Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia.

Van Baarle, Floor L.F.; Van De Weerdt, Emma K.; Van Der Velden, Walter J.F.M.; Ruiterkamp, Roelof A.; Tuinman, Pieter R.; Ypma, Paula F.; Van Den Bergh, Walter M.; Demandt, Astrid M.P.; Kerver, Emile D.; Jansen, A. J.Gerard

Published in:
New England Journal of Medicine

DOI:
10.1056/NEJMoa2214322

Publication date:
2023

ORIGINAL ARTICLE

Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia

F.L.F. van Baarle, E.K. van de Weerdt, W.J.F.M. van der Velden, R.A. Ruiterkamp, P.R. Tuinman, P.F. Ypma, W.M. van den Bergh, A.M.P. Demandt, E.D. Kerver, A.J.G. Jansen, P.E. Westerweel, S.M. Arbous, R.M. Determann, W.N.K.A. van Mook, M. Koeman, A.B.U. Mäkelburg, K.P. van Lienden, J.M. Binnekade, B.J. Biemond, and A.P.J. Vlaar

ABSTRACT

BACKGROUND

Transfusion guidelines regarding platelet-count thresholds before the placement of a central venous catheter (CVC) offer conflicting recommendations because of a lack of good-quality evidence. The routine use of ultrasound guidance has decreased CVC-related bleeding complications.

METHODS

In a multicenter, randomized, controlled, noninferiority trial, we randomly assigned patients with severe thrombocytopenia (platelet count, 10,000 to 50,000 per cubic millimeter) who were being treated on the hematology ward or in the intensive care unit to receive either one unit of prophylactic platelet transfusion or no platelet transfusion before ultrasound-guided CVC placement. The primary outcome was catheter-related bleeding of grade 2 to 4; a key secondary outcome was grade 3 or 4 bleeding. The noninferiority margin was an upper boundary of the 90% confidence interval of 3.5 for the relative risk.

RESULTS

We included 373 episodes of CVC placement involving 338 patients in the per-protocol primary analysis. Catheter-related bleeding of grade 2 to 4 occurred in 9 of 188 patients (4.8%) in the transfusion group and in 22 of 185 patients (11.9%) in the no-transfusion group (relative risk, 2.45; 90% confidence interval [CI], 1.27 to 4.70). Catheter-related bleeding of grade 3 or 4 occurred in 4 of 188 patients (2.1%) in the transfusion group and in 9 of 185 patients (4.9%) in the no-transfusion group (relative risk, 2.43; 95% CI, 0.75 to 7.93). A total of 15 adverse events were observed; of these events, 13 (all grade 3 catheter-related bleeding [4 in the transfusion group and 9 in the no-transfusion group]) were categorized as serious. The net savings of withholding prophylactic platelet transfusion before CVC placement was $410 per catheter placement.

CONCLUSIONS

The withholding of prophylactic platelet transfusion before CVC placement in patients with a platelet count of 10,000 to 50,000 per cubic millimeter did not meet the predefined margin for noninferiority and resulted in more CVC-related bleeding events than prophylactic platelet transfusion. (Funded by ZonMw; PACER Dutch Trial Register number, NL5534.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Vlaar can be contacted at a.p.vlaar@amsterdamumc.nl or at the Department of Intensive Care Medicine, Rm. C3-415, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

N Engl J Med 2023;388:1956-65.
DOI: 10.1056/NEJMoa2214322

CME at NEJM.org

Central venous catheter (CVC) placement is a frequently performed invasive procedure that allows for the administration of vasoactive drugs, irritating or hypertonic solutions (e.g., parenteral nutrition), simultaneous infusion of multiple medications, as well as for hemodialysis and hemodynamic monitoring.[1] Overall, approximately 18% of hospitalized patients undergo CVC placement during admission, and the number is greater on the hematology ward or in the intensive care unit (ICU), where patients also frequently have thrombocytopenia.[2-5]

The reported risk of major bleeding complications after CVC placement among patients with severe thrombocytopenia is very low, although recommendations are based mainly on evidence from retrospective cohort studies that lacked standardized platelet-transfusion protocols or validated bleeding assessment tools.[6,7] The lack of good-quality evidence has resulted in the use of varying platelet-transfusion thresholds ranging from 20,000 to 50,000 per cubic millimeter, both in guidelines and in clinical practice.[8-15] Important predictors of bleeding complications are operator experience and the use of ultrasound guidance.[1,6] The introduction of routine ultrasound guidance for CVC placement has greatly reduced the risk of complications, including the occurrence of periprocedural hemorrhage.[16,17] Consequently, retrospective studies suggest safe ultrasound-guided CVC placement even in patients with a platelet count of less than 20,000 per cubic millimeter.[6,18]

Meanwhile, concern has been growing over transfusion-related morbidity and mortality. Transfusion-related adverse events include acute lung injury, circulatory overload, infection, allergic reaction, and alloimmunization, all of which are more likely to occur in patients who are treated on the hematology ward or in the ICU.[19-21] In addition to the risk of serious side effects, blood products are both scarce and expensive, and the aging of the population is projected to further increase scarcity. Among blood products, platelet concentrates are especially scarce since their short life span makes it difficult to maintain an adequate supply.[22-24]

The question arises as to whether the use of prophylactically transfused platelet concentrates is necessary to prevent CVC-related bleeding complications in patients with severe thrombocytopenia. We performed the Randomized, Controlled Trial on Prophylactic Platelet Transfusion Prior to Central Venous Catheter Placement in Patients with Thrombocytopenia (PACER) trial to evaluate the hypothesis that the omission of prophylactic platelet transfusion before CVC placement in patients with a platelet count of 10,000 to 50,000 per cubic millimeter would not increase the risk of catheter-related bleeding.

