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Safety and Efficacy of Acute Normovolemic Hemodilution in Female Patients

A Secondary Analysis of the ANH Trial

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IMPORTANCE Female patients undergoing cardiac surgery have a higher transfusion burden, yet they remain underrepresented in randomized clinical trials. Although the ANH trial showed no significant reduction in the proportion of patients receiving allogeneic blood transfusions with acute normovolemic hemodilution, evidence regarding its efficacy and safety specifically in female patients remains limited.

OBJECTIVE To evaluate the efficacy and safety of acute normovolemic hemodilution (ANH) compared with usual care in female patients undergoing elective cardiac surgery with cardiopulmonary bypass.

DESIGN, SETTING, AND PARTICIPANTS This was a post hoc secondary analysis of the multicenter, randomized ANH trial, which was conducted at 32 centers in 11 countries from April 2019 to December 2024. Of 2010 patients in the original ANH trial, 405 were women and were included in this analysis; 219 had been randomized to receive ANH and 186 to usual care. This secondary analysis was conducted from August 2025 to January 2026.

INTERVENTION Withdrawal of at least 650 mL whole blood with crystalloids replacement and reinfusion after cardiopulmonary bypass.

MAIN OUTCOMES AND MEASURES The primary outcome was the occurrence of at least 1 allogeneic packed red blood cell (pRBC) transfusion during the index hospitalization. Safety outcomes included intraoperative hypotension, intensive care unit (ICU) length of stay, hospital length of stay, mortality, and other perioperative complications.

RESULTS The median (IQR) age of the participants was 62 (54-69) years. The occurrence of allogeneic pRBC transfusion was similar in the ANH and usual care groups (38.8% vs 44.6%, respectively; relative risk [RR], 0.87; 95% CI, 0.69-1.10; *P* = .24). Intraoperative hypotension occurred more frequently with ANH (16.0% vs 4.8% in usual care; RR, 3.30; 95% CI, 1.62-6.74; *P* = .02). Patients receiving ANH also had longer ICU stays (mean difference, 21.13 hours; 95% CI, 1.89-40.38; *P* = .03) and hospital stays (mean difference, 1.92 days; 95% CI, 0.14-3.70; *P* = .04). No significant differences were observed in mortality or other postoperative complications.

CONCLUSIONS AND RELEVANCE In this post hoc secondary analysis of a randomized clinical trial, ANH was not associated with a reduction in allogeneic pRBC transfusion among women undergoing cardiac surgery and was associated with more frequent intraoperative hypotension and longer ICU and hospital stay. These exploratory findings warrant confirmation in adequately powered studies specifically designed to evaluate female patients undergoing cardiac surgery.

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Visual Abstract
Invited Commentary
Supplemental content

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Women remain underrepresented in randomized trials performed in cardiac surgery, comprising 20% to 25% of participants, and the generalizability of trial results to this population is often limited,[1] requiring specific studies and analyses to validate data. Moreover, although there are no sex-specific complications to our knowledge, female patients have shown higher rates of short-term mortality after coronary artery bypass graft, cerebrovascular events, acute kidney injury, wound infection, and packed red blood cell (pRBC) transfusions.[2-4] Indeed, although allogeneic pRBC transfusions are common after cardiac surgery in both men and women,[4-6] transfusion requirements vary significantly by sex, with women being more frequently exposed. This underscores the need for effective blood-sparing strategies.[5-7]

Within multimodal patient blood management, acute normovolemic hemodilution (ANH) is an appealing strategy[8] supported by current international guidelines.[9,10] Acute normovolemic hemodilution involves removing autologous whole blood after general anesthesia induction simultaneous with crystalloid administration to achieve controlled hemodilution and maintain normovolemia. The removed blood is later reinfused after cardiopulmonary bypass separation, thereby potentially reducing the exposure to allogeneic red cells[11] and other blood product transfusions.

