A Multicenter, Open-Label, Randomized Controlled Trial of a Conservative Fluid Management Strategy Compared With Usual Care in Participants After Cardiac Surgery: The Fluids After Bypass Study*

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OBJECTIVES: There is little evidence to guide fluid administration to patients admitted to the ICU following cardiac surgery. This study aimed to determine if a protocolized strategy known to reduce fluid administration when compared with usual care reduced ICU length of stay following cardiac surgery.

DESIGN: Prospective, multicenter, parallel-group, randomized clinical trial.

SETTING: Five cardiac surgical centers in New Zealand conducted from November 2016 to December 2018 with final follow-up completed in July 2019.

PATIENTS: Seven-hundred fifteen patients undergoing cardiac surgery; 358 intervention and 357 usual care.

INTERVENTIONS: Randomization to protocol-guided strategy utilizing stroke volume variation to guide administration of bolus fluid or usual care fluid administration until desedation or up to 24 hours. Primary outcome was length of stay in ICU. Organ dysfunction, mortality, process of care measures, patient-reported quality of life, and disability-free survival were collected up to day 180.

MEASUREMENTS AND MAIN RESULTS: Overall 666 of 715 (93.1%) received at least one fluid bolus. Patients in the intervention group received less bolus fluid (median [interquartile range], 1,000 mL [250–2,000 mL] vs 1,500 mL [500–2,500 mL]; $p < 0.0001$) and had a lower overall fluid balance (median [interquartile range], 319 mL [−284 to 1,274 mL] vs 673 mL [38–1,641 mL]; $p < 0.0001$) in the intervention period. There was no difference in ICU length of stay between the two groups (27.9 hr [21.8–53.5 hr] vs 25.6 hr [21.9–64.6 hr]; $p = 0.95$). There were no differences seen in development of organ dysfunction, quality of life, or disability-free survival at any time points. Hospital mortality was higher in the intervention group (4% vs 1.4%; $p = 0.04$).

CONCLUSIONS: A protocol-guided strategy utilizing stroke volume variation to guide administration of bolus fluid when compared with usual care until desedation or up to 24 hours reduced the amount of fluid administered but did not reduce the length of stay in ICU.

KEY WORDS: cardiac surgery; critical care; hemodynamic monitoring; intravenous fluid; randomized controlled trial; stroke volume variation

***See also p. 529.**

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Cardiac surgery is one of the most frequently performed major surgical procedures worldwide. Demand for cardiac surgery has increased, and combined with increased case mix complexity and advancing age, demand for limited surgical services often exceeds availability of resources (1, 2). "Bed block," whereby patient flow through the surgical system is restricted due to patients using a hospital bed for longer than expected, is a common occurrence. In some healthcare systems, in particular, restricted availability of ICU and postoperative surgical ward beds leads to frequent cancelations in operating lists, delay in transfer from the ICU to the ward, and increases in costs associated with delays (3, 4).

IV fluid therapy is one of the most common treatments administered to patients in the ICU with wide variation in practice and prescribing reported (5–7). Fluid administration has been shown to be commonplace in patients following cardiac surgery with 93% of patients receiving at least one fluid bolus in the postoperative period (8). Impaired microcirculation and multiple organ dysfunction may result due to inadequate cardiac output and reduced organ perfusion has been shown in patients after cardiac surgery (9). Although IV fluids are administered with the intention of correcting hypovolemia and improving cardiac output, this may result in a positive fluid balance that has been associated with adverse outcomes in other surgical populations (10–13).

Studies in other patient populations have shown improvements in patient outcomes such as improved wound healing and reduction in length of stay (LOS) when a restrictive fluid regime is used (10, 13), while the Restrictive versus liberal fluid therapy for major abdominal surgery study found surgical site infection, acute kidney injury at 30 days and renal replacement therapy at 90 days was more common in the restrictive fluid group (14). However, no such evidence existed within the cardiac surgical population.

We previously reported a single-center feasibility study, which showed a protocolized strategy, avoiding unnecessary fluid administration, was easy to implement, significantly reduced fluid loading, and led to reductions in ICU LOS (15).

We hypothesized that in participants with a European system for cardiac operative risk evaluation (EuroSCORE II) greater than or equal to 0.9 undergoing cardiac surgery utilizing cardiopulmonary bypass, the use of a protocolized strategy to guide fluid administration would reduce ICU LOS and improve participant outcomes.

MATERIALS AND METHODS

The Fluids After Bypass (FAB) trial was prospectively registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12616001301459 first registered September 16, 2016) and the protocol and statistical analysis plan has been previously published (16).

Design and Setting

The FAB trial was an investigator-initiated, prospective, multicenter, parallel-group, open-label, randomized controlled superiority trial. The trial was undertaken in five publicly funded cardiac surgical centers in New Zealand between November 2016 and July 2019. All ICUs are closed units with 24/7 staffing by intensivists and trainees. All units allowed nursing staff to administer some IV fluids by standing order.

