ORIGINAL ARTICLE

Randomized Trial of Platelet-Transfusion Thresholds in Neonates

Anna Curley, M.D., Simon J. Stanworth, F.R.C.P., D.Phil., Karen Willoughby, B.Sc.,
Susanna F. Fustolo-Gunnink, M.D., Vidheya Venkatesh, M.D., Cara Hudson, M.Sc.,
Alison Deary, M.Sc., Renate Hodge, M.Sc., Valerie Hopkins, B.Sc.,
Beatriz Lopez Santamaria, M.Sc., Ana Mora, Ph.D., Charlotte Llewelyn, Ph.D.,
Angela D'Amore, M.D., Rizwan Khan, M.R.C.P.I., Wes Onland, M.D., Ph.D.,
Enrico Lopriore, M.D., Ph.D., Karin Fijnvandraat, M.D., Ph.D.,
Helen New, F.R.C.Path., Ph.D., Paul Clarke, M.D., and Timothy Watts, M.D.,
for the PlaNeT2 MATISSE Collaborators*

ABSTRACT

BACKGROUND

Platelet transfusions are commonly used to prevent bleeding in preterm infants with thrombocytopenia. Data are lacking to provide guidance regarding thresholds for prophylactic platelet transfusions in preterm neonates with severe thrombocytopenia.

METHODS

In this multicenter trial, we randomly assigned infants born at less than 34 weeks of gestation in whom severe thrombocytopenia developed to receive a platelet transfusion at platelet-count thresholds of 50,000 per cubic millimeter (high-threshold group) or 25,000 per cubic millimeter (low-threshold group). Bleeding was documented prospectively with the use of a validated bleeding-assessment tool. The primary outcome was death or new major bleeding within 28 days after randomization.

RESULTS

A total of 660 infants (median birth weight, 740 g; and median gestational age, 26.6 weeks) underwent randomization. In the high-threshold group, 90% of the infants (296 of 328 infants) received at least one platelet transfusion, as compared with 53% (177 of 331 infants) in the low-threshold group. A new major bleeding episode or death occurred in 26% of the infants (85 of 324) in the high-threshold group and in 19% (61 of 329) in the low-threshold group (odds ratio, 1.57; 95% confidence interval [CI], 1.06 to 2.32; P=0.02). There was no significant difference between the groups with respect to rates of serious adverse events (25% in the high-threshold group and 22% in the low-threshold group; odds ratio, 1.14; 95% CI, 0.78 to 1.67).

CONCLUSIONS

Among preterm infants with severe thrombocytopenia, those randomly assigned to receive platelet transfusions at a platelet-count threshold of less than 50,000 per cubic millimeter had a significantly higher rate of death or major bleeding within 28 days after randomization than those in the group that received less than 25,000 per cubic millimeter. (Funded by the National Health Service Blood and Transplant Research and Development Committee and others; Current Controlled Trials number, ISRCTN87736839.)

PROPHYLACTIC PLATELET TRANSFUSIONS are commonly administered to preterm infants to reduce the risk of bleeding.[1-5] Policies regarding neonatal platelet transfusion vary widely among clinicians and institutions, reflecting the broad nature of consensus-based guideline recommendations.[5-8] A randomized trial comparing prophylactic platelet-transfusion thresholds in neonates showed no benefit of maintaining a "normal" platelet count (150,000 per cubic millimeter) to prevent intraventricular hemorrhage in 152 preterm infants.[9] It excluded infants with severe thrombocytopenia (defined as a platelet count of <50,000 platelets per cubic millimeter). Most current clinical decisions to transfuse platelets are made for infants with platelet counts below this threshold.[5,10,11] More restrictive transfusion thresholds have become common, despite the lack of outcome data.[8] In one study, 42% of transfusions were administered in patients with platelet counts of less than 25,000 per cubic millimeter, and 92% were administered in those with counts of less than 50,000 per cubic millimeter.[6]

Data are lacking from randomized trials to compare clinically relevant outcomes associated with currently used platelet count thresholds in preterm infants with thrombocytopenia. We performed a multicenter, randomized trial to assess whether a policy of prophylactic platelet transfusion in preterm infants, based on a platelet-count threshold of less than 50,000 per cubic millimeter, as compared with less than 25,000 per cubic millimeter, reduced the risk of death and major bleeding.

METHODS

ELIGIBILITY CRITERIA

Parents and guardians of infants who had a platelet count of less than 100,000 per cubic millimeter were identified. Randomization occurred after written informed consent was received if the infant was receiving care in a participating neonatal intensive care unit and the following criteria were met: a gestational age at birth of less than 34 weeks, a platelet count of less than 50,000 per cubic millimeter, and cranial ultrasonography performed within 6 hours before randomization that did not show a major intraventricular hemorrhage. Exclusion criteria were a major or life-threatening congenital malformation, major bleeding within the previous 72 hours, fetal intracranial hemor-

rhage, immune thrombocytopenia, no administration of parenteral vitamin K, or a low probability of survival beyond several hours. Preterm infants with major bleeding became eligible for randomization 72 hours later provided there was no further major bleeding.