A recent large, multinational, pragmatic, randomized study (the ANH trial) enrolling 2010 adult patients undergoing elective on-pump cardiac surgery found no benefit with ANH in reducing the proportion of patients receiving at least 1 allogeneic pRBC unit during hospitalization (27.3% in ANH vs 29.2% in usual care),[6] with similar neutral conclusions reported in a meta-analysis[12] of randomized clinical trials. Although the results of the ANH trial somewhat mitigated the enthusiasm on ANH and discouraged its routine implementation in cardiac surgery, some subgroups of patients might still benefit from this allogeneic blood-sparing strategy.[13]

Given their typical smaller body size (corresponding to a lower estimated blood volume [EBV]), lower body mass index (BMI), and lower hemoglobin and hematocrit levels, female patients more frequently meet relative contraindications to ANH and have less capacity for large-volume blood removal when ANH is feasible. However, while male patients carry the potential for larger absolute blood volume removal, female patients may achieve greater relative blood withdrawal for a given volume and, potentially, a more effective hemodilution.[14] Therefore, we conducted a secondary post hoc analysis of the ANH trial to assess the efficacy and safety of ANH with respect to the need for allogeneic pRBC in women undergoing on-pump cardiac surgery.

Key Points

Question What are the effects of acute normovolemic hemodilution (ANH) in female patients undergoing cardiac surgery?

Findings In this post hoc analysis of 405 women enrolled in the ANH trial, ANH was not associated with a reduction in allogeneic packed red blood cell transfusions compared with usual care. ANH was associated with a higher incidence of intraoperative hypotension and longer intensive care unit and hospital length of stay.

Meaning These exploratory findings suggest that ANH may not reduce transfusion requirements in female patients undergoing cardiac surgery and warrant further investigation in adequately powered studies.

Methods

Study Design and Population

This was a post hoc secondary analysis of the ANH trial[6] based on the planned sex subgroup analysis. The ANH trial was a pragmatic, multinational, randomized clinical trial comparing ANH with usual care in adults undergoing elective cardiac surgery with cardiopulmonary bypass across 32 centers in 11 countries. The full ANH trial design is described elsewhere,[6,11] and the trial protocol is available in Supplement 1. The ANH trial was registered at ClinicalTrials.gov website (NCT03913481). Ethical approval and written informed consent were obtained for the ANH trial as previously reported.[6,11] The Consolidated Standards of Reporting Trials (CONSORT) reporting guideline[15] was followed. Briefly, from April 2019 to December 2024, 2010 adult patients scheduled for elective cardiac surgery with cardiopulmonary bypass were randomized to receive ANH (n = 1010) or usual care without ANH (n = 1000). Randomization was not stratified by sex. The ANH trial had 2-level screening with specific exclusion criteria assessment first at the time of first patient evaluation (eg, the day before surgery) and in the operating theater after anesthesia induction and before randomization. The first screening excluded patients who had unstable coronary disease, critical perioperative state, pregnancy, or antiplatelet therapy use (only aspirin therapy was allowed). The operating room screening excluded patients who had predictable hemodynamic instability, pre-cardiopulmonary bypass anemia, or cardiopulmonary bypass anemia caused by ANH volume withdrawal (eTable 1 in Supplement 2). In the ANH group, at least 650 mL of whole blood was withdrawn after general anesthesia induction, while crystalloids were infused to maintain normovolemia. Autologous blood was then reinfused after cardiopulmonary bypass separation and heparin reversal. Patients randomized to usual care had the same intraoperative and postoperative management without ANH. In this secondary analysis, we excluded male patients from the entire trial population, yielding a population of 405 female patients, 219 of whom had been randomized to ANH and 186 to usual care (**Figure**).

