EDITORIAL

Choosing the Best Blood Pressure Target for Vasopressor Therapy

John C. Marshall, MD

Medical research drives innovation and improves outcomes. In cardiology, advances in diagnosis, prevention, and treatment reduced the 30-day mortality from acute myocardial infarction from 20% to 12.4% between 1995 and 2014.[1] Similarly, for women diagnosed with breast cancer, 5-year survival has increased from 74% to 88.5% over the past 4 decades[2] in parallel with advances in diagnosis and targeted therapy, including chemotherapeutic regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF), trastuzumab, and aromatase inhibitors.[3]

Related article

However, patient outcomes also improve in the absence of specific technological advances. For example, it is estimated that between 1990 and 2017, the global number of deaths from sepsis declined from 15.7 million (95% uncertainty intervals [UI], 14.7-16.7 million) to 11.0 million (95% UI, 10.0-12.1 million).[4] This improvement has not occurred because of new drugs and new procedures but rather from improved approaches to resuscitation and physiologic support and from understanding the effects of often subtle variability in management strategies that translate into better patient outcomes. A recurring theme of these insights is that although physiologic support is good, restraint in providing that support is often better, for example, controlling blood glucose levels but not too rigidly using insulin[5]; administering transfusions but accepting a lower hemoglobin threshold at which to make the decision to transfuse[6]; or providing ventilator support but limiting distention of the lungs.[7] Underlying this theme is an emerging recognition that in acute critical illness, what is normal is not necessarily optimal and that interventions bring both benefits and harms.

In this issue of *JAMA*, Lamontagne and colleagues[8] report the results of the 65 trial, an evaluation of blood pressure targets to guide vasopressor therapy. The emergency hemodynamic management of septic shock includes administration of fluids to restore a relative intravascular volume deficit, and the use of vasopressor agents such as norepinephrine to increase blood pressure when fluid alone is insufficient to do so. Increased blood pressure is thought to result in augmented tissue perfusion, although the optimal threshold is unknown. Previous guidelines of the Surviving Sepsis Campaign had recommended that a mean arterial pressure (MAP) threshold of 65 mm Hg should be targeted,[9] based on observational data that tissue perfusion is maintained at a MAP as low as 65 mm Hg.[10] Implicit in that recommendation is an assumption that harm is only a consequence of a MAP that is too low, and not one that is too high. Prior studies have suggested that a higher blood pressure may be harmful[11,12] and that targeting a MAP of 65 mm Hg results in MAP levels of 75 mm Hg or higher because infusions are increased when the pressure is lower than the target but not necessarily reduced when it is higher than the target blood pressure level.[12] Moreover, the physiologic objective is not pressure but flow, and for a given pressure, flow is increased when resistance is reduced, as it is in septic shock.

Building on the findings of an earlier pilot trial,[13] the 65 trial investigators tested the hypothesis that targeting a MAP of 60 to 65 mm Hg in older patients would be more effective than usual care as reflected in reduced all-cause mortality at 90 days. Patients older than 65 years with vasodilatory hypotension were randomized to receive vasopressors guided either by MAP target (60-65 mm Hg, permissive hypotension) (n = 1291) or to receive usual care (at the discretion of the treating clinician) (n = 1307). The researchers showed satisfactory adherence with the intervention, as reflected in an 11.3% occurrence of nonadherence and in the separation of the mean blood pressures achieved (although MAPs for the permissive hypotension group appeared to average around 65 mm Hg).

At 90 days, 500 of 1221 (41.0%) patients in the permissive hypotension group had died compared with 544 of 1242 (43.8%) in the usual care group (absolute risk difference, −2.85%; 95% CI, −6.75 to 1.05; *P* = .15), which favored the permissive hypotension approach but failed to meet prespecified criteria for superiority (an absolute risk reduction of 6%). The duration of vasopressor usage and the amount of drug administered were reduced in the permissive hypotension group, with a difference in mean duration of vasopressors of −9.9 hours (95% CI, 62; -14.3 to −5.5 hours) and a difference in median dose of vasopressors of (8.7 mg, 95% CI, −12.8 to −7.6 mg, norepinephrine equivalent). Both a prespecified analysis adjusted for imbalances in key baseline variables and a post hoc subgroup analysis of patients with chronic hypertension at baseline yielded odds ratios (ORs) suggesting the possibility of better survival associated with permissive hypotension, with an adjusted OR of 0.82 (95% CI, 0.68 to 0.98), and an adjusted relative risk of 0.84 (95% CI, 0.71 to 0.99), respectively. As importantly, there was no evidence that a lower blood pressure target was associated with later ischemic sequelae such as acute kidney injury or cognitive impairment in survivors.

