

Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery

P.S. Myles, R. Bellomo, T. Corcoran, A. Forbes, P. Peyton, D. Story, C. Christophi, K. Leslie, S. McGuinness, R. Parke, J. Serpell, M.T.V. Chan, T. Painter, S. McCluskey, G. Minto, and S. Wallace, for the Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

Guidelines to promote the early recovery of patients undergoing major surgery recommend a restrictive intravenous-fluid strategy for abdominal surgery. However, the supporting evidence is limited, and there is concern about impaired organ perfusion.

METHODS

In a pragmatic, international trial, we randomly assigned 3000 patients who had an increased risk of complications while undergoing major abdominal surgery to receive a restrictive or liberal intravenous-fluid regimen during and up to 24 hours after surgery. The primary outcome was disability-free survival at 1 year. Key secondary outcomes were acute kidney injury at 30 days, renal-replacement therapy at 90 days, and a composite of septic complications, surgical-site infection, or death.

RESULTS

During and up to 24 hours after surgery, 1490 patients in the restrictive fluid group had a median intravenous-fluid intake of 3.7 liters (interquartile range, 2.9 to 4.9), as compared with 6.1 liters (interquartile range, 5.0 to 7.4) in 1493 patients in the liberal fluid group ($P < 0.001$). The rate of disability-free survival at 1 year was 81.9% in the restrictive fluid group and 82.3% in the liberal fluid group (hazard ratio for death or disability, 1.05; 95% confidence interval, 0.88 to 1.24; $P = 0.61$). The rate of acute kidney injury was 8.6% in the restrictive fluid group and 5.0% in the liberal fluid group ($P < 0.001$). The rate of septic complications or death was 21.8% in the restrictive fluid group and 19.8% in the liberal fluid group ($P = 0.19$); rates of surgical-site infection (16.5% vs. 13.6%, $P = 0.02$) and renal-replacement therapy (0.9% vs. 0.3%, $P = 0.048$) were higher in the restrictive fluid group, but the between-group difference was not significant after adjustment for multiple testing.

CONCLUSIONS

Among patients at increased risk for complications during major abdominal surgery, a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen and was associated with a higher rate of acute kidney injury. (Funded by the Australian National Health and Medical Research Council and others; RELIEF ClinicalTrials.gov number, NCT01424150.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Myles at the Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, Commercial Rd., Melbourne, VIC 3004, Australia, or at p.myles@alfred.org.au.

*A list of participating centers and investigators in the RELIEF trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 10, 2018, at NEJM.org.

N Engl J Med 2018;378:2263-74.

DOI: 10.1056/NEJMoa1801601

Copyright © 2018 Massachusetts Medical Society.

EACH YEAR, AT LEAST 310 MILLION patients undergo major surgery worldwide,¹ procedures that involve the administration of intravenous fluids. Clinicians have traditionally administered generous amounts of intravenous fluids perioperatively to correct for preoperative fasting and other fluid deficits, anesthesia-induced vasodilation, hemorrhage, and accumulation of fluid in extravascular spaces² and to enhance tissue oxygen delivery and maintain urine output.³⁻⁵ Occult hypovolemia may occur in up to 60% of such patients.^{4,6,7}

Traditional intravenous-fluid regimens that are administered during abdominal surgery deliver up to 7 liters of fluid on the day of surgery.⁸⁻¹⁰ Such regimens can lead to tissue edema and weight gain of 3 to 6 kg.^{8,11,12} Some small trials have shown that a more restrictive fluid regimen led to fewer complications and a shorter hospital stay,^{9,11,13} and recent consensus statements support fluid restriction.^{12,14,15} Restricting fluids to achieve zero balance is also a key component of enhanced recovery after surgery (ERAS) pathways, a perioperative care guideline that is designed to promote early recovery among patients undergoing major surgery.^{12,14,16} However, the evidence for fluid restriction during and immediately after abdominal surgery is inconclusive.^{12,15-17} Fluid restriction could increase the risk of hypotension and decrease perfusion in the kidney and other vital organs, leading to organ dysfunction, but excessive intravenous-fluid infusion may increase the risk of pulmonary complications,¹⁸ acute kidney injury,¹⁹ sepsis,²⁰ and poor wound healing.²¹

Since the most effective intravenous-fluid regimen is unclear,^{12,22} we conducted the Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) trial to compare a restrictive fluid regimen with a more traditional (liberal) regimen in patients who had an increased risk of complications while undergoing major abdominal surgery. Our primary hypothesis was that a restrictive fluid regimen in adults undergoing such surgery would lead to a lower rate of complications and a higher rate of disability-free survival than a liberal fluid regimen.²²

METHODS

TRIAL DESIGN

The RELIEF trial was an international, randomized, assessor-blinded trial comparing a restric-

tive intravenous-fluid regimen with a liberal regimen that represented traditional care in patients undergoing major abdominal surgery. The rationale and design of our trial have been reported previously.²² The trial was funded by the Australian National Health and Medical Research Council, the Health Research Council of New Zealand, the Australian and New Zealand College of Anaesthetists, and Monash University. The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each site.

The members of the steering committee (who are listed in the Supplementary Appendix, available at NEJM.org) designed the trial, gathered and analyzed the data, prepared the manuscript, and together with their coauthors made the decision to submit the manuscript for publication. The members of the steering committee vouch for the accuracy and completeness of the data set and adherence to the trial protocol and statistical analysis plan. There was no commercial involvement in the trial.

