Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Monday March 2, 2015
1800 HOURS

LOCATION:
Aqua Terra
1 Johnson Street

PRESENTING ARTICLES:
Dr. Tarit Saha & Dr. James Cheng

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SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
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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, who will be expected to contribute pending suspension of bar privileges.

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?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

Section Editor: **Martin J. London**

CME

The Impact of Anesthesiologists on Coronary Artery Bypass Graft Surgery Outcomes

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BACKGROUND: One of every 150 hospitalized patients experiences a lethal adverse event; nearly half of these events involves surgical patients. Although variations in surgeon performance and quality have been reported in the literature, less is known about the influence of anesthesiologists on outcomes after major surgery. Our goal of this study was to determine whether there is significant variation in outcomes between anesthesiologists after controlling for patient case mix and hospital quality.

METHODS: Using clinical data from the New York State Cardiac Surgery Reporting System, we conducted a retrospective observational study of 7920 patients undergoing isolated coronary artery bypass graft surgery. Multivariable logistic regression modeling was used to examine the variation in death or major complications (Q-wave myocardial infarction, renal failure, stroke) across anesthesiologists, controlling for patient demographics, severity of disease, comorbidities, and hospital quality.

RESULTS: Anesthesiologist performance was quantified using fixed-effects modeling. The variability across anesthesiologists was highly significant ($P < 0.001$). Patients managed by low-performance anesthesiologists (corresponding to the 25th percentile of the distribution of anesthesiologist risk-adjusted outcomes) experienced nearly twice the rate of death or serious complications (adjusted rate 3.33%; 95% confidence interval [CI], 3.09%–3.58%) as patients managed by high-performance anesthesiologists (corresponding to the 75th percentile) (adjusted rate 1.82%; 95% CI, 1.58%–2.10%). This performance gap was observed across all patient risk groups.

CONCLUSIONS: The rate of death or major complications among patients undergoing coronary artery bypass graft surgery varies markedly across anesthesiologists. These findings suggest that there may be opportunities to improve perioperative management to improve outcomes among high-risk surgical patients. (Anesth Analg 2015;120:526–33)

It is widely believed that anesthesia-related mortality has decreased dramatically during the past 25 to 50 years.[1] In a seminal study from the 1950s based on nearly 600,000 anesthetics, Beecher and Todd[2] estimated that anesthesia was the primary cause of death in 1 of 2680 cases. In its report, *To Err Is Human: Building a Safer Health Care System*, the Institute of Medicine (IOM) reports that anesthesia mortality rates have decreased from 1 in 10,000 to 1 in 200,000 to 300,000.[3] The accuracy of the low mortality estimate cited in the IOM report has been strongly challenged. Lagasse[4] estimates that the anesthesia mortality rate is 20 times higher than the IOM estimate: 1 death per 10,000 anesthetics, rather than 1 in 200,000.

Using a narrow definition of anesthesia-related outcomes, which includes only very rare complications such as esophageal intubation or cardiac arrest on induction, creates the impression that anesthesiology is safer than it actually is. If, in fact, the commonly cited statistic of 1 death in 200,000 to 300,000 anesthetics[3] is accurate, then the practical limits of what is achievable for anesthesia patient safety may already have been attained. However, if more common but still major complications, such as acute kidney injury, postoperative myocardial infarction (MI), respiratory failure, and stroke, are caused as much by anesthesia as by surgical management,[5] then surgery can be made safer by further improving anesthesia care. One of every 150 hospitalized patients experiences a lethal adverse event, and nearly half of these events involves surgical patients.[6] More than 50% of surgical adverse events may be preventable.[7] If surgical outcomes vary across anesthesiologists, then further improvements in

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Reprints will not be available from the authors.

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anesthesia management could improve surgical outcomes. Quantifying the variability in performance across anesthesiologists will provide us with an estimate of the potential improvements in surgical outcomes that might be attainable by improving anesthesia care.

The goal of this study was to determine whether there is significant variation in mortality and major complication outcomes among anesthesiologists in patients undergoing isolated coronary artery bypass graft (CABG) surgery using clinical data from the New York State Department of Health. Our goal is to help fill a critical gap in our understanding of the impact of anesthesiologists on surgical outcomes in patients undergoing high-risk surgery.

METHODS

Data Source

This study was based on population-based data from the New York State Cardiac Surgery Reporting System for patients undergoing isolated CABG surgery in New York State between 2009 and 2010. (Anesthesiologist identifiers were first available for the secondnhalf of 2009 and all of 2010).[a] The database includes comprehensive clinical information on patient demographics; encrypted[b] anesthesiologist, surgeon, and hospital identifiers; preoperative risk factors; and in-hospital mortality and major postoperative complications (stroke, Q-wave MI,[c] deep sternal wound infection, bleeding requiring reoperation, sepsis or endocarditis, gastrointestinal bleeding, perforation, or infarction; renal failure; respiratory failure; unplanned cardiac reoperation or interventional procedure).[8] This database does not include any information on physician (e.g., board certification, fellowship training) or hospital structural variables (teaching status, nurse staffing) and cannot be linked to outside datasets to obtain such information. These clinical data were collected prospectively by clinical data collectors and were submitted to the New York State Department of Health.[9] Comprehensive audit mechanisms are in place to ensure the accuracy and validity of the data.[9] Hospitals with a high reported prevalence of cardiac risk factors compared with the state average (e.g., a hospital reporting a high percentage of patients requiring emergency surgery) were subject to auditing.[9] Our study was approved by the IRB at the University of Rochester and by the New York State Department of Health. The requirement for informed consent was waived by the IRB at the University of Rochester.

Study Sample

We identified 14,390 patients who underwent isolated CABG. We excluded 63 cases with missing information on left ventricular ejection fraction and 19 with missing hematocrit values. We excluded 188 anesthesiologists with case volumes <50 (4817 cases). Because fixed-effects logistic regression is conditional on each panel member (anesthesiologist) having at least 1 success and 1 failure, we also excluded 21 anesthesiologists (1308 cases) with observed outcome rates equal to 0; their performance cannot be estimated using a fixed-effects model. Because high-quality physicians are less likely to have failures (death or major complications), they are less likely to be included in the estimation sample, resulting in selection bias. If the performance of these anesthesiologists was in fact close to perfect, then our analysis may have led to an underestimation of the variability in performance across anesthesiologists. Finally, hospitals in the resulting sample cohort with only 1 anesthesiologist meeting the above inclusion criteria were excluded (263 cases) because the anesthesiologist and hospital effect could not be separately identified. The final study cohort consisted of 7920 CABG cases managed by 91 anesthesiologists and 97 surgeons in 23 New York State hospitals.

Analysis

For our primary analysis, we defined the occurrence of a composite outcome of in-hospital mortality or major in-hospital complication (Q-wave MI,[d] renal failure,[e] or stroke[f]). We estimated a fixed-effects logistic regression model that included both anesthesiologist and hospital fixed-effects specified as intercept shifts. We assumed that anesthesiologists were nested within hospitals and then parameterized the anesthesiologist fixed effect so that each anesthesiologist was compared with the overall weighted average of the anesthesiologists working in the same hospital.[10] By specifying anesthesiologist fixed effects in this manner, we also controlled for hospital fixed effects. The adjusted odds ratio (AOR) for each anesthesiologist represents the odds of mortality or major complication attributable to a specific anesthesiologist relative to the average anesthesiologist working within the same hospital adjusted for patient risk conditional on hospital effects. We also assumed that anesthesiologists were randomly assigned to work with surgeons within their hospital so that the correlation between surgeon quality and anesthesiologist quality is small. We justified this assumption based on the widespread practice that cardiac anesthesiologists are assigned cases without consideration of surgeon quality. Our approach for estimating physician performance differs from the conventional approach for calculating the observed-to-expected mortality ratio of individual surgeons because the latter does not control for hospital quality[11] and therefore assumes that surgeon performance is the principal determinant of patient outcomes (other than severity of disease).

A priori, we included patient risk factors that are thought to be associated with death or major complications to include in our baseline prognostic model. To minimize omitted-variable bias, we created a nonparsimonious model for the composite outcome and retained some risk factors that did not achieve statistical significance but were judged to be clinically important. The predictor variables we included were age, sex, obesity (body mass index [BMI] ≥30), underweight (BMI ≤18.5), severity-of-disease (ejection fraction, emergency, unstable [requires pharmacologic or mechanical support to maintain arterial blood pressure or cardiac index], congestive heart failure, previous MI, calcified aorta, or previous open-heart surgery), and comorbidities (valvular disease, renal failure, cerebrovascular

[a]2010 data were the most recent data available.

[b]Anesthesiologists, surgeons, and hospitals are identified in the CABG database.

[c]Non--Q-wave MI is not included in the registry.

[d]New Q waves occurring within 48 hours after surgery.

[e]The need for temporary or permanent dialysis.

[f]Permanent new neurologic deficit.

Table 1. Characteristics of Patients Undergoing Isolated Coronary Artery Bypass Graft Surgery According to Anesthesiologist Performance

Patient characteristics	All patients (91 anesthesiologists, 7920 patients)	Anesthesiologist performance		*P* value
		High performance (23 anesthesiologists, 1889 patients)	Low performance (23 anesthesiologists, 1884 patients)	
Patient demographics				
Age, mean (y)	66.5	66.6	66.7	0.269
Female (%)	25.8	26.1	25.7	0.832
Body mass index (%)				
Underweight	0.76	0.64	0.69	0.84
Overweight	39.2	38.9	39.1	0.92
Obese	39.9	40.9	39.8	0.49
Severity of disease (%)				
Left ventricular ejection fraction (%)	48.9	48.9	48.7	0.73
Unstable	0.66	0.58	1.22	0.038
Emergency	3.91	4.24	3.61	0.32
Congestive heart failure	12.1	13.6	14.3	0.52
Previous MI <1 d	2.42	2.22	2.07	0.75
Previous MI 1–7 d	18.6	18.3	20.2	0.15
Previous MI 8–20 d	5.03	4.39	6.05	0.022
Previous MI 21 d or more	23.0	24.3	23.4	0.55
Calcified aorta	4.77	5.24	5.04	0.78
Open heart surgery (prior)	3.31	3.07	2.60	0.39
Comorbidities (%)				
Aortic stenosis, moderate or severe	0.77	1.01	0.96	0.88
Tricuspid insufficiency, moderate or severe	1.83	1.64	1.65	0.99
Renal failure, creatinine >1.5 mg/dL	9.32	9.95	9.13	0.39
Renal failure, requiring dialysis	2.23	2.91	1.91	0.045
Cerebrovascular disease	19.4	19.8	18.6	0.34
Peripheral vascular disease	12.5	13.2	11.8	0.18
COPD	26.9	26.6	26.8	0.90
Hematocrit	37.0	36.8	36.7	0.44
Composite risk (%)				
Low risk	50.0	48.5	48.7	0.692
Intermediate risk	25.0	25.3	24.2	
High risk	25.0	26.2	27.1	
Outcomes (%)				
Death or major complication	2.89	2.22	4.46	<0.001
Death	1.45	1.22	2.12	0.030
Q-wave myocardial infarction	0.19	0.16	0.32	0.32
Renal failure	0.82	0.37	1.27	0.002
Stroke (within 24 h of CABG)	0.45	0.32	0.58	0.22
Stroke (over 24 h)	1.01	0.79	1.22	0.19

