

PERSPECTIVE

International Collaboration in Real-World Evidence Generation for Direct Acting Oral Anti-Coagulants

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Clinical trials of direct acting oral anticoagulants (DOACs) did not provide comprehensive evidence for some patient groups. Observational studies were planned to further characterize the safety profile of these products. The European Medicines Agency (EMA), Health Canada, and the US Food and Drug Administration (FDA) have long collaborated in medicine's regulation and we leveraged this to coordinate bigger observational studies. Here, we report on this collaboration and draw conclusions on benefits and challenges of a multiregional approach.

BENEFIT RISK OF DOACS

Results of observational studies of DOACs conducted in the European Union and Canada¹ and in the United States² have been published. These real-world data studies followed discussions within the respective regulatory authorities and collaboration between those authorities and academia. Collectively, the studies provide information on real-world safety and effectiveness of DOACs. Real-world data studies on DOACs are important because the DOACs are widely used³ and studies have shown that they prevent deaths and serious disability from thrombosis and embolism.⁴ However, it is well known from

pivotal clinical trials that all anticoagulants and antiplatelet agents increase the risk of bleeding, including serious bleeding and death; these adverse drug reactions constitute one of the most common causes of drug-induced harm.⁵ The evidence base for thrombosis and embolus prevention and for serious bleeding events has come from clinical trials carried out in a highly selected group of patients who may not be fully representative of those being treated in clinical practice. Patients exposed to DOACs in a community setting are often older, have compromised renal function and other comorbidities, and may be taking other medicines, factors that can

affect drug plasma concentrations and potentially increase the risk of bleeding and thrombosis.² There have been no head-to-head randomized clinical trials to determine if any of the DOACs differed from the others with respect to these outcomes, only indirect comparisons from network meta-analyses of randomized clinical trials showing varying levels of bleeding risk among DOACs, with apixaban generally having a lower risk than other DOACs,^{6,7} and meta-analysis of real-world data showing lower major bleeding risk for apixaban and dabigatran compared with vitamin K antagonists (VKas).⁸

At the time of authorization, the different DOACs had high-quality clinical trial evidence supporting their positive benefit risk balance. However, additional studies were imposed on these products by some jurisdictions because of the limitations related to the duration and nature of the clinical trial exposure, and some uncertainties related to their safe and effective use, including the optimal dose, use in patients with renal impairment, and use in at-risk populations. To take stock of the knowledge on the products and to catalyze the generation of information to fill knowledge gaps, the EMA organized an expert workshop on November 25, 2015. Among the conclusions of the workshop was the request for further research in real life patients to support the safe use of anticoagulants in clinical practice outside the setting of a clinical trial. On this basis, the EMA commissioned independent research from academia in the European Union and embarked on collaboration with Health Canada through the Drug Safety and Effectiveness Network and with the FDA on real-world studies of DOACs.

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METHODOLOGY

Regulatory authorities rely on analyses using longitudinal healthcare databases to understand the use and performance of medical products in routine care. Against this background, we believe that an appropriate approach to assess the safety and even effectiveness of medicines in the real world of clinical care is to apply a variety of tools to assess and analyze data from that setting. Such a hybrid approach draws on evidence from different sources, including registries for specialist use products, one-off studies using classical epidemiological techniques for complex causality questions, and common protocol approaches to address questions across multiple databases, which may be combined with using a common data model. Different real-world data sources and technological approaches have different strengths and weaknesses and these differences can be harnessed to address different research use cases.

In the case of DOACs, the real-world data studies used different methodological approaches, each with strengths and weaknesses. The approach taken in the European Union and Canada was to use a common protocol applied across multiple datasets, four in the European Union and six in Canada, and perform a meta-analysis

on the results obtained in each dataset. The meta-analysis confirmed that the risk of major bleeding of DOACs compared to VKa is not increased when combining all DOACs, with a pooled hazard ratio (HR) of 0.94 (95% confidence interval (CI) 0.87–1.02). However, a modest higher risk of major bleeding was found for rivaroxaban (HR 1.11, 95% CI 1.06–1.16), whereas lower risks of major bleeding were observed for apixaban (HR 0.76, 95% CI 0.69–0.84) and dabigatran (HR 0.85, 95% CI 0.75–0.96) when compared to VKa. A common protocol had the strengths of securing a large sample size by supporting participation of many datasets and harmonizing the choices in the study design, the definition, and the coding of outcomes and exposures. However, the common protocol cannot fully remove the variability between different coding systems and in the interpretation of certain aspects of the protocol, such as definition of inclusion and exclusion criteria, exposure, outcome, and confounders by local investigators. In contrast, the US study, initiated before the EU-Canadian study, used a single data set, the Medicare claims data covering the entire target population, which allowed for analysis of a large amount of information available in the database to assess benefits

and harms based on a large propensity model. However, this study design limited the assessment to the effects of the products within the patient population covered by this payer system.

INTERNATIONAL COLLABORATION

The real-world data studies conducted in the European Union, Canada, and the United States followed extensive dialogue and collaboration between regulators and researchers in those regions. The collaboration was motivated by the perceived benefits of conducting studies in multiple jurisdictions. Potential benefits of a multi-regional approach are given in **Box 1**, whereas challenges of such an approach are given in **Box 2**.

IMPLICATIONS AND NEXT STEPS

We have seen real-world evidence collaboration between academics and industry across different regions of the world, but this collaboration is one of the first of this scale of real-world evidence generation on a safety issue by regulatory authorities. It has provided a strong evidence base upon which to make informed decisions, for example, the study results were the subject of a major review by the EMA Committee on Human Medicinal Products.⁹

Box 1 Potential benefits of a multiregional approach to conducting observational studies of product safety and effectiveness

- increased study size,
- increased external validity,
- increased impact of results,
- ability to compare effects between regions,
- fostering methods for the specific studies through dialogue and comparison,
- fostering the development of new methods,
- fostering the development of networks and infrastructure,
- allows to compare questions dependent on the healthcare system or country-specific questions, for example, the effectiveness of risk minimization measures.

Box2 Potential challenges of a multiregional approach to conducting product monitoring studies

- complexity and number of actors involved,
- complexity of governance,
- challenges in data sharing including confidentiality issues,
- time and resource required to address complexities,
- addressing healthcare system or country-specific questions, for example, the effectiveness of risk minimization measures,
- capturing relevant differences in healthcare practices across regions that might impact results.

Different real-world data sources assessed using different methodologies to examine health outcomes of patients treated with DOACs have shown consistent results across observational studies and randomized clinical trials. This consistency has increased our confidence as regulators in drawing conclusions with implications for regulation and health care.

This work provides a foundation for future and better international collaboration, as demonstrated by the agreement at the International Coalition of Medicines Regulatory Authorities (ICMRA) to collaborate on coronavirus disease 2019 (COVID-19) observational research.¹⁰ The EMA, Health Canada, and the FDA will further collaborate to consider the implications of this work for the development of new methods and infrastructure to enable better, faster, and more extensive international collaboration on important public health questions in the future.

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

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