ANESTHESIOLOGY

Prolonged Blood Storage and Risk of Posttransfusion Acute Kidney Injury

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Erythrocyte transfusions are independently associated with postoperative acute kidney injury
- Prolonged erythrocyte storage produces progressive shape abnormalities, biochemical changes, and release of proinflammatory cytokines—all of which might promote kidney injury

What This Article Tells Us That Is New

- In a planned subanalysis of a large trial that evaluated mortality in hospitalized patients randomized to either the freshest or the oldest available erythrocyte units, there was no difference in the incidence of posttransfusion acute kidney injury

ABSTRACT

Background: Erythrocyte transfusions are independently associated with acute kidney injury. Kidney injury may be consequent to the progressive hematologic changes that develop during storage. This study therefore tested the hypothesis that prolonged erythrocyte storage increases posttransfusion acute kidney injury.

Methods: The Informing Fresh *versus* Old Red Cell Management (INFORM) trial randomized 31,497 patients to receive either the freshest or oldest available matching erythrocyte units and showed comparable mortality with both. This *a priori* substudy compared the incidence of posttransfusion acute kidney injury in the randomized groups. Acute kidney injury was defined by the creatinine component of the Kidney Disease: Improving Global Outcomes criteria.

Results: The 14,461 patients included in this substudy received 40,077 erythrocyte units. For patients who received more than one unit, the mean age of the blood units was used as the exposure. The median of the mean age of blood units transfused per patient was 11 days [interquartile range, 8, 15] in the freshest available blood group and 23 days [interquartile range, 17, 30] in the oldest available blood group. In the primary analysis, posttransfusion acute kidney injury was observed in 688 of 4,777 (14.4%) patients given the freshest available blood and 1,487 of 9,684 (15.4%) patients given the oldest available blood, with an estimated relative risk (95% CI) of 0.94 (0.86 to 1.02; $P = 0.132$). The secondary analysis treated blood age as a continuous variable (defined as duration of storage in days), with an estimated relative risk (95% CI) of 1.00 (0.96 to 1.04; $P = 0.978$) for a 10-day increase in the mean age of erythrocyte units.

Conclusions: In a population of patients without severely impaired baseline renal function receiving fewer than 10 erythrocyte units, duration of blood storage had no effect on the incidence of posttransfusion acute kidney injury.

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Acute kidney injury (AKI) is characterized by elevated serum creatinine or decreased urine output. The incidence of AKI ranges from 7 to 18% in hospitalized patients, including patients having surgery.[1–5] Many factors contribute to developing AKI including hypotension, altered cardiac function, anemia, hypoxia, nephrotoxins, and preexisting renal disease. Erythrocyte transfusions are also independently associated with AKI after endovascular and surgical procedures.[6–9]

Development of posttransfusion AKI may be consequent to the hematologic changes that develop with longer erythrocyte storage times. Specifically, prolonged erythrocyte storage duration produces progressive shape abnormalities and a host of biochemical disturbances.[10–12] For example, sodium and glucose concentrations decrease, while concentrations of potassium, lactate, and proinflammatory cytokines increase considerably. Furthermore, the erythrocytes themselves increasingly aggregate, become rigid, and adhere to endothelial cells, which may impede their ability to flow through small capillaries to deliver oxygen.[13,14] These changes are collectively termed the erythrocyte "storage lesion."

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The Informing Fresh *versus* Old Red Cell Management (INFORM) trial was a pragmatic randomized trial that found no significant difference in the mortality of patients who were randomly transfused with the freshest available or oldest available matching erythrocyte units.[15,16] However, it remained unclear whether transfusion with older blood increased the risk of AKI. Many previous studies addressing this question were observational or had small sample sizes, which made their conflicting results difficult to interpret (appendix).[17–32] Notably, 10 of 11 studies with sample sizes greater than 500 patients did not find an association between blood age and AKI,[23–32] and 4 of 5 studies published after the year 2015 also did not find an association.[18,20,27,30,31] Furthermore, the three randomized trials all showed no difference in renal adverse events based on blood age.[27,30,31] However, the studies tended to focus on particular subsets of patients, such as those in the intensive care unit or undergoing cardiac surgery. We therefore tested the hypothesis that the transfusion of older blood increases the risk of AKI in a more general population of hospitalized patients.

Materials and Methods

Study Design

We performed a planned substudy of the INFORM trial.[15,33] Because the original study did not assess kidney function, this substudy required the collection of additional laboratory data—creatinine and hemoglobin—from blood sample measurements before and after transfusion. INFORM recruited patients from six hospitals in four countries, all of which participated in our substudy: Hamilton General Hospital (Canada), Juravinski Hospital (Canada), St. Joseph's Healthcare Center (Canada), Cleveland Clinic (United States), Flinders Medical Center (Australia), and Meir Medical Center (Israel). This substudy was approved by the institutional review board at each participating site.

