POSTER HTA105

Use of Real-World Evidence to Support Direct Oral Anti-Coagulant Reimbursement and Implementation in Atrial Fibrillation: a Comparison of Experiences in Three Markets

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INTRODUCTION

Our work, and that of other researchers, has highlighted the barriers to the optimal use of real-world evidence (RWE) in health technology assessment (HTA). When RWE has been used, particularly to address questions of relative effectiveness in HTA, it has commonly been mistrusted. This is in part because problems nearly always arise that are particular to the use of particular data sources, answering particular questions.

In this case study, we consider how RWE was used in the assessment of direct oral anticoagulants (DOACs) in atrial fibrillation (AF) in both pre- and post-approval stages of their use. We chose DOACs for two reasons: they are an example of a drug class which has received much attention in the literature and by HTA agencies, with a relative wealth of published material; and there is a great deal of data, both trial and RWD, relating to their effectiveness. They could be considered as a 'best case' scenario in terms of the availability of evidence to answer a range of important questions – they have positive trial data, evidence of direct superiority compared to warfarin for two DOACs, well documented issues with their main comparator (warfarin) and a range published evidence. Such a range of good evidence might be expected to support optimal reimbursement and speedy and appropriate patient access, but this has not proved to be the case.

BACKGROUND & OBJECTIVES

EUreccA

This work was carried out as part of a wider collaboration, EUreccA, which is a European think tank aiming to advance constructive engagement on the challenges faced by stakeholders within the healthcare system. In collaboration with Novartis, it established an RWE Steering Group (EUreccA RWE SG) to review existing barriers for effective use of RWE in bringing new medicines to patients quickly.

Several topics and case studies were selected by the RWE steering group and approved by a panel of HTA experts (Advisory Board), one case study being RWE use for Direct Oral Anti-Coagulants (DOACs) HTA submissions in atrial fibrillation (AF). DOACs are an example of a primary care drug with substantial published evidence and RWE included as part of HTA submissions.

Four DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) were approved in the US and Europe within the last decade for AF. These approvals were based on pivotal randomized controlled trials (RCTs) demonstrating non-inferiority versus warfarin in stroke prevention in AF, see Table 1.

Table 1. DOAC pivotal trials

DOAC	Type	Trial, NCT number, study
Pradaxa (*dabigatran*)	Direct thrombin inhibitor	RELY, NCT00262600 (randomized, parallel assignment. non-inferiority, comparator: warfarin) Connolly (2009)[1]
Xarelto (*rivaroxaban*)	Factor Xa inhibitor	ROCKET-AF, NCT00403767 (non-inferiority, comparator: warfarin) Patel (2011)[2]
Eliquis (*apixaban*)		ARISTOTLE, NCT00412984 (non-inferiority, comparator: warfarin) Granger (2011)[3]
Savaysa (*edoxaban*)		ENGAGE, AF-TIMI 48 NCT00781391 (non-inferiority, comparator: warfarin) Giugliano (2013)[4]

Key: AF, atrial fibrillation; DOAC, direct oral anticoagulant.

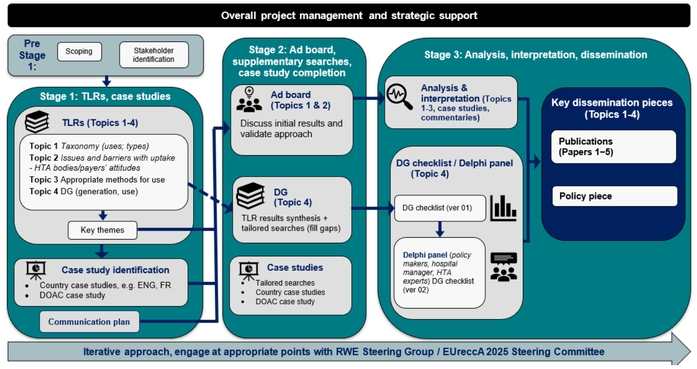
Using this case study, we sought to answer the following research questions:

Research questions:
1. What can we learn from the first four DOACs approved for use in atrial fibrillation (AF) in 3 European markets (France, England and Spain)?
2. How was RWE used to support HTA and post-HTA decision making?

METHODS

To support the development of our research questions, we conducted several scoping searches to identify key topics and case studies which could help us understand and begin to address the barriers to optimal RWE use in HTA. We conducted an Advisory Board with European HTA experts to validate our overall approach (including the selection of our case studies) before progressing our investigation. See Figure 1 for details.

Figure 1: Summary of overall project approach



Case study methods used:

1. **Pragmatic literature review of DOAC pairings***
   - Aim: To support our interviews and discussion on lessons learned
2. Inclusion of relevant literature from our **targeted literature reviews** from the broader project, see Figure 1.
   - Aim: To support our interviews
3. **Interviews** with experts from each of our countries of interest (**France, England and Spain**)
   - Aim: To consider how RWE was used to support HTA and post-HTA decision making and to provide lessons from across these jurisdictions.

