0.24%/yr [n = 40/9120] ELIQUIS vs 0.47%/yr [n = 78/9081] warfarin, HR = 0.51 [95% CI: 0.35-0.75]) and ischemic strokes with hemorrhagic conversion (0.07%/yr [n = 12/9120] ELIQUIS vs 0.12%/yr [n = 20/9081] warfarin, HR = 0.60 [95% CI: 0.29-1.23]) compared with warfarin. Purely ischemic strokes (0.83%/yr [n = 140/9120] ELIQUIS vs 0.82%/yr [n = 136/9081] warfarin, HR = 1.02 [95% CI: 0.81-1.29]) occurred with similar rates on both drugs
- In another clinical trial (AVERROES), ELIQUIS was associated with an increase in major bleeding compared with aspirin that was not statistically significant (1.41%/yr vs 0.92%/yr, 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

*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.

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

IMPORTANT SAFETY INFORMATION (*continued*)

WARNINGS AND PRECAUTIONS (*continued*)

- **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.

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Additionally, ELIQUIS (apixaban) demonstrated a superior reduction in the risk of death versus warfarin (3.52%/yr [n = 603/9120] vs 3.94%/yr [n = 669/9081], HR = 0.89; 95% CI, 0.80-0.998; $P = 0.046$).[7,11] Cardiovascular deaths (1.80%/yr vs 2.02%/yr, 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 versus warfarin.[11,12] The incidence of nonvascular mortality was similar in patients taking ELIQUIS to that in patients taking warfarin (1.14%/yr vs 1.22%/yr, HR = 0.93; 95% CI, 0.77-1.13).[11]

ELIQUIS demonstrated lower rates in select bleeding outcomes versus warfarin (**FIGURE 2**), including significantly fewer intracranial hemorrhage (ICH) events (ELIQUIS vs warfarin: 0.33%/yr vs 0.82%/yr, HR = 0.41; 95% CI, 0.30-0.57) and significantly fewer fatal bleeding events (ELIQUIS vs warfarin: 0.06%/yr vs 0.24%/yr, HR = 0.27; 95% CI, 0.13-0.53).[7,13,14] There were also fewer gastrointestinal bleeding events versus warfarin (ELIQUIS vs warfarin: 0.83%/yr vs 0.93%/yr, HR = 0.89; 95% CI, 0.70-1.14), but the difference was not statistically significant.[7] Additionally, there were numerically higher rates of intraocular bleeding events versus warfarin (ELIQUIS vs warfarin: 0.21%/yr vs 0.14%/yr, HR = 1.42; 95% CI, 0.83-2.45).[13] Specifically, for the components of ICH events, there were fewer hemorrhagic stroke and other ICH events for ELIQUIS versus warfarin:

- Hemorrhagic stroke[c]: 0.24%/yr (n = 38/9088) versus 0.49%/yr (n = 74/9052), HR = 0.51; 95% CI, 0.34-0.75[7]
- Other ICH: 0.10%/yr (n = 15/9088) versus 0.34%/yr (n = 51/9052), HR = 0.29; 95% CI, 0.16-0.51[7]

Specifically, for the components of fatal bleeding, there were fewer intracranial and nonintracranial events for ELIQUIS versus warfarin:

- Intracranial: 0.03%/yr (n = 4/9088) versus 0.20%/yr (n = 30/9052), HR = 0.13; 95% CI, 0.05-0.37[7]
- Nonintracranial: 0.04%/yr (n = 6/9088) versus 0.05%/yr (n = 7/9052), HR = 0.84; 95% CI, 0.28-2.15[7]

ELIQUIS resulted in significantly fewer clinically relevant nonmajor bleeding (CRNM) events compared with warfarin (2.08%/yr [n = 318/9088] vs 3.00%/yr [n = 444/9052], HR = 0.70; 95% CI, 0.60-0.80; $P < 0.0001$).[14] CRNM was defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy.[11]

