Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB
Via Zoom

Thursday, 28 October, 2021
1630-1800 HOURS

PRESENTING ARTICLES:
Dr. Kendra Derry & Dr. Dana Archibald

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

JAMA | Original Investigation

Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery
The FIBRES Randomized Clinical Trial

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IMPORTANCE Excessive bleeding is a common complication of cardiac surgery. An important cause of bleeding is acquired hypofibrinogenemia (fibrinogen level <1.5-2.0 g/L), for which guidelines recommend fibrinogen replacement with cryoprecipitate or fibrinogen concentrate. The 2 products have important differences, but comparative clinical data are lacking.

OBJECTIVE To determine if fibrinogen concentrate is noninferior to cryoprecipitate for treatment of bleeding related to hypofibrinogenemia after cardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial at 11 Canadian hospitals enrolling adult patients experiencing clinically significant bleeding and hypofibrinogenemia after cardiac surgery (from February 10, 2017, to November 1, 2018). Final 28-day follow-up visit was completed on November 28, 2018.

INTERVENTIONS Fibrinogen concentrate (4 g; n = 415) or cryoprecipitate (10 units; n = 412) for each ordered dose within 24 hours after cardiopulmonary bypass.

MAIN OUTCOMES AND MEASURES Primary outcome was blood components (red blood cells, platelets, plasma) administered during 24 hours post bypass. A 2-sample, 1-sided test for the ratio of the mean number of units was conducted to evaluate noninferiority (threshold for noninferiority ratio, <1.2).

RESULTS Of 827 randomized patients, 735 (372 fibrinogen concentrate, 363 cryoprecipitate) were treated and included in the primary analysis (median age, 64 [interquartile range, 53-72] years; 30% women; 72% underwent complex operations; 95% moderate to severe bleeding; and pretreatment fibrinogen level, 1.6 [interquartile range, 1.3-1.9] g/L). The trial met the a priori stopping criterion for noninferiority at the interim analysis after 827 of planned 1200 patients were randomized. Mean 24-hour postbypass allogeneic transfusions were 16.3 (95% CI, 14.9 to 17.8) units in the fibrinogen concentrate group and 17.0 (95% CI, 15.6 to 18.6) units in the cryoprecipitate group (ratio, 0.96 [1-sided 97.5% CI, −∞ to 1.09; $P < .001$ for noninferiority] [2-sided 95% CI, 0.84 to 1.09; $P = .50$ for superiority]). Thromboembolic events occurred in 26 patients (7.0%) in the fibrinogen concentrate group and 35 patients (9.6%) in the cryoprecipitate group.

CONCLUSIONS AND RELEVANCE In patients undergoing cardiac surgery who develop clinically significant bleeding and hypofibrinogenemia after cardiopulmonary bypass, fibrinogen concentrate is noninferior to cryoprecipitate with regard to number of blood components transfused in a 24-hour period post bypass. Use of fibrinogen concentrate may be considered for management of bleeding in patients with acquired hypofibrinogenemia in cardiac surgery.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03037424

Visual Abstract

Editorial page 1958

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 2019

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Excessive bleeding necessitating blood component transfusion is common after cardiac surgery and is associated with increased risk of morbidity and mortality and associated costs.[1] The pathophysiology of cardiac surgery-related bleeding is often multifactorial but includes acquired hypofibrinogenemia (fibrinogen level <1.5-2.0 g/L), which is associated with excessive bleeding in children[2] and adults.[3] In cases of excessive bleeding and acquired hypofibrinogenemia, guidelines recommend treatment with either cryoprecipitate or fibrinogen concentrate.[4,5]

Although both products are plasma-derived, they have distinct features. Cryoprecipitate is a nonpurified product; hence, in addition to fibrinogen it contains fibronectin and platelet microparticles, as well as coagulation factors VIII, XIII, and von Willebrand factor.[6] Its fibrinogen content varies widely (from 3-30 g/L per unit); in most cases it must be maintained and shipped in a frozen state and then thawed and pooled (typically 5-10 unit pools) before administration; and it has a limited shelf life after thawing (<4-6 hours), increasing wastage.[7,8] Fibrinogen concentrates are pathogen-reduced and purified; have standardized fibrinogen content (20 g/L); are lyophilized, allowing for easy storage, reconstitution, and administration; and have longer shelf life after reconstitution (up to 24 hours), which reduces wastage. There is divergent practice regarding the preferred product for fibrinogen replacement.[9] Cryoprecipitate remains the therapy of choice in many areas (including North America). In many European countries, however, fibrinogen concentrates have replaced cryoprecipitate, even though very few studies have directly compared these products.[10,11]

In this multicenter randomized clinical trial in patients undergoing cardiac surgery and requiring fibrinogen replacement because of clinically significant bleeding related to acquired hypofibrinogenemia, the objective was to determine if fibrinogen concentrate was noninferior to cryoprecipitate as measured by the amount of allogeneic blood components (red cells, platelets, and plasma) administered.

Key Points

Question Is fibrinogen concentrate noninferior to cryoprecipitate for treatment of bleeding related to acquired hypofibrinogenemia in cardiac surgery?

Findings In this randomized trial of 735 adult patients who underwent cardiac surgery and developed clinically significant bleeding and hypofibrinogenemia post cardiopulmonary bypass, the mean number of blood components transfused within 24 hours post bypass was 16.3 units in the fibrinogen concentrate group and 17.0 units in the cryoprecipitate group; ratio of the mean number of units transfused was 0.96, which met the prespecified noninferiority margin ratio of less than 1.2.

Meaning For management of cardiac surgery–associated bleeding related to acquired hypofibrinogenemia, fibrinogen concentrate may be considered for fibrinogen replacement.

Methods

Trial Oversight

This was an investigator-initiated, multicenter, randomized clinical trial conducted at 11 centers in Canada. The trial design and methodology have been previously published[12]; the study protocol and statistical analysis plan are available in Supplement 1, and aspects of the trial design and methodology are included in the eMethods in Supplement 2. The trial coordinating center was the Department of Anesthesia and Pain Management Clinical Trials Unit at the University Health Network (Toronto, Ontario, Canada). The trial was overseen by an independent data and safety monitoring committee, which reviewed adverse events after every 100 patients and reviewed a preplanned interim analysis performed after approximately 600 evaluable patients were enrolled. Study monitors independently reviewed all primary outcomes and adverse events. The trial was performed in accordance with the principles of the Declaration of Helsinki and applicable regulatory requirements. Research ethics board approval was obtained at each site before trial initiation, including approval of a delayed written consent process. Consent was delayed until after treatment (in accordance with the Canadian Tri-Council Policy Statements on the ethical conduct of research involving humans),[13] in part because it is not possible to reliably predict before surgery which patients will require fibrinogen replacement for bleeding control during or after surgery, at which time there is a need for rapid access to therapy.

Patients

Adult patients undergoing cardiac surgery with cardiopulmonary bypass for whom fibrinogen replacement was ordered in response to clinically significant postbypass bleeding deemed related to acquired hypofibrinogenemia (fibrinogen plasma level <2.0 g/L by the Clauss method or FIBTEM [fibrin-based thromboelastometry test extrinsically activated with tissue factor and containing the platelet inhibitor cytochalasin D]-derived clot amplitude at 10 minutes <10 mm by thromboelastometry) were eligible for enrollment.[14,15] In line with clinical practice, patients with bleeding were also eligible if hypofibrinogenemia was suspected but plasma fibrinogen levels were unavailable at the time of decision-making.

Blood bank technologists screened and randomized eligible patients if they had none of the following exclusion criteria: receipt of fibrinogen concentrate or cryoprecipitate within 24 hours before surgery; history of severe allergic reaction to fibrinogen concentrate or cryoprecipitate; refusal of blood components for religious or other reasons; plasma fibrinogen level greater than 3.0 g/L within 30 minutes of treatment order (to avoid increasing levels above the upper limit of normal [4.0 g/L]); and known pregnancy.

Trial Procedures

Participants were randomly assigned (1:1) to study groups using a pseudorandom number generator (PROC PLAN procedure in SAS) in randomly permuted blocks of 4, stratified by center. Allocation was blinded; randomization schedule was kept at the blood banks in sequentially numbered opaque sealed envelopes (prepared by Ergomed GmbH), which were opened when the order for fibrinogen replacement was received. Patients in the fibrinogen concentrate group received 4 g of fibrinogen concentrate (Fibryga; Octapharma AG), to be infused over

approximately 10 minutes, and those in the cryoprecipitate group received 10 units of cryoprecipitate, to be infused according to local practice. The dosages for fibrinogen concentrate[16-18] and cryoprecipitate[19,20] were consistent with recently published trials and guidelines. Cryoprecipitate dose in Canada is standardized at 10 units per dose,[21] and although the amount of fibrinogen in each unit of cryoprecipitate is variable, on average each 10-unit pool contains approximately 4 g of fibrinogen (Canadian Blood Services data; Dana Devine, PhD, Canadian Blood Services, email communication, September 2019).

Patients were to only receive the allocated product for 24 hours after cardiopulmonary bypass, after which only cryoprecipitate was used for fibrinogen replacement. It was not feasible to blind clinicians involved in product administration, but clinicians not involved in product administration, patients, data collectors, and outcome assessors were blinded. To maintain blinding, chart labels for both products stated "Fibrinogen Study Product 4 grams." Data on race were collected for descriptive purposes as reported by patients based on predefined categories.