INTERVENTION

Infants were randomly assigned to receive a platelet transfusion (at a dose of 15 ml per kilogram of body weight) when the platelet count was less than 25,000 per cubic millimeter (the low-threshold group) or less than 50,000 per cubic millimeter (the high-threshold group). One Dutch trial site administered platelet hyperconcentrates in a dosage of 10,000 to 20,000 × 10^6 platelets per kilogram. Platelet products conformed to national standards in the United Kingdom, Ireland, and the Netherlands. The protocol (available with the full text of this article at NEJM.org) permitted additional platelet transfusions for clinically significant bleeding or surgery or invasive procedures. Treating clinicians and parents and guardians were aware of the treatment assignments, but neonatologists adjudicating the outcomes were unaware of these assignments.

OUTCOMES

The primary outcome was a composite of death or major bleeding up to and including day 28. Prespecified secondary outcomes were the following: survival up to day 28 after a major bleeding episode, death up to day 28, the rate and time from randomization to major bleeding up to day 28, at least one minor bleeding episode up to day 14, at least one moderate bleeding episode up to day 14, a major bleeding episode after red-cell transfusion, chronic lung disease (dependency on oxygen or respiratory support at >36 weeks of postmenstrual age) up to the end of the trial, stage 2 retinopathy of prematurity (unilateral or bilateral) up to 38 weeks of corrected gestational age, retinopathy of prematurity leading to laser or bevacizumab therapy up to 38 weeks of corrected gestational age, discharge by 38 weeks of corrected gestational age, the number of platelet-transfusion episodes per participant up to day 28, receipt of at least one platelet transfusion, the median platelet-count nadir before a major bleeding episode, the median platelet count closest to that of a major bleeding episode, a new sepsis event up to end of the trial, a new necrotizing enterocolitis

event up to the end of the trial, a serious adverse event up to the end of the trial, and platelet transfusion–related adverse events up to the end of the trial. An additional secondary outcome was the neurodevelopmental outcome at 2 years; these data were not available as of this writing.

A bleeding-assessment tool was designed and validated for use in this trial.[12] Grading of bleeding as minor, moderate, major, or severe was assigned centrally with the use of a computer algorithm and based on a modified version of the World Health Organization grading system used in other platelet-transfusion trials[12-14] (see the Supplementary Appendix, available at NEJM.org). The outcome of "major bleeding" included intracranial hemorrhage (leading to neurosurgical intervention or radiologic imaging showing midline shift), intraventricular hemorrhage filling 50% or more of the cerebral ventricle, pulmonary hemorrhage (fresh bleeding through an endotracheal tube with increased ventilatory requirements), frank rectal bleeding, and severe bleeding (fatal bleeding, life-threatening bleeding associated with shock, or bleeding requiring fluid boluses or red-cell transfusion). Our definition of rectal bleeding was pragmatic; we defined any amount of fresh visible blood as rectal bleeding; we also performed a prespecified sensitivity analysis excluding rectal-only bleeding as a component of the primary outcome.

DATA COLLECTION

A bleeding-assessment form was completed daily for 14 days after randomization. Thereafter, data on infants who were not discharged or transferred were collected weekly. For infants transferred to another hospital before day 28, primary outcome data up to and including day 28, as a minimum, were documented. Reporting of safety outcomes was mandatory only at participating hospitals.

RANDOMIZATION

A Web-based service (www.sealedenvelope.com) assigned infants randomly in a 1:1 ratio. Minimization was used for the factors of intrauterine growth restriction and gestational age, with a 60% chance of simple random assignment. Intrauterine growth restriction was defined as birth weight in less than the 10th percentile in conjunction with an estimated fetal weight crossing percentiles downward during pregnancy, ultrasonographic evidence of uteroplacental insufficiency, or both.

OVERSIGHT

This trial was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by independent ethics committees in the United Kingdom, the Netherlands, and Ireland. An independent data and safety monitoring committee reviewed the interim data analysis and monitored patient safety in 6 monthly data review sessions. The first two authors take responsibility for the accuracy and completeness of data and the fidelity of the trial to the protocol. The statistical analysis plan is available with the protocol at NEJM.org.

STATISTICAL ANALYSIS

Data on the frequency of bleeding outcomes in infants with severe thrombocytopenia were available from the observational Platelets for Neonatal Transfusion–Study 1 (PlaNeT-1),[6] in which 30 of 169 infants (18%) died or had a major bleeding episode. However, that study included term infants, and therefore overall mortality and the incidence of new major bleeding episodes were expected to be higher in our trial. We estimated that the assignment of 329 infants to each group would provide 80% power (with the use of a two-sided test, at a 5% significance level), assuming an event rate for the primary outcome of 20% in the low-threshold group, to detect a difference of 8 percentage points (assuming that the event rate in the high-threshold group was 12%). This number of infants was rounded to a total of 660. At the time of the preplanned interim analysis after 87 infants were enrolled, the event rate in the low-threshold group was 18%, suggesting that the sample-size calculation was adequate.

