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Will Real-World Data Sway Course Of Novel Anticoagulant Market?

By Emily Hayes

A WAVE OF DATA TO SUPPORT use of novel anticoagulants in real-world settings was presented at the European Society of Cardiology Congress, but the question is whether this will alter the course of the market still dominated by warfarin and trailed by J&J/Bayer's Xarelto.

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Sponsors are increasingly turning to real-world data to support novel oral anticoagulants, as was highlighted at the recent European Society of Cardiology Congress, but questions remain about how it might change a market dominated by the mainstay warfarin.

Four novel anticoagulants have been introduced since 2010 and since then they have been trying to upend the warfarin standard of care. There's plenty of positive clinical trial data, including evidence of direct superiority, but with warfarin so entrenched and generic, the novel oral anticoagulants (NOACs) haven't swept the market. Evidence of downstream economic benefits could help sponsors make their case.

The first NOAC on the market was **Boehringer Ingelheim GMBH**'s direct thrombin inhibitor *Pradaxa* (dabigatran). The other three are Factor Xa inhibitors: **Johnson & Johnson/Bayer AG**'s *Xarelto* (rivaroxaban), **Bristol-Myers Squibb Co./Pfizer Inc.***Eliquis* (apixaban), and – the last to win approval – **Daiichi Sankyo Co. Ltd.**'s *Savaysa* (edoxaban).

J&J/Bayer's strategy of developing a once-daily agent for a very broad range of indications appears to have paid off. Xarelto is the top-selling NOAC with $4.36bn in worldwide sales in 2015, followed by twice-daily Eliquis with $1.86bn, twice-daily Pradaxa with €1.29bn ($1.4bn) and once-daily Savaysa with $134.9m.

Datamonitor Healthcare's survey of specialists in major markets suggests that warfarin is still the most popular choice for the leading indications for novel anticoagulants – stroke prevention in non-valvular atrial fibrillation and prevention and treatment of venous thromboembolism. Xarelto is the second choice for these indications and has had broad uptake in major markets.

Datamonitor analyst Jack Allen noted in a July 13 report about the market for anticoagulants in preventing stroke in patients with atrial fibrillation that cardiology guidelines are open-ended for this indication and consequently, "many physicians have decided to prescribe warfarin at first-line," which he said was likely due to familiarity and comfort.

Xarelto is the preferred medication for second-line therapy for stroke prevention in patients who have a CHADS-VASc risk score of 1 or higher, he noted. "The drug's simple dosing regimen and lack of dietary restrictions likely drive its strong uptake in this treatment setting," he added. Savaysa is given once daily, but FDA labeling restricts its use based on renal status.

Roger Longman, CEO of reimbursement intelligence company Real Endpoints, expects that real world evidence will impact payers less than prescribers. The novel anticoagulants are "pretty widely available" and these data are unlikely to "pry open access much more," but the data may help sway prescribing, giving doctors more incentive to move away from warfarin, he said.

It also may highlight differences between NOACs. Though investors had closely analyzed every difference

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in trial results during clinical development, cardiologists were more likely to see similarities between the NOACs, especially in the absence of head-to-head trials. A *Lancet* meta-analysis in 2013 described efficacy and safety across the board for novel anticoagulants in preventing stroke in atrial fibrillation. *(Also see "Anticoagulant Market Spoiled By Choice? Cost May Be True Differentiator" - Pink Sheet, 9 Dec, 2013.)*

Room To Grow

Reimbursement and access are good in the US and Europe, but King's College hematology specialist Alexander Cohen points out that there are variations regionally in terms of funding that affect prescribing patterns for novel anticoagulants, plus some restrictions on prescribing; for example, based on whether a doctor is in primary care or in the hospital setting. Cohen has received research funding as an investigator for hospital utilization analyses from Bristol-Myers Squibb.

At its annual meeting in April, Boehringer pointed out that that there is still room to grow the atrial fibrillation market. Registry data show that only 44.9% of US patients with atrial fibrillation were given an anticoagulant, usually warfarin, and global registry data show that in newly diagnosed atrial fibrillation patients, 38% were not given anticoagulants.