A Quick Take is available at NEJM.org

Methods

Trial Design and Oversight

This noninferiority trial was conducted on hematology wards and in ICUs at 10 hospitals in the Netherlands (7 academic and 3 general hospitals). The trial was funded by ZonMw, part of the Dutch Research Council. The institutional review board of the Amsterdam University Medical Center at the University of Amsterdam approved the trial protocol, which has been published previously[25] and is available with the full text of this article at NEJM.org. An independent data and safety monitoring board reviewed the trial conduct. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

All CVC placement procedures involving patients with thrombocytopenia who had a platelet count of 10,000 to 50,000 per cubic millimeter within 24 hours before the procedure were eligible for inclusion. CVCs were required to be in place for at least 24 hours. Exclusion criteria were the use of a therapeutically administered anticoagulant, a history of congenital or acquired coagulation factor deficiency or bleeding risk, or a spontaneously prolonged international normalized ratio (INR) of 1.5 or more. After the occurrence of two thirds of the trial events, the initial INR upper limit was adjusted to 3.0 after the emergence of new evidence of the safety of CVC placement at higher INR levels.[26] Data from multiple placement episodes could be included in the analysis but not within 24 hours after the previous randomization in order to secure adequate follow-up (Table S1 in the Supplementary Appendix, available at NEJM.org).

Table 1. CVC-Related Bleeding.*

Bleeding Grade	Definition
Grade 0	No bleeding
Grade 1	Oozing; hematoma; bleeding that results in <20 min of manual compression to stop
Grade 2	Bleeding that results in minor interventions to stop, such as prolonged manual compression (>20 min)
Grade 3	Bleeding that results in radiologic or elective operative intervention or red-cell transfusion without hemodynamic instability
Grade 4	Bleeding associated with severe hemodynamic instability (hypotension, defined as a decrease of >50 mm Hg or >50% in either systolic or diastolic blood pressure), with associated tachycardia (heart rate increase, >20% for 20 min) and resulting in increased red-cell transfusion or fatal bleeding

* CVC denotes central venous catheter.

INFORMED CONSENT

The trial involved two distinct categories of informed consent. Patients who were being treated on the hematology ward provided written informed consent before inclusion, whereas a deferred-consent procedure was allowed for patients in the ICU, in whom CVC placement was often an emergency procedure shortly after admission. These patients were provisionally included in the trial, after which informed consent was obtained from either the patient or a legal representative at the earliest possible time. If informed consent was denied, patients were excluded from the trial and their data were not used. If a patient died before informed consent could be obtained, their data were included in the analyses.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive either one unit of platelet concentrate or no platelet transfusion before CVC placement. The trial-group assignment was performed in an unblinded manner for the patient and treating physician. It was required that CVC placement be guided by ultrasound and be performed by an experienced operator; such experience was defined as a history of having performed at least 50 CVC placements. The operator was unaware of the trial-group assignment if possible, and all catheters were placed approximately 1 hour after randomization. Otherwise, CVCs were placed according to local clinical practice and could be of any diameter, could be either tunneled or nontunneled, and could be placed in the internal jugular vein, subclavian vein, or femoral vein. Randomization was stratified according to the trial center and catheter type (large-bore dialysis catheter or regular catheter).

OUTCOMES

The primary outcome was the occurrence of catheter-related bleeding of grade 2 to 4 within 24 hours after CVC placement. Bleeding was assessed according to the bleeding scale previously used by Zeidler et al. (Table 1),[27] an adaptation of the Common Terminology Criteria for Adverse Events.[28] The occurrence of bleeding and any related treatments were recorded by trained staff members at each site immediately after CVC placement and at 1 hour and 24 hours thereafter.

A key secondary outcome was major (grade 3 or 4) bleeding. Other secondary outcomes were grade 1 bleeding, platelet and red-cell transfusions within 24 hours after CVC placement, hemoglobin level and platelet count at 1 hour and 24 hours after CVC placement, allergic transfusion reaction within 24 hours after CVC placement, the onset of acute lung injury within 48 hours after CVC placement, the length of ICU and hospital stay, in-hospital mortality, and financial costs.

STATISTICAL ANALYSIS

On the basis of existing evidence, we expected that in the transfusion group, 1% of the patients would have grade 2 bleeding and that no patients would have grade 3 or 4 bleeding.[27] The noninferiority margin was determined as an absolute increase of 2.5 percentage points in the risk of grade 2 to 4 bleeding in the no-transfusion group, which corresponded to an upper boundary of the confidence interval of 3.5 for the relative risk. The noninferiority margin was determined on the basis of the findings of a trial of prophylactic plasma transfusion before invasive procedures.[29] We determined that 196 CVC placements in each trial group would provide a power of 80% to determine the noninferiority of the no-transfusion strategy, with a one-sided alpha level of 0.05. We anticipated no loss to follow-up, given the short duration of data collection for the primary analysis.

