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Assisted Fluid Management Software Guidance for Intraoperative Fluid Administration

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Intraoperative fluid management, restrictive or liberal fluid administration, and goal-directed protocols are controversial
- Automated software using artificial intelligence techniques is being developed for various intraoperative management tasks

What This Article Tells Us That Is New

- This multicenter, prospective study of investigational fluid management software in patients with an arterial catheter evaluated the fraction of software-recommended boluses producing a target increase in stroke volume
- A higher percentage of software-recommended boluses met the target increase, compared to a historical reference rate and to clinician-initiated boluses

ABSTRACT

Background: Excessive or inadequate fluid administration causes complications, but despite this, fluid administration during noncardiac surgery is highly variable. Goal-directed management helps optimize the amount and timing of fluid administration; however, implementation is difficult because algorithms are complex. The authors therefore tested the performance of the Acumen Assisted Fluid Management software (Edwards Lifesciences, USA), which is designed to guide optimal intravenous fluid administration during surgery.

Methods: In this multicenter, prospective, single-arm cohort evaluation, the authors enrolled 330 adults scheduled for moderate- to high-risk noncardiac surgery that required arterial catheter insertion and mechanical ventilation. Clinicians chose a fluid strategy based on a desired 10%, 15%, or 20% increase in stroke volume (SV) in response to a fluid bolus. Dedicated fluid management software prompted "test" or "recommended" boluses, and clinicians were free to initiate a "user" bolus of 100 to 500 ml of crystalloid or colloid. Clinicians were free to accept or decline the software prompts. The authors primarily compared the fraction of software-recommended boluses that produced suitable increases in SV to a 30% reference rate. On an exploratory basis, we compared responses to software-recommended and clinician-initiated boluses.

Results: Four hundred twenty-four of 479 (89%) software-recommended fluid boluses and 508 of 592 (86%) clinician-initiated fluid boluses were analyzed per protocol. Of those, 66% (95% CI, 62 to 70%) of delivered fluid boluses recommended by the software resulted in desired increases in SV, compared with the 30% reference rate, whereas only 41% (95% CI, 38 to 44%) of clinician-initiated boluses did ($P < 0.0001$). The mean ± SD increase in SV after boluses recommended by the software was 14.2 ± 13.9% *versus* 8.3 ± 12.1% ($P < 0.0001$) for those initiated by clinicians.

Conclusions: Fluid boluses recommended by the software resulted in desired SV increases more often, and with greater absolute SV increase, than clinician-initiated boluses. Automated assessment of fluid responsiveness may help clinicians optimize intraoperative fluid management during noncardiac surgery.

(ANESTHESIOLOGY 2021; XXX:00–00)

Each year, more than 313 million major noncardiac surgical procedures are performed worldwide, including more than 40 million in the United States alone.[1] High-risk surgeries comprise approximately 10% of these major noncardiac surgical procedures, but account for nearly 80% of perioperative deaths and a high burden of postoperative complications.[2] Maintaining adequate intraoperative cardiac output and oxygen delivery during surgery can prevent damage to vital organs and resultant complications.[3] Hemodynamic-guided fluid management, also called goal-directed therapy, helps optimize cardiac output and may improve outcomes in high-risk surgical patients.[4–7]

Goal-directed therapy requires clinicians to follow standardized algorithms that determine when fluids should be given. A common feature of most algorithms is an effort to maintain a predefined stroke volume (SV) and keep SV variation less than 12%.[4,8] Goal-directed therapy protocols have been developed and endorsed by multiple organizations, including medical societies in some European countries.[9,10] However, the complexity and variety of goal-directed therapy algorithms make them challenging to implement; consequently, adherence to such algorithms is often poor.[11,12] For example, in one of the largest goal directed therapy trials, only 30% of fluid boluses resulted in an appropriate SV increase, highlighting poor assessment of fluid responsiveness with an SV maximization protocol.[13] To overcome these challenges, Acumen Assisted Fluid Management software (Edwards Lifesciences, USA) was developed to automate the assessment of fluid responsiveness.[14] Using invasive

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arterial pressure information, the software recommends a fluid administration when patients are likely to respond to fluid bolus with a predefined increase in SV.

We evaluated the effectiveness of the Assisted Fluid Management software in predicting fluid responsiveness in moderate- to high-risk noncardiac surgical patients who required invasive arterial pressure monitoring. We hypothesized that automated assessment of hemodynamic status and prompting specific fluid recommendations may facilitate intraoperative fluid management during surgery. Specifically, we evaluated the percentage of software-recommended boluses that resulted in a targeted change in SV compared with a 30% reference value. Additionally, we compared responses to software-recommended and clinician-initiated fluid boluses.

Materials and Methods

Study Design

Our single-arm, prospective cohort study was an investigational device evaluation designed to evaluate safety and effectiveness data for a premarket approval application to the U.S. Food and Drug Administration (Silver Spring, Maryland). The study was approved by a private commercial Western Institutional Review Board No. (WCG IRB; Puyallup, Washington) and local Institutional Review Boards and was registered with ClinicalTrials.gov (NCT03469570). Written informed consent was obtained from each subject. Subjects were recruited at nine hospitals across the United States, and no site exceeded 20% of the total enrollment. Two pilot subjects (pilot cohort) were permitted per site for training purposes before formal data acquisition began.

