the first two methods.[4] It would better to use the IPTW method to estimate treatment effects of PNB. Moreover, selecting similar propensity scores during matching allows the high and low propensity scores to be discarded. We are concerned that this portion will not represent all patients who have undergone TKA. The IPTW method would solve this problem.

## Competing Interests

The authors declare no competing interests.

**Jung-Won Hwang, M.D., Ph.D., Young-Tae Jeon, M.D., Ph.D.** Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea (Y.-T.J.). ytjeon@snubh.org

## References

1. McIsaac DI, McCartney CJL, van Walraven C: Peripheral nerve blockade for primary total knee arthroplasty: A population-based cohort study of outcomes and resource utilization. Anesthesiology 2017; 126:312–20
2. Kerr DR, Kohan L: Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: A case study of 325 patients. Acta Orthop 2008; 79:174–83
3. El Bitar YF, Illingworth KD, Scaife SL, Horberg JV, Saleh KJ: Hospital length of stay following primary total knee arthroplasty: Data from the Nationwide Inpatient Sample Database. J Arthroplasty 2015; 30:1710–5
4. Rubin DB: On principles for modeling propensity scores in medical research. Pharmacoepidemiol Drug Saf 2004; 13:855–7

*(Accepted for publication June 7, 2017.)*

*In Reply:*

We thank Drs. Hwang and Jeon and Drs. Kehlet and Jørgensen for their letters and welcome the opportunity to discuss the strengths and limitations of our study.[1]

As stated in the letter from Drs. Hwang and Jeon and acknowledged in our article,[1] we were unable to identify whether each nerve block studied was actually clinically effective. When considered from the perspective of an explanatory research question, this is clearly a limitation. However, because the aim of our study was comparative effectiveness, our specific objective was in the realm of pragmatic research, that is, how effective and generalizable might the intervention be in real-world practice.[2] From this perspective, we hope that our measures of association provide useful insights into the impact that the peripheral nerve blocks have on system outcomes across a generalizable large sample of patients across an entire healthcare system.

With respect to the assertion by Drs. Hwang and Jeon that our lack of control for intraoperative and postoperative variables and complications is a limitation, we would argue the contrary. In observational comparative effectiveness research, efforts must be made to adjust for indication bias and confounding bias (among other sources). When selecting variables that may be confounders, one must ensure that they meet the definition of a confounder, specifically that they differentially impact exposure (*i.e.*, receipt of a block), differentially impact outcome, and are not on the causal pathway.[3] Therefore, although complications may contribute to differences in length of stay (LOS), they are not true confounders because they occur after exposure and are likely on the causal pathway to prolonged LOS. Furthermore, it has been shown that control for variables such as these that are not true confounders can lead to spurious associations.[4]

Finally, we agree with Drs. Hwang and Jeon that the choice of analytic approach when performing propensity score–based analyses impacts interpretation of study results.[5] Specifically, matched analyses such as ours estimate the average treatment effect in the treated (ATT), because some individuals are excluded if they received treatment but no adequate match was available or if they were untreated and again went unmatched to a treated subject. Although this may decrease overall generalizability, it may also decrease bias. In contrast, methods such as inverse probability of treatment weighting (IPTW) or regression analysis provide an average treatment effect (ATE), that is, what might happen if the entire population was shifted from untreated to treated.[6] Although the ATT and ATE are typically similar in direction and magnitude, this is not always the case. In fact, in the case of IPTW, including individuals who were treated despite a very low propensity for treatment can greatly over-weight their contribution to the analysis, especially if extreme tails of the distribution are not trimmed.[5] Furthermore, matched analyses can provide an estimate of the absolute risk difference, as opposed to IPTW and regression-based approaches that are typically limited to estimating relative outcome differences. Lastly, in our sensitivity analysis we used a regression-based multilevel multivariable regression analysis, which estimated an ATE for single shot blocks that was identical in direction and magnitude to the ATT estimated from the propensity score–matched analysis.

We would also like to thank Drs. Kehlet and Jørgensen for their commentary regarding our publication[1] and in particular their interest in promoting improvements in reporting, analysis, and overall research efforts related to LOS. First, we agree that different patterns of care between jurisdictions or individual hospitals can skew LOS findings. As Hart *et al.*[7] outlined in an analysis of Canadian *versus* American total joint arthroplasty outcomes, LOS in Canadian hospitals tends to be approximately 1.3 to 1.4 days longer, a finding that may be attributable to a 21 to 27% increase in rates of discharge to short-term rehabilitation from American hospitals. Data from Hart *et al.*[7] also suggest a mean LOS after joint replacement in Canadian hospitals of slightly more than four days, a figure consistent with mean LOS reported in our study, which included a larger cross-section of hospitals than would have been included in the National Surgical Quality Improvement Program data file.