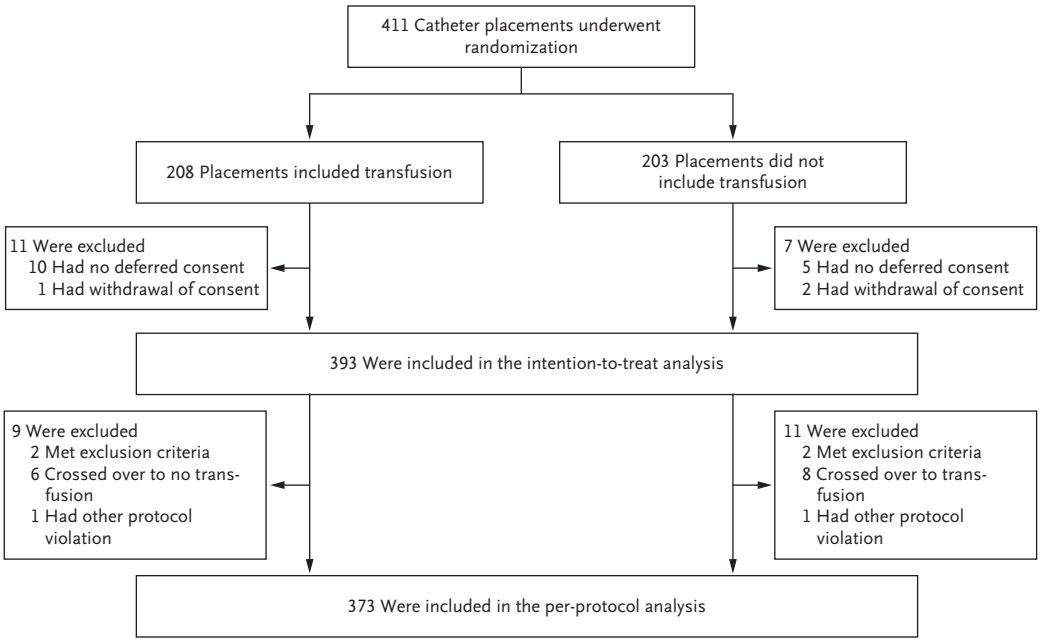

Figure 1. Randomization and Analyses.

Randomization was performed according to the placement of a central venous catheter (CVC) with or without prophylactic platelet transfusion because each patient could have more than one placement. Included in the per-protocol analysis were 373 episodes of CVC placement involving 338 patients.

The primary outcome was reported as a relative risk with a two-sided 90% confidence interval. We calculated two-sided 95% confidence intervals for the secondary outcomes and subgroup analyses, which were not adjusted for multiplicity and may not be used in place of hypothesis testing. Relative risks, mean differences for skewed outcomes, and rate ratios for count variables were calculated with a Poisson mixed-effects model, and mean differences for continuous variables were calculated with a linear mixed-effects model. The trial group and catheter type were modeled as fixed effects, and the trial site as a stratification factor was modeled as a random effect.

A multiple-imputation approach was used for any outcome variable with more than 5% missing data, with a complete-case approach used in a sensitivity analysis. Otherwise, only a complete case analysis was performed. For the primary outcome and bleeding-related secondary outcomes, we performed both a per-protocol analysis and an intention-to-treat analysis with the same assumption for the noninferiority margin. Other secondary outcomes were analyzed in the intention-to-treat population. Additional details are provided in the Methods section of the Supplementary Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From February 2016 through March 2022, a total of 393 CVC placements involving 358 patients were included in the trial (197 in the transfusion group and 196 in the no-transfusion group). Of these CVC placements, 373 were included in the per-protocol analysis after the exclusion of 20 placements owing to protocol violations (Fig. 1). No loss to follow-up occurred; the percentage of missing data for the primary outcome was 7.2% (Table S2). The characteristics of the patients at the time of CVC placement were well balanced between the trial groups (Table 2 and Table S3). A total of 15 adverse events were observed; of these events, 13 (all grade 3 catheter-related bleeding [i.e., leading to red-cell transfusion]) were categorized as serious; 4 events were in the

Table 2. Characteristics of the Patients at Baseline.*

Characteristic	Transfusion (N=188)	No Transfusion (N=185)
Median age (IQR) — yr	58 (47–65)	59 (50–65)
Female sex — no. (%)	63 (33.5)	70 (37.8)
Median body-mass index (IQR)†	25.3 (22.6–28.4)	25.4 (23.0–29.0)
Median platelet count (IQR) — per mm^3	30,000 (20,000–38,000)	30,000 (20,000–37,000)
Median international normalized ratio (IQR)	1.1 (1.0–1.3)	1.1 (1.0–1.2)
Median activated partial thromboplastin time (IQR) — sec	29 (25–34)	31 (26–35)
Median hemoglobin (IQR) — g/dl	8.2 (7.4–9.2)	8.5 (7.7–9.5)
Hospital department — no. (%)		
Hematology ward	108 (57.4)	104 (56.2)
ICU	80 (42.6)	81 (43.8)
Catheter type — no. (%)		
Regular	155 (82.4)	155 (83.8)
Dialysis	33 (17.6)	30 (16.2)
Tunneled catheter — no. (%)	20 (10.6)	18 (9.7)
Catheter site — no. (%)		
Internal jugular vein	93 (49.5)	93 (50.3)
Subclavian vein	71 (37.8)	70 (37.8)
Femoral vein	24 (12.8)	22 (11.9)
Platelet transfusion <6 hr before randomization — no. (%)	16 (8.5)	19 (10.3)

* Characteristics are described per catheter placement in the multiply imputed per-protocol population. ICU denotes intensive care unit, and IQR interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

transfusion group and 9 in the no-transfusion group (Table S4).