The 65 trial is an example of what has been disparagingly called a "negative" or "null" trial,[14] yet it is also an important contribution to knowledge that will likely change practice and may help to reduce mortality. How can this be possible?

The concept that a trial is either positive or negative derives from trials of novel drugs or technologies. The investigators posit a minimally important treatment effect that either is or is not achieved when the intervention is applied; the result is a categorical decision about efficacy. Such a dichotomous decision is appropriate when the intervention is untested: in that case, not only is the intervention new and a departure from standard care, it carries unknown risks and costs, so the threshold for adoption is high.

In contrast, the 65 trial explored the merits of an intervention that is in widespread clinical use—vasopressor therapy—but for which optimal titration is uncertain. This uncertainty reflects inherent variability in clinical practice and changing clinical perspectives on the validity of conventional wisdom. Declining rates of acute gastrointestinal stress bleeding, for example, have led investigators to ask whether the harms of prophylaxis may outweigh the benefits[15]; concerns that the oxygen-carrying capacity of red blood cells might be jeopardized by prolonged storage led to trials of fresh vs conventionally stored red blood cells,[16] and speculation that oxygen may be harmful during acute inflammation has prompted analyses of reduced oxygen targets in critical illness.[17] The outcomes of these trials were far from predictable, and practice variability reflects uncertainty in understanding optimal therapy in the context of profoundly disrupted homeostasis. This variability is what makes clinical trials in critical care so important but also so potentially controversial.[18]

There are 2 common approaches to the design of a clinical trial that evaluates practice variability. Investigators might first seek to measure the spectrum of that variability through preliminary observational studies or studies of clinician attitudes and then define study groups that represent 2 plausible but separate approaches along a spectrum of practice.[6] Alternatively, the investigators might opt to evaluate a specific interventional strategy and compare this with a "usual care" control, as was done in the 65 trial. Both approaches have shortcomings. Definition of 2 different treatment groups based on 2 discrete points on a spectrum of practice possibilities (for example, a liberal vs a conservative approach) potentially opens the trialists to accusations that one or other intervention is widely divergent from usual care and thus unethical or that the optimal approach is in the middle.[19] On the other hand, the use of a usual care control assumes that standard care is optimal care and risks contamination of the experiment because of secular changes in practice over time.[20] In many cases, usual care is often far from standardized care, as the substantial variability around MAP readings in the usual care group of the 65 trial attests.

So how should the results of the 65 trial be incorporated into clinical practice? From a scientific perspective, the trial was indeterminate. It failed to support its primary hypothesis, although it generated findings that were consistent with that hypothesis and suggested that further work might well be informative. But for the clinician caring for a patient with vasodilatory shock, the message is different. Nothing in the results suggests that artificially raising the blood pressure by administering more vasopressors provides benefit for patients; in fact, the signal suggests that this deliberate intervention may be harmful, particularly among patients for whom expert opinion had previously recommended such an approach,[9] those with preexisting hypertension. Clinicians could be reassured in the finding that assiduously targeting an arbitrary blood pressure is not helpful; scientists could ask whether interventions should be titrated to pressure at all but and instead should focus on physiologic variables that reflect flow, such as capillary refill.[21] Clearly, caution must be exercised in avoiding a blood pressure that is too low to enable perfusion, but the 65 trial raises the question, "Should an upper limit be placed on a MAP target?"

Randomized clinical trials yield insight, not instructions. The message of the 65 trial by Lamontagne et al is not that all patients should be treated the same, rather that treatment decisions can be individualized around a somewhat lower mean MAP comfort point. A MAP target of 60 to 65 mm Hg appears to be more than adequate for most older patients with vasodilatory shock, and, contrary to conventional wisdom, it is possible that a lower target threshold may be more beneficial in older patients with preexisting hypertension. Some "negative" trials can contribute to changes in clinical practice.

ARTICLE INFORMATION

Author Affiliation: The Keenan Research Centre for Biomedical Science, the Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

Corresponding Author: John C. Marshall, MD, St Michael's Hospital, 30 Bond St, Fourth Floor Bond Wing, Room 4-007, Toronto, ON M5B 1W8, Canada (john.marshall@unityhealth.to).

