AN AUDIENCE WITH…

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The US Food and Drug Administration (FDA) approval of Boehringer Ingelheim's dabigatran for stroke prevention in atrial fibrillation last year was a key success in a long hunt for oral anticoagulants. A year and a half on, however, the drug's place in the anticoagulant armamentarium still remains unclear. The jury is out on how the direct thrombin inhibitor fares versus warfarin in the real-world setting, and how it stacks up against oral factor Xa inhibitors like Bayer's rivaroxaban and Bristol-Myers Squibb/Pfizer's apixaban (the FDA is due to rule on approval for apixaban in June). To answer these questions, Boehringer Ingelheim has now launched one of the world's largest registries, GLORIA-AF, to follow the use of anticoagulants — including dabigatran and its competitors — in 56,000 patients. Co-chairing the steering committee of the study is Gregory Lip, a cardiologist at the University of Birmingham Centre for Cardiovascular Sciences, UK. He discusses the changing anticoagulant landscape with **Asher Mullard**.

How has the treatment landscape changed with the approval of new oral anticoagulants?
I think we are in quite an important time in relation to stroke prevention in atrial fibrillation (AF). Before the approval of these drugs, our only option for treating AF was the rather inconvenient drug warfarin, and so there was a lot of reluctance to prescribe it or to only use it in 'high-risk' patients. But data from a Danish cohort study have recently shown that whereas many major guidelines suggest that anticoagulation therapy is not necessary for patients with $CHADS_2$ scores [which estimate the risk of stroke in patients with AF] of between 0 and 1, even these patients have stroke rates that can be as high as 3.2% per year. Given the availability now of oral anticoagulants — and of better strategies for managing warfarin — these findings are leading us to rethink the use of anticoagulant therapies: our focus now is not on identifying high-risk patients who are in need of treatment, but is instead on identifying the low-risk patients who don't need therapy.

At the same time, there is also an increasing amount of data showing that aspirin is only minimally effective for stroke prevention in AF and may not be any safer than warfarin therapy.

Taken together, these findings mean that for a standard AF population more patients need to be on therapy.

Hence the need for the registry?
We have important data from Phase III trials of novel oral anticoagulants, but the question on everyone's mind is whether the data from these clinical trials will echo what happens in clinical practice. And often, when new drugs come along, many clinicians tend to use the new therapies to treat their most difficult patients. So the registry has two main goals. Initially it will act sort of like a post-marketing surveillance approach to see which sorts of patients are being initiated on dabigatran. But the ultimate intention will be to look at how all the new anticoagulants — dabigatran, rivaroxaban and apixaban — are used and how they compare in the real-world setting versus warfarin.

The registry seems unusual in that whereas companies will often launch registries to track the use of their own drugs, this one will also track the use of competitors' candidates. Why is this?
With the introduction of any new drug, there is the need for post-marketing surveillance of some sort to see how the drug is being used in clinical practice and how its efficacy and safety in the real world fares in comparison with pivotal clinical trial data. In a sense, it is not unreasonable to broaden this out to also follow other drugs, given that other good drugs are, or will shortly be, available as well. It just seems sensible to see how all the new anticoagulants fare in clinical practice.

Is the fact that Boehringer Ingelheim is funding the collection of data on the use, efficacy and safety of competitor drugs at all problematic?
The registry just reports what's going on. And although Boehringer Ingelheim is funding the registry, the study has an independent steering committee that is chaired by Menno Huisman, from the Leiden University Medical Center, who is involved in running the study. So the important thing is that the registry will shine a light on real-world clinical practice with these drugs.

When will the results be available?
The study is anticipated to conclude by 2020. But we hope that there will be preliminary readouts before then.

With the third oral anticoagulant up for approval in the United States this month, what is the next frontier for these drugs?
There are lots of therapeutic opportunities where these new anticoagulants may perhaps provide further benefit. One of the questions that is frequently asked is whether they might be used in patients with prosthetic heart valves? There are also some data emerging from the use of these drugs in patients with severe heart failure, leading us to ask whether oral anticoagulants are the way to go in this setting? And are there subsets of acutely medically ill patients who might be suitable for treatment?

Last but not least is the possibility of using these drugs in patients with acute coronary syndrome (ACS). Rivaroxaban has already given us some very exciting data in this setting. Low-dose treatment on top of antiplatelet therapy reduced adverse outcomes, including mortality, although as expected it was also associated with a small rise in bleeding. Given how common ACS is, I think this is quite an important group of patients to continue to study.

In summary, there are still a lot of possibilities with these new drugs.