PRIMARY OUTCOME

Grade 2 to 4 catheter-related bleeding occurred in 9 of 188 patients (4.8%) in the transfusion group and in 22 of 185 patients (11.9%) in the no-transfusion group. Noninferiority of the no-transfusion strategy was not shown, with an absolute risk difference of 7.1 percentage points (90% confidence interval [CI], 1.3 to 17.8) and a relative risk of 2.45 (90% CI, 1.27 to 4.70) (Table 3 and Table S5). The results of sensitivity analyses were consistent with those of the primary analysis (Table S6). Results were also similar in a post hoc analysis that included a variable of operator awareness of trial-group assignments (Table S7). In a secondary analysis, the risk of grade 2 to 4 CVC-related bleeding increased with lower platelet counts (Table S8).

OTHER BLEEDING-RELATED OUTCOMES

No grade 4 bleeding complications were reported (Table S9). The risk of grade 3 or 4 CVC-related bleeding complications was lower in the transfusion group than in the no-transfusion group (2.1% vs. 4.9%), with relative risks consistent with the primary outcome (Table 3 and Table S5). The differences in grade 1 CVC-related bleeding complications and hematoma occurrence also favored the transfusion group. The number of red-cell transfusions within 24 hours after CVC placement was similar in the two groups, although the no-transfusion group received more red-cell transfusions specifically for CVC-related bleeding (16 vs. 6) (Table S10).

OTHER OUTCOMES

The platelet count was higher in the transfusion group than in the no-transfusion group both at 1 hour and at 24 hours after CVC placement

Table 3. Primary and Secondary Outcomes.*

Outcome	Transfusion (N=188)	No Transfusion (N=185)	Effect Size (90% or 95% CI)
Primary outcome			
Grade 2–4 catheter-related bleeding — no./total no. (%)	9/188 (4.8)	22/185 (11.9)	2.45 (1.27 to 4.70)†
Bleeding-related secondary outcomes			
Catheter-related bleeding — no./total no. (%)			
Grade 3–4	4/188 (2.1)	9/185 (4.9)	2.43 (0.75 to 7.93)†
Grade 1	88/188 (46.8)	106/185 (57.3)	1.22 (0.91 to 1.61)†
Hematoma — no./total no. (%)	23/188 (12.2)	35/185 (18.9)	1.62 (0.94 to 2.80)†
Median hematoma size (IQR) — cm	4.0 (2.2–5.9)	2.1 (1.8–4.3)	1.34 (0.96 to 1.86)‡
Rate of red-cell transfusion in ≤24 hr	0.48±0.76	0.49±0.75	1.02 (0.76 to 1.37)§
Hemoglobin level after CVC placement — g/dl			
After 1 hr	8.1±1.4	8.5±1.3	0.34 (0.06 to 0.62)¶
After 24 hr	8.4±1.4	8.5±1.2	0.09 (–0.17 to 0.35)¶
Other secondary outcomes			
Rate of platelet transfusion in ≤24 hr	0.14±0.44	0.47±0.65	3.29 (2.16 to 5.03)§
Median platelet count after CVC placement (IQR) — per mm^3			
After 1 hr	54,000 (42,000 to 66,000)	26,000 (18,000 to 37,000)	–26.8 (–31.4 to –22.3)¶
After 24 hr	36,000 (27,000 to 49,000)	26,000 (18,000 to 40,000)	–9.5 (–13.9 to –5.1)¶
Allergic transfusion reaction — no./total no. (%)	2/197 (1.0)	1/196 (0.5)	0.50 (0.05 to 5.51)†
Acute lung injury — no./total no. (%)	1/197 (0.5)	0/196	0.50 (0.05 to 5.48)†
Median length of stay (IQR) — days‖			
In ICU	9 (3 to 17)	7 (2 to 16)	0.84 (0.76 to 0.91)‡
In hospital	24 (13 to 34)	24 (9 to 33)	0.94 (0.90 to 0.98)‡
Death — no./total no. (%)			
ICU	38/67 (56.7)	43/83 (51.8)	0.92 (0.59 to 1.42)†
Hospital	50/177 (28.2)	57/180 (31.7)	0.99 (0.84 to 1.16)†

* Plus–minus values are means ±SD. The confidence interval for the primary outcome is two-sided 90% (one-sided 95%). The confidence intervals for the secondary outcomes are two-sided 95% and have not been adjusted for multiplicity, so they may not be used in place of hypothesis testing. The primary outcome and bleeding-related secondary outcomes were analyzed in both the per-protocol population (shown here) and the intention-to-treat population (shown in the Supplementary Appendix). Other secondary outcomes were analyzed only in the intention-to-treat population. CVC denotes central venous catheter.