All analyses were performed according to the intention-to-treat principle with adjustments for trial site as a random effect, gestational age, and intrauterine growth restriction. All tests were two-sided; a P value of less than 0.05 was considered to indicate statistical significance. SAS software, version 9.4 (SAS Institute), was used to conduct the analyses. All odds ratios and hazard ratios are presented as the high-threshold group as compared with the low-threshold group.

The primary outcome was analyzed with the use of a mixed logistic-regression model and was compared with the use of cranial imaging performed within the period from day 23 to day 38 (5 days before to 10 days after day 28), and details of any major bleeding were reported up to day 28.

Missing primary outcomes were inferred by investigators who were unaware of the treatment assignments. For example, if an infant was discharged before day 28 and was not readmitted within the 28-day period, we assumed that no major bleeding had occurred (details are provided in the statistical analysis plan and the Supplementary Appendix).

Further prespecified sensitivity analyses were performed, including a per-protocol analysis, an analysis that excluded rectal bleeding, and an analysis that assessed sensitivity to missing primary outcome data. Binary outcomes were analyzed with the use of logistic regression, and count variables were analyzed with the use of negative binomial regression with an offset to account for the number of days of follow-up. Several secondary outcomes were analyzed with the use of Cox proportional-hazards regression to allow for differing numbers of days of follow-up. Data on infants who were transferred to nonparticipating hospitals and who had not had an event were censored at the time of transfer. The number of platelet transfusions administered to each group and platelet counts at which transfusions were administered were analyzed to assess adherence to the protocol.

RESULTS

TRIAL POPULATION

Between June 2011 and August 2017, a total of 3731 infants who were assessed for eligibility, of whom 660 were randomly assigned (331 to the low-threshold group and 329 to the high-threshold group) (Fig. 1). Of these infants, 563 in the United Kingdom (85%), 83 in the Netherlands (13%), and 14 in Ireland (2%) were enrolled across 43 trial sites. We obtained written informed consent from the parent or guardian of, on average, 3 infants (when the platelet count was <100,000 per cubic millimeter) for every 1 infant in whom severe thrombocytopenia developed. Baseline characteristics were well matched between the treatment groups (Table 1). The overall median birth weight was 740 g (range, 360 to 2490), and the median gestational age was 26.6 weeks (range, 22.7 to 33.9). A total of 37% of the infants underwent randomization on or before 5 days of life, and 59% underwent randomization by day 10 (Fig. S1 in the Supplementary Appendix shows randomization according to day of age). A total of 247 of 634 infants with available data (39%)

(121 in the low-threshold group and 126 in the high-threshold group) received at least one platelet transfusion before randomization.

DATA COMPLETENESS AND ADHERENCE TO TRANSFUSION PROTOCOL

The primary outcome assessment was completed for 653 infants (99%). Six infants (2 in the low-threshold group and 4 in the high-threshold group) were withdrawn because the consenting process was not followed, duplicate randomizations occurred in error, or randomization that was performed in error despite major hemorrhage in the infant. Of the infants for whom primary outcome data were available, 523 (79%) underwent cranial ultrasonography within 5 days before and 10 days after day 28. Of the 130 infants who did not undergo cranial ultrasonography in this period, 77 died before day 28, and the primary outcome was inferred for 53 on the basis of prespecified clinical criteria (see the Supplementary Appendix). Bleeding-assessment forms were completed up to day 14 for 84% of the infants in the low-threshold group and 81% in the high-threshold group. A total of 97% of the transfusions (93% in the low-threshold group and 99% in the high-threshold group) were conducted according to the protocol. A total of 88% were performed according to the treatment-group threshold (75% in the low-threshold group and 97% in the high-threshold group). On 124 occasions (30 in the low-threshold group and 94 in the high-threshold group), a platelet transfusion was indicated according to the protocol but was not administered.

A total of 128 new major bleeding episodes occurred in 80 infants between randomization and day 28. These episodes occurred in 14% of infants (45 of 328) in the high-threshold group and 11% of infants (35 of 330) in the low-threshold group. Of these episodes, 7 major bleeding episodes that occurred during the trial led to death or withdrawal of intensive care (3 in the high-threshold group and 4 in the low-threshold group).