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Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension
A Randomized Clinical Trial

François Lamontagne, MD; Alvin Richards-Belle, BSc; Karen Thomas, MSc; David A. Harrison, PhD; M. Zia Sadique, PhD; Richard D. Grieve, PhD; Julie Camsooksai, BSc; Robert Darnell, BA; Anthony C. Gordon, MD; Doreen Henry, MSc; Nicholas Hudson, BA; Alexina J. Mason, PhD; Michelle Saull, BSc; Chris Whitman, BSc; J. Duncan Young, DM; Kathryn M. Rowan, PhD; Paul R. Mouncey, MSc; for the 65 trial investigators

Visual Abstract
Editorial
Video and Supplemental content

IMPORTANCE Vasopressors are commonly administered to intensive care unit (ICU) patients to raise blood pressure. Balancing risks and benefits of vasopressors is a challenge, particularly in older patients.

OBJECTIVE To determine whether reducing exposure to vasopressors through permissive hypotension (mean arterial pressure [MAP] target, 60-65 mm Hg) reduces mortality at 90 days in ICU patients aged 65 years or older with vasodilatory hypotension.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, pragmatic, randomized clinical trial was conducted in 65 ICUs in the United Kingdom and included 2600 randomized patients aged 65 years or older with vasodilatory hypotension (assessed by treating clinician). The study was conducted from July 2017 to March 2019, and follow-up was completed in August 2019.

INTERVENTIONS Patients were randomized 1:1 to vasopressors guided either by MAP target (60-65 mm Hg, permissive hypotension) (n = 1291) or according to usual care (at the discretion of treating clinicians) (n = 1307).

MAIN OUTCOME AND MEASURES The primary clinical outcome was all-cause mortality at 90 days.

RESULTS Of 2600 randomized patients, after removal of those who declined or had withdrawn consent, 2463 (95%) were included in the analysis of the primary outcome (mean [SD] age 75 years [7 years]; 1387 [57%] men). Patients randomized to the permissive hypotension group had lower exposure to vasopressors compared with those in the usual care group (median duration 33 hours vs 38 hours; difference in medians, −5.0; 95% CI, −7.8 to −2.2 hours; total dose in norepinephrine equivalents median, 17.7 mg vs 26.4 mg; difference in medians, −8.7 mg; 95% CI, −12.8 to −4.6 mg). At 90 days, 500 of 1221 (41.0%) in the permissive hypotension compared with 544 of 1242 (43.8%) in the usual care group had died (absolute risk difference, −2.85%; 95% CI, −6.75 to 1.05; $P = .15$) (unadjusted relative risk, 0.93; 95% CI, 0.85-1.03). When adjusted for prespecified baseline variables, the odds ratio for 90-day mortality was 0.82 (95% CI, 0.68 to 0.98). Serious adverse events were reported for 79 patients (6.2%) in the permissive care group and 75 patients (5.8%) in the usual care group. The most common serious adverse events were acute renal failure (41 [3.2%] vs 33 [2.5%]) and supraventricular cardiac arrhythmia (12 [0.9%] vs 13 [1.0%]).

CONCLUSIONS AND RELEVANCE Among patients 65 years or older receiving vasopressors for vasodilatory hypotension, permissive hypotension compared with usual care did not result in a statistically significant reduction in mortality at 90 days. However, the confidence interval around the point estimate for the primary outcome should be considered when interpreting the clinical importance of the study.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: 65 Trial investigators are listed at the end of the article.

Corresponding Author: François Lamontagne, MD, Université de Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada (francois.lamontagne@usherbrooke.ca).

Section Editor: Derek C. Angus, MD, MPH, Associate Editor, *JAMA* (angusdc@upmc.edu).

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Vasopressors are commonly administered to patients in intensive care units (ICUs)[1,2] to avoid hypotension associated with myocardial injury, kidney injury, and death.[3,4] Vasopressors, however, may reduce blood flow in vasoconstricted vascular beds and are associated with effects on cardiac, metabolic, microbiome, and immune function.[5] Balancing risks of hypotension with risks from vasopressors is, therefore, a challenge when managing patients in ICUs.

Blood pressure is used to guide administration of vasopressors. The 2012 Surviving Sepsis Campaign Guidelines recommended an initial mean arterial pressure (MAP) target of 65 mm Hg with a higher target for older patients, and for those with chronic hypertension and coronary artery disease.[6] Although the 2016 update[7,8] acknowledged no evidence for targeting MAP values greater than 65 mm Hg in any patient group, MAP values reported in observational studies are systematically higher than 65 mm Hg,[9,10] possibly because clinicians also use other targets.

