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EDITORIAL COMMENT

Target trial emulations: bridging the gap between clinical trial and real-world data

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This article refers to 'Stopping mineralocorticoid receptor antagonists after hyperkalaemia: trial emulation in data from routine care' by M. Trevisan *et al.*, published in this issue on pages 1698–1707.

Clinical guidelines have designated mineralocorticoid receptor antagonists (MRAs) as a class I indicated treatment for patients with heart failure with reduced ejection fraction in the absence of contraindications.[1,2] Despite this, MRAs have consistently been underutilized in clinical practice. Indeed, data from observational studies have demonstrated that 40–70% of guideline-eligible patients are not prescribed MRAs, primarily because of fear of hyperkalaemia and worsening renal failure.[3,4] Hyperkalaemia is indeed a common adverse effect of MRAs; evidence from clinical trials shows that MRA users have over twice the risk of hyperkalaemia compared with patients on placebo.[5] MRA therapy is frequently discontinued after an episode of hyperkalaemia, which further exacerbates the problem of MRA underuse.[6]

Whether to discontinue MRAs after an event of hyperkalaemia has remained a topic of debate. Mild-to-moderate hyperkalaemia is known to be associated with an increase in the risk of mortality. With *primum non nocere* as a goal, the risk of future hyperkalaemia episodes should be weighed against the increased risk of hospitalization and mortality yielded by terminating MRA therapy. In the absence of concrete evidence, risk perception is likely to play a role in clinical decisions, with the imminent risk of hyperkalaemia seemingly outweighing the long-term risk of poor clinical outcomes. This highlights the need for high quality evidence to optimize and standardize therapy after an event of hyperkalaemia. Conducting a randomized controlled trial (RCT) to compare discontinuation vs. continuation of MRAs after hyperkalaemia would be challenging. For all comers, less than 20% of MRA users experience hyperkalaemia which would make it difficult to conduct a clinical outcomes trial.[7] Additionally, obtaining consent could be difficult in the very high risk individuals.

Given this background, Trevisan and colleagues must be congratulated on their excellent analysis published in this issue of the Journal.[8] The authors utilized a novel technique, *target trial emulation*, to assess the effect of MRA discontinuation after hyperkalaemia on clinical outcomes and incidence of hyperkalaemia. Target trial emulation refers to the application of design principles from RCTs to the analysis of observational data in an attempt to reduce biases that customarily plague generalized observational studies. Amongst 39 518 new MRA users in the SCREAM (Stockholm CREAtinine Measurements) healthcare utilization cohort, the authors identified 7408 patients who experienced an index hyperkalaemia event. MRA discontinuation was defined as no new dispensation of MRA in a 6-month grace period following the index hyperkalaemia event, while MRA continuation was defined as at least 6 months of MRA use following the hyperkalaemia event. Randomization was statistically emulated, and a weighted Cox proportional hazards model was used to estimate the 2-year risk of adverse clinical outcomes and hyperkalaemia. Amongst patients with an index hyperkalaemia event, 3782 (51%) continued MRA therapy, while 2222 (30%) discontinued. The remaining patients died or were censored before the 6-month grace period. The results showed that patients who stopped MRAs had a nominal but significantly increased risk of the composite of death or hospitalization for cardiovascular events when compared with patients who continued therapy. Similarly, patients who discontinued MRA therapy had a significantly higher risk of major adverse cardiac events and all-cause death. In contrast, these patients were significantly less likely to experience recurrent hyperkalaemia. The results were similar in a subgroup of heart failure patients.

The findings of the study in question are in line with previous observational studies which have also demonstrated poorer clinical outcomes in patients who discontinue MRAs or other renin–angiotensin–aldosterone inhibitors after an event of hyperkalaemia.[9,10] However, by emulating a target trial, Trevisan and colleagues minimize various limitations found in previous analyses, as discussed below.

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Addressing the disconnect between clinical trial and real-world data

Randomized controlled trials have long been considered the gold standard for guiding clinical practice. The controlled environment allows investigators to reduce bias and confounding and assess the presence of a causal association. However, there have been increasing concerns that this internal validity is achieved at the expense of external validity, i.e. generalizability.[11] Observational studies frequently claim to test the hypotheses of RCTs in the 'real world'. If the results of these studies are consistent with those of RCTs, it is often assumed that the methodology and design of the observational study is valid. At the same time, it is assumed that the findings of the clinical trial are applicable in the real world. However, the methodologies of both clinical trials and observational studies need to be evaluated closely. Naïve observational studies often have several methodological differences and biases which invalidate direct comparison with RCTs; these include but are not limited to lack of randomization and confounding, per-protocol analysis, immortal-time bias, outcome ascertainment bias, and poorer quality data.