Participants

Participants were 16 years old or older, having elective cardiac surgery with planned use of cardiopulmonary bypass and a preoperative EuroSCORE II of 0.9 or more. They were excluded if they had a contraindication to the use of stroke volume variation (SVV) monitoring or an indication for specific fluid management postoperatively. Patients with a EuroSCORE less than or equal to 0.9 were excluded as we had previously demonstrated that they were less likely to benefit from the intervention (16). A full list of inclusion and exclusion criteria can be found in the **Supplementary Appendix** (http://links.lww.com/CCM/G121).

Ethics Approval and Consent

The study was approved by the Northern B New Zealand Health and Disability Ethics Committee (16/NTB/153). Written informed consent to participate was obtained from all study participants by appropriately trained research staff prior to enrollment.

Randomization

Participants were randomized preoperatively in a 1:1 ratio to one of the two groups stratified by hospital. Randomization was achieved using sequentially numbered, opaque, sealed envelopes prepared by a person

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not involved with the study. A permuted block randomization method of variable block size was generated by the study statistician.

Trial Interventions

Study treatment was administered from time of admission to the ICU until the time that routine postoperative sedation was stopped or for a period of 24 hours (whichever occurred first).

The intervention arm used a protocol-guided strategy (**Fig. 1**) for administering bolus fluids. This protocol used SVV to guide fluid administration and had been previously tested in a feasibility study (15). This protocol asked bedside clinicians first of all to assess if the participant had an inadequate cardiac output before administering bolus fluid. If so, they then used SVV to assess the likelihood of the participant being volume responsive (17), the aim being to administer fluid only to those who were objectively determined to have an inadequate cardiac output and be likely to respond to IV fluid.

In the usual care arm, participants received IV bolus fluid as determined by local protocols and the bedside clinician.

All other ICU care was as per usual practice at individual sites, including the choice of fluid and use of blood management protocols.

Outcome Measures

The primary outcome was ICU LOS to day 28 postenrollment.

Secondary outcomes measures included process of care measures, complications and mortality, quality of life, and disability-free survival to day 180 postsurgery (16). A full list of outcomes can be found in the Supplementary Appendix (http://links.lww.com/CCM/G121).