Results from an individual patient data meta-analysis of 2 trials evaluating MAP targets, the SEPSISPAM (Sepsis and Mean Arterial Pressure) trial,[11] and the OVATION (Optimal Vasopressor Titration) pilot trial,[12] suggest that increased exposure to vasopressors resulting from higher MAP targets is potentially associated with an increased risk of death in a subgroup of older patients (≥65 years).[13] In this subgroup, 28-day mortality was 37.2% compared with 45.8% (odds ratio, 1.42; 95% CI, 0.98-2.04). This led to the biological rationale that greater exposure to vasopressors may harm older patients by overwhelming their more limited physiological reserve.

This randomized clinical trial tested the hypothesis that reducing vasopressor exposure through permissive hypotension (using a MAP target of 60-65 mm Hg) among patients treated in the ICU aged 65 years or older with vasodilatory hypotension and receiving vasopressors compared with usual vasopressor exposure reduces 90-day mortality (**Video**).

Key Points

Question What is the effect on mortality at 90 days of reducing the exposure to vasopressors through permissive hypotension (mean arterial pressure target of 60-65 mm Hg) in intensive care unit (ICU) patients aged 65 years or older receiving vasopressors for vasodilatory hypotension?

Findings In this randomized clinical trial that included 2600 patients aged 65 years or older with vasodilatory hypotension, treatment with permissive hypotension resulted in death at 90 days among 41.0% of patients compared with 43.8% of those receiving usual care, a difference that was not statistically significant.

Meaning Reducing the exposure to vasopressors through permissive hypotension did not significantly reduce mortality at 90 days.

Methods

Trial Design and Oversight

The 65 trial[14] was a pragmatic, open, multicenter, parallel group, randomized clinical trial. The South Central-Oxford C Research Ethics Committee and the United Kingdom Health Research Authority approved the trial protocol, which is available in Supplement 1. The research ethics committee granted an emergency waiver of consent. The UK National Institute for Health Research (NIHR) convened an independently chaired (and majority independent) trial steering committee and an independent data monitoring and ethics committee. The Clinical Trials Unit at the UK Intensive Care National Audit & Research Centre (ICNARC) managed the trial.

Sites and Patients

The trial was conducted in 65 UK National Health Service (NHS) adult, general, ICUs that participate in the Case Mix Programme—the national clinical audit for adult ICUs across England, Wales, and Northern Ireland. Patients aged 65 years or older admitted to a participating ICU were eligible if they were randomized within 6 hours of commencing a vasopressor infusion (to minimize exposure to vasopressors prior to randomization) for vasodilatory hypotension, with adequate fluid resuscitation (as assessed by the treating clinician) completed or ongoing and vasopressors were expected to continue for 6 hours or more. In an earlier version of the protocol, randomization was permitted from the point of making the decision to commence a vasopressor infusion (**Figure 1**). Exclusion criteria included contraindications to permissive hypotension (eMethods in Supplement 2).

Screening was conducted by the clinical-research teams at each ICU. Randomization occurred as soon as possible once eligibility was confirmed. Patients were allocated in a 1:1 ratio, via a concealed central 24-hour telephone-web randomization system, to permissive hypotension or usual care. Randomization was stratified by site using permuted blocks with variable block lengths (of 4, 6, and 8).

Trial Interventions

Patients in the permissive hypotension group received vasopressors with administration guided by a MAP target of 60 to 65 mm Hg to reduce or discontinue exposure to vasopressors. The MAP target was reinforced through trial-specific prompts on infusion pumps and in medical notes and setting of upper MAP alarms. Patients in the usual care group received vasopressors at the discretion of treating clinicians allowing a more personalized approach (eg, in function of patient characteristics and markers of perfusion). Choice of vasopressor, as well as all other interventions, were also at the discretion of treating clinicians. Norepinephrine, vasopressin, terlipressin, phenylephrine, epinephrine, dopamine, and metaraminol were considered as vasopressors.