**Note: Combinations of questions and possible data sources we call 'pairings'.*

RESULTS

We summarise three key concerns regarding DOAC HTA submission and post-HTA submission for France, Spain and England and where RWE was used to alleviate these concerns. This is summarised in Table 2 and discussed below.

Safety concerns and a lack of local data

- At the time of the first DOAC submission, concern regarding safety was a predominant issue compared with the potential benefits in the number of avoided strokes. As a result, it was deemed essential for HTA bodies to identify the profile of patients at high risk of bleeds with DOACs.

Table 2. RWE needed to overcome key concerns identified by our experts

Country	Safety concerns (lack of local safety data)	Potentially large budget impact	Implementation concerns (e.g. no warfarin clinics)
			
			
			

Key: BI, Budget Impact; **Red** = Main concern; **Orange** = Secondary concern.

- This was a key issue in France and Spain where several RW studies were commissioned locally to better support HTA decision-making and provide answers to those uncertainties. For example in France, the ANSM asked the Sickness Fund to perform a study using a national claims data base (SNDS) to investigate the comparative incidence of haemorrhages after 90 days of treatment with patients naïve to any anticoagulation and treated either with dabigatran, rivaroxaban and VKAs for all indications (NACROA). A secondary objective was to compare the incidence of any arterial thrombosis, strokes, systemic embolisms and acute myocardial infarction. The study concluded that there were no excess bleeds or arterial thrombosis.[4] Thus, there were partial reassuring data on safety. This first study also played an important role in comforting clinicians with DOAC use. These studies were used by the CT alongside RWE provided by the companies to inform their decision making.

A primary care drug, large eligible population and budget impact

- This was a key issue in Spain. Once concerns around safety were alleviated locally, it was broadly expected that most patients would switch from warfarin to a DOAC. This was mainly because it is considered simpler to use (e.g., frequent international normalised ratio (INR) monitoring not required) and more effective (based on trial data).
- However, expectation of a simple switch from warfarin was not realized in Spain, for example, it was not clear how many patients were using warfarin at the time, how many were not appropriately managed on warfarin or how many were eligible to switch. There was a concern about how agencies in Spain were going to manage this, based on the potential volumes. The Authorities in Spain commissioned several RW studies to gather this information. In addition, there was uncertainty around the potential benefit (long-term data needed) and the cost was high compared to warfarin. Due to this lack of data to answer questions appropriately, initial approval was restricted requiring new patients to try warfarin prior to dabigatran.

Implementation concerns

- In England, it took a long time for DOAC manufacturers to proactively resolve the questions beyond those asked by the European Medicines Agency (EMA) and the National Institute for Health and Care Excellence (NICE, England's HTA body) for DOACs. At the time, the DOAC manufacturers did not foresee the extent of the questions which prescribers, clinicians, payers or patients had and did not provide robust answers using RWE in a timely manner.
- For example, INR measurement would no longer be needed with DOACs, and patients would no longer need to attend warfarin clinics. However, some patients wanted to continue attending these clinics for a variety of clinical and non-clinical reasons.
- Therefore, local health authorities organized their own confirmatory work (RWE studies) to gain a level of confidence to allow for the required pathway changes to be made. These typically took the form of clinical audits.
- These may not have been robust studies with the statistical rigour reflected in RWE guidance but were fit for purpose. In this case, they were rigorous enough to answer the question being posed and, importantly, to allow for the question to be answered in a timely manner.

DISCUSSION AND CONCLUSIONS

- This case study was chosen because at the time of HTA submission there was a great deal of data, both RCT and RWD, relating to DOAC effectiveness, providing a 'best case' scenario in terms of the wealth of evidence available to answer a range of important HTA questions. These circumstances might be expected to support speedy decision-making, reimbursement and patient access.
- Our results suggest that in practice this was not the case. There were several unanswered questions. Many of these were not about effectiveness but about practicalities of organization and delivery. There were delays in DOAC reimbursement in Spain and France and although there was no delay with reimbursement in England, there was a delay in DOAC implementation and uptake.
- The timing of HTA submission, whether the drug is a primary care drug (potentially a large budget impact), the trial design, safety concerns and the issues related to its implementation can all contribute to uncertainty and concerns regarding HTA decision making.
- Our results highlight the usefulness of RWE to fill gaps in the original DOAC trials, to reduce uncertainty and to answer questions important to local decision makers.
- This case study highlights that early planning is recommended to support a clearer understanding of the additional evidence needs and to generate fit for purpose RWE and ultimately support faster access for patients.
- We have recently published 5 papers in Value in Health which discuss **Using Real-World Data in the Health Technology Assessment of Pharmaceuticals**: https://www.sciencedirect.com/journal/value-in-health/vol/26/issue/4/suppl/S

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