Low-performance anesthesiologists were defined as those whose adjusted performance corresponded to the lower 25th percentile, and high-performance anesthesiologists were defined as those whose adjusted performance corresponded to the top 75th percentile.
Underweight = body mass index (BMI) ≤18.5; overweight = BMI ≥25 and BMI <30; obese = BMI ≥30.
COPD = chronic obstructive pulmonary disease; MI = myocardial infarction.

disease, peripheral vascular disease, chronic obstructive pulmonary disease, and hematocrit). The discrimination of the prognostic model was assessed using the C statistic. Model calibration was assessed using the Hosmer-Lemeshow statistic. Fractional polynomials were used to determine the optimal specification of continuous predictor variables to ensure that the model was linear in the logit for continuous variables.[12]

To quantify the independent contribution of very-low–performance (90th percentile), low-performance (75th percentile), average-performance (50th percentile), high-performance (25th percentile), and very-high–performance (10th percentile) anesthesiologists on the risk of death or major complications after CABG, we performed a simulation in which we calculated the predicted probability of death for all the patients in the sample cohort based on the estimated distribution of the anesthesiologist fixed-effects within hospitals. This approach simulates the hypothetical outcomes for the sample cohort, assuming that all patients receive care from anesthesiologists with the same level of performance leaving the hospital site unchanged. To further illustrate the importance of the anesthesiologist on clinical outcomes, we also estimated the impact of very-low–, low–, average–, high–, and very-high–performance anesthesiologists on groups of low- (risk ≤1.85%), intermediate- (1.85 < risk ≤3.37), and high-risk patients (>3.37%): corresponding to the 50th, 51st to 75th, and >75th percentile of risk. Individual risk (probability of death or major complications) was calculated after re-estimating the baseline model without including anesthesiologist and hospital fixed effects.

We performed additional analyses to examine the assumption that surgeon and anesthesiologist performance was not correlated. We used the same approach described in the Analysis section to estimate the risk-adjusted performance for individual surgeons using a fixed-effects logistic regression model that included a separate surgeon identifier for

each surgeon. The AOR for each surgeon represents the odds of mortality or major complications relative to the average surgeon working in the same hospital adjusted for patient risk and hospital effects. We then estimated the correlation coefficient for anesthesiologist and surgeon performance.

Data management and statistical analyses were performed using STATA SE/MP Version 13.0 (STATA Corp., College Station, TX). Robust variance estimators were used to account for the clustering of observations within anesthesiologists.[13] All statistical tests were 2 tailed, and P values <0.05 were considered significant.

RESULTS

There were no clinically significant differences in age, gender, BMI, severity of disease, or comorbidities between patients treated by high-performance and low-performance anesthesiologists (Table 1). Table 2 displays the AORs and 95% confidence intervals (CIs) for the composite outcome models. The fixed-effects model exhibited good discrimination, with a C statistic of 0.78 and acceptable calibration (P > 0.05) (Table 2). A caterpillar plot displaying the variability in anesthesiologist performance is shown in Figure 1.

After adjusting for patient characteristics and hospital effects, we found that the variability across anesthesiologists was highly significant (P < 0.001). In our simulation, we found that patients managed by low-performance anesthesiologists (adjusted rate 3.33%; 95% CI, 3.09%–3.58%) had a 1.8-fold higher risk of death or serious complications than patients managed by high-performance anesthesiologists (adjusted rate, 1.82%; 95% CI, 1.58%–2.10%) conditional on hospital effects (Table 3 and Fig. 2).

When patients were stratified by their baseline preoperative risk (low risk, bottom 50th percentile of risk; intermediate risk, 51st to 75th percentile; and high risk, >75th percentile), we still found an approximately 2-fold higher rate of death or major complications in patients treated by low-performance anesthesiologists compared with high-performance anesthesiologists across all risk categories (Table 3 and Fig. 3).

In our additional analysis to examine the assumption that surgeon and anesthesiology quality is uncorrelated, we found that the correlation between anesthesiologist and surgeon risk-adjusted performance was poor (correlation coefficient = 0.14).

DISCUSSION

To date, no large-scale study has analyzed the effects of different anesthesiologists on patient outcomes. In this population-based study of patients undergoing isolated CABG surgery in New York State, we found evidence of substantial variability in death or major complications across anesthesiologists. After adjusting for patient risk and hospital quality, we found that patients cared for by low-performance anesthesiologists had approximately a 2-fold higher risk of in-hospital death or major complications relative to patients cared for by high-performance anesthesiologists. Patients in our sample experienced an absolute risk of death or major complications that was approximately 1.5 percentage points higher if they were managed by a low-performance anesthesiologist compared with a high-performance anesthesiologist. The performance gap was observed across multiple hospitals and all patient risk groups. This

Table 2. Baseline Model Parameters

Risk factors	Patient risk factors		Patient risk factors + anesthesiologist fixed effects	
	AOR	*P*	AOR	*P*
Patient demographics				
Age	1.04 (1.02–1.05)	<0.001	1.04 (1.02–1.06)	<0.001
Body mass index				
Obese	1.32 (0.97–1.78)	0.073	1.34 (0.98–1.84)	0.066
Severity of disease				
Ejection fraction	0.99 (0.98–1.00)	0.11	0.99 (0.98–1.00)	0.13
Unstable	2.95 (1.33–6.52)	0.008	2.55 (1.10–5.93)	0.030
Emergency	1.60 (0.80–3.18)	0.18	1.69 (0.88–3.25)	0.11
Congestive heart failure	1.80 (1.24–2.61)	0.002	1.85 (1.25–2.74)	0.002
Previous MI <1 d	2.34 (1.10–4.97)	0.027	2.22 (1.02–4.83)	0.044
Previous MI 1–7 d	1.54 (1.00–2.38)	0.051	1.52 (0.96–2.40)	0.071
Previous MI 8–20 d	1.59 (0.99–2.54)	0.055	1.48 (0.91–2.40)	0.11
Previous MI 21 d or more	1.45 (1.00–2.13)	0.053	1.45 (0.99–2.15)	0.059
Calcified aorta	1.18 (0.78–1.78)	0.45	1.17 (0.75–1.82)	0.49
Open heart surgery	1.39 (0.75–2.56)	0.29	1.40 (0.75–2.58)	0.29
Comorbidities				
Renal failure, creatinine >1.5 mg/dL	0.98 (0.66–1.45)	0.90	0.97 (0.64–1.47)	0.89
Renal failure, requiring dialysis	1.82 (0.91–3.63)	0.088	2.02 (1.01–4.02)	0.045
Cerebrovascular disease	1.54 (1.15–2.06)	0.004	1.58 (1.17–2.15)	0.003
Peripheral vascular disease	1.75 (1.22–2.52)	0.003	1.81 (1.25–2.61)	0.002
COPD	1.44 (1.09–1.91)	0.010	1.45 (1.07–1.97)	0.015
Hematocrit	0.97 0.94–0.99)	0.009	0.97 (0.94-0.99)	0.006
Model performance				
C statistic	0.75		0.78	
Hosmer-Lemeshow statistic	6.18 (*P* = 0.63)		12.02 (*P* = 0.15)	

The anesthesiologist fixed-effects are not presented in the table.
AOR = adjusted odds ratio; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease.

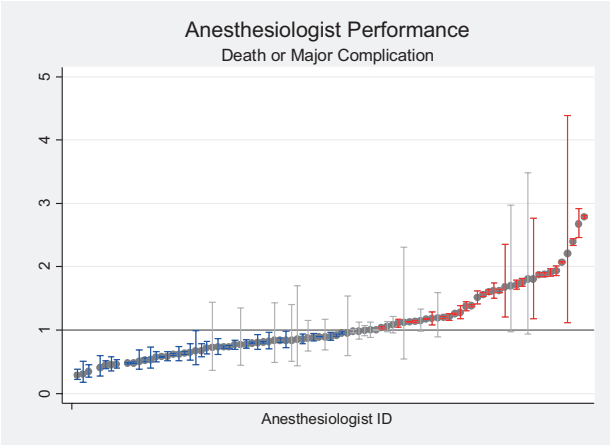

Figure 1. Plot of adjusted odds ratios (AORs) with 95% confidence interval (error bar) for individual anesthesiologists enrolled in the New York State cardiac surgery registry. Anesthesiologists with AORs significantly >1 are considered low-performance outliers, whereas anesthesiologists with AORs significantly <1 are considered high-performance outliers. This figure illustrates the variability of anesthesiologist performance and does not adjust for multiple comparisons.

performance gap is similar to the absolute difference in mortality between high- and low-volume surgeons performing CABG surgery.[14] To the best of our knowledge, this is the first large-scale study to systematically examine the impact of anesthesiologist performance on a patient's risk of experiencing death or a serious complication.

The variability of outcomes across anesthesiologists may not be surprising to experienced anesthesiologists and surgeons but is likely to be overlooked by most patients and many clinicians. General anesthesia is the induction of a reversible drug-induced coma accompanied by the loss of brainstem function, resulting in apnea and atonia in addition to cardiovascular depression.[15] The practice of anesthesia is complex and includes controlling the airway, respiratory care, hemodynamic monitoring and management, fluid and blood administration, pharmacologic manipulation, preoperative evaluation and optimization, and postoperative care, all while ensuring adequate pain control and unconsciousness. There is increasing evidence that anesthetic management may impact short-, intermediate-, and long-term outcomes.[16,17] Most major complications, such as acute kidney injury, postoperative MI, respiratory failure, and stroke, are likely to be affected by both anesthesia and surgical management.[5] The need for large clinical studies to develop a more robust evidence base for perioperative medicine is clear.[18] By highlighting the variability in outcomes across anesthesiologists, our findings reinforce the need to better understand the factors in the management of surgical patients that drive perioperative outcomes, including factors such as teamwork between anesthesiologists and surgeons.

Twenty years ago, DeAnda and Gaba[19] reported that the level of performance of anesthesiologists responding to simulated intraoperative critical incidents was highly variable. Nonetheless, there are little published data examining variability in surgical outcomes attributable to anesthesiologists. One early study, examining the association between perioperative myocardial ischemia and postoperative MI, reported that of 9 anesthesiologists, 1 was an outlier with respect to the incidence of postoperative MIs.[20] A second single-center study, based on 1300 CABG surgery patients, examined the impact of anesthesiologists on aspartate aminotransferase levels, a biomarker for MI. That study found that different anesthesiologists were associated with higher levels of aspartate aminotransferase than others.[21] However, that study used only very limited risk adjustment. Two studies have examined the impact of anesthesiologist board certification on mortality.[22,23] Silber et al.[23] documented that death and failure-to-rescue (death after a major complication) in patients undergoing general surgical or orthopedic procedures were higher in patients cared for by anesthesiologists who were not board certified.