† The effect size is the relative risk for binary outcomes. The relative risk for acute lung injury was calculated with 1 event added to each cell in the two-by-two table to circumvent the analytic problem of no events in the control group.

‡ The effect size is the mean difference for skewed variables.

§ The effect size is the rate ratio for count variables.

¶ The effect size is the between-group difference for continuous variables, as calculated with a linear mixed-effects model.

‖ The lengths of stay in the ICU and in the hospital were counted from randomization.

(Table 3). The no-transfusion group received more platelet transfusions in the 24 hours after CVC placement than the transfusion group, especially in patients with lower platelet counts and in those being treated on the hematology ward (Table S11). Three allergic transfusion reactions (two in the transfusion group and one in the no-transfusion group) and one case of transfusion-related acute lung injury were reported. The length of stay in the ICU was slightly shorter in the no-transfusion group, and mortality was similar in the two groups.

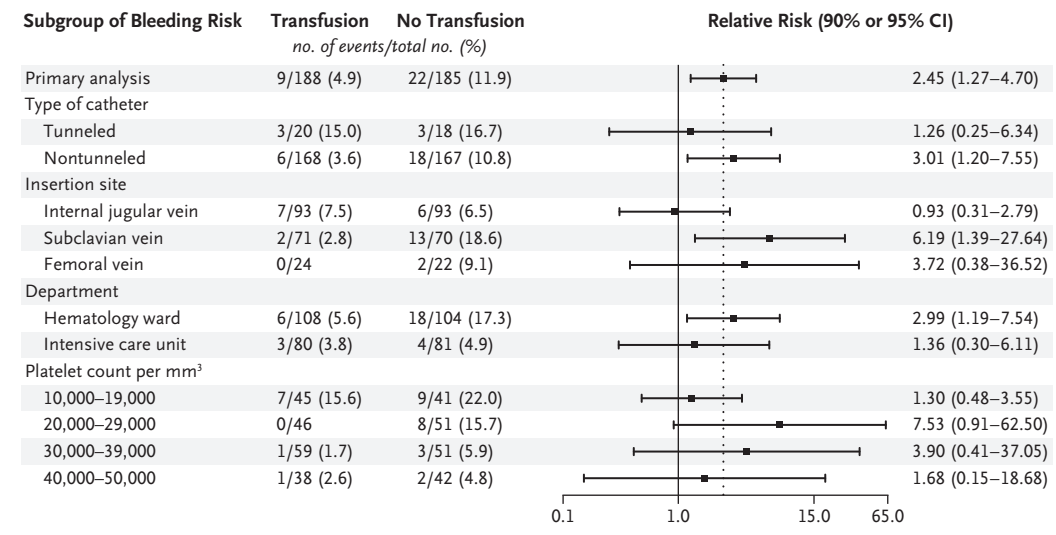

Figure 2. Bleeding Risk in Primary and Subgroup Analyses.

Shown is a forest plot of the risk of bleeding of grade 2 to 4 among patients with severe thrombocytopenia who had received prophylactic platelet transfusion and among those who had not received a platelet transfusion, according to overall numbers of central venous catheter (CVC) placements in the primary analysis and in prespecified exploratory subgroup analyses. The vertical dotted line represents the relative risk in the primary analysis (per-protocol population). A two-sided 90% confidence interval was calculated for the primary analysis and two-sided 95% confidence intervals for the subgroup analyses. The confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Relative risks in two subcategories — femoral vein placement and a platelet count of 20,000 to 29,000 per cubic millimeter — were calculated with 1 event added to each cell in the two-by-two table (used to evaluate the association between a possible risk factor and an outcome) to circumvent the analytic problem of no events in the control group.

SUBGROUP ANALYSES

The results of prespecified exploratory subgroup analyses were similar to the findings of the primary analysis (Fig. 2 and Fig. S1). In the two groups, the bleeding risk among the patients being treated on the hematology ward was higher than that among patients in the ICU, as was the bleeding risk with the use of tunneled catheters as compared with nontunneled catheters.

COST ANALYSIS

Overall costs related to transfusion and bleeding events were higher in the transfusion group than in the no-transfusion group (total cost difference per catheter placement, $410 [95% CI, 285 to 545]), a difference that was mainly driven by the up-front cost of $682 per prophylactic platelet transfusion (Table S10). However, the transfusion costs in the 24 hours after CVC placement were higher in the no-transfusion group because of higher frequencies of platelet transfusion and transfusions related to bleeding.

DISCUSSION

In this randomized, controlled trial involving patients with severe thrombocytopenia who were undergoing ultrasound-guided CVC placement, prophylactic platelet transfusion was associated with a lower risk of bleeding than the withholding of transfusion. The noninferiority of withholding transfusion was not shown for the primary outcome of grade 2 to 4 bleeding. Other secondary outcomes, such as grade 3 or 4 bleeding, grade 1 bleeding, and hematoma occurrence, consistently indicated that bleeding risk was higher in the no-transfusion group, whereas the number of transfusion reactions was low.