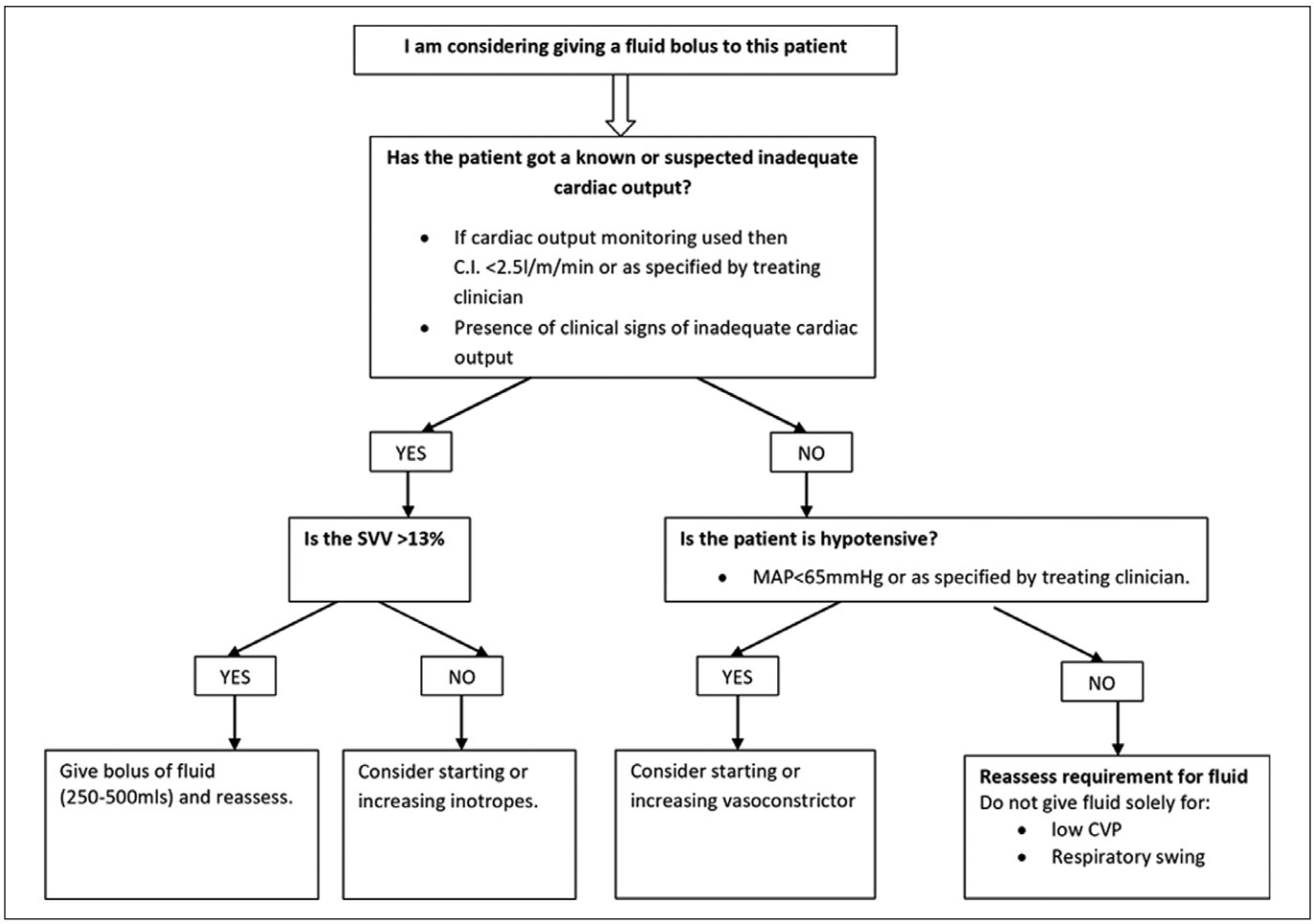

Figure 1. Fluid administration protocol from admission to the ICU until the time that routine postoperative sedation is stopped or for a period of 24 hr (whichever occurred first). CI = cardiac index, CVP = central venous pressure, MAP = mean arterial pressure, SVV = stroke volume variation.

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While participants were blinded to treatment allocation, blinding of treating clinicians was not feasible. We minimized bias by ensuring concealment of allocation prior to randomization, by protocolizing treatment in the intervention arm, and by using a robust outcome measure (ICU LOS) as recorded in the clinical information systems at each site and collected by blinded research staff. The statistical analysis plan was published a priori (16).

Sample Size Calculation

Sample size calculations were based on findings from our pilot study in which there was a median difference in ICU hours between treatment and intervention arms that was greater than 20 hours for participants with a EuroSCORE II greater than or equal to 0.9 (15). Based on an observed SD of 56, with 590 participants, this study had 90% power (two-sided $p = 0.05$) to detect a 15-hour difference and 80% power (two-sided $p = 0.05$) to detect a 13-hour difference in ICU hours. Differences of this magnitude were both conservative in comparison to what we had previously observed and clinically relevant as they would enable participants to be discharged from the ICU on or before the morning of the second postoperative day, enabling a new participant to be admitted on that day and thus resolving a principal barrier to increasing cardiac surgical participant throughput. By recruiting a total of 700 completely eligible participants, we further allowed for inflation due to one interim analysis, a 3% drop-out rate, and 15% for potential non-normality in ICU LOS (18).

Data Management

Data were collected and entered into an electronic database by trained research nurses at each site using a secure Research Electronic Data Capture database hosted by the Medical Research Institute of New Zealand.

Statistical Analysis Plan

Primary analysis was conducted in accordance with a pre-published analysis plan (16) following an intention to treat principle including all randomized patients. All data were assessed for normality. Between-group comparisons were performed using chi-square tests for equal proportion, student *t* tests for normally distributed data, and Wilcoxon rank-sum tests otherwise, with results reported as *n* (%), mean (SD), or median (interquartile range [IQR]), respectively. To account for potential heterogeneity between sites and baseline imbalance ($p < 0.2$), the primary outcome (ICU LOS) was log-transformed and analyzed using hierarchical mixed regression with results reported as geometric means (95% CI) and a ratio of geometric means. To account for survival bias, these results were additionally reported for survivors only (Supplementary Appendix, http://links.lww.com/CCM/G121). Further sensitivity analyses were performed on a modified intention to treat population, excluding all patients that met secondary screening criteria (which identify patients in whom the use of SVV is not reliable) following admission to the ICU postoperatively. Longitudinal data were analyzed using mixed linear modeling, fitting main effects for treatment and time and an interaction between the two to determine if treatment behaved differently over time. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC) and a two-sided *p* value of 0.05 was used to indicate statistical significance.

Study Management and Data Monitoring

An independent data safety monitoring committee (DSMC) was appointed prior to the commencement of the study and comprised three senior academic clinicians with experience in undertaking randomized controlled clinical trials. A blinded interim analysis was conducted by the DSMC after 50% of participants were enrolled and subsequently discharged from the ICU. The recommendation was to continue with no change.