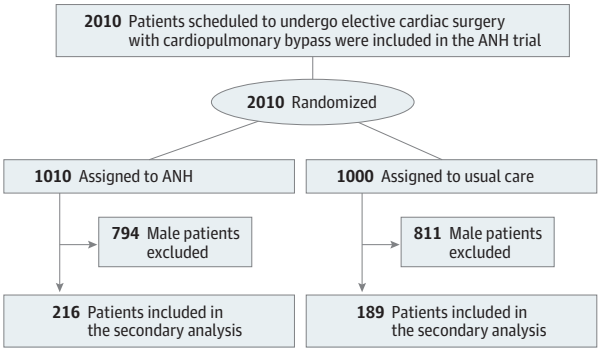
Outcomes

The end points of this study were the efficacy and safety on ANH in female population. The efficacy was evaluated as the number of patients receiving at least 1 unit of allogeneic pRBC during hospitalization. Safety was assessed by the occurrence of hypotensive events, as identified and recorded according to the clinical judgment of the attending anesthesiologist at each participating center. Moreover, we investigated all-cause mortality at 30 days, bleeding complications (such

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Figure. Patient Selection Flow Diagram



as need for surgical revision and total blood loss), ischemic complications (myocardial infarction, stroke, thromboembolic events), acute kidney injury, the occurrence of cardiogenic shock, the number of patients with prolonged vasopressor or inotropic therapy (>48 hours), the need for mechanical circulatory support, sepsis, septic shock, acute respiratory distress syndrome, kidney replacement therapy rate, duration of mechanical ventilation, intensive care unit (ICU) and hospital length of stay, ICU and hospital mortality, and hospital readmission within 30 days. Finally, we performed unplanned exploratory subgroup analyses for female patients according to BMI and baseline EBV. BMI was stratified by World Health Organization categories and by median value, while EBV analysis was divided into quartiles. Outcome definitions were provided in supplementary material of the ANH trial.[6,11]

Statistical Analysis

The primary analysis was conducted according to the intention-to-treat principle, including all randomized female patients according to their assigned treatment group. A per-protocol sensitivity analysis was also performed after excluding patients with at least 1 major protocol deviation. Descriptive statistics were used to summarize baseline characteristics of the study population. Categorical variables were reported as counts and percentages. The distribution of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed variables were reported as means with SDs and compared between groups using the *t* test, whereas skewed variables were reported as medians with corresponding IQRs and compared using the Wilcoxon rank sum test. Categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate. For binary outcomes, between-group differences were quantified as relative risks (RRs) with 95% CIs, while continuous outcomes were quantified as absolute mean differences with corresponding 95% CIs. We analyzed 30-day mortality using Kaplan-Meier methods to estimate survival and the 2-sided log-rank test to compare groups. Patients who did not experience death were censored at the last available follow-up. We performed a Cox proportional hazards model to estimate hazard ratios (HRs) with 95% CIs. We performed additional exploratory analyses in the overall trial cohort using multivariable models adjusted for all baseline characteristics reported in **Table 1**. Hypotension was analyzed using modified Poisson regression and reported as RRs with 95% CIs, whereas ICU stay and hospital stay were analyzed using linear regression and reported as mean differences with 95% CIs. For all models, we reported the interaction *P* value between treatment group and sex. Analyses were conducted using Stata version 19.0 (StataCorp) and R version 4.4.1 (R Foundation for Statistical Computing).

Results

Characteristics of Included Population

The population of the present study consisted of 405 women, who had been randomized to the ANH group (n = 219) and usual care group (n = 186) (Figure). The median (IQR) age was 62 (54-69) years. Arterial hypertension was the most frequent comorbidity and 1 of 4 patients had New York Heart Association Class III or IV. Valvular surgery was performed in 75% of procedures and coronary artery bypass graft in 26%. The median preoperative hemoglobin level was 14 g/dL and the median EBV was 4 liters. Although randomization was not stratified by sex, the 2 groups had comparable baseline characteristics (Table 1). The number of female patients stratified by country is shown in eFigure 1 in Supplement 2. All patients assigned to the intervention group underwent ANH, although 4 patients had plasmapheresis instead of whole blood withdrawal. The median amount of blood removed was 650 mL, corresponding to a median of 16.7% of EBV. The ANH group showed a higher median volume of crystalloids infused before cardiopulmonary bypass than in the usual care group (850 mL vs 600 mL) (**Table 2**).