The proportionally higher bleeding risk that we found in patients with a lower platelet count after transfusion further supports the idea that a sufficient platelet count (and by extension, platelet transfusion) is important in preventing CVC-related bleeding. Although the platelet count has poor predictive power for bleeding

complications, it is one of very few variables that has been associated with spontaneous hemorrhage among patients in the ICU and in those with a hematologic cancer.[30-32] In this trial, the highest incidence of bleeding occurred in patients on the hematology ward, in those with a platelet count of 10,000 to 20,000 per cubic millimeter, and in those receiving a tunneled catheter, findings that indicate the importance of platelet transfusion in these patient groups before CVC placement. Differences in CVC-related bleeding risk between catheter placement in the ICU and on the hematology ward are expected, because patients in the ICU more often have consumptive thrombocytopenia whereas patients with hematologic issues more often have hypoproliferative thrombocytopenia.[33]

As compared with previously published data, the bleeding incidence in our trial was markedly higher, which may be explained by the prospective and structured manner of bleeding assessment that was used. Previous studies of CVC-related bleeding risk in patients with thrombocytopenia were mostly retrospective cohort studies, which depended on accurate recording of bleeding in patients' medical records.[18,27,34-38] On the basis of these retrospective studies, the most recent platelet transfusion guidelines from the Association for the Advancement of Blood and Biotherapies, the British Committee for Standards in Haematology, and the Society of Interventional Radiology now recommend prophylactic platelet transfusion before CVC placement when the platelet count is below 20,000 per cubic millimeter.[8-10] However, the Association of Anaesthesists of Great Britain and Ireland, the American Society of Clinical Oncology, and the Dutch guidelines on blood transfusion recommend a platelet transfusion threshold of 40,000 to 50,000 per cubic millimeter. The European Society of Intensive Care Medicine makes no recommendation either way for patients with a platelet count of 10,000 to 50,000 per cubic millimeter who are undergoing CVC placement.[11-14]

Besides bleeding risk, the scarcity and costs of platelet concentrates are important considerations when recommending the routine use of prophylactic platelet transfusion. Because of the short life span of platelet concentrates, maintaining an adequate supply is a logistic challenge, especially in countries with aging populations where the supply is decreasing and the demand is increasing.[22,23] Moreover, a shortage of blood products already exists in low- and middle-income countries, where the risk of pathogenic contamination is another limiting factor on the supply side.[24] Another strategy could be to withhold prophylactic platelet transfusion but actively monitor patients with thrombocytopenia who are undergoing CVC placement and transfuse after the procedure whenever substantial bleeding occurs. Although in our trial the withholding of prophylactic platelet transfusion before CVC placement led to an overall cost reduction, it should also be considered that the majority of patients in the no-transfusion group who had a platelet count of 10,000 to 30,000 per cubic millimeter still received a platelet transfusion within 24 hours after CVC placement, which was more common on the hematology ward. Consequently, a thoughtful clinical strategy may be to prophylactically transfuse patients in the lower platelet-count ranges and in those with downward platelet-count trends before CVC placement. These patients are likely to need a platelet transfusion anyway, and the benefit is highest before the procedure.

Our trial has several limitations. First, although this was a multicenter trial performed at academic and general hospitals, it was conducted only in the Netherlands, which may hamper comparisons with other health care systems. Although ultrasound guidance is now becoming standard practice, barriers to its use exist in high-income as well as low- and middle-income settings.[39,40] Second, this was a single-blind trial, which may have introduced some bias. However, an effort was made to keep the operator unaware of trial-group assignments during the CVC placement procedure, and no effect modification was seen between procedures according to group awareness among the operators. Third, our transfusion strategy consisted of one unit of platelet concentrate regardless of the baseline platelet count and without verification of the platelet increment after transfusion. Although this procedure reflects regular clinical practice, we cannot exclude the possibility that patients in the lower range of platelet counts might have needed multiple units to reach a sufficient level. And fourth, the clinical relevance of an increased risk of grade 2 bleeding complications could be

questioned. However, because the relative risk of grade 3 bleeding complications was similar to the relative risk of grade 2 bleeding complications and the overall incidence of both levels of bleeding was higher than previously described, we consider these results to be clinically relevant.

A strength of the trial is the broad patient population, with both hematology and ICU patients, both tunneled and nontunneled catheters, both large-bore dialysis catheters and smaller regular catheters, and insertions in internal jugular veins as well as subclavian veins and femoral veins. These features reflect the variety of CVCs that practitioners typically encounter in clinical practice, so their inclusion improves the generalizability of the results.

Despite our overall findings regarding CVC-related bleeding complications in all patients with a platelet count of 10,000 to 50,000 per cubic millimeter, we would advocate for a more personalized approach. We would consider prophylactic platelet transfusion in patients with a platelet count of less than 30,000 per cubic millimeter, especially on the hematology ward, because these patients are likely to require a platelet transfusion within 24 hours anyway. For patients in the ICU with lower platelet counts, we would consider a no-transfusion strategy with intensive monitoring and a low threshold for the therapeutic use of blood products. The patients in the ICU had a lower bleeding risk than those on the hematology ward, and the ICU setting allows for more intensive monitoring. We would consider raising platelet-count thresholds for tunneled catheter insertion as opposed to nontunneled catheter insertion, because the bleeding risk associated with tunneled catheters was considerably higher. Finally, we would consider performing a follow-up trial to investigate the prophylactic transfusion of multiple units of platelet concentrate in patients with a platelet count of less than 20,000 per cubic millimeter, because their bleeding risk remained high even after one unit of platelets.