There are two potential solutions to bridge the gap between real-world and clinical trial evidence. First, is to design RCTs to be more 'pragmatic' by loosening restrictions and focusing on maximal possible heterogeneity in treatment, patient population, and healthcare providers so that the efficacy of the intervention in the full spectrum of everyday clinical settings can be assessed.[11] The second approach is to conduct observational studies with the design principles of RCTs; this is where target trial emulations come in, as descried by Hernán and Robins.[12] Common biases and limitations across the spectrum of clinical studies are summarized in *Figure 1*.

Target trial emulations allow a more accurate comparison of clinical trial and real-world data. They may be particularly useful in guiding clinical practice when RCTs are not expected in the near future, or at all. In cases where naïve observational studies disagree with RCTs, it has been shown that re-analysis of the same observational data using a target trial emulation technique yields findings similar to RCTs.[13,14] Target trial emulations have gained traction over the past decade; however, these studies are few and far between in the field of cardiology.

The 'trial' element in target trial emulations

Similar to RCTs, target trial emulations also have a well-defined 'time zero'. Time zero is the point at which three events occur: application of eligibility criteria, initiation of a particular treatment strategy, and start of outcome assessment. In contrast, in naive observational studies, groups are often assigned based on exposure status (i.e. users vs. non-users), rather than initial treatment assignment (initiators vs. non-initiators). This strategy results in the inclusion of patients who continue to adhere to the therapy due to observed benefit or lack of adverse effects, and exclusion of patients who discontinued treatment — thereby falsely inflating positive effects of the treatment (prevalent user bias). Furthermore, in naïve observational studies, group assignment is often based on exposure information that is observed after the patient enters the study (after time zero), for example when a patient receives a new drug dispensation at some point after the start of the study. This, by design, means that patients in the treatment

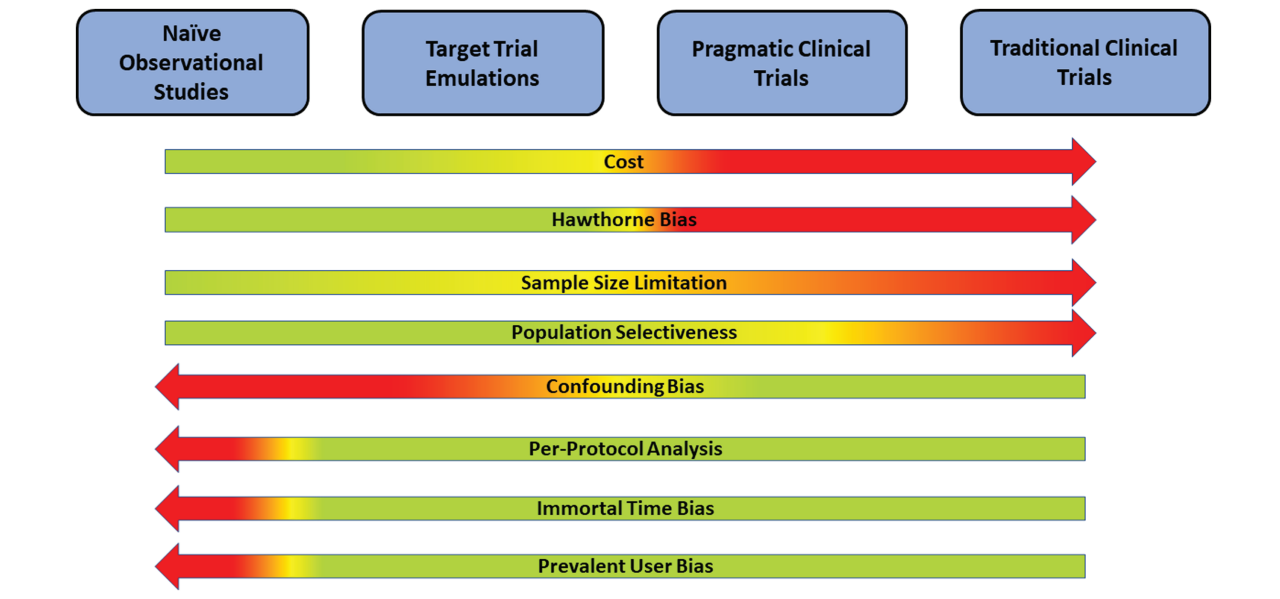


Figure 1 Common biases and limitations in each type of clinical study.

