

## Benefits and Risks of Intraoperative High Inspired Oxygen Therapy: Firm Conclusions Are Still Far Off

To the Editor:

We read with great interest the recent systematic review and meta-analysis by Hovaguimian *et al.*<sup>1</sup> on the advisability of intraoperative administration of a high inspired oxygen fraction ( $F_{IO_2}$ ). The authors analyzed randomized trials comparing high supplemental oxygen (defined as  $F_{IO_2} \geq 50\%$ , preferably 80%) with a lower fraction ( $F_{IO_2} < 50\%$ ) for reducing surgical site infection (SSI) and postoperative nausea and vomiting.

Previous meta-analyses had reached inconsistent conclusions regarding the effect on SSI.<sup>2-7</sup> This new meta-analysis<sup>1</sup> found evidence (in nine trials including 5,103 patients) that SSI risk decreased by 23% when a high  $F_{IO_2}$  was applied during all types of surgery (risk ratio [RR], 0.77; 95% CI, 0.59 to 1.00). However, moderately large heterogeneity ( $I^2$ , 54%;  $P = 0.03$ ) was also detected.<sup>1</sup> Moreover, in a subgroup analysis of colorectal surgery (1,977 patients in eight trials), the effect of supplemental oxygen was statistically borderline (RR, 0.78; 95% CI, 0.60 to 1.02), but as heterogeneity was not significant ( $I^2$ , 39%;  $P = 0.11$ ), the authors did demonstrate a statistically significant overall effect (RR, 0.79; 95% CI, 0.65 to 0.97) under a fixed-effects model.

As a result, we feel that these data should not be taken to suggest that additional trials or meta-analyses are unnecessary, that is, we believe that we should not take the reduction in SSI to have been demonstrated. Nothing could be farther from the truth. We believe deeper analysis, with greater power to account for the detected heterogeneity may still call into question the translation of these findings to clinical practice. It is noteworthy that all the included trials enrolled relatively small numbers of patients with colorectal surgery, and most (six of eight) lacked sufficient power to determine potential differences. To illustrate this concern, we note that in a hypothetical meta-analysis that assumes a baseline SSI rate of 17.5% and an effect size of 22% (RR, 0.78), more than 3,200 patients would be required for an alpha of 0.05 and 80% power.<sup>8</sup> The implication is that to detect such an effect, 1,200 more cases would be needed in a future meta-analysis.

The extent of heterogeneity in analyzed studies partly determines how difficult it is to draw overall conclusions. Analysts do not generally explore potential causes of heterogeneity by incorporating study-level covariates in random-effects regressions, sometimes because of limited data provided in the selected trials. Conflicting conclusions on SSI in the analyzed studies<sup>2-7</sup> may derive from variations in patient characteristics (*e.g.*, baseline differences in risk factors for SSI) or varying surgical procedures or outcome assessments across trials. The implication of such differences in past trials is that future analyses should look at the distribution of potential effect modifiers when the body of evidence permits.

Results can also be usefully reported with a prediction interval (PI), a novel statistical proposal which assesses the degree of heterogeneity and its likely effect by predicting a range for the

treatment effect in future studies.<sup>9</sup> To differentiate the information provided by the more familiar CI from the information given by the PI, consider that the CI confirms that a sample mean has been reasonably well estimated whereas the PI tells us where 95% of the future data points should lie. Thus, the PI gives us a more complete picture of the degree of uncertainty around our current inferences. When we calculated the PI for the data provided by Hovaguimian *et al.*,<sup>1</sup> the upper and lower limits included the null value of 1, and so we can expect that in some settings applying a high  $F_{IO_2}$  may actually be ineffective for reducing SSI (RR, 0.77; 95% PI, 0.38 to 1.57). Given such a large PI, further research is needed until the causes of heterogeneity can be controlled for. Meanwhile, we can only tentatively conclude, based on these results and a solid pathophysiological foundation,<sup>10,11</sup> that applying a high  $F_{IO_2}$  is very likely to reduce SSI and may provide protection in many surgeries.

In summary, it seems to us that further research is still needed if we are to clarify the specific effects of perioperative high  $F_{IO_2}$  so that we can confidently generalize results to a range of populations and clinical situations. However, it is already clear that new trials have to reduce heterogeneity by including standard measures of SSI<sup>12</sup> and postoperative nausea and vomiting<sup>13</sup> and by recruiting primarily patients at high risk for these events. Meanwhile, this meta-analysis brings us closer to closing the debate and helping us realize what is still needed.

### Competing Interests

The authors declare no competing interests.