Our findings indicate a clinically important gap in quality between low-performing and high-performing anesthesiologists. This observation has important implications for patient safety and quality of care. This performance gap is a previously unrecognized opportunity to improve surgical outcomes in the highest-risk patients. Widespread generation of massive amounts of digital data in electronic health records, including data on intraoperative events and processes of care, could be harnessed to provide the "Big Data" platform for comparative effectiveness research in surgical outcomes.[24] This will only be possible through data sharing in an environment of "open science."[25] Big data could be used to discover differences in decision making among anesthesiologists that result in such substantial differences in patient outcomes. Large national outcomes registries, such as the National Anesthesia Clinical Outcomes Registry,[5] American College of Surgeons National Surgical Quality Improvement Program,[26] and Society of Thoracic Surgeons (STS) registry,[27] should be merged with intraoperative data from anesthesia information management systems to create vast digital learning laboratories for discovering best practices in perioperative medicine. The partnership between STS and the Society of Cardiovascular Anesthesiologists, in which a cardiac anesthesia module was added to the STS registry, is a model for other collaborations between anesthesiologists and surgeons to create comprehensive outcome registries. Efforts to improve perioperative outcomes are most likely to succeed when surgeons and anesthesiologists join forces, such as in the FOCUS (Flawless Operative Cardiovascular Unified Systems) initiative,[28] to improve patient outcomes.

Our study has several potential limitations. First, we were not able to examine whether anesthesiologists identified as low performance remained low performance over time. The sample size available for this study was not sufficient to assess whether patients treated by anesthesiologists identified as performance outliers using data from previous years were as likely to experience adverse outcomes as those managed by nonoutlier anesthesiologists. The consistency of hospital or physician quality over time is a new approach for judging the validity of quality metrics. In theory, if performance measures capture hospital quality, then contemporary patients treated at hospitals identified as low performance using historical data should have worse outcomes than patients treated in average- or high-performance hospitals.[29,30] The ability of quality measures to predict future performance has been examined recently for noncardiac surgery[31] and common medical conditions[32] but is not yet a standard approach for evaluating the

Table 3. Coronary Artery Bypass Graft Surgery Outcomes Versus Anesthesiologist Performance Stratified by Patient Risk of Death or Major Complications

	Very-high performance 10th percentile (*n* =9)	High performance 25th percentile (*n* = 14)	Average performance 50th percentile (*n* = 45)	Low performance 75th percentile (*n* = 13)	Very-low performance 90th percentile (*n* = 10)
	Adjusted rate (95% CI)	Adjusted rate (95% CI)	Adjusted rate (95% CI)	Adjusted rate (95% CI)	Adjusted rate (95% CI)
Patient risk					
All patients	1.31 (1.28–1.34)	1.82 (1.58–2.10)	2.55 (2.5–2.55)	3.33 (3.09–3.58)	4.57 (3.10–6.66)
Low risk	0.49 (0.47–0.50)	0.68 (0.59–0.79)	0.91 (0.85–0.97)	1.29 (1.19–1.39)	1.81 (1.19–2.74)
Intermediate risk	1.09 (1.06–1.12)	1.53 (1.32–1.77)	2.03 (1.91–2.17)	2.86 (2.65–3.09)	4.01 (2.66–6.00)
High risk	3.18 (3.10–3.25)	4.39 (3.81–5.04)	5.73 (5.40–6.09)	7.86 (7.32–8.44)	10.7 (7.34–15.2)

The risk of major complications or death (%) of patients treated by very-low–, low-, average-, high-, and very-high–performance anesthesiologists, conditional on patient risk and hospital quality.

n = refers to the number of anesthesiologists in each group.

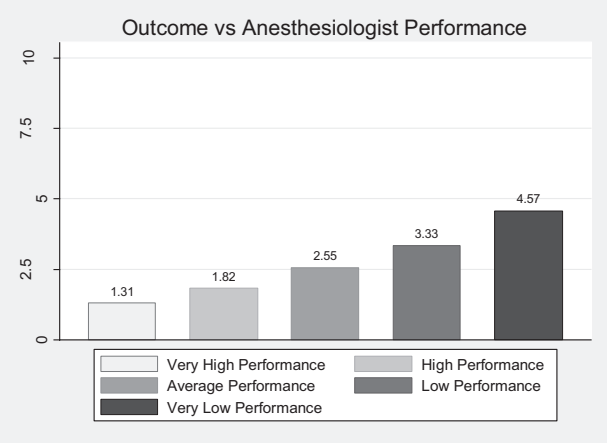

Figure 2. Estimated rate of death or major complications in sample cohort if all patients were treated by very-high–, high-, average-, low-, or very-low–performance anesthesiologists.

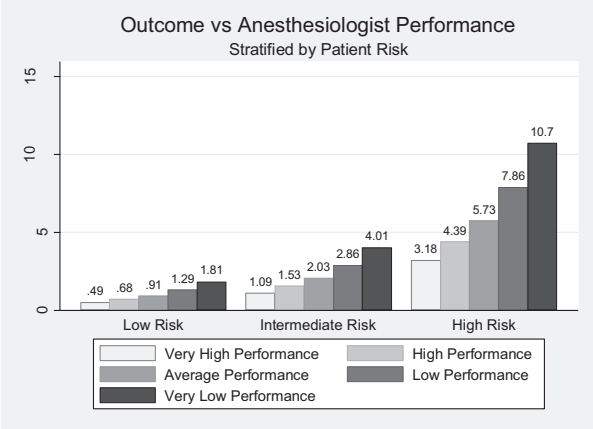

Figure 3. Estimated rate of mortality or major complications in sample cohort if all patients were treated by very-high–, high-, average-, low-, or very-low–performance anesthesiologists, stratified by patient risk.

performance of report cards. We have shown previously that past hospital performance predicts future performance for CABG surgery in New York State.[33] Although risk adjustment is an inexact science, the finding that the past performance of a hospital predicts the outcomes of future patients suggests that performance metrics have face validity. The recent finding by Birkemeyer et al.[34] that the independent assessment of surgeon technical skill is associated with risk-adjusted complication rates also suggests that quantifying the variability in physician performance has face validity.

Second, we excluded anesthesiologists with either low case volumes or no deaths or major complications. The adjusted outcomes for anesthesiologists with no bad outcomes cannot be estimated using fixed-effects modeling, whereas the adjusted outcomes for low-volume anesthesiologists would have been very imprecise and unlikely to reflect physician quality. Third, because it was not possible to simultaneously control for both surgeon and hospital effects within a fixed-effects model, we assumed that surgeon and anesthesiologist quality were not correlated, and that our estimate of anesthesiologist performance was independent of surgeon quality. We justified this assumption based on the widespread practice that cardiac anesthesiologists are assigned cases without consideration of surgeon quality, and the finding that surgeon and anesthesiologist performance were poorly correlated in our sample.

Fourth, it is possible that some of the variability in outcomes among anesthesiologists was caused by unobserved differences in severity of disease that were not adequately controlled by risk adjustment. The comprehensiveness of the New York State database and the good statistical performance of our multivariable model in our analyses mitigate, but do not eliminate, this limitation. Fifth, attending anesthesiologists frequently supervise anesthesiology residents, fellows, and certified registered nurse anesthetists, and these personnel were not included in our analytic model. To the degree that other anesthesiology personnel influence the management of CABG patients, this may bias the attending anesthesiologist's impact on mortality toward the null, leading us to underestimate the variability in anesthesiologist performance. Furthermore, the anesthesiologist of record may transfer his/her case to another attending anesthesiologist at the end of the day. By omitting other anesthesia personnel, our study may underestimate the overall impact of anesthesia management on CABG mortality. Sixth, the accuracy of the complication data in the New York State registry may not be as accurate as that of other data elements. We cannot exclude the possibility that some of the variation in outcomes across anesthesiologists may be attributable to systematic differences in coding accuracy of complications at the hospital level. Seventh, because our

data did not include information on anesthetic processes of care, we could not explore possible clinical explanations for this observed variation. In the future, it may be possible to link the New York State data with intraoperative information (e.g., drug, fluid, and blood product administration) to identify best practices in intraoperative management.

Finally, it could be argued that we should have used hierarchical as opposed to a fixed-effect modeling to quantify the variability in anesthesiologist performance. However, the use of hierarchical modeling and shrinkage estimators to assess provider quality is controversial. Proponents of hierarchical modeling argue that hierarchical modeling is better able to accommodate providers with low case volume. Although it is true that nonhierarchical models are likely to lead to more extreme values of the point estimates for low-volume providers, the wider CIs surrounding the point estimates for low-volume providers with "extreme" performance make it easy to differentiate between true outliers and providers with "average" performance when using nonhierarchical modeling. The other argument favoring the use of hierarchical modeling is that it properly adjusts for clustering of observations by providers.[35] However, robust variance estimators can be used to adjust for clustering of observations in nonhierarchical modeling.[13]

Hierarchical models have important disadvantages. The most important is that low-volume providers are "shrunk" to average performers and grouped with high-volume providers whose performance is truly average. The rationale for shrinkage is that, a priori, we know very little about the true performance of low-volume providers, and hence, we should "assume" that in the absence of sufficient provider case volume, low-volume providers have average performance. Some dispute this approach, arguing that because in many cases, low provider volumes are associated with worse outcomes, shrinkage toward the mean leads to biased estimates of performance. This approach is particularly problematic for public reporting, in which the goal is to promote transparency and accountability because low-volume providers who may be actually providing low-quality care tend to be classified as average performers because of the use of shrinkage estimators in hierarchical modeling.[36] On a practical level, because virtually all of the anesthesiologists are low-volume providers, their performance will be shrunk to the mean if we were to use hierarchical modeling in our analysis. Thus, the use of shrinkage estimators will present a biased estimate of the variation of anesthesiologist quality. Shrinkage estimators are a very conservative approach for assessing provider quality and will typically lead to very few providers being identified as quality outliers, even among a group of hospitals with high case volumes. Finally, hierarchical models require the assumption that there is no correlation between the patient characteristics and the quality of the anesthesiologists (or surgeons or hospitals), a set of assumptions not required with fixed-effects models. Thus, the assumptions of hierarchical modeling are frequently violated when used to estimate provider quality because hierarchical modeling assumes that the random effect (provider effect) is not correlated with patient risk. If, in fact, some anesthesiologists take care of sicker patients than others, then hierarchical modeling may lead to biased estimates of provider effects.

CONCLUSIONS

We report important and clinically significant variation in performance across anesthesiologists, thus demonstrating that the perioperative outcomes of patients undergoing CABG surgery might be improved by changes in management by anesthesiologists. We found that low-performance anesthesiologists had a nearly 2-fold higher rate of deaths or major complications compared with average-performance anesthesiologists. This observation should encourage anesthesiologists and surgeons to increase their efforts to develop evidence-based strategies for improving perioperative care. With the rapid adoption of intraoperative electronic medical records that capture granular information on all aspects of intraoperative management and patient physiology, it should be feasible to create and analyze vast digital libraries of clinical information and use these data to identify best practices in perioperative medicine. Overcoming the myth that anesthesiology is a "six sigma specialty"[37] that has minimal room for improvement should encourage anesthesiologists and surgeons to work collaboratively to further develop the science behind perioperative medicine and to successfully bridge the quality chasm in surgery.