AVERROES TRIAL STUDY DESIGN

Another study, AVERROES, was a phase 3, double-blind, RCT, designed to compare the effects of ELIQUIS (2.5 mg[d] or 5 mg twice daily, n = 2807) or aspirin (81 mg to 324 mg once daily, n = 2791) in reducing the risk of stroke and SE in 5598 patients with NVAF thought not to be candidates for warfarin therapy. The primary efficacy endpoint was the occurrence of stroke or SE, while the primary safety endpoint was major bleeding.[15] Participants had at least 1 risk factor for stroke, including prior stroke or transient ischemic attack, age 75 years or older, arterial hypertension (receiving treatment), diabetes mellitus (receiving treatment), heart failure greater than or equal to New York Heart Association Class 2 at the time of enrollment, and left ventricular ejection fraction less than or equal to 35%, or documented peripheral artery disease.[7,15] Patients could not be receiving VKA therapy (e.g., warfarin), either because it had already been demonstrated or expected to be unsuitable to them.[7,15] The 2 treatment groups were well balanced with respect to baseline characteristics, including age, stroke risk at entry as measured by $CHADS_2$ score,[e] and prior use of

[c]On-treatment analysis based on the safety population, compared to intent-to-treat analysis presented in efficacy population.

[d]A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: age at least 80 years, body weight less than or equal to 60 kg, or serum creatinine at least 1.5 mg/dL.

[e]Scale from 0 to 6 to estimate stroke risk, with higher scores predicting greater risk.

IMPORTANT SAFETY INFORMATION (*continued*)

WARNINGS AND PRECAUTIONS (*continued*)

- **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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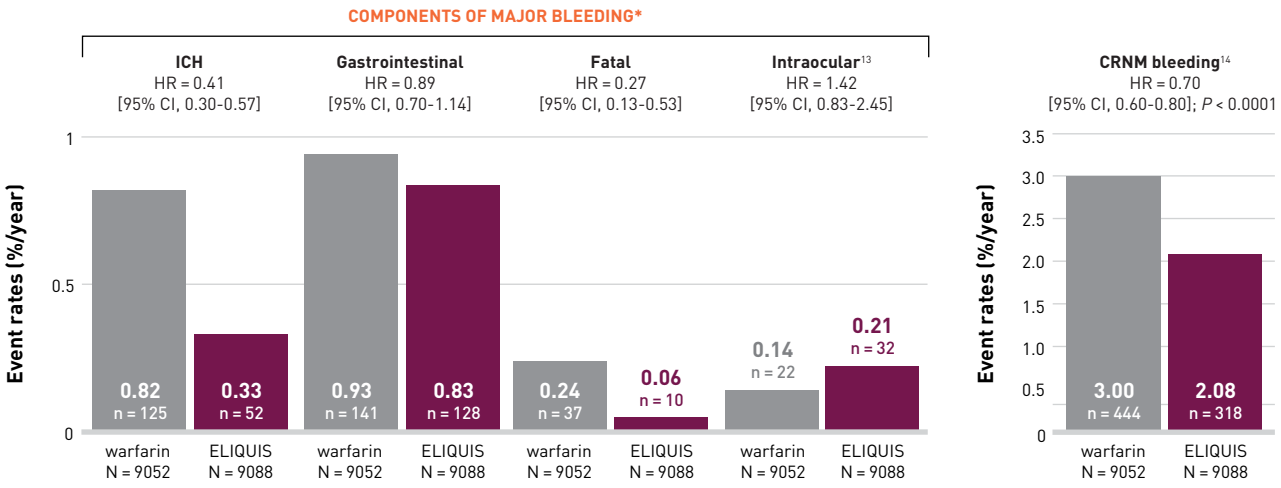
FIGURE 2. ARISTOTLE: Bleeding Components[7,13,14]*



ELIQUIS (apixaban) 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%/yr vs 0.92%/yr, HR = 1.54 [95% CI: 0.96-2.45]; *P* = 0.07)
- The most common reason for treatment discontinuation in ARISTOTLE and AVERROES was for 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

*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.

