

ORIGINAL ARTICLE

A Randomized Trial of Acute Normovolemic Hemodilution in Cardiac Surgery

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ABSTRACT

BACKGROUND

Patients undergoing cardiac surgery often receive red-cell transfusions, along with the associated risks and costs. Early intraoperative normovolemic hemodilution (i.e., acute normovolemic hemodilution [ANH]) is a blood-conservation technique that entails autologous blood collection before initiation of cardiopulmonary bypass and reinfusion of the collected blood after bypass weaning. More data are needed on whether ANH reduces the number of patients receiving allogeneic red-cell transfusion.

METHODS

In a multinational, single-blind trial, we randomly assigned adults from 32 centers and 11 countries who were undergoing cardiac surgery with cardiopulmonary bypass to receive ANH (withdrawal of ≥ 650 ml of whole blood with crystalloids replacement if needed) or usual care. The primary outcome was the transfusion of at least one unit of allogeneic red cells during the hospital stay. Secondary outcomes were death from any cause within 30 days after surgery or during the hospitalization for surgery, bleeding complications, ischemic complications, and acute kidney injury.

RESULTS

A total of 2010 patients underwent randomization; 1010 were assigned to ANH and 1000 to usual care. Among patients with available data, 274 of 1005 (27.3%) in the ANH group and 291 of 997 (29.2%) in the usual-care group received at least one allogeneic red-cell transfusion (relative risk, 0.93; 95% confidence interval, 0.81 to 1.07; $P=0.34$). Surgery for postoperative bleeding was performed in 38 of 1004 patients (3.8%) in the ANH group and 26 of 995 patients (2.6%) in the usual-care group. Death within 30 days or during hospitalization occurred in 14 of 1008 patients (1.4%) in the ANH group and 16 of 997 patients (1.6%) in the usual-care group. Safety outcomes were similar in the two groups.

CONCLUSIONS

Among adults undergoing cardiac surgery, ANH did not reduce the number of patients receiving allogeneic red-cell transfusion. (Funded by the Italian Ministry of Health; ANH ClinicalTrials.gov number, NCT03913481.)

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RED-CELL TRANSFUSION IS COMMON IN modern clinical practice,¹⁻⁴ with one study estimating that more than 10 million red-cell units are transfused in the United States each year.⁵ However, this procedure is affected by three main concerns: costs, shortages, and transfusion-related complications. The median cost of red cells ranges from \$150 to \$634 per unit depending on the country, which results in substantial expenses for hospitals and health care systems.⁶⁻⁸ In addition, the availability of red cells fluctuates over time, with periods of shortage potentially leading to postponement of nonurgent surgeries. Such delays affect patients' health and, again, costs.⁹ Finally, red-cell transfusion carries risks spanning from mild fever, chills, and allergic reactions¹⁰ to more-severe side effects such as infections, transfusion-related lung injury, and transfusion-associated circulatory overload, which occurs in 1 to 5% of transfusions.¹¹

Patients who undergo cardiac surgery are at high risk for allogeneic red-cell transfusion.^{12,13} More than two million patients undergo cardiac surgery annually worldwide, and approximately 35% receive at least one unit of red cells.¹⁴⁻¹⁶ Transfusion during cardiac surgery is a risk factor for adverse perioperative outcomes and death.¹⁷⁻²⁰ Early intraoperative normovolemic hemodilution (known as acute normovolemic hemodilution, or ANH) is a well-known technique that is performed in approximately 20% of cardiac surgery departments in the United States.²¹ It is also performed by 26.7% of cardiac anesthesiologists and in 13.7% of patients worldwide.²² ANH allows for the reinfusion of the patient's whole blood, which is withdrawn before the patient receives heparin and undergoes cardiopulmonary bypass.²³ This technique improves the coagulation profile after cardiopulmonary bypass and reduces activation of inflammatory pathways, consumption of clotting factors and platelets owing to activation of circuit contacts, the need for allogeneic red-cell transfusion, and blood viscosity, thereby contributing to improved microcirculatory perfusion.^{12,24-28}

A retrospective study involving 18,000 patients in the United States who had undergone cardiac surgery compared outcomes with ANH only, retrograde autologous priming only, both interventions, and neither intervention, showing that the ANH-only group had the lowest percentage of patients who underwent intraoperative transfusion.²¹

A meta-analysis of 29 randomized, controlled trials of cardiac surgery performed in the United States and 10 other countries showed a reduced overall need for red-cell transfusion when ANH was performed, which was magnified when a large volume of blood (e.g., ≥650 ml) was withdrawn preoperatively.²⁹ Another meta-analysis of randomized, controlled trials showed a significant reduction in the percentage of patients who received a transfusion and the number of units of red cells transfused when patients underwent ANH.³⁰ The 2021 American Clinical Practice Guidelines on Patient Blood Management state that "ANH is a reasonable method to reduce bleeding and transfusion" (American College of Cardiology and American Heart Association class of recommendation, IIa; level of evidence, A).³¹ Similarly, the 2024 European Guidelines on Patient Blood Management in Adult Cardiac Surgery suggest that "ANH may be considered to reduce postoperative transfusions" (class of recommendation, IIB; level of evidence, A).¹² A recent consensus statement, however, noted that most studies were not powered to assess safety, and that hemodilution procedures varied among studies.³²