**F. Javier Belda, M.D., Ph.D., Ferrán Catalá-López, Pharm.D., M.P.H., Ph.D., Robert Greif, M.D., M.M.E., F.E.R.C., Jaume Canet, M.D., Ph.D.** Hospital Universitari Germans Trias i Pujol, Badalona, Spain (J.C.). jcanet.germanstrias@gencat.cat

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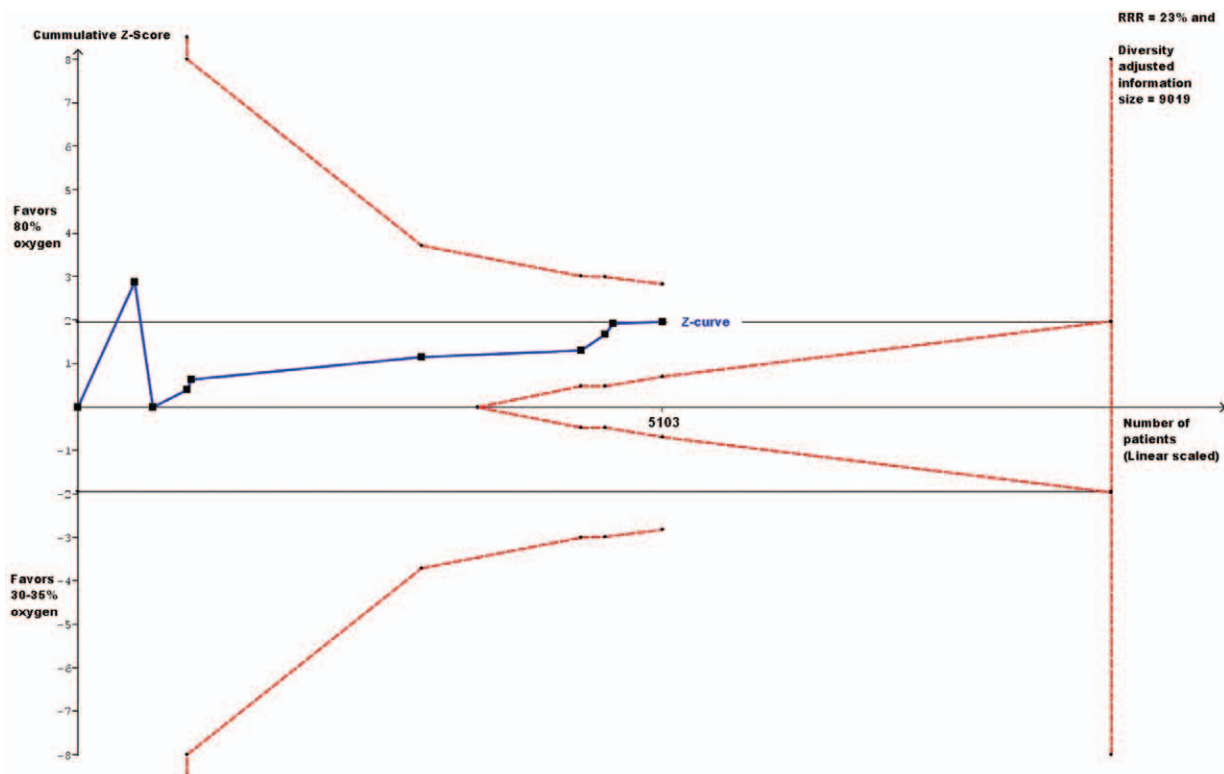
## Intraoperative High Inspired Oxygen Fraction: Are There Real Benefits?

To the Editor:

We read with interest the meta-analysis by Hovaguimian *et al.*<sup>1</sup> on the effects of a high perioperative inspiratory oxygen fraction. The positive conclusions in terms of decreased

risk of surgical site infection (SSI), weak prophylactic effect on nausea, and no increased risk of atelectasis raise several methodological concerns.

First, the preventive effect on SSI was reported for patients receiving prophylactic antibiotics although the observed difference was not statistically significant (upper 95% CI, 1.00). Moreover, the actual rates of patients receiving antibiotics were only reported in four of the nine trials,<sup>2–5</sup> leaving the conclusion to be based on protocol information from five trials, and a separate analysis of antibiotics *versus* no antibiotics was omitted. The large body of evidence demonstrating no significant effect on SSI from perioperative hyperoxia to 1,966 patients for caesarean section was excluded from the current meta-analysis, because the intervention was delivered through nonrebreathing masks during neuraxial anesthesia,<sup>6</sup> although such face masks are able to deliver a fraction of inspired oxygen ( $F_{IO_2}$ ) greater than 0.60 inducing an adequate high-to-normal  $F_{IO_2}$  ratio. The Evaluation of Nitrous Oxide In the Gas Mixture for Anaesthesia (ENIGMA) trial, favoring hyperoxia *versus* nitrous oxide to prevent SSI, was included without restrictions in the meta-analysis, suggesting that there is no difference between nitrous oxide and nitrogen in this context.<sup>5</sup> However, a randomized trial of 197 patients<sup>7</sup> receiving five different interventions, including a perioperative  $F_{IO_2}$  of 0.80, was excluded because data could not be extracted. Data seem to be available, and the significantly increased risk of SSI in the intervention group in that study would further have challenged the primary conclusion of this meta-analysis.



**Fig. 1.** Trial sequential analysis of the nine trials included in the meta-analysis of hyperoxia to prevent surgical site infection by Hovaguimian *et al.*<sup>1</sup> Solid line = cumulative Z-curve. Dashed line = trial sequential monitoring boundary. RRR = relative risk reduction.