DISCLOSURES

Name: Laurent G. Glance, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Laurent G. Glance has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Arthur L. Kellermann, MD, MPH.
Contribution: This author helped conduct the study and write the manuscript.
Attestation: Arthur L. Kellermann reviewed the analysis of the data and approved the final manuscript.
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Attestation: Yue Li reviewed the analysis of the data and approved the final manuscript.
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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Andrew W. Dick has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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REFERENCES

1. Gaba DM. Anaesthesiology as a model for patient safety in health care. BMJ 2000;320:785–8
2. Beecher HK, Todd DP. A study of the deaths associated with anesthesia and surgery: based on a study of 599,548 anesthesias in ten institutions 1948-1952, inclusive. Ann Surg 1954;140:2–35
3. Institute of Medicine (US) Committee on Quality of Health Care in America. Kohn LT, Corrigan JM, Donaldson MS, eds. To Err Is Human: Building a Safer Health System. Washington, DC: National Academies Press, 2000
4. Lagasse RS. Anesthesia safety: model or myth? A review of the published literature and analysis of current original data. Anesthesiology 2002;97:1609–17
5. Glance LG, Neuman M, Martinez EA, Pauker KY, Dutton RP. Performance measurement at a "tipping point." Anesth Analg 2011;112:958–66
6. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care 2008;17:216–23
7. Gawande AA, Thomas EJ, Zinner MJ, Brennan TA. The incidence and nature of surgical adverse events in Colorado and Utah in 1992. Surgery 1999;126:66–75
8. Cardiac Surgery Report, Adult – Instructions and Data Element Definitions Rennsselaer, NY: New York State Department of Health, 2009
9. Hannan EL, Cozzens K, King SB 3rd, Walford G, Shah NR. The New York State cardiac registries: history, contributions, limitations, and lessons for future efforts to assess and publicly report healthcare outcomes. J Am Coll Cardiol 2012;59:2309–16
10. DeLong ER, Peterson ED, DeLong DM, Muhlbaier LH, Hackett S, Mark DB. Comparing risk-adjustment methods for provider profiling. Stat Med 1997;16:2645–64
11. Hannan EL, Siu AL, Kumar D, Kilburn H Jr, Chassin MR. The decline in coronary artery bypass graft surgery mortality in New York State. The role of surgeon volume. JAMA 1995;273:209–13
12. Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parameteric modeling. Appl Stat 1994;43:429-67
13. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica 1980;48:817–30
14. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349:2117–27
15. Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med 2010;363:2638–50
16. Sessler DI. Long-term consequences of anesthetic management. Anesthesiology 2009;111:1–4
17. Hunt LP, Ben-Shlomo Y, Clark EM, Dieppe P, Judge A, MacGregor AJ, Tobias JH, Vernon K, Blom AW; National Joint Registry for England, Wales and Northern Ireland. 90-day mortality after 409,096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. Lancet 2013;382:1097–104
18. Devereaux PJ, Chan MT, Eisenach J, Schricker T, Sessler DI. The need for large clinical studies in perioperative medicine. Anesthesiology 2012;116:1169–75
19. DeAnda A, Gaba DM. Role of experience in the response to simulated critical incidents. Anesth Analg 1991;72:308–15
20. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14
21. Merry AF, Ramage MC, Whitlock RM, Laycock GJ, Smith W, Stenhouse D, Wild CJ. First-time coronary artery bypass grafting: the anaesthetist as a risk factor. Br J Anaesth 1992;68:6–12
22. Silber JH, Williams SV, Krakauer H, Schwartz JS. Hospital and patient characteristics associated with death after surgery. A study of adverse occurrence and failure to rescue. Med Care 1992;30:615–29
23. Silber JH, Kennedy SK, Even-Shoshan O, Chen W, Mosher RE, Showan AM, Longnecker DE. Anesthesiologist board certification and patient outcomes. Anesthesiology 2002;96:1044–52
24. Murdoch TB, Detsky AS. The inevitable application of big data to health care. JAMA 2013;309:1351–2
25. Ross JS, Krumholz HM. Ushering in a new era of open science through data sharing: the wall must come down. JAMA 2013;309:1355–6
26. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals. Ann Surg 2009;250:363–76
27. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1–coronary artery bypass grafting surgery. Ann Thorac Surg 2009;88:S2–22
28. Gurses AP, Kim G, Martinez EA, Marsteller J, Bauer L, Lubomski LH, Pronovost PJ, Thompson D. Identifying and categorising patient safety hazards in cardiovascular operating rooms using an interdisciplinary approach: a multisite study. BMJ Qual Saf 2012;21:810–8
29. Jha AK, Epstein AM. The predictive accuracy of the New York State coronary artery bypass surgery report-card system. Health Aff (Millwood) 2006;25:844–55
30. Glance LG, Mukamel DB, Osler TM, Dick AW. Ranking trauma center quality: can past performance predict future performance? Ann Surg 2014;259:682–6
31. Dimick JB, Staiger DO, Hall BL, Ko CY, Birkmeyer JD. Composite measures for profiling hospitals on surgical morbidity. Ann Surg 2013;257:67–72
32. Chen LM, Staiger DO, Birkmeyer JD, Ryan AM, Zhang W, Dimick JB. Composite quality measures for common inpatient medical conditions. Med Care 2013;51:832–7
33. Glance LG, Dick AW, Mukamel DB, Li Y, Osler TM. How well do hospital mortality rates reported in the New York State CABG report card predict subsequent hospital performance? Med Care 2010;48:466–71
34. Birkmeyer JD, Finks JF, O'Reilly A, Oerline M, Carlin AM, Nunn AR, Dimick J, Banerjee M, Birkmeyer NJ; Michigan Bariatric Surgery Collaborative. Surgical skill and complication rates after bariatric surgery. N Engl J Med 2013;369:1434–42
35. Krumholz HM, Brindis RG, Brush JE, Cohen DJ, Epstein AJ, Furie K, Howard G, Peterson ED, Rathore SS, Smith SC Jr, Spertus JA, Wang Y, Normand SL; American Heart Association; Quality of Care and Outcomes Research Interdisciplinary Writing Group; Council on Epidemiology and Prevention; Stroke Council; American College of Cardiology Foundation. Standards for statistical models used for public reporting of health outcomes: an American Heart Association Scientific Statement from the Quality of Care and Outcomes Research Interdisciplinary Writing Group: cosponsored by the Council on Epidemiology and Prevention and the Stroke Council. Endorsed by the American College of Cardiology Foundation. Circulation 2006;113:456–62
36. Mukamel DB, Glance LG, Dick AW, Osler TM. Measuring quality for public reporting of health provider quality: making it meaningful to patients. Am J Public Health 2010;100:264–9
37. Chassin MR. Is health care ready for Six Sigma quality? Milbank Q 1998;76:565–91, 510

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Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery

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Editor's key points

- The perioperative use of colloid solutions has potential benefits in cardiac surgical patients, but may affect coagulation.
- In this randomized study of 240 patients, the use of high volumes of colloid (50 ml kg^{-1} day^{-1}) had no effect on the primary outcome measure, blood loss from chest drains.
- However, blood transfusion requirements were lower when a crystalloids-only fluids regimen was used.
- The infusion of high volumes of colloids caused more haemodilution and had greater adverse effects on coagulation.

Background. Infusion of 5% human albumin (HA) and 6% hydroxyethyl starch 130/0.4 (HES) during cardiac surgery expand circulating volume to a greater extent than crystalloids and would be suitable for a restrictive fluid therapy regimen. However, HA and HES may affect blood coagulation and could contribute to increased transfusion requirements.

Methods. We randomly assigned 240 patients undergoing elective cardiac surgery to receive up to 50 ml kg^{-1} day^{-1} of either HA, HES, or Ringer's lactate (RL) as the main infusion fluid perioperatively. Study solutions were supplied in identical bottles dressed in opaque covers. The primary outcome was chest tube drainage over 24 h. Blood transfusions, thromboelastometry variables, perioperative fluid balance, renal function, mortality, intensive care unit, and hospital stay were also assessed.

Results. The median cumulative blood loss was not different between the groups (HA: 835, HES: 700, and RL: 670 ml). However, 35% of RL patients required blood products, compared with 62% (HA) and 64% (HES group; $P=0.0003$). Significantly, more study solution had to be administered in the RL group compared with the colloid groups. Total perioperative fluid balance was least positive in the HA group [6.2 (2.5) litre] compared with the HES [7.4 (3.0) litre] and RL [8.3 (2.8) litre] groups ($P<0.0001$). Both colloids affected clot formation and clot strength and caused slight increases in serum creatinine.

Conclusions. Despite equal blood loss from chest drains, both colloids interfered with blood coagulation and produced greater haemodilution, which was associated with more transfusion of blood products compared with crystalloid use only.

Keywords: blood loss; coagulation; colloids; fluid regime; Ringer's lactate; rotation thromboelastometry; transfusion

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Controversy exists about the optimal perioperative fluid management in patients undergoing major surgery. Prevention of fluid overload intraoperatively has been associated with less postoperative complications.[1] In addition, the transfusion of packed red blood cells (PRBCs) is associated with increased morbidity and mortality after cardiac surgery.[2] Thus, avoiding transfusion might also be important to improve outcome of patients undergoing cardiac procedures.

Crystalloids, in the form of Ringer's lactate (RL), and colloids such as hydroxyethyl starches and 5% human serum albumin (HA) are commonly used for intraoperative fluid management during heart surgery. The latter two have a more profound volume expansion effect than crystalloids and would therefore be more suitable for a restrictive fluid therapy.[3] However, hydroxyethyl starch solutions have been shown to impair coagulation[4 5] and renal function.[6–11] Six per cent hydroxyethyl starch 130/0.4 [Voluven®] (HES) is a newer generation tetrastarch formulation with a lower molecular weight, which might affect coagulation to a lesser degree than hydroxylethyl starch solutions with higher molecular weight.[12–15] However, a recent meta-analysis stated that insufficient data are available for the effect of HES on the bleeding tendency in cardiac patients.[16] In comparison with HES, HA has been used since the 1970s during cardiac surgery mainly for two reasons: first, HA is able to coat the fluid pathway surface and thereby reduces platelet activation and consumption

with concomitant release of inflammatory mediators.[3 17–19] Secondly, HA prevents a substantial decrease in colloid oncotic pressure.[20] Likewise, RL has also been used for many years during heart surgery, either as the sole replacement fluid or in combination with HA or HES.[21] Since large volumes are generally administered throughout the procedure, even RL might influence coagulation via dilution of coagulation factors.

We hypothesized that 6% HES 130/0.4 would increase blood loss from the chest drains. Thus, the main objective of our study was to compare external blood loss from chest drains between groups receiving HA 5%, 6% HES 130/0.4, or RL as the main infusion during cardiac surgery. Blood transfusions, total perioperative fluid balance, thromboelastometry variables, course of serum creatinine and platelet count, intubation time, intensive care unit (ICU), and hospital stay were also assessed.