Accordingly, we performed the Acute Normovolemic Hemodilution in High-Risk Cardiac Surgery Patients (ANH) trial, a multinational, single-blind, randomized, pragmatic trial involving adult patients undergoing cardiac surgery with cardiopulmonary bypass. We aimed to test the hypothesis that ANH would reduce the need for allogeneic red-cell transfusion.³³

METHODS

TRIAL DESIGN

We conducted a phase 3, single-blind, randomized trial at 32 centers in 11 countries in North America, South America, Europe, and Asia. The ethics committee at the coordinating center and at each participating center approved the trial protocol (available with the full text of this article at NEJM.org). All the patients provided written informed consent before enrollment. Details of the rationale and design of the trial and the statistical analysis plan were previously published.³³ The full list of the participating centers is available in the Supplementary Appendix (available at NEJM.org). The trial was conducted in accordance with local regulations and the principles of the Declaration of Helsinki and Good Clinical Practice

guidelines and is reported in accordance with the Consolidated Standards of Reporting Trials guidelines.³⁴

The ANH trial was funded by the Italian Ministry of Health, which had no role in the conception or design of the trial, the collection or analysis of the data, or the writing of the manuscript. The first, last, and contact authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Data were stored in an electronic case report form and deidentified by a unique numeric code that was assigned to each patient.

An independent data and safety monitoring committee reviewed the data and performed prespecified blinded interim analyses. A steering committee designed and oversaw the trial. Data collection and outcome assessment were conducted by designated personnel at each site.

PATIENTS

All adult patients who were scheduled to undergo cardiac surgery with cardiopulmonary bypass underwent screening for eligibility. The main exclusion criteria were unstable coronary artery disease, critical perioperative state (e.g., hemodynamic instability or a need for mechanical ventilation), emergency surgery, or inadequate suspension of anticoagulant or antiplatelet therapy before surgery; the use of low-dose aspirin was permitted. During a second screening evaluation performed in the operating room immediately before randomization, patients were excluded if they were at risk for hemodynamic instability or anemia after ANH; the risk of anemia was assessed with the use of formulas to predict the resulting hematocrit level after ANH and after hemodilution due to priming for cardiopulmonary bypass (Supplementary Appendix).

RANDOMIZATION AND BLINDING

After anesthesia was induced and the hematocrit level was assessed, eligible patients were randomly assigned to receive ANH or the best available treatment without ANH (i.e., usual care). Randomization was performed by means of a Web-based system with the use of computer-generated, permuted-block sequences, with stratification according to site. Patients, investigators, data collectors, outcome assessors, and statisticians were unaware of the trial-group assignments. The at-

tending anesthesiologists were aware of the assignment but were not involved in data collection or data analysis.

TRIAL INTERVENTION

After randomization, each patient was assigned a unique trial number. Patients in the ANH group had at least 650 ml of whole blood withdrawn before the administration of heparin. At the discretion of the attending anesthesiologist, patients received an infusion of up to 3 ml of crystalloid solution for every 1 ml of blood withdrawn. Collected blood samples were stored at room temperature and reinfused after cardiopulmonary bypass weaning and after the effects of heparin were reversed with the use of 1 mg of protamine for every 100 units of heparin administered. Blood was most commonly withdrawn from a large-bore, central, rapid-infusion catheter and stored in blood bags for autologous use with citrate-phosphate-dextrose-adenine that was already in use at each center or was provided by the coordinating center. Patients in the usual-care group were treated according to standard local procedures without ANH.

For both trial groups, we recommended, but did not mandate, the following thresholds for hematocrit level to determine whether a transfusion was warranted: less than 28% before cardiopulmonary bypass, less than 20% during cardiopulmonary bypass, less than 25% immediately after cardiopulmonary bypass weaning, and less than 27% during the postoperative hospital stay.¹⁴ If patients in the ANH group became anemic before or during cardiopulmonary bypass, the anesthesiologist transfused the ANH blood before transfusing allogeneic red cells.

DATA COLLECTION AND FOLLOW-UP

We collected data on demographic characteristics and coexisting conditions at baseline, surgical procedure and intraoperative care, postoperative course in the intensive care unit (ICU) and during the hospital stay, major outcomes, safety outcomes, and protocol deviations with respect to the need for allogeneic red-cell transfusions. Trained investigators unaware of group assignments performed follow-up 30 days after randomization through telephone, the patient's surgeon, the patient's general practitioner, the city register office, or the patient's electronic hospital records.