PATIENT SELECTION AND RANDOMIZATION

We studied adults who had an increased risk of complications while undergoing major abdominal surgery that included a skin incision, an expected operative duration of at least 2 hours, and an expected hospital stay of at least 3 days. Surgical-risk criteria included an age of at least 70 years or the presence of heart disease, diabetes, renal impairment, or morbid obesity. (Details regarding the categories of increased risk are provided in the Supplementary Appendix.) Patients were excluded if they were undergoing urgent or time-critical surgery, liver resection, or less extensive surgery (e.g., laparoscopic cholecystectomy) or if they had end-stage kidney failure requiring dialysis. All the patients provided written informed consent.

After enrollment, on the day of surgery, patients were asked to complete the 12-item World Health Organization Disability Assessment Schedule (WHODAS).²³ They were then randomly assigned in a 1:1 ratio to a trial group in permuted blocks and stratified according to site and planned postoperative destination (critical care or hospital ward) by means of a Web-based service.

TRIAL TREATMENTS

The liberal intravenous-fluid regimen was designed to reflect traditional practices for abdomi-

nal surgery.^{8-10,24,25} A bolus of a balanced salt crystalloid solution was administered at a dose of 10 ml per kilogram of body weight during the induction of anesthesia, followed by a dose of 8 ml per kilogram per hour until the end of surgery. The perioperative dose could be further reduced after 4 hours if clinically indicated. For patients with a body weight of more than 100 kg, fluid volumes were calculated on the basis of a maximal body weight of 100 kg. Fluid infusion was continued postoperatively at a dose of 1.5 ml per kilogram per hour for at least 24 hours, but this dose could be reduced if there was evidence of fluid overload and no hypotension, or increased if there was evidence of hypovolemia or hypotension.

The restrictive intravenous-fluid regimen was designed to provide a net zero fluid balance.^{9,11,14} Induction of anesthesia was accompanied by an intravenous-fluid bolus of no more than 5 ml per kilogram; no other intravenous fluids were to be administered before surgery unless indicated if using a goal-directed device (esophageal Doppler or pulse wave analyzer). An infusion of a balanced salt crystalloid solution at a dose of 5 ml per kilogram per hour was administered until the end of surgery. Intravenous fluids were continued postoperatively at a dose of 0.8 ml per kilogram per hour. The rate of postoperative fluid replacement could be adjusted as outlined for the liberal fluid group, except that the use of vasopressors could first be considered for treating hypotension without evidence of hypovolemia. The total administration of fluid during the first 24-hour period was expected to be approximately half that in the liberal fluid group.

Bolus colloid or blood could be used intraoperatively in the two groups to replace blood loss (milliliter for milliliter). Alternative fluid types (other crystalloid, dextrose, or colloid) and electrolytes were allowed postoperatively to account for local preferences and blood biochemical findings. Oliguria was not used as an indication for the additional administration of intravenous fluid. All other perioperative care was performed according to the discretion and practices of local clinicians (see the Supplementary Appendix).

BLINDING AND DATA QUALITY

The attending anesthesiologist and most medical and nursing staff members who were caring for patients on the ward had knowledge of the group assignments. All research staff members

who were responsible for the primary outcome assessment were not aware of group assignments.

Members of a clinical end-points committee who did not participate in the trial adjudicated all secondary outcome events in a blinded manner. The committee members conducted trial-center visits with random audits during the trial, and a data-quality committee monitored data completion and accuracy. An independent data safety and monitoring committee monitored the trial for safety, which included a review of the results of a formal interim analysis that was performed after 1632 patients had undergone randomization.

MEASUREMENTS AND PATIENT FOLLOW-UP

Patients were followed during their hospital admission and up to 1 year after surgery.²² We measured the quality of the recovery of each patient using a validated 15-item quality-of-recovery scale (QoR-15).²⁶ On day 30, the medical records of all the patients were reviewed, and the patients were contacted to ascertain whether any of the primary or secondary outcomes had occurred. Research staff members collated source documentation for any outcome events. The QoR-15 and WHODAS questionnaires were repeated on day 30,²³ and the WHODAS questionnaire was repeated at 3 months, 6 months, and 12 months after surgery to ascertain survival status and new-onset disability. Source documentation was required to confirm the occurrence of surgical-site infection, pneumonia, or other septic complications up to 30 days after surgery; renal-replacement therapy up to 90 days; and death during the first year (see the Supplementary Appendix).

TRIAL OUTCOMES

The primary outcome was disability-free survival up to 1 year after surgery. Disability was defined as a persistent impairment in health status (lasting ≥ 6 months), as measured by a score of at least 24 points on the WHODAS questionnaire, which reflects a disability level of at least 25% (the threshold point between “disabled” and “not disabled”).^{23,27} The WHODAS questionnaire was completed by the patient or by a proxy (a spouse or caregiver) if the patient was not able to complete it. The date of onset of any new disability was recorded (see the Supplementary Appendix).

The secondary outcomes were acute kidney injury, a composite of 30-day mortality or major septic complications (sepsis, surgical-site infec-

tion, anastomotic leak, or pneumonia), serum lactate level (at 6 and 24 hours), peak C-reactive protein level, blood transfusion, duration of stay in the intensive care unit (ICU) and hospital, unplanned admission to the ICU, and quality of recovery. Acute kidney injury was defined according to the criteria of the Kidney Disease: Improving Global Outcomes group, on a scale of 1 to 3, with higher values indicating increased severity.²⁸ We also recorded the incidence of renal-replacement therapy up to day 90. We adjusted creatinine measurements on day 1 and day 3 according to the patient's fluid balance at 1 day and 3 days after surgery (see the Supplementary Appendix).^{22,29}

STATISTICAL ANALYSIS

We performed all the analyses in a modified intention-to-treat population, which included all the patients who had undergone both randomization and induction of general anesthesia for eligible surgery. All the patients were followed for the duration of the trial, unless they withdrew consent. In the latter case, data were censored at the time that consent was withdrawn.