There were no other alterations to patient care. Each hospital had an established protocol for bleeding management that was not altered for the purposes of this study. Tranexamic acid use was routine at all centers. Administration of blood components and hemostatic agents (other than cryoprecipitate and fibrinogen concentrate), use of cell salvage, and viscoelastic testing were based on local hospital protocols.

Outcomes

The primary efficacy outcome was cumulative allogeneic blood component units (red blood cells, platelets, and plasma) administered for 24 hours after termination of cardiopulmonary bypass. Since 2 types of platelets are issued in Canada (75% standard buffy-coat pools from 4 allogeneic donors and 25% apheresis units from a single allogeneic donor), both types were counted as a 4-unit transfusion. Secondary outcomes included individual blood component units administered for 24 hours after termination of cardiopulmonary bypass, all transfusions from beginning of surgery to postoperative day 7, bleeding severity (according to the universal definition of perioperative bleeding [UDPB])[22] during the 24 hours after cardiopulmonary bypass, and pretreatment and posttreatment fibrinogen levels. The UDPB components "delay in chest closure" and "cryoprecipitate or fibrinogen concentrate administration" were not used. Postoperative follow-up was 28 days. Adverse events were classified using the *Medical Dictionary for Regulatory Activities* (version 21.1) system of nomenclature. Adverse events that started or worsened on or after the first dose of the investigational product were classified as treatment-emergent. Data on duration of mechanical ventilation, intensive care unit stay, and hospitalization after surgery were also collected.

Statistical Analysis

Sample size was based on demonstrating noninferiority of fibrinogen concentrate relative to cryoprecipitate with respect to the primary efficacy outcome. Determination of noninferiority was based on a 1-sided type I error probability of .025 and a noninferiority margin of 20% for the ratio of mean number of units transfused per group. A 20% margin was deemed by an expert panel to be a plausible trade-off in efficacy in exchange for the potential advantages of fibrinogen concentrate relative to those of cryoprecipitate. An empirical distribution function was calculated based on a mean of 16 units and a standard deviation of 14 units (derived from a recent study on bleeding management in cardiac surgery)[23] and was used to estimate power by performing 10 000 simulations for each of the possible sample sizes. Calculations showed that 1200 patients would provide an empirical power greater than 90% (assuming a 10% dropout rate and equal mean units transfused per group).

The primary analysis set comprised all randomized patients who had undergone cardiac surgery with cardiopulmonary bypass, received at least 1 (partial or complete) dose of either treatment, and for whom informed consent was obtained. The per-protocol analysis excluded patients who did not undergo cardiac surgery with cardiopulmonary bypass, received the incorrect treatment, received less than 80% of the planned dose, or received the first treatment more than 24 hours after cardiopulmonary bypass. The prespecified subgroups for analysis were elective vs nonelective surgery, simple vs complex surgery, and a subgroup excluding patients who were in critical state before surgery (blinded adjudication based on predefined conditions such as acute aortic dissection or cardiac arrest immediately before surgery). Post hoc subgroups analyzed were patients undergoing nonelective surgery and not in critical state before surgery, patients who had a fibrinogen measurement before product administration, patients with confirmed hypofibrinogenemia (with Clauss method) before product administration, and patients with at least moderate blood loss according to the UDPB.[22]

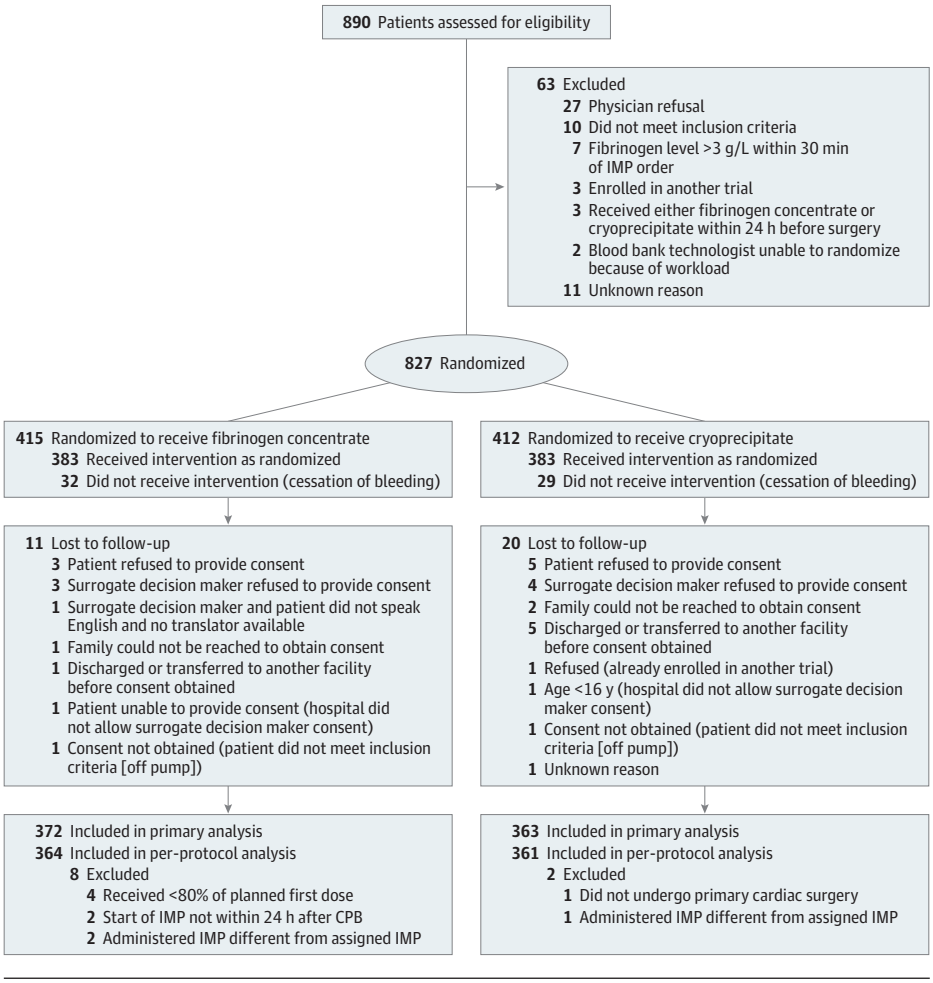
A 2-sample, 1-sided test of the null hypothesis that the treatment group fibrinogen concentrate to cryoprecipitate ratio of the mean number of allogenic blood components was 1.2 or greater (ie, 20% noninferiority margin) was used to evaluate noninferiority using Poisson regression modeling for count data. Noninferiority would be demonstrated if the upper limit of the model-derived 1-sided 97.5% CI was less than 1.2. If noninferiority was demonstrated, an analogous test for superiority was to be performed, testing the hypothesis that the treatment group ratio of the mean number of allogenic blood components was 1.0 or greater against the alternative that it was less than 1.0, at a 1-sided type I error level of $\alpha = .025$. No α adjustment was made because of the hierarchical ordering of the tests. This analysis was repeated for the secondary allogeneic blood component transfusion outcomes.

There was 1 prespecified interim analysis after approximately 50% of the planned 1200 evaluable patients were enrolled, which used an adjusted type I error rate of .00258 according to the O'Brien-Fleming method[24] for a noninferiority stop. The trial was also to be stopped for futility if the predictive power for the test of noninferiority was less than 0.25.

Secondary outcomes were examined using descriptive statistics, the Wilcoxon rank-sum test, point estimates and risk ratios with 2-sided 95% CIs, and the Hodges-Lehmann estimator of median differences with 95% CIs, where appropriate. Kaplan-Meier estimates for time-to-death distribution were calculated and graphically presented. Comparisons were prespecified as superiority analyses with $\alpha = .05$.

Several post hoc analyses were performed: (1) noninferiority was assessed for the outcome of cumulative allogeneic

Figure 1. Patient Flow in the FIBRES Study of the Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery



CPB indicates cardiopulmonary bypass; IMP, investigational medicinal product.

blood component units administered from investigational product administration to 24 hours after cardiopulmonary bypass; (2) treatment × site interaction was accounted for by including site in the model for the primary outcome as a fixed-effect variable (as 3 categories based on number of patients enrolled: <40; 40-99; >99); and (3) the relationship of critical state before surgery was explored by adjusting for it in the comparisons for the primary outcome and mortality. The results of secondary outcomes and post hoc analyses should be interpreted as exploratory, as no correction for type I error was made.

Variables with missing values are noted where applicable and patients with missing values were excluded from the relevant analyses. All analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Patient recruitment continued from February 10, 2017, to November 1, 2018, with the final follow-up visit on November 28, 2018. The trial was stopped based on the recommendation of the independent data and safety monitoring committee for meeting the criterion for noninferiority at the interim analysis. Of the 15 412 patients who underwent cardiac surgery at the 11 participating sites, 827 (5.3%) were screened and randomized (**Figure 1**). Sixty-one randomized patients were not treated because of cessation of bleeding. Informed consent could not be obtained for 31 treated patients, leaving 735 patients in the primary analysis set (n = 372 for fibrinogen concentrate, n = 363 for cryoprecipitate). After excluding 10 patients with major protocol deviations, 725 patients were included in the per-protocol analysis (Figure 1). No patients in the primary analysis set had missing transfusion or adverse event information; thus, they were all included in the relevant analyses.