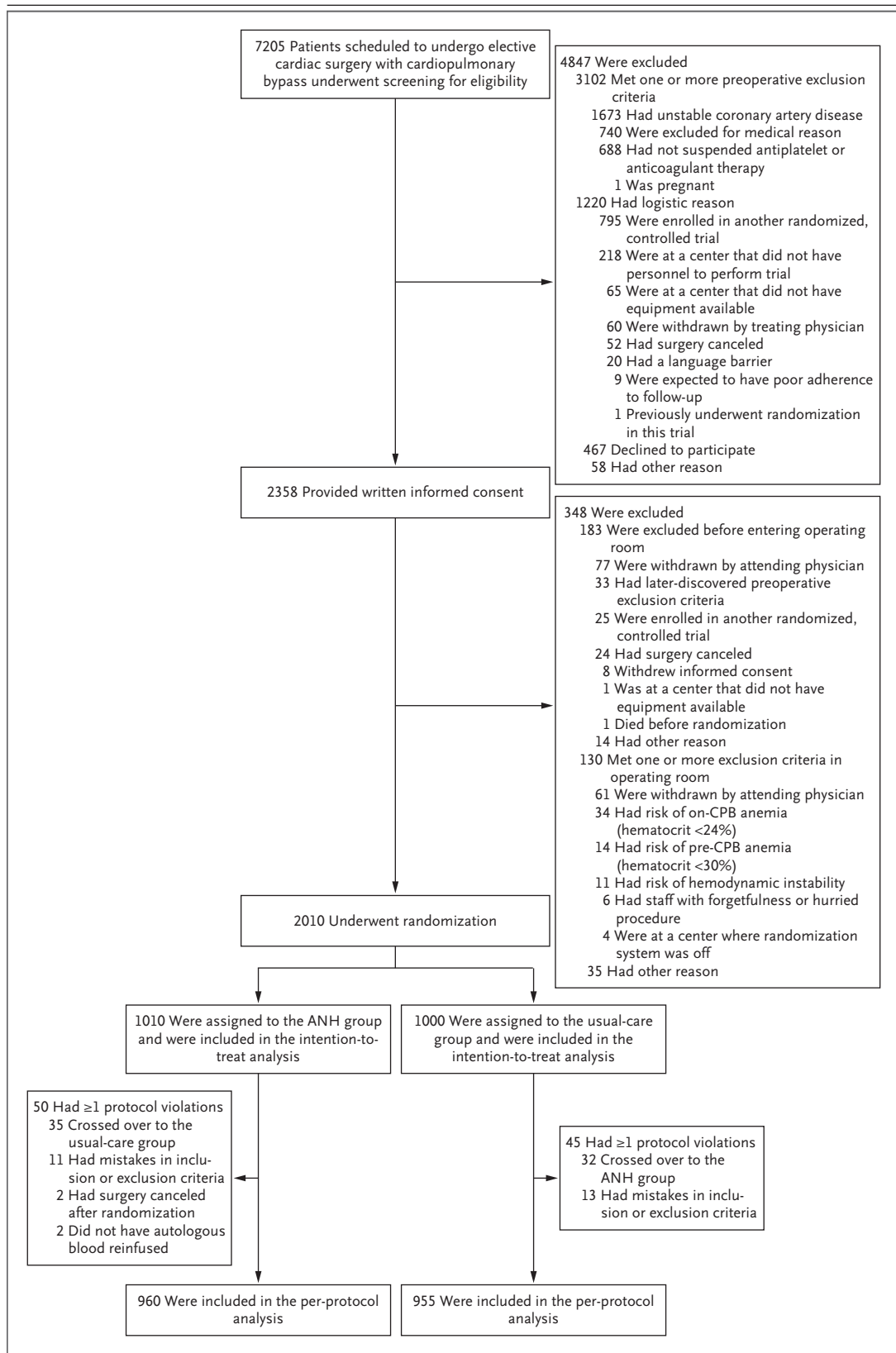


Figure 1 (facing page). Screening and Randomization.

Patients receiving low-dose aspirin (i.e., 75 to 100 mg daily) were included in the trial as specified in the protocol and were not among the 688 patients who were excluded because they had not discontinued antiplatelet or anticoagulant medication. ANH denotes acute normovolemic hemodilution.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the transfusion of at least one unit of allogeneic red cells from randomization until hospital discharge. Prespecified secondary outcomes were acute kidney injury, bleeding-related and ischemic complications, and death from any cause within 30 days after surgery or during the hospitalization in which the surgery was performed (trial outcomes are defined in the Supplementary Appendix).

PRESPECIFIED SAFETY OUTCOMES

Prespecified intraoperative and postoperative safety outcomes included cardiogenic shock, inotropic drug use for more than 48 hours, mechanical circulatory support, sepsis, septic shock, lowest hematocrit level occurring in the ICU, and death (see the Supplementary Appendix for detailed criteria). We also obtained data on any possible complication of the trial intervention and on protocol deviations. The cause of death was classified according to validated criteria (see the Supplementary Appendix).³⁵

STATISTICAL ANALYSIS

On the basis of two previous large, international trials (Transfusion Requirements in Cardiac Surgery [TRICS III] and Aspirin and Tranexamic Acid for Coronary Artery Surgery [ATACAS]), which showed incidences of postsurgical transfusion of 52% and 38%, respectively,^{13,14} and of a meta-analysis of randomized, controlled trials of ANH that identified transfusion rates of 56% in the control group and 42% in the ANH group,²⁹ we conservatively hypothesized that 35% of the patients in the usual-care group would undergo transfusions. We estimated that a sample of 1000 patients per group (a total of 2000 patients) would provide the trial with 90% power to detect a 20% lower relative risk of red-cell transfusion with ANH than with usual care at a two-sided alpha level of 0.05.³⁶ This sample size accounted for the three interim analyses (for which O'Brien–Fleming sequential tests were used with P values

for early interruption of the effect of treatment on the primary outcome of <0.000015, <0.003, and <0.02 after enrollment of 25%, 50%, and 75% of the patients, respectively),³⁷ withdrawal of patients from the trial, and rounding (see the Supplementary Appendix).

