

there was no effect on TmP per GFR because at 10 hours the data were based on nonfasting samples and serum phosphorous had returned to baseline levels by 21 hours. The rise in serum levels of 1,25-dihydroxyvitamin D is probably due to the direct stimulatory effect of calcitonin on renal  $1\alpha$ -hydroxylase.<sup>3</sup> Recently, Gooi et al. reported that osteocytes express the calcitonin receptor and respond to calcitonin with an increase in sclerostin production.<sup>4</sup> Since the primary source of FGF-23 is osteocytes, these findings imply that the decline in FGF-23 levels that we observed in patients with X-linked hypophosphatemia was due to the direct effect of calcitonin on osteocytes in this disease. Our study raises the possibility that calcitonin is a therapeutic option for patients with X-linked hypophosphatemia.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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## Increased 36-Week Survival with High Oxygen Saturation Target in Extremely Preterm Infants

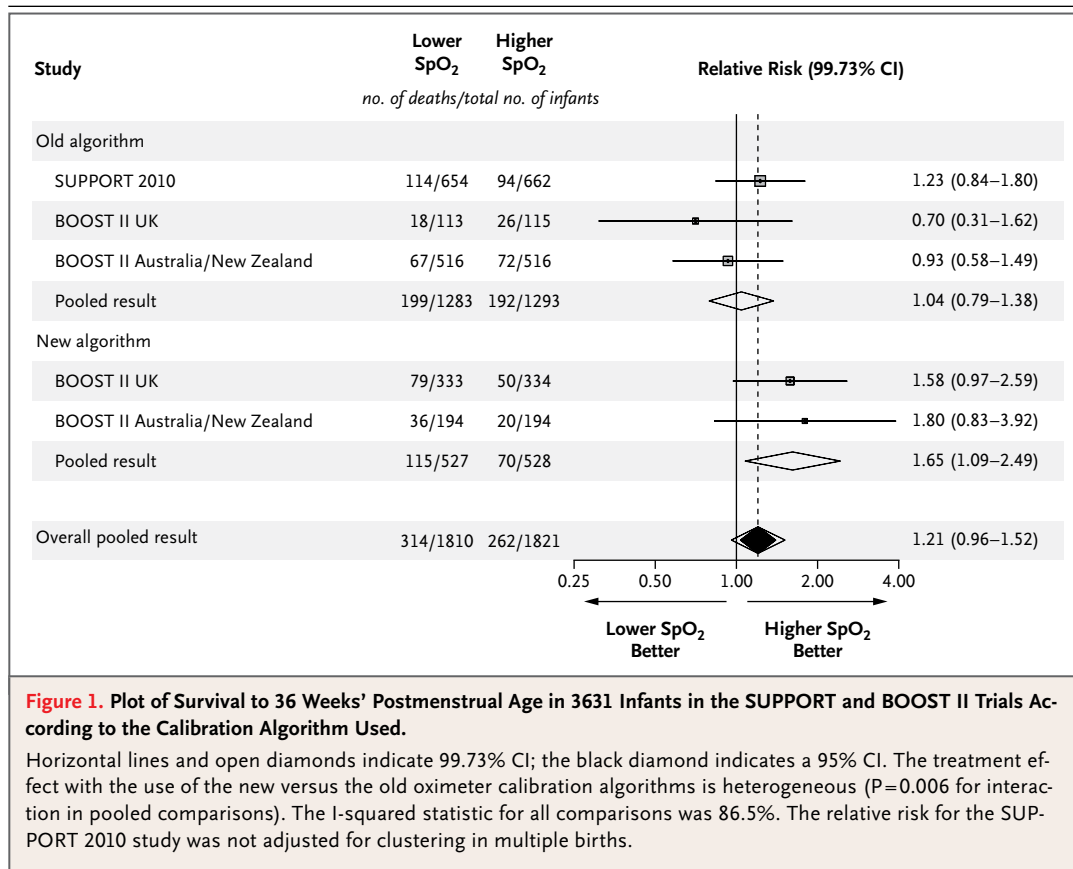
**TO THE EDITOR:** Following advice from the Data Monitoring Committees (DMCs), recruitment to the U.K. and Australian Benefits of Oxygen Saturation Targeting (BOOST II) trials has closed early after a joint safety analysis showed higher survival rates at 36 weeks postmenstrual age in infants born at less than 28 weeks<sup>7</sup> of gestation and randomly assigned to oxygen saturation (SpO<sub>2</sub>) targets of 91 to 95% rather than 85 to 89% while breathing supplemental oxygen.