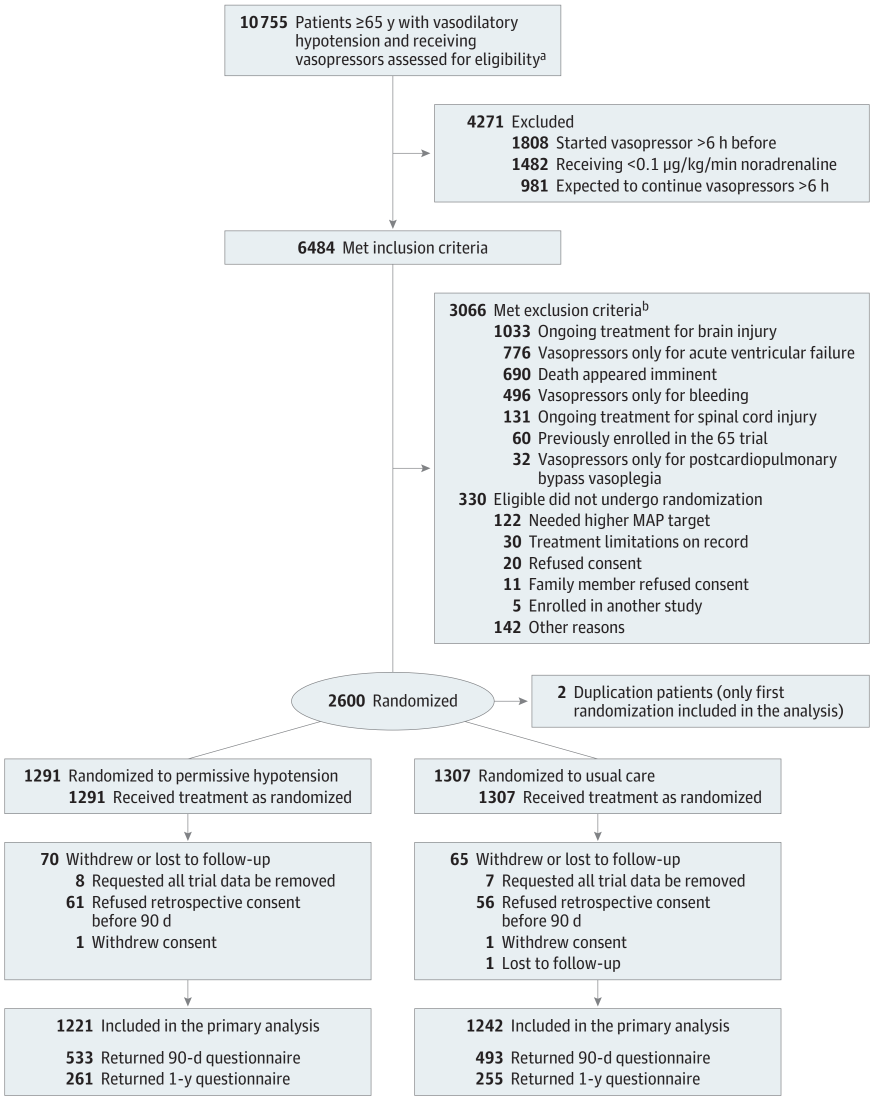
Monitoring of Adherence

Adherence was defined as appropriate reduction in dose (or discontinuation) of vasopressors when the MAP was higher than the upper target limit (65 mm Hg). Deviation was defined by failure to reduce (or discontinue) vasopressors while the MAP remained higher than 65 mm Hg for 3 consecutive hours.

Consent Procedures

For patients who did not have the mental capacity to give verbal consent prior to randomization, a "research without prior consent" approach was used. Agreement was obtained from

Figure 1. Screening, Randomization, and Follow-up of Patients in the 65 Trial



[a] As assessed by the treating clinician.

[b] Some patients met more than 1 criterion.

a personal or nominated consultee as soon as appropriate following randomization. Informed consent was obtained from patients if they regained mental capacity. Data collected up to refusal or withdrawal of consent were retained. All procedures are provided in the eMethods section in Supplement 2.

Outcome Measures

The primary outcome was all-cause mortality at 90 days after randomization.