Subject Selection

We enrolled adults 18 yr or older who were scheduled for elective major noncardiac surgical procedures including abdominal surgery, combined abdominal/pelvic surgery, or major peripheral vascular surgery expected to last 2 h or more. All were American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status III or IV and required intraoperative mechanical ventilation and arterial catheterization for continuous blood pressure monitoring as part of their anesthetic care plan. We excluded patients who had a body mass index greater than or equal to 35 kg/m^2; aortic stenosis; moderate-to-severe mitral stenosis; moderate-to-severe aortic or mitral regurgitation; atrial fibrillation; planned ventilation with tidal volume less than 8 ml/kg of ideal body weight; and those scheduled for liver resection, neurosurgical procedures, or open-chest procedures.

Software

An open-loop fluid management workflow was employed for this protocol using the EV1000 Clinical Platform (Edwards Lifesciences, USA) with Acumen Assisted Fluid Management software. Clinicians were thus guided by the software but retained full control of fluid administration. The main functions of the software were to (1) integrate all monitored hemodynamic variables and continuously analyze patients' fluid responsiveness; (2) analyze the response to fluid boluses; and (3) predict patients' current fluid responsiveness and, when appropriate, prompt clinicians to consider a fluid bolus.

Figure 1 provides a block diagram of the software algorithm. Its inputs are the user settings that include choice of fluid strategy and surgery approach, hemodynamic data from arterial pressure waveform-based analyses, and the fluid delivery details provided by the clinician *via* the monitor's user interface. Users were asked to specify their desired change in SV (10%, 15%, or 20%) resulting from a 500-ml fluid bolus, allowing the clinician to choose between a liberal fluid management strategy with the 10% setting or a conservative fluid management strategy with the 20% setting. However, clinicians were allowed to select any bolus fluid volume between 100 and 500 ml. If the clinician delivered a fluid bolus with a volume other than 500 ml, the expected change in SV was proportionately scaled by the software. The relationship between the bolus volume and the scaling factor was experimentally derived from animal studies and corroborated with previously described definitions of fluid responsiveness.[15–17] The surgical approach options were "Open" or "Laparoscopic/Prone," where selecting the latter informs the algorithm that SV variation may be elevated secondary to these procedure characteristics. Hemodynamic data included measured variables such as heart rate, mean arterial pressure, and estimated advanced variables using pulse contour analysis including SV, SV variation, and systematic vascular resistance. We recorded the start and end time of each bolus, along with the fluid type and volume.

Fluid bolus analysis uses the fluid delivery data and the hemodynamic data to estimate the percent change in SV (*i.e.*, change in SV) resulting from a fluid bolus. Whenever

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Part of the work presented in this article has been presented as "Assisted Fluid Management Trial Results" at the New Findings from the Outcomes Research Consortium of the Anesthesiologists' annual meeting on October 3, 2020.

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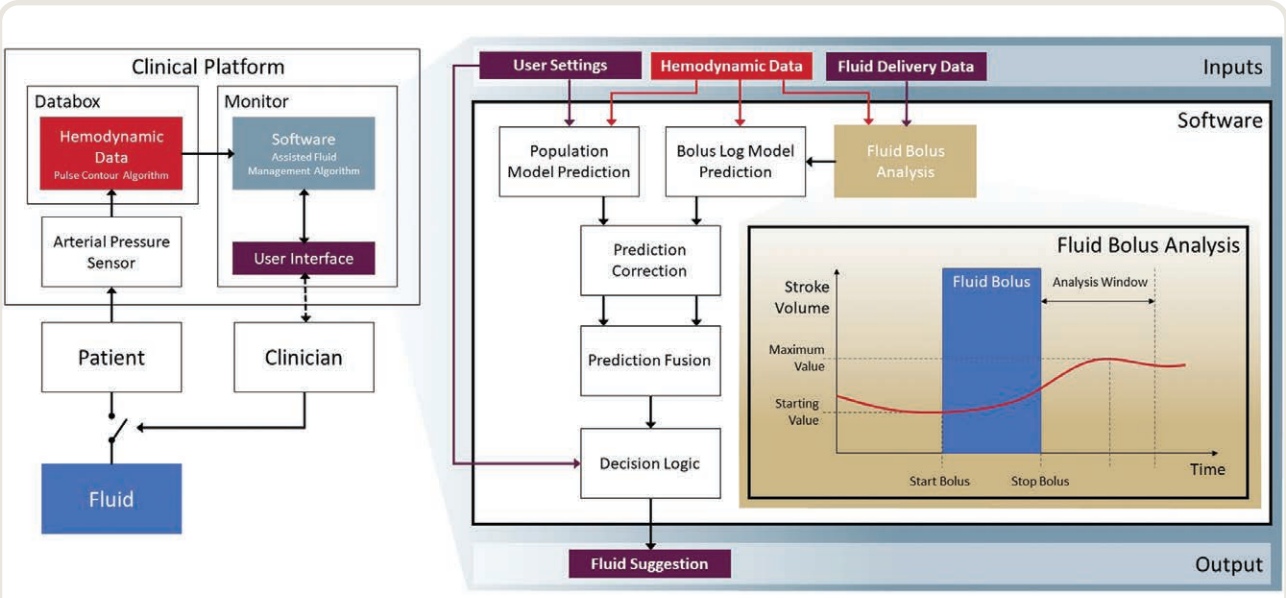