Baseline demographics and surgical characteristics were well balanced except for critical state before surgery (**Table 1**). Patients received a median of 4 (interquartile range [IQR], 4-4) g of fibrinogen concentrate and 10 (IQR, 10-10) units of cryoprecipitate (**Table 2**; eTable 1 in Supplement 2).

Transfusions

In the primary analysis set, mean allogeneic blood component units administered were 16.7 (SD, 16.4) units within

Table 1. Characteristics of the Study Population at Baseline

Characteristic	No. (%) Fibrinogen Concentrate (n = 372)	No. (%) Cryoprecipitate (n = 363)
Age, median (IQR), y	65 (54-72)	64 (53-72)
Sex		
Women	113 (30.4)	105 (28.9)
Men	259 (69.6)	258 (71.1)
Race		
White	287 (77.2)	273 (75.2)
Asian	51(13.7)	58 (16.0)
Black	3 (0.81)	6 (1.6)
Aboriginal	5 (1.3)	2 (0.55)
Other[a]	26 (7.0)	24 (6.6)
Body mass index, median (IQR)[b]	22.2 (19.6-25.4)	22.8 (19.6-25.6)
NYHA class[c]		
I (least severe)	104 (27.9)	112 (30.8)
II	110 (29.6)	108 (29.8)
III	110 (29.6)	103 (28.4)
IV (most severe)	48 (12.9)	40 (11.0)
Myocardial infarction, d		
No.	367	358
None	294 (80.1)	299 (83.5)
0-90	39 (10.6)	30 (8.4)
>90	34 (9.3)	29 (8.1)
Ejection fraction, %		
No.	357	347
>50	256 (71.7)	263 (75.8)
31-50	51 (14.3)	57 (16.4)
21-30	28 (7.8)	12 (3.5)
<21	22 (6.2)	15 (4.3)
Pulmonary pressure, mm Hg		
No.	308	303
≤30	225 (73.1)	215 (71.0)
31-55	58 (18.8)	68 (22.4)
>55	25 (8.1)	20 (6.6)
Hypertension	234 (62.9)	240 (66.1)
Dyslipidemia	185 (49.7)	185 (51.0)
Congestive heart failure	113 (30.4)	91 (25.1)
Atrial fibrillation	81 (21.8)	80 (22.0)
Diabetes mellitus	80 (21.5)	74 (20.4)
Chronic lung disease	53 (14.3)	37 (10.2)
Stroke/TIA	46 (12.4)	49 (13.5)
Peripheral vascular disease	37 (10.0)	34 (9.4)
Active endocarditis	19 (5.1)	18 (5.0)
CCS class IV angina	15 (4.0)	13 (3.6)
Dialysis (preoperative)	9 (2.4)	14 (3.9)
Intra-aortic balloon pump	10 (2.7)	3 (0.8)
VAD/ECMO	9 (2.4)	9 (2.5)
Critical state before surgery[d]	63 (16.9)	38 (10.5)
Preoperative laboratory values, median (IQR)		
Creatinine, μmol/L	88 (72-107) [n = 359]	86 (72-106) [n = 352]
Hemoglobin, g/dL	13.4 (11.6-14.6) [n = 366]	13.5 (11.7-14.8) [n = 356]
Platelet count, $\times 10^3/\mu L$	189 (154-235) [n = 365]	185 (152-230) [n = 356]
International normalized ratio	1.02 (0.98-1.20) [n = 335]	1.03 (0.98-1.15) [n = 334]
Surgical factors		
Nonelective surgery	141 (37.9)	128 (35.3)
Complex surgery[e]	267 (71.8)	260 (71.6)
Procedure (% of procedures)[f]	653 (100.0)	612 (100.0)
Aortic valve procedure	165 (25.3)	146 (23.9)
Surgery on aorta	161 (24.7)	177 (28.9)
CABG surgery	153 (23.4)	146 (23.9)
Mitral valve procedure	68 (10.4)	70 (11.4)
Tricuspid valve procedure	31 (4.7)	35 (5.7)
ASD/VSD repair	20 (3.1)	8 (1.3)
Heart transplant	18 (2.8)	10 (1.6)
Complex congenital	11 (1.7)	11 (1.8)
Other[g]	26 (4.0)	9 (1.5)
Cardiopulmonary bypass duration, median (IQR), min	143 (102-209)	134 (99-200)

Abbreviations: ASD, atrial septal defect; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; NYHA, New York Heart Association; TIA, transient ischemic attack; VAD, ventricular assist device; VSD, ventricular septal defect.

[a] Other races marked as unknown or not applicable.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] NYHA functional classification: I = no limitation of physical activity and no symptoms; II = slight limitation of physical activity (ordinary physical activity results in fatigue, palpitation, dyspnea); III = marked limitation of physical activity (less than ordinary activity causes fatigue, palpitation, or dyspnea); IV = unable to carry on any physical activity without discomfort (symptoms of heart failure at rest).

[d] Determined by blinded adjudication for patients who underwent emergency surgery deemed to be in a critical state, based on criteria outlined in Supplement 2.

[e] Procedures other than CABG surgery only, single valve only, or repair of atrial septal defect only.

[f] Totals exceed 100% because some patients underwent more than 1 procedure.

[g] Examples of other procedures included aortic root enlargement, left ventricular aneurysmectomy, and left atrial appendage resection.

24 hours after termination of cardiopulmonary bypass and 22.4 (SD, 23.1) units from beginning of surgery to postoperative day 7. The mean 24-hour postbypass cumulative allogeneic blood component transfusions were 16.3 (95% CI, 14.9 to 17.8) units in the fibrinogen concentrate group and 17.0 (95% CI, 15.6 to 18.6) units in the cryoprecipitate group, and the mean ratio was 0.96 (1-sided 97.5% CI, −∞ to 1.09; $P < .001$ for nonferiority; 2-sided 95% CI, 0.84 to 1.09; $P = .50$ for superiority]) (**Table 3** and **Figure 2**).

Table 2. Details of Intervention, Perioperative Laboratory Values, Fibrinogen Levels, and Bleeding

Variable	Median (IQR)	
	Fibrinogen Concentrate (n = 372)	Cryoprecipitate (n = 363)
Dosage of investigational product		
Mean (SD)	4.8 (2.1) g	12.9 (8.5) units
Median (IQR)	4 (4-4) g	10 (10-10) units
Doses of investigational product, No. (%)		
1	309 (83.1)	296 (81.5)
2	49 (13.2)	49 (13.5)
3	10 (2.7)	10 (2.8)
≥4	4 (1.1)	8 (2.2)
Time from start of surgery to order of first dose, h	5.8 (4.5-7.3)	5.8 (4.6-7.1)
Time from order of first dose to administration, min	45 (32-62)	47 (37-60)
Time from end of CPB to administration of first dose, min	97 (52-159)	104 (59-160)
Plasma fibrinogen level, g/L		
Pretransfusion	1.6 (1.3-1.9) [n = 352]	1.6 (1.3-1.9) [n = 346]
Posttransfusion	2.5 (2.1-2.9) [n = 324]	2.3 (2.0-2.6) [n = 296]
Change from pretransfusion	0.90 (0.6-1.2) [n = 306]	0.70 (0.5-1.0) [n = 280]
Blood components transfused before randomization, mean (SD), units	4.3 (6.1)	4.5 (6.0)
Cell salvage blood, mL	373 (0-918)	400 (0-876)
Nadir hematocrit during cardiopulmonary bypass, %	26 (23-30)	25 (23-30)
Hemoglobin, g/dL		
Intraoperative post-CPB	9.1 (8.3-9.9) [n = 348]	8.9 (8.2-9.7) [n = 342]
Day of surgery (last recorded value)	9.6 (8.6-10.9) [n = 365]	9.5 (8.7-10.7) [n = 356]
Postoperative day 1 (last recorded value)	9.0 (8.3-9.9) [n = 367]	9.0 (8.3-10.0) [n = 361]
Platelet count, $\times 10^3/\mu L$		
Intraoperative post-CPB	107 (84-136) [n = 280]	103 (81-129) [n = 278]
Day of surgery (last recorded value)	132 (107-165) [n = 362]	133 (107-163) [n = 353]
Postoperative day 1 (last recorded value)	117 (91-145) [n = 366]	115 (92-143) [n = 359]
International normalized ratio		
Intraoperative post-CPB	1.6 (1.4-1.8) [n = 295]	1.6 (1.5-1.8) [n = 277]
Day of surgery (last recorded value)	1.3 (1.2-1.4) [n = 355]	1.3 (1.2-1.4) [n = 340]
Postoperative day 1 (last recorded value)	1.2 (1.1-1.4) [n = 342]	1.2 (1.1-1.3) [n = 335]
Bleeding categories according to modified UDPB classification, No. (%)[a]		
≥2 (moderate to massive)	349 (93.8)	347 (95.6)
<2 (insignificant to mild)	23 (6.2)	16 (4.4)
24-h chest tube drainage, mL	800 (500-1350)	830 (540-1350)
Reexploration, No. (%)	53 (14.2)	44 (12.1)
Prothrombin complex concentrate, No. (%)	110 (29.6)	98 (27.0)
Recombinant factor VII, No. (%)	35 (9.4)	28 (7.7)

Abbreviations: CPB, cardiopulmonary bypass; IQR, interquartile range; UDPB, universal definition of perioperative bleeding.