The planned statistical analyses were published before trial completion.³³ The primary analyses were performed according to the intention-to-treat principle and reported without imputation, with the number of available observations used as the denominator. Two sensitivity analyses of the primary outcome with different methods of imputation of missing data were performed, together with a post hoc sensitivity analysis that adjusted for center as a covariate. A per-protocol analysis was also performed.

Categorical measures are presented as percentages and compared with the use of the two-tailed chi-square test or Fisher's exact test when appropriate, and the results of the comparisons are presented as relative risks with 95% confidence intervals. Continuous measures with skewed distribution are expressed as medians with interquartile ranges. Measures with symmetric distribution are expressed as means with standard deviations. Between-group comparisons are reported as mean differences with 95% confidence intervals.

We performed prespecified subgroup analyses stratified according to the type of surgery, duration of cardiopulmonary bypass (median, >102 minutes vs. ≤102 minutes), sex, age (≤65 years vs. >65 years), preoperative chronic kidney disease (yes vs. no), previous cardiac surgery (yes vs. no), preoperative anemia (hemoglobin level, <12 vs. 12 to 14 vs. >14 g per deciliter), and use of preoperative antithrombotic drugs (yes vs. no). The results of the subgroup analyses are presented as relative risks with 95% confidence intervals. We also performed two post hoc subgroup analyses on management of preoperative anemia and on patients at high risk for bleeding, the results of which are expressed as relative risks with 95% confidence intervals. We used the Kaplan–Meier estimator to perform a prespecified time-to-event analysis of death within 30 days after surgery or during hospitalization for surgery with the corresponding 95% confidence intervals.

Data were analyzed with the use of Stata software, version 18 (StataCorp). A two-sided P value of less than 0.05 indicated statistical signifi-

cance. The widths of the confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing.

were well balanced between the two groups (Tables 1 and 2 and Table S3 in the Supplementary Appendix).

RESULTS

PATIENTS

From April 2019 through December 2024, a total of 7205 patients underwent screening for eligibility. Of these, 2358 provided informed consent and 2010 underwent randomization (1010 patients were assigned to the ANH group and 1000 to the usual-care group) (Fig. 1). Demographic and clinical characteristics at baseline, type of scheduled surgery, and intraoperative management

TRIAL INTERVENTION

The median volume of blood withdrawn in the ANH group was 650 ml (interquartile range, 650 to 700) (Table 2). In 45 of 1006 patients with available data (4.5%), the volume of withdrawn blood was less than 650 ml (see Table S5 for specific reasons). No adverse events were recorded, and the withdrawn blood was reinfused in all patients except two; blood was not reinfused in one patient owing to bag rupture and in one owing to blood coagulation within the bag. Among

Table 1. Characteristics of Patients at Baseline.*

Characteristic	ANH Group (N=1010)	Usual-Care Group (N=1000)
Median age (IQR) — yr	59 (52–66)	61 (53–68)
Female sex — no. (%)	219 (21.7)	186 (18.6)
Median body-mass index (IQR)†	26 (24–30)	27 (24–30)
Race — no. (%)‡		
White	792 (78.4)	778 (77.8)
Asian	195 (19.3)	198 (19.8)
Other	23 (2.3)	20 (2.0)
Median hemoglobin concentration (IQR) — g/dl	14 (14–15)	15 (14–15)
New York Heart Association class III or IV for heart failure — no. (%)	236 (23.4)	273 (27.3)
Medical condition — no. (%)		
Previous myocardial infarction	160 (15.8)	168 (16.8)
Atrial fibrillation	168 (16.6)	149 (14.9)
Arterial hypertension	626 (62.0)	668 (66.8)
Chronic kidney disease	65 (6.4)	64 (6.4)
Regular medications before surgery — no. (%)		
Aspirin	389 (38.5)	396 (39.6)
Beta-blockers	540 (53.5)	557 (55.7)
ACE inhibitors, ARB agents, or both	458 (45.3)	472 (47.2)
Diuretics	409 (40.5)	397 (39.7)
Surgery type — no./total no. (%)		
Valve§	619/1005 (61.6)	594/998 (59.5)
Coronary-artery bypass graft	384/1003 (38.3)	394/998 (39.5)
Ascending aorta or aortic arch	97/1004 (9.7)	109/997 (10.9)

* Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ANH acute normo-volemic hemodilution, ARB angiotensin-receptor blocker, and IQR interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race was reported by the patients.

§ Patients had undergone at least one of the following surgeries: aortic-valve, mitral-valve, or tricuspid-valve surgery.

Table 2. Trial Interventions and Intraoperative Characteristics.*

Variable	ANH Group (N = 1010)	Usual-Care Group (N = 1000)
Trial interventions		
Median volume of blood withdrawn during ANH (IQR) — ml†	650 (650–700)	0
Plasmapheresis instead of withdrawal of whole blood — no./total no. (%)	18/1003 (1.8)	0
Crystalloids administered before cardiopulmonary bypass — no./total no. (%)	976/1004 (97.2)	962/994 (96.8)
Median volume of crystalloids infused before cardiopulmonary bypass (IQR) — ml‡	1000 (500–1200)	700 (500–1000)
Other fluids administered before cardiopulmonary bypass — no./ total no. (%)§	2/1004 (0.2)	2/994 (0.2)
Intraoperative characteristics		
Median duration of cardiopulmonary bypass (IQR) — min¶	102 (75–134)	98 (71–131)
Hypotension — no./total no. (%)	114/1005 (11.3)	46/994 (4.6)
Tachyarrhythmia — no./ total no. (%)	27/1005 (2.7)	21/994 (2.1)

* Percentages may not total 100 because of rounding.