Even in higher-risk patients, oral anticoagulant prescribing did not exceed 50%, Jonathan Hsu of the **University of California, San Diego**, and colleagues reported in *JAMA Cardiology* in April.

Hsu concluded that the "lack of guideline-adhering prescription of OACs for stroke prophylaxis ... should draw attention to a treatment gap in patients who may most appropriately need OAC therapy."

Boehringer is counting on this opportunity, plus the availability of a reversal agent, to drive Pradaxa growth this year. *(Also see "Barner Goes Out On A High As Boehringer Ingelheim Returns To Growth" - Scrip, 19 Apr, 2016.)* The firm's *Praxbind* (idarucizumab) won accelerated approval from FDA in October for use in reversing the effects of dabigatran on an emergency basis. *(Also see "BI's Praxbind US Approval May Boost Pradaxa Sales" - Scrip, 16 Oct, 2015.)*

Portola Pharmaceuticals Inc. has developed a reversal agent for Factor Xa inhibitors called *AndexXa* (andexanet), but the company had a major setback in August when FDA issued a complete response letter, which will require Portola to take more time to get a new submission together. *(Also see "Portola Seeks Narrower Label For AndexXa Antidote After FDA Rebuff" - Scrip, 18 Aug, 2016.)* Interim results from the Phase III ANNEXA-4 study presented at the ESC meeting appear to support approval.

Boehringer is also counting on real-world data to build the case for Pradaxa.

Real-world studies are especially needed when a new class of drugs is introduced, Sabine Luik, senior vice president of medicine and regulatory affairs, said in an interview.

The field of novel anticoagulants is one of the first areas where we see a plethora of safety and effectiveness data coming out after pivotal studies, she said. "From a patient perspective, that is incredibly important confirmation of data from clinical trials in a real-world setting," Luik said.

The limitations of randomized trial data are well-appreciated. Clinical trials are too short and too small, and the participants may not be reflective of the real-world population in terms of age, comorbidities or concomitant medications, King's College's Cohen said.

In recent years, however, some 100 observational studies have been published on real-world use of anticoagulants, Cohen told *Scrip*. The US studies typically use claims databases from Medicare and Medicaid, and the European trials involve use of national databases – either for all patients or for a segment of millions within a population.

The trials vary in terms of size and strengths and weaknesses, but it is important to look at the full range of results, rather than individual trials, he said.

"It's very clear these drugs behave in the real world as they did in the clinical studies," he said.

Safety and effectiveness have been consistent and when it comes to the most feared complication of anticoagulation treatment – bleeding into the brain – all of

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the novel anticoagulants show reduced risk compared to warfarin, Cohen said.

Bristol/Pfizer Bolster Eliquis

Though Eliquis had a slower start than originally expected, the drug has been doing very well recently. Bristol reported that sales of Eliquis grew 78% year-over-year in the second quarter, rising to $777m. *(Also see "Bristol's HCV Bump Catalyzes Strong Quarter, But Not Expected To Last" - Scrip, 28 Jul, 2016.)* The company explained that Eliquis's growth is due to a solid trend in new prescriptions.

It's unclear to what extent real-world data have helped spur sales so far, but Bristol is stressing the potential value of these analyses.

The Bristol-Myers and Pfizer Alliance notes that it has gathered 500,000 real-world patient records, including more than 50,000 for patients prescribed Eliquis. These data come on top of the results accumulated for 18,000 who took part in the pivotal ARISTOTLE program.

Bristol says that "this shows our commitment to real world analysis," but also notes that there are large real-world analyses that have been done independently of pharma and have been peer reviewed.

Real-world data are important because they can provide valuable information about the safety and effectiveness of a drug in clinical practice, said Christoph Koenen, head of Cardiovascular Medical at Bristol.

"They generally draw upon larger sample sizes than data from clinical trials and can sometimes provide other types of information about the use of anticoagulants by patients in real-world settings, such as adherence rates," the exec told *Scrip.*

Real-world data have limitations, notably the lack of randomization, but they can complement registrational trials, he explained.

The European Society of Cardiology (ESC) Congress, held Aug. 27-31 in Rome, featured many real-world datasets that complement registrational data (*see table next page*).