Methods

Participants

This randomized, double-blind, single-centre trial, which was conducted over the course of four consecutive years at our department was approved by the institutional review board and reported to the national regulatory authority (Gov Identifier: NCT 01174719). All 240 patients provided written informed consent before inclusion. Inclusion criteria were: patients undergoing elective cardiovascular surgery [i.e. coronary artery bypass grafting (CABG), valve repair or replacement, and surgery of the ascending aorta] on cardiopulmonary bypass (CPB). Exclusion criteria were known allergy to hydroxyethyl starch or albumin, preoperative anaemia, emergencies, treatment with acetylsalicylic acid <3 days before surgery, GPIIbIIIa antagonists use <7 days before surgery, coagulation disorders [i.e. INR >1.2, activated partial thromboplastin time (aPTT) >40 s, platelet count <100 g litre^{-1}], BMI >40 kg m^{-2}, left ventricular ejection fraction $<20\%$, renal dysfunction defined as serum creatinine >1.5 mg dl^{-1}, proven heparin-induced thrombocytopenia, and danaparoid or lepirudin treatment during the month before the operation.

Randomization, fluid regimen, and blinding

Eligible patients were randomized into three groups comprising 80 patients each with the following fluid regimens:

HA group: 5% albumin up to 50 ml kg^{-1} day^{-1}, additional RL as required;
HES group: 6% HES 130/0.4 up to 50 ml kg^{-1} day^{-1}, additional RL as required;
RL group: RL up to 50 ml kg^{-1} day^{-1}, additional RL as required.

An independent IT specialist was in charge of randomization, which was performed using a random number generator. The local pharmacy prepared the study solutions that were supplied in identical 250 ml bottles. Blinding was performed with the help of opaque covers that were placed around the bottles and the infusion sets.

Procedures

Anaesthesia was induced with midazolam (0.1 mg kg^{-1}), propofol (1.0–1.5 mg kg^{-1}), fentanyl (3–10 μg kg^{-1}), and cisatracurium (0.2 mg kg^{-1}) and maintained with sevoflurane (target BIS value 40–50), and fentanyl (0.05–0.1 μg kg^{-1} min^{-1}). Fluid administration was started with 250–500 ml of the study solution during induction of anaesthesia. The CPB circuit was primed with 1500 ml study solution together with 5000 IE heparin, and 100 ml mannitol 20%. Patients received either aprotinin (10^6 IU after anaesthesia induction plus 10^6 IU added to the CBP prime) or tranexamic acid (either 1.0 or 1.5 g after anaesthesia induction plus the same dosage in the CPB prime according to the patient's body weight and renal function). Tranexamic acid was used as antifibrinolytic after November 2007 when sale of aprotinin was suspended by Bayer. After anticoagulation with heparin (300 IE kg^{-1}) and achieving an activated clotting time (ACT) >400 s, CPB was performed using non-pulsatile flow at 2.5 litre min^{-1} m^{-2}, a non-heparin-coated circuit, and a membrane oxygenator (Quadrox™, Maquet, Hirrlingen, Germany, or Dideco Compactflow™, Mirandola, Italy). Mild-to-moderate hypothermia was induced (30–34°C) and norepinephrine was given if necessary to maintain a mean arterial pressure >60 mm Hg. Buckberg cardioplegic solution was used for myocardial preservation. Additional RL was added to the extracorporeal circuit when filling of the CPB reservoir was insufficient. During and after weaning from CPB, transoesophageal echocardiography was used to monitor myocardial performance and the impact of fluid loading and inotropic support on ventricular function. Further fluid management and also vasopressors and/or inotropic use was at the discretion of the attending consultant and not controlled by protocol. All study cases were performed by experienced cardiac anaesthesia fellows supervised by senior cardiac anaesthesiologists. Intraoperative fluid therapy with study solution was restricted to two-thirds of the maximally allowed daily dose (i.e. 33.3 ml kg^{-1}). It was assumed that anaesthesia and surgery would require a greater fluid load than the immediate postoperative period. Additional fluid requirements were met with RL in order to avoid accidental overdosage of either of the two colloids. The last third of the study solution (i.e. 16.7 ml kg^{-1}) was kept for the initial volume replacement in the ICU that also guaranteed that the total permitted dose would not be administered within a short period of time.

Rotation thromboelastometry (ROTEM® Pentapharm CO, Munich, Germany) *ex vivo* coagulation variables were examined using predefined tests: INTEM (ellagic acid activated intrinsic pathway) and FIBTEM (with platelet inhibitor cytochalasin D, evaluating the contribution of fibrinogen to clot formation).[22] The samples were analysed within 120 s after blood was drawn from the central venous catheter and coagulation was initiated with activators using a semi-automated electronic pipette system according to the manufacturer's instructions. Coagulation was allowed to proceed for 50 min. Automatic ROTEM variables were: clotting time (CT), clot formation time (CFT), α-angle, maximum clot firmness (MCF), and clot lysis.

These variables have been validated using standard coagulation tests.[22 23] ROTEM quality control measures were undertaken weekly by our laboratory staff. Reference ranges for ROTEM thromboelastometry variables were taken from a multi-centre investigation.[24]

Blood transfusion was performed according to STS-SCA transfusion guidelines.[25 26] Transfusion triggers for the transfusion of PRBCs were: haemoglobin (Hb) concentrations of $\leq$7.0 g dl^{-1} during and $\leq$8.0–9.0 g dl^{-1} after CPB.

Administration of fresh-frozen plasma, platelets, and coagulation factors was based predominantly on ROTEM variables and the pre- and postoperative coagulation profile of each patient. After appropriate reversal of residual heparin, fresh-frozen plasma and factor concentrates were given in the presence of prolonged CT and CFT_{INT} and normal ACT. Fibrinogen was given when MCF_{FIB} was $<$8 mm, and platelets were transfused when MCF_{FIB} was $>$8 mm. In the ICU, Normotest® $>$1.5, aPTT $>$60 s, fibrinogen concentration $<$1 g litre^{-1}, and platelet count $<50\times10^9$ litre^{-1} prompted transfusion of fresh-frozen plasma, platelets, or both.

Outcome variables

The primary outcome variables were clinical bleeding based on chest tube drainage over the first 24 h after CPB. Secondary outcomes were transfusion of PRBCs, fresh-frozen plasma, platelets, fibrinogen, factor concentrate, changes in Hb, thromboelastometry variables, and the total amount of study solution, total amount of administered fluid, fluid balance, intubation time, and length of hospital stay. Furthermore, the units of PRBC transfused within the second and the sixth postoperative day (POD), and also the course of Hb, platelets, and creatinine until POD 6 were compared between the groups. Δ creatinine was calculated as maximal creatinine value within 48 h minus baseline creatinine.[27] Since aprotinine was replaced by tranexamic acid during the investigation period, we also compared utilization of these agents between the groups. Hb levels were compared at the start of anaesthesia (baseline), after release of the aortic cross-clamp (surgery), upon arrival in the ICU, 24 h after surgery, and on the morning of the sixth POD. The length of stay in the ICU and mortality within 90 days were recorded as safety variables.

Statistical analysis

The sample size calculation was based on data from our institutional data bank, where the actual blood loss from 99 CABG patients was found to be 714 ml with a standard deviation (SD) of 370 ml. The study was powered to detect a difference in blood loss of 185 ml (i.e. half SD) between the active control (RL) and HA or HES with a type I error rate of 0.05 and a power of 0.08 for a two-sided *t*-test with correction for multiple comparisons. Consequently, a sample size of 80 patients per group was required.

Data are given as mean (SD). Non-normally distributed variables are expressed as median (25% and 75% percentiles). Non-parametric statistical tests were used for analysis if no normal distribution could be achieved by log transformation.

Analyses of variance models were used for comparison of the log-transformed cumulative blood loss over 24 h after surgery, the infused study medication, and the cumulative postoperative fluid balance over 24 h between the three groups. Repeated-measures analyses of covariance (ANCOVA) models were used to test for differences in the log-transformed MCF_{FIB} and CFT_{INT} values between study groups, considering baseline values as covariates and time (arrival at the ICU *vs* 24 h after surgery) as repeated factor. Repeated-measure ANCOVA was also used for comparison of Hb, platelets, and creatinine levels between the groups, additionally considering values during surgery in the model. For all pair-wise comparisons between the study groups, the Tukey *post hoc* test was used to adjust for multiple comparisons. The non-parametric Kruskal–Wallis test was used to test for differences in non-study fluids, cumulative dose of study fluid expressed as ml kg^{-1} day^{-1}, crystalloid to colloid ratio, intubation time, urine output, and Δ creatinine values between the groups. The χ^2 test was used to compare frequencies of patients receiving PRBC, FFP, platelets, fibrinogen, and factor concentrates between study groups. All *P*-values are reported as results of two-sided tests and values of $<$0.05 were considered statistically significant.

Results

A total of 240 patients randomized into three groups were included in the study. Patients' characteristics and intra- and postoperative data are shown in Table 1. Four patients were excluded for the following reasons: one patient from the HA group developed urticaria after induction of anaesthesia and the study was terminated as a possible allergic reaction to the study solution could not be ruled out. Another three patients, two from the HA group and one from the RL group, were either haemodynamically unstable or became hypoxaemic after CPB and required either support with an intraaortic balloon pump or ECMO. Minor violations of the study protocol occurred in two patients. One patient mistakenly received 1000 ml Voluven® and another patient 600 ml of HA during the ICU stay within the study period, without being excluded from the study. Unblinding revealed that both patients were in the HES group. However, in the first patient, the cumulative amount of colloids (HES as study solution and additional Voluven®) did not exceed 50 ml kg^{-1} day^{-1}. In the second patient, the sum of the administered study solution and the given HA was also within the tolerable range of 50 ml kg^{-1} day^{-1}. Owing to inappropriate filling of an HA bottle with HES by our pharmacy, the HES group comprised 81 patients and the HA group only 79; of whom, three patients had to be excluded as mentioned above. The recruitment profile is depicted as a CONSORT flow diagram in Figure 1.