Fig. 1. Block diagram of Assisted Fluid Management algorithm. Fluid Bolus Analysis computes the percent change in stroke volume (*i.e.*, change in stroke volume) for a fluid bolus. The Population Model Prediction and the Bolus Log Model Prediction estimate the patient's current fluid responsiveness. The Population Model describes the relationship between stroke volume variation and predicted change in stroke volume. The Bolus Log Model uses the hemodynamic responses to past fluid boluses to determine whether a patient is fluid responsive. Prediction Correction compares the measured change in stroke volume to the predicted change in stroke volume from past boluses and corrects the current prediction for systematic biases. Prediction Fusion averages the Population Model Prediction and the Bolus Log Prediction, weighted by the quality of the information in Bolus Log Model to produce a Final Prediction. Decision Logic compares the Final Prediction to the current Fluid Strategy setting to determine whether a fluid bolus suggestion should be generated.

fluid is given within prescribed limits (volume, 100 to 500 ml; rate, 1 to 10 l/h), the algorithm calculates the expected change in SV by overlaying the start time and stop time of the fluid bolus on top of the SV measurements (Supplemental Digital Content, fig. 1, http://links.lww.com/ALN/C609).

The algorithm prediction of the patient's current fluid responsiveness combines predictions from the population model and the bolus log model (fig. 1). The population model describes the relationship between SV variation and predicted change in SV. The bolus log model uses the hemodynamic responses to past fluid boluses to determine whether a patient is fluid responsive. It generates a predicted change in SV by identifying boluses that were given in a similar hemodynamic state and aggregating those responses.

In Prediction Correction, the algorithm compares the measured change in SV to the predicted change in SV for those boluses being used in the bolus log model and corrects the prediction model for systematic biases (*i.e.*, the model is either overestimating or underestimating the patient's response to fluid). In Prediction Fusion, the average of the population model prediction and the bolus log prediction is weighted by the quality of the information in the bolus log model to produce a final prediction. In Decision Logic, the final prediction is compared to the current Fluid Strategy setting to determine whether a fluid bolus suggestion should be generated. If the predicted change in SV is greater than the selected Fluid Strategy setting, the output of the algorithm is a fluid suggestion prompt that is displayed on the clinical monitor.

Protocol

The software was activated after confirming a good quality arterial waveform signal using a square wave test. Clinicians then selected a restrictive or liberal fluid strategy based on a 10%, 15%, or 20% desired increase in SV. The software prompted a "test" bolus when the available information was insufficient to predict fluid responsiveness or prompted a "recommended" bolus; both are herein collectively referred to as "software-prompted boluses." Clinicians were free to accept or decline software-prompted boluses (for an example of the user interface, see Supplemental Digital Content, fig. 2, http://links.lww.com/ALN/C609), and they could also administer "clinician-initiated" boluses of 100 to 500 ml of crystalloid or colloid at their own discretion. Not all bolus prompts resulted in analyzed boluses; figure 3 in the Supplemental Digital Content (http://links.lww.com/ALN/C609) presents the complete fluid bolus workflow and describes the transition between prompted, declined, accepted, discarded, completed, and analyzed boluses. A declined prompt prevented additional prompts for 5 min. A fluid bolus can only be analyzed by

the software if it was delivered within the prescribed rate and volume limits and has the required information to assess the hemodynamic response to the fluid. If fluid bolus was not completed as prescribed, the clinicians were asked to exclude the fluid bolus from analysis by marking "discard" in the clinical platform. The software performance (see Study Endpoints) was conditionally dependent on two variables: the fraction of times a clinician chose to accept software-prompted boluses and the fraction of times the delivered bolus achieved the desired SV change.

Study Endpoints

The primary endpoint was the fraction of software-prompted boluses that resulted in the desired increase in SV. When SV did not increase by the designated amount, the episode was considered to be nonresponsive. This effective response rate for software-prompted boluses was compared with a 30% response rate previously published in the literature. Additionally, we performed an exploratory comparison with clinician-initiated boluses.

Adverse events were collected and summarized. The primary safety endpoint was serious adverse events attributed to the software. An independent Clinical Events Committee reviewed event narratives, patient profiles, and hemodynamics, and adjudicated all adverse events for attribution, severity, and relatedness to fluid management recommendations, classified as "not related," "possibly related," or "related" to the software use, as per U.S. Food and Drug Administration guidelines. The Clinical Events Committee comprised four independent members (three anesthesiologists and one surgeon) who were experts in scientific disciplines needed to interpret the data and ensure study participant safety.

Statistical Analysis

A data analysis and statistical plan was written, date-stamped, and recorded in the investigators' files before data were accessed. The statistical analysis plan was also included in the final protocol approved by the U.S Food and Drug Administration on January 11, 2019. Our study was a pragmatic single-arm study powered to compare the response rate generated as a result of the Assisted Fluid Management software's recommendation to a reference 30% response rate. Response rate was defined as the fraction of fluid boluses resulting in an appropriate SV change. A planned exploratory analysis was to compare response rate after the Assisted Fluid Management–recommended bolus *versus* clinician-initiated boluses.