With an expected probability of 1-year disability-free survival of 65%^{30,31} and a type I error of 0.05, we calculated that the enrollment of 2650 patients (with 850 events of death or disability) was required to provide a power of 90% to detect a hazard ratio of 0.80 using the log-rank test. The sample size was inflated to 2800 patients to account for withdrawals and loss to follow-up. The steering committee met on June 30, 2016, to discuss the results of a review by the data-quality committee and the accruing incidence of disability. With the randomization of 2578 patients (1443 with complete follow-up), 300 primary outcome events had occurred, with a greater-than-expected probability of 1-year disability-free survival of 85%. We therefore increased the sample size to 3000 (with ≥ 380 events) to provide a power of 80% to detect a hazard ratio of 0.75. In actuality, 533 events were observed in the trial (event-free rate, 82%), which provided a power of 80% to detect a hazard ratio of 0.78.

We used the Kaplan–Meier method to calculate the probability of the primary outcome. Hazard ratios for the time until the occurrence of disability or death between the two groups were estimated with the use of a Cox proportional-hazards model, in which data for patients

without an event were censored at the date of the last contact, with assessment of proportionality of hazards based on Schoenfeld residuals testing (see the Supplementary Appendix). Analyses of the time until death or a new onset of disability were performed similarly.

For outcomes that were measured on a binary scale, we used log-binomial regression to estimate risk ratios directly or exact logistic regression to approximate these values if the number of events in either group was fewer than 10. In the analyses of end points regarding acute kidney injury, we used multiply imputed fluid-balance measurements if such values were missing (see the Supplementary Appendix). Outcomes regarding the duration and length of hospital stay in the two groups were compared with the use of the Wilcoxon–Breslow–Gehan test, with data censored at 30 days and in-hospital deaths assigned the longest duration of stay. Continuous outcomes were analyzed with the use of linear regression with robust standard errors; these were first log-transformed if the values were right-skewed, or median regression was used if the values were left-skewed. A post hoc procedure to control for multiple testing was applied to all secondary outcomes with the use of the Holm–Bonferroni method,³² with a family-wise significance level of 0.049 to account for the interim analysis. Sensitivity analyses with respect to missing data are provided in the Supplementary Appendix.

Data for patients were analyzed in subgroups that included sex, age quartile, location of trial center (country), presence or absence of colorectal surgery, and use or nonuse of a goal-directed device. Analyses of heterogeneity of effects across subgroups were performed with the use of treatment-by-covariate terms added to the Cox regression models.

RESULTS

PATIENT ENROLLMENT AND FOLLOW-UP

From May 2013 through September 2016, a total of 5223 patients met the eligibility requirements for enrollment at 47 centers in seven countries. Of these patients, we randomly assigned 3000 patients to a restrictive fluid regimen (1501 patients) or a liberal fluid regimen (1499 patients) (Table S1 and Fig. S1 in the Supplementary Appendix). Of these patients, 2983 (99.4%) met the

inclusion criteria for the modified intention-to-treat population (1490 in the restrictive fluid group and 1493 in the liberal fluid group). The mean number of patients per site was 64 (range, 1 to 227). The mean age was 66 years, 43% underwent colorectal surgery, and 64% underwent cancer surgery. There were no significant differences between the groups at baseline (Table 1, and Table S2 in the Supplementary Appendix). Among the patients who had undergone randomization, 1-year outcome data were available for 2901 (96.7%) (Table 1, and Fig. S1 in the Supplementary Appendix).

TRIAL TREATMENT

The volumes of fluids that were administered to patients in each group are presented in Table 2, and in Tables S3 to S5 in the Supplementary Appendix. During surgery, the median rate of fluid infusion was 6.5 ml per kilogram per hour (interquartile range, 5.1 to 8.4) in the restrictive fluid group and 10.9 ml per kilogram per hour (interquartile range, 8.7 to 13.5) in the liberal fluid group. On postoperative day 1, the median rate of fluid infusion was 0.9 ml per kilogram per hour (interquartile range, 0.7 to 1.2) in the restrictive fluid group and 1.5 ml per kilogram per hour (interquartile range, 1.2 to 1.7) in the liberal fluid group.

Selected ERAS elements that were aimed at improving outcomes were not clinically different across groups (Table S6 in the Supplementary Appendix). Patients in the restrictive fluid group were more likely than those in the liberal fluid group to receive vasopressor support ($P=0.02$), have lower urine output ($P<0.001$), and have a higher incidence of oliguria or anuria ($P<0.001$) but were less likely to require red-cell transfusion ($P=0.02$) or gain weight during the first 2 days after surgery (Table S7 in the Supplementary Appendix).

PRIMARY OUTCOME

The median follow-up time was 366 days in each group. The rate of disability-free survival at 1 year was 81.9% in the restrictive fluid group and 82.3% in the liberal fluid group (hazard ratio for death or disability, 1.05; 95% confidence interval, 0.88 to 1.24; $P=0.61$) (Table 3 and Fig. 1, and Fig. S2 in the Supplementary Appendix). Death or persistent disability occurred in 267 patients (95 deaths and 172 cases of persistent disability)

in the restrictive fluid group and in 261 patients (96 deaths and 165 cases of persistent disability) in the liberal fluid group. The effect of restrictive fluid therapy on the risk of disability-free survival was consistent across subgroups, including planned use of a goal-directed device ($P=0.37$), with the exception of sex and country, including a significant between-group difference among residents of New Zealand (Fig. 2). The distributions of baseline variables in female patients and residents of New Zealand are provided in Tables S8 and S9 in the Supplementary Appendix, respectively.