[a] UDPB determinants used in this study include postoperative chest tube output; units of red blood cells, plasma, and platelets transfused; use of factor concentrates; and surgical reexploration (classification scheme included in the eAppendix in Supplement 2).[22] For this study the following components of the UDPB score were not used: delay in chest closure and use of cryoprecipitate or fibrinogen concentrate. One intraoperative death was included in the severe or massive category in the fibrinogen concentrate group.

Noninferiority was also observed for the secondary outcomes of individual 24-hour and cumulative 7-day blood component transfusions (Table 3), as well as in the post hoc outcome of cumulative transfusions measured from product administration to 24 hours after termination of cardiopulmonary bypass (mean units, 8.6 [95% CI, 7.5 to 9.9] in the fibrinogen concentrate group vs 8.9 [95% CI, 7.8 to 10.2] in the cryoprecipitate group; mean ratio, 0.97 [1-sided 97.5% CI, −∞ to 1.18; $P = .02$ for noninferiority) and after accounting for treatment × site interaction ($P < .001$) (eFigure 1 in Supplement 2) on the primary outcome (mean ratio, 1.00 [1-sided 97.5% CI, −∞ to 1.13; $P = .003$ for noninferiority). Noninferiority was also observed for all defined subgroups except for the nonelective group, which included all patients in critical state before surgery (Figure 2; eTable 2 in Supplement 2).

Fibrinogen Levels

Timing and number of doses of investigational product were similar between groups. Fibrinogen response was slightly greater in the fibrinogen concentrate group (median increase, 0.9 [IQR, 0.6-1.2] g/L vs 0.7 [IQR, 0.5-1.0] g/L; $P < .001$) (Table 2; eTable 1 in Supplement 2).

Table 3. Primary and Secondary Outcomes: Allogeneic Blood Component Transfusions

Population	Fibrinogen Concentrate No.	Fibrinogen Concentrate Median (IQR)	Fibrinogen Concentrate LS Mean (95% CI)	Cryoprecipitate No.	Cryoprecipitate Median (IQR)	Cryoprecipitate LS Mean (95% CI)	Mean Difference (95% CI)	Unadjusted Ratio of LS Means (1-Sided 97.5% CI)	Noninferiority *P* Value
Primary Outcome: Cumulative Allogeneic Blood Components Transfused Within 24 h After Cardiopulmonary Bypass[a]									
Primary analysis set	372	12.0 (5.5 to 22.0)	16.3 (14.9 to 17.8)	363	14.0 (7.0 to 23.0)	17.0 (15.6 to 18.6)	−0.73 (−3.10 to 1.64)	Unadjusted 0.96 (−∞ to 1.09)	<.001
								Adjusted 0.91 (−∞ to 1.03)[c]	<.001
Per-protocol set[b]	364	12.0 (6.0 to 22.0)	16.4 (15.0 to 18.0)	361	14.0 (7.0 to 22.0)	16.9 (15.5 to 18.5)	−0.50 (−2.90 to 1.89)	Unadjusted 0.97 (−∞ to 1.10)	<.001
								Adjusted 0.92 (−∞ to 1.05)[c]	<.001
Secondary Outcome: Red Blood Cell Transfusions Within 24 h After Cardiopulmonary Bypass									
Primary analysis set	372	2.0 (0.0 to 5.0)	3.3 (3.0 to 3.7)	363	2.0 (1.0 to 5.0)	3.3 (2.9 to 3.7)	0.23 (−0.55 to 1.00)	1.00 (0 to 1.18)	.02
Per-protocol set	364	2.0 (0.0 to 5.0)	3.3 (3.0 to 3.7)	361	2.0 (1.0 to 5.0)	3.3 (2.9 to 3.7)	0.25 (−0.53 to 1.03)	1.01 (0 to 1.18)	.02
Secondary Outcome: Platelet Transfusions Within 24 h After Cardiopulmonary Bypass									
Primary analysis set	372	8.0 (4.0 to 12.0)	9.1 (8.3 to 9.9)	363	8.0 (4.0 to 12.0)	9.7 (8.9 to 10.5)	−0.46 (−1.70 to 0.78)	0.94 (−∞ to 1.06)	<.001
Per-protocol set	364	8.0 (4.0 to 12.0)	9.1 (8.3 to 10.0)	361	8.0 (4.0 to 12.0)	9.6 (8.8 to 10.5)	−0.31 (−1.56 to 0.93)	0.95 (−∞ to 1.08)	<.001
Secondary Outcome: Plasma Transfusions Within 24 h After Cardiopulmonary Bypass									
Primary analysis set	372	2.0 (0.0 to 6.0)	3.9 (3.5 to 4.4)	363	3.0 (0.0 to 6.0)	4.1 (3.6 to 4.6)	−0.04 (−0.97 to 0.89)	0.96 (−∞ to 1.15)	.008
Per-protocol set	364	2.0 (0.0 to 6.0)	4.0 (3.5 to 4.5)	361	3.0 (0.0 to 6.0)	4.0 (3.6 to 4.6)	0.04 (−0.91 to 0.98)	0.98 (−∞ to 1.17)	.01
Secondary Outcome: Cumulative Allogeneic Blood Components Transfused Within 7 d After Start of Surgery									
Primary analysis set	372	15.5 (6.0 to 29.5)	22.5 (20.5 to 24.7)	363	17.0 (9.0 to 28.0)	22.3 (20.3 to 24.5)	0.21 (−3.14 to 3.55)	Unadjusted 1.01 (0 to 1.15)	.005
								Adjusted 0.96 (−∞ to 1.09)[c]	<.001
Per-protocol set	364	15.5 (6.0 to 29.0)	22.5 (20.5 to 24.8)	361	17.0 (9.0 to 28.0)	22.2 (20.2 to 24.5)	0.31 (−3.07 to 3.70)	Unadjusted 1.01 (0 to 1.16)	.007
								Adjusted 0.96 (−∞ to 1.09)[c]	<.001

Abbreviation: LS, least-squares.

[a] Units of allogenic blood components counted as follows: each red blood cell unit = 1 unit, each 250-mL plasma unit = 1 unit, each 500-mL plasma unit = 2 units, each platelet dose = 4 units.

[b] Per-protocol set excluded patients who did not undergo cardiac surgery with cardiopulmonary bypass, received the incorrect treatment, received less than 80% of the planned dose, or received the first treatment more than 24 hours after cardiopulmonary bypass.

[c] Adjusted for critical state before surgery (post hoc analysis).

Adverse Events and Other Outcomes

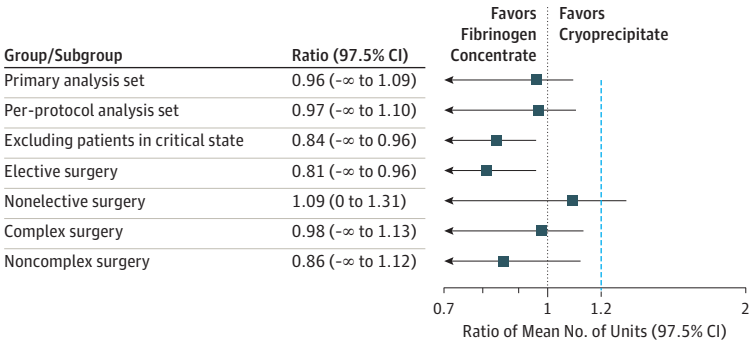
Treatment-emergent adverse event profiles were similar (**Table 4**; eTable 3 in Supplement 2), as were the duration of intubation, intensive care unit stay, and hospital stay (Table 4). There were 35 deaths (9.4%) in the fibrinogen concentrate group and 27 (7.4%) in the cryoprecipitate group (unadjusted hazard ratio, 1.28 [95% CI, 0.77 to 2.12]; $P = .35$) (Kaplan-Meier curves shown in eFigures 2 and 3 in Supplement 2). Death rates were also not significantly different when stratified by critical state before surgery (fibrinogen concentrate vs cryoprecipitate: 19/63 [30.2%] vs 12/38 [31.6%] in critical state patients; 16/309 [5.2%] vs 15/325 [4.6%] in remaining patients) and after risk adjustment for critical state (post hoc analysis hazard ratio, 1.03 [95% CI, 0.62 to 1.70]; $P = .92$) (results from post hoc analyses reported in eTables 4 and 5 in Supplement 2). Thromboembolic adverse events were observed in 26 patients (7.0%) in the fibrinogen group and 35 patients (9.6%) in the cryoprecipitate group (unadjusted odds ratio, 0.70 [95% CI, 0.42 to 1.20]) (Table 4).

Discussion

In this study of patients who experienced bleeding after cardiac surgery and required fibrinogen replacement as part of routine clinical practice, the primary finding was that fibrinogen concentrate was noninferior to cryoprecipitate as measured by the number of blood components transfused.

The study protocol, which did not modify clinical practice and used a delayed (postintervention) consent process, successfully randomized the small proportion of patients with bleeding who were ordered fibrinogen replacement (comprising approximately 5% of patients who underwent cardiac surgery at participating centers during the study period). The groups were well balanced for baseline variables except for critical state before surgery, an important prognostic variable that was more prevalent in the fibrinogen concentrate group. The occurrence of adverse events was comparable between the groups, although there was

Figure 2. Ratio of Mean Number of Allogeneic Blood Components Transfused in the 24 Hours After Cardiopulmonary Bypass for the Primary Analysis Set, Per-Protocol Analysis Set, and A Priori–Defined Subgroups



All patients in critical state were in the nonelective subgroup. Blue dashed line at x = 1.2 indicates the noninferiority margin.