CI = confidence interval; CRNM = clinically relevant nonmajor; HR = hazard ratio; ICH = intracranial hemorrhage.

IMPORTANT SAFETY INFORMATION (*continued*)

WARNINGS AND PRECAUTIONS (*continued*)

- **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.

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VKA within 30 days before screening. The mean follow-up period was approximately 1.1 years.[15]

RANDOMIZED CLINICAL TRIALS VERSUS REAL-WORLD EVIDENCE

RCTs are considered the gold standard in evaluating the efficacy and safety of therapeutic interventions and are designed to show causality.[16,17] Some strengths of RCTs include randomization to minimize bias/confounding, prospective design with prespecified endpoints, blinding, and high integrity of data, all leading to high acceptance by decision makers.[16,18] However, certain patient populations may be underrepresented in RCTs, given the highly controlled environment and explicit exclusion criteria.[17,19] RWE can help address this information gap by evaluating how an intervention works in a large array of patients.[17]

While RCTs provide the highest level of evidence for drug efficacy and safety, RWE can be used to evaluate treatment effectiveness, safety, and other clinical and economic outcomes observed in routine clinical practice.[16,20] Real-world data (RWD) is data acquired from sources outside of RCTs, including electronic medical records (EMRs), administrative claims data, registries, hospital claims data, and health surveys.[20,21] Results from the analysis of RWD comprise RWE and may be used to supplement RCTs to help inform decision making for clinicians.[20,22] For example, RWE can serve to bridge the gap between RCTs and real-world clinical practice[20] by analyzing treatment effectiveness,[23] including a larger population, investigating adherence and persistence, and analyzing treatment patterns across certain conditions.[16,21] RWE studies are usually observational or noninterventional studies that can be prospective or retrospective.[16]

Given the growing interest in RWE and pursuant to the 21st Century Cures Act, the US Food and Drug Administration (FDA) has created a framework for evaluating the potential use of RWE to help support the approval of a new indication in already-approved drugs and to help support or satisfy postapproval study requirements.[24,25]

Important limitations exist among RWE. Some challenges associated with RWE include identifying the right database for the analysis, designing the appropriate methodology, identifying the right data elements, and understanding differences in the description of a real-life event versus an event in a clinical trial.[21] Additionally, the source and type of data used may limit the generalizability of the findings.[26] Data quality is also a concern for RWE due to the fact that data collection is often not undertaken with the research purpose in mind and therefore inconsistent collection, misclassification of electronic data, and missing data are possibilities.[20,21] Finally, RWE studies are useful in evaluating associations but cannot determine causality regarding the effects of treatment, mainly because RWE studies lack randomization, subjecting them to the effects of confounding and various types of bias.[16,20]

Health care economic information (HCEI) can be based on RWD and can be used by formulary decision makers to help inform decisions on a population health basis. For example, HCEI can be useful to formulary decision makers in examining costs and utilization management based on claims, EMRs, charts, or registries.[20] Specifically, HCEI can provide a realistic estimate of the resource use and direct and indirect costs associated with therapy.[20]

Guidance has evolved to help ensure HCEI is used appropriately by formulary decision makers. When evaluating HCEI, the FDA considers existing current good research practices for substantiation developed by authoritative bodies such as International Society for Pharmacoeconomics and Outcomes Research, International Society for Pharmacoepidemiology, Patient-Centered Outcomes Research Institute, and Agency for Healthcare Research and Quality.[28]

While initial formulary coverage decisions are usually made before RWE studies are conducted, RWE can be used to inform future formulary placement decisions.[27] However, the time, resources, and skills needed to evaluate RWE within the full body of evidence of a given therapy may be a barrier to RWE use.[27]

FROM CLINICAL TRIALS TO THE CLINICAL SETTING: AN EXAMPLE OF A REAL-WORLD, OBSERVATIONAL, RETROSPECTIVE ANALYSIS

This piece features the ARISTOPHANES analysis, the largest retrospective, observational, real-world database analysis examining

IMPORTANT SAFETY INFORMATION (*continued*)

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.