Efficacy Outcomes

Acute normovolemic hemodilution was not effective in reducing the occurrence of allogeneic pRBC transfusion in 85 of 219 participants in the ANH group (38.8%) and 83 of 186 in the usual care group (44.6%) (RR, 0.87; 95% CI, 0.69-1.10; *P* = .24) (**Table 3**). These results were confirmed in subgroups by BMI and EBV quartiles (eFigures 2 and 3 in Supplement 2). We also found no difference in the number of allogeneic blood component (pRBC, fresh frozen plasma, and platelets) units among patients receiving transfusion during hospital stay (Table 3). Methodological issues are detailed in eTable 2 in Supplement 2, and efficacy results remained unchanged in the corresponding per-protocol analysis (eTable 3 in Supplement 2).

Safety and Additional Outcomes

We observed an increased occurrence of intraoperative hypotensive events in the ANH group (35/219 [16%] vs 9/186 [4.8%]; RR, 3.30; 95% CI, 1.62-6.74; *P* = .02) (**Table 4**). No difference was detected in bleeding or ischemic complications. Increases were observed in the median (IQR) duration of mechanical ventilation (ANH: 7 [4-15] vs usual care 8 [5-14]; mean difference, 11.46 hours; 95% CI, 1.33-21.59; *P* = .03), as well as the median (IQR) duration of ICU length of stay (ANH: 39 [20-69] vs usual care 38 [21-66]; mean dif-

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Table 1. Baseline Characteristics of Female Participants

Characteristic	ANH group (n = 219)	Usual care group (n = 186)	Overall (N = 405)
Age, median (IQR), y	62 (54-69)	63 (55-69)	62 (54-69)
Body mass index, median (IQR)	26 (23-31)	26 (22-31)	26 (23-31)
Race and ethnicity, No. (%)			
Asian	29 (13.2)	30 (16.1)	59 (14.6)
White	185 (84.5)	155 (83.3)	340 (84.0)
Other	5 (2.3)	1 (0.5)	6 (1.5)
Estimated blood volume, median (IQR), L	4.0 (3.7-4.5)	4.0 (3.7-4.5)	4.0 (3.6-4.4)
Hemoglobin concentration, median (IQR), g/dL	14 (13-14)	13 (13-14)	14 (13-14)
New York Heart Association class III-IV, No. (%)	58 (26.5)	54 (29.0)	112 (27.7)
Medical condition, No. (%)			
Previous myocardial infarction	21 (9.6)	18 (9.7)	39 (9.6)
Atrial fibrillation	46 (21.0)	49 (26.3)	95 (23.5)
Arterial hypertension	125 (57.1)	117 (62.9)	242 (59.8)
Chronic kidney disease	14 (6.4)	11 (5.9)	25 (6.2)
Regular medications prior to surgery, No. (%)			
Aspirin	65 (29.7)	46 (24.7)	111 (27.4)
β-Blockers	130 (59.4)	120 (64.5)	250 (61.7)
ACE inhibitors/ARB agents	88 (40.2)	73 (39.2)	161 (39.8)
Diuretics	103 (47.0)	82 (44.1)	185 (45.7)
Surgery type, No. (%)			
Valve	159 (72.6)	144 (77.4)	303 (74.8)
CABG	66 (30.1)	38 (20.4)	104 (25.7)
Ascending aorta[a]	21 (9.6)	15 (8.1)	36 (8.9)

Abbreviations: ACE, angiotensin-converting enzyme; ANH, acute normovolemic hemodilution; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft.

[a] Data were missing for 1 patient in the usual care group.

