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EDITORIAL

Residual confounding in observational studies: new data from the old DIG trial

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This editorial refers to 'Digoxin–mortality: randomized vs. observational comparison in the DIG trial'†, by L. Aguirre Dávila *et al.*, on page 3336.

Heart failure (HF) is frequently diagnosed and affects ~1–2% of the population in European countries.[1] The prognosis of patients with HF is very poor, with a 5-year survival rate of <50%.[2] HF is a chronic disease and, despite advances in medical and device therapy, the majority of patients show progression of the disease. Digoxin is one of the oldest drugs, widely available and very cheap, but only one large randomized placebo-controlled trial [Digoxin Investigation Group (DIG)] has studied this drug.[3] This trial proved a neutral effect on the endpoint mortality, but reported a beneficial effect on rehospitalization for HF. Post-hoc analyses of this trial showed a favourable outcome, particularly for patients with lower doses of digoxin and consequently lower serum concentrations of digoxin.[4,5] Yet, the DIG trial was performed >25 years ago, during a time when there were hardly any other HF treatments available besides angiotensin-converting enzyme inhibitors. Consequently, after the introduction of beta-blockers, mineralocorticoid receptor antagonists, and, recently, valsartan–sacubitril (all drugs with a class I recommendation in the treatment of HF), the use of digoxin declined. Besides the introduction of other HF drugs as a reason for its decline in use, several observational studies questioned the safety of digoxin.

For example, in a recently published substudy of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial,[6] the authors compared atrial fibrillation patients with newly prescribed digoxin during follow-up with patients who had not received digoxin during the trial. The researchers found a significantly higher mortality in patients receiving digoxin in the unadjusted, but also in the propensity-matched group. Based on these observational data, they concluded that digoxin should preferably be avoided in patients with atrial fibrillation regardless of HF. It is questionable whether such bold statements can be made based on only observational data. In all observational studies, patients using digoxin were sicker, indicating an important risk for prescription bias.

In a large meta-analysis, a decreasing risk ratio of digoxin for mortality was observed in unadjusted analyses, adjusted analyses, propensity-matched studies, and randomized controlled trials (RCTs), respectively.[7] Studies with a lower risk of bias were more likely to report a neutral association of digoxin with mortality. This again raises suspicion that maybe digoxin is not the causal factor for these findings, but (residual) confounding factors are.

Last year, a comprehensive comparison on the differences between outcome of HF drugs in RCTs and observational studies was published.[8] All established medications in HF with reduced ejection fraction (HFrEF) had at least one RCT to demonstrate its effect, and several observational studies with variable outcomes. No other drug showed as many contradictory outcomes as digoxin. These authors make a strong case against drawing conclusions on therapeutic effects from associations found in observational studies.

In the current issue of the *European Heart Journal*, Aguirre Dávila and colleagues add further evidence to this discussion. In an elegant way they study whether it is possible to control for prescription bias in patients treated with digoxin. They used the original DIG study and focused on the 44% of the participants in the trial who had previously been treated with digoxin and underwent randomized withdrawal in the original trial.[9] This gave the authors the opportunity to see what the true effect is of digoxin in that population. Patients treated with digoxin before randomization showed important differences in baseline characteristics, with previous digoxin users having more signs and symptoms of advanced HF, lower ejection fraction, and higher use of diuretics, among others. As a logical consequence, they confirm that previous use of digoxin was associated with higher mortality. These findings stood irrespective of whether patients eventually received digoxin or placebo and, more importantly, also persisted