Patient Population

Between April 2012 and October 2015, the INFORM trial enrolled 31,497 patients. They were randomized 1:2 to receive either the freshest available blood (experimental group) or the oldest available blood (control group), up to the maximum accepted shelf life of 42 days. No other aspect of patient management was controlled.

Adults were eligible for INFORM if they required an erythrocyte transfusion during their hospital admission (surgery was not required). The trial excluded patients expected to receive massive transfusions, patients who required uncrossmatched erythrocyte units or autologous erythrocyte units, patients with complex antibody profiles, and patients deemed to have a clinical indication for the freshest available blood. Among the randomized patients, 24,736 met all enrollment criteria and were included in the original INFORM analysis. No crossovers occurred during the study.

For this substudy, we additionally excluded patients who did not have both pretransfusion and posttransfusion serum creatinine measurements, had baseline creatinine greater than 4.0 mg/dl, had an estimated glomerular filtration rate of less than 30 ml/min based on the Modification of Diet in Renal Disease equation, were dependent on renal dialysis, had procedures on the urinary system, or received 10 erythrocyte units or more during their hospital admission. Patients with inadequate serum creatinine measurements or severely impaired baseline renal function were excluded because we would have been unable to calculate our primary outcome of posttransfusion AKI. Patients who received 10 erythrocyte units or more during their hospital admission were also excluded because the transfused erythrocyte units would likely span a large range of storage durations, which would blur the separation we were trying to achieve between patients who received fresh *versus* old blood.

Outcomes

Our primary exposure was transfusion with either the freshest available blood (short-term storage group) or the oldest available blood (long-term storage group). Our primary outcome was the development of posttransfusion AKI, defined using the creatinine component of the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[34] The baseline creatinine value was defined as the mean serum creatinine measurement in the week before transfusion. AKI was defined as an increase of at least 1.5 times the baseline creatinine or an increase of 0.3 mg/dl in any rolling 48-h window in the 7 days after transfusion.[34] Therefore, at minimum, patients needed to have a baseline serum creatinine measurement and another serum creatinine measurement within 7 days of transfusion to be included in our study. We chose to limit our timing to 7 posttransfusion days—rather than including serum creatinine measurements from the entire hospital stay—to remain consistent with the KDIGO criteria. Furthermore, we excluded patients with baseline serum creatinine values greater than 4.0 mg/dl or who were already on renal dialysis because their baseline renal function was so poor that they were already classified as having the most severe AKI under KDIGO guidelines, so we would be unable to calculate further injury using the KDIGO definitions. Since we did not have data regarding urine output, we did not use this parameter for an alternative definition of AKI. Nonetheless, serum creatinine is both sufficient and more common for AKI definition.

Statistical Analysis

In the primary analysis, we tested the association between treatment group (short-term *vs.* long-term storage) and AKI using a log-binomial regression to report relative risk in this randomized trial. We assessed whether the treatment effect varied across levels of various baseline factors, including age, sex, patient blood type, and study site, by assessing interaction between treatment group and the baseline factor. Likelihood ratio tests were used to test for heterogeneity of the treatment effect.

For the secondary analysis, we analyzed blood storage duration as a continuous variable. The mean duration of erythrocyte storage was used for patients who received more than one unit. A log-binomial model was fitted with AKI as the outcome and the actual age of the erythrocytes (in days) as the exposure. This model was adjusted for hospital site and patient blood type to account for imbalance. The time interval for the erythrocyte transfusions to be included in the analysis was the time from the first erythrocyte transfusion to the earliest time at which patients were determined to meet the criteria for AKI or 7 days from the first transfusion (for subjects who did not meet the criteria for AKI).

Additionally, a sensitivity analysis was conducted using the age of the oldest erythrocyte unit (in days) given to each patient as the exposure. The model was adjusted for hospital site, patient blood type, and number of erythrocyte transfusions to account for imbalance. A Poisson regression model (with AKI as the outcome) with robust error variance was fitted for this analysis in lieu of the log-binomial model, which failed to converge. Poisson regression models are usually used for estimating relative rates for count data. This can be easily extended to binomial data, in which case the relative rates can be thought of as relative risks. However, Poisson regression tends to be conservative when applied to binomial data. This can be rectified by using robust error variances obtained using sandwich estimation. The time interval for erythrocyte transfusions to be considered for inclusion in the sensitivity analysis was the same as that for the secondary analysis.

For the primary analysis, balance of demographic and clinical characteristics between the randomized groups was assessed using absolute standardized difference. The absolute standardized difference is roughly the absolute difference between means or proportions divided by the pooled SD.[35,36] For the secondary and sensitivity analyses, balance was assessed using absolute Pearson correlation (for continuous and ordinal covariates) or absolute standardized difference (for nominal covariates), because the exposures (*e.g.*, blood storage duration) were continuous.[37] The absolute standardized difference in this case was calculated by treating the nominal covariates as the stratifying groups and the treatment variables as the outcome. For both primary and secondary analyses, an absolute standardized difference or absolute Pearson correlation greater than 0.1 indicated imbalance between the two treatment groups, and covariate adjustment would be used to account for the imbalance.