† Data were missing for 25 patients in the ANH group.

‡ Data were missing for 1 patient in the usual-care group.

§ Patients received noncrystalloid fluids only.

¶ Data were missing for 9 patients in the ANH group and for 6 patients in the usual-care group.

1006 patients with available data, reinfusion of blood occurred before aortic cross-clamping in 7 patients (0.7%) and during cardiopulmonary bypass in 69 patients (6.9%). Off-pump surgery was performed in 8 of 1006 patients with available data (0.8%) in the ANH group and in 13 of 997 patients with available data (1.3%) in the usual-care group. No patients withdrew consent. Crossover occurred in 67 of the 2010 patients (3.3%) across trial groups (Fig. 1).

PRIMARY AND SECONDARY OUTCOMES

At the time of hospital discharge, transfusion of at least one unit of allogeneic red cells had occurred in 274 of 1005 patients with available data (27.3%) in the ANH group and in 291 of 997 with available data (29.2%) in the usual-care group (relative risk, 0.93; 95% confidence interval [CI], 0.81 to 1.07; $P=0.34$) (Table 3). The median number of transfused red-cell units was 2 (interquartile range, 1 to 4) in the ANH group and 2 (interquartile range, 1 to 3) in the usual-care group, with a total number of transfused red-cell units of 880 and 791, respectively. Death from any cause within 30 days after surgery or during hospitalization for surgery occurred in 14 of 1008 patients with available data (1.4%) who underwent ANH and in 16 of 997 patients with available data (1.6%) who received usual care

(Table 3). The median volume of blood drained from chest tubes at 12 hours after surgery was 290 ml (interquartile range, 190 to 423) in the ANH group and 300 ml (interquartile range, 200 to 450) in the usual-care group. Surgery for post-operative bleeding was performed in 38 of 1004 patients with available data (3.8%) in the ANH group and in 26 of 995 patients with available data (2.6%) in the usual-care group. The results were similar in the per-protocol analysis and all sensitivity analyses (Tables S6 and S7).

The risks of acute kidney injury, bleeding-related and ischemic complications, hospital readmission, and death within 30 days after surgery or during hospitalization for surgery with ANH as compared with usual care are shown in Table 3. The results of the prespecified and post hoc subgroup analyses appeared to be generally consistent across the subgroups with the exception of duration of cardiopulmonary bypass (Figs. S4 and S5). The occurrence of blood transfusion stratified according to trial center is shown in Figure S3, and details of blood transfusions at different time points are shown in Tables S8 and S9.

SAFETY OUTCOMES

Data on safety outcomes in the two groups are shown in Table 4 and Table S4. Overall, 152 of 1005 patients with available data (15.1%) in the

Table 3. Clinical Outcomes.

Outcomes	ANH Group (N = 1010)	Usual-Care Group (N = 1000)	Relative Risk or Absolute Mean Difference (95% CI)*
Primary outcome			
Receipt of at least one allogeneic red-cell transfusion — no./total no. (%)	274/1005 (27.3)	291/997 (29.2)	0.93 (0.81 to 1.07)†
Secondary outcomes			
Death within 30 days after surgery or during hospitalization — no./total no. (%)	14/1008 (1.4)	16/997 (1.6)	0.87 (0.42 to 1.76)
Bleeding complications			
Surgical revision for bleeding — no./total no. (%)	38/1004 (3.8)	26/995 (2.6)	1.45 (0.89 to 2.37)
Median volume of blood drained from chest tubes at 12 hr after surgery (IQR) — mL‡	290 (190–423)	300 (200–450)	–11.66 (–35.54 to 12.22)
Ischemic complications — no./total no. (%)			
Myocardial infarction	10/1005 (1.0)	9/996 (0.9)	1.10 (0.45 to 2.70)
Stroke, transient ischemic attack, or both	11/1005 (1.1)	12/996 (1.2)	0.91 (0.40 to 2.05)
Thromboembolic event	5/1005 (0.5)	7/996 (0.7)	0.71 (0.23 to 2.22)
Acute kidney injury — no./total no. (%)	85/1005 (8.5)	89/996 (8.9)	0.95 (0.71 to 1.26)
Median no. of units of allogeneic blood component in patients receiving transfusion during hospital stay (IQR)			
Red cells	2 (1–4)	2 (1–3)	0.50 (–0.03 to 1.03)
Fresh frozen plasma	2 (1–4)	2 (1–4)	0.24 (–0.26 to 0.74)
Platelets	1 (1–3)	1 (1–3)	0.17 (–0.59 to 0.93)

* Data are presented as relative risks for dichotomous outcomes and as absolute mean differences for continuous outcomes. The relative risk was calculated as the ratio of event probability in the ANH group to event probability in the usual-care group. The absolute mean difference was calculated as the mean of the ANH group minus the mean of the usual-care group. The widths of the 95% confidence intervals presented in this table have not been adjusted for multiplicity; therefore, inferences drawn from these intervals may not be reproducible.

† P=0.34.

‡ Data were missing for 10 patients in the ANH group and for 11 patients in the usual-care group.