Regarding differences in practice between hospitals, we fully acknowledge that our data sources do not allow us to measure whether specific fast-track processes of care were used at certain hospitals and for specific patients in our study; this is a limitation. For this reason, we ensured that all of our analyses accounted for clustering of patients within hospitals to allow us to account for unmeasured variation between hospitals, both in the use of perioperative processes of care as well as discharge patterns. In our propensity score–matched analysis this involved direct matching within hospitals along with a propensity score, a method that has been shown to decrease both bias and error in estimating causal effects relative to simply matching on the propensity score.[8] In our sensitivity analysis, which used regression analysis, we accounted for clustering of patients in hospitals using a multivariable-adjusted generalized linear model and generalized estimating equation methods. We certainly encourage the use of analytic strategies that account for hierarchal data in all comparative effectiveness research where between-center variation is a consideration.

In summary, across a universal healthcare system we report the population-based association between peripheral nerve block exposure and LOS using best-practice methods for comparative effectiveness research and report a LOS consistent with other reports from our jurisdiction. We agree that our data, like any observational data set, have limitations that must be considered when appraising our findings. We also agree that understanding why patients remain in the hospital after surgery is a high-priority area of research and that minimizing variation and instituting best practices should lead to improved patient and system outcomes.

## Competing Interests

The authors declare no competing interests.

**Daniel I. McIsaac, M.D., M.P.H., F.R.C.P.C., Colin J. L. McCartney, M.B.Ch.B., Ph.D., F.R.C.A., F.C.A.R.C.S.I., F.R.C.P.C., Carl van Walraven, M.D., F.R.C.P.C., M.Sc.** The Ottawa Hospital, Ottawa, Ontario, Canada (D.I.M.). dmcisaac@toh.ca

## References

1. McIsaac DI, McCartney CJL, van Walraven C. Peripheral nerve blockade for primary total knee arthroplasty: A population-based cohort study of outcomes and resource utilization. Anesthesiology 2017; 126:312–20
2. Koppenaal T, Linmans J, Knottnerus JA, Spigt M: Pragmatic vs. explanatory: An adaptation of the PRECIS tool helps to judge the applicability of systematic reviews for daily practice. J Clin Epidemiol 2011; 64:1095–101
3. Weinberg CR. Toward a clearer definition of confounding. Am J Epidemiol 1993; 137:1–8
4. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: An application to birth defects epidemiology. Am J Epidemiol 2002; 155:176–84
5. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, Robins JM: Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. Am J Epidemiol 2006; 163:262–70
6. Austin PC, Laupacis A: A tutorial on methods to estimating clinically and policy-meaningful measures of treatment effects in prospective observational studies: A review. Int J Biostat 2011; 7:6
7. Hart A, Bergeron SG, Epure L, Huk O, Zukor D, Antoniou J: Comparison of US and Canadian perioperative outcomes and hospital efficiency after total hip and knee arthroplasty. JAMA Surg 2015; 150:990–8
8. Gayat E, Thabut G, Christie JD, Mebazaa A, Mary JY, Porcher R: Within-center matching performed better when using propensity score matching to analyze multicenter survival data: Empirical and Monte Carlo studies. J Clin Epidemiol 2013; 66:1029–37

*(Accepted for publication June 13, 2017.)*

# Combining Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blocker for Clinical Decision-making Lacks Vision

*To the Editor:*

We read with interest the study by Roshanov *et al.*[1] comparing outcomes in patients undergoing noncardiac surgery, following the withholding or continuing of an Angiotensin-converting Enzyme Inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB). Although this was a large and comprehensive retrospective study, several key issues should be considered when reviewing this article.

First and foremost is the practice of combining of both ACEis and ARBs for study analysis. ACEi and ARBs are two distinct classes of medications acting at very different regulatory points within the renin-angiotensin system.[2] Moreover, their actions at these regulatory points produce distinct end effects.

A dual action enzyme, angiotensin-converting enzyme is responsible for both the conversion of angiotensin I to angiotensin II and the breakdown of bradykinin into non-active molecules. As a result, ACEi prevents the generation of angiotensin II and increases circulating levels of bradykinin.[3,4] While many of the beneficial effects of ACEi therapy have been attributed to reductions in angiotensin II, these benefits appear to be due to increased levels of bradykinin.[5]

Moreover, it is known that chronic ACEi use does not alter circulating levels of angiotensin II.[6–9] Escape pathways of angiotensin II production exist; including chymase-mediated production, which result in production of angiotensin II and a return to pretreatment plasma levels during chronic ACEi use.[10,11] The duration of ACEi use prior to surgery is not addressed in this study. This could significantly affect circulating angiotensin levels and, therefore, the interpretation of study results.

On the other hand, ARBs are highly specific antagonists of the angiotensin type 1 ($AT_1$) receptor and block downstream signaling of these G-protein coupled receptors.[3,12] While the classic actions of angiotensin II (salt