Relative risk and 95% CI were obtained from all models. The confidence level for all tests was set at 95% ($P < 0.05$ was considered significant). This study had 4,777 patients in the short-term storage group (treatment) and 9,684 patients in the long-term storage group (lower). Using the observed control group incidence of 15.4%, we had 90% power to detect a relative risk of 0.86 or lower at the 0.05 significance level. The analyses were conducted using R version 4.0.2 (https://www.R-project.org/, accessed December 22, 2020).

Results

Patients

A total of 24,736 patients from the INFORM study were considered for this substudy. After excluding patients who did not meet the inclusion criteria, 14,461 patients were left for analysis. Among them, 4,777 were randomized to receive the freshest available blood (short-term storage group) and 9,684 to receive the oldest available blood (long-term storage group; fig. 1). The average age of the patients was 67 yr, and most had blood types O and A. Before transfusion, the average serum creatinine was approximately 1.0 mg/dl, hemoglobin was approximately 8.0 g/dl, and approximately 7% of the patients in each group had a history of chronic kidney disease. Overall, the patients in the two treatment groups were well balanced at baseline for the primary analysis (all with an absolute standardized difference of less than 0.10; table 1).

For the secondary and sensitivity analyses, balance on potential confounding variables was assessed separately, because the exposures (mean age of transfused erythrocytes and age of the oldest erythrocyte unit) were continuous (table 2). Imbalance was detected for hospital site and patient blood type for both of these exposures. Imbalance of the number of erythrocytes transfused was also detected for the age of the oldest erythrocyte unit. These variables were thus adjusted for in the corresponding analyses.

Transfusion Data

The 14,461 patients included in our analysis received a total of 40,077 erythrocyte units: 13,202 in the short-term storage group and 26,875 in the long-term storage group (fig. 2). Patients in each group received a median of 2 erythrocyte units [interquartile range, 1 to 3]. For patients who received more than one erythrocyte unit, we determined both the mean age of the transfused units and the age of the oldest unit. The median of the mean age of erythrocyte units transfused per patient was 11 days [interquartile range, 8 to 15] in the short-term storage group and 23 days [interquartile range, 17 to 30] in the long-term storage group. The median of the oldest erythrocyte unit transfused per patient was 12 days [interquartile range, 9 to 18] in the short-term storage group and 26 days [interquartile range, 18 to 35] in the long-term storage group. The proportion of patients who received other transfusions—platelets, plasma, and cryoprecipitate—was similar in each group (table 3).

Outcomes

The criteria for AKI were met by 688 of 4,777 patients (14.4%) in the short-term storage group and 1,487 of 9,684 patients (15.4%) in the long-term storage group. We did not find an association between the treatment group and AKI in the primary analysis, with an estimated relative risk (95% CI) of 0.94 (0.86 to 1.02; $P = 0.132$). The estimated CI suggests that the risk of developing AKI in the short-term storage group ranged from 14% lower to 2% higher than in the