ANH group and 145 of 995 with available data (14.6%) in the usual-care group received vasopressor or inotropic drugs for more than 48 hours. Cardiogenic shock occurred in 37 of 1006 patients with available data (3.7%) in the ANH group and 32 of 995 with available data (3.2%) in the usual-care group. The lowest hematocrit value while in the ICU was 32% (interquartile range, 28 to 36) in the ANH group and 32% (interquartile range, 29 to 36) in the usual-care group (Table 4).

DISCUSSION

In this multinational, pragmatic, randomized trial, we compared the use of ANH with usual care without hemodilution in adult patients scheduled for elective cardiac surgery with cardiopulmonary bypass. We found that ANH did not reduce the

number of patients who received allogeneic red-cell transfusions, so it cannot be recommended as a blood-conservation strategy in patients undergoing cardiac surgery. Moreover, ANH did not appear to modify the risk of surgical revision for bleeding or decrease the total amount of blood loss from chest drainage during the first 12 hours after surgery. Finally, ANH did not appear to be associated with any difference in safety outcomes.

The use of ANH has been reported in more than 30 countries, including the United States.^{21,22,29,30,38} Several previous randomized, controlled trials evaluated ANH; however, most were small (≤ 40 patients) and involved a single center. Moreover, the volume of blood that was withdrawn was heterogeneous among the trials. A meta-analysis of 29 randomized, controlled trials involving 2439 patients showed a reduction in the num-

Table 4. Safety Outcomes.*

Outcome	ANH Group (N = 1010)	Usual-Care Group (N = 1000)	Relative Risk or Absolute Mean Difference (95% CI)†‡	P Value
Cardiogenic shock — no./total no. (%)	37/1006 (3.7)	32/995 (3.2)	1.14 (0.72 to 1.82)	0.57
Vasopressor or inotropic drugs for >48 hr — no./total no. (%)	152/1005 (15.1)	145/995 (14.6)	1.04 (0.84 to 1.28)	0.73
Mechanical circulatory support — no./total no. (%)‡	27/1006 (2.7)	23/996 (2.3)	1.16 (0.67 to 2.01)	0.59
Sepsis — no./total no. (%)	6/1006 (0.6)	5/995 (0.5)	1.19 (0.36 to 3.88)	0.99
Septic shock — no./total no. (%)	5/1006 (0.5)	3/995 (0.3)	1.65 (0.40 to 6.88)	0.73
Acute respiratory distress syndrome — no./total no. (%)	4/1003 (0.4)	2/995 (0.2)	1.98 (0.36 to 10.81)	0.69
Median lowest hematocrit level while in ICU (IQR) — %§	32 (28–36)	32 (29–36)	−0.04 (−0.50 to 0.43)	0.60
AKI with need for renal replacement therapy — no./total no. (%)	15/1005 (1.5)	14/996 (1.4)	1.06 (0.51 to 2.19)	0.87
Median duration of ventilation (IQR) — hr¶	7 (4–14)	7 (4–13)	3.26 (−0.31 to 6.82)	0.97
Median duration of ICU stay (IQR) — hr	38 (20–68)	40 (21–66)	6.23 (−0.02 to 12.47)	0.82
Died in the ICU — no./total no. (%)	11/1008 (1.1)	10/997 (1.0)	1.09 (0.46 to 2.55)	0.85
Median duration of hospital stay (IQR) — days**	8 (6–11)	8 (6–11)	0.50 (−0.20 to 1.20)	0.50
Died in the hospital — no./total no. (%)	14/1008 (1.4)	14/997 (1.4)	0.99 (0.47 to 2.06)	0.98
Hospital readmission within 30 days after randomization — no./total no. (%)	61/1008 (6.1)	59/997 (5.9)	1.02 (0.72 to 1.45)	0.90

* AKI denotes acute kidney injury, and ICU intensive care unit.

† Data are presented as relative risks for dichotomous outcomes and as absolute mean differences for continuous outcomes. The relative risk was calculated as the ratio of event probability in the ANH group to event probability in the usual-care group. The absolute mean difference was calculated as the mean of the ANH group minus the mean of the usual-care group. The widths of the 95% confidence intervals presented in this table have not been adjusted for multiplicity; therefore, inferences drawn from these intervals may not be reproducible.

‡ Mechanical circulatory support device included at least one of the following: intraaortic balloon pump, Impella, or venous-arterial extracorporeal membrane oxygenator.

§ Data were missing for 22 patients in the ANH group and for 18 patients in the usual-care group.

¶ Data were missing for 13 patients in the ANH group and for 12 patients in the usual-care group.

|| Data were missing for 6 patients in the ANH group and for 4 patients in the usual-care group.

** Data were missing for 5 patients in the ANH group and for 5 patients in the usual-care group.

ber of transfused red-cell units,²⁹ but the included trials were of low quality, which suggests the need for a large, high-quality, randomized, controlled trial. In this regard, our trial had a sample size almost equivalent to the overall number of patients enrolled in these previous trials.

Most recent European and U.S. guidelines on blood management among patients undergoing cardiac surgery mention ANH as a reasonable³¹ strategy that may be considered¹² to reduce the likelihood of needing an allogeneic blood transfusion. However, the key data supporting this suggestion are from the previously mentioned meta-analysis.²⁹ Two recent studies have shown promising results with ANH; however, one was a retrospective, single-center study that included only 51 patients,³⁹ and the other was a small, single-center trial (55 patients in both groups).⁴⁰

In contrast, our trial was based on broad and reproducible inclusion criteria and involved a representative population of adult patients who underwent cardiac surgery. In addition, subgroup analyses were performed in populations that are theoretically at higher risk for anemia. Finally, the data supporting a lack of effectiveness were consistent for all outcomes.