Although there was a trend towards lower blood loss over chest tubes in the RL group, the primary study endpoint, namely chest tube drainage over 24 h after surgery, was not significantly different between the groups (P=0.085; Table 2). There was, however, a significant group difference in the quantity of blood transfusion (P=0.0004). Patients in the RL group

Table 1 Patients' characteristics and perioperative data. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate; ESL, logistic EuroSCORE; BMI, body mass index; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; VR, valve replacement or reconstruction; Combined procedure: valve and CABG surgery, or double valve replacement or valve replacement with composite graft; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; ICU, intensive care unit; vasopressors use is defined according to SOFA score; RRT, renal replacement therapy. Values are either: numbers (*n*), percentages (%), means (SD), medians (25/75% percentile), or medians (lowest–highest value). *$P<0.05$ compared with colloid groups

	HA ($n=76$)	HES ($n=81$)	RL ($n=79$)
Patient characteristics			
Male/female (*n*)	53/23	52/29	61/18
Age (yr)	66 (23–85)	67 (28–87)	67 (24–87)
BMI (kg m^{-2})	27 (4)	27 (4)	27 (4)
ESL	5 (6)	6 (6)	5 (5)
LVEF (%)			
>50	33	34	33
30–50	29	36	35
<30	34	33	33
Type of surgery (%)			
CABG	37	33	30
VR	29	37	34
Combined procedure	32	32	36
Duration (min)			
Anaesthesia	333 (74)	328 (76)	314 (55)
CPB	107 (32)	99 (42)	105 (40)
ACC	70 (23)	64 (29)	71 (28)
Use of antifibrinolytics (*n*)			
Aprotinin	24	24	25
Tranexamic acid	52	55	54
Use of vasopressors (%)	70	75	72
Low	59	54	56
High	11	21	16
Postoperative data			
Time to extubation (min)	580 (455/735)	562 (485/824)	530 (450/725)
ICU stay (day)	1 (1/16)	1 (1/48)	1 (1/16)
Hospital stay (day)	14 (7/66)	14 (8/55)	13 (6/164)
Δ $Creatinine_{0-48\,h}$ (mg dl^{-1})	0.06 (−0.02/0.15)	0.02 (−0.05/0.11)	−0.02* (−0.13/0.07)
RRT (*n*)	2	1	0
Mortality 90 day (*n*)	2	1	0

received fewer PRBCs compared with HA ($P=0.0015$) and HES patients ($P=0.0002$). In addition, the percentage of patients receiving either PRBCs or any blood product was significantly lower in the RL group. In contrast, there was no difference for both variables when HA and HES patients were compared (Table 2). Most units of PRBC were given perioperatively during the first 24 h. There were no significant group differences in the number of PRBC units transfused within PODs 2–6 [HA: 2.04 (0.45); HES: 2.14 (0.79); RL: 2.15 (0.91) $P=0.544$]. Most PRBC units transfused during this period were ordered between POD 3 and 5. No significant inter-group differences were noted for transfused FFP and platelets. A greater percentage of patients in both colloid groups received fibrinogen. Regarding the amount of coagulation factor concentrates, no significant differences were found between the three groups.

Changes in Hb levels over time and between the groups were significantly different (Fig. 2). During surgery, Hb significantly declined from baseline in all groups. However, patients in the RL group showed the least decline during surgery ($P<0.0001$) and at arrival in the ICU ($P<0.0001$). Twenty-four hours after surgery, patients in the HA group presented with the lowest Hb values compared with the HES ($P<0.0001$) and the RL group ($P<0.0001$). No difference was observed between HES and RL patients at this time point. Likewise, no difference was noted in Hb values among the three groups on POD 6 [HA: 10.1 (1.3), HES: 10.3 (1.1) RL: 10.2 (1.1)]. Similar changes were found for platelet count until POD 6 (Fig. 3B).

ROTEM thromboelastometry variables are depicted in Table 3. MCF_{FIB} values decreased in all groups during surgery but remained within the reference range in the HA and the RL groups. The lowest value was observed in the HES group at arrival in the ICU ($P<0.0001$). An increase in MCF_{FIB} values was found in all groups between arrival in the ICU and 24 h after surgery ($P<0.0001$). Values in the HA group were

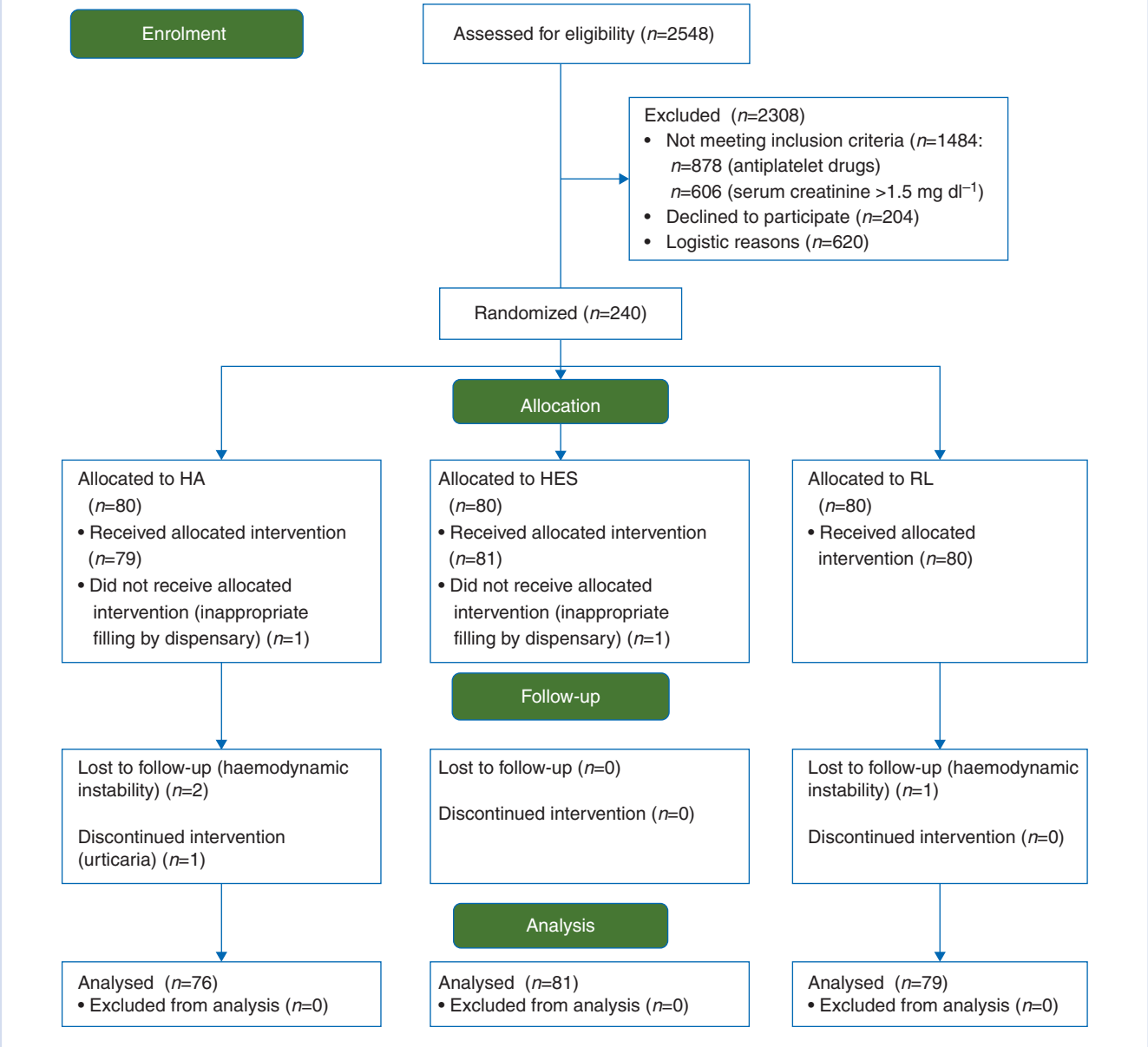

Fig 1 Consort 2010 flow diagram.

significantly lower at this time point when compared with the HES ($P=0.027$) and the RL group ($P<0.001$). No statistically significant difference was found between the RL and the HES groups ($P=0.083$). CFT_{Int} values increased intraoperatively. They were significantly different ($P<0.0001$) between the groups on ICU arrival with the highest values being detected in the HES group and the lowest in the RL group. Twenty-four hours after surgery, the HA group showed significantly prolonged CFT_{Int} than patients of the RL ($P<0.0001$) and the HES groups ($P=0.004$). No significant difference was found between the HES and the RL groups at this time ($P=0.193$).

We recorded statistically significant group differences regarding the total amount of infused study solution ($P=0.0024$). We observed no difference between the colloid groups but significant differences between HA and RL ($P=0.0051$), and also HES and RL, respectively ($P=0.0016$; Table 4). Similarly, the fluid balance was significantly different between the groups ($P<0.0001$). The HES group had a more positive total fluid balance than the HA group ($P=0.0116$), and the RL group an increased fluid balance compared with both HES ($P=0.0262$) and HA ($P<0.0001$). The crystalloid to colloid ratio was lower in the HA relative to the HES group ($P=0.028$). There were no group differences regarding urine output ($P=0.952$, Table 4). Serum creatinine levels were significantly higher in the HA group immediately after surgery when compared with the HES and RL groups and remained elevated

Table 2 Chest tube drainage and transfusions until the first 24 h after surgery. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate; PRBCs, packed red blood cells; FFP, fresh frozen plasma. Chest tube drainage and PRBCs are expressed as median (25/75% percentiles). All other variables are depicted as percentages. *P*-value as determined by univariate analysis

	HA ($n=76$)	HES ($n=81$)	RL ($n=79$)	*P*-value
Chest tube drainage (ml)	835 (545/1253)	700 (540/1090)	670 (455/1015)	0.0850
PRBCs (ml)	300 (0/600)	300 (0/600)	0 (0/300)	0.0004
PRBCs (units)	1 (0/2)	1 (0/2)	0 (0/1)	0.0004
PRBCs intraoperative (ml)	0 (0/600)	0 (0/600)	0 (0/300)	0.0119
PRBCs postoperative (ml)	0 (0/275)	0 (0/250)	0 (0/0)	0.0333
FFP (%)	8	10	5	0.5152
Platelets (%)	7	14	5	0.1186
Fibrinogen (%)	12	16	4	0.0383
Factor concentrate (%)	3	6	3	0.3921
Percentage of patients receiving				
PRBCs (%)	58	61	34	0.0013
Any blood product (%)	62	64	35	0.0003

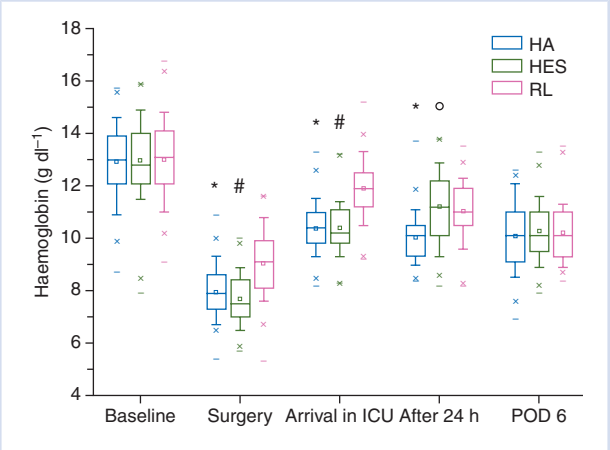

Fig 2 Course of Hb concentration. *$P<0.05$ HA *vs* RL; #$P<0.05$ HES *vs* RL; ○$P<0.05$ HES *vs* HA.

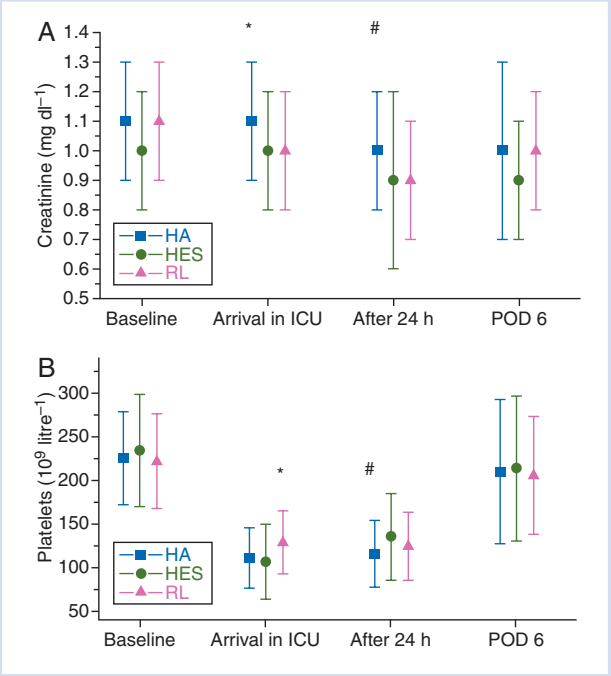

Fig 3 Time course of creatinine (A). *$P<0.01$ HA *vs* HES and RL; #$P<0.0248$ HA *vs* RL and platelets (B). *$P<0.0001$ RL *vs* HA and HES; #$P<0.0156$ HA *vs* HES.

in relation to the RL group 24 h after surgery (Fig. 3A). Δ Creatinine only increased in the colloid groups (Table 1).