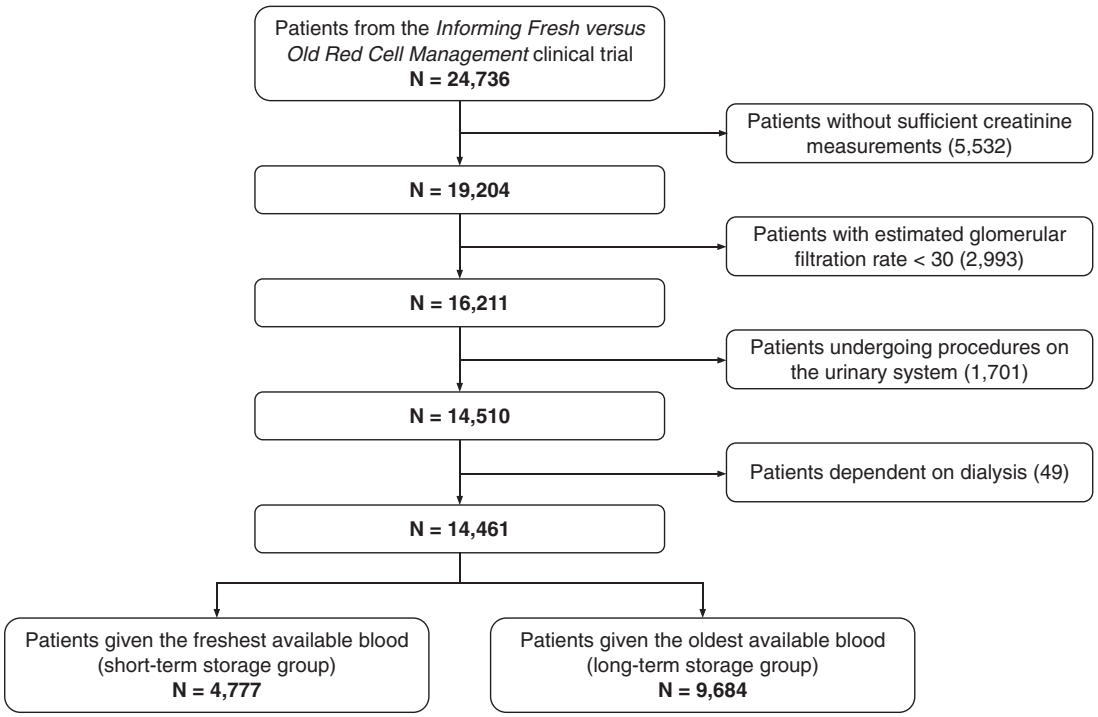

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

long-term storage group. No significant interactions were found between treatment assignment and baseline factors such as age, sex, patient blood type, and study site (fig. 3).

For the secondary analysis, after adjusting for hospital site and patient blood type, the mean age of erythrocytes was not associated with AKI ($P = 0.978$), with an estimated relative risk (95% CI) of 1.00 (0.96 to 1.04) for a 10-day increase in the mean age of erythrocytes. Similarly, for the sensitivity analysis, after adjusting for hospital site, patient blood type, and number of erythrocyte transfusions, the age of the oldest erythrocyte unit was not associated with AKI ($P = 0.885$), with an estimated relative risk (95% CI) of 1.00 (0.96 to 1.04) for a 10-day increase in the age of the oldest erythrocyte unit.

Discussion

Among hospitalized adults without severely impaired baseline renal function who received fewer than 10 erythrocyte transfusions, the duration of blood storage had no appreciable effect on the incidence of AKI. This finding was consistent when comparing patients who were randomized to receive either the freshest or oldest available blood and when comparing the actual age of the transfused blood cells. It is thus unlikely that erythrocyte storage influences renal function over the typical range of storage durations.

Previous studies investigated the potential renal consequences of transfusing older blood (appendix).[17–32] Most were observational and focused on particular subsets of patients, such as those having cardiac surgery[19,22,25–28,32] or needing intensive care.[24,30,31] Some of the older studies reported conflicting results, perhaps because of small sample sizes and the heterogeneous definitions of blood age and kidney injury. Notably, most of the studies with greater than 500 patients (and all three randomized trials) have shown that there is no significant association between blood storage duration and adverse renal outcomes.

Our trial was by far the largest assessing erythrocyte storage duration and kidney injury. The enrollment of a broad patient population, regardless of reason for transfusion or surgical status, allows our results to be generalized to most hospitalized patients. Additionally, with our pragmatic design, we achieved a 12-day separation between the two randomized treatment groups, which was better than the 10 days targeted by the original INFORM trial. With this large, broad patient sample and adequate storage-duration separation achieved between the treatment groups, we found no effect of blood storage duration on AKI in our primary analysis. Furthermore, there was no evidence of harm in our continuous analysis even at extreme durations, up to the 42-day storage limit allowed in most developed countries. We therefore conclude that blood storage duration has no clinically meaningful effect on kidney injury in patients who do not have severely impaired renal function at baseline, which is consistent with the underlying INFORM trial that clearly showed no difference in mortality. Given that blood is a limited and valuable resource, it is reassuring to find that the patients in our study could safely receive erythrocyte units of any age, according to the current storage practices. Based on these findings, the way we maintain our blood supply appears to be safe,

Table 1. Demographic and Clinical Characteristics of the Patients by Erythrocyte Storage Duration Group

Characteristic	Short-term Storage Group (N = 4,777)	Long-term Storage Group (N = 9,684)	Absolute Standardized Difference
Age, mean (SD)	67 (16)	67 (16)	0.003
Male sex, no. (%)	2,500 (52.3)	5,063 (52.3)	0.001
Blood type, no. (%)			0.015
O	2,109 (44.1)	4,297 (44.4)	
A	1,926 (40.3)	3,926 (40.5)	
B	563 (11.8)	1,121 (11.6)	
AB	179 (3.7)	340 (3.5)	
Hospital site, no. (%)			0.020
Australia	1,181 (24.7)	2,418 (25.0)	
Canada site 1	1,012 (21.2)	2,057 (21.2)	
Canada site 2	664 (13.9)	1,315 (13.6)	
Canada site 3	224 (4.7)	480 (5.0)	
United States	1,630 (34.1)	3,269 (33.8)	
Israel	66 (1.4)	145 (1.5)	
Days to transfusion, median [interquartile range]	2.6 [1.4, 6.3]	2.6 [1.4, 6.5]	0.024
Baseline serum creatinine (mg/dl), mean (SD)	0.98 (0.38)	1.00 (0.38)	0.038
Lowest baseline hemoglobin (g/dl), mean (SD)	8.02 (1.73)	8.06 (1.72)	0.024
Chronic kidney disease, no. (%)	357 (7.5)	715 (7.4)	0.003
Category of disease diagnosis, no. (%)			0.064
Circulatory system	1,501 (31.4)	3,029 (31.3)	
Injury, poisoning, or external causes, including trauma	790 (16.5)	1,616 (16.7)	
Neoplasms	648 (13.6)	1,342 (13.9)	
Digestive system	626 (13.1)	1,259 (13.0)	
Musculoskeletal system and connective tissue	253 (5.3)	473 (4.9)	
Respiratory system	191 (4.0)	392 (4.0)	
Blood and blood-forming organs and immune-system disorders	186 (3.9)	378 (3.9)	
Certain infectious and parasitic diseases	128 (2.7)	213 (2.2)	
Symptoms, signs, and abnormal clinical and laboratory findings	113 (2.4)	208 (2.1)	
Endocrine, nutritional, and metabolic	110 (2.3)	224 (2.3)	
Genitourinary system	56 (1.2)	109 (1.1)	
Factors influencing health status and contact with health services	53 (1.1)	125 (1.3)	
Pregnancy, childbirth, and puerperium	34 (0.7)	71 (0.7)	
Other	88 (1.8)	245 (2.5)	