Table 4. Treatment-Emergent Adverse Events and Other Measured Outcomes at 28-Day Follow-up

Outcome	No. (%)	
	Fibrinogen Concentrate (n = 372)	Cryoprecipitate (n = 363)
Any adverse event	248 (66.7)	264 (72.7)
No. of events	623	673
Any serious adverse event	117 (31.5)	126 (34.7)
No. of events	224	264
Thromboembolic adverse events[a]	26 (7.0)	35 (9.6)
No. of events	27	39
Stroke/TIA	17 (4.6)	18 (5.0)
DVT/PE	5 (1.3)	9 (2.5)
Myocardial infarction	3 (0.8)	4 (1.1)
Other vessel thrombosis	0	7 (1.9)
Amaurosis fugax	0	1 (0.3)
Disseminated intravascular coagulation	1 (0.3)	0
Thrombophlebitis	1 (0.3)	0
Acute kidney injury[b]	48 (12.9)	48 (13.2)
Hepatobiliary disorders[c]	32 (8.6)	37 (10.2)
Duration of mechanical ventilation, median (IQR), d	1.3 (0.7-5.0) [n = 337]	1.3 (0.7-4.2) [n = 342]
Duration of intensive care unit stay, median (IQR), d	2.9 (1.4-5.7) [n = 352]	2.8 (1.2-5.6) [n = 345]
Duration of hospitalization, median (IQR), d	8.2 (6.3-13.0) [n = 314]	9.0 (6.3-13.3) [n = 308]

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

[a] Patients who experienced more than 1 event are counted only once in the total.

[b] Acute kidney injury was defined as greater than a 2-fold increase in creatinine or kidney failure requiring hemodialysis within 28 days of surgery.

[c] Hepatobiliary disorders were defined by the *Medical Dictionary for Regulatory Activities* (version 21.1) system of nomenclature.

a nonsignificant difference of 2.0% in mortality. This seemed to be related to the between-group imbalance in the number of patients in critical state before surgery.

The study objective was to compare the 2 currently recommended therapies for fibrinogen replacement[4,5] under usual conditions of clinical care. Thus, it did not include a placebo group to determine the efficacy of fibrinogen replacement per se, nor did it attempt to identify the appropriate threshold for fibrinogen replacement.[16] A recent systematic review comparing fibrinogen concentrates with cryoprecipitate in patients with bleeding[10] identified 1 randomized trial (with high risk for bias)[19] and 3 observational studies[25-27] and concluded that there was insufficient evidence to recommend one product over the other. Another review of trauma, obstetric, and gastrointestinal bleeding populations reached similar conclusions.[9] This study provides further data regarding the comparative efficacy and adverse event profile of these 2 products.

The noninferiority finding can inform the choice of cryoprecipitate or fibrinogen concentrate for treatment of bleeding related to acquired hypofibrinogenemia. A core tenet and major regulatory driver in transfusion medicine is the precautionary principle that requires risk-mitigation strategies to be instituted even if there is only a theoretical risk of harm.[28] Consistent with this principle, the US Food and Drug Administration blood safety strategy recommends the use of pathogen-reduced blood products when feasible.[28] Currently, there are no known impending infectious threats for

recipients of cryoprecipitate; however, the history of blood pathogens suggests that plasma-derived products have transmitted pathogens in the past and may do so in the future.[29] In addition, mathematical models of emerging pathogens suggest that the association of plasma-derived products (such as cryoprecipitate) with outcomes and costs may be substantial.[30] In this regard, fibrinogen concentrate may be preferred to cryoprecipitate because it is pathogen-reduced. Another advantage of fibrinogen concentrate is that in most situations it can be logistically simpler to deliver to the bedside of a patient with bleeding. One important consideration is the cost differential that currently favors cryoprecipitate, but this varies across regions, and the most recent economic analysis failed to include the costs of future emerging pathogens and did not include comprehensive activity-based costing.[31]

Limitations

This study has several limitations. First, since the aim was to compare the 2 products when used under usual conditions of care, it was not logistically possible to institute a standardized transfusion protocol across the sites or to blind clinicians to treatment assignment. Although a post hoc analysis showed that there were treatment × site interactions, accounting for the interactions did not have a material effect on the primary outcome. Moreover, postoperative hemoglobin, platelet count, and coagulation measures were similar between groups (Table 2), suggesting that transfusion practice was consistent in both groups. In addition, the results were consistent when transfusions were measured from beginning of surgery to postoperative day 7 (a priori analysis) or after administration of investigational product (post hoc analysis), which suggests that lack of blinding did not influence the timing of transfusions relative to product administration. Of note, to ensure that all transfusions and adverse events were collected without bias, patients and outcome assessors were blinded to treatment allocation and independent monitors reviewed all transfusion and adverse events. Second, while the study had few exclusion criteria, it included only patients undergoing cardiac surgery with bleeding, and its findings may therefore not be generalizable to other settings where fibrinogen replacement is required. This would primarily be other types of surgery, trauma, and postpartum hemorrhage,[32] but most evidence suggests that the role of fibrinogen is similar in these settings.[33,34] Third, because of the pragmatic design of the study, strict timing of laboratory assessments could not be enforced. However, only less than 5% of patients had no measured fibrinogen levels before product administration. Related to this, a small proportion of patients had fibrinogen values above recommended thresholds when treatment order was received. However, this is consistent with recent experience in major bleeding,[32] and ongoing bleeding from sample collection to therapy means that actual fibrinogen levels at the time of therapy were likely lower than measured values. Fourth, fibrinogen content is standardized in fibrinogen concentrate but is highly variable in cryoprecipitate. As a result, some patients in the cryoprecipitate group likely received much less or much more than 4 g of fibrinogen. While this is one of the inherent limitations of cryoprecipitate, observed differences in pretreatment and posttreatment fibrinogen levels suggest that on average both groups received clinically similar amounts of fibrinogen.

Conclusions

In patients undergoing cardiac surgery who develop clinically significant bleeding and hypofibrinogenemia after cardiopulmonary bypass, fibrinogen concentrate is noninferior to cryoprecipitate with regard to number of blood components transfused in a 24-hour period post bypass. Use of fibrinogen concentrate may be considered for management of bleeding in patients with acquired hypofibrinogenemia in cardiac surgery.

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ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

ABSTRACT

BACKGROUND

It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU.

METHODS

We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.

RESULTS

Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline; the two groups had similar baseline characteristics. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; P=0.87). The proportion of patients with new single-organ and multiple-organ failure was similar in the two groups (P=0.85). There were no significant differences between the groups in the mean (±SD) numbers of days spent in the ICU (6.5±6.6 in the albumin group and 6.2±6.2 in the saline group, P=0.44), days spent in the hospital (15.3±9.6 and 15.6±9.6, respectively; P=0.30), days of mechanical ventilation (4.5±6.1 and 4.3±5.7, respectively; P=0.74), or days of renal-replacement therapy (0.5±2.3 and 0.4±2.0, respectively; P=0.41).

CONCLUSIONS

In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.

The Saline versus Albumin Fluid Evaluation (SAFE) Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australian Red Cross Blood Service, and the George Institute for International Health. The writing committee (Simon Finfer, M.B., B.S., Rinaldo Bellomo, M.B., B.S., M.D., Neil Boyce, M.B., B.S., Ph.D., Julie French, R.N., John Myburgh, M.B., B.Ch., Ph.D., and Robyn Norton, Ph.D., M.P.H.) takes responsibility for the content of this article. Address reprint requests to Dr. Finfer at ANZICS CTG, Level 3, 10 Ievers St., Carlton, VIC 3053, Australia, or at ctg@anzics.com.au.

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THE ADMINISTRATION OF INTRAVENOUS fluids to maintain or increase intravascular volume is a common intervention in the intensive care unit (ICU), but there is uncertainty whether the choice of fluid significantly influences patients' outcomes.[1-7] In particular, no adequately powered randomized, controlled trials have examined the effect of fluid choice on the survival of patients in the ICU. In the absence of such trials, a number of meta-analyses have examined how the choice of crystalloid or colloid solution and of albumin-containing or albumin-free fluid affects survival in critically ill patients and in patients who are less severely ill.[1-3,7] A meta-analysis published by the Cochrane Injuries Group Albumin Reviewers included 24 studies involving a total of 1419 patients and suggested that the administration of albumin-containing fluids resulted in a 6 percent increase in the absolute risk of death when compared with the administration of crystalloid solutions.[1] However, a subsequent meta-analysis of 55 trials involving a total of 3504 patients examined the effect of resuscitation with albumin-containing fluid on the risk of death in a general population of patients and did not find a significant increase in the risk of death.[3]

The conflicting results of such meta-analyses have left many clinicians unsure about the effect of albumin-containing fluids on survival in critically ill patients. To address this uncertainty, we conducted the Saline versus Albumin Fluid Evaluation (SAFE) Study in 16 ICUs in Australia and New Zealand. We tested the hypothesis that when 4 percent albumin is compared with 0.9 percent sodium chloride (normal saline) for intravascular-fluid resuscitation in patients in the ICU, there is no difference in the 28-day rate of death from any cause.