Ten patients, seven in the HES and three in the HA group, required reexploration for bleeding, either on the day of surgery or on POD 1. One patient in the HES and one in the HA group, and also two patients of the RL group had reoperations after POD 5. Three patients died within 90 days, one in the HES group (1.2%) and two in the HA group (2.5%) (Table 1).

Usage of the two different antifibrinolytic agents was not significantly different between the groups ($P=0.982$; Table 1).

Discussion

This is the first randomized controlled trial that directly compares the new-generation 6% hydroxyethyl starch 130/0.4 [Voluven®] (HES) and HA against RL for fluid management during cardiac surgery. Two hundred and forty patients were included and randomized in three groups with 80 patients per group. We used large volumes of fluid, as 50 ml kg^{-1} day^{-1} is the upper recommended daily limit for HES. We deliberately chose this dosage to maximize the chance of demonstrating a significant effect. We found that fluid therapy with neither study solution caused increased external blood loss via chest tubes after operation. However, transfusion of PRBC and transfusion of any blood product during the first 24 h of the study were increased in both colloid groups, both intraoperatively and after operation.

Table 3 Thromboelastometry analysis. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate; CFT, clot formation time; MCF, maximal clot firmness. *P*-values are given as determined by univariate analysis. *$P<0.05$ RL *vs* HES; #$P<0.05$ HA *vs* RL; †$P<0.05$ HES *vs* HA; NS, not significant (according to *post hoc* analysis). Values are expressed as medians (25/75% percentile)

	HA ($n=76$)	HES ($n=81$)	RL ($n=79$)	*P*-value
CFT_{INT} (reference range: 40–100 s)				
Baseline	69 (57/82)	69 (57/81)	74 (64/83)	NS
Arrival in ICU	137 (111/175)#	185 (137/253)†	107 (85/138)*	<0.0001
After 24 h	100 (85/125)#	89 (75/112)†	84 (71/109)	0.0042
MCF_{FIB} (reference range: 9–25 mm)				
Baseline	19 (15/22)	19 (15/22)	18 (15/21)	NS
Arrival in ICU	10 (9/13)#	7 (6/10)†	13 (11/17)*	<0.0001
After 24 h	15 (13/19)#	18 (14/21)†	18 (16/20)	0.0266

Table 4 Perioperative fluids, fluid balance, and urine output. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate. Values for fluid balance are expressed as means (SD). Study solution, non-study fluids, cumulative doses of study solution as ml kg^{-1} day^{-1}, crystalloid to colloid ratio, and urine output as non-normally distributed values are expressed as medians (25/75% percentile). *P*-value is given for the univariate analysis. Non-study fluids are including crystalloid solutions, analgesics, antibiotics, and glucose–electrolytes. Fluid balance was calculated from infused study solution, non-study fluids, transfusions, fibrinogen, factor concentrate, and urine output and also blood loss from drainage

	HA ($n=76$)	HES ($n=81$)	RL ($n=79$)	*P*-value
Study solution (ml)				
Intraoperative	2500 (2250/3000)	2500 (2250/2750)	3000 (2500/3500)	<0.0001
Postoperative	750 (500/1000)	625 (500/1000)	750 (500/1000)	0.7717
Total	3250 (2750/3750)	3000 (2750/3500)	3500 (3000/4000)	0.0027
Non-study fluids				
Intraoperative	2800 (2250/3557)	2350 (1900/2900)	3450 (2474/4350)	<0.0001
Postoperative	4757 (3102/5407)	5450 (4380/7090)	5570 (4350/6800)	0.0003
Total	7504 (5378/9147)	7870 (6902/10 220)	8700 (7419/11 143)	0.0006
Fluid balance (ml)				
Intraoperative	3969 (1173)	3573 (1125)	4836 (1298)	<0.001
Postoperative	2272 (1874)	3755 (2454)	3565 (2190)	0.0114
Total	6228 (2456)	7365 (2980)	8336 (2810)	<0.0001
Study solution (ml kg^{-1} day^{-1})	44 (34/49)	42 (35/48)	47 (41/49)	0.0084
Crystalloid to colloid ratio	1.4 (0.9/2)	1.7 (1.2/2.5)	NA	0.0281
$Urine\ output_{0-24\ h}$ (ml)	2705 (2010/3455)	2734 (1980/3400)	2930 (2070/3540)	0.9518

Our results are in line with published studies and meta-analyses comparing crystalloids and colloids for cardiac surgery. Colloids at all times produced a less positive fluid balance yet postoperative bleeding often did not differ between crystalloids and colloids.[3 28] Studies comparing albumin with non-protein colloids during cardiac surgery were in the majority in favour of albumin regarding transfusion requirements and mortality.[29–31] However, in those studies, older generation starches were used which consisted of high molecular weight molecules with high molar substitution and the new-generation HES 130/0.4 6% was not included. In contrast, perioperative volume replacement with up to 50 ml kg^{-1} HES or 50 ml kg^{-1} 4% human serum albumin in children undergoing congenital heart surgery resulted in fewer allogenic blood transfusions in the HES group compared with the albumin group (median: 18 *vs* 29 ml kg^{-1}).[32] This was explained by a more profound haemodilution induced by 4% albumin. Both colloids were, however, not compared against a crystalloid solution.

In a recent meta-analysis by Navickis and colleagues, it was concluded that hydroxyethyl starches were associated with increased blood loss, reoperation for bleeding, and blood product transfusion in relation to albumin after adult cardiac surgery. However, insufficient data still are available for HES.[16] Previous trials investigating blood loss and transfusion requirements in adult cardiac surgery patients to date either compared HES with hydroxyethyl starch 200/0.5[33 34] or HES with crystalloids.[35 36] In two smaller studies ($n=15$ per group), Schramko and colleagues compared HES with Ringer's acetate and 4% gelatine[37] and with hydroxyethyl starch 200/0.5 and 4% albumin, respectively.[34] The latter, however, had no study arm with a crystalloid solution as an active control. No difference in blood loss and transfusion

requirement was found between HES and hydroxyethyl starch 200/0.5 given at a median dose of 33 ml kg^{-1}. After dual antiplatelet therapy, Lee and colleagues also could not find a difference in perioperative blood loss between crystalloids and HES when administered up to 30 ml kg^{-1}. Furthermore, Tiryakioglu and colleagues did not observe a negative effect on chest tube drainage and need for transfusion when 1500 ml HES was used for CPB prime instead of Ringer. Although the novel HES preparation was reported to have only a minimal effect on haemostasis,[15] HES impaired fibrin formation and clot strength after cardiac surgery following a total dose of 15 and 28 ml kg^{-1} but did not negatively affect blood loss.[34 37] Similarly, in the study by Choi and colleagues,[38] both 500 ml HES and 500 ml HA in the pump prime negatively affected blood coagulation in patients undergoing mitral valve surgery. In contrast to data published by Schramko and colleagues,[34] both colloids (i.e. HA as well) equally prolonged fibrin formation and fibrin build-up, depressed the α-angle, depressed the maximal amplitude, and shear elastic modulus. Presumably, the HES and HA groups therefore also showed no difference in intra- and postoperative blood loss, in the amount of co-administered colloids and crystalloids, in urine output, and in the amount of transfused units of PRBC, FFP, and platelets. Again, both colloids were not compared against a crystalloid solution.

In contrast, patients in this trial received up to 50 ml kg^{-1} study solution. Therefore, dilution of coagulation factors and also platelets and platelet dysfunction should even be more pronounced. This could account for the increased CFT_{INT} in both colloid groups and the decreased MCF_{FIB} in the HES group on arrival in the ICU. A slight increase in CFT_{INT} was also noticed in the RL group. The median CFT_{INT} values returned to normal in all groups after 24 h. Changes of CFT_{INT} and MCF_{FIB} were most distinct in the HES group, whereas in the RL group, changes were least. We chose these two ROTEM variables as they were most affected after infusion of HES—even at smaller doses.[37] All patients in our study routinely received antifibrinolytic drugs and hyperfibrinolysis was not observed in any patient. Whereas enhancement of fibrinolysis,[39] depletion of circulating coagulation factors[40] and reduced platelet count can be detected by ROTEM, impairment of platelet function due to CPB,[41] and the administration of HES[14 42] and HA[18] might be better tracked by specific platelet function tests.[41] As we did not perform such tests, we cannot comment on the impact of both colloids on platelet function in the present trial.

Nevertheless, the difference in transfusion requirements in our study can be explained either by the negative impact of the two colloids on blood coagulation but also by the more profound haemodiluting effect, which decreased Hb levels earlier below 7.0 and below 8–9 g dl^{-1}, which were our triggers to give PRBC during and after CPB, respectively. This would explain the fact that more units of PRBC were transfused in the HES and HA groups, both intraoperatively and immediately after operation. In contrast, fluid management with RL in this study was associated with the lowest rate for transfusion of blood products, but also with a more positive fluid balance. Albumin, HES, and RL are not considered equipotent intravascular volume expanders, but their relative potencies are variable. Crystalloids are generally considered to be less potent volume expanders than colloids, which initially increase plasma oncotic pressure, preload, and cardiac output. Albumin had a plasma volume expanding potency that is 40% higher than that of saline.[43] In relation to HA, the volume expansion effect of HES seems to be rather small.[10 11] Accordingly, fluid balance in this study was highest in the RL group and lowest in the HA group, whereas fluid balance in the HES group was intermediate. This is also reflected by the crystalloid to colloid ratio that was lower in the HA group in relation to HES. The volume expansion effect was mainly pronounced intraoperatively, where more non-study fluids had to be given in the RL group, particularly to maintain adequate filling of the CPB reservoir. Vasopressor use was not different between our groups, which is in line with previous studies that compared HES with control fluids.[11 44 45]

As has been shown previously, perioperative transfusion of PRBCs and the necessity for reexplorations are strongly associated with increased mortality, and also pulmonary and infectious complications.[2] Although mortality was low in our trial, which was not powered to detect group differences in mortality, the three patients who died within 90 days had been allocated to the HES and the HA groups, respectively. Similarly, reoperations due to bleeding complications were numerically higher in the two colloid groups.