The absolute standardized difference is roughly defined as the absolute difference between means or proportions divided by the pooled standard deviation. An absolute standardized difference of greater than 0.10 indicates imbalance.

and we see no reason to routinely discard or limit the use of older blood if it has not yet reached the storage limit of 42 days.

The most common indication for erythrocyte transfusion is anemia, which is inherently associated with AKI. In addition, patients with preexisting renal disease may be more susceptible to further kidney injury. Thus, it was important to assess for balance of anemia and baseline kidney function because these are potential confounders. It was reassuring that both absolute standardized difference analyses and absolute Pearson correlations showed that pretransfusion hemoglobin and creatinine were similar for patients in the primary, secondary, and sensitivity analyses. It is important to note that we excluded patients with baseline serum creatinine values greater than 4.0 mg/dl or who were already on renal dialysis because we were unable to calculate further kidney injury in these patients. Our study population, therefore, was made of patients who were considered "sick" enough to warrant measuring their serum creatinine, but not so sick that they had severely impaired renal function at baseline.

We included patients with all ABO blood types in our analysis, although most had type O or A, and we expected patients with type B and AB to be more likely to receive non–type-specific units. Patient blood types were comparably distributed between the treatment groups of the primary analysis, but we observed slight imbalances in the secondary and sensitivity analyses. Imbalances were unsurprising because while the primary analysis was based on randomization of patient allocation, the secondary and sensitivity analyses used the actual blood storage duration. We therefore adjusted for patient blood type in our secondary and sensitivity models. Notably, the treatment effect for our primary outcome was similar across all blood types.

Because this is a substudy of the INFORM trial, we were limited in the variables we could include in our analysis. The original INFORM trial did not systematically record detailed information on coexisting illnesses, reasons for transfusion, and concomitant interventions. We also did not have information on which patients were surgical *versus* nonsurgical, although the underlying pathophysiology is often different between those patient populations. We were therefore unable to adjust for those possible confounders or perform those subgroup analyses with our models. However, in a large randomized trial, it is highly unlikely that baseline characteristics and ancillary treatments differed systematically between the groups.

Table 2. Balance of Potential Confounders on Exposures for the Secondary and Sensitivity Analyses

Characteristic	Mean Age of Transfused Blood	Age of Oldest Blood Transfused
Absolute standardized difference		
Sex	0.03	0.06
Hospital site	0.32*	0.31*
Patient blood type	0.18*	0.16*
Disease diagnosis	0.09	0.09
Absolute Pearson correlation		
Age	0.01	0.01
Days to transfusion	0.00	0.01
Baseline serum creatinine	0.01	0.01
Lowest baseline hemoglobin	0.02	0.01
Chronic kidney disease	0.04	0.04
No. of erythrocyte units transfused	0.01	0.13*
No. of platelet transfusions	0.01	0.07
No. of plasma transfusions	0.00	0.05
No. of cryoprecipitate transfusions	–0.04	0.00

*An absolute standardized difference or absolute Pearson correlation of greater than 0.10 indicates imbalance.

Because we were using a different outcome than the original INFORM study, we observed a significant percentage of missing outcome data. Specifically, 14,461 of 24,736 (58.5%) of the original INFORM patients remained available for analysis in this substudy, which invites the possibility that our patient population might have different characteristics than the INFORM study population. Most patients were excluded for missing serum creatinine measurements, so it seems very unlikely that there was a systematic bias in the missing data related to the patient's allocation. Additionally, we maintained our 1:2 allocation ratio, which further highlights the unlikeliness of bias; however, this cannot be ruled out conclusively and should be noted as a limitation of the study.