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group who die or experience an event in the follow-up period prior to exposure ascertainment would likely be incorrectly assigned to the 'untreated' group or excluded — once more distorting the results in favor of the treatment group (immortal time bias). The presence of these biases in naïve observational studies has previously resulted in largely implausible conclusions, which were later disproven by RCTs.[15]

Unlike confounding bias which cannot be eliminated with certainty in observational studies, prevalent user bias and immortal time bias are often self-inflicted problems which can be solved by emulating target trials. Trevisan and colleagues eliminated prevalent user bias by considering only patients who were new users of MRA (by imposing a minimum of 12 months of MRA free period prior to the first MRA dispensation). The risk of immortal time bias was reduced by ensuring that patients who died in the period where exposure status was unknown contributed to events in both groups. Additionally, target trial emulations do not impose any specific treatment after the assignment period, thus emulating an intention-to-treat analysis, which is commonly used in RCTs. Naïve observational studies, in contrast, generally employ a per-protocol analysis.

The 'real-world' element in target trial emulations

There are certain elements which make trial emulations more suited to study applicability of treatments in the real world, compared with clinical trials. First, trial emulations can potentially have larger sample sizes given the use of a sufficiently large database. For example, funding and patient recruitment constraints make it unlikely that an RCT designed to study the effects of MRA discontinuation after hyperkalaemia would have a sample size comparable to that reported by Trevisan and colleagues. Second, fewer ethical and design restrictions can allow trial emulations to include a more heterogeneous group of patients, similar to what is seen in a clinical setting. RCTs frequently have narrower eligibility criteria; for example, patients with multiple comorbidities are often excluded to maintain homogeneity and patient safety. Furthermore, RCTs tend to enrol patients with more severe disease to ensure higher event rates. These factors limit the ability of RCTs to identify potential effect modifiers. Additionally, both physicians and patients must consent to participating in a clinical trial, which leads to further selection.

Unlike RCTs, target trial emulations are also free from the risk of Hawthorne bias — which can lead to higher levels of treatment adherence than seen in real-world settings. Additionally, trial emulations also do not have blinding — which is not necessarily a limitation if the goal is to study treatment efficacy in real-world settings.

Limitations of target trial emulations

An ideal trial emulation would require that the treatment strategy varies from patient to patient on a random basis. However, such a scenario is improbable in the real world, and selection of treatment strategy often depends on several patient baseline, prognostic and physician-related factors. Although randomization is statistically emulated in target trial emulations, the efficacy of this is dependent on the presence of data on a rich set of confounders. Even then, residual confounding is always a possibility. Furthermore, sufficient data on exposure time are required to accurately specify a time zero. Thus, the quality of a target trial emulation is entirely dependent on the quality and quantity of registry data available.

Although the SCREAM healthcare utilization cohort is a very comprehensive database, absence of certain data limits the interpretability of the current study. For example, data on MRA dosage were not available — it is very likely that the dose of MRA was reduced in the 'continuation' arm after a hyperkalaemia event. Similarly, data on dosage of other heart failure medications (such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) were also unavailable. Furthermore, there were no data on reasons other than hyperkalaemia to stop MRAs (e.g. pedal oedema). Thus, although Trevisan and colleagues convincingly demonstrate that continuing MRAs after an episode of hyperkalaemia is associated with better long-term clinical outcomes, future studies are required to identify appropriate dosages of MRA and other heart failure medications to continue with.

Conclusion

Target trial emulations are methodologically superior to naïve observational studies, and often yield findings similar to RCTs. Thus, they serve as an important compromise in the absence of RCTs. We congratulate Trevisan *et al.* for answering a critical question in heart failure medicine using the target trial emulation technique, and we believe their findings are reliable and relevant to clinical practice.

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