In patients with severe thrombocytopenia, we found that withholding prophylactic platelet transfusion before CVC placement in those with a platelet count of 10,000 to 50,000 per cubic millimeter did not meet the predefined margin for noninferiority and resulted in more CVC-related bleeding than prophylactic platelet transfusion.

Supported by ZonMw, part of the Dutch Research Council (project number, 843002625).

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Floor L.F. van Baarle, M.D., Emma K. van de Weerdt, M.D., Ph.D., Walter J.F.M. van der Velden, M.D., Ph.D., Roelof A. Ruiterkamp, M.Sc., Pieter R. Tuinman, M.D., Ph.D., Paula F. Ypma, M.D., Ph.D., Walter M. van den Bergh, M.D., Ph.D., Astrid M.P. Demandt, M.D., Emile D. Kerver, M.D., A.J. Gerard Jansen, M.D., Ph.D., Peter E. Westerweel, M.D., Ph.D., Sesmu M. Arbous, M.D., Ph.D., Rogier M. Determann, M.D., Ph.D., Walther N.K.A. van Mook, M.D., Ph.D., Mirelle Koeman, M.D., Ph.D., Anja B.U. Mäkelburg, M.D., Ph.D., Krijn P. van Lienden, M.D., Ph.D., Jan M. Binnekade, Ph.D., Bart J. Biemond, M.D., Ph.D., and Alexander P.J. Vlaar, M.D., Ph.D.

The authors' affiliations are as follows: the Departments of Intensive Care Medicine (F.L.F.B., E.K.W., J.M.B., A.P.J.V.) and Hematology (B.J.B.) and the Laboratory of Experimental Intensive Care and Anesthesiology (F.L.F.B., E.K.W., A.P.J.V.), Amsterdam University Medical Centers location University of Amsterdam, the Department of Intensive Care Medicine, Amsterdam University Medical Centers location Vrije Universiteit Amsterdam (P.R.T.), and the Departments of Oncology (E.D.K.) and Intensive Care Medicine (R.M.D.), OLVG, Amsterdam, the Department of Hematology, Radboud University Medical Center, Nijmegen (W.J.F.M.V., R.A.R.), the Departments of Hematology (P.F.Y.) and Intensive Care Medicine (M.K.), Haga Ziekenhuis, the Hague, the Departments of Critical Care (W.M.B.) and Hematology (A.B.U.M.), University Medical Center Groningen, University of Groningen, Groningen, the Departments of Hematology (A.M.P.D.) and Intensive Care Medicine (W.N.K.A.M.), Maastricht University Medical Center, Maastricht, the Department of Hematology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam (A.J.G.J.), the Department of Internal Medicine, Albert Schweitzer Ziekenhuis, Dordrecht (P.E.W.), the Department of Intensive Care Medicine, Leiden University Medical Center, Leiden (S.M.A.), and the Department of Interventional Radiology, St. Antonius Ziekenhuis, Nieuwegein (K.P.L.) — all in the Netherlands.

REFERENCES

1. Taylor RW, Palagiri AV. Central venous catheterization. Crit Care Med 2007;35:1390-6.
2. Rebulla P, Finazzi G, Marangoni F, et al. The threshold for prophylactic platelet transfusion in adults with acute myeloid leukemia. N Engl J Med 1997;337:1870-5.
3. Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. Lancet 2012;380:1309-16.
4. Levi M, Sivapalaratnam S. Hemostatic abnormalities in critically ill patients. Intern Emerg Med 2015;10:287-96.
5. Pérez-Granda MJ, Guembe M, Rincón C, Muñoz P, Bouza E. Effectiveness of a training program in compliance with recommendations for venous lines care. BMC Infect Dis 2015;15:296.
6. van de Weerdt EK, Biemond BJ, Baake B, et al. Central venous catheter placement in coagulopathic patients: risk fac-