Another limitation was the lack of blinding because regulatory agencies require all erythrocyte products to be labeled with the date of collection or expiration. However, lack of blinding seems unlikely to influence transfusion practice, because clinicians would not know blood age until the requested units arrived at the transfusion venue, and at that point, the blood age would be unlikely to influence a previous decision to transfuse.

In summary, there was no difference in the incidence of posttransfusion AKI in our study population of patients who received the freshest available blood compared to patients who received the oldest available blood. This result aligns with the standard blood bank inventory management practice of providing the oldest available blood for routine transfusions.

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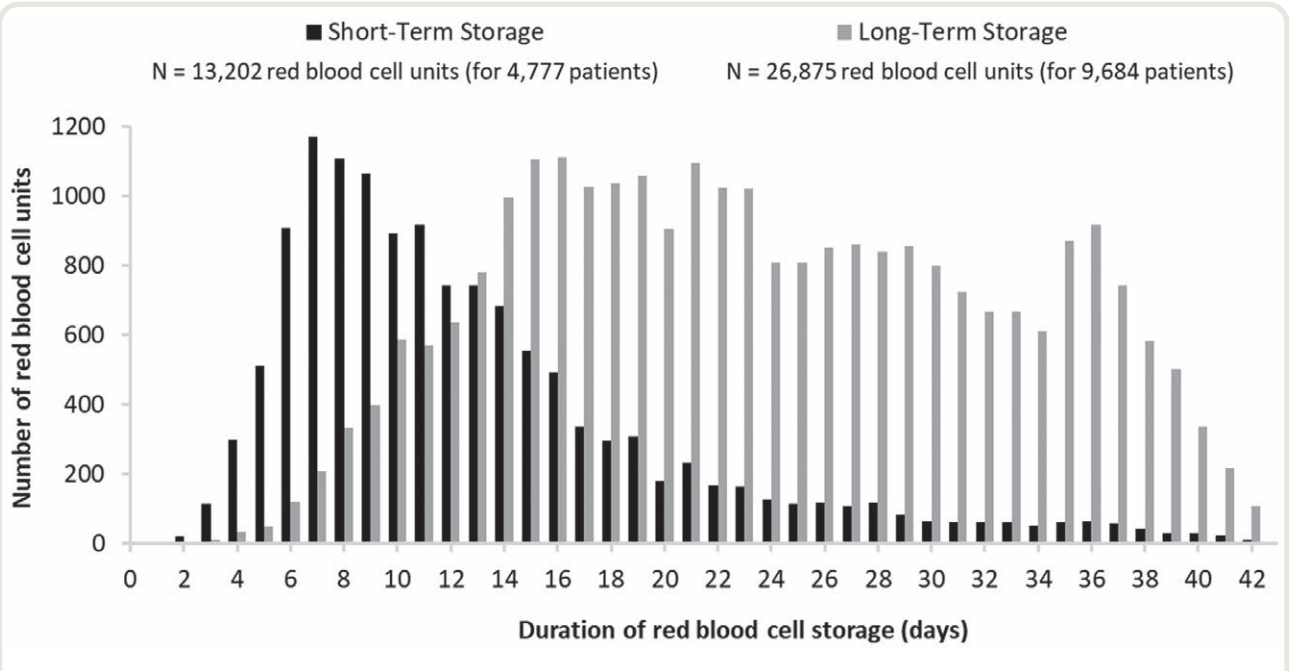

Fig. 2. Duration of erythrocyte storage before transfusion. Shown is a histogram of erythrocyte storage duration for the two groups: short-term storage (N = 13,202 erythrocyte units for 4,777 patients) and long-term storage (N = 26,875 erythrocyte units for 9,684 patients). The median [interquartile range] number of units transfused per patient was 2 [1, 3] in both groups. The median [interquartile range] of the mean age of transfused units was 11 [8, 15] in the short-term storage group and 23 [17, 30] in the long-term storage group (table 3).

Table 3. Transfusion Data by Erythrocyte Cell Storage Duration Group

Characteristics	Short-term Storage Group (N = 4,777)	Long-term Storage Group (N = 9,684)	Absolute Standardized Difference
Age of first erythrocyte unit transfused per patient, median [interquartile range]	11 [8, 15]	23 [17, 32]	1.458
Number of erythrocyte units transfused per patient, median [interquartile range]	2 [1, 3]	2 [1, 3]	0.004
Mean age of erythrocyte units transfused per patient, median [interquartile range]	11 [8, 15]	23 [17, 30]	1.504
Age of oldest erythrocyte unit transfused per patient, median [interquartile range]	12 [9, 18]	26 [18, 35]	1.327
Other transfusions, no. (%)			
Platelets	861 (18.0)	1,803 (18.6)	0.015
Plasma	724 (15.2)	1,491 (15.4)	0.007
Cryoprecipitate	254 (5.3)	494 (5.1)	0.01

An absolute standardized difference of greater than 0.10 indicates imbalance.