The removal of blood at the beginning of surgery has been investigated in other clinical settings. A recent randomized, controlled trial showed that hypovolemic phlebotomy effectively reduced the need for red-cell transfusions during hepatic surgery.⁴¹ It is possible that the efficacy in that trial was mostly due to the hypovolemia and resulting hypotension, which could reduce hepatic venous bleeding, but such hypovolemia can be harmful in patients undergoing cardiac surgery.

Our trial had several limitations. First, the percentage of female patients was lower than in other studies of cardiac surgery,^{39,40,42-47} possibly because of safety concerns related to a lower level of hemoglobin at baseline.⁴⁸ Second, we did not mandate a common transfusion protocol. Consequently, centers had the option to apply their institutional protocols. Third, we included all types of cardiac surgery regardless of the associated bleeding risk. Finally, we observed protocol deviations (e.g., crossover, off-pump surgery) owing to the pragmatic design, but the findings were robust in the per-protocol analyses.

In this trial involving adult patients scheduled to undergo elective cardiac surgery with cardiopulmonary bypass, ANH was not associated with an increased risk of adverse events but did not reduce the number of patients receiving allogeneic red-cell transfusion.

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We dedicate this work to our dear friend and mentor, Prof. Rinaldo Bellomo, whose inexhaustible enthusiasm and work to improve the care of our patients will live on through the many colleagues he touched.

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REFERENCES

- Goodnough LT, Shieh L, Hadhazy E, Cheng N, Khari P, Maggio P. Improved blood utilization using real-time clinical decision support. *Transfusion* 2014;54:1358-65.
- Kanagasabai U, Selenic D, Chevalier MS, et al. Evaluation of the WHO global database on blood safety. *Vox Sang* 2021;116:197-206.
- Anthes E. Evidence-based medicine: save blood, save lives. *Nature* 2015;520:24-6.
- Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. *N Engl J Med* 2017;377:1261-72.
- Free RJ, Sapiiano MRP, Chavez Ortiz JL, Stewart P, Berger J, Basavaraju SV. Continued stabilization of blood collections and transfusions in the United States: findings from the 2021 National Blood Collection and Utilization Survey. *Transfusion* 2023;63:Suppl 4:S8-S18.
- Rigal J-C, Riche VP, Tching-Sin M, et al. Cost of red blood cell transfusion: evaluation in a French academic hospital. *Transfus Clin Biol* 2020;27:222-8.
- Jacobs JW, Diaz M, Arevalo Salazar