Secondary outcomes were mortality at discharge from ICU and from the treating acute care hospital; duration of survival to longest available follow-up; duration of advanced respiratory and renal support during ICU stay; days alive and free of advanced respiratory support and renal support within first 28 days; duration of ICU and treating acute care hospital stay; cognitive decline assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, short version)[15] in survivors at 90 days and 1 year; and health-related quality of life (QOL), assessed using the EuroQoL 5-dimension 5-level (EQ-5D-5L) questionnaire,[16] in survivors, at 90 days and 1 year. IQCODE scores are calculated as the mean of the scores from the 16 items that range from 1 (much improved) to 5 (much worse). The EQ-5D-5L utility scale ranges from −0.285 to 1 with lower scores indicating worse health-related QOL, anchored at 0 (death) and 1 (perfect health). No studies have been conducted to establish a minimally clinically important difference (MCID) for critically ill patients aged 65 years or older with vasodilatory hypotension on either the IQCODE or EQ-5D-5L. Adverse events were monitored to ICU discharge. All definitions are in listed in the eMethods section in Supplement 2. The integrated economic evaluation for the trial will be reported separately.

Data Collection

Patients' trial data were linked to both Case Mix Programme data, including baseline data and ICU outcomes, and NHS death registrations, for survival data. Data not contained in the Case Mix Programme—such as hourly vasopressor dose and MAP—were collected prospectively. Detailed vasopressors and MAP data are based on the first episode of vasopressors, with the end of an episode defined as a 24-hour period without receipt of vasopressors, discharge from the ICU, or death (whichever occurred first). Cognitive decline and health-related QOL were ascertained by mailed questionnaires, with telephone follow-up. Follow-up for patient-reported 1-year outcomes was stopped when the last patient reached 90 days.

Statistical Analysis

Using Case Mix Programme data, the final sample size calculation assumed a 90-day mortality of 35% for usual care with a 2.5% withdrawal or loss to follow-up; a sample size of 2600 patients (1300 per group) had 90% power to detect a 6% absolute risk reduction—approximately two-thirds of the observed absolute risk reduction in the individual patient data meta-analysis[13]—to 29% for permissive hypotension. An initial sample-size calculation based on the same assumptions but powered to detect an 8% absolute risk reduction was updated following the internal pilot phase on the recommendation of the trial steering committee (eMethods in Supplement 2). A single interim analysis on the primary end point was conducted after recruitment and 90-day follow-up of 500 patients, using a Peto-Haybittle stopping rule ($P < .001$) for early termination due to either effectiveness or harm.

Patients were analyzed according to their randomized group, following a prespecified statistical analysis plan.[17] A P value of less than .05 was considered statistically significant. All tests were 2-sided with no adjustment for multiple comparisons. Doses for each vasopressor, except metaraminol, were converted to norepinephrine equivalents.[18]

The Fisher exact test was used to compare between-group differences in the primary outcome. Absolute risk reduction is reported with 95% CIs without adjustment as the primary effect estimate. Secondary analyses of the primary outcome included unadjusted relative risk reduction; and adjusted analysis (using multilevel logistic regression) for prespecified baseline variables (age, sex, chronic hypertension, chronic heart failure, atherosclerotic disease, dependency on assistance for daily activities, location prior to ICU admission and urgency of surgery, ICNARC physiology score,[19] Sepsis-3,[20] receipt of vasopressors at randomization, and duration of vasopressors prior to randomization), and site (as a random effect). Sensitivity analyses repeating the primary analysis including only patients deemed eligible in the final version of the protocol; best- and worst-case scenario analysis assuming all patients with missing primary outcome data had survived if randomized to permissive hypotension and died if randomized to usual care, and vice versa; and adherence-adjusted analysis defining adherence as a binary variable, 0 for all patients allocated to permissive hypotension with 1 or more deviation, or 1 if not, and using a structural mean model with an instrumental variable of allocated treatment to estimate the complier average causal effect of treatment.

Secondary outcomes were analyzed using unadjusted t tests or Wilcoxon rank sum test and multilevel linear regression for continuous outcomes (duration of advanced respiratory and renal support, days alive and free of advanced respiratory and renal support at day 28, duration of ICU and treating acute care hospital stay, cognitive decline, and health-related QOL at 90 days and 1 year), Fisher exact test and multilevel logistic regression for binary outcomes (mortality at discharge from ICU and treating acute care hospital), and log-rank test and Cox proportional-hazard models with shared frailty at the site level for duration of survival from randomization to longest available follow-up (proportionality was assessed visually using Kaplan-Meier curves).

Prespecified, subgroup analyses of the primary outcome testing interactions for age, chronic hypertension, chronic heart failure, atherosclerotic disease, ICNARC risk of death,[19] Sepsis-3,[20] and receipt of vasopressors at randomization were conducted. Likelihood ratio tests were used to compare models, with and without the relevant interaction terms. One subgroup, chronic hypertension, was also tested (prespecified) for interaction with the effect of permissive hypotension across the in-hospital secondary outcomes.

