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EDITORIAL

The Complementary Role of Real World Evidence: Focus on Oral Anticoagulants

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A large number of real world evidence (RWE) analyses have been published in the past few years, including a retrospective analysis of outpatient data from Germany in this journal [1]; but, what is 'real world evidence'? It may include: prospective non-interventional clinical studies, prospective and retrospective patient registries, retrospective clinical studies and retrospective (claims) database analyses [2–5]. These help to assess the effectiveness, safety, persistence and adherence of medical therapies in large numbers of patients, often with multiple co-morbidities, who would otherwise not have been included in clinical trials, and to evaluate treatment beyond the time course of the randomised trials [6]. The 2016 US Food and Drug Administration (FDA) landmark paper on RWE states: ''We believe it refers to information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records, claims and billing data, product and disease registries, and data gathered through personal devices and health applications" [7].

Real world evidence should be viewed as complementary to rigorous randomised controlled trials (RCTs), which are the gold standard for evaluating and answering medical questions about the efficacy and safety of new therapies [2,3,6]. Real world evidence studies have different strengths and weaknesses (Figure 1) [8]. Claims analyses are retrospective studies and dependent on the completeness and quality of coding in the database whilst prospective registries have the advantage of pre-defined endpoints (e.g. definition for bleeding) and more rigorous data collection including the ability to adjudicate events [6,8]. Post-marketing studies can be useful when assessing the use of a drug in routine clinical practice, such as: effectiveness and safety, treatment adherence, prescriber expectation, practical treatment benefits and comparison with other treatment options (Table 1) [2,3,6].

Early in drug development, RWE may expedite the generation of hypotheses to inform the design of clinical studies and enable identification of subpopulations with higher risk-benefit ratios to target development efforts, avoid adverse events and unnecessary delays and allow targeted and efficient patient recruitment for RCTs [6]. Because of the large numbers of patients involved, RWE can improve the generalisability of RCTs with data from a more diverse group of patients in different practice settings and longer follow-up than targeted, tightly controlled populations, to gain better insights on safety and effectiveness [6]. Once a product has been approved, RWE may also inform decisions regarding value and reimbursement [6]. The US FDA also declared: '' . . . although we are optimistic about long-term prospects for the evolution of mature, robust methodologic approaches to the incorporation of RWE into therapeutic development and evaluation given the intensive efforts now under way, caution is still needed . . . " [7]

Recently in *Heart, Lung and Circulation*, Coleman et al. [1] reported a retrospective analysis of a database, which is limited in that it is observational and tries to propensity match patients according to specific parameters (such as age, gender, CHA_2DS_2VASc score and number of co-morbidities in this analysis) aimed to reduce confounding due to one group being different to the other 'intervention' group [1]. This type of RWE study (which in this analysis compared

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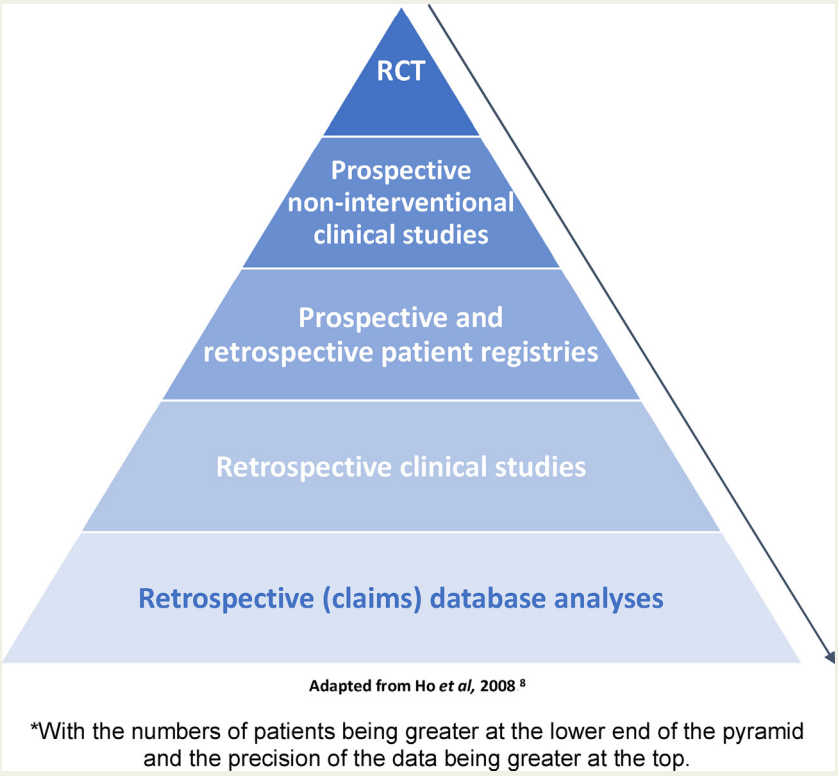

Figure 1 Different types of real world evidence*.

outcomes between apixaban and vitamin K antagonist users with non-valvular atrial fibrillation), should yield more patients than an RCT (which in this case it does not); and, have longer follow-up than a RCT, (which in this case it was not) (Table 1). Patients may be included who have co-morbidities which excluded them from a RCT and doses are at the discretion of the treating physician [2,3]. However, there may be under-dosing in the apixaban group, or the time in the therapeutic range (TTR) in the vitamin K antagonist group may be sub-optimal. Potential negative points include funding from pharmaceutical companies, lack of adjudication of endpoints and the lack of blinding of the physician and patient whereby, despite propensity matching, there may be a prescriber bias towards one treatment for patients who are less well and another for patients who are more robust [2,3].

Coleman et al. [1] presents a well conducted retrospective database analysis, although the number of patients treated with apixaban or vitamin K antagonist who were excluded because they were not able to be propensity matched is not stated. Real world evidence data is intended to reflect patterns of care which may differ from an RCT. The cohort in this article is older than the patients in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [9], there was a higher percentage of female patients, and all patients were anticoagulant naïve [1,9]. The $CHADS_2$ score and the proportion of patients taking aspirin was similar to the ARISTOTLE trial [1,9]. The proportion of patients on each of the doses of apixaban is not mentioned nor is the TTR [1]. However, the small number of events reported is most likely related to the relatively small number of 1670 patients versus 18,201 in the ARISTOTLE trial as well as the shorter duration of follow-up of 1 year versus a mean of 1.8 years in the ARISTOTLE trial [1,9]. As RCTs such as the ARISTOTLE trial are felt to be the gold standard, unless a retrospective database analysis can evaluate many more patients and/or with much longer follow-up, its additional value is limited.

Comparing the article by Coleman et al. [1] to other RWE studies evaluating non-vitamin K oral anticoagulants (NOACs), the number of patients is significantly greater in the other RWE studies, for example Graham et al. analysed 134,414 patients [10], Larsen et al. 48,137 [11], Seeger et al. 44,672 [12], and Yao et al. 28,614 [13], to name a few. These were similar analyses with longer follow-up and because of their numerical power, the number of events were greater and more tangible conclusions could be drawn. None of the composite endpoints in Coleman et al. showed statistically significant differences between the two types of therapy but this was almost certainly because the study was under-powered [1]. Comparisons to the ARISTOTLE study are hypothesis generating, at best. However, longer follow-up may produce further information; and, the data generated from this RWE study could be included in a meta-analysis with other trials to increase their statistical power.