In 2010, outcomes at hospital discharge in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT trial), a randomized trial comparing the same SpO<sub>2</sub> ranges among 1316 infants, were reported in the *Journal*.<sup>1</sup> Infants randomly assigned to the lower target of 85 to 89% had a lower risk of retinopathy of prematurity than did those in the higher target group (8.6% vs. 17.9%; relative risk, 0.52; 95% confidence interval [CI], 0.37 to 0.73; P<0.001), but they also had a lower rate of survival to hospital discharge (mortality, 19.9% vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; P=0.04). The U.K., Australian, and New Zealand BOOST II trials were designed to compare SpO<sub>2</sub> targets of 85 to 89% versus 91 to 95%, with a primary outcome of survival without dis-

ability at 2 years corrected for gestation. A prospective meta-analysis of all the neonatal oxygen trials is planned.<sup>2</sup> After the results of SUPPORT were published, the DMCs of the other trials separately reviewed their interim data and found no reason to stop recruitment.<sup>3</sup>

In the U.K. and Australian trials, infants have been managed with the use of Masimo oximeters similar to those used in the SUPPORT trial except that, by early 2009, all oximeters were fitted with a revised calibration algorithm.<sup>4</sup> Both the original and revised calibration algorithms perform within the recommended standards for accuracy, but the revised algorithm is associated with improved SpO<sub>2</sub> targeting, more closely resembles the calibration algorithms in other oximeters,<sup>4</sup> and is now the current standard algorithm in Masimo oximeters (see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

In December 2010, a joint safety analysis of survival at 36 weeks<sup>7</sup> postmenstrual age was undertaken, pooling 2315 infants in the U.K., Australian, and New Zealand trials with the 1316 infants in the SUPPORT trial,<sup>1</sup> as provided for in the U.K. protocol.<sup>5</sup> Guidelines prespecified that investigators be told the results if the



**Figure 1. Plot of Survival to 36 Weeks' Postmenstrual Age in 3631 Infants in the SUPPORT and BOOST II Trials According to the Calibration Algorithm Used.**

Horizontal lines and open diamonds indicate 99.73% CI; the black diamond indicates a 95% CI. The treatment effect with the use of the new versus the old oximeter calibration algorithms is heterogeneous ( $P=0.006$  for interaction in pooled comparisons). The I-squared statistic for all comparisons was 86.5%. The relative risk for the SUPPORT 2010 study was not adjusted for clustering in multiple births.

difference in 36-week survival between groups for all infants, or for those recruited after introducing the new calibration algorithm, exceeded 3 SE (equivalent to 99.73% CI, with  $P=0.003$ ).<sup>5</sup> Among all 3631 infants, those randomly assigned to an SpO<sub>2</sub> of 91 to 95% had a higher survival rate than those assigned to an SpO<sub>2</sub> of 85 to 89% (mortality, 17.3% vs. 14.4%; relative risk for survival associated with higher SpO<sub>2</sub> target, 1.21; 99.73% CI, 0.96 to 1.52;  $P=0.015$ ). Among the 1055 infants in the U.K. and Australian trials who were treated after the change in the calibration algorithm, survival differences were greater (mortality, 21.8% vs. 13.3%; relative risk for survival associated with higher SpO<sub>2</sub> target, 1.65; 99.73% CI, 1.09 to 2.49;  $P<0.001$ ; test for interaction for pooled comparisons of old vs. new algorithm,  $P=0.006$ ) (Fig. 1). The DMCs reported these results to the trial steering groups. Because of the findings in the 1055 infants on the new algorithm, both trials closed recruitment. Detailed reports on outcomes up to the time of hospital discharge are planned.