Data were summarized using standard frequentist methods as appropriate per data type. The primary effectiveness analysis was conducted on the per-protocol population, as the amount of potential missing data was unknown at the time of study planning. Histograms and boxplots were used to check distributions and for possible outliers of continuous variables. The response rates and one-sided 97.5% CIs reported for the primary effectiveness endpoint were computed at the event level using a bootstrap methodology. The response rate was compared using a chi-square for a difference in proportions or the Fisher exact test, as appropriate. The change in SV was compared using a paired *t* test or Wilcoxon signed-rank test, as appropriate.

In accordance with the suggestions of Samuelson and Petrick[18] that a minimum of 4,000 bootstraps are recommended for an $\alpha = 0.025$, 10,000 iterations were used for this analysis. Bias was calculated as the difference between the sample mean and bootstrapped population mean to the accuracy of the bootstrapped estimate (bias = $2.7e^{-7}$). This approach was used for all estimations of statistical inference since it accommodates correlated data. All bootstrapping followed a procedure as discussed by Davison and Hinkley.[19]

Statistical analyses were conducted using SAS v9.4 (SAS Institute, USA).

Sample Size Estimate

We assumed a 50% response rate following a software-prompted bolus and compared that to a 30% response rate reported by MacDonald *et al.*[13] With a planned enrollment of 330 subjects and 300 subjects qualifying for per-protocol analysis, we had 90% power for detecting a 20% difference in response rates with an $\alpha = 0.025$. Potential impact of change in SV (10%, 15%, 20%) stratification was not addressed as the proportion of subjects within each of these strata were not known *a priori*. These thresholds were captured as part of the data collection and analyzed. No *a priori* power calculation was conducted for exploratory comparison between Assisted Fluid Management–recommended boluses and clinician-initiated bolus.

Because the correlation between time points for the software was initially unknown, we used an approximate method using intraclass correlation and cluster size as described by Gelman and Hill.[20] We used a standard error of 0.1 and an intraclass correlation of 0.04 for establishing power and sample size. The potential impact of having multiple sites was considered but found to have a trivial impact on the power calculations. Given intraclass correlation was calculated from the between-group variation (squared standard error) divided by the total variation, and the total variation can be approximated from $p1 \times (1 - p1)$ given the binomial outcome. All power and sample size calculations were conducted using R (v3.4.2) and the R package CRTSize[21] and verified using PASS 15 (NCSS Statistical Software, USA) using the *t* test for one-sample proportions procedure.

Results

A total of 1,017 subjects were screened for eligibility, of whom 637 failed to meet the entry criteria (fig. 2). Among 380 consenting subjects, 330 were enrolled and had surgery in which Assisted Fluid Management software was

used: 307 were deemed "per protocol" and were included in the final analysis for the primary effectiveness endpoint. The median age was 66 yr, 58% were male, and 92% were American Society of Anesthesiologists Physical Status III (tables 1 and 2).

Clinicians using the software represented a range of experience and familiarity with goal-directed therapy. All were new to the software. A breakdown of the clinicians' backgrounds is shown in table 1 of the Supplemental Digital Content (http://links.lww.com/ALN/C609).