SECONDARY OUTCOMES

Acute kidney injury occurred in 124 patients (8.6%) in the restrictive fluid group and in 72 patients (5.0%) in the liberal fluid group ($P<0.001$), as calculated from the average of 10 multiply imputed data sets (Table 3). Renal-replacement therapy was performed in 13 patients (0.9%) and 4 patients (0.3%), respectively (unadjusted $P=0.048$; threshold level for statistical significance after adjustment for multiple comparisons, $P=0.004$) (Table 3, and Table S12 in the Supplementary Appendix). The risk of acute kidney injury was largely unaffected by the assigned treatment if postoperative creatinine values were not adjusted according to fluid balance or with the use of additional methods to account for missing data (Tables S10 and S11 in the Supplementary Appendix).

Septic complications or death up to 30 days after surgery occurred in 323 patients (21.8%) in the restrictive fluid group and 295 patients (19.8%) in the liberal fluid group ($P=0.19$). Surgical-site infection occurred in 245 patients (16.5%) in the restrictive fluid group and in 202 patients (13.6%) in the liberal fluid group (unadjusted $P=0.02$; threshold level for statistical significance after adjustment for multiple comparisons, $P=0.003$) (Table 3, and Table S12 in the Supplementary Appendix). There were no other significant between-group differences in the rates of trial outcomes (Table 3, and Tables S6 and S13 in the Supplementary Appendix).

SENSITIVITY ANALYSES

In sensitivity analyses, the proportion of patients who were alive and free of new-onset disability at 1 year was 81.4% in the restrictive fluid group and 83.3% in the liberal fluid group ($P=0.13$ by

Table 1. Demographic and Perioperative Characteristics of the Patients at Baseline.*

Characteristic	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)
Mean age \pm SD — yr	66 \pm 13	66 \pm 13
Male sex — no. (%)	771 (51.7)	783 (52.4)
Median body weight (IQR) — kg	84 (68–102)	83 (69–102)
ASA physical status — no. (%) [†]		
1	25 (1.7)	21 (1.4)
2	542 (36.4)	540 (36.2)
3	849 (57.0)	868 (58.1)
4	74 (5.0)	64 (4.3)
Median preoperative WHODAS score (IQR) [‡]	15 (13–21)	15 (13–21)
Country — no. (%)		
Australia	836 (56.1)	841 (56.3)
Canada	250 (16.8)	247 (16.5)
United Kingdom	141 (9.5)	134 (9.0)
Hong Kong	111 (7.4)	116 (7.8)
United States	74 (5.0)	75 (5.0)
New Zealand	46 (3.1)	48 (3.2)
Italy	32 (2.1)	32 (2.1)
Coexisting medical condition — no. (%)		
Hypertension	899 (60.3)	908 (60.8)
Coronary artery disease	212 (14.2)	250 (16.7)
Heart failure	57 (3.8)	47 (3.1)
Previous myocardial infarction	122 (8.2)	146 (9.8)
Peripheral vascular disease	95 (6.4)	92 (6.2)
Current smoker	194 (13.0)	204 (13.7)
History of stroke or TIA	105 (7.0)	115 (7.7)
Chronic obstructive pulmonary disease	244 (16.4)	254 (17.0)
Moderate or severe renal disease	101 (6.8)	108 (7.2)
Perioperative care — no. (%)		
Neuraxial block	409 (27.4)	385 (25.8)
Invasive blood-pressure monitoring	1070 (71.8)	1080 (72.3)
CVP monitoring	276 (18.5)	272 (18.2)
Type of surgery — no. (%)		
Esophageal or gastric	286 (19.2)	257 (17.2)
Hepatobiliary	133 (8.9)	139 (9.3)
Colorectal	646 (43.4)	651 (43.6)
Urologic or renal	220 (14.8)	223 (14.9)
Gynecologic	135 (9.1)	139 (9.3)
Other	70 (4.7)	84 (5.6)
Surgical method — no. (%)		
Open	818 (54.9)	788 (52.8)
Laparoscopic	458 (30.7)	463 (31.0)
Laparoscopic-assisted	214 (14.4)	242 (16.2)

Characteristic	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)
Median duration of surgery (IQR) — hr	3.3 (2.4–4.6)	3.3 (2.5–4.5)
Planned postoperative care in HDU or ICU — no. (%)	416 (27.9)	418 (28.0)

* There were no significant differences between the groups at baseline. CVP denotes central venous pressure, HDU high-dependency unit, ICU intensive care unit, IQR interquartile range, and TIA transient ischemic attack.

† The American Society of Anesthesiologists (ASA) criteria for physical status include a classification for normal health (1), mild systemic disease (2), severe systemic disease (3), and severe systemic disease that is a constant threat to life (4).

‡ The score on the World Health Organization Disability Assessment Schedule (WHODAS) estimates the amount of disability, with scores of 24 or greater indicating at least moderate disability.

Variable	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)	P Value
During surgery			
Median intraoperative blood loss (IQR) — ml	200 (100 to 400)	200 (100 to 500)	0.14†
Median intraoperative fluid administration (IQR) — ml			
Crystalloid	1677 (1173 to 2294)	3000 (2100 to 3850)	<0.001
Colloid‡	500 (250 to 800)	500 (400 to 1000)	0.01
Median infusion rate (IQR) — ml/kg/hr	6.5 (5.1 to 8.4)	10.9 (8.7 to 13.5)	<0.001
In PACU§			
Median administration of fluid (IQR) — ml			
Crystalloid	160 (90 to 302)	300 (160 to 500)	<0.001
Colloid‡	400 (250 to 500)	500 (250 to 500)	0.27
Postoperative day 1, post-PACU			
Median administration of fluid (IQR) — ml			
Crystalloid	1556 (1200 to 1960)	2600 (2052 to 3150)	<0.001
Colloid‡	500 (250 to 1000)	500 (400 to 750)	0.89
Median infusion rate (IQR) — ml/kg/hr	0.9 (0.7 to 1.2)	1.5 (1.2 to 1.7)	<0.001
At 24 hr after surgery			
Median cumulative total for intravenous fluids (IQR) — ml	3671 (2885 to 4880)	6146 (5000 to 7410)	<0.001
Median fluid balance (IQR) — ml¶	1380 (540 to 2338)	3092 (2010 to 4241)	<0.001†
Median weight gain (IQR) — kg	0.3 (-1.0 to 1.9)	1.6 (0.0 to 3.6)	ND

* ND denotes not done, and PACU postanesthesia care unit.