PRIMARY OUTCOME

The primary outcome occurred in 26% of the infants in the high-threshold group (85 of 324 infants) and 19% of the infants in the low-threshold group (61 of 329) (Table 2). With adjustment for gestational age and intrauterine growth restriction as covariates and trial site as a random effect, the
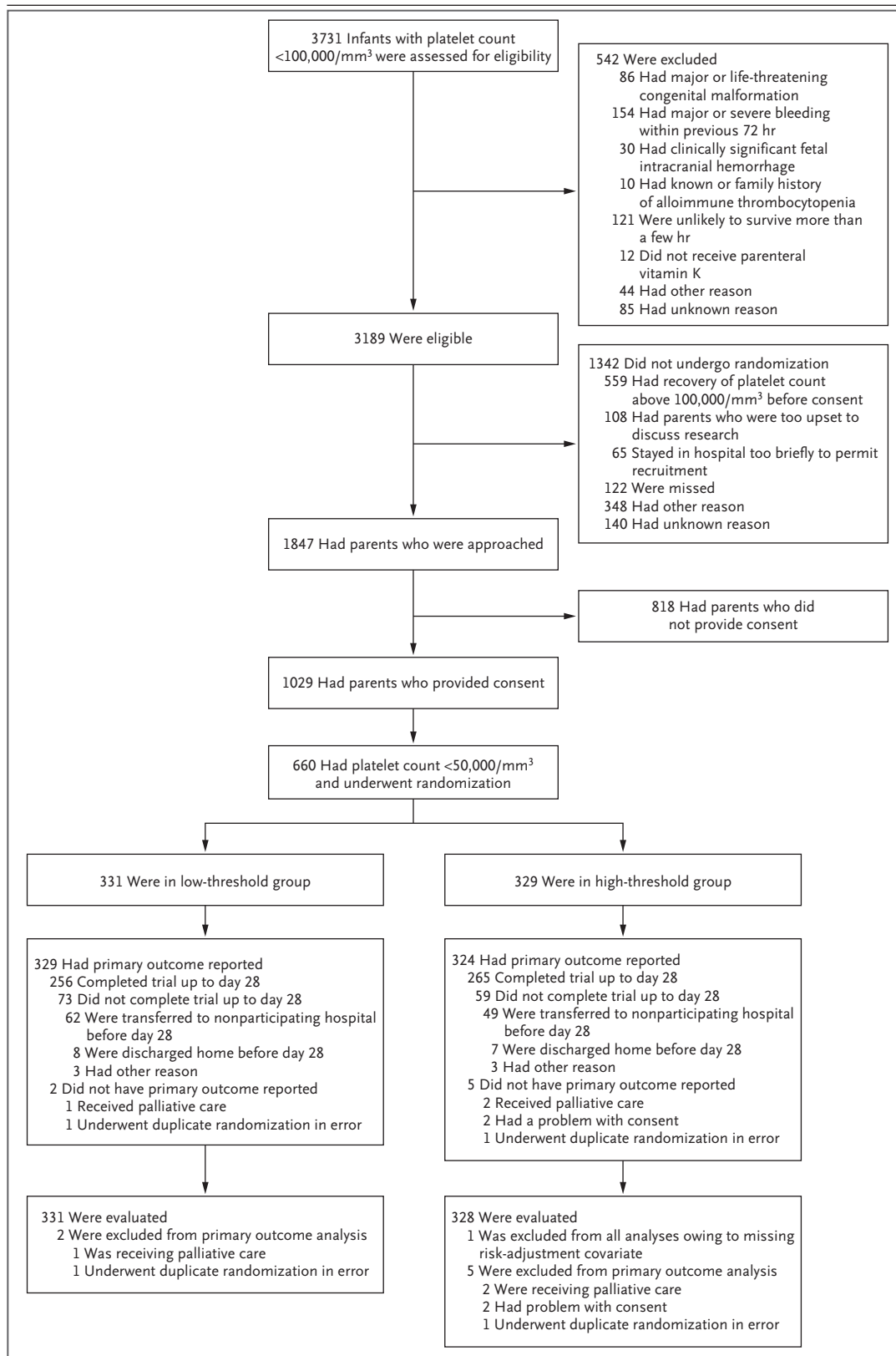
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┌────────────────────────────────────────────┐
│ 3731 Infants with platelet count            │
│ <100,000/mm³ were assessed for eligibility  │
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542 Were excluded
  86 Had major or life-threatening congenital malformation
  154 Had major or severe bleeding within previous 72 hr
  30 Had clinically significant fetal intracranial hemorrhage
  10 Had known or family history of alloimmune thrombocytopenia
  121 Were unlikely to survive more than a few hr
  12 Did not receive parenteral vitamin K
  44 Had other reason
  85 Had unknown reason

3189 Were eligible

1342 Did not undergo randomization
  559 Had recovery of platelet count above 100,000/mm³ before consent
  108 Had parents who were too upset to discuss research
  65 Stayed in hospital too briefly to permit recruitment
  122 Were missed
  348 Had other reason
  140 Had unknown reason

1847 Had parents who were approached

818 Had parents who did not provide consent

1029 Had parents who provided consent

660 Had platelet count <50,000/mm³ and underwent randomization

331 Were in low-threshold group

329 Were in high-threshold group

329 Had primary outcome reported
  256 Completed trial up to day 28
  73 Did not complete trial up to day 28
    62 Were transferred to nonparticipating hospital before day 28
    8 Were discharged home before day 28
    3 Had other reason
2 Did not have primary outcome reported
  1 Received palliative care
  1 Underwent duplicate randomization in error

324 Had primary outcome reported
  265 Completed trial up to day 28
  59 Did not complete trial up to day 28
    49 Were transferred to nonparticipating hospital before day 28
    7 Were discharged home before day 28
    3 Had other reason
5 Did not have primary outcome reported
  2 Received palliative care
  2 Had a problem with consent
  1 Underwent duplicate randomization in error

331 Were evaluated
  2 Were excluded from primary outcome analysis
    1 Was receiving palliative care
    1 Underwent duplicate randomization in error

328 Were evaluated
  1 Was excluded from all analyses owing to missing risk-adjustment covariate
  5 Were excluded from primary outcome analysis
    2 Were receiving palliative care
    2 Had problem with consent
    1 Underwent duplicate randomization in error

Figure 1. Eligibility, Randomization, and Follow-up.