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the rates of stroke/SE and major bleeding among commercial and Medicare patients with NVAF who initiated oral anticoagulants (OACs).[29] The results presented are only for ELIQUIS (apixaban) versus warfarin. The analysis, which was funded by BMS and Pfizer, evaluated data from the Centers for Medicare and Medicaid Services Fee-for-service Medicare data and 4 US commercial insurance claims databases that cover more than 180 million beneficiaries each year (approximately 56% of the population in the US).[29] It illustrates how RWE can supplement RCT results, in this case, related to the effectiveness and safety of ELIQUIS for stroke risk/SE reduction in patients with NVAF.

Objective and Methods of Analysis

The objective of this retrospective observational analysis was to compare rates of stroke/SE and major bleeding outcomes among a large number of patients with NVAF on newly prescribed OACs. The study included matched cohorts for all the OAC comparisons, although, as mentioned, only the ELIQUIS versus warfarin data will be discussed here. Data for this analysis is from patients identified between January 1, 2013, and September 30, 2015, from the US Centers for Medicare and Medicaid Services Fee-for-Service Medicare data, the Truven MarketScan Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database (MarketScan), the IMS PharMetrics Plus Database (PharMetrics), the Optum Clinformatics Data Mart (Optum), and the Humana Research Database (Humana).[29]

Patients with at least 1 pharmacy claim for ELIQUIS or warfarin during the study period were selected for inclusion. The first day of treatment was the index date. Patients were required to have an AF diagnosis, determined based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes, on or before the index date and have continuous medical and pharmacy health plan enrollment for at least 12 months prior to the index date.[29] Patients were excluded if they had been treated with any OAC within 12 months before the index date, evidence of valvular heart disease, venous thromboembolism, transient AF (pericarditis, hyperthyroidism, thyrotoxicity), or a heart valve replacement/transplant during the baseline period; pregnancy during the study; or hip or knee replacement surgery within 6 weeks prior to the index date.[29]

Outcome measures were time to first stroke/SE (including ischemic stroke, hemorrhagic stroke, and SE) and time to first major bleeding (including gastrointestinal bleeding, intracranial hemorrhage, and major bleeding at other locations). These were based on hospitalizations with stroke/SE or major bleeding as the principle or first listed diagnosis. Patients were followed from the day after the index date to the earliest of the following: switch date, death (only inpatient death for the commercial databases and all-cause death for Medicare database), 30 days after the discontinuation date, end of continuous medical or pharmacy plan enrollment, or end of study period. The mean follow-up was 187.6 days and 242.3 days for ELIQUIS and warfarin, respectively.[29]

One to one propensity score matching (PSM) was conducted to balance demographics and clinical characteristics. Subgroup analyses were also conducted, and the balance of baseline characteristics was evaluated and adjusted for if needed. Data not shown.[29] Cox proportional hazard models with robust sandwich estimates were used to compare the rate of stroke/SE and major bleeding in each PSM cohort. Sensitivity analyses were conducted for the primary analysis by restricting the follow-up period to 1 year to help balance the follow-up period between the cohorts. Multivariate Cox proportional hazards models were conducted on all the patients meeting eligibility criteria with all covariates used for propensity score estimation. Results of both were consistent with the main analysis.[29]

Limitations of Analyses

There are important limitations inherent to RWD analyses. Due to the nature of retrospective, observational cohort studies, no causal relations could be inferred, and only statistical associations were assessed. Diagnoses, outcomes, comorbidities, and components of

IMPORTANT SAFETY INFORMATION (*continued*)

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.