Targeting neonatal SpO<sub>2</sub> is imprecise.<sup>4</sup> These

data allow no inferences about risks and benefits of other targets. Until longer-term data on survival and morbidity are available, we consider it prudent not to target an SpO<sub>2</sub> of 85 to 89% in infants born earlier than 28 weeks of gestation. Final recommendations await information on the primary outcomes of disability-free survival, anticipated in 2014 (Current Controlled Trials number, ISRCTN00842661 [U.K. trial] and Australian New Zealand Clinical Trials Registry numbers, ACTRN12605000055606 [Australian trial] and ACTRN12605000253606 [New Zealand trial]).<sup>2</sup>

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## CORRECTIONS

Case 7-2011 — A 52-Year-Old Man with Upper Respiratory Symptoms and Low Oxygen Saturation Levels (March 10, 2011; 364:957-66). In the Causes of Low Oxygen Saturation on Pulse Oximetry subsection of the Differential Diagnosis section, the unit of measure for wavelengths should have been nm, rather than mm, in two instances: in the first sentence under Hypoxemia (page 959) and in the second sentence of the second paragraph under Dapsone and Methemoglobinemia (page 960). The article is correct at NEJM.org.

Lying Low (Clinical Problem-Solving article, March 3, 2011; 364:871-5, and Interactive Medical Case, February 10, 2011; 364:e10). In the thirteenth paragraph of the Clinical Problem-Solving article, beginning “A fast was initiated . . .” (page 873), the third sentence should have given the patient’s insulin level in  $\mu\text{IU}$  per milliliter, rather than mIU per milliliter. In the tenth slide of the Interactive Medical Case, insulin should have been reported in  $\mu\text{IU}/\text{ml}$ , rather than mIU/ml. Both the article and the interactive case are correct at NEJM.org.

A Syndrome with Congenital Neutropenia and Mutations in G6PC3 (January 1, 2009;360:32-43). In Table 1 (page 35), the genotype for Patient 8 should have been “c.[778G→C]+[778G→C], p.[Gly260Arg]+[Gly260Arg],” rather than “c.[784G→C]+[784G→C], p.[Gly262Arg]+[Gly262Arg].” In the G6PC3 Mutations in Other Patients subsection of Results (page 40), the fourth sentence should have begun, “The two other missense mutations . . .,” rather than, “The three other missense mutations . . .,” and the fifth sentence should have read, “None of these additional patients with G6PC3 mutations had mutations in ELA2 or HAX1, with the exception of a monoallelic genetic variant in HAX1 (p.Val172Ile) in Patient 10. Monoallelic mutations in HAX1 have never been associated with congenital neutropenia. Therefore, these three genetic defects represent distinct variants of severe congenital neutropenia,” rather than, “None of these additional patients with G6PC3 mutations had mutations in ELA2 or HAX1, a finding suggesting that these three genetic defects are distinct variants of severe congenital neutropenia.” The article is correct at NEJM.org.

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The symposium will be held in West Hartford, CT, May 4 and 5.

Contact the Hoffman Heart and Vascular Institute of Connecticut, Saint Francis Hospital and Medical Center, 114 Woodland St., Hartford, CT 06105-1299; or call (860) 714-4019; or fax (860) 714-8001; or e-mail [jwesche@stfranciscare.org](mailto:jwesche@stfranciscare.org).

### 4TH INTERNATIONAL SYMPOSIUM ON CANCER METASTASIS & THE LYMPHOVASCULAR SYSTEM: BASIS FOR RATIONAL THERAPY

The symposium will be held in New York, May 12–14.

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### JOEL AND BARBARA ALPERT LECTURE IN GENERAL PEDIATRICS

The lecture, entitled “Bending the Disparities Curve,” will be held in Boston on May 19.

Contact Melissa Brennan, Boston University School of Medicine, 771 Albany St., Suite 3509, Boston, MA 02118; or call (617) 414-7424; or fax (617) 414-3833; or e-mail [melissa.brennan@bmc.org](mailto:melissa.brennan@bmc.org).

### INTENSIVE BIOETHICS COURSE 37

The course will be offered in Washington, DC, June 6–10.

Contact the Joseph and Rose Kennedy Institute of Ethics, Healy Hall, 4th Floor, Georgetown University, Washington, DC 20057; or call (202) 687-8099; or see <http://kennedyinstitute.georgetown.edu/programs>.

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