RESULTS

Participants

This study enrolled 715 participants over 25 months at five sites, 358 randomized to the intervention arm and 357 to the usual care arm (**Table S1**, http://links.lww.com/CCM/G121). Of those, 27 in the intervention arm and 21 in the usual care arm were documented as meeting one of the exclusion criteria on return to the ICU postoperatively such as new onset atrial fibrillation, insertion of an intra-aortic balloon pump, open chest, or they were not expected to survive for the next 24 hours. There were also a number in each group (14 intervention vs 14 usual care participants) who were

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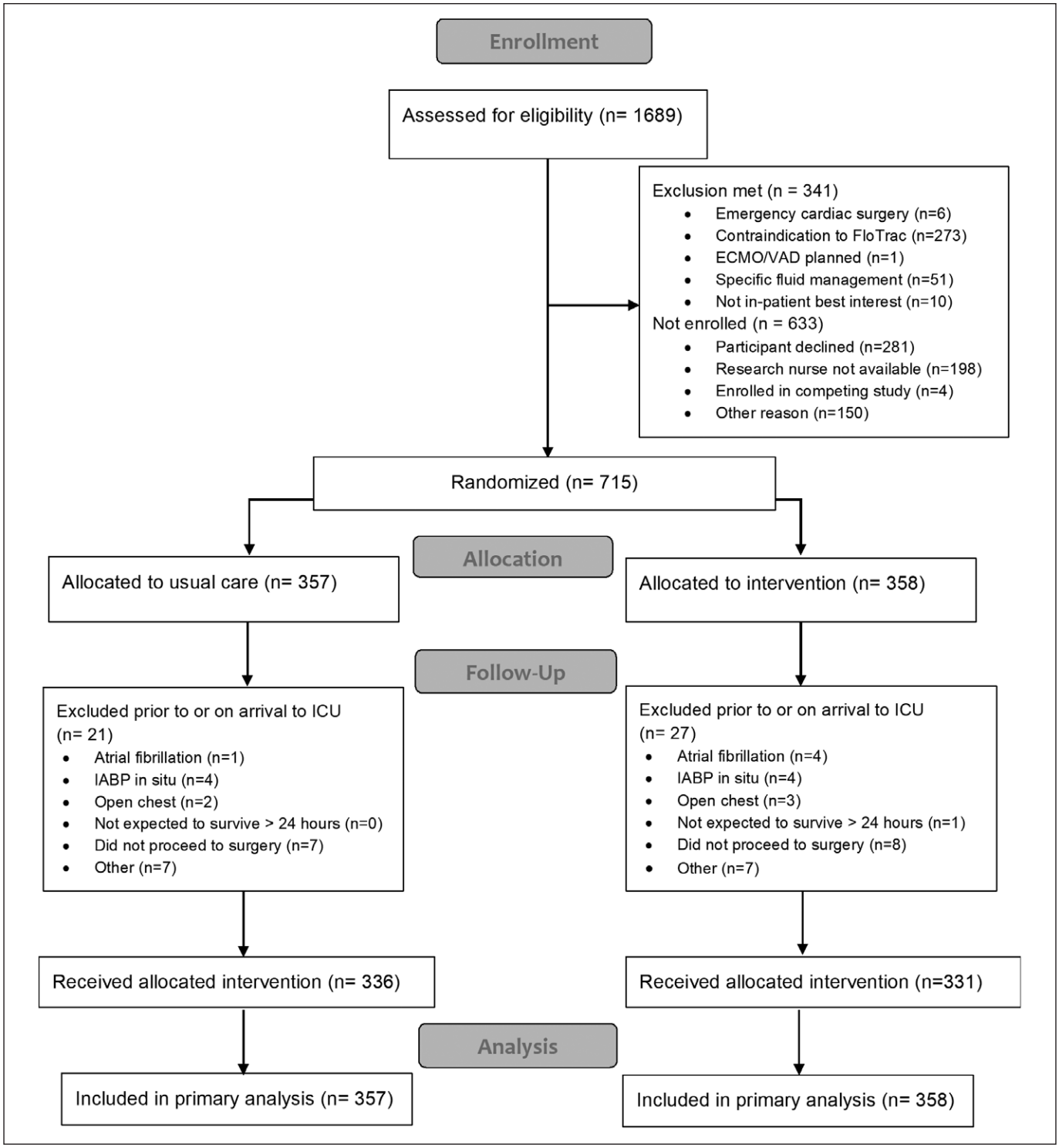

Figure 2. Screening, randomization, and follow-up of participants in the Fluids After Bypass trial. ECMO = extracorporeal membrane oxygenation, IABP = intra-aortic balloon pump, VAD = ventricular assist device.

excluded for other reasons including having surgery canceled, late change to percutaneous procedure, or transferred to nonparticipating private hospitals for surgery due to long waiting lists in the publicly funded cardiac centers (**Fig. 2**).

Did not proceed to surgery includes those patients who either had a planned change in procedure, for example, from surgical aortic valve replacement to transcatheter aortic valve implantation and those who were transferred for surgery to a nonstudy hospital.