METHODS

STUDY DESIGN AND TREATMENT PROTOCOL

Patients 18 years of age or older who had been admitted to the closed, multidisciplinary ICUs of 16 academic tertiary hospitals in Australia and New Zealand between November 2001 and June 2003 were assessed for eligibility for the study. Eligible patients were those whom the treating clinician judged to require fluid administration to maintain or increase intravascular volume, with this decision supported by the fulfillment of at least one objective criterion. Patients admitted to the ICU after cardiac surgery, after liver transplantation, or for the treatment of burns were excluded. Details of the inclusion and exclusion criteria are given in Table S1 of the Supplementary Appendix (available with the full text of this article at www.nejm.org). A detailed description of the study design has been published elsewhere.[8]

The study protocol was approved by the ethics committees of the University of Sydney and of each participating institution. Written informed consent was to be obtained from all competent patients; in cases in which prior consent could not be obtained from the patient because of critical illness or the use of sedative or anesthetic drugs, consent could be delayed, and a provision for delayed consent was applied. In such cases, the patient or his or her surrogate decision maker was informed of the study as soon as practicable, and consent was sought to continue the study procedures and to access the participant's medical records for study-related data. The patients or their legal surrogates were informed of their right to request that the study procedures be discontinued and their right to refuse the study-related use of their medical records.

Eligible patients were randomly assigned to receive either 4 percent albumin (Albumex, CSL) or normal saline, with the random assignments stratified according to institution and according to whether there was a diagnosis of trauma on admission to the ICU. Randomization was carried out centrally with the use of a minimization algorithm, and the service was accessed on the Internet through a secure Web site. Study fluids were supplied in identical 500-ml bottles, and blinding was ensured through the use of specially designed masking cartons and specially designed and manufactured administration sets.[8] The effectiveness of the blinding was confirmed in a formal study before the trial was initiated. The treating clinicians determined the amount and rate of fluid administration according to each patient's clinical status and response to treatment. The allocated study treatment was to be used for all fluid resuscitation in the ICU until death or discharge or until 28 days after randomization. The administration of intravenous fluids outside the ICU was not controlled.

In addition to the study fluid, patients received maintenance fluids, specific replacement fluids, enteral or parenteral nutrition, and blood products at the discretion of the treating clinicians. The monitoring of central venous pressure, pulmonary-artery catheterization, and all other aspects of patient care were performed at the discretion of the treating clinicians.

BASELINE ASSESSMENT AND FOLLOW-UP DATA COLLECTION

Data collected at baseline included the Acute Physiology and Chronic Health Evaluation II score,[9] as well as information pertaining to diagnostic criteria for severe sepsis[10] (Table S2 of the Supplementary Appendix) and for the acute respiratory distress syndrome.[11] Patients were identified as having traumatic brain injury at baseline if they had a history of trauma, a Glasgow Coma Score[12] while not sedated of less than 14, and an abnormality consistent with traumatic brain injury on a computed tomographic scan of the head. The cardiovascular, respiratory, renal, hematologic, and hepatic components of the Sequential Organ-Failure Assessment (SOFA) score,[13] as described in Table S3 of the Supplementary Appendix, were recorded at the time of randomization, daily for the next seven days, and then every third day until discharge from the ICU or until day 28. After randomization, the heart rate, central venous pressure, mean arterial blood pressure, volume of study fluid administered, volume of nonstudy fluid and blood products administered, net fluid balance (calculated as the total fluid input minus the total fluid output), use of mechanical ventilation, and use of renal-replacement therapy (intermittent or continuous hemodialysis, hemofiltration, or hemodiafiltration) were recorded daily until discharge from the ICU or death or until day 28.

OUTCOME MEASURES

The primary outcome measure was death from any cause within 28 days after randomization. Secondary outcome measures were the survival time during the first 28 days, the proportion of patients who had one, two, three, four, or five new organ failures (defined as a documented change in the cardiovascular, respiratory, renal, hematologic, or hepatic component of the SOFA score from 0, 1, or 2 at baseline to 3 or 4 during the ICU stay, where higher scores indicate increasingly severe organ dysfunction), the duration of mechanical ventilation, the duration of renal-replacement therapy, and the duration of the ICU and hospital stay.

Death from any cause within 28 days after randomization was also examined in six predefined subgroups according to the presence or absence of trauma, the presence or absence of severe sepsis, and the presence or absence of the acute respiratory distress syndrome at baseline.

STUDY AND DATA MANAGEMENT

Two preplanned interim analyses were performed by an independent statistician after recruitment of the first 2333 patients (33 percent of the planned total) and the first 4666 patients (67 percent), and the results were reviewed by the independent data-monitoring committee.

The George Institute for International Health at the University of Sydney performed the data management, the site management, and the data analysis, independently of the funding agencies. The manuscript was prepared by the writing committee and was revised by the study investigators, who approved the final manuscript.

STATISTICAL ANALYSIS

The trial was designed to enroll 7000 patients, thereby providing a power of 90 percent to detect a 3 percent difference in absolute mortality rates between the two groups from an estimated baseline mortality rate of 15 percent. The data were exported from the study database and analyzed with the use of SPSS software (version 11.5). All analyses were performed on an intention-to-treat basis. Where data were missing, we report the number of available observations, and we make no assumptions about the missing data.

Proportions were compared by means of the chi-square test or Fisher's exact test, and continuous variables were compared by means of unpaired t-tests. The results of comparisons of event rates in the two groups are presented as relative risks with 95 percent confidence intervals. Survival times were compared by means of the log-rank test and are presented as Kaplan–Meier curves without adjustment for baseline covariates. Heterogeneity of treatment effects among subgroups was assessed with the use of the test for a common relative risk.[14]

RESULTS

STUDY PATIENTS

Seven thousand random assignments to a study treatment were made (3499 to the albumin group and 3501 to the saline group). Three patients mistakenly underwent randomization twice within 28 days; they were followed for 28 days beginning at the time of the first randomization, and for purposes of data analysis were considered part of the group to which they were first assigned. Thus, the study population comprised 6997 patients, 3497 of whom

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Albumin Group	Saline Group
Age — yr	58.6±19.1	58.5±18.7
Female sex — no. (%)	1424 (40.7)	1376 (39.3)
Reason for admission to ICU — no. (%)		
Surgical	1473 (43.0)	1465 (42.8)
Medical	1955 (57.0)	1958 (57.2)
Source of admission to ICU — no. (%)		
Emergency department	948 (27.7)	977 (28.5)
Hospital floor	614 (17.9)	573 (16.7)
Another ICU	63 (1.8)	66 (1.9)
Another hospital	323 (9.4)	341 (10.0)
Operating room (emergency surgery)	801 (23.4)	780 (22.8)
Operating room (elective surgery)	662 (19.3)	678 (19.8)
Same ICU (readmission)	17 (0.5)	8 (0.2)
Predefined subgroups — no. (%)		
Trauma	597 (17.4)	590 (17.2)
Severe sepsis	603 (18.1)	615 (18.4)
Acute respiratory distress syndrome	61 (1.8)	66 (1.9)
APACHE II score†	18.7±7.9	19.0±8.0
Physiological variables		
Heart rate — beats/min	91.4±23.5	92.3±23.5
Mean arterial pressure — mm Hg	77.8±16.4	78.2±16.3
Central venous pressure — mm Hg	9.0±4.7	8.6±4.6‡
Urine output — ml/hr	89.7±132.4	95.0±161.4
Serum albumin — g/liter	27.4±7.8	27.7±7.9
Organ failure— no. (%)§		
No failure	1962 (57.2)	1885 (55.1)
1 organ	1075 (31.4)	1148 (33.5)
2 organs	335 (9.8)	329 (9.6)
3 organs	50 (1.5)	57 (1.7)
4 organs	5 (0.1)	4 (0.1)
5 organs	1 (<0.1)	0
Mechanical ventilation — no. (%)	2186 (63.8)	2217 (64.8)
Renal-replacement therapy — no. (%)	45 (1.3)	41 (1.2)
Albumin in previous 72 hr — no. (%)	127 (3.7)	135 (3.9)

* Plus–minus values are means ±SD. Percentages were calculated according to the number of patients for whom data were available: for sex, 3497 in the albumin group and 3500 in the saline group; for severe sepsis, 3339 in the albumin group and 3338 in the saline group; and for all the other variables, 3428 in the albumin group and 3423 in the saline group. Because of rounding, not all percentages total 100. ICU denotes intensive care unit, and APACHE II Acute Physiology and Chronic Health Evaluation II.

† Higher scores on APACHE II indicate more severe illness.

‡ P=0.03 for the comparison with the value in the albumin group (without correction for multiple-hypothesis testing).

§ Organ failure was defined as a Sequential Organ-Failure Assessment score[13] of 3 or 4 for any individual organ system.

were assigned to receive albumin and 3500 of whom were assigned to receive saline. The majority of the patients (6628 [94.7 percent] — 3312 of those in the albumin group [94.7 percent] and 3316 of those in the saline group [94.7 percent]) were enrolled with the use of the provision for delayed consent. Delayed consent was obtained from the patient in 2713 cases (38.8 percent) and from a surrogate decision maker (a relative, a legally recognized surrogate, or an institutional ethics committee) in the remaining cases. Prior consent was obtained from the patient in 45 cases (0.6 percent) and from a surrogate decision maker in 335 cases (4.8 percent).