Missing values were imputed using multivariate imputation by chained equation (MICE)[21] for all baseline variables included in the adjusted model and for cognitive decline and health-related QOL at 90 days and at 1 year (in patients known to be alive at each relevant time point). Models were fitted across all the imputed data sets and results combined using the Rubin rules.[22] Further details of variables considered for imputation are provided in eTable 1 in Supplement 2. Stata/SE version 14.2 was used for all effectiveness analyses, and Stata/SE version 16.0 for multiple imputation (StataCorp LP).

Post hoc analyses included estimation of the absolute risk difference for the primary outcome adjusted for site only, using a generalized estimating equations (GEE) model with a binomial link and robust standard error estimates, estimation of the adjusted relative risk for the primary outcome, adjusted for the same baseline variables as previously specified, and calculation of the adjusted relative risk by prespecified subgroups, which was done using a GEE model with a Poisson link and robust standard error estimates. Mortality at days 28 and 60 was also reported as a binary outcome using only patients with nonmissing primary outcome data.

Results

Sites and Patients

Across 65 sites, a total of 10 755 patients aged 65 years or older with vasodilatory hypotension and receiving vasopressors were screened and 6484 deemed to have met the inclusion criteria. After applying the exclusion criteria, 2930 were potentially eligible and 2600 were enrolled between July 3, 2017, and March 16, 2019. Two patients were randomized twice (in error) leaving 2598 unique patients (1291 permissive hypotension, 1307 usual care) (Figure 1; and eFigures 1 and 2 in Supplement 2). Randomization occurred 24 hours a day, 7 days a week (eFigure 3 in Supplement 2). Deferred consent was used, and retrospective consent was obtained for 2461 (95%) of patients (eFigures 4 and 5 in Supplement 2), of whom 2 later

Table 1. Patient Baseline Characteristics

Characteristic	No./Total (%) of Patients	
	Permissive Hypotension (n = 1283)[a]	Usual Care (n = 1300)[a]
Age, median (IQR), y	75.2 (70.4-80.5)	74.8 (70.1-80.8)
Sex		
Women	520/1216 (42.8)	547/1239 (44.1)
Men	696/1216 (57.2)	692/1239 (55.8)
Comorbidities[b]		
Chronic hypertension	590/1283 (46.0)	597/1299 (46.0)
Atherosclerotic disease	187/1283 (14.6)	189/1299 (14.5)
Chronic heart failure	143/1283 (11.1)	143/1298 (11.0)
Chronic renal replacement therapy at ICU admission	16/1204 (1.3)	18/1224 (1.5)
Daily activities status before admission to acute hospital		
No assistance	794/1211 (65.6)	850/1230 (69.1)
Minor or major assistance	409/1211 (33.8)	375/1230 (30.5)
Total assistance with all activities	8/1211 (0.7)	5/1230 (0.4)
Location prior to ICU admission and urgency of surgery		
Emergency department and not in hospital	432/1219 (35.4)	420/1239 (33.9)
Operating room		
Elective and scheduled surgery	53/1219 (4.3)	60/1239 (4.8)
Emergency and urgent surgery	259/1219 (21.2)	264/1239 (21.3)
Other ICU	14/1219 (1.1)	22/1239 (1.8)
Ward or intermediate care area	461/1219 (37.8)	473/1239 (38.2)
APACHE II score, mean (SD) [No.][c]	20.9 (6.5) [1218]	20.6 (6.1) [1239]
ICNARC physiology score, mean (SD) [No.][d],	23.9 (8.8) [1213]	23.5 (8.8) [1239]
$ICNARC_{H-2015}$ predicted risk of death, median (IQR) [No.][e]	0.33 (0.15-0.60) [1213]	0.32 (0.14-0.61) [1239]
Sepsis-3[f]		
No sepsis	263/1216 (21.6)	275/1239 (22.2)
Sepsis (not in shock)	364/1216 (29.9)	369/1239 (29.8)
Septic shock	589/1216 (48.4)	595/1239 (48.0)
Mean arterial pressure at randomization, mm Hg[g],		
Mean (SD)	69.9 (10.1)	71.1 (11.5)
Median (IQR) [No.]	69 (64-75) [1281]	70 (64-77) [1300]
Vasopressor infusion(s) received at time of randomization		
Norepinephrine only	761/1265 (60.2)	766/1280 (59.8)
Metaraminol only	406/1265 (32.1)	409/1280 (32.0)
Phenylephrine only	37/1265 (2.9)	38/1280 (3.0)
Epinephrine only	3/1265 (0.2)	5/1280 (0.4)
Vasopressin only	0/1265 (0.0)	2/1280 (0.2)
Dopamine only	0/1265 (0.0)	1/1280 (0.1)
Other or combination	43/1265 (3.4)	34/1280 (2.7)
None[g]	15/1265 (1.2)	25/1280 (2.0)
Norepinephrine equivalent dose[h]		
<0.1 μg/kg/min[i]	153/1265 (12.1)	155/1280 (12.1)
≥0.1 μg/kg/min	676/1265 (53.4)	677/1280 (52.9)
Duration of vasopressor infusion prior to randomization, median (IQR), min [No.][j]	186 (102-277) [1247]	186 (104-284) [1262]

