Editorial

The use of instrumental variables: An alternative to traditional modeling?

We read with interest the article “Can We Account for Selection Bias? A Comparison of Bare Metal and Drug-Eluting Stents in Belgium,” especially because the authors, together with a team of experts from the Belgian Health Care Knowledge Centre (KCE), previously published a health technology assessment (HTA) report and economic evaluation on this subject using the same data [1,2].

Both assessments are made for the Belgian population. The two studies, however, used a different methodological approach. The KCE analysis applied the “traditional” modeling approach to calculate the cost-effectiveness of drug-eluting stents (DES) versus bare metal stents (BMS). The “alternative” approach used Ordinary Least Squares (OLS) and Instrumental Variable (IV) methods to compare costs between DES and BMS treatments.

It is fascinating to observe that using those two different analysis methods can lead to completely opposite conclusions. The KCE report concluded that DES was not cost effective, due to the combination of a relatively high price for DES and the rather good results obtained with BMS. In contrast, the econometric approach found no significant cost differences for diabetic patients and cost savings with DES for the non-diabetic population (if the cost for dual-antiplatelet therapy was excluded).

Arguments both in favor and against different approaches can be considered. It is not our aim to list these. The results of the IV analysis, however, are intuitively hard to understand. We illustrate this with “a back of the envelope” calculation (for which the exact calculations and details can be found in the full HTA report). In the real-world Belgian population, the cumulative probability for a repeat percutaneous coronary intervention (PCI) within 1 year was on average 15% in patients actually receiving a BMS (n = 11,453). Less than 50% of these re-interventions were due to restenosis (defined in the study as a re-PCI in the same vessel as the initial intervention). Based on randomized controlled trials it was assumed that approximately two-thirds of these re-interventions could be avoided if patients would receive a DES instead of a BMS. Consequently, this would result in an absolute treatment effect of 5% fewer PCI re-interventions at the most.

With a re-PCI cost of about €7000, the initial extra cost for the health care payer of €1000 for a DES per patient is difficult to be outweighed. Furthermore, extra costs for antiplatelet treatment have to be taken into account (which was done in the KCE cost-effectiveness analysis). Even with an optimistic 100% treatment effect to avoid all restenosis, cost savings would still not be reached with current DES charges due to the relatively good results with BMS. Translating the large relative treatment effect on a relatively small baseline risk for re-interventions is translated in small absolute gains, which eventually determine the intervention’s cost effectiveness.

So why do we observe this difference using two radically different research methods? In theory, the instrumental variable approach can measure the treatment effect using observational data and adjusting for observable and non-observable confounding factors. However, the practical use of this approach depends on the quality of the instrument, which is difficult to assess. As the authors mentioned, it cannot be ruled out that the treatment effect model does not correct for all observed or unobserved characteristics and that the estimated treatment effect is biased, possibly due to weak instruments. The contrast with the traditional, but more transparent, approach confirms this and indicates that one has to be careful using this approach to make policy recommendations.

This discussion demonstrates that clever techniques should be used carefully and special attention to bias should be monitored that would favor instruments leading to “positive” findings. Nevertheless, we are also confident that econometric approaches using OLS, instrumental variables or other techniques could have their merits, e.g., to try to estimate causal relationships when controlled experiments are not feasible or to formulate hypotheses that need further research. It is necessary to investigate the validity and limitations of these approaches. However, with current knowledge, cost-effectiveness calculations preferably use transparent techniques and should use data from well-performed RCTs (if available) to reflect the relative treatment effect.

Funding: The authors have no financial relationships to disclose.
REFERENCES