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risk scores were based on ICD-9-CM codes, which is different from the clinical trials and without further adjudication of outcomes using precise clinical criteria. The presence of a claim for a filled prescription does not indicate whether the medication was consumed or taken as prescribed. Also, there is no guarantee that patients were dosed according to the US prescribing information for ELIQUIS (apixaban) and warfarin.[29]

Although cohorts were propensity-score matched, potential residual confounders exist, which are not available in the dataset. Additionally, observed and unobserved heterogeneity may exist across the 5 data sources.[29]

Claims for laboratory values, such as international normalized ratio measurements, are not available in the database; therefore, the authors were unable to determine time in therapeutic range for patients who were prescribed warfarin. Creatinine measurements were not available to evaluate renal function. The claims databases, excluding Centers for Medicare and Medicaid Services Medicare data, did not include complete death information. There was no evaluation of the dose-reduction criteria for DOACs due to the absence of comprehensive data on body weight or serum creatinine/creatinine clearance. Additionally, use of over-the-counter aspirin and nonsteroidal anti-inflammatory drugs are not available in the database.[29]

Results may not be generalizable to the overall NVAF population in the US because the study did not include uninsured patients and patients solely covered by other public health insurance plans. The follow-up period was not uniform, which may have introduced bias into the results. Finally, compared with clinical trials, the average follow-up period for each cohort in this analysis was also shorter, which may impact the results.[29]

Effectiveness and Safety Results

For ELIQUIS versus warfarin, baseline characteristics after 1 to 1 PSM resulted in 100,977 matched pairs, with a mean age of 76.1 and 76 for ELIQUIS and warfarin, respectively, and a mean CHA_2DS_2-VASc score of 3.9. The effectiveness analysis for ELIQUIS versus warfarin yielded the following HR (95% CI): 0.64 (0.58-0.70) for the primary effectiveness outcome of stroke/SE (**FIGURE 3**).[29] The safety analysis for ELIQUIS versus warfarin yielded the following HR (95% CI): 0.60 (0.56-0.63) for the primary safety outcome of major bleeding (**FIGURE 4**).[29] The analysis also evaluated components of effectiveness and safety outcomes that are not included here.

Important to note, ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding. ELIQUIS is not indicated for the treatment of coronary artery disease with or without NVAF. Apparent homogeneity or heterogeneity across subgroups should not be overinterpreted. No adjustments for multiple comparisons were made. Formal power calculations for subgroup analyses were not performed. Some analyses may lack adequate power to detect significant differences. The definitions of stroke and major bleeding, follow-up period, and the patient population in ARISTOTLE were different than in these analyses.[7,11,29] Please note that retrospective, observational analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables; causality cannot be established in observational analyses.[30]

CLOSING REMARKS

Based on registrational clinical trials, ELIQUIS has been approved and indicated for patients with NVAF to reduce the risk of stroke/SE.[7-10] RWE may supplement RCT data and may be able to provide information about the heterogeneous patient populations that may be often underrepresented in clinical trials.[16] In addition to clinical trials, RWE-based analyses can be useful to stakeholders in the health care industry to help inform decision-making regarding clinical use and formulary decisions. The use of RWE is also becoming more widespread because massive amounts of RWD are electronically available today, and there is an increased ability to conduct quality analyses with these data.[20] RWE is not without limitations, including lack of randomization, introduction of bias and confounders, and inability to determine causality.[16,20] Also, RWD is not collected with

IMPORTANT SAFETY INFORMATION (*continued*)

DRUG INTERACTIONS (*continued*)

- **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 with 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.