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Excludes 15 patients who refused permission of data use.

[b] Comorbidities were selected a priori because they may constitute effect modifiers.

[c] The Acute Physiology and Chronic Health Evaluation (APACHE) II score (range, 0-71; higher scores indicate greater severity) was calculated using physiology readings in the first 24 hours of ICU admission.[23]

[d] The Intensive Care National Audit & Research Centre (ICNARC) score (range, 0-100; higher scores indicate greater severity) was calculated using physiology readings in the first 24 hours of ICU admission.[24]

[e] $ICNARC_{H-2015}$ predicted risk is calculated using physiology reading in the first 24 hours of ICU admission with age, comorbidities, dependency, and location before and reason for admission.

[f] Sepsis-3 criteria requires evidence of infection and 2 or more points on the Sequential Organ Failure Assessment (SOFA) score, which is based on data in the first 24 hours of ICU admission.

[g] Patients starting vasopressors or receiving metaraminol or terlipressin boluses could be recruited for the protocol's version 2.0, which specified their starting a vasopressor infusion at least 1 hour before randomization.

[h] Norepinephrine equivalent doses were calculated according to the method described in Khanna et al,[18] using the conversion factors: epinephrine μg/kg/min (× 1), dopamine μg/kg/min (/150), phenylephrine μg/kg/min (× 0.1) and vasopressin U min –1 (× 2.5).

[i] Both groups had 118 patients receiving less than 0.1 μg/kg/min of norepinephrine were eligible for recruitment prior to the protocol's version 2.0, which specified that, for patients receiving norepinephrine, then they must fulfill a minimum dose of 0.1 μg/kg/min at the time of randomization. A minimum dose was not required for other vasopressors.

withdrew consent, and 1 was lost to follow-up by 90 days, leaving 2458 patients. Five patients declined retrospective consent after 90 days and were included in the analysis until that point. As a result, 2463 patients (1221 permissive hypotension, 1242 usual care) were included in the analysis of the primary outcome. Follow-up was completed in August 2019.

The randomized groups were well matched at baseline (**Table 1**), except for the proportion of patients dependent on assistance for daily activities (417 [34.4%] in permissive hypotension, 380 [30.9%] in usual care group). Immediately prior to randomization, the mean MAP was 69.9 mm Hg in the permissive hypotension and 71.1 mm Hg in the usual care group.

Table 2. Vasopressor Use After Randomization by Group

	Permissive Hypotension (n = 1261)[a]	Usual Care (n = 1276)[a]	Difference (95% CI)
Total duration of vasopressors after randomization, median (IQR), h	33.0 (15.0 to 56.0)	38.0 (19.0 to 67.0)	-5.0 (-7.8 to -2.2)
Vasopressor usage, No. (%)			
Norepinephrine	992 (78.7)	997 (78.1)	0.9 (−2.3 to 4.1)
Metaraminol	395 (31.3)	418 (32.8)	−1.3 (−4.9 to 2.4)
Vasopressin	123 (9.8)	126 (9.9)	−0.1 (−2.4 to 2.3)
Epinephrine	40 (3.2)	42 (3.3)	−0.1 (−1.5 to 1.3)
Phenylephrine	32 (2.5)	33 (2.6)	−0.0 (−1.3 to 1.2)
Terlipressin	10 (0.8)	14 (1.1)	−0.3 (−1.1 to 0.5)
Dopamine	1 (0.1)	2 (0.2)	−0.1 (−0.3 to 0.2)
Norepinephrine equivalents[b]			
Total dose, mg			
Median (IQR) [No.