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Editorial

Digoxin and mortality: lessons for observational studies

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Digoxin decreases hospital admissions for heart failure and has no effect on all-cause mortality [1]. After years of discussion, it appears that a meta-analysis of randomized and observational studies by Ziff *et al*. [1] confirms this conclusion. In the meta-analysis, the randomized trials showed no effect on mortality, while the observational studies all demonstrated that digoxin increased mortality. Ziff *et al*. [1] discussed that observational studies should only be interpreted as hypothesis generating (compared with randomized trials being definitive), and in an accompanying editorial, Cole and Francis even stated that 'trials are best, ignore the rest' [2]. These provoking statements need some nuance.

Randomization is the most important measure to counteract confounding bias. In a well-performed randomized, double blind trial, quantitative causal relationships between drugs and intended or unintended effects are directly observable. In observational studies, when studying the causal effects of drugs, it is important to distinguish between intended and unintended effects. For intended effects, observational studies suffer from the huge problem of confounding by indication. The reason(s) to start administering a drug is related to the perceived prognosis of a patient and therefore a comparison with a group of patients with the same indication but, whether untreated or treated with another drug, will potentially suffer from confounding bias [3]. Statistical adjustment for potential confounders will reduce such bias but often it is impossible to capture all relevant prognostic factors; e.g. they might simply be missing from health record databases but, in addition, we will never know the exact considerations that led the prescriber to start a treatment. This leaves room for residual confounding.

For unintended drug effects, this is completely different, in as far as the adverse effects are not predictable at the start of treatment. For these side effects, there are no prognostic factors at the start of treatment and therefore we can speak of some kind of natural randomization of the treatment in relation to the side effect. When potential information and selection biases are adequately counteracted, causal relationships can be derived. When the adverse effect is predictable at the start of treatment – for instance, a patient has a contraindication [e.g. the use of a nonsteroidal anti-inflammatory drug (NSAID) in a patient with a history of an upper gastrointestinal (GI) bleeding] – obviously, there will be the problem of confounding by contraindication, similar to the confounding explained for the intended effects in observational studies.

From the perspective of intended and unintended effects, the case of the digoxin effect on mortality in heart failure patients is interesting. On the one hand, one of the intended effects of digoxin for heart failure is to improve survival by a positive inotropic effect. On the other hand, an unintended effect of digoxin is that it increases the risk of fatal cardiac arrhythmias. Thus, the outcome all-cause mortality includes a digoxin-related composite outcome of intended and unintended effects. By studying the causes of death, we will obtain more insight into the separate mortality risks of digoxin.

When planning an observational study, it is important that the biological mechanisms underlying the relationships between drugs and effects are taken into account in the design phase of the study. In a randomized controlled trial, when patients are mostly constantly exposed to the drug, this is less relevant provided that the study is long enough to allow the outcomes under study to occur. In daily practice, however, the adherence and persistence of drugs is lower than in randomized studies.

Thus, when in an observational study acute effects are being studied – for instance, the relationship between NSAIDs and upper GI bleeding – it is important to know whether a patient was exposed to the drug at the time of the bleed. For cancer, with regard to the adverse effects of drugs (for instance, cyclosporine and skin cancer), the cumulative exposure of the drug prior to the event is relevant, rather than the exposure at the moment of the cancer

diagnosis. So, a first step in observational studies is to measure the exposure to the drug during a relevant timeframe, based on prior knowledge of the biological mechanism. In the meta-analysis of Ziff *et al*. [1], the observational studies that handled digoxin exposure in a time-dependent fashion were excluded. Only studies that classified patients as exposed or unexposed to digoxin at baseline (the start of digoxin therapy) were included. Obviously, exposure definitions like this will completely hamper the study of the effect of digoxin on mortality. There are several modelling techniques described in the literature that allow drug exposure to be evaluated in a time-dependent way – for instance, the use of Cox models with time-varying covariates or weighted cumulative exposure techniques [4, 5].

Observational studies are not a replacement for randomized controlled trials; they should be complementary. The study of long-term side effects with low frequency can only be approached by using observational studies. Such studies should also be used for investigating patients in daily practice who might respond differently to the – often highly selected – patients studied in randomized controlled trials. In line with the learning *vs*. confirming concept of Sheiner [6], observational studies are more useful for learning, and randomized trials for confirming what has been learned. It is impossible to state whether the observational studies indicating a higher mortality rate by digoxin were completely wrong. For instance, frailer patients treated in daily practice, perhaps with dosages that are too high in relation to their kidney function and potassium levels, might receive more harm than benefit when exposed to digoxin for heart failure.

In conclusion, it is important that observational studies are complementary to randomized controlled trials when studying drug effects. They should be directed at unknown, unpredictable side effects, especially those that occur with low frequency and need long-term exposure to occur. Furthermore, they should be directed at patient groups which might respond differently to patients studied in randomized controlled trials. The case of digoxin and mortality teaches us, again, that the biological mechanisms underlying causal relations between drugs and effects should be taken into account when designing and analysing observational studies.

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