At baseline, the only statistically significant difference between the two groups was a higher mean (±SD) central venous pressure in the albumin group (9.0±4.7 mm Hg, vs. 8.6±4.6 mm Hg in the saline group; P=0.03). The baseline characteristics of the 6997 patients are summarized in Table 1, and their progress through the study is summarized in Figure S1 of the Supplementary Appendix.

Study fluid was administered to all but 197 patients (2.8 percent), including 90 in the albumin group and 107 in the saline group. Resuscitation fluids in addition to the allocated study fluid were administered to 309 patients in the albumin group (8.8 percent) and 375 in the saline group (10.7 percent). The most common reason for the administration of nonstudy resuscitation fluid was error (in 189 patients in the albumin group [5.4 percent] and 190 in the saline group [5.4 percent]). Clinicians' preference for a specific nonstudy resuscitation fluid was the reason for its administration in 68 patients in the albumin group (1.9 percent) and 103 in the saline group (2.9 percent). At the completion of the trial, information on vital status 28 days after randomization was unavailable for 67 patients (1.0 percent), including 26 in the albumin group and 41 in the saline group. In 56 of these 67 cases, vital status was missing because the patient or his or her legal surrogate had withheld or withdrawn consent.

FLUIDS ADMINISTERED AND TREATMENT EFFECTS

On each of the first three study days, the patients who had been randomly assigned to receive albumin received significantly less study fluid than did those assigned to saline, resulting in a significantly greater net positive fluid balance in the saline group on each of those days (Table 2). The ratios of the volume of albumin to the volume of saline administered during the first four days were as follows: 1:1.3 on day 1, 1:1.6 on day 2, 1:1.3 on day 3, and 1:1.2 on

Table 2. Fluids Administered and Physiological Effects of Treatment.*

Variable	Albumin Group		Saline Group		P Value†
	No. of Patients	Value	No. of Patients	Value	
Study fluid (ml)					
Day 1	3410	1183.9±973.6	3418	1565.3±1536.1	<0.001
Day 2	3059	602.7±892.7	3068	954.0±1484.4	<0.001
Day 3	2210	268.0±554.5	2202	348.3±753.5	0.03
Day 4	1686	192.3±427.0	1664	228.6±642.6	0.57
Nonstudy fluid (ml)					
Day 1	3392	1459.4±1183.2	3405	1505.6±1254.3	0.30
Day 2	3051	2615.9±1372.5	3057	2707.3±1435.7	0.009
Day 3	2199	2618.5±1346.5	2191	2660.9±1319.3	0.15
Day 4	1680	2691.5±1228.7	1656	2707.7±1255.4	0.36
Packed red cells (ml)					
Day 1	3411	97.8±360.7	3415	71.7±296.8	<0.001
Day 2	3066	106.5±321.4	3074	61.1±235.2	<0.001
Day 3	2217	59.8±225.5	2210	49.5±190.8	0.30
Day 4	1692	43.6±167.5	1668	46.0±189.0	0.77
Net positive fluid balance (ml)					
Day 1	3363	1543.6±1619.7	3382	1990.5±2061.7	<0.001
Day 2	3044	1015.3±1826.9	3052	1505.1±2215.9	<0.001
Day 3	2190	422.1±1633.3	2182	553.0±1732.3	0.007
Day 4	1671	137.2±1491.0	1649	155.7±1650.6	0.70
Mean arterial pressure (mm Hg)					
Day 1	3406	81.4±14.4	3408	80.9±14.5	0.14
Day 2	3068	84.4±15.1	3075	84.2±15.7	0.49
Day 3	2215	87.2±15.3	2209	86.9±16.1	0.62
Day 4	1688	88.3±15.9	1666	88.4±16.3	0.87
Heart rate (beats/min)					
Day 1	3398	88.0±20.2	3406	89.7±20.8	<0.001
Day 3	3071	88.5±19.5	3075	89.5±19.2	0.06
Day 3	2216	88.8±19.1	2213	89.7±18.8	0.10
Day 4	1691	89.5±18.9	1668	89.9±18.5	0.52
Central venous pressure (mm Hg)					
Day 1	2204	11.2±4.8	2270	10.0±4.5	<0.001
Day 2	2095	11.6±4.9	2135	10.4±4.3	<0.001
Day 3	1531	11.4±4.8	1589	10.7±4.4	<0.001
Day 4	1221	11.1±4.8	1230	10.5±4.4	<0.001
Serum albumin (g/liter)					
Day 1	2081	28.7±7.0	2061	24.7±6.5	<0.001
Day 2	2708	30.8±6.4	2703	24.5±5.9	<0.001
Day 3	1921	30.0±6.4	1905	23.6±5.6	<0.001
Day 4	1498	29.0±6.2	1478	23.1±5.5	<0.001

* Plus–minus values are means ±SD.
† P values are for the comparison between the two means for each variable at each time point.

day 4. The overall ratio of the volume of albumin to the volume of saline administered during the first four days was approximately 1:1.4. Patients in the two groups received similar volumes of other fluids during the first four days, except on days 1 and 2, when the patients in the albumin group received a greater volume of packed red cells than did those in the saline group; on average, during the first four days, patients assigned to receive albumin received 71.0 ml more packed red cells than those assigned to receive saline. On day 2, patients in the saline group received a greater volume of nonstudy fluids than did those in the albumin group (Table 2). After day 4, there were no differences between the two groups in the volume of study fluids administered. There were no significant differences between the groups in the mean arterial pressure measured at the end of each of the first four days of the study. The patients assigned to receive albumin had a lower heart rate at the end of the first day than those as-

signed to receive saline. Central venous pressure was significantly higher in the albumin group than in the saline group at all time points during the first four days, and the serum albumin concentration was higher in the albumin group throughout the study period (Table 2).

OUTCOMES

Within 28 days after randomization, 726 of 3473 patients in the albumin group (20.9 percent) and 729 of 3460 patients in the saline group (21.1 percent) had died. For the albumin group as compared with the saline group, the absolute difference in mortality was –0.2 percent (95 percent confidence interval, –2.1 to +1.8 percent). The relative risk of death among patients assigned to receive albumin as compared with those assigned to receive saline was 0.99 (95 percent confidence interval, 0.91 to 1.09; P=0.87). At 28 days, 111 patients in the albumin group (3.2 percent) and 87 patients in the saline group (2.5 percent) remained in the ICU (relative risk, 1.27; P=0.09); 793 (22.8 percent) and 848 (24.5 percent), respectively, remained in the hospital (relative risk, 0.93; 95 percent confidence interval, 0.86 to 1.01; P=0.10) (Table 3). There was no significant difference in survival times between the two groups (Fig. 1).

The number of patients who had new single-organ or multiple-organ failure, assessed according to their SOFA scores, was similar in the two groups (P=0.85 by Fisher's exact test) (Table 3). During the 28-day study period the mean length of stay in the

Table 3. Primary and Secondary Outcomes.*

Outcome	Albumin Group	Saline Group	Relative Risk (95% CI)	Absolute Difference (95% CI)	P Value
Status at 28 days — no./total no. (%)					
Dead	726/3473 (20.9)	729/3460 (21.1)	0.99 (0.91 to 1.09)		0.87
Alive in ICU	111/3473 (3.2)	87/3460 (2.5)	1.27 (0.96 to 1.68)		0.09
Alive in hospital†	793/3473 (22.8)	848/3460 (24.5)	0.93 (0.86 to 1.01)		0.10
Length of stay in ICU — days	6.5±6.6	6.2±6.2		0.24 (–0.06 to 0.54)	0.44
Length of stay in hospital — days†	15.3±9.6	15.6±9.6		–0.24 (–0.70 to 0.21)	0.30
Duration of mechanical ventilation — days	4.5±6.1	4.3±5.7		0.19 (–0.08 to 0.47)	0.74
Duration of renal-replacement therapy — days	0.48±2.28	0.39±2.0		0.09 (–0.0 to 0.19)	0.41
New organ failure — no. (%)‡					0.85§
No failure	1397 (52.7)	1424 (53.3)			
1 organ	795 (30.0)	796 (29.8)			
2 organs	369 (13.9)	361 (13.5)			
3 organs	68 (2.6)	75 (2.8)			
4 organs	18 (0.7)	17 (0.6)			
5 organs	2 (0.1)	0			
Death within 28 days according to subgroup — no./total no. (%)					
Patients with trauma	81/596 (13.6)	59/590 (10.0)	1.36 (0.99 to 1.86)		0.06
Patients with severe sepsis	185/603 (30.7)	217/615 (35.3)	0.87 (0.74 to 1.02)		0.09
Patients with acute respiratory distress syndrome	24/61 (39.3)	28/66 (42.4)	0.93 (0.61 to 1.41)		0.72

* Plus–minus values are means ±SD. CI denotes confidence interval, and ICU intensive care unit.
† The data include the numbers of patients in the ICU or the length of stay in the ICU.
‡ Data were available for 2649 patients in the albumin group and 2673 patients in the saline group. New organ failure was defined as a Sequential Organ-Failure Assessment score[13] of 0, 1, or 2 in any individual organ system at baseline, followed by an increase in the score to 3 or 4 in the same system.
§ The P value pertains to the comparison between the albumin and saline groups in the numbers of patients who had no new organ failure or new failure of one, two, three, four, or five organs.

ICU was 6.5±6.6 days in the albumin group and 6.2±6.2 days in the saline group (P=0.44). The mean length of stay in the hospital was 15.3±9.6 days and 15.6±9.6 days, respectively (P=0.30). The numbers of days of mechanical ventilation and days of renal-replacement therapy were similar in the two groups (Table 3).