Please see additional **Important Safety Information** on the following pages and click for **Full Prescribing Information**, including **Boxed WARNINGS.**

FIGURE 3. ARISTOPHANES: ELIQUIS Versus Warfarin, Effectiveness Outcome: Stroke/SE[29]

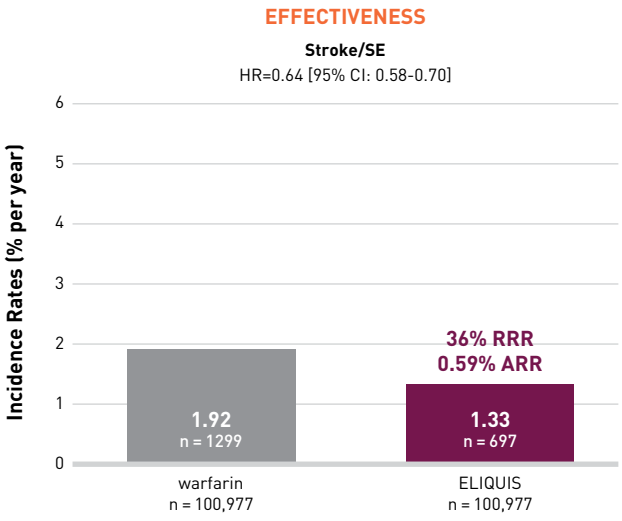
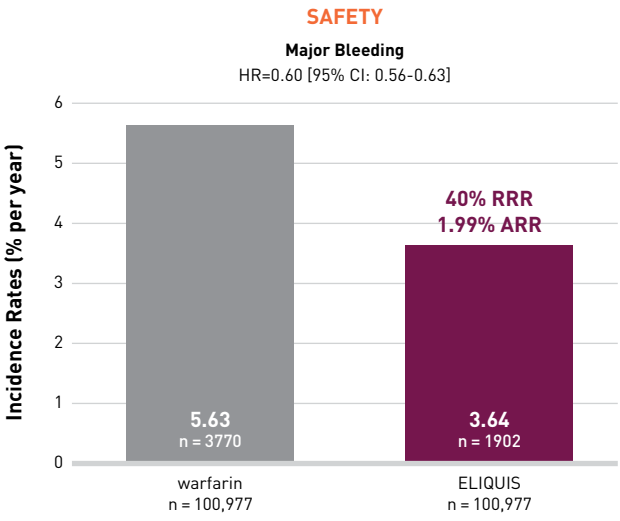


FIGURE 4. ARISTOPHANES: ELIQUIS Versus Warfarin, Safety Outcome: Major Bleeding[29]



Please note that ELIQUIS (apixaban) increases the risk of bleeding and can cause serious, potentially fatal, bleeding

The definitions of stroke and major bleeding, follow-up period, and the patient population in ARISTOTLE were different than in these analyses.

Retrospective, observational analyses are not intended for direct comparison with clinical trials and are designed to evaluate associations among variables; causality cannot be established in observational analyses.

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

research in mind, resulting in potential coding errors and missing data.[20,26] Additionally, guidelines for the use and interpretation of RWE continue to be developed.[28] Keeping these important limitations in mind, members of the health care community continue to utilize the information that can be collected and analyzed about product use, safety, and effectiveness. ●

IMPORTANT SAFETY INFORMATION (*continued*)

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

ELIQUIS is available in 2.5 mg and 5 mg tablets.

Please see additional **Important Safety Information** on the following pages and click for **Full Prescribing Information**, including **Boxed WARNINGS.**

Q & A With STEVEN DEITELZWEIG, MD, on Real-world Evidence

STEVEN B. DEITELZWEIG, MD, MMM, SFHM, FACP, FACC
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System Chairman, Hospital Medicine
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Ochsner Health System, New Orleans, Louisiana, USA

Dr Deitelzweig was compensated by Bristol Myers Squibb and Pfizer for his participation.

What is real-world data (RWD)?