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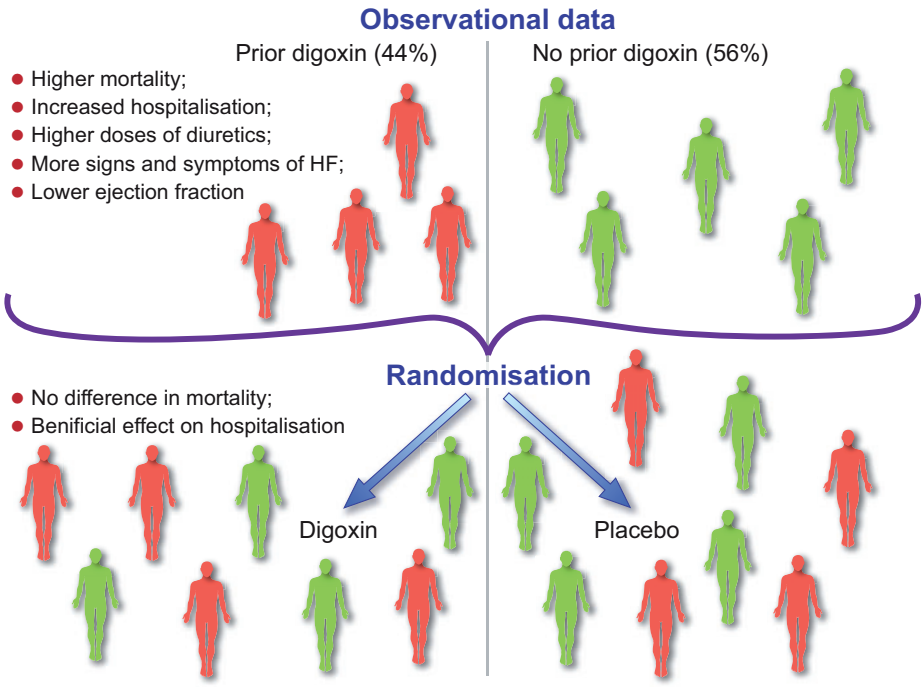

Figure 1 Visual representation of differences found in observational and randomized data.

after rigorous correction for a variety of baseline covariates associated with worse prognosis (29 in total, all with a *P*-value <0.2 in baseline comparison). Through the division of the randomized groups into new categories (i.e. previously treated with digoxin vs. no previous digoxin treatment), the authors created an observational study within the same data set. They were not able to find the same treatment effect in the observational approach as in the randomized approach. Most strikingly, in the observational cohort, previous digoxin use was associated with a higher risk for re-hospitalization, whereas, in the original DIG study, randomization to digoxin resulted in a significantly lower risk for hospitalization. This underlines the limitations of associations found in non-randomized studies (*Figure 1*).

In the course of deterioration of clinical status, physicians are inclined to prescribe additional drugs, thereby identifying sicker patients in a way that multivariable analysis cannot correct for. Even with extensive correction for known variables of more advanced disease, important prognostic variables remain unmeasured simply because we do not know which they are. In the current study, the authors corrected rigorously for all differences at baseline, but they did not perform propensity score matching. This type of analysis is a technique used to match different patients in categories based on their probability of being in that particular category. Whether the results of the current study would be different had propensity matching been done is unclear, but, given the extensive correction for baseline factors, this seems unlikely. The same holds for inclusion of more extensive baseline characteristics, including echocardiographic data and circulating biomarkers. In the current analysis, only two circulating biomarkers have been used: serum creatinine and potassium. It remains unclear, therefore, whether the inclusion of more well-established HF biomarkers would have led to a different outcome. In the same vein of circulating biomarkers, measurements of serum digoxin have already shown their value. Patients with lower serum levels of digoxin (concentrations between 0.5 and 0.9 ng/mL) had a better prognosis compared with placebo-treated patients, whereas mortality was higher in patients with digoxin levels above 1.0 ng/mL.[4]

The DIG study is still the only randomized trial and, even though the current HF arsenal has been expanded, present recommendations are made based on this older trial. Therefore, adequately powered RCTs on the effect of digoxin in the current era are warranted, especially focusing on lower dosages of digoxin. The results of two large RCTs in patients with HF will hopefully help to position the place of digoxin in modern HF treatment. The first is the DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure (DIGIT-HF trial),[10] an RCT on the effects of concentrations of digitoxin in a range of 8–18 ng/mL on the composite of HF hospitalization and all-cause mortality in advanced chronic HFrEF (EudraCT: 2013-005326-38). A potential limitation of this study is the uncertainty of whether results on digitoxin can be extrapolated to known data on digoxin. The second trial is Digoxin Evaluation in Chronic heart failure: Investigational Study In Outpatients in the Netherlands (DECISION ClinicalTrials.gov Identifier: NCT03783429). A double-blind placebo-controlled trial on the effects of low-dose digoxin (aiming for concentrations within the 0.5–0.9 ng/mL range) on the composite of (repeated) HF hospitalizations and cardiovascular mortality in ambulatory HF patients. Both trials aim to include a significant proportion of patients with atrial fibrillation, another important, but unexplored, terrain in digoxin research.

Aguirre Dávila and colleagues demonstrate elegantly that one cannot fully adjust for prescription bias and have already untangled a part of the mystery on the safe use of digoxin in HF. Hopefully the results of future large ongoing RCTs will further help to determine the place of digoxin in HF.

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