SUBGROUP ANALYSES

During the 28-day study period, the relative risk of death among patients with trauma in the albumin group as compared with such patients in the saline group was 1.36; the corresponding relative risk of death among patients without trauma was 0.96 (P=0.04 by the test for a common relative risk). This difference in the relative risk of death was due to the greater number of patients with trauma and an associated brain injury who died after random assignment to albumin as opposed to saline: 59 of 241 such patients in the albumin group died (24.5 percent), as compared with 38 of 251 such patients in the saline group (15.1 percent) (relative risk, 1.62; 95 percent confidence interval, 1.12 to 2.34; P=0.009). Among patients who had trauma without brain injury, there was no difference between the groups in terms of mortality: 22 such patients in the albumin group (6.2 percent) and 21 in the saline group (6.2 percent) died (relative risk, 1.00; 95 percent confidence interval, 0.56 to 1.79; P=1.00). Among all the patients who had trauma (596 in the albumin group and 590 in the saline group), there were 81 (13.6 percent) deaths in the albumin group and 59 (10.0 percent) in the saline group (relative risk, 1.36; 95 percent confidence interval, 0.99 to 1.86; P=0.06) (Fig. 2 and Table 3).

In a subgroup analysis of patients with severe sepsis, the relative risk of death during the 28-day study period among those randomly assigned to receive albumin as opposed to saline was 0.87, as compared with a corresponding relative risk of 1.05 among patients without severe sepsis (P=0.06 by the test for a common relative risk). Of the 603 patients with severe sepsis who had been assigned to receive albumin, 185 (30.7 percent) died, and of the 615 patients with severe sepsis who had been assigned to receive saline, 217 (35.3 percent) died (relative risk, 0.87; 95 percent confidence interval, 0.74 to 1.02; P=0.09) (Table 3). In a subgroup analysis of patients with the acute respiratory distress syndrome, the relative risk of death among those assigned to receive albumin as opposed to saline was 0.93; the corresponding relative risk among patients without this syndrome was 1.00 (P=0.74 by the test for a common relative risk).

DISCUSSION

In this randomized trial, we found that the use of 4 percent albumin or normal saline for intravascular volume resuscitation in a heterogeneous population of patients in the ICU resulted in equivalent rates of death from any cause during the 28-day study period. Requirements for mechanical ventilation and renal-replacement therapy, time spent in the ICU and in the hospital during the 28-day study period, and the time until death (among the patients who died) were also equivalent. The proportion of patients in the two groups in whom new single-organ or multiple-organ failure developed were similar. Our findings do not support the results of the Cochrane Injuries Group Albumin Reviewers' meta-analysis, which suggested that the use of albumin was associated with an increased mortality rate among critically ill patients.[1]

Our study was conducted as a double-blind, randomized trial. Albumin and saline are not considered equipotent intravascular volume expanders, but their relative potencies have not previously been examined in an adequately powered, blinded trial. In our study, patients who were resuscitated with albumin received less fluid than those who were resuscitated with saline. During the first four days,

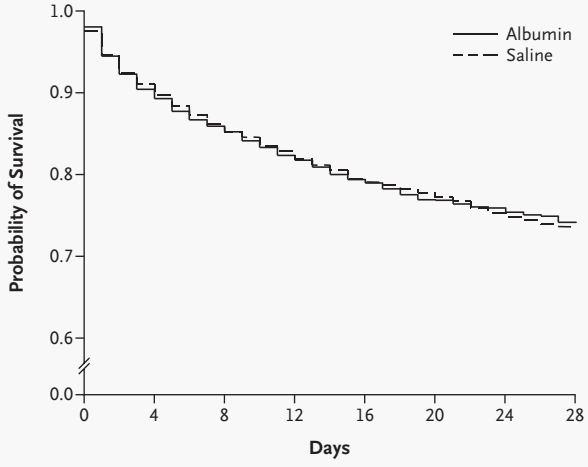

Figure 1. Kaplan–Meier Estimates of the Probability of Survival.
P=0.96 for the comparison between patients assigned to receive albumin and those assigned to receive saline.

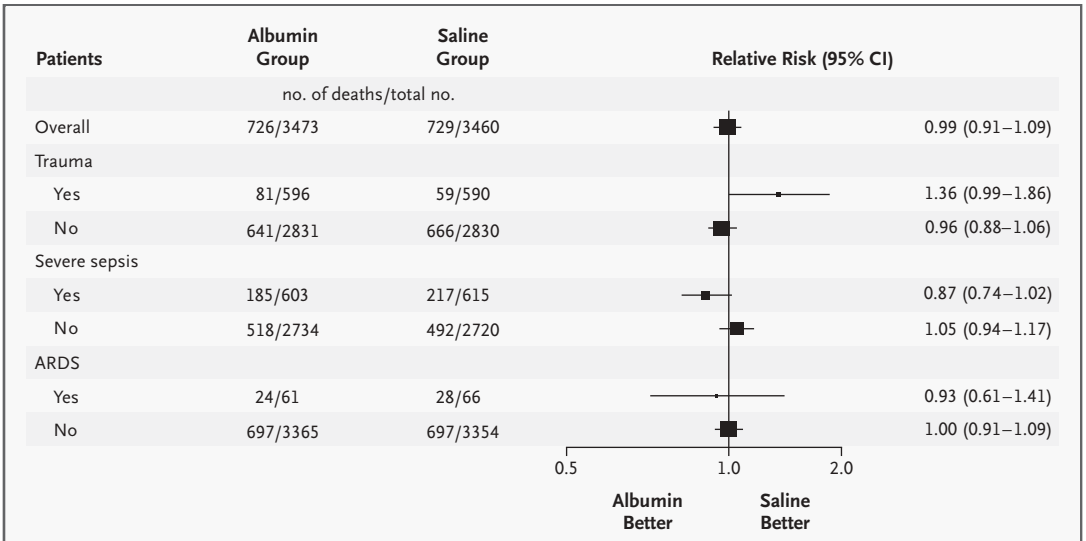

Figure 2. Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups.

The size of each symbol indicates the relative number of events in the given group. The horizontal bars represent the confidence intervals (CI). ARDS denotes the acute respiratory distress syndrome.

the ratio of albumin administered to saline administered was approximately 1:1.4. However, there was no significant difference in mean arterial pressure between the groups, and the differences in central venous pressure and heart rate were small. Thus, we believe that the patients in the two groups were resuscitated to similar and acceptable end points.

Our study was also a large, pragmatic study in a population of patients subject to a large number of concurrent interventions. We did not collect information on all concurrent interventions performed in the ICU. However, randomization was stratified according to participating institution, so that each institution treated equal numbers of patients assigned to saline or to albumin. As a result, we do not believe that an imbalance in concurrent interventions could have influenced the results.

Patients who were assigned to albumin received a significantly greater volume of packed red cells during the first two days of the study. The reasons for this difference remain speculative but may include greater hemodilution with albumin than with saline or increased blood loss with albumin due to transient alterations in coagulation. In a study of transfusion requirements in critically ill patients conducted by Hébert and colleagues, a liberal transfusion policy resulted in the administration of an excess of 3.0 units of packed red cells. This was associated with an increase in in-hospital mortality of 5.9 percentage points.[15] During the first four days of our study, the excess volume of fluid transfused in the albumin group averaged 71.0 ml per patient (less than one quarter of a unit). Accordingly, we do not believe this small excess in transfused volume influenced the results.

Given that our study had insufficient power to detect small but important differences in mortality among the predefined subgroups, the results provide only limited evidence that the treatment effects varied among these subgroups. The finding that patients with trauma might benefit more from resuscitation with saline than patients without trauma appears to be consistent with the results of a meta-analysis by Choi et al., who suggested that colloid resuscitation was associated with increased mortality in patients with trauma.[2] In our study, however, the increased relative risk of death among patients with trauma as compared with those without trauma resulted from a small excess number of deaths among patients who had trauma with brain injury, whereas the meta-analysis by Choi et al. did not include studies in patients with brain injury.[2]

In our study, the difference in mortality between the albumin and saline groups among patients with trauma involving brain injury should be interpreted

with caution. Patients with traumatic brain injury constituted only 7 percent of the study population, and the excess number of deaths in the albumin group was only 21. In large studies, such subgroup differences frequently occur by chance.[16] In addition, the rate of death from any cause over a 28-day period is not considered the most appropriate outcome measurement with which to assess treatment effects in patients with brain injury. Assessment of mortality and functional neurologic status at least six months after injury is recommended.[17] In contrast with our findings in patients with trauma, the comparison of the relative risk of death among patients with severe sepsis and those without severe sepsis provides limited evidence of a treatment effect that favors albumin in patients with severe sepsis. It should be noted that such differences between subgroups frequently occur by chance and that only specifically designed and appropriately powered studies can determine whether any such treatment effects are real.

In conclusion, our study provides evidence that albumin and saline should be considered clinically equivalent treatments for intravascular volume resuscitation in a heterogeneous population of patients in the ICU. Whether either albumin or saline confers benefit in more highly selected populations of critically ill patients requires further study. According to the current state of knowledge, factors that may influence the choice of resuscitation fluid for a critically ill patient include the individual clinician's preference, the tolerability of the treatment, its safety, and its cost.

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Dr. A. Davies and Dr. D. Stephens report owning shares in CSL.

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APPENDIX

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