Appendix 3 (as supplied by the authors): Probabilistic sensitivity analysis for evaluating the impact of outcome misclassification

Method

We used methods proposed by Lash, Fox, and Fink,[1] to conduct a probabilistic sensitivity analysis (PSA) evaluating the impact of outcome misclassification on our observed estimates. Use of ICD-9 diagnosis codes to identify cases of VTE is reported to have predictive positive values in the range of 65% to 95%.[2] Based on this range, we calculated corresponding measures for sensitivity and specificity assuming a true underlying prevalence of 0.025 for VTE. Using the resulting ranges of sensitivity (0.75 to 0.95) and specificity (0.990 to 0.999), we conducted 1,000 Monte-Carlo simulations for this PSA. In each simulation, we used uniform distribution to randomly sample values of sensitivity and specificity of the outcome from the pre-specified ranges and calculated corrected risk ratios (RRs) based on summary level exposure and outcome data.

Results

In the following table, we report median, 2.5th and 97.5th percentile of the corrected RRs to demonstrate the impact of outcome misclassification on our estimates.

Outcome misclassification scenario	**Corrected RR estimates-Median (2.5th-97.5th percentile)**	**Quantitative estimate of the impact of misclassification (Based on the reported relative risk of 0.78)**
Non-differential between two exposure groups	0.53 (0.04 – 0.76)	47% underestimation of the effect of TNF-α inhibitors on the risk of VTE
Differential (sensitivity of VTE algorithm higher in the TNF-α inhibitor group)	0.56 (0.05 – 6.89)	39% underestimation of the effect of TNF-α inhibitors on the risk of VTE
Differential (sensitivity of VTE algorithm lower in the TNF-α inhibitor group)	0.61 (0.05 – 5.59)	28% underestimation of the effect of TNF-α inhibitors on the risk of VTE

Conclusion

Based on the results from this analysis, we note that low PPV of the algorithm to identify VTE is unlikely to explain our primary finding. If anything, we would expect the reported results to be underestimating the true effect of TNF-α inhibitors on the risk of VTE due to outcome misclassification.

Appendix to: Desai RJ, Gagne JJ, Lii J, et al. Comparative risk of incident venous thromboembolism in patients with inflammatory bowel disease initiating tumour necrosis factor-α inhibitors or nonbiologic agents: a cohort study. CMAJ 2017. doi: 10.1503/cmaj.161485.

References

1. Lash TL, Fox MP, Fink AK. Applying quantitative bias analysis to epidemiologic data. 2011; Springer Science & Business Media.

2. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. *Pharmacoepi Drug Saf*. 2012 Jan 1;21(S1):154-62.