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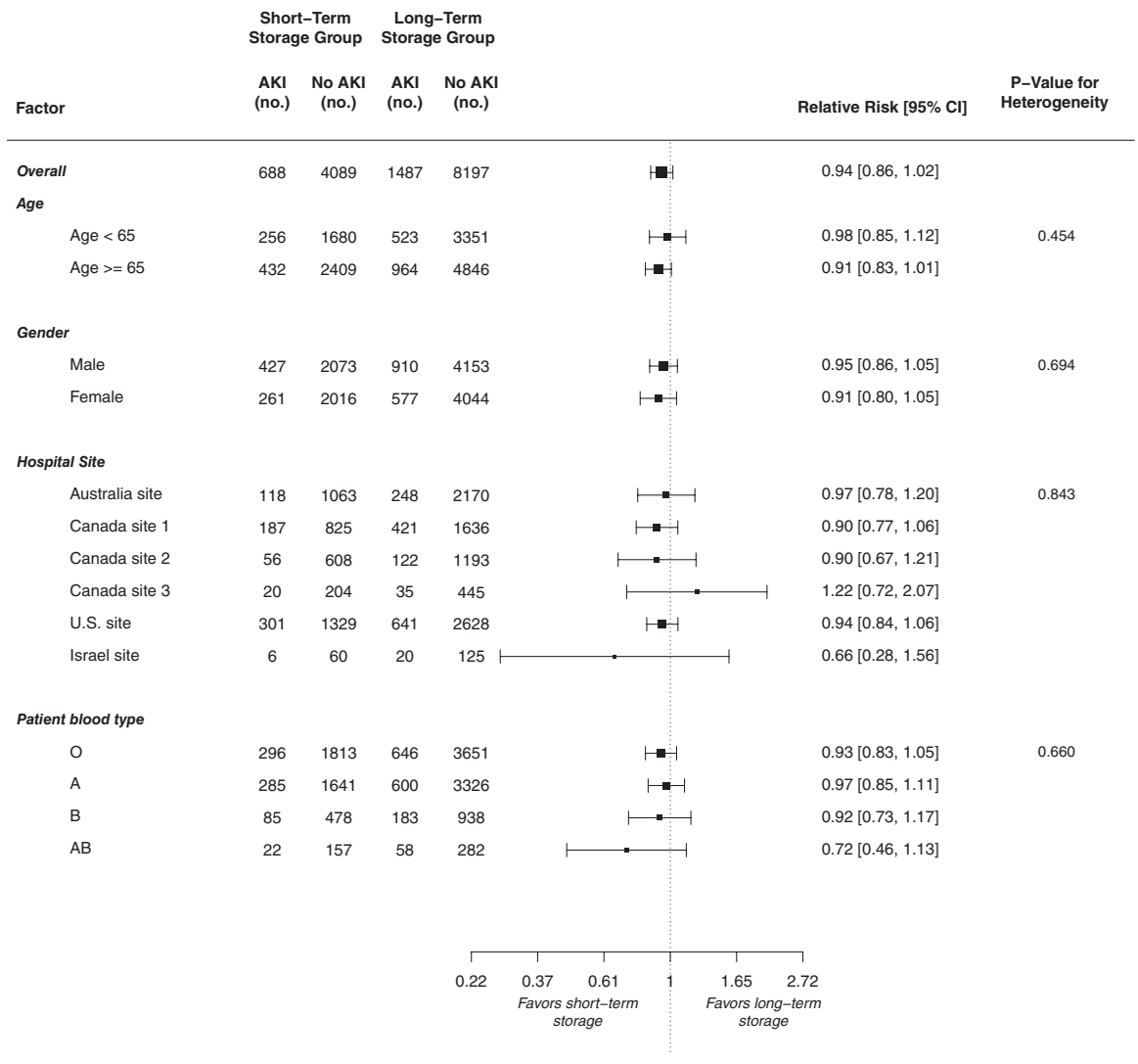

Fig. 3. Heterogeneity of treatment effect on posttransfusion acute kidney injury (AKI) for the primary analysis. The forest plot displays treatment effect heterogeneity across levels of various prespecified baseline factors, assessed using log-binomial models.

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Competing Interests

Dr. Eikelboom has financial relationships with Astra-Zeneca (Cambridge, United Kingdom), Bayer (Leverkusen, Germany), Boehringer-Ingelheim (Ingelheim am Rhein, Germany), Bristol-Myer-Squibb (New York, New York), Daiichi-Sankyo (Chuo City, Tokyo, Japan), Eli-Lilly (Indianapolis, Indiana), Glaxo-Smith-Kline (Brentford, United Kingdom), Pfizer (New York, New York), Janssen (Beerse, Belgium), Sanofi-Aventis (Paris, France), and Servie (Porsgrunn, Norway). Dr. Heddle has financial relationships with Canadian Institute of Health Research (Ottawa, Ontario, Canada), Haemonetics (Braintree, Massachusetts), and CSL Behring (Ottawa, Ontario, Canada). The other authors declare no competing interests.