The University of Birmingham's Gregory Lipp and colleagues presented data from a real-world observational study funded by Bristol and Pfizer of bleeding rates in 45,361 atrial fibrillation patients insured by Medicare and commercial plans at the ESC meeting and published results in the journal *Thrombosis and Haemostasis* online on Aug. 19. Those on warfarin were older and sicker based on standard cardiovascular test scores, but researchers used propensity-scored matching (PSM) to "ensure comparability of patient populations in relation to outcomes," Lipp and colleagues noted in their journal report.

Eliquis was associated with a significantly lower rate of major bleeding compared to warfarin – with a 47% reduced risk – and Pradaxa was associated with a 31% reduced risk for bleeding. Major bleeding was similar for Xarelto and warfarin. The authors noted that the reduction in major bleeding for Eliquis relative to warfarin was consistent with the pivotal ARISTOTLE study.

"As far as we are aware, no other US-based observational study has evaluated the risk of major bleeding between multiple NOACs and warfarin using PSM.... In general, real-world data have provided complementary evidence on the efficacy and safety of the NOACs compared to warfarin. Some real-world results regarding dabigatran and rivaroxaban use have been published with no comparator or only compared to warfarin," Lipp and colleagues stated in the article.

In June, Xiaoxi Yao of the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery and colleagues published real-world outcomes data for Pradaxa, Xarelto and Eliquis in patients with nonvalvular atrial fibrillation in the *Journal of the American Heart Association*. Bristol describes the study, which was sponsored by the Mayo Clinic, as the "largest and most robust" real-world efficacy and safety data study published to date.

Eliquis was associated with a significant 33% lower risk for stroke or systemic embolism compared to warfarin.

The researchers also reported that in line with registrational trial results, all three novel anticoagulants "were associated with lower intracranial bleeding than

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Real-World Evidence Studies Of Anticoagulants

Sponsor/funding	Description	Key Findings
Boehringer Ingelheim	GLORIA-AF registry of non-valvular atrial fibrillation patients, analysis of about 3,000 newly diagnosed patients observed over two years; results presented at ESC meeting.	Rate of major bleeding was 1.12% and rate of life-threatening bleeding was 0.54%. Rate of stroke low at 0.63%. Results consistent with data from registrational studies.
Bristol-Myers Squibb/Pfizer	Retrospective US study of Eliquis, Pradaxa and Xarelto using electronic health record data in 63,430 patients with non-valvular atrial fibrillation, 47,215 of whom were on warfarin; presented at ESC.	Matched cohort analyses indicated Eliquis and Pradaxa were associated with large, significant reductions in risk for bleeding – 19% and 30% respectively – compared to warfarin, while Xarelto was similar to warfarin.
Bristol/Pfizer	Outcomes for use of Pradaxa, Xarelto and Eliquis compared to warfarin in 36,652 elderly patients with non-valvular atrial fibrillation, subgroup of electronic health records study; presented at ESC.	Pradaxa and Eliquis both associated with significantly lower bleeding – 12% and 17%, respectively – while Xarelto was associated with a numerically higher risk of 16%.
Bristol/Pfizer	Real-world observational study of bleeding rates in 45,361 atrial fibrillation patients insured by Medicare and commercial health plans. Presented at ESC and published in *Thrombosis and Haemostasis* Aug. 19. Those on warfarin were older and sicker based on standard cardiovascular test scores, but researchers used propensity-scored matching to "ensure comparability of patient populations in relation to outcomes."	Eliquis associated with a significantly lower rate of major bleeding compared to warfarin – with a 47% reduced risk – and Pradaxa a 31% lower risk for bleeding. Major bleeding similar for Xarelto and warfarin. Reduction in major bleeding for Eliquis similar to results in pivotal ARISTOTLE study.
Mayo Clinic	Real-world outcomes data for Pradaxa, Xarelto and Eliquis in patients with nonvalvular atrial fibrillation. Claims data taken from the OptumLabs Data Warehouse compared each anticoagulant to warfarin using private and Medicare insurance records from 2010 to 2015; total of 125,243 patients. Results published in *Journal of the American Heart Association* June 13.	Eliquis associated with a significant 33% lower risk for stroke or systemic embolism compared to warfarin. Pradaxa associated with a 2% numerically lower risk and Xarelto with a 7% lower risk, also not significant. Eliquis had significantly lower risk for major bleeding (55% lower). Patients on Pradaxa were also at significantly lower risk, by 21%. Xarelto patients had similar risk as warfarin.
Obel Family Foundation, unrestricted grant	Independent real world anticoagulant study of Danish databases examined novel anticoagulants and warfarin in 61,678 patients with non-valvular atrial fibrillation. Results published in the *British Medical Journal* June 16.	No significant difference in rates of ischemic stroke between novel anticoagulants and warfarin. However, 17% lower rate of stroke plus systemic embolism for Xarelto. Lower mortality for Pradaxa and Eliquis compared to warfarin, with reduced risk of death at 37% and 35% respectively. Any or major bleeding was also significantly lower for both of these drugs, but not for Xarelto.
Bayer/J&J	Observational safety study drawn from Swedish databases. Examined records for 57,498 adult patients (7,273 rivaroxaban and 50,225 warfarin) with non-valvular AF in Sweden. Presented at ESC.	Similar rates of major bleeding with Xarelto and warfarin at 3.40 vs. 3.32 bleeds per 100 patient-years. Significantly lower rate of intracranial bleeding for Xarelto versus warfarin: 0.62 vs. 0.88 bleeds per 100 patient-years, respectively (HR 0.63).