This study has several limitations. It was conducted as a double-blind, randomized, controlled trial to detect significant group differences in external blood loss via the inserted chest tubes. It was not powered to detect differences in major complications (e.g. re-exploration, renal replacement therapy), and mortality. Much larger trials would have been needed to answer those questions. However, the observed positive Δ creatinine values in both colloid groups indicate that these patients were at increased risk for renal replacement therapy and greater mortality.[27] Furthermore, group differences in transfusion of any blood product and PRBC were highly significant, which signifies that the trial was sufficiently powered to detect such differences. Although there was no strict protocol for volume substitution when compared with vasopressor use, fluid administration in all groups was guided by the results from the transoesophageal echo exam and by clinical experience of a senior staff anaesthesiologist who had profound knowledge in transoesophageal echocardiography. The incidence of pruritus, a patient-relevant safety outcome variable, whose pathogenetic mechanism is tissue storage of starch molecules,[46] was not recorded. In a previous study that specifically addressed this issue, we found that 4.6% of patients treated with HES were affected.[47] However, several weeks may elapse after exposure to hydroxyethyl starches until onset of pruritus, which complicates proper assessment of groups at risk.

We conclude that all three fluid therapies did not affect our main outcome variable, namely chest tube drainage over 24 h after cardiac surgery with CPB. However, the transfusion rate of PRBCs or of any blood product was higher in both colloid groups, since the transfusion trigger was reached earlier due to more profound haemodilution in conjunction with a negative impact of HES and HA on blood coagulation. In addition, as Δ

creatinine increase solely occurred in these two groups, patients treated with these agents may also face an increased likelihood for kidney injury. Consequently, the use of large amounts of HES and HA in elective cardiovascular surgery, as it was the case in this trial, might be harmful, since it appears to be associated with an increased risk for blood transfusion and the need for renal replacement therapy.

Authors' contributions

K.S.: patient recruitment, data collection, and writing manuscript. E.M.B.: generation of study protocol, administration of study for Ethics committee and local authority, patient recruitment, writing and editing manuscript, and corresponding author. A.L.: generation of study protocol and editing manuscript. A.K.: statistical analysis. S.L.: data collection and preparation of tables and figures. M.D.: patient recruitment and manuscript editing. M.J.H.: generation of study protocol and fund raising.

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Declaration of interest

None declared.

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References

1 Holte K, Kehlet H. Fluid therapy and surgical outcomes in elective surgery: a need for reassessment in fast-track surgery. *J Am Coll Surg* 2006; **202**: 971–89

2 Surgenor SD, Kramer RS, Olmstead EM, *et al.* The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. *Anesth Analg* 2009; **108**: 1741–6

3 Russell JA, Navickis RJ, Wilkes MM. Albumin versus crystalloid for pump priming in cardiac surgery: meta-analysis of controlled trials. *J Cardiothorac Vasc Anesth* 2004; **18**: 429–37

4 Treib J, Haass A, Pindur G. Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997; **78**: 974–83

5 de Jonge E, Levi M, Buller HR, Berends F, Kesecioglu J. Decreased circulating levels of von Willebrand factor after intravenous administration of a rapidly degradable hydroxyethyl starch (HES 200/0.5/6) in healthy human subjects. *Intensive Care Med* 2001; **27**: 1825–9

6 Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; **348**: 1620–2

7 Dart AB, Mutter TC, Ruth CA, Taback SP. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *Cochrane Database Syst Rev* 2010; **1**: CD007594

8 Schortgen F, Girou E, Deye N, Brochard L. The risk associated with hyperoncotic colloids in patients with shock. *Intensive Care Med* 2008; **34**: 2157–68

9 Zarychanski R, Abou-Setta AM, Turgeon AF, *et al.* Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. *J Am Med Assoc* 2013; **309**: 678–88

10 Perner A, Haase N, Guttormsen AB, *et al.* Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124–34

11 Myburgh JA, Finfer S, Bellomo R, *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; **367**: 1901–11

12 Jungheinrich C, Sauermann W, Bepperling F, Vogt NH. Volume efficacy and reduced influence on measures of coagulation using hydroxyethyl starch 130/0.4 (6%) with an optimised in vivo molecular weight in orthopaedic surgery: a randomised, double-blind study. *Drugs R D* 2004; **5**: 1–9

13 Konrad CJ, Markl TJ, Schuepfer GK, Schmeck J, Gerber HR. In vitro effects of different medium molecular hydroxyethyl starch solutions and lactated Ringer's solution on coagulation using SONOCLOT. *Anesth Analg* 2000; **90**: 274–9

14 Franz A, Braunlich P, Gamsjager T, Felfernig M, Gustorff B, Kozek-Langenecker SA. The effects of hydroxyethyl starches of varying molecular weights on platelet function. *Anesth Analg* 2001; **92**: 1402–7

15 Kozek-Langenecker SA. Effects of hydroxyethyl starch solutions on hemostasis. *Anesthesiology* 2005; **103**: 654–60

16 Navickis RJ, Haynes GR, Wilkes MM. Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials. *J Thorac Cardiovasc Surg* 2012; **144**: 223–30

17 Palanzo DA, Zarro DL, Manley NJ, Montesano RM, Quinn M, Gustafson PA. Effect of surface coating on platelet count drop during cardiopulmonary bypass. *Perfusion* 1999; **14**: 195–200

18 Adrian K, Mellgren K, Skogby M, Friberg LG, Mellgren G, Wadenvik H. The effect of albumin priming solution on platelet activation during experimental long-term perfusion. *Perfusion* 1998; **13**: 187–91

19 DiNardo J. Physiology and techniques of extracorporeal circulation in the pediatric patient. *Pediatric Cardiac Anesthesia*, 4th Edn. Lippincott Williams & Wilkins, 2005; 228–52

20 Ohqvist G, Settergren G, Bergstrom K, Lundberg S. Plasma colloid osmotic pressure during open-heart surgery using non-colloid or colloid priming solution in the extracorporeal circuit. *Scand J Thorac Cardiovasc Surg* 1981; **15**: 251–5

21 Sade RM, Stroud MR, Crawford FA Jr, Kratz JM, Dearing JP, Bartles DM. A prospective randomized study of hydroxyethyl starch, albumin, and lactated Ringer's solution as priming fluid for cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1985; **89**: 713–22

22 Theusinger OM, Nurnberg J, Asmis LM, Seifert B, Spahn DR. Rotation thromboelastometry (ROTEM) stability and reproducibility over time. *Eur J Cardiothorac Surg* 2010; **37**: 677–83

23 Rugeri L, Levrat A, David JS, *et al.* Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *J Thromb Haemost* 2007; **5**: 289–95

24 Lang T, Bauters A, Braun SL, *et al.* Multi-centre investigation on reference ranges for ROTEM thromboelastometry. *Blood Coagul Fibrinolysis* 2005; **16**: 301–10

25 Ferraris VA, Brown JR, Despotis GJ, *et al.* 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg* 2011; **91**: 944–82

26 Ferraris VA, Ferraris SP, Saha SP, *et al.* Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg* 2007; **83**: S27–86

27 Lassnigg A, Schmid ER, Hiesmayr M, *et al.* Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? *Crit Care Med* 2008; **36**: 1129–37

28 Himpe D. Colloids versus crystalloids as priming solutions for cardiopulmonary bypass: a meta-analysis of prospective, randomised clinical trials. *Acta Anaesthesiol Belg* 2003; **54**: 207–15

29 Wilkes MM, Navickis RJ, Sibbald WJ. Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. *Ann Thorac Surg* 2001; **72**: 527–33

30 Sedrakyan A, Gondek K, Paltiel D, Elefteriades JA. Volume expansion with albumin decreases mortality after coronary artery bypass graft surgery. *Chest* 2003; **123**: 1853–7

31 Knutson JE, Deering JA, Hall FW, *et al.* Does intraoperative hetastarch administration increase blood loss and transfusion requirements after cardiac surgery? *Anesth Analg* 2000; **90**: 801–7

32 Hanart C, Khalife M, De Ville A, Otte F, De Hert S, Van der Linden P. Perioperative volume replacement in children undergoing cardiac surgery: albumin versus hydroxyethyl starch 130/0.4. *Crit Care Med* 2009; **37**: 696–701

33 Kasper SM, Meinert P, Kampe S, *et al.* Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with hydroxyethyl starch 200/0.5 at recommended doses. *Anesthesiology* 2003; **99**: 42–7

34 Schramko AA, Suojaranta-Ylinen RT, Kuitunen AH, Kukkonen SI, Niemi TT. Rapidly degradable hydroxyethyl starch solutions impair blood coagulation after cardiac surgery: a prospective randomized trial. *Anesth Analg* 2009; **108**: 30–6

35 Lee JS, Ahn SW, Song JW, Shim JK, Yoo KJ, Kwak YL. Effect of hydroxyethyl starch 130/0.4 on blood loss and coagulation in patients with recent exposure to dual antiplatelet therapy undergoing off-pump coronary artery bypass graft surgery. *Circ J* 2011; **75**: 2397–402

36 Tiryakioglu O, Yildiz G, Vural H, Goncu T, Ozyazicioglu A, Yavuz S. Hydroxyethyl starch versus Ringer solution in cardiopulmonary bypass prime solutions (a randomized controlled trial). *J Cardiothorac Surg* 2008; **3**: 45

37 Schramko A, Suojaranta-Ylinen R, Kuitunen A, Raivio P, Kukkonen S, Niemi T. Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: a prospective randomized trial. *Br J Anaesth* 2010; **104**: 691–7

38 Choi YS, Shim JK, Hong SW, Kim JC, Kwak YL. Comparing the effects of 5% albumin and 6% hydroxyethyl starch 130/0.4 on coagulation and inflammatory response when used as priming solutions for cardiopulmonary bypass. *Minerva Anestesiol* 2010; **76**: 584–91

39 Jamnicki M, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR. Compromised blood coagulation: an in vitro comparison of hydroxyethyl starch 130/0.4 and hydroxyethyl starch 200/0.5 using thrombelastography. *Anesth Analg* 1998; **87**: 989–93

40 Schols SE, Lance MD, Feijge MA, *et al.* Impaired thrombin generation and fibrin clot formation in patients with dilutional coagulopathy during major surgery. *Thromb Haemost* 2010; **103**: 318–28

41 Velik-Salchner C, Maier S, Innerhofer P, *et al.* An assessment of cardiopulmonary bypass-induced changes in platelet function using whole blood and classical light transmission aggregometry: the results of a pilot study. *Anesth Analg* 2009; **108**: 1747–54

42 Stogermuller B, Stark J, Willschke H, Felfernig M, Hoerauf K, Kozek-Langenecker SA. The effect of hydroxyethyl starch 200 kD on platelet function. *Anesth Analg* 2000; **91**: 823–7

43 Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350**: 2247–56

44 Bayer O, Reinhart K, Kohl M, *et al.* Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: a prospective sequential analysis. *Crit Care Med* 2012; **40**: 2543–51

45 Brunkhorst FM, Engel C, Bloos F, *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125–39

46 Bork K. Pruritus precipitated by hydroxyethyl starch: a review. *Br J Dermatol* 2005; **152**: 3–12

47 Base EM, Standl T, Lassnigg A, *et al.* Efficacy and safety of hydroxyethyl starch 6% 130/0.4 in a balanced electrolyte solution (Volulyte) during cardiac surgery. *J Cardiothorac Vasc Anesth* 2011; **25**: 407–14

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