oxygen and low oxygen arms of the Vento et al study. The exact pressures used by Dekker et al were not mentioned but more efficient use of the mask ventilation with better seal might explain higher SpO_2 achieved in this study. Although an increase in alveolar PaO_2 is expected with 90% oxygen, presence of right-to-left shunts might attenuate the rate of increase in SpO_2. Finally, cord management differed between the 2 studies. These differences in study design and possible differences in efficacy of mask ventilation might have contributed to the differences in SpO_2 observed between the 2 studies. Similar to Kapadia et al,[4] Vento et al observed a reduction in bronchopulmonary dysplasia with the low oxygen strategy.

Dekker et al ask: should we recommend a change in guidelines to start with higher fraction of inspired oxygen ($FiO_2 \sim 1.0$) in extremely preterm infants based on a physiological sound but small, randomized trial of 44 infants and what is the optimal primary outcome of neonatal clinical trials evaluating resuscitation at birth?

Two systematic reviews conducted by the International Liaison Committee on Resuscitation Neonatal Task Force and Cochrane database prior to publication of the Dekker et al study concluded that the ideal FiO_2 for preterm newborns is still not known and no advantage of high vs low initial FiO_2 was demonstrated.[5,6] More studies evaluating this topic are needed to reach an evidence-based consensus. Recommending 1.0 FiO_2 for initial resuscitation for a short period during mask ventilation may be physiologically appropriate, but needs to be substantiated by a higher number of enrolled subjects and preferably by a systematic review.

There is considerable debate regarding the optimal primary outcome and endpoint for neonatal clinical trials in general and trials evaluating short-term measures in the delivery room. The use of death or neurodevelopmental impairment (NDI) at approximately 2 years has been considered the gold standard in many recent neonatal trials. We agree with Dekker et al that a large sample size will be needed for a short intervention during resuscitation to have an impact on death/NDI at 2 years. However, should we be implementing interventions that result in short-term transient improvements but do not influence mortality, morbidity (such as intraventricular hemorrhage or bronchopulmonary dysplasia) or long-term NDI? The Food and Drug Administration guidelines recommend clinical endpoints should be a direct measure of improved survival, a benefit that was detectable by the patient (improvement in symptoms or functional capacity) or decreased chances of developing a condition or disease complication that is itself apparent to the patient and is undesirable (https://www.fda.gov/media/84987/download).

The neonatal community needs more studies such as Dekker et al[1] so that appropriate systematic reviews can be conducted to enable International Liaison Committee on Resuscitation Neonatal Task Force to provide evidence-based recommendations for optimal initial oxygenation of extremely preterm infants that improve clinically relevant endpoints.

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Clarification of aOR calculation

To the Editor:

Foglia et al reported that changes in oxygen saturation (SpO_2) policies had no impact on the incidence of retinopathy of prematurity (ROP).[1] Their assertion is based on the finding of significant reduction of any ROP incidence during epoch 2 among the hospitals that did not change their SpO_2 policies as well as among those that did change their SpO_2 policies with aORs of 0.57 and 0.71, respectively, resulting in a nonsignificant interaction term for this outcome.

Table II of this report reveals that the magnitude of difference between aOR (0.57) and the unadjusted OR (0.97) is approximately 40% for any ROP among hospitals that did not change their SpO_2 policy. This degree of difference between adjusted and unadjusted ORs is not seen for any other

outcome between the epochs in the 2 groups of hospitals. This raises the possibility of a statistical calculation error because the authors do not provide an explanation for this degree of deviation of aOR from the raw unadjusted OR. If the aOR for this measure is indeed insignificant, then the author's conclusion that SpO_2 policy changes had no impact on any ROP incidence needs to be revised.

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Reference

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Reply

To the Editor:

Dr Srivatsa voiced concerns about our report investigating the impact of changing oxygen saturation alarm limit policies on neonatal outcomes among extremely preterm infants. Dr Srivatsa correctly notes that the magnitude of difference between the unadjusted ORs and aORs for the outcome of "any retinopathy of prematurity (ROP)" was approximately 40% for infants in hospitals without a policy change. This magnitude of difference was not seen for other outcomes.

In fact, the aORs are less than the unadjusted ORs across epochs for most outcomes assessed in both hospital groups. We could speculate about exactly why the degree of difference is higher for the outcome of "any ROP," but we know it is due to adjustment for 1 or more of the important baseline covariates included in the model. Many of these covariates varied significantly between epochs. We confirm that the observed difference was not due to a calculation or reporting error.

Further, we dispute the notion that our conclusion need be revised. The strength of our study design is that we included hospitals without a policy change as a comparison group. This allowed us to isolate the impact of the policy change itself from secular trends in practice and outcomes that would be observed in a traditional before/after study following a policy change. Although the aOR for "any ROP" suggested improved outcomes in epoch 2 for both groups, the interaction between hospital group and epoch was not significant. This supports our conclusion that a policy change was not associated with meaningful improvements in the outcome of any ROP.

In conclusion, the difference between the unadjusted ORs and aORs is due to the adjustment for covariates that may have differentially impacted the outcomes, leading to different degrees of difference between the unadjusted ORs and aORs across outcomes.

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Do B-type natriuretic peptide levels accurately predict outcome in infants with congenital diaphragmatic hernia?

To the Editor:

We have read with interest the study by Guslits et al that investigated the prognostic effect of B-type natriuretic peptide (BNP) in predicting the outcomes of infants with congenital diaphragmatic hernia (CDH).[1] Infants with atrial septal defect, ventricular septal defect, or patent ductus arteriosus were included. However, it may be important to exclude subjects with any other disease that influences ventricular volume expansion and pressure overload, because BNP is a cardiac neurohormone secreted by the ventricles in response to volume expansion and pressure overload.[2] We are very interested in the echocardiographic parameters of those infants, to understand if these heart diseases could have an impact on their right volume and pressure. Alternatively, an additional control group with similar heart diseases but without CDH could be included.

In the present study, the authors sought additional biomarkers that could longitudinally assess illness severity due to pulmonary vascular disease and right ventricle