† This P value was calculated from 10 imputations of missing values.

‡ Colloid was administered during the perioperative period in 369 patients in the restrictive fluid group and 309 patients in the liberal fluid group (P=0.008); in the PACU in 130 patients and 92 patients, respectively (P=0.006); and on postoperative day 1 after leaving the PACU in 207 patients and 127 patients, respectively (P<0.001).

§ Patients who bypassed the PACU and were admitted directly to the ICU or HDU included 116 in the restrictive fluid group and 106 in the liberal fluid group.

¶ Data regarding fluid balance were missing for 179 patients in the restrictive fluid group and 161 in the liberal fluid group. Results were not meaningfully different after multiple imputation.

|| Data regarding weight gain were missing for 1036 patients in the restrictive fluid group and 999 in the liberal fluid group; the P value was not calculated.

Table 3. Primary and Secondary Outcomes.*

Outcome	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)	Hazard or Risk Ratio (95% CI) [†]	P Value
Primary outcome				
Disability-free survival at 1 yr — no. (%) [‡]	1223 (81.9)	1232 (82.3)	1.05 (0.88–1.24)	0.61
Death or persistent disability — no.	267	261		
Death	95	96		
Persistent disability	172	165		
Secondary outcomes[§]				
Composite septic outcome or death — no./total no. (%) [¶]	323/1481 (21.8)	295/1487 (19.8)	1.10 (0.96–1.27)	0.19
Surgical-site infection — no./total no. (%)	245/1481 (16.5)	202/1487 (13.6)	1.22 (1.03–1.45)	0.02
Sepsis — no./total no. (%)	157/1481 (10.6)	129/1487 (8.7)	1.22 (0.98–1.52)	0.08
Anastomotic leak — no./total no. (%)	49/1481 (3.3)	35/1487 (2.4)	1.41 (0.92–2.16)	0.12
Pneumonia — no./total no. (%)	54/1481 (3.6)	57/1487 (3.8)	0.95 (0.66–1.37)	0.79
Acute kidney injury — no./total no. (%) ^{**}	124/1443 (8.6)	72/1439 (5.0)	1.71 (1.29–2.27)	<0.001
Renal-replacement therapy — no./total no. (%)	13/1460 (0.9)	4/1462 (0.3)	3.27 (1.01–13.8)	0.048
Pulmonary edema — no./total no. (%)	20/1481 (1.4)	32/1487 (2.2)	0.63 (0.36–1.09)	0.10
Unplanned admission to ICU — no./total no. (%)	161/1487 (10.8)	145/1491 (9.7)	1.11 (0.90–1.38)	0.32
Median peak serum lactate level (IQR) — mmol per liter ^{††}	1.6 (1.1–2.5)	1.6 (1.1–2.4)	NA	NA
Median C-reactive protein level on day 3 (IQR) — mg per liter ^{‡‡}	136 (82–198)	133 (80–200)	NA	0.66
Median duration of mechanical ventilation (IQR) — hr ^{§§}	17 (5–65)	14 (3–31)	NA	0.07
Median score on quality-of-recovery scale (IQR) ^{¶¶}	106 (89–121)	107 (90–122)	NA	0.31
Median duration of stay in HDU or ICU (IQR) — days	1.8 (1.0–3.1)	1.4 (0.9–2.9)	NA	0.13
Median duration of hospital stay (IQR) — days	6.4 (3.6–10.6)	5.6 (3.6–10.5)	NA	0.26
Death — no. (%)[‡]				
At 90 days	31 (2.1)	18 (1.2)	1.73 (0.97–3.10)	0.06
At 12 mo	95 (6.5)	96 (6.6)	1.03 (0.78–1.36)	0.86

* NA denotes not applicable.

[†] The hazard ratio or risk ratio is for the restrictive fluid group as compared with the liberal fluid group.

[‡] Percentages in this category were estimated with the use of the Kaplan–Meier method. Among the patients who died, 9 in the restrictive fluid group and 12 in the liberal fluid group had persistent disability before death at 12 months. The risks of death at 90 days and at 12 months are listed in the table as predefined secondary outcomes.

[§] All the secondary outcomes were assessed up to 30 days after surgery, with the exception of renal-replacement therapy and the duration of mechanical ventilation, which were assessed at 90 days.

[¶] The composite septic outcome includes surgical-site infection, anastomotic leak, pneumonia, and sepsis.

^{||} The P value was not significant after adjustment for multiple comparisons, with a threshold level of P=0.004 for renal-replacement therapy and P=0.003 for surgical-site infection.

^{**} Values for acute kidney injury are the average number of events across 10 imputations in which fluid balance was imputed after adjustment for serum creatinine values on day 1 and day 3. Details regarding these analyses and sensitivity analyses are provided in the Supplementary Appendix.

^{††} Data regarding the peak serum lactate level were missing for 1057 patients in the restrictive fluid group and in 1086 in the liberal fluid group; the P value was not calculated.

^{‡‡} Data regarding the C-reactive protein level were missing for 422 patients in the restrictive fluid group and 420 in the liberal fluid group.

^{§§} Data regarding mechanical ventilation are for 102 patients in the restrictive fluid group and 100 in the liberal fluid group.