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TABLE 1.
Demographic and Clinical Characteristics of Participants at Baseline

	All ($n = 715$)	Usual Care ($n = 357$)	Intervention ($n = 358$)
Gender (female), *n* (%)	189 (26.4)	87 (24.4)	102 (28.5)
Age, yr, median (IQR)	70 (61–75)	68 (59–74)	70 (59–74)
Weight, kg, median (IQR)	82.9 (72–94.2)	84.4 (73.8–96.5)	80 (71–93)
European system for cardiac operative risk evaluation, median (IQR)	1.8 (1.3–2.9)	1.8 (1.2–2.82)	1.97 (1.4–3.11)
Ethnicity, *n* (%)			
New Zealand European	574 (80.3)	281 (78.7)	293 (81.8)
Māori	61 (8.5)	31 (8.7)	30 (8.4)
Pacific	33 (4.6)	18 (5)	15 (4.2)
Asian	31 (4.3)	19 (5.3)	12 (3.4)
Middle Eastern/Latin American/African	3 (0.4)	3 (0.8)	0 (0)
Other	13 (1.8)	5 (1.4)	8 (2.2)
Creatinine, µmol/L, mean (SD)	91.7 (25.1)	92.3 (23.8)	91.2 (26.4)
Hemoglobin, g/L, mean (SD)	137 (16.3)	136 (17.4)	137 (15.2)
On diuretic prior to hospital admission, *n* (%)	130 (18.2)	72 (20.2)	58 (16.2)
Preoperative health score, mean (SD)	69.2 (21.5)	69.3 (21.4)	69.1 (21.6)
Operation, *n* (%)			
Isolated CABG	310 (43.4)	155 (43.4)	155 (43.3)
Single valve	138 (19.3)	72 (20.2)	66 (18.4)
Multivalve surgery	37 (5.2)	18 (5)	19 (5.3)
CABG + valve	143 (20)	71 (19.9)	72 (20.1)
Other	72 (10.1)	34 (9.5)	38 (10.6)
Bypass duration, min, mean (SD)	118 (57.4)	118 (57.8)	118 (57.1)
Cross-clamp time, min, mean (SD)	85.2 (45.4)	85.5 (45.6)	84.8 (45.2)
Pulmonary artery catheter at admission to ICU, *n* (%)	152 (21.8)	83 (23.8)	69 (19.8)
Sequential Organ Failure Assessment total at ICU admission, median (IQR)	5 (4–6)	5 (4–6)	5 (4–6)

CABG = coronary artery bypass surgery, IQR = interquartile range.

The groups were well matched at baseline with the exception being a significantly higher ($p = 0.01$) EuroSCORE II score in the intervention group as compared with the usual care group (**Table 1**; and **Tables S2** and **S4**, http://links.lww.com/CCM/G121). Age, baseline weight, and New York Heart Association score were also significantly different. The cohort was on average 70 years old (61–75 yr old), 26% women, 80% New Zealand European, and 8.5% New Zealand Maori and an average EuroSCORE II 1.84 (1.3–2.94). The majority underwent isolated coronary artery bypass surgery (43.3%) or single valve surgery (19.3%) with

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TABLE 2.
Fluid and Vasopressor Administration by Group

	Usual Care ($n = 357$)	Intervention ($n = 358$)	p
Fluids from admission to extubation, median (IQR)			
All fluids administered, mL	2,190 (1,216–3,341)	1,506 (666–2,853)	< 0.0001
Bolus fluid administered, mL	1,500 (500–2,500)	1,000 (250–2,000)	< 0.0001
All fluid losses, mL	1,283 (835–1,935)	1,205 (785–1,822)	0.23
Blood loss, mL	270 (175–400)	250 (150–425)	0.25
Urine output, mL	970 (585–1,515)	900 (550–1,392)	0.14
Overall fluid balance, mL	673 (38–1,641)	319 (-284 to 1,274)	< 0.0001
Fluids from admission to 24 hr			
All fluids administered, mL, median (IQR)	3,580 (2,300–5,174)	3,187 (2,002–4,617)	0.02
Bolus fluid administered, mL, median (IQR)	2,400 (1,045–3,500)	2,000 (1,000–3,183)	0.03
All fluid losses, mL, median (IQR)	2,440 (1,869–3,220)	2,235 (1,760–2,918)	0.007
Blood loss, mL, median (IQR)	500 (340–725)	470 (300–700)	0.17
Urine output, mL, median (IQR)	1,775 (1,370–2,525)	1,669 (1,245–2,308)	0.01
Overall fluid balance, mL, mean (SD)	1,821 (1,853)	1,687 (1,787)	0.33
Number of fluid boluses, median (IQR)	8 (4–12)	7 (3–11)	0.02
Vasopressor requirement on day 1, *n* (%)			
Received vasopressors day 1	323 (92.6)	323 (92.8)	0.89
Dopamine	183 (56.7)	187 (57.9)	0.75
Dobutamine	2 (0.6)	5 (1.5)	0.25
Noradrenaline	267 (82.7)	271 (83.9)	0.67
Adrenaline	37 (11.5)	27 (8.4)	0.19
Milrinone	59 (18.3)	46 (14.2)	0.17
Vasopressin	25 (7.7)	18 (5.6)	0.27
Other	27 (8.4)	17 (5.3)	0.12

IQR = interquartile range.

a mean (SD) bypass duration of 118 minutes (57 min) (Table 1).