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Appendix

Table A1. Previous Literature about the Effect of Age of Transfused Blood Components on Renal Status

Title	N	Method	Patients	Blood Age	Results
Age of transfused blood is an independent risk factor for postinjury multiple organ failure (Zallen *et al.*, 1999)[17]	63	Case control	Trauma	Mean erythrocyte storage duration as continuous variable (mean 24 *vs.* 30 days)	Mean age of transfused blood was greater in patients with multiple organ failure
Transfusion of older red blood cells increases the risk of acute kidney injury after orthotopic liver transplantation: A propensity score analysis (Wang *et al.*, 2018)[18]	137	Retrospective cohort	Liver transplant	Less than 14 days *versus* 14 days or more	Incidence of severe AKI was higher in the older blood group
Red blood cell storage is associated with length of stay and renal complications after cardiac surgery (Sanders *et al.*, 2011)[19]	176	Prospective cohort	Cardiac surgery	14 days or less *versus* more than 14 days	Incidence of renal complications were higher in the older blood group
Red cell storage duration does not affect outcome after massive blood transfusion in trauma and nontrauma patients: A retrospective analysis of 305 patients (Bautista *et al.*, 2017)[20]	305	Retrospective cohort	Massive transfusion	Mean erythrocyte storage duration as continuous variable (range, 8 to 36 days)	Mean storage time of erythrocytes was not associated with AKI
Transfusions in the less severely injured: Does age of transfused blood affect outcomes? (Weinberg *et al.*, 2008)[21]	430	Retrospective cohort	Trauma	Less than 14 days *versus* 14 days or more	Incidence of renal failure was higher in the older blood group
Influence of storage time and amount of red blood cell transfusion on postoperative renal function: An observational cohort study (Shimmer *et al.*, 2013)[22]	492	Retrospective cohort	Cardiac surgery	Less than 14 days *versus* 14 days or more	Renal function was worse in the older blood group
Storage age of transfused red blood cells during liver transplantation and its intraoperative and postoperative effects (Chen *et al.*, 2012)[23]	525	Retrospective cohort	Liver transplant	Less than 14 days *versus* 14 days or more	Age of erythrocytes was not associated with acute renal dysfunction or failure
Age of red blood cells and outcome in acute kidney injury (Kaukonen *et al.*, 2013)[24]	652	Prospective cohort	ICU	1st quartile versus 2nd through 4th quartiles (median, 12 *versus* 21 days)	Age of erythrocytes was not associated with incidence of stage III AKI
Age of transfused red cells and early outcomes after cardiac surgery (Yap *et al.*, 2008)[25]	670	Retrospective cohort	Cardiac surgery	Mean erythrocyte age, oldest erythrocyte unit, storage more than 30 days	Using multiple logistic regression analyses, no erythrocyte storage variable was associated with renal failure
Association between red blood cell storage duration and clinical outcome in patients undergoing off-pump coronary artery bypass surgery: A retrospective study (Min *et al.*, 2014)[26]	1,072	Retrospective cohort	Cardiac surgery	Mean erythrocyte age, oldest erythrocyte unit, storage more than 14 days	Using multiple logistic regression analyses, no erythrocyte storage variable was associated with renal failure
Effects of red-cell storage duration on patients undergoing cardiac surgery (Steiner *et al.*, 2015)[27]	1,098	Randomized trial	Cardiac surgery	10 days or less *versus* 21 days or more	Age of erythrocytes was not associated with renal or urinary disorder adverse events
Age of transfused blood is not associated with increased postoperative adverse outcome after cardiac surgery (McKenny *et al.*, 2011)[28]	1,153	Prospective cohort	Cardiac surgery	14 days or less *versus* more than 14 days	Age of erythrocytes was not associated with renal complications
The effects of "old" red blood cell transfusion on mortality and morbidity in elderly patients with hip fractures: A retrospective study (Kadar *et al.*, 2013)[29]	1,381	Retrospective cohort	Hip fracture surgery	Less than 14 days *versus* more than 14 days	Age of erythrocytes was not associated with renal failure
Age of transfused blood in critically ill adults (Lacroix *et al.*, 2015)[30]	2,430	Randomized trial	ICU	Less than 8 days *versus* oldest available	Age of erythrocytes was not associated with renal replacement therapy
Age of red cells for transfusion and outcomes in critically ill adults (Cooper *et al.*, 2017)[31]	4,919	Randomized trial	ICU	Freshest available *versus* oldest available (mean, 12 *vs.* 22 days)	Age of erythrocytes was not associated with renal replacement therapy
Duration of red-cell storage and complications after cardiac surgery (Koch *et al.*, 2008)[32]	6,002	Retrospective cohort	Cardiac surgery	Less than 14 days *versus* more than 14 days	Incidence of renal failure was higher in the older blood group

The results are sorted by sample size.

AKI, acute kidney injury; ICU, intensive care unit.

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