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CORRESPONDENCE
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Preventing immortal time bias in observational studies: a matter of design

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We thank Diab and colleagues for raising awareness for immortal time bias (ITB) in studies on cardiosurgical treatments in the European Heart Journal.[1] The authors elaborate on ITB in research on infective endocarditis (IE) and tricuspid regurgitation (TR), stating that a prospective, intention-to-treat design is the only practical way to detect and avoid ITB. In this letter, we elaborate on the causes of ITB and outline additional methods to prevent this bias in observational studies.

ITB is introduced when researchers deviate from basic principles of study design. At the start of follow-up (i.e. 'time-zero'), treatment status should be determined and eligibility criteria should be met for all participants. For a fair comparison, time-zero should be similar for all treatments arms, for example, the day of IE or TR diagnosis. However, when future information is used to assign treatment status at time-zero, ITB lures,[2] because—by design—participants have to survive until they undergo the future treatment.

If, however, at time-zero a clinical decision is made between two strategies (e.g. early vs. late surgery), a comparison between those intended strategies is not hampered by ITB. A prerequisite is that follow-up still starts at time-zero for all participants, who are then included in the analysis according to the made clinical decision. That decision reflects the intention for a particular treatment, thus the term intention-to-treat is used, even in an observational study.

Analysis of the treatment that was actually received—i.e. the 'per-protocol' effect—requires alternative methodology in case of early vs. late surgery for IE. For example cloning and censoring, where patients are cloned and each clone is randomly assigned a treatment strategy at time-zero.[2] All patients/clones are then followed until they discontinue the strategy that was assigned to them at baseline, and censored afterwards. A late surgery strategy patient/clone that does not reach the actual late surgery, would then still contribute (follow-up) information to the analysis.

When interest lies in comparing surgery vs. medical treatment for TR, several other approaches exist to prevent ITB, for example an analysis of treatment options as time-dependent variables.[3] A patient who undergoes surgery contributes person-time to the medical treatment group until surgery is performed, and to the surgery group afterwards. An alternative approach is a landmark analysis. At a certain 'landmark' timepoint, e.g. 1 month after diagnosis of severe TR, all patients who are still at risk are classified according to surgery performed until the landmark.[3]

Observational studies of medical treatments are prone to bias from different sources (e.g. confounding, missing data, misclassification). ITB is a self-inflicted bias resulting from misaligning time-zero with treatment assignment. Various methods beyond intention-to-treat designs exist to estimate valid treatment effects, even in retrospective studies, however, these methods target different research questions. Cardiovascular researchers should be aware of the problem of ITB and consider analytical solutions to prevent this bias.

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References

1. Diab M, Bonaros N, Doenst T. Immortal time bias: the hidden confounder in assessing cardiosurgical treatment effects. *Eur Heart J* 2023;**44**:3149–3151.
2. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol* 2016;**79**:70–75.
3. Dekkers OM, Groenwold RHH. When observational studies can give wrong answers: the potential of immortal time bias. *Eur J Endocrinol* 2021;**184**:E1–E4.

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