Circulation: Cardiovascular Quality and Outcomes

EDITORIAL

Exposure Misclassification in Observational Studies

Setting New Standards

See Article by Krumme et al

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In recent years, there has been considerable investment in the use of observational data, including registry, electronic medical records, and insurance claims-based databases, to complement randomized trials for evaluating medical therapies and devices. Observational analyses of therapeutic interventions have been used to assess treatment effectiveness in more broadly representative populations, provide longer duration of follow-up, and offer an opportunity for potential cost savings compared with prospective trials.[1] However, these studies are not without limitations. In particular, the lack of random assignment of treatment as well as challenges in accurately characterizing treatment status can introduce hidden biases that impact the validity of study results.[2]

In the accompanying study, Krumme et al[3] attempt to address a common limitation of observational studies evaluating the effectiveness of different medications: difficulty in accurately defining medication exposure leading to misclassification bias. As highlighted by the authors, traditional methods of defining medication exposure status have relied on the use of the landmark method, or by definition, a specific time point in which a patient is determined to either be on or off therapy. However, the use of a single time point may not accurately capture a patient's true exposure status, particularly when evaluating prescription medications.[4] As such, the authors attempted to determine whether they could reduce the influence of exposure misclassification by altering how medication exposure was defined.

To do so, the authors used the evaluation of prolonged dual antiplatelet therapy (DAPT) >12 months after coronary stenting as a test case. This example was chosen as a recent large randomized clinical trial, the Dual Antiplatelet Therapy Study,[5] evaluated a similar question, whereas prior observational studies evaluating the long-term treatment effects of DAPT have used the landmark method to define exposure status.[6] The authors studied a proprietary linked electronic health record and insurance database, which included pharmacy claims data, to compare 12 months of DAPT versus more prolonged therapy, and used similar inclusion and exclusion criteria as the Dual Antiplatelet Therapy Study. Starting with the landmark method, the authors applied increasingly restrictive criteria in an attempt to better identify a population of DAPT continuers and discontinuers. Results from each nested cohort were compared with that of the Dual Antiplatelet Therapy Study. In addition, the authors evaluated whether they achieved improvement in DAPT exposure status by assessing the proportion of days covered, or PDC, among continuers and discontinuers in the 12 to 18 month time period.

We commend the authors for an elegantly performed analysis that raises the bar for defining treatment exposure status in future analyses. With each sequential set of restrictions, the authors were able to better define a population that were either

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continued or discontinued on DAPT after 12 months. This was represented by a substantial increase in PDC for DAPT continuers and decrease in PDC among the DAPT discontinuers between the most (cohort 4) and least (cohort 1) restrictive cohorts. Furthermore, among increasingly restrictive cohorts, hazard ratios for major adverse cardiovascular or cerebrovascular events and myocardial infarction more closely approached that of the results of the Dual Antiplatelet Therapy Study, accomplishing their goal of approximating the results of a gold standard randomized trial.

The reduction in misclassification bias can in part be attributed to narrowing the population to those for whom the filling versus nonfilling of prescriptions was indicative of greater intent. For instance, requiring enrollees to have a cardiology visit in the preceding 2 months before continuation or discontinuation made the assignment of exposure status at 12 months more purposeful. As such, this methodology allowed the authors to more closely mimic what is performed in randomized clinical trials. This likely also accounts for the authors' ability to estimate treatment effects more similar to that of the Dual Antiplatelet Therapy Study.

Importantly, as each cohort became increasingly restricted, the cohorts, as a consequence, became healthier and more adherent. Patients who fulfill a year of DAPT, have no events in the year after coronary stenting, and attend a cardiology visit at 1 year are inherently different than all others. As such, although the restricted study population allows the authors to better define treatment exposure status, these results may become less generalizable to the broader real-world patient population. As evidence of this, with each overlay of new criteria, the overall event rates in the study sample declined. Although the hazard ratios for major adverse cardiovascular or cerebrovascular events and myocardial infarction more closely aligned with the Dual Antiplatelet Therapy Study results, event rates actually become more disparate. The more restrictive criteria also greatly diminished the available sample, leading to widening and overlapping confidence intervals. A similar effect was observed when examining the effect of DAPT on bleeding, with the most stringent criteria failing to find statistically significant increases in bleeding with prolonged DAPT—a finding that has been demonstrated numerous times in even modestly powered randomized trials.[7]

Last, focusing this analysis on misclassification bias may be akin to focusing on one elephant in the room and ignoring another. A major limitation of comparative analyses of therapeutic interventions in observational data is that of confounding by indication. Although there have been a plethora of recent DAPT trials that have improved our understanding of the optimal duration of DAPT after coronary stenting, the decision to continue or discontinue treatment at 12 months remains at the discretion of the treating provider.[8] Often there are patient characteristics, such as frailty,[9] that are unmeasured in registry and claims-based databases but have substantial influence on both the decision to treat and outcomes. Furthermore, patient and procedural characteristics, such as presentation with myocardial infarction and stent type and diameter, are important determinants of the duration of treatment[10] yet were not controlled for in this analysis. The authors do acknowledge this limitation and reference alternative statistical methodologies, such as instrumental variable methodology, that have been used to overcome this issue.[11] How the methods put forward here might be combined with these other techniques to simultaneously address exposure misclassification and confounding by indication remains an area of great interest.

Overall, the study offers an important step forward at expanding the methodology used to define medical treatment exposure in observational analyses. These methods ought to be considered by pharmaco-epidemiologists entertaining the future use of landmark analysis to define treatment exposure. However, it is important to note that the presence of a well-powered randomized trial was required to evaluate the method against a gold standard. Whether these methods will be enough to lend credibility to observational comparative effectiveness studies in the absence of randomized data remains to be seen.

ARTICLE INFORMATION

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Disclosures

None.

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