Table 2. Acute Normovolemic Hemodilution (ANH) Trial Interventions and Intraoperative Characteristics of the Female Population

Variable	ANH group (n = 219)	Usual care group (n = 186)
Trial interventions		
Volume of blood withdrawn during ANH, median (IQR), mL	650 (650-700)	0
Estimated blood volume withdrawn during ANH, median (IQR), %	16.7 (14.7-18.6)	0
Volume of crystalloids infused before cardiopulmonary bypass, median (IQR), mL	850 (500-1100)	600 (500-1000)
Duration of cardiopulmonary bypass, median (IQR), min	99 (71-129)	98 (71-129)

ference, 21.13 hours; 95% CI, 1.89-40.38; P = .03) and hospital length of stay (ANH: 8 [6-12] vs usual care 8 [6-11]; mean difference, 1.92 days; 95% CI, 0.14-3.70; P = .04). We found no differences in the need for mechanical circulatory support (4.1% vs 2.7%; RR, 1.53, 95% CI, 0.52-4.48; P = .44), need for inotropic or vasopressor agents (>48 h) (16.4% vs 10.8%; RR, 1.52, 95% CI, 0.91-2.53; P = .10), and need for renal replacement therapy (2.7% vs 0.5%; RR, 5.07, 95% CI, 0.62-41.72; P = .13) (Table 4). Safety outcomes were consistent in the per-protocol analysis (eTable 4 in Supplement 2). All-cause mortality at 30 days was 2.3% in the ANH group and 2.7% in the usual care group, with an RR of 0.85 (95% CI, 0.25-2.87; P = .79) (Table 4). The time-to-event analysis on mortality is displayed in eFigure 4 in Supplement 2. No significant difference was found in any additional outcomes (eTable 5 in Supplement 2). Additional multivariable analyses performed in the overall ANH trial cohort confirmed an independent association between ANH and hypotension (adjusted RR, 2.33; 95% CI, 1.61-3.38; P < .001). Furthermore, significant treatment-by-sex interactions were observed for ICU stay (ANH vs usual care: adjusted mean difference, 0.09; 95% CI, − 0.60 to 8.98; P = .36; female vs male: adjusted mean difference, 1.26; 95% CI, −11.41 to 13.92; P = .85; interaction P = .04) and hospital stay (ANH vs usual care: adjusted mean difference, 0.09; 95% CI, −0.60 to 0.79; P = .80; female vs male: adjusted mean difference -1.91; 95% CI, −3.41 to -0.42; P = .01; interaction P = .03). In contrast, no significant interaction was observed for hypotension (ANH vs usual care, adjusted RR, 2.33; 95% CI, 1.61 to 3.38; P < .001; female vs male: adjusted RR, 1.14; 95% CI, 0.51 to 2.53; P = .75; interaction P = .35), despite higher adjusted probabilities of hypotension among female compared with male patients receiving ANH (17.1% vs 10.3%) (eTables 6-8 in Supplement 2).

Discussion

Key Findings

In this post hoc analysis of the ANH trial, we found that ANH did not reduce the occurrence of allogeneic transfusions in female patients compared with usual care treatment. Notably, ANH was associated with an increased rate of hypotension together with prolonged durations of

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Table 3. Efficacy Outcomes for Female Patients

Outcome	ANH group (n = 219)	Usual care group (n = 186)	Relative risk (95% CI)	*P* value
Patients receiving ≥1 allogeneic pRBC transfusion, No. (%)	85 (38.8)	83 (44.6)	0.87 (0.69 to 1.10)	.24
Allogeneic blood component units in transfused patients during hospital stay, median (IQR), units				
Red blood cell	2 (1-4)	2 (1-2)	0.56 (−0.38 to 1.51)	.24
Fresh frozen plasma	3 (2-4)	3 (1-3)	0.11 (−1.34 to 1.56)	.88
Platelets	2 (1-3)	1 (1-3)	0.84 (−1.04 to 2.73)	.36

Abbreviations: ANH, acute normovolemic hemodilution; pRBC, packed red blood cell.