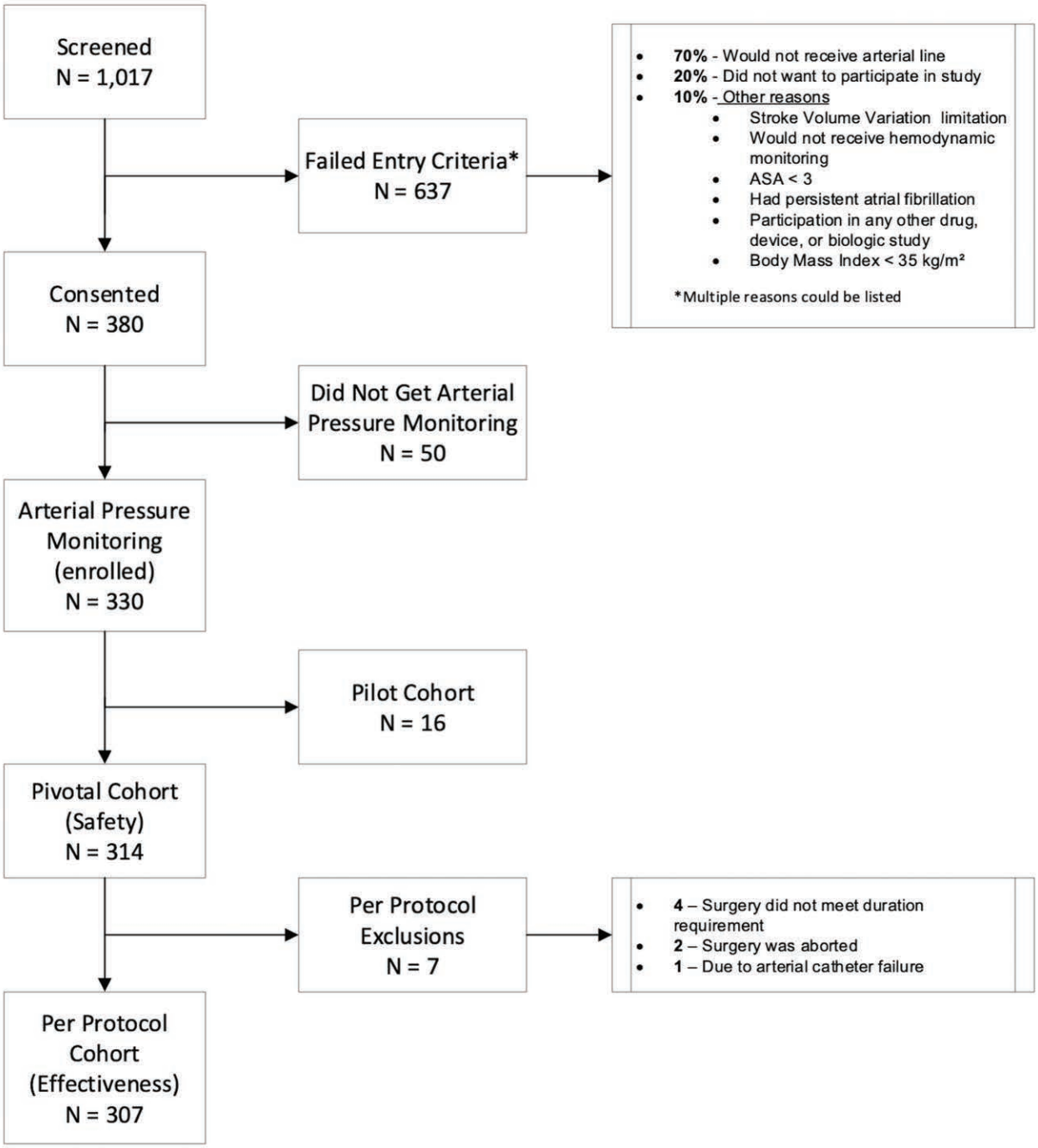

Fig. 2. Subject accountability flowchart. A total of 1,017 subjects were evaluated for eligibility criteria; 637 failed to meet the eligibility criteria. Of the 380 subjects who consented, 330 were enrolled and underwent surgery with intraoperative use of the software.

Table 1. Subject Demographics and Surgical Characteristics (N = 314)

Factor	
Age, yr	66 (59–73)
Female	131 (41.7)
Male	183 (58.3)
Race	
Asian	2 (0.6)
Black	22 (7.0)
White	284 (90.7)
Other	5 (1.6)
Body mass index, kg/m^2	25.9 (22.5–29.3)
American Society of Anesthesiologists Physical Status	
III	289 (92.0)
IV	25 (8.0)
Medical history	
Systemic hypertension	190 (61.1)
Coronary artery disease	44 (14.2)
Peripheral vascular disease	34 (11.0)
Arrhythmia	27 (8.7)
Cerebrovascular accident	18 (5.8)
Myocardial infarction	13 (4.2)
Congestive heart failure	9 (2.9)
Heart valve disease	9 (2.9)
Thoracic aortic aneurysm	5 (1.6)
Cancer	215 (69.8)
Hyperlipidemia	130 (41.4)
Gastrointestinal abnormality	116 (37.7)
History of smoking or tobacco use within last 10 yr	90 (29.4)
Current smoker	51 (16.7)
Hypercholesterolemia	34 (11.1)
Diabetes	79 (26.2)
Renal insufficiency	50 (16.1)
Chronic obstructive pulmonary disease	41 (13.2)
Liver disease	18 (5.8)
Coagulopathy or bleeding disorder	16 (5.2)
Surgery characteristics	
Colorectal	15 (4.7)
General	120 (38.2)
Hepatobiliary	19 (6.0)
Orthopedic	15 (4.7)
Urology	77 (24.5)
Vascular	37 (11.7)
Other	42 (13.3)

Data are number (percentage) or median (interquartile range).

Table 2. Intraoperative and Postoperative Data

Intraoperative Characteristics (N = 314)	
Hemodynamics	
Cardiac index, l · min^{-1} · m^{-2}	2.8 ± 0.8
Stroke volume variation, %	10.4 ± 5.3
Mean arterial pressure, mmHg	83.1 ± 14.4
Inputs/outputs	
Crystalloids, l	3.5 ± 3.7
Colloids, l	2.7 ± 1.6
Norepinephrine, %	5.7
Phenylephrine, %	52.1
Ephedrine, %	7.8
Vasopressin, %	1.5
Total maintenance fluid volume infused, ml	1,200 (697–2,000)
Estimated blood loss, ml	300 (100–600)
Urine output, ml	337 (200–600)
Duration of surgery, min	296 (226–385)
Postoperative data	
All serious adverse events at 30 days	88 (28)
Length of stay, days	5 (3–10)

Data are number, number (percentage), mean ± SD, or median (interquartile range).

Fluid Boluses

Of the 2,550 software prompts, 1,209 (47%) were declined by the clinician (table 3). The most common reason noted for declining the software prompts was the presence of normal blood pressure at the time of the prompt; other reasons for not accepting the prompts are given in table 4. Among the 1,341 software-prompted boluses that were accepted and fluid bolus was administered, 168 were discarded by the clinician mostly due to vasoactive drug administration during the fluid bolus or other abrupt physiologic changes, resulting in a total of 1,173 software-prompted boluses completed and 1,165 boluses analyzed.