^{¶¶} Data regarding the quality of recovery on day 3 were missing for 73 patients in the restrictive fluid group and 75 in the liberal fluid group. The scores on this scale range from 0 (extremely poor) to 150 (excellent).

^{|||} Data regarding the duration of stay in the HDU or ICU data are for 485 patients in the restrictive fluid group and 473 in the liberal fluid group who were admitted at any time postoperatively.

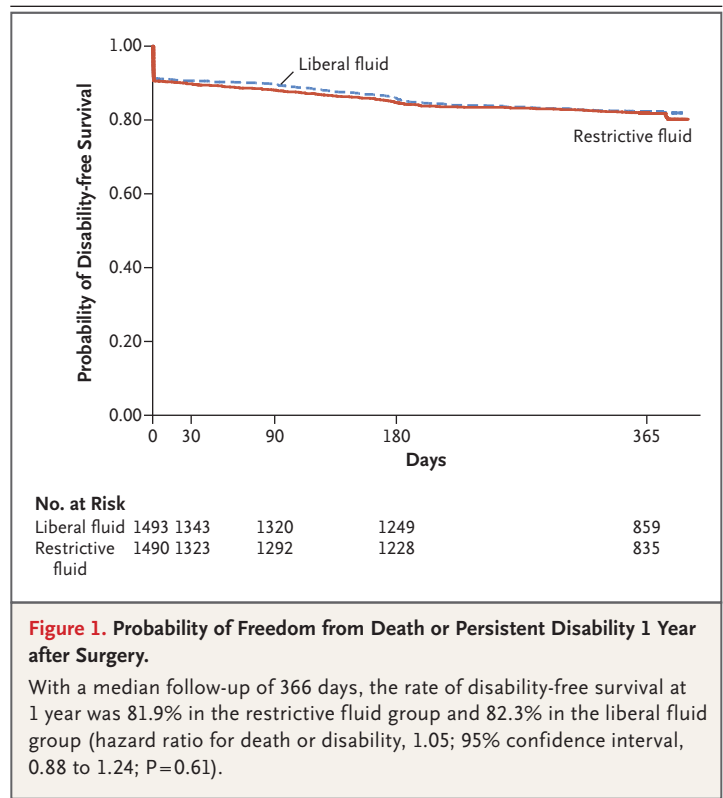
Cox regression); modifications to the disability definition did not meaningfully change the results (Tables S14 and S15 and Figs. S3 and S4 in the Supplementary Appendix). Results were largely unchanged after adjustment for stratification factors that were used in randomization (Tables S16 and S17 in the Supplementary Appendix).

DISCUSSION

In this international trial evaluating disability-free survival and rates of serious complications among at-risk patients undergoing major abdominal surgery, we compared a restrictive regimen for the administration of intravenous fluid (designed to achieve zero balance during surgery and the 24-hour postoperative period) with a liberal fluid regimen. At 1 year, the rate of disability-free survival was not significantly higher with the restrictive fluid regimen than with the liberal fluid regimen. However, patients in the restrictive fluid group had a significantly higher risk of acute kidney injury than those in the liberal fluid group.

Perioperative intravenous-fluid therapy serves to restore and maintain body water, electrolytes, and organ perfusion to achieve homeostasis.^{14,33} Avoiding too much intravenous fluid is commonly recommended in ERAS programs.^{12,14,16,33,34} Some small trials have supported a restrictive fluid regimen.^{9,11,13} However, inappropriate fluid-balance approaches can be harmful.^{24,35} In particular, acute kidney injury may result from inadequate administration of fluid (renal hypoperfusion)²⁸ or excessive administration (renal interstitial edema).¹⁹ Our findings may resolve this uncertainty, since we found that restricting intravenous-fluid administration with the aim of zero balance increased the risk of acute kidney injury.

Intravenous-fluid regimens for abdominal surgery have been classified as restrictive (<1.75 liters per day), balanced (1.75 to 2.75 liters per day), and liberal (>2.75 liters per day).³³ In our trial, the patients who were assigned to the restrictive fluid group received a median of 1.7 liters intraoperatively and an additional 1.9 liters during the 24-hour postoperative period. Patients in the liberal fluid group received 3.0 liters during surgery and an additional 3.0 liters during the first 24 hours (similar to the amount recorded in



registry data²⁴ and pooled analyses of trials).^{10,25} In previous studies, intraoperative restrictive fluid replacement varied from 1.0 to 2.7 liters, as compared with 2.8 to 5.4 liters in liberal fluid regimens.³⁴ Current recommendations suggest avoiding a weight gain of more than 2.5 kg,^{14,16} a cutoff that was achieved in a majority of the patients in our trial, including those in the liberal fluid group.

Our findings should not be used to support excessive administration of intravenous fluid. Rather, they show that a regimen that includes a modestly liberal administration of fluid is safer than a restrictive regimen. There is a belief that fluid-induced edema impairs wound healing. In contrast, we identified a higher rate of surgical-site infection in the restrictive fluid group, possibly because of wound or anastomotic hypoperfusion. Fluid restriction will inevitably increase the need for vasopressor therapy unless hypotension is ignored.