tors and incidence of bleeding complications. Transfusion 2017;57:2512-25.
7. Cabrini L, Pappacena S, Mattioli L, et al. Administration of blood products to prevent bleeding complications associated with central venous catheter insertion in patients at risk: a systematic review. Br J Anaesth 2017;118:630-4.
8. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2015;162:205-13.
9. Estcourt LJ, Birchall J, Allard S, et al. Guidelines for the use of platelet transfusions. Br J Haematol 2017;176:365-94.
10. Patel IJ, Rahim S, Davidson JC, et al. Society of Interventional Radiology consensus guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions. II. Recommendations. J Vasc Interv Radiol 2019; 30(8):1168.e1-1184.e1.
11. Klein AA, Arnold P, Bingham RM, et al. AAGBI guidelines: the use of blood components and their alternatives 2016. Anaesthesia 2016;71:829-42.
12. Schiffer CA, Bohlke K, Delaney M, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2018;36:283-99.
13. Vlaar AP, Oczkowski S, de Bruin S, et al. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. Intensive Care Med 2020;46:673-96.
14. Federatie Medisch Specialisten. Trombocytenwaarde voor profylactische trombocytentransfusie. October 15, 2020 (https://web.archive.org/web/20211021052556/https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/trombocytentransfusies/trombocytenwaarde_voor_profylactische_trombocytentransfusie.html).
15. van de Weerdt EK, Peters AL, Goudswaard EJ, et al. The practice of platelet transfusion prior to central venous catheterization in presence of coagulopathy: a national survey among clinicians. Vox Sang 2017;112:343-51.
16. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization. Cochrane Database Syst Rev 2015;1:CD006962.
17. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for subclavian or femoral vein catheterization. Cochrane Database Syst Rev 2015;1:CD011447.
18. Cavanna L, Citterio C, Di Nunzio C, Orlandi E, Toscani I, Ambroggi M. Central venous catheterization in cancer patients with severe thrombocytopenia: ultrasound-guide improves safety avoiding prophylactic platelet transfusion. Mol Clin Oncol 2020;12:435-9.
19. Vlaar APJ, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet 2013;382:984-94.
20. Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. Lancet 2016; 388:2825-36.
21. Aubron C, Flint AW, Bailey M, et al. Is platelet transfusion associated with hospital-acquired infections in critically ill patients? Crit Care 2017;21:2.
22. Williamson LM, Devine DV. Challenges in the management of the blood supply. Lancet 2013;381:1866-75.
23. Greinacher A, Weitmann K, Schönborn L, et al. A population-based longitudinal study on the implication of demographic changes on blood donation and transfusion demand. Blood Adv 2017;1: 867-74.
24. Roberts N, James S, Delaney M, Fitzmaurice C. The global need and availability of blood products: a modelling study. Lancet Haematol 2019;6(12):e606-e615.
25. van de Weerdt EK, Biemond BJ, Zeerleder SS, et al. Prophylactic platelet transfusion prior to central venous catheter placement in patients with thrombocytopenia: study protocol for a randomised controlled trial. Trials 2018;19:127.
26. van Baarle FLF, Tisheh A, Jhingoeriesingh SS, Vlaar APJ, Biemond BJ. Contribution of coagulopathy on the risk of bleeding after central venous catheter placement in critically ill thrombocytopenic patients. Crit Care Explor 2022;4(1): e0621.
27. Zeidler K, Arn K, Senn O, Schanz U, Stussi G. Optimal preprocedural platelet transfusion threshold for central venous catheter insertions in patients with thrombocytopenia. Transfusion 2011;51:2269-76.
28. National Cancer Institute. Common terminology criteria for adverse events v3.0 (CTCAE). August 9, 2006 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).
29. Müller MC, Arbous MS, Spoelstrade Man AM, et al. Transfusion of fresh-frozen plasma in critically ill patients with a coagulopathy before invasive procedures: a randomized clinical trial (CME). Transfusion 2015;55:26-35.
30. Estcourt LJ, Stanworth SJ, Harrison P, et al. Prospective observational cohort study of the association between thromboelastometry, coagulation and platelet parameters and bleeding in patients with haematological malignancies — the ATHENA study. Br J Haematol 2014;166: 581-91.
31. Russell L, Holst LB, Kjeldsen L, Stensballe J, Perner A. Risks of bleeding and thrombosis in intensive care unit patients with haematological malignancies. Ann Intensive Care 2017;7:119.
32. Russell L, Madsen MB, Dahl M, Kampmann P, Perner A. Prediction of bleeding and thrombosis by standard biochemical coagulation variables in haematological intensive care patients. Acta Anaesthesiol Scand 2018;62:196-206.
33. Zarychanski R, Houston DS. Assessing thrombocytopenia in the intensive care unit: the past, present, and future. Hematology Am Soc Hematol Educ Program 2017;2017:660-6.
34. Haas B, Chittams JL, Trerotola SO. Large-bore tunneled central venous catheter insertion in patients with coagulopathy. J Vasc Interv Radiol 2010;21:212-7.
35. Doerfler ME, Kaufman B, Goldenberg AS. Central venous catheter placement in patients with disorders of hemostasis. Chest 1996;110:185-8.
36. Duffy SM, Coyle TE. Platelet transfusions and bleeding complications associated with plasma exchange catheter placement in patients with presumed thrombotic thrombocytopenic purpura. J Clin Apher 2013;28:356-8.
37. Vinson DR, Ballard DW, Hance LG, et al. Bleeding complications of central venous catheterization in septic patients with abnormal hemostasis. Am J Emerg Med 2014;32:737-42.
38. Rocha LL, Neto AS, Pessoa CMS, et al. Comparison of three transfusion protocols prior to central venous catheterization in patients with cirrhosis: a randomized controlled trial. J Thromb Haemost 2020;18:560-70.
39. Zaver F, Boniface K, Wachira B, Wanjiku G, Shokoohi H. International scope of emergency ultrasound: barriers in applying ultrasound to guide central line placement by providers in Nairobi, Kenya. Emerg Med Int 2018;2018:7328465.
40. Scholten HJ, Ten Bloemendal E, Botter B, Korsten HHM, Bouwman RA. Barriers to ultrasound guidance for central venous access: a survey among Dutch intensivists and anaesthesiologists. J Clin Monit Comput 2019;33:1023-31.