- DE, et al. United States blood pricing: a cross-sectional analysis of charges and reimbursement at 200 US hospitals. *Am J Hematol* 2023;98:E179-E182.
8. İndelen C, Uygun Kizmaz Y, Kar A, Shander A, Kirali K. The cost of one unit blood transfusion components and cost-effectiveness analysis results of transfusion improvement program. *Türk Gogus Kalp Damar Cerrahisi Derg* 2021;29:150-7.
 9. Ranucci M. Bank blood shortage, transfusion containment and viscoelastic point-of-care coagulation testing in cardiac surgery. *Br J Anaesth* 2017;118:814-5.
 10. Carson JL, Brooks MM, Hébert PC, et al. Restrictive or liberal transfusion strategy in myocardial infarction and anemia. *N Engl J Med* 2023;389:2446-56.
 11. Roubinian NH, Hendrickson JE, Triulzi DJ, et al. Incidence and clinical characteristics of transfusion-associated circulatory overload using an active surveillance algorithm. *Vox Sang* 2017;112:56-63.
 12. Casselman FPA, Lance MD, Ahmed A, et al. 2024 EACTS/EACTAIC guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP. *Eur J Cardiothorac Surg* 2024 October 10 (Epub ahead of print).
 13. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med* 2017;377:2133-44.
 14. Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med* 2017;376:136-48.
 15. Dixon B, Santamaria JD, Reid D, et al. The association of blood transfusion with mortality after cardiac surgery: cause or confounding? *Transfusion* 2013;53:19-27.
 16. Huang D, Chen C, Ming Y, et al. Risk of massive blood product requirement in cardiac surgery: a large retrospective study from 2 heart centers. *Medicine (Baltimore)* 2019;98(5):e14219.
 17. Ivascu Girardi N, Cushing MM, Evered LA, et al. Incidence and impact of a single-unit red blood cell transfusion: analysis of the Society of Thoracic Surgeons Database 2010-2019. *Ann Thorac Surg* 2023;115:1035-41.
 18. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. *Ann Thorac Surg* 2002;74:1180-6.
 19. Ranucci M, Bozzetti G, Ditta A, Cotza M, Carboni G, Ballotta A. Surgical reexploration after cardiac operations: why a worse outcome? *Ann Thorac Surg* 2008;86:1557-62.
 20. Paone G, Likosky DS, Brewer R, et al. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. *Ann Thorac Surg* 2014;97:87-94.
 21. Stammers AH, Mongero LB, Tesdahl E, Stasko A, Weinstein S. The effectiveness of acute normovolemic hemodilution and autologous prime on intraoperative blood management during cardiac surgery. *Perfusion* 2017;32:454-65.
 22. Guarracino F, Bonizzoni MA, Losiggio R, Paternoster G. Acute normovolemic hemodilution in cardiac surgery and the power of global collaboration in advancing research. *Signa Vitae* 2025 May 26 (Epub ahead of print).
 23. Goldberg J, Paugh TA, Dickinson TA, et al. Greater volume of acute normovolemic hemodilution may aid in reducing blood transfusions after cardiac surgery. *Ann Thorac Surg* 2015;100:1581-7.
 24. Patel PA, Fabbro M II. Expanding the utilization of acute normovolemic hemodilution. *J Cardiothorac Vasc Anesth* 2020;34:1761-2.
 25. Mirhashemi S, Ertefai S, Messmer K, Intaglietta M. Model analysis of the enhancement of tissue oxygenation by hemodilution due to increased microvascular flow velocity. *Microvasc Res* 1987;34:290-301.
 26. Pries AR, Secomb TW. Rheology of the microcirculation. *Clin Hemorheol Microcirc* 2003;29:143-8.
 27. Henderson RA, Judd M, Strauss ER, et al. Hematologic evaluation of intraoperative autologous blood collection and allogeneic transfusion in cardiac surgery. *Transfusion* 2021;61:788-98.
 28. Flom-Halvorsen HI, Øvrum E, Øystese R, Brosstad F. Quality of intraoperative autologous blood withdrawal used for retransfusion after cardiopulmonary bypass. *Ann Thorac Surg* 2003;76:744-8.
 29. Barile L, Fominskiy E, Di Tomasso N, et al. Acute normovolemic hemodilution reduces allogeneic red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis of randomized trials. *Anesth Analg* 2017;124:743-52.
 30. Li S, Liu Y, Zhu Y. Effect of acute normovolemic hemodilution on coronary artery bypass grafting: a systematic review and meta-analysis of 22 randomized trials. *Int J Surg* 2020;83:131-9.
 31. Tibi P, McClure RS, Huang J, et al. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. *J Cardiothorac Vasc Anesth* 2021;35:2569-91.
 32. Salenger R, Arora RC, Bracey A, et al. Cardiac surgical bleeding, transfusion, and quality metrics: joint consensus statement by the Enhanced Recovery After Surgery Cardiac Society and Society for the Advancement of Patient Blood Management. *Ann Thorac Surg* 2025;119:280-95.
 33. Monaco F, Guarracino F, Vendramin I, et al. Acute normovolemic hemodilution in cardiac surgery: rationale and design of a multicenter randomized trial. *Contemp Clin Trials* 2024;143:107605.
 34. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med* 2010;8:18.
 35. Ridgeon E, Bellomo R, Myburgh J, et al. Validation of a classification system for causes of death in critical care: an assessment of inter-rater reliability. *Crit Care Resusc* 2016;18:50-4.
 36. DeMets DL, Lan G. The alpha spending function approach to interim data analyses. *Cancer Treat Res* 1995;75:1-27.
 37. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
 38. Henderson RA, Mazzeffi MA, Strauss ER, et al. Impact of intraoperative high-volume autologous blood collection on allogeneic transfusion during and after cardiac surgery: a propensity score matched analysis. *Transfusion* 2019;59:2023-9.
 39. Takahashi Y, Yoshii R, Amaya F, Sawa T, Ogawa S. Effect of acute normovolemic hemodilution in patients undergoing cardiac surgery with remimazolam anesthesia. *J Anesth* 2024;38:98-104.
 40. Ming Y, Zhang F, Yao Y, et al. Large volume acute normovolemic hemodilution in patients undergoing cardiac surgery with intermediate-high risk of transfusion: a randomized controlled trial. *J Clin Anesth* 2023;87:111082.
 41. Martel G, Carrier FM, Wherrett C, et al. Hypovolaemic phlebotomy in patients undergoing hepatic resection at higher risk of blood loss (PRICE-2): a randomised controlled trial. *Lancet Gastroenterol Hepatol* 2025;10:114-24.
 42. Landoni G, Monaco F, Ti LK, et al. A randomized trial of intravenous amino acids for kidney protection. *N Engl J Med* 2024;391:687-98.
 43. Landoni G, Lomivorotov VV, Alvaro G, et al. Levosimendan for hemodynamic support after cardiac surgery. *N Engl J Med* 2017;376:2021-31.
 44. Hahn RT, Makkar R, Thourani VH, et al. Transcatheter valve replacement in severe tricuspid regurgitation. *N Engl J Med* 2025;392:115-26.
 45. Généreux P, Schwartz A, Oldemeyer JB, et al. Transcatheter aortic-valve replacement for asymptomatic severe aortic stenosis. *N Engl J Med* 2025;392:217-27.
 46. Baldus S, Doenst T, Pfister R, et al. Transcatheter repair versus mitral-valve surgery for secondary mitral regurgitation. *N Engl J Med* 2024;391:1787-98.
 47. Coylewright M, Grubb KJ, Arnold SV, et al. Outcomes of balloon-expandable transcatheter aortic valve replacement in younger patients in the low-risk era. *JAMA Cardiol* 2025;10:127-35.
 48. Ripoll JG, Smith MM, Hanson AC, et al. Sex-specific associations between preoperative anemia and postoperative clinical outcomes in patients undergoing cardiac surgery. *Anesth Analg* 2021;132:1101-11.

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