Our trial has certain limitations. Obviously, clinicians could not administer intravenous fluids in a blinded manner. This lack of blinding may

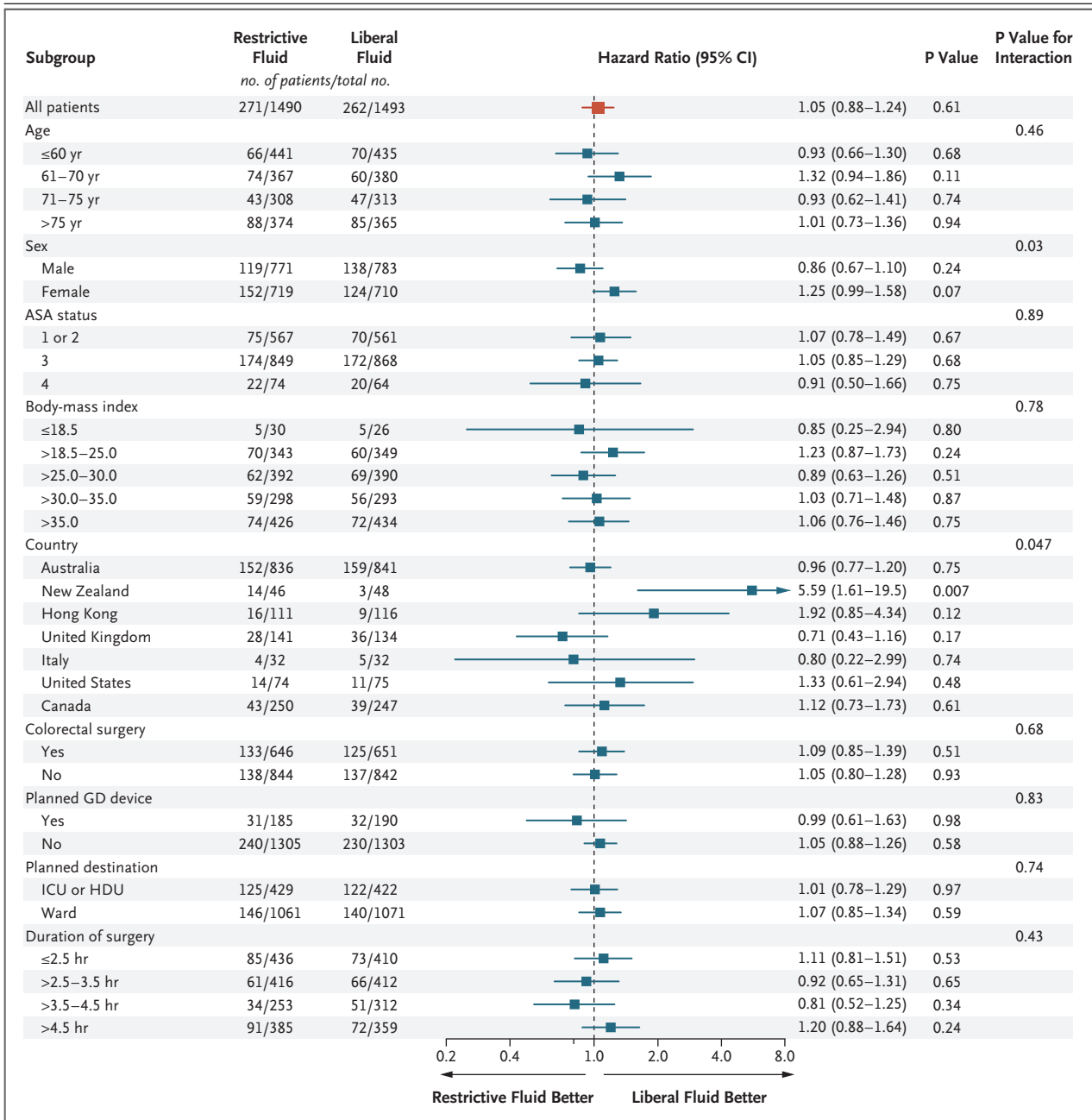


Figure 2. Hazard Ratios for Death or Disability in Prespecified Subgroups.

The only significant interactions between group assignment and subgroup were for sex and country, with a significant between-group difference for residence in New Zealand. The body-mass index is the weight in kilograms divided by the square of the height in meters. The American Society of Anesthesiologists (ASA) criteria for physical status include a classification for normal health (1), mild systemic disease (2), severe systemic disease (3), and severe systemic disease that is a constant threat to life (4). GD denotes goal-directed, HDU high-dependency unit, and ICU intensive care unit.

have introduced bias in documentation and some outcome monitoring. The trial was pragmatic and included a range of abdominal surgeries with an aim toward generalizability. Less than half of the patients were treated according to ERAS principles, a factor that did not influence the overall effects of the fluid intervention. The trial dictated the administration of fluid therapy

during and for the first 24 hours after surgery, when most intravenous fluid is given; however, the administration of later fluid therapy was not controlled. Many patients could not be weighed on days 1 to 3. We identified a lower risk of disability-free survival in the restrictive fluid group among patients in New Zealand. This secondary finding was based on a small number of events and cannot be explained by baseline imbalance, so it may be spurious. Some of the results for secondary outcomes may be spurious because of an alpha-level error. However, the risk of acute kidney injury in the restrictive fluid group was highly significant and was coherent in the context of oliguria and the use of renal-replacement therapy.

In conclusion, in patients at increased risk for complications while undergoing major abdomi-

nal surgery, a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen 1 year after surgery. However, the restrictive regimen was associated with a higher rate of acute kidney injury.

Supported by a grant (ID1043755) from the Australian National Health and Medical Research Council (NHMRC), the Australian and New Zealand College of Anaesthetists, Monash University, a grant (ID14/222) from the Health Research Council of New Zealand, and the United Kingdom National Institute of Health Research. Drs. Myles and Bellomo are supported by Australian NHMRC Practitioner Fellowships.

Disclosure forms provided by the authors are available at NEJM.org.

We thank Adam Meehan for data management, construction of the Web-accessed electronic database, and provision of the Web-based randomization service; Monty Mythen and David McIlroy and all the members of the committees overseeing the trial; and the Australian and New Zealand College of Anaesthetists Clinical Trials Network.

