

# Using Reference-Arm Adjustment to Reduce Bias in Outcomes of Bucher Indirect Comparison: A Case Study

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## Objectives

Indirect treatment comparison (ITC) has been widely used for investigating comparative effectiveness of target interventions when head-to-head studies are not available<sup>1</sup>.

Theoretically, ITC could produce valid estimations with assumptions in study homogeneity, similarity and evidence consistency. However, in an anchored ITC, relative effects of interventions to their reference arms could be influenced by unmeasured confounders and lead to biased comparison results<sup>2</sup>.

The aim of this study was to explore whether using reference-arm adjustment can help to reduce the biases in outcomes.

## Methods

We followed Bucher et al.'s ITC method to evaluate efficacy and safety between eltrombopag and hetrombopag for treatment of immune thrombocytopenia using placebo as a common comparator.

Outcomes evaluated by ITC included incidence of any grade bleeding symptom and safety profile. Odds ratio (OR) was used as effect measure and its 95% confidence interval (CI) was calculated.

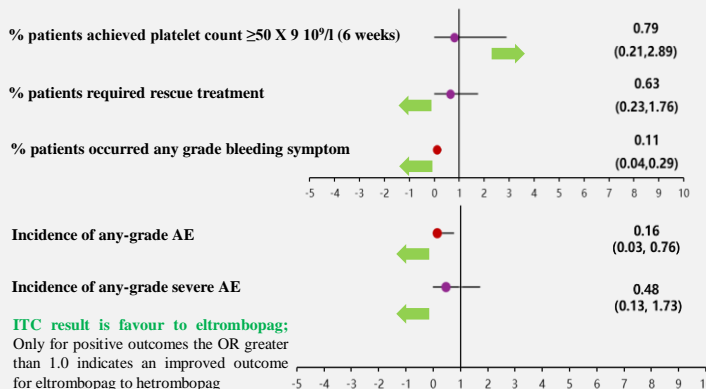
The consistency of results was investigated between ITC analysis that adjusted for reference arms and base-case ITC analysis without reference-arm adjustment.

## Results

A systematic literature search was conducted up to October 2021 and two eligible randomized controlled trials were analyzed<sup>3-4</sup>.

- Our analysis found that reference arms (i.e., placebo) of these trials had significant difference in efficacy, which indicated unmeasured confounders may exist within base-case ITC analysis.
- When reference-arm adjustment was applied in ITC, eltrombopag showed a significantly reduced risk for any grade bleeding symptom and any grade AE compared with hetrombopag (OR=0.11, 95% CI 0.04–0.29 and OR=0.16, 95% CI 0.03–0.76, respectively).
- While in base-case analysis, no significant difference was observed between eltrombopag and hetrombopag.

### Forest plots of indirect comparison of efficacy outcomes and safety profile Eltrombopag vs Hetrombopag



## Conclusions

Our study found that cross-trial differences in reference arms can introduce bias to ITC results.

Reference-arm adjustment can be considered to ensure ITC yields credible results.

## Bibliography

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