Table 4. Safety Outcomes

Outcome	ANH group (n = 219)		Usual care group (n = 186)		RR or absolute MD, value (95% CI)	*P* value
	Value	No. with missing data	Value	No. with missing data		
Intraoperative hypotension, No./total No. (%)	35/219 (16.0)	0	9/186 (4.8)	0	RR, 3.30 (1.62 to 6.74)	.02
Tachyarrhythmia, No./total No. (%)	9/219 (4.1)	0	6/186 (3.2)	0	RR, 1.27 (0.46 to 3.51)	.64
Bleeding complications						
Surgical revision for bleeding, No. (%)	6 (2.8)	1	3 (1.6)	1	RR, 1.70 (0.43 to 6.69)	.52
Blood loss at 12 h postsurgery, median (IQR), mL	230 (150-350)	1	233 (170-350)	4	MD, 19.51 (−24.50 to 63.51)	.19
Ischemic complications, No. (%)	12 (5.5)	0	4 (2.1)	1	2.55 (0.84 to RR, 7.77)	.12
Myocardial infarction	5 (2.3)	0	1 (0.5)	1	RR, 4.22 (0.50 to 35.83)	.23
Stroke/transient ischemic attack	5 (2.3)	0	3 (1.6)	1	RR, 1.41 (0.34 to 5.81)	.73
Thromboembolic event	2 (0.9)	0	0	1	Not estimable	.50
Acute kidney injury, No. (%)	15 (6.9)	0	15 (8.1)	1	RR, 0.85 (0.42 to 1.68)	.63
Need for renal replacement therapy, No. (%)	6 (2.7)	0	1 (0.5)	1	RR, 5.07 (0.62 to 41.72)	.13
Cardiogenic shock, No. (%)	12 (5.5)	0	14 (7.6)	1	RR, 0.72 (0.34 to 1.53)	.39
Vasopressors or inotropic drugs >48 h, No. (%)	36 (16.4)	0	20 (10.8)	1	RR, 1.52 (0.91 to 2.53)	.10
Mechanical circulatory support, No. (%)	9 (4.1)	0	5 (2.7)	0	RR, 1.53 (0.52 to 4.48)	.44
Sepsis, No. (%)	4 (1.8)	0	0	1	Not estimable	.13
ARDS, No. (%)	2 (0.9)	0	1 (0.5)	1	RR, 1.69 (0.15 to 18.48)	.66
Duration of ventilation, median (IQR), h	7 (4-15)	3	8 (5-14)	3	MD, 11.46 (1.33 to 21.59)	.03
Duration of ICU stay, median (IQR), h	39 (20-69)	1	38 (21-66)	1	MD, 21.13 (1.89 to 40.38)	.03
Duration of hospital stay, median (IQR), d	8 (6-12)	0	8 (6-11)	1	MD, 1.92 (0.14 to 3.70)	.04
Hospital readmission at 30 d, No. (%)	15 (6.9)	0	12 (6.5)	1	RR, 1.06 (0.51 to 2.20)	.88
ICU mortality, No. (%)	5 (2.3)	0	3 (1.6)	1	RR, 1.41 (0.34 to 5.81)	.63
Mortality at 30 d, No. (%)	5 (2.3)	0	5 (2.7)	1	RR, 0.85 (0.25 to 2.87)	.79

Abbreviations: ANH, acute normovolemic hemodilution; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MD, mean difference; RR, relative risk.

mechanical ventilation and ICU and hospital stays in female patients receiving ANH, without effect on mortality. Results were consistent in the per-protocol analysis. Although no significant treatment-by-sex interaction was observed for hypotension, adjusted multivariable analyses confirmed an increased risk of hypotension associated with ANH, with higher probability among female than male individuals.

