A post approval look at anticoagulants

Journal:	*British Journal of Clinical Pharmacology*
Manuscript ID	ED-00004-19
Manuscript Type:	Editorial
Date Submitted by the Author:	03-Jan-2019
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Key Words:	Clinical Pharmacology, Anticoagulants < Haematology, Cardiology
Abstract:	n/a

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Someone once described serendipity as looking for a needle in a haystack and finding the farmer's daughter (or son)[1]. Pharmaco-epidemiologists are often trying to find the needle without picking up a lot of other things.

Although all experimental trialist would like to answer everything using a controlled clinical trial, the rarity of some endpoints just defies practical execution as the trials simply become too large or too lengthy. Picking up signals from observation is therefore inevitable-and inevitably biased.

The trick is to control the bias as much as possible and to sort the signals from the noise. Anton Pottegard(1) and colleagues from Boston and Odense published recently about a new method to identify signals of interest called sequence symmetry analysis. How does this work? Basically, the analysis uses the assumption that when a treatment is associated with an increased risk of a certain disease there will be more incidences of the disease following the drug than vice versa. They attempted to use this technique in a database of all prescriptions and health care contacts in Danes born before 1950. Other than just looking for drug-disease pairs they also studied drug – drug associations, as the use of one drug may

[1] Julius Comroe, Jr., as quoted in What Does That Mean? : Exploring Mind, Meaning, and Mysteries (2010) by Eldon Taylor, p. 9

lead to another. They did identify these, for instance the use of paracetamol was more often followed by an opioid, reflecting good practice. A more frequently occurring drug after another one may of course also mean the previous medicine caused side effects and this was a reflection of a change in therapy. The Danish database yielded 200 billion sequences of events from which they filtered about 45000 event sequences that were suspicious. Whichever technique used there must be some way in which noise can be filtered out. The authors suggest using a different design in addition to sequence symmetry analysis, and dose response evaluations to add plausibility to these often-complex analyses of datasets with a not fully assured quality.

In no area is finding this epidemiological needle in the data haystack more important than for anticoagulants. The bleeding or thrombotic events are relatively infrequent. This makes it hard even for gargantuan trials to detect a difference between two active treatments, in an unbiased manner, with sufficient statistical power. Especially with new anticoagulants these questions are particularly relevant because clinical experience is not yet sufficient, especially with groups of patients that were not involved in the trials. The new Direct Oral Anticoagulants (DOAC's) were shown to be non-inferior and sometimes superior to warfarin in non-valvular atrial fibrillation. Luca Monaco and his team went to the VigiBase database from the Uppsala monitoring center of adverse drug reactions from many countries to study this again in a bigger and less well-defined population compared to the clinical trials.(2) After much controlling of potential bias their analysis was at least partly validated by the fact that they got similar results to others but also managed to get a picture of differential effects of the three new DOACs. Compared to warfarin they found a reduced incidence of intracranial hemorrhage for the DOACS, but, interestingly an increased risk of myocardial infarction for

dabigatran and rivaroxaban. Such analyses should not be interpreted a causal, but rather taken as a reason for caution and possibly further systematic research (as randomized evidence will not be forthcoming).

Tanja Mueller and a group of researchers from Glasgow approached the same problem but this time in Scotland and the results were not exactly similar showing the problems of the non -randomized approach(3). In this study the DOAC's did not differ in risks of stroke or systemic embolism or death. Apixaban-which in the previous study has a slightly worse safety record-had a higher associated risk of myocardial infarction but a lower risk of pulmonary embolism than rivaroxaban. From this study it appeared that the bleeding risk was higher after rivaroxaban than the other DOAC's and the treating clinician is left baffled. Are these findings the needle in the haystack or the farmer's daughter?

Finally, this was also approached in a group of atrial fibrillation patients in France, where the ones on dabigatran 110 or 150 mg were compared to the ones on Vitamin K antagonists. (4)The patient groups were well matched, and this study demonstrated that dabigatran was overall safer and more effective than the Vitamin K antagonists. So, they may have gotten the farmer's daughter (or son) out of the haystack and found the needle. The end of this story is course that there is no end. We always have to keep monitoring new and old medicines in broader populations to see if unexpected but rare adverse effects emerge in groups that have not been studied before in randomized controlled trials and these studies reflect some of the ways it can be done. Are they perfect? Obviously not, but not doing this is infinitely worse. There are many health care interventions that are not medicines which are launched upon patients without such careful monitoring. A good example are the metal-

on-metal hip prostheses(5), but that is another story. So we need to keep looking for the needle in the haystack-even though we may come upon surprising and sometimes inappropriate discoveries.

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