Clinical Management of Participants

Overall, 666 of 715 participants (93.1%) received a fluid bolus. Participants in the intervention group received less bolus fluid (median [IQR], 1,000 mL [250–2,000 mL] vs 1,500 mL [500–2,500 mL]; $p < 0.0001$) and had a lower overall fluid balance (median [IQR], 319 mL [–284 to 1,274 mL] vs 673 mL [38–1,641 mL]; $p < 0.0001$) while on study protocol than those allocated to usual care (**Table 2;** and **Table S5**, http://links.lww.com/CCM/G121). There was no significant difference between groups in the requirement for vasopressor therapy. A total of 12,399 reasons were recorded

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for fluid bolus administration (multiple reasons could be chosen by the bedside clinician administering the fluid bolus [**Fig. F1**, http://links.lww.com/CCM/G121]). The most commonly recorded reasons for fluid bolus administration were hypotension (33.2% of all fluid bolus episodes), low central venous pressure (14.4%), SVV greater than 13 (9.5%), poor perfusion (8.9%), and respiratory swing on arterial trace (6.8%).

Effectiveness of the Intervention

There was no statistically significant difference in ICU LOS—measured as both actual LOS (from admission to ICU to actual discharge from ICU and subject to delay due to availability of beds in the postoperative ward 27.9 hr [21.8–53.5 hr] intervention group vs 25.6 hr [21.9–64.6 hr] usual care group; $p = 0.95$) and "ready for discharge" time (measured from time of admission to ICU to time judged fit for discharge to the postoperative ward by the duty clinician 21.2 hr [18.3–44.7 hr] intervention group vs 21.1 hr [18.4–46.4 hr] usual care group; $p = 0.94$) (**Table 3**; and **Tables S6, S7, S9, S10, S11,** and **S12,** http://links.lww.com/CCM/G121). These results remain unchanged when adjusted for site and baseline imbalance (**Table S8**, http://links.lww.com/CCM/G121).

Other Outcomes

There were no differences seen in development of organ dysfunction, quality of life, or disability-free survival at any time points. Hospital mortality was higher in the intervention group (4% vs 1.4%; $p = 0.035$) and this was due to higher ICU mortality (3.4% vs 0.8%; $p = 0.019$). Four deaths occurred in the operating room while other reasons for death included gut ischemia ($n = 3$), empyema ($n = 1$), right heart failure secondary to aortic regurgitation ($n = 1$), and neurologic complications ($n = 2$).

With regards patient-reported quality of life and disability-free survival, the only significant difference was in pain/discomfort levels at 3 months as reported using the EuroQol-5D (EQ5D5L) ($p = 0.023$). There were no differences in the EQ5D5L domains of mobility, personal care, usual activities, or anxiety or depression at any time point or in pain/discomfort at hospital discharge or 6 months (**Fig. F2**, http://links.lww.com/CCM/G121). There were no significant differences between groups with regards those identifying as having none or mild disability at each time point as measured using the World Health Organisation Disability assessment schedule (WHODAS) 2.0 and classed as WHODAS % less than 25. At baseline, 75.5% of all participants were classed as having none or mild disability; at hospital discharge, this reduced to 48.5%, at 3 months rose to 91%, and at 6 months to 92.1% (**Fig. F3**, http://links.lww.com/CCM/G121).

There were no serious adverse events related to the intervention recorded.

DISCUSSION

This prospective, multicenter, open-label, parallel-group, randomized clinical trial tested a novel strategy utilizing SVV to guide administration of bolus fluid compared with usual care fluid administration until desedation or up to 24 hours. The intervention reduced the amount of fluid administered to participants but did not find a significant difference in ICU LOS in participants undergoing cardiac surgery. Furthermore, there was no difference in patient-reported quality of life, disability-free survival, or mortality at 3 and 6 months postsurgery.