Relationship to Previous Studies and Future Perspectives

To our knowledge, this is the largest study focused on ANH in female patients undergoing cardiac surgery. However, previous data came from nonrandomized large cohort studies since no female-only randomized clinical trials (RCTs) were performed in cardiac surgery. Notably, the ANH trial was, to our knowledge, the only trial reporting data on female population in this setting. In 2025, Martel and colleagues[16] found benefit with ANH on allogeneic transfusions in patients undergoing hepatic surgery, with women representing 44% of the trial population.

With most international guidelines and RCTs supporting the safety of ANH,[9,10] we believe this is one of the first studies to suggest that ANH might be associated with some detrimental effects.[9,10] Female patients are frequently considered less-than-ideal ANH candidates due to a higher baseline level of anemia, which could be worsened with ANH. However, patients were carefully screened, and only patients without anemia were enrolled.

Goldberg et al[17] reported greater benefit with ANH in patients from whom large volumes of blood (>800 mL) were removed compared with lower volumes, thereby promoting discussion on the appropriateness of the chosen minimum

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value in the ANH trial. In the present analysis, the collection of at least 650 mL of whole blood required by the ANH trial protocol might have been too much for female participants, likely causing an increased incidence of intraoperative hypotension in the ANH group (16% vs 4%).[3] Moreover, the amount of 650 mL of blood corresponded to 16.7% of EBV, which is a large removal, especially when considering that previous RCT protocols planned a blood removal of 10% to 15% of EBV. Similarly, a pair-matched study[13] suggested a volume-dependent association between ANH and a reduction of allogeneic transfusion rates (all blood products combined).

A few considerations warrant attention. First, participants in these studies were predominantly male. Second, subgroup analyses on BMI and EBV were consistent with primary outcome main results, with a direction in favor of ANH when the EBV was higher (thus corresponding to a relatively lower percentage of blood removed). In line with previous literature and pathophysiology, we expected to find improved outcomes in female patients with greater blood removal and hemodilution, which should theoretically reduce cardiopulmonary bypass–related coagulopathy. Instead, we found no difference in the primary outcome and possible signals of harm from ANH in the exploratory outcomes. Accordingly, we recommend using caution when considering ANH in female patients undergoing cardiac surgery. Future work should focus solely on female patients and use tailored ANH protocols.

Limitations

This study has several limitations. First, women represented only 20% of the overall ANH trial population because randomization was stratified by center and not by sex. Consequently, although treatment allocation was balanced in the overall randomized cohort, balance was not necessarily preserved within this post hoc female subgroup, resulting in an unequal number of women in the 2 treatment groups. Although this proportion is consistent with the representation of women in contemporary randomized trials in cardiac surgery, the sample size provided limited statistical power to detect differences in relatively infrequent outcomes. Notably, given the 5.8% absolute difference observed for the primary outcome (38.8% in the ANH group and 44.6% in the usual care group), more than 2000 patients would have been required to achieve 80% statistical power, whereas the present study had an estimated power of only 22%. Therefore, the absence of statistically significant differences for some outcomes should be interpreted cautiously. Second, as a subpopulation of a multinational pragmatic trial, the present study shares similar limitations to the larger study, including possibly heterogeneity sources due to different transfusion protocols, surgical practice and perioperative patients' management. Third, this secondary analysis was not prespecified in the initial study protocol. However, considering the little existing evidence on ANH in female cardiac surgery patients, sex-specific data and analysis is warranted. This is likely the largest randomized clinical trial looking at ANH in female cardiac surgical patients. Fourth, the pragmatic nature of the ANH trial may also have introduced heterogeneity related to differences in local transfusion protocols, perioperative management strategies, and clinical practice across participating countries.

Conclusions

In this post hoc secondary analysis of a randomized clinical trial, ANH was not associated with a reduction in the occurrence of allogeneic pRBC transfusion in female patients undergoing cardiac surgery, with increased intraoperative hypotension and prolonged length of stay. Therefore, while we await adequately powered studies specifically designed to evaluate female population, the implementation of ANH in female cardiac surgical patients should be carefully assessed.

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