DEITELZWEIG: Not only is RWD being utilized more, but its being defined more broadly. Various professional organizations have developed different definitions. For example, the International Society for Pharmacoeconomics and Outcomes Research considers everything that goes beyond what is normally collected in phase III clinical trial programs to be RWD. According to the FDA, any data derived from sources other than traditional clinical trials are RWD. RWD could include retrospective cohort studies, pragmatic clinical trials, disease-specific registries linked to insurance claims, and registry-based studies. These examples give you the flavor for the expansiveness of this type of work.

What do you think about RWD and real-world evidence (RWE) in relation to randomized clinical trials (RCTs) to help inform decisions about patient care?

DEITELZWEIG: This is an area that has potential utility for HCPs and ultimately their patients as there is increasing access to large amounts of electronic health data. RWD is now being used by regulatory bodies, scientific communities, payers, and others to supplement RCT data. RCTs are the gold standard for providing efficacy and safety of medication, because they're rigorous, randomized, and often blinded. While RCTs are conducted in a well-controlled setting, RWD can assess a larger population including various types of data from actual clinical populations, as well as may be done at a lower cost and faster rate as the data often has already been collected and organized in a database. However, the RWD is not generally collected with research in mind and hence important limitations exist.

RWD analyses can apply rigorous methodologies to help minimize certain limitations inherent to RWD and observational research. People recognize that RWD can be useful because it can provide insights about topics such as effectiveness, safety, patterns of therapy use, adherence, and persistence over time. Often, payers use various data sources, including RCTs, RWE, and HCEI, to assess elements of the value equation, which can help weigh the clinical outcomes of a therapy versus the health care costs associated with that therapy.

What are the biggest limitations of RWE studies?

DEITELZWEIG: RWE studies are observational in nature, so the biggest limitations include lack of randomization when comparing different interventions and potential introduction of biases and confounders. Therefore, it is important to note that one can't claim causality based on RWD since only associations can be evaluated. Additionally, data is not collected with research in mind, which may result in misclassification of data, inconsistencies, and missing data.

How does RWE fit into the hierarchy of clinical evidence? Has its position changed recently in that there is so much more attention on RWE and guidance for how to use it?

DEITELZWEIG: Well-designed RCTs are considered the highest level of evidence, and RWE can help supplement RCTs. RWE and RCTs have their advantages and disadvantages, but the real takeaway point is RWE can supplement RCTs by providing insights on treatment effectiveness and safety. From my perspective, RCTs and RWE can be used together to provide insights to help clinicians care for patients, which is an essential point.

When evaluating RWE, there are a couple of areas to look at to assess if it's good quality RWD. For example, looking at sample size and adequate power in RWE can help to understand if a difference can be detected, not just due to chance. Additionally, there are other important methodological considerations.

As a person who's a reviewer for some of the journals, I'll look for whether they use propensity score matching or regression analyses appropriately to balance baseline characteristics between groups. Did they use the right tools and assessments for how they looked at the risk of bias and confounders? Regarding the outcomes of interest, is it in the original data set that was being studied, or did they develop a proxy outcome requiring validation? Was the study itself designed in a transparent and prespecified manner? These are all important questions to think about when looking at these data. Those analyzing data look at something called PICOS, which is the population, intervention, comparators, outcome, and study design.

The simple answer is yes, there are many ways in which we can benefit from RWE in addition to the foundational RCT information, but additional scrutiny needs to be given to RWD studies.

Could you provide an example of how you use RWE?

DEITELZWEIG: First, I should emphasize that RWE is not meant to stand alone but is meant to supplement RCTs. One way that I use

RWE is in identifying the most practical therapeutic approach to look at adherence, persistence, or different practice settings. You might be able to detect a safety signal that an RCT wasn't conducted long enough to detect. Usually, RCTs are 6 months or a year in length, but patients who are on medications such as anticoagulants are going to be on these medications for longer. RWE may be a way to observe patients on therapies over a longer length of time. In addition, you can evaluate complex therapies. For example, RWE is useful in evaluating patients who are taking several different medications at the same time and also have a couple of different comorbidities, which may be underrepresented in RCTs. These are health care data collected in routine clinical settings to help support our clinical decision-making as clinicians; the data tend to be more descriptive than predictive.