Fluid bolus administration is often one of the first-line treatments delivered postoperatively to patients in the ICU after cardiac surgery (8). The reasons surrounding this are complex. They may relate to the ease of administration of IV fluids by bedside staff; difficulty for staff in determining whether or not fluid administration is the best option with no clear evidence available to inform practice. The response to fluid administration is often quick and easy to identify, appealing to those who want to see an instant response, perhaps in terms of increasing blood pressure. Oftentimes though, there is no thought given to the long-term sequelae of fluid administration. This program of research developed in response to an observation from the postoperative ward staff that patients were often fluid overloaded as seen by increased postoperative weight and concerns regarding edema causing wound dehiscence, difficulty mobilizing, and increased use of diuretics. Accumulating evidence shows that a positive fluid balance is associated with worse outcomes, longer ICU admission, and increased mortality (19, 20).

There remains a paucity of high-level evidence regarding the optimal approach to fluid therapy (21).

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TABLE 3.
Primary and Secondary Outcomes

	Usual Care ($n = 357$)	Intervention ($n = 358$)	p
Primary outcome, median (IQR)			
ICU length of stay–actual, hr	25.6 (21.9–64.6)	27.9 (21.8–53.5)	0.95
ICU length of stay–ready for discharge, hr	21.1 (18.4–46.4)	21.2 (18.3–44.7)	0.94
Secondary outcomes, *n* (%)			
Intra-aortic balloon pump postoperative	4 (1.1)	8 (2.3)	0.24
Return to theater for bleeding	16 (4.6)	18 (5.2)	0.72
Reintubation required	5 (1.4)	12 (3.4)	0.09
Readmission to ICU	17 (4.9)	13 (3.7)	0.46
New onset atrial fibrillation	133 (38)	135 (38.7)	0.85
Use of renal replacement therapy			
In ICU	5 (1.4)	8 (2.3)	0.4
At 6 mo	3 (0.9)	2 (0.6)	1
Renal function			
Highest creatinine measured in hospital, µmol/L, mean (SD)	115 (49)	109 (39.8)	0.08
Highest creatinine corrected for fluid balance, µmol/L, mean (SD)	119 (52.2)	114 (42.6)	0.11
Developed AKI from baseline, *n* (%)	105 (29.4)	96 (26.8)	0.44
Developed AKI from baseline (adjusted for fluid balance), *n* (%)	118 (33.1)	117 (32.7)	0.92
KDIGO stage 1, *n* (%)	89 (24.9)	83 (23.2)	0.59
KDIGO stage 2, *n* (%)	13 (3.6)	5 (1.4)	0.06
KDIGO stage 3, *n* (%)	3 (0.84)	8 (2.2)	0.13
Other clinical outcomes			
Length of ventilation, hr, median (IQR)	8.2 (5.2–16.3)	7.6 (5.3–15.7)	0.5
Hospital length of stay, d, median (IQR)	7.0 (6.0–9.1)	7.0 (5.2–9.0)	0.18
Use of vasoactive drugs in first 3 d, *n* (%)	325 (93.1)	324 (93.1)	0.99
On diuretic at hospital discharge, *n* (%)	137 (45.1)	121 (42.3)	0.5
Disability free (World Health Organisation Disability assessment schedule % < 25, none or mild disability), *n* (%)			
Baseline	260 (73.4)	275 (77.5)	0.21
At hospital discharge	152 (45.9)	166 (51.1)	0.19
At 3 mo	292 (90.7)	286 (91.4)	0.76
At 6 mo	291 (92.1)	284 (92.2)	0.96
Mortality, *n* (%)			
Died prior to ICU discharge	5 (1.4)	14 (3.9)	0.04
Dead at 3 mo	5 (1.4)	13 (3.7)	0.06
Dead at 6 mo	10 (2.8)	19 (5.3)	0.09

AKI = acute kidney injury, IQR = interquartile range, KDIGO = Kidney disease: improving global outcomes.

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We found that the most common reason for administering a fluid bolus was hypotension. This is in agreement with other studies that report commonly used indicators such as blood pressure, urine output, cardiac output, and central venous pressure (22, 23). It is interesting to note that this was true in patients with or without cardiac output monitoring suggesting that the default management of hypotension is fluid administration.

It should be recognized that differences exist between cardiac surgical patients and that a "one size fits all" approach to fluid management may not be appropriate (24). For instance, those undergoing elective versus emergent surgery; those undergoing surgery utilizing cardiopulmonary bypass versus those without. Furthermore, management on return to the ICU may differ depending on postoperative condition—the difference between the standard "warm, wake, and wean" cardiac surgical patient and the complicated postoperative course marked by cardiogenic shock, vasoplegia, or the development of multiple organ failure. The aim of the algorithm used in this trial was to prevent fluid administration to patients who were unlikely to be fluid responsive as demonstrated by a low SVV. This differs from most goal-directed therapy studies, which aim to maximize cardiac output by giving fluid challenges. Trials of goal-directed fluid therapy in the cardiac ICU have shown reductions in ICU and hospital LOS, as well as frequency of pneumonia and mediastinal infection (9, 25–31). In contrast, our study did not demonstrate any difference in these outcomes. It should be recognized though that other studies have employed different protocols and targets as part of goal-directed therapy, so interventions or results may not be consistent or directly comparable.