APPENDIX

The authors' full names and academic degrees are as follows: Paul S. Myles, M.P.H., D.Sc., Rinaldo Bellomo, M.D., Tomas Corcoran, M.D., Andrew Forbes, Ph.D., Philip Peyton, M.D., Ph.D., David Story, M.D., Chris Christophi, M.B., B.S., Kate Leslie, M.D., Shay McGuinness, M.B., Ch.B., Rachael Parke, M.P.H., Jonathan Serpell, M.D., Matthew T.V. Chan, M.B., B.S., Thomas Painter, M.B., Ch.B., Stuart McCluskey, M.D., Ph.D., Gary Minto, M.B., Ch.B., and Sophie Wallace, M.P.H.

The authors' affiliations are as follows: Alfred Hospital (P.S.M., J.S., S.W.), Monash University (P.S.M., R.B., T.C., A.F., K.L., J.S., S.W.), and the University of Melbourne (R.B., P.P., D.S., C.C., K.L.), Melbourne, VIC, Austin Hospital, Heidelberg, VIC (R.B., P.P., D.S., C.C.), Royal Perth Hospital and the University of Western Australia, Perth (T.C.), Royal Melbourne Hospital, Parkville, VIC (K.L.), and Royal Adelaide Hospital and Discipline of Acute Care Medicine, University of Adelaide, Adelaide, SA (T.P.) — all in Australia; Auckland City Hospital, Auckland, and the Medical Research Institute of New Zealand, Wellington — both in New Zealand (S. McGuinness, R.P.); the Chinese University of Hong Kong, Hong Kong (M.T.V.C.); University Health Network, Toronto (S. McCluskey); and Derriford Hospital, Plymouth, United Kingdom (G.M.).

REFERENCES

- Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* 2015; 385:Suppl 2:S11.
- Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. *Ann Surg* 1961;154:803-10.
- Arkilic CF, Taguchi A, Sharma N, et al. Supplemental perioperative fluid administration increases tissue oxygen pressure. *Surgery* 2003;133:49-55.
- Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. *Intensive Care Med* 1994;20:203-9.
- Davies SJ, Wilson RJ. Preoperative optimization of the high-risk surgical patient. *Br J Anaesth* 2004;93:121-8.
- Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993;270:2699-707.
- Wilson J, Woods I, Fawcett J, et al. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. *BMJ* 1999;318:1099-103.
- Tambyraja AL, Sengupta F, MacGregor AB, Bartolo DC, Fearon KC. Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection. *World J Surg* 2004;28:1046-51.
- Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003;238:641-8.
- Boland MR, Noorani A, Varty K, Coffey JC, Agha R, Walsh SR. Perioperative fluid restriction in major abdominal surgery: systematic review and meta-analysis of randomized, clinical trials. *World J Surg* 2013;37:1193-202.
- Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002;359:1812-8.
- Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. *Clin Nutr* 2012;31:783-800.
- Nisanevich V, Felsenstein I, Almog G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005;103:25-32.
- Feldheiser A, Aziz O, Baldini G, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand* 2016;60:289-334.
- Intravenous fluid therapy in adults in hospital: clinical guideline CG174. London: National Institute for Health and Care Excellence, 2017 (<https://www.nice.org.uk/guidance/cg174>).
- Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: a review. *JAMA Surg* 2017;152:292-8.
- Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg* 2012; 114:640-51.
- Arief AI. Fatal postoperative pulmo-

- nary edema: pathogenesis and literature review. *Chest* 1999;115:1371-7.
19. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nat Rev Nephrol* 2010;6:107-15.
 20. Ratner AJ, Lysenko ES, Paul MN, Weiser JN. Synergistic proinflammatory responses induced by polymicrobial colonization of epithelial surfaces. *Proc Natl Acad Sci U S A* 2005;102:3429-34.
 21. Lang K, Boldt J, Suttner S, Haisch G. Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. *Anesth Analg* 2001;93:405-9.
 22. Myles P, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy in major abdominal surgery (RELIEF): rationale and design for a multicentre randomised trial. *BMJ Open* 2017;7(3):e015358.
 23. World report on disability: technical appendix C. Geneva: World Health Organization, 2011:287-94 (http://www.who.int/disabilities/world_report/2011/report.pdf).
 24. Thacker JK, Mountford WK, Ernst FR, Krukas MR, Mythen MM. Perioperative fluid utilization variability and association with outcomes: considerations for enhanced recovery efforts in sample US surgical populations. *Ann Surg* 2016;263:502-10.
 25. Rahbari NN, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. *Br J Surg* 2009;96:331-41.
 26. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332-40.
 27. Shulman MA, Myles PS, Chan MT, McLroy DR, Wallace S, Ponsford J. Measurement of disability-free survival after surgery. *Anesthesiology* 2015;122:524-36.
 28. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary. *Crit Care* 2013;17:204.
 29. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med* 2011;39:2665-71.
 30. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. *BMJ* 2011;342:d1491.
 31. Mamidanna R, Burns EM, Bottle A, et al. Reduced risk of medical morbidity and mortality in patients selected for laparoscopic colorectal resection in England: a population-based study. *Arch Surg* 2012;147:219-27.
 32. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat* 1979;6:65-70.
 33. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. *Proc Nutr Soc* 2010;69:488-98.
 34. Bundgaard-Nielsen M, Secher NH, Kehlet H. 'Liberal' vs. 'restrictive' perioperative fluid therapy — a critical assessment of the evidence. *Acta Anaesthesiol Scand* 2009;53:843-51.
 35. Bellamy MC. Wet, dry or something else? *Br J Anaesth* 2006;97:755-7.

Copyright © 2018 Massachusetts Medical Society.

ARTICLE METRICS NOW AVAILABLE

Visit the article page at NEJM.org and click on Metrics to view comprehensive and cumulative article metrics compiled from multiple sources, including Altmetrics. www.nejm.org/about-nejm/article-metrics.