The complete fluid bolus workflow and associated terminology are presented in figure 3 of the Supplemental Digital Content (http://links.lww.com/ALN/C609). Similarly, there were 592 boluses given by clinicians without a software prompt, of which 81 were discarded, 511 completed, and 508 analyzed (fig. 3).

The predominant fluid type delivered was crystalloid (82% software-prompted *vs.* 56% clinician-initiated), followed by colloids (13% software-prompted *vs.* 29% clinician-initiated) and a small proportion of "other" fluid types (5% software-prompted *vs.* 14% clinician-initiated) that included blood products. Software-prompted boluses and clinician-initiated boluses both had median volumes of 200 ml (table 3).

Performance Results

The response rate for software-recommended boluses was 66% (97.5% bootstrapped CI, 62 to 70%). The response rate for the clinician-initiated fluid boluses was 41% (97.5% bootstrapped CI, 38 to 44%; table 3). The mean ± SD SV change after software-recommended boluses was 14.2 ± 13.9% *versus* 8.3 ±12.1% for clinician-initiated fluid boluses. The results were similar irrespective of the selected fluid strategy (table 3). Each patient spent 73% of the time with an SV variation less than or equal to 12%, otherwise known as mean SV variation time-in-target.

Safety Results

Nine serious adverse events occurred in six (2%) subjects that were adjudicated by the Clinical Events Committee to be possibly related to the software (table 5). Four patients developed acute kidney injury (which resolved before discharge in three cases), one patient had an intraoperative hypotensive episode associated with significant blood loss, and one patient had a brief episode of atrial fibrillation followed by lactic acidosis and sepsis in the postoperative

Table 3. Primary Analysis, Stroke Volume Change in Response to a Fluid Bolus

Bolus Category	Software-Prompt: Test* (n = 741)	Software-Prompt: Recommended* (n = 424)	Clinician Initiated† (n = 508)
Analyzed boluses			
Total bolus volume delivered, ml	170 ± 84	190 ± 81	218 ± 97
	150 (100, 500)	200 (100, 500)	200 (100, 500)
Resulting change in stroke volume, %	16 ± 26‡	14 ± 14‡	8 ± 12
	11 (–26, 361)	11 (–16, 80)	7 (–26, 134)
Primary effectiveness endpoint at event level			
Mean response, % (97.5% bootstrapped CI)	60 (58, 63)	66 (62, 70)§	41 (38, 44)§
No. of boluses/subjects	741/278	424/143§	508§
Selected fluid strategy‖			
10%	4 (32%)	9 (40%)	6 (30%)
15%	76 (566%)	88 (371%)	72 (364%)
20%	19 (143%)	3 (13%)	22 (114%)

Unless otherwise specified, data are mean ± SD, median (minimum, maximum), or number (percentage).

*Software-recommended and software test boluses are collectively referred to as software-prompted boluses. †Clinician Initiated refers to clinician-initiated fluid boluses. ‡One bolus lacked a starting stroke volume due to an unreliable pressure signal, preventing the calculation of percent change in stroke volume. §$P < 0.0001$. The change in stroke volume was compared using a paired t test or Wilcoxon signed-rank test, as appropriate. The response rate was compared using a chi-square test for a difference in proportions or a Fisher exact test, as appropriate. Significance is estimated using $\alpha = 0.05$. ‖Selected fluid strategy refers to clinician-targeted stroke volume change in response to fluid bolus.

Table 4. Reasons Cited for Declining Software Prompts

Reasons Software Prompt Was Declined	n/N (%)*
Hemodynamic condition	
The subject was normotensive at the time	598/1,451 (41)
Clinician preferred to use vasoactive agent instead at the time	103/1,451 (7)
Fluid was contraindicated by the procedure at present time	102/1,451 (7)
Clinician does not think subject will be fluid responsive	95/1,451 (7)
Other	67/1,451 (5)
Clinician believed the hemodynamic changes were temporary and due to surgical manipulation	39/1,451 (3)
Patient was hypertensive at the time	34/1,451 (2)
Wanted to further review hemodynamics before deciding to give fluid	18/1,451 (1)
Actively managing blood pressure	17/1,451 (1)
Brief period of arrhythmia and felt bolus was not needed	11/1,451 (1)
Clinician was concerned about right ventricular dysfunction	1/1,451 (0.1)
Workflow issues	
Clinician busy engaging in other tasks	54/1,451 (4)
Clinician was starting to close the case at the time of the prompt	53/1,451 (4)
The bolus recommendation was suspect and/or based on recent artifactual data	52/1,451 (4)
Arterial blood gas/lab draw	39/1,451 (3)
Clinician was administering fluid (blood or other) outside of software	34/1,451 (2)
Patient was waiting for erythrocyte administration	29/1,451 (2)
Fluid was recently administered and still within observation period	26/1,451 (2)
Patient recently received fluid but was not responsive	18/1,451 (1)
Questionable pressure tracing	16/1,451 (1)
Clinician was concerned about dilutional anemia at the time	7/1,451 (0.5)
Clinician mistakenly declined the prompt	6/1,451 (0.4)
Surgical condition	
There was a change in subject positioning and clinician would prefer to wait and see	28/1,451 (2)
There was an expected change with insufflation which was thought to be brief	3/1,451 (0.2)

*The denominator reflects the fact that more than one reason could be provided for why an Assisted Fluid Management prompt was declined.

period. None of the serious adverse events were deemed definitively related to the software or subsequent clinical actions.