Restriction of IV fluid in the intervention arm may lead to an increase in the use of vasopressor drugs that often cannot be delivered in the postoperative surgical ward, which in turn could lead to increased ICU LOS. This concern proved to be unfounded as this study showed no difference in the amounts of vasopressor drugs given in each group, and so we do not feel that this impacted on LOS in the ICU or high dependency unit. Previous studies have suggested that restrictive fluid regimes may be associated with an increased risk of renal injury or a change in diuretic use (14), but we did not see any evidence of this in this study. A previous single-center, retrospective observational study suggested a positive fluid balance was associated negatively with acute kidney injury and requirement for de novo dialysis in patients undergoing cardiac surgery (32). In this multicenter randomized controlled trial, we found no evidence of an increase in acute kidney injury with a moderately restrictive fluid regime.

Although there was no difference in mortality at 3 and 6 months, there was a significant difference in deaths prior to discharge from the ICU ($p = 0.04$). Although the low overall mortality rate at this time point (2.6%) suggests that this is a chance finding, six out of 19 deaths were attributable to cardiogenic shock and three out of 19 were due to gut ischemia. Although all nine of these patients were in the intervention group, the number of events is too small to attribute causality (**Table S3**, http://links.lww.com/CCM/G121).

There is concern in the ICU community that increased amounts of IV fluid may indeed be harmful in certain patient groups (33), although to our knowledge, this has not been tested in patients undergoing cardiac surgery. In fact, there still remains a glaring gap in the evidence base regarding perioperative fluid administration for cardiac surgical patients. This study has shown a protocolized bedside algorithm can reduce the amount of fluid given; however, this has not translated into reduced time in the ICU.

One of the reasons we may have failed to find a difference in this study is that there appears to have been a shift in the practice of fluid administration over time. In the program of research leading up to this RCT, consisting of observational studies and a feasibility study, we had found that usual practice had changed over time. The volume of fluid administered in the usual care arm in this study was again found to be lower than that recorded previously by our group (8, 15). This study found a median of 1,500 mL (IQR, 500–2,500 mL) bolus fluid administered up to extubation in the usual care arm in comparison to 2,520 mL (1,440–5,250 mL) in our feasibility study, a reduction of 40%. We also saw a reduction in the median (IQR) amount of all fluids administered up to 24 hours in this study of 3,580 mL (2,300–5,174 mL) compared with 5,080 mL (3,930–7,320 mL) in the feasibility study, a reduction of 30%. Although this change may explain the lack of efficacy compared with our earlier study, a more likely explanation is that the findings of the small single-center feasibility study represent a type I error.

This trial has several strengths. First, it was conducted in all five publicly funded cardiac surgical

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centers in New Zealand; thus, the study findings are representative of, and generalizable to, those patients that present for surgery in this country. Second, the trial assessed patient-reported quality of life and disability up to 6 months following randomization and subsequent cardiac surgery. This provides an unprecedented picture of how patients recover following cardiac surgery, which has previously not been reported. Third, the study was completed on time, and there was no loss to follow-up. A complete data set was available for analysis. Fourth, we analyzed both actual ICU LOS and the time from admission to ICU to "ready for ICU discharge" in order to allow for any effect of extended stay in the ICU for participants due to bed block on the postoperative wards.

There are some limitations. First, that we only permitted bedside clinicians to access SVV data obtained by the FloTrac system to guide patient management and not cardiac output. Although a SVV value of 14% for predicting fluid responsiveness has been widely used, we did not explore the utility of alternative values for this (17). Second, the protocol guiding fluid administration was only able to be delivered while the patient was sedated and ventilated due to the restrictions of using SVV, there was some evidence of "catch-up" fluid administration to the intervention arm after cessation of algorithm guided fluid administration. Third, the intervention was not blinded, but the risk of bias was mitigated by a robust randomization process, allocation concealment of group assignment to participants and outcome assessors, and the use of both methods of calculating ICU LOS. Last, there was no attempt to control or measure fluid balance in the operating room prior to ICU admission. This was because SVV cannot be used with an open chest and accurately assessing fluid balance during surgery with cardiopulmonary bypass is unreliable. We have assumed that intraoperative fluid management in both groups was similar, and we ensured that the allocated intervention was commenced promptly at admission to ICU to maximize treatment difference.

CONCLUSIONS

In patients undergoing cardiac surgery using cardiopulmonary bypass, a protocol-guided strategy utilizing SVV to guide administration of bolus fluid when compared with usual care fluid administration until desedation or up to 24 hours reduced the amount of fluid administered but did not significantly reduce the LOS in ICU.

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