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Sponsor/funding	Description	Key Findings
Bayer/J&J	Data from XAPASS – a prospective observational post-authorization study of Xarelto. Enrolled more than 11,000 patients in Japan. Results presented at ESC.	Incidence of any bleeding event with Xarelto was 4.84 per 100 patient-years, major bleeding was 1.02 per 100 patient-years and intracranial hemorrhage rate was 0.43 per 100 patient-years. Incidence of the composite endpoint of stroke, systemic embolism, or myocardial infarction was 1.35 per 100 patient-years, and rate of ischemic stroke was 0.90 per 100 patient-years. Findings similar to Phase III J-ROCKET AF.
Bayer/J&J	US retrospective study REVISIT-US of claims data. Results presented at ESC.	Xarelto associated with a non-significant 29% decrease in ischemic stroke and significant 47% reduction in intracranial hemorrhage compared to warfarin.

Source: Company statements, ESC abstracts, journal reports

warfarin." Intracranial bleeding is the most severe complication for anticoagulants.

Boehringer Looks To The Future

Real-world evidence has also come into play in terms of identifying post-market safety concerns. Following real-world reports of bleeding, FDA evaluated Pradaxa's safety using its Sentinel drug safety surveillance network. *(Also see "Pradaxa Medicare Study: Observing a Slow Attitude Change at FDA on Observational Studies" - Pink Sheet, 29 May, 2014.)* Observational data gained through Sentinel helped support Pradaxa's safety following damaging lawsuits and press reports.

The Sentinel program still has the largest set of observational data for Pradaxa, Luik noted, but Boehringer also places a high priority on its own real-world studies and presented data from the GLORIA-AF study at the ESC meeting.

Patient populations in the real world differ from clinical trials, which apply enrollment criteria, and yet "everything we have seen so far goes in the same direction – and we have seen really a broad set of evidence and data which supports our clinical trial results," Luik said.

Boehringer has enrolled 34,500 patients in GLORIA-AF and plans to include a total of 56,000 in the registry. On Aug. 15, the company announced that it would be developing another registry called RE-VECTO to monitor real-world use of the reversal agent Praxbind.

Luik said that she expects that "real-world data will inform drug development much more in the future"

So far the company has been running traditional observational studies, but as with other companies, it is considering ways of doing prospective pragmatic trials in the future. Possibilities as the field evolves include running a real-world trial to support supplemental indication filings with FDA.

"That, to me, is a future area we are all thinking about," Luik said.

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Editor's Note: The Datamonitor report on stroke prevention in atrial fibrillation cited in this article was published by analyst Jack Allen on July 13. Please see Datamonitor Healthcare website for more information.

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