Discussion

Clinicians routinely give fluids intraoperatively to maintain vascular volume and vital organ perfusion. Fluids are usually given per clinician judgment, based on blood pressure, heart rate, urine output, blood loss, and informal assessments of pulse pressure variation. The difficulty is that most of these physiologic variables are lagging indicators of patient volume status. For example, patients can lose up to 20% of blood volume before blood pressure decreases. Furthermore, arbitrary restrictive or liberal fluid administration strategies can lead to poor patient outcomes.[22,23] A more formal approach is to use some sort of goal-directed algorithm, typically based on SV changes in response to fluid boluses. The goal is usually to give enough fluid to maximize SV and optimize tissue perfusion. A challenge with this approach is determining when fluid boluses are likely to increase SV (*i.e.*, be beneficial) rather than representing an excessive (unhelpful) fluid load.[13]

Artificial intelligence–based tools in anesthesiology are under development with varied success for various perioperative applications: depth in anesthesia monitoring, anesthetic delivery, adverse event detection, ultrasound guidance, and pain management.[24] With the promise of automating assessment of fluid responsiveness, our artificial intelligence–based Assisted Fluid Management software was successful in recommending fluid bolus when needed. SV increased more after software-recommended boluses than after clinician-initiated ones, and desired SV goals were more often met when following the software's recommendations.

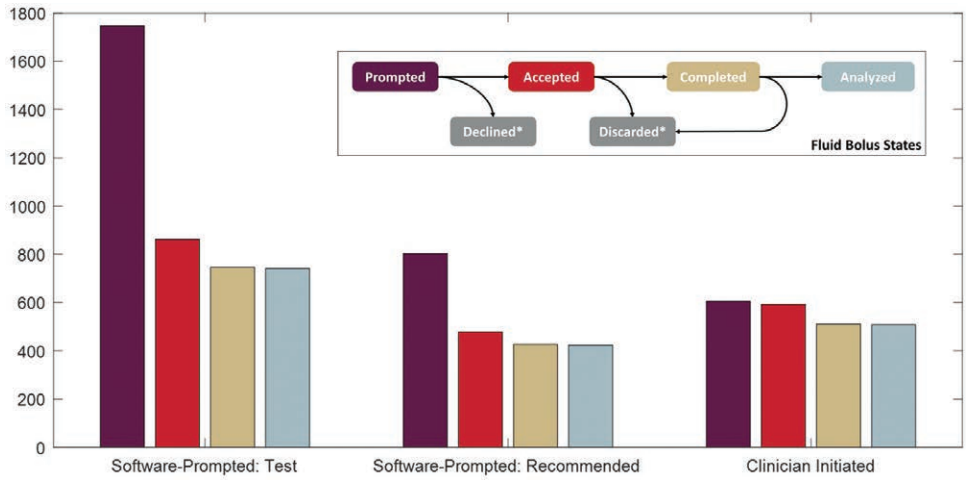

Fig. 3. The number of fluid bolus prompts grouped by origin (software test prompts, software-recommended prompts, or clinician-initiated) are represented by the *purple bars*. The number of these prompts that were accepted, completed, and analyzed are represented by *red*, *tan*, and *blue bars*, respectively. A declined software prompt places the system in a 5-min quiet period when no new notifications are presented to the clinician. A fluid bolus can be analyzed by the software if it was delivered within the prescribed rate and volume limits and has the required information to assess the hemodynamic response to the fluid.

Only 41% of the clinician-initiated fluid boluses in our patients resulted in *a priori*–specified SV increases. The remaining boluses might represent excessive volume administration that might have been better avoided or were given in response to ongoing blood loss. In contrast, fluid boluses recommended by the software led to desired SV increases in 66% of the instances, representing a relative 60% improvement over clinician-initiated boluses. Furthermore, the absolute increase in SV after software-recommended boluses was 40% greater than after clinician-initiated boluses. Software-guided fluid administration therefore increased both the fraction of beneficial boluses and their efficacy.

An assumption behind guided fluid management is that titrating fluid administration to SV improves outcomes. In fact, the evidence supporting the benefit is weak.[3,13,25] But to the extent that guided management might improve fluid titration, the complexity of goal-directed protocols is a barrier to implementation in clinical practice.[7] By automating assessment of fluid responsiveness, objective guidance by the software has the potential to improve adherence to goal-directed protocols.