Do you and your colleagues consider RWE to be useful?

DEITELZWEIG: Today, RWE is being used more and more and, in my opinion, has potential in various aspects of our clinical practice. I think it is very emblematic that societies are using it and publishing real-world analyses in peer-reviewed papers that are being promulgated.

RWE could provide useful insights that may have an impact if you ask the right questions, design the analysis appropriately, and interpret the results in the right way, even though it's not randomized. Although causality won't be established, it's recognized that the associations that can be determined from RWE might be useful. My colleagues around the US and abroad are becoming much more sophisticated in the use of RWE and how it can help them and, eventually, their patients.

Additionally, the FDA has committed to explore the potential use of RWE to help support the approval of a new indication for a drug already approved.

Do you have any colleagues who are hesitant to use RWE?

DEITELZWEIG: There are some who have hesitations with RWE, but the more my colleagues see this information being presented in prominent peer-reviewed journals and think about their patient population, they realize that RWE can be insightful. What is very important to consider is whether the information from different sources is consistent so that they can use it in their practice. In other words, is it consistent with data from the claims database? Is it consistent with data from electronic medical records? Is it consistent with data from registries? When I'm giving presentations, I often say that when you're an academic, it's publish or perish. In this space of RWE, it's replicate or perish. If the data is not consistent with not just the RCTs but with other RWD, and you can't explain why, that's an issue; replicability is very important. Additionally, unexpected findings can be considered for hypothesis generation.

What can you tell us about different sources of RWD/RWE?

DEITELZWEIG: It is important to remember that whether it's claims data, electronic medical records, or registries, all of them have pros and cons. Therefore, it is important to learn what's most useful for what you're trying to accomplish.

In focusing on health economics outcomes research, I started working with different large data sets to make myself familiar with what they can offer. For the United States, I often use Optum® Clinformatics®, which is one of the largest databases, but some other databases I also use include IBM® MarketScan®, IQVIA® PharMetrics® Plus, and Humana®. Premier® is one of the largest hospital databases. Medicare data is often used in RWE, but there is usually a lag in availability. Some other RWD databases include the Veterans Affairs EHR data, CERNER®, Flatiron® and many more.

What is your experience in using databases to answer questions?

DEITELZWEIG: My colleagues and I definitely use databases and recognize the advantages and limitations within each data set. Claims data are useful for long periods of time, but often they don't have the granularity of the clinical detail. For example, the claims data may not have a blood pressure reading, a creatinine value, or an international normalized ratio if the patient is on warfarin. That's a limitation. But you could use an electronic medical record, and that medical record may be able to provide the necessary granularity, as may registries. Plus, there are patient case report forms, which capture information in a prespecified and prospective manner. Those are all types of RWE. A lot of it does depend on the quality of the design and the data source; is it a reliable data source? That's key. And limitations still exist due to how the data is collected, potentially resulting in misclassification of data, inconsistencies, and missing data.

In addition to RCTs, how do you use RWE to inform treatment decisions specifically, for reducing the risk of stroke in patients with NVAF?

DEITELZWEIG: That has been an area of important research from a lot of people around the world, myself included, because atrial fibrillation is the most common type of heart arrhythmia that increases risk of stroke and oral anticoagulants are commonly given to reduce this risk. RWE can be used to evaluate effectiveness and safety issues [such as major and minor bleeding], as well as examine costs associated with clinical events. With anticoagulants, it's common to worry about the bleeding burden and if it matters that patients are on multiple medications or have comorbidities. All of these are important characteristics of patients, and some of this information has been captured in RWD for patients with NVAF, which have been included in either congress communications or peer-reviewed publications. Therefore, these data in patients with NVAF are being recognized as useful research in the RWE space. •

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