Table 1. Characteristics of the Trial Population.*

Variable	Low-Threshold Group (N=331)	High-Threshold Group (N=329)
Intrauterine growth restriction — no./total no. (%)†‡	125/331 (38)	120/328 (37)
Antenatal glucocorticoids — no./total no. (%)	289/329 (88)	292/326 (90)
Full course of glucocorticoids, ≥2 doses — no./total no. (%)	191/281 (68)	194/281 (69)
Clinical evidence of chorioamnionitis — no./total no. (%)	26/330 (8)	28/322 (9)
Cesarean delivery — no./total no. (%)†	201/329 (61)	208/328 (63)
Female sex — no./total no. (%)†	140/331 (42)	123/328 (38)
Median weight at birth (IQR) — g†	743 (605–990)	728 (600–940)
Median gestation at birth (IQR) — wk†	26.7 (24.9–28.7)	26.6 (24.9–28.9)
Median corrected gestational age at randomization (IQR) — wk†	28.9 (26.9–31.6)	29.0 (27.2–31.5)
Median weight at randomization (IQR) — g§	892 (670–1190)	860 (668–1170)
Median postnatal age at randomization (IQR) — days†	7.0 (3.7–18.9)	8.4 (4.0–21.0)
Randomization ≤5 days of age — no./total no. (%)	125/331 (38)	116/328 (35)
Was receiving treatment for necrotizing enterocolitis at randomization — no./total no. (%)†¶	49/331 (15)	58/328 (18)
Was receiving antibiotic treatment for sepsis at randomization — no./total no. (%)†	206/331 (62)	209/328 (64)
Major bleeding before randomization — no./total no. (%)† ‖	62/331 (19)	60/328 (18)
Pulmonary bleeding — no./total no. (%)	31/62 (50)	22/60 (37)
Frank rectal bleeding — no./total no. (%)	8/62 (13)	9/60 (15)
Intraventricular hemorrhage — no./total no. (%)**	40/59 (68)	39/58 (67)
Intracranial hemorrhage — no./total no. (%)	10/62 (16)	7/60 (12)
Other bleeding — no./total no. (%)	7/62 (11)	4/60 (7)
Median platelet count at randomization (IQR) — × 10⁻³ per cubic millimeter†	38 (28–44)	38 (29–44)

* There were no significant differences between the groups in this post hoc analysis. IQR denotes interquartile range.
† Data were missing for one infant in the high-threshold group.
‡ Intrauterine growth restriction was defined as a birth weight below the 10th percentile and an estimated fetal weight crossing percentiles downward during pregnancy with or without ultrasonographic evidence of uteroplacental insufficiency.
§ Data were missing for one infant in the low-threshold group.
¶ In infants with necrotizing enterocolitis of stage IIa or higher (abdominal distention, tenderness, absent bowel sounds, and radiologic finding of pneumatosis intestinalis), necrotizing enterocolitis was defined with the use of the Modified Bell's staging criteria.[15]
‖ Some infants had more than one bleeding episode before randomization.
** Intraventricular hemorrhage was defined as intraventricular hemorrhage filling of at least 50% of a cerebral ventricle.

odds ratio was 1.57 (95% confidence interval [CI], 1.06 to 2.32; P=0.02).

SECONDARY OUTCOMES

There were no significant differences between the groups with respect to the rates of minor or worse bleeding. Time to major bleeding or death is shown in Figure 2. A total of 48 infants (15%) died in the high-threshold group and 33 (10%) died in the low-threshold group (odds ratio, 1.56; 95% CI, 0.95 to 2.55).

The percentage of infants surviving with bronchopulmonary dysplasia at 36 weeks of corrected age was 63% in the high-threshold group and 54% in the low-threshold group (odds ratio, 1.54; 95% CI, 1.03 to 2.30). A post hoc analysis of the composite outcome of death or bronchopulmonary dysplasia (to allow for deaths before a possible diagnosis of bronchopulmonary dysplasia) yielded a similar odds ratio. There were no significant differences between the groups with respect to rates of survival with retinopathy

Table 2. Primary and Secondary Outcomes, According to Treatment Group.

Outcome	Low-Threshold Group (N=331)	High-Threshold Group (N=329)	Odds Ratio or Hazard Ratio (95% CI)*
Primary outcome			
Death or major bleeding episode through trial day 28 — no./total no. (%)	61/329 (19)	85/324 (26)	OR, 1.57 (1.06–2.32)†
Secondary outcomes‡			
Death through trial day 28 — no./total no. (%)	33/330 (10)	48/326 (15)	OR, 1.56 (0.95–2.55)
At least one major bleeding episode through trial day 28 — no./total no. (%)	35/330 (11)	45/328 (14)	HR, 1.32 (1.00–1.74)
Survival with bronchopulmonary dysplasia at 36 wk — no./total no. (%)§	153/281 (54)	169/269 (63)	OR, 1.54 (1.03–2.30)
Post hoc outcome of death or bronchopulmonary dysplasia at 36 wk — no./total no. (%)	200/329 (61)	224/324 (69)	OR, 1.56 (1.07–2.27)
Discharge by 38 wk of corrected gestational age — no./total no. (%)	41/328 (12)	29/326 (9)	HR, 0.68 (0.46–1.00)
Survival with unilateral or bilateral retinopathy of prematurity of stage ≥2 at 38 wk of corrected gestational age — no./total no. (%)¶	71/297 (24)	82/279 (29)	OR, 1.37 (0.91–2.08)
Unilateral or bilateral retinopathy of prematurity of stage ≥2 treated with laser or bevacizumab therapy — no./total no. (%)	29/295 (10)	36/278 (13)	OR, 1.38 (0.79–2.42)
New sepsis event after randomization — no./total no. (%)‖	175/326 (54)	181/324 (56)	HR, 1.10 (0.92–1.33)
New necrotizing enterocolitis event after randomization — no./total no. (%)**	54/326 (17)	42/324 (13)	HR, 0.72 (0.37–1.41)
At least one major bleeding episode through trial day 28 — no./total no. (%)	14/330 (4)	11/328 (3)	HR, 0.80 (0.40–1.60)
At least one minor or worse bleeding episode through trial day 14 — no./total no. (%)	232/328 (71)	225/324 (69)	HR, 0.96 (0.84–1.09)
At least one moderate or worse bleeding episode up to trial day 14 — no./total no. (%)	114/328 (35)	111/324 (34)	HR, 1.01 (0.86–1.18)
At least one platelet transfusion — no./total no. (%)	177/331 (53)	296/328 (90)	HR, 2.75 (2.36–3.21)
No. of platelet transfusions administered in infants who received at least one transfusion — median (IQR)	2 (1–3)	2 (1–3)	

* Odds ratios (ORs) are a relative measure of the odds of the binary outcome occurring by the end of the time period in the high-threshold group as compared with the low-threshold group. Hazard ratios (HRs) are a relative measure of the hazard (instantaneous event rate) of the outcome occurring at any time over the time period in the high-threshold group as compared with the low-threshold group. The odds ratios have been adjusted for trial site as a random effect, intrauterine growth restriction, and gestational age at birth and are based on marginal effects. The hazard ratios have been adjusted for trial site, intrauterine growth restriction, and gestational age at birth and are based on marginal Cox models.
† Values for the risk-adjustment covariates were missing for 1 infant in the high-threshold group, and that infant was excluded from the analysis. Outcome data were missing for 7 infants (2 in the low-threshold group and 5 in the high-threshold group). Outcome data were inferred for 47 infants (27 in the low-threshold group and 20 in the high-threshold group). P=0.02 for the comparison of the two groups.
‡ The widths of the confidence intervals for secondary outcomes have not been adjusted for multiplicity of analyses, so the intervals should not be used to infer definitive treatment effects.
§ Data are shown for infants who were alive at 36 weeks.
¶ Data are shown for infants who were alive 4 weeks after birth.
‖ The hazard ratio was also adjusted for sepsis at randomization.
** The hazard ratio was also adjusted for necrotizing enterocolitis at randomization.

of prematurity or in the rates of other complications of prematurity (Table 2).

A total of 90% of the infants (296 of 328) in the high-threshold group and 53% (177 of 331) in the low-threshold group received at least one platelet transfusion (hazard ratio, 2.75; 95% CI, 2.36 to 3.21) (Table 2). A total of 10% (32 of 328 infants) in the high-threshold group did not receive a transfusion indicated by a low platelet count owing to an increase in the platelet count to more than 50,000 per cubic millimeter while awaiting planned transfusion. There was a wide separation between the groups in the numbers of platelet transfusions on the first trial day (Fig. 3).

SENSITIVITY ANALYSES AND SUBGROUP ANALYSES

Results were materially unchanged in a per-protocol analysis (odds ratio for the primary outcome, 1.68; 95% CI, 1.11 to 2.55), in an analysis excluding rectal-only bleeding (odds ratio, 1.75; 95% CI,
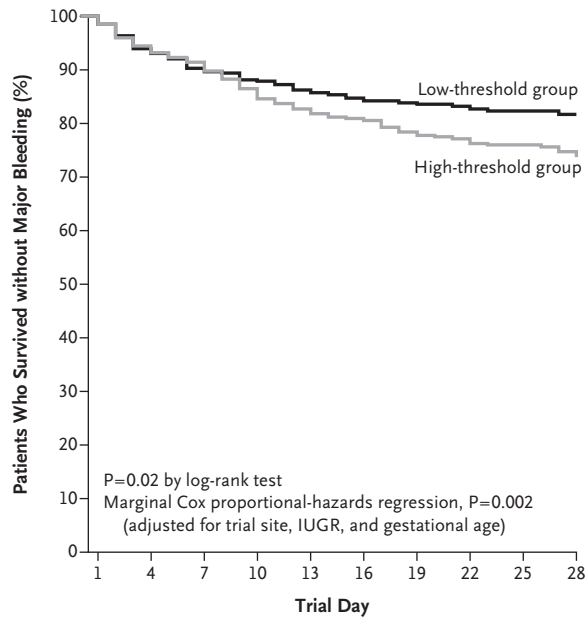
Figure 2. Patients Who Survived without Major Bleeding to Trial Day 28, According to Treatment Group.

IUGR denotes intrauterine growth restriction.

the investigators to be possibly related to the transfusion.

DISCUSSION

This large, multicenter, randomized trial involving preterm infants with severe thrombocytopenia showed that more deaths, major bleeding, or both occurred when a higher prophylactic platelet-count transfusion threshold of 50,000 per cubic millimeter was used than when a threshold of 25,000 per cubic millimeter was used. The recruited cohort comprised high-risk infants with a median gestational age of 26.6 weeks and birth weight of 740 g. They were often critically unwell, evidenced by their high background incidence of necrotizing enterocolitis and sepsis at recruitment, overall mortality, and incidence of major bleeding. The respective difference in event rate (26% vs. 19%) between the high-threshold and low-threshold treatment groups implies that reducing the transfusion trigger from 50,000 per cubic millimeter to 25,000 per cubic millimeter may prevent death or major bleeding in 7 of 100 preterm neonates with severe thrombocytopenia.

Potential limitations of our trial require consideration. A total of 3.2% (45 of 1393) of platelet transfusions were additional transfusions that were not indicated by the protocol, but overall, adherence to the protocol was good. The results were similar in direction for the analysis of components of the primary outcome separately, and the trial findings remained consistent in a per-protocol analysis. The rate of rectal bleeding, a component of the primary outcome, may not have been clinically significant; however, the results were materially unchanged when these bleeding episodes were excluded in a sensitivity analysis. Only 37% of the infants were recruited on or before 5 days of life, but this is probably because necrotizing enterocolitis and late-onset sepsis, both clinically significant causes of severe neonatal thrombocytopenia, are less common in the first postnatal week than at later ages.

Our trial highlights the importance of trials of platelet transfusion involving patients with conditions other than hematologic cancers.[16] It adds to previous data indicating a tenuous relationship between platelet count and bleeding.[1,6,13] Although retrospective studies have suggested that platelet transfusions may cause harm in neonates independently of the disease process, data from

1.14 to 2.67), and in analyses assessing sensitivity to missing data (Tables S5 and S6 in the Supplementary Appendix). In subgroup analyses, there were no significant interactions between treatment and the presence of intrauterine growth restriction, gestational age, or postnatal age at randomization (Table S4 in the Supplementary Appendix).
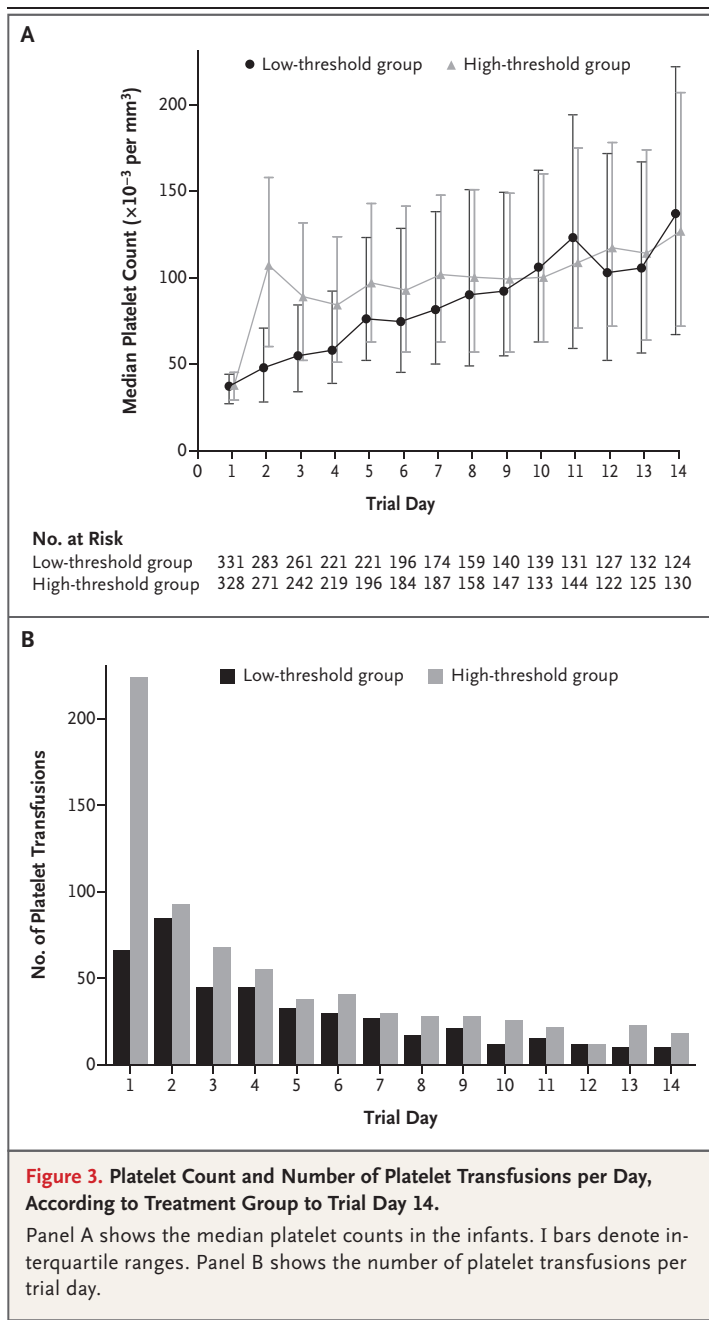
SERIOUS ADVERSE EVENTS

Not including major bleeding, 92 serious adverse events were reported in 74 infants in the low-threshold group and 91 serious adverse events were reported in 81 infants in the high-threshold group; these included multiorgan failure, necrotizing enterocolitis, renal failure, respiratory failure, and sepsis. There was no significant difference in rates of serious adverse events between the groups (25% in the high-threshold group and 22% in the low-threshold group; odds ratio, 1.14; 95% CI, 0.78 to 1.67) (Table 2, and Table S3 in the Supplementary Appendix). One serious adverse event (respiratory deterioration attributed to transient acute lung inflammation) was considered by

randomized, controlled trials to support this are lacking.[17] A recent randomized trial of platelet transfusion (added to standard care) in adults with intracranial bleeding associated with antiplatelet agents showed increased rates of death or dependence (defined as a score of 4 to 6 on the modified Rankin scale [a measure of disability in which scores range from 0 to 6, with higher scores indicating greater disability and a score of 6 indicating death]) with platelet transfusions.[18] Associations between platelet transfusion and increased risks of thrombosis and death have been reported in large retrospective studies involving adult patients with platelet-consumptive disorders.[19]

In our trial, the reasons for the between-group differences in mortality and major bleeding are unknown. Platelets have recognized immunologic and inflammatory effects, outside of effects on hemostasis.[20,21] The effect of transfusing adult platelets to a delicately balanced neonatal hemostatic system with relatively hypofunctional platelets is also poorly understood.[22] Inflammatory consequences after transfusion of platelet components as biologic agents, hemodynamic shifts related to platelet-transfusion volume, or both, coupled with fragility of the germinal matrix and disturbances in organ and brain blood flow could have contributed to an increased risk of hemorrhage.[23-25] Preterm lungs, with a large capillary bed and abundant immune cells, may be vulnerable to proinflammatory injury mediated by platelet transfusion–derived bioreactive components.[26] Rates of bronchopulmonary dysplasia appeared to be higher in the group that received transfusions at a threshold of 50,000 per cubic millimeter than in the group that received transfusions at a threshold of 25,000 per cubic millimeter, although the lack of adjustment for multiplicity must be considered in interpreting differences between groups in secondary outcomes. Other potential causes of adverse outcomes include platelet-derived reactive oxygen species and proangiogenic factors that may aggravate the aberrant angiogenesis characterizing bronchopulmonary dysplasia, a common complication of prematurity.[27] Vessel occlusion by platelet microthrombi could also compromise collateral blood flow.

In conclusion, among preterm infants with severe thrombocytopenia, the use of a platelet-count threshold of 50,000 per cubic millimeter for prophylactic platelet transfusion resulted in a higher rate of death or major bleeding than a restrictive threshold of 25,000 per cubic millimeter within 28 days after randomization.

Figure 3. Platelet Count and Number of Platelet Transfusions per Day, According to Treatment Group to Trial Day 14.

Panel A shows the median platelet counts in the infants. I bars denote interquartile ranges. Panel B shows the number of platelet transfusions per trial day.

APPENDIX

The authors' affiliations are as follows: the Department of Neonatology, National Maternity Hospital, Dublin (A.C.), and University Maternity Hospital Limerick, Limerick (R.K.) — both in Ireland; Department of Transfusion Medicine, National Health Service (NHS) Blood and Transplant, the Department of Haematology, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, the Radcliffe Department of Medicine, University of Oxford, and Oxford Biomedical Research Centre Haematology Theme, Oxford (S.J.S.), the Department of Obstetrics and Gynaecology, University of Cambridge (K.W.), NHS Blood and Transplant, Clinical Trials Unit (K.W., C.H., A. Deary, R.H., V.H., A.M., C.L.), and the Neonatal Intensive Care Unit, Cambridge University Hospitals NHS Trust (A. D'Amore), Cambridge, the Neonatal Intensive Care Unit, Evelina London Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust (B.L.S., T.W.), NHS Blood and Transplant (H.N.), and the Department of Hematology, Imperial College London (H.N.), London, and the Neonatal Intensive Care Unit, Norfolk and Norwich University Hospitals NHS Foundation Trust, and Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich (P.C.) — all in the United Kingdom; the Center for Clinical Transfusion Research, Sanquin Blood Supply (S.F.F.-G., K.F.), and the Departments of Epidemiology (S.F.F.-G.) and Neonatology (E.L.), Leiden University Medical Center, Leiden, and the Departments of Pediatric Hematology (S.F.F.-G., K.F.) and Neonatology (W.O.), Emma Children's Hospital, Academic Medical Center, Amsterdam — both in the Netherlands; and the Neonatal Intensive Care Unit, Cloudnine Hospital, Bangalore, India (V.V.).

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