Table 5. Serious Adverse Events and Their Association with Study Device

Event (N = 314)	Not Related m, n (n/N)*	Possibly Related to Device m, n (n/N)*	Related to Device m, n (n/N)*
Cardiac disorders	16, 8 (3%)		0, 0 (0%)
Arrhythmia	11, 5 (2%)	1, 1 (0.3%)	0, 0 (0%)
Infections and infestations	40, 31 (10%)		0, 0 (0%)
Sepsis	8, 8 (3%)	1, 1 (0.3%)	0, 0 (0%)
Injury, poisoning, and procedural complications	18, 18 (6%)		0, 0 (0%)
Postoperative ileus	3, 3 (1%)	1, 1 (0.3%)	0, 0 (0%)
Metabolism and nutrition disorders	7, 7 (2%)		0, 0 (0%)
Lactic acidosis	1, 1 (0.3%)	1, 1 (0.3%)	0, 0 (0%)
Renal and urinary disorders	11, 11 (4%)		0, 0 (0%)
Acute kidney injury	8, 8 (3%)	4, 4 (1%)	0, 0 (0%)
Vascular disorders	17, 14 (5%)		0, 0 (0%)
Hypotension	4, 4 (1%)	1, 1 (0.3%)	0, 0 (0%)
All site-reported serious adverse events	170, 88 (28%)	9, 6 (1.9%)	0, 0 (0%)

m is the number of events; n is the number of subjects with the event; N is the total number of patients in the study. Since a subject can have multiple types of events within the same category, the number of unique subjects with an event in the main category may not add up to the number of subjects with an event in the individual subcategories.

*Events captured up until 30 days after surgery.

Half of all software prompts were declined by clinicians and could not be analyzed. The major reason software recommendations were declined was that blood pressure was normal for the clinical situation or clinicians preferred to use vasopressors, suggesting that the clinicians believed that both pressure and flow are necessary for adequate perfusion. A complete list of the reasons for declined prompts is presented in table 4. Presumably, if all recommended boluses are accepted and fluid boluses given, there will be fewer subsequent recommendations because initial boluses will replete the vascular space. Clinicians' compliance with software prompts may have affected mean time-in-target for SV variation, which was only 73% in our study. In contrast, Joosten *et al*. reported high (92%) time-in-target with high compliance with software prompts.[14] Clinical practice variability may affect compliance with study protocol and thus response rate. But response rates were similar across various hospital centers (Supplemental Digital Content, table 2, http://links.lww.com/ALN/C609), supporting our primary conclusion. Changes in surgical or patient condition during bolus are unavoidable. For example, surgical or patient conditions may change quickly after acceptance of bolus prompts. Clinicians were instructed to mark "discard" in the clinical platform to remove an accepted/delivered bolus record from the analysis if a drug like a vasopressor was given or a surgical condition like patient position changed during bolus administration. The fact that nearly half of the software-recommended prompts were declined, presumably due to lack of trust in this novel software, is unsurprising. But changes in surgical or patient condition during bolus is unavoidable, making it impossible to determine true effect of the recommended bolus. System performance should be further evaluated in various clinical settings and with clinicians who more often accept the software recommendations. Additionally, anesthetic level, surgical stimulation, vasoactive medications, and baseline cardiovascular can affect the decision to administer fluid bolus and the subsequent SV response. While we don't have the data on anesthetic level or surgical condition, we did evaluate the impact of timing of vasopressor on the primary endpoint. The SV change did not differ much when vasoactive medications were given within 15 min of fluid bolus administration, supporting our primary conclusion. Also, we evaluated the variance in response rate based on the sites and the clinicians nested within sites. While the response rate varied between sites, it did not appear to have a large impact on the outcome. Consistent with previous reports on fluid management practices, most of the variance is attributed to clinician experience.[26]

The Acumen Assisted Fluid Management software and monitoring system rely on accurate information from both the arterial pressure waveform and an engaged clinician who needs to provide bolus details. The combination of information from SV variation and the information from past hemodynamic responses to fluid boluses helps the software discriminate between fluid-responsive and nonresponsive events. For example, in situations when a patient might be considered fluid-responsive (*i.e.*, SV variation is elevated), but has not responded to past fluid boluses, with all else equal, the software learns to withhold additional fluid bolus prompts. This learning mimics clinical thinking and is a desirable feature of the software. On the other hand, the software adds work to the normal clinical routine. For example, clinicians need to document start time, stop time, and volume of administered boluses.

Our study was designed to assess the software's effectiveness as a decision support tool for clinicians by providing individualized recommendations for fluid administration in moderate- to high-risk surgery patients. We showed that SV increased more after software-recommended boluses than after clinician-initiated ones and that desired SV goals were more often met when following the software's recommendations. However, the generalizability of our findings is limited by our focus on moderate- to high-risk surgical patients, the requirement to ventilate patients with more than 8 ml/kg ideal body weight, and the exclusion of patients with a body mass index greater than or equal to 35 kg/m^2, valvular heart disease, and atrial fibrillation, among others. Also, the clinical importance of these intermediate outcomes remains unclear. For that matter, it remains unclear whether targeted fluid management improves substantive outcomes.[3,13,25] A robust randomized trial is needed to determine the extent to which software-guided fluid management might improve important outcomes.

In conclusion, during major noncardiac surgical procedures, fluid boluses recommended by the Assisted Fluid Management software substantively increased SV about 60% more often than clinician-initiated boluses. Furthermore, the absolute increase in SV after software-recommended boluses was 40% greater than after clinician-initiated boluses. The software guidance thus appears to be a useful complement to clinical judgment in determining when fluid boluses are needed during major noncardiac surgery.

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Competing Interests

Drs. Maheshwari, Sessler, and Miller are consultants for Edwards Lifesciences (Irvine, California). Dr. Ramsingh was a consultant for Edwards Lifesciences during the study period and took on a paid position within the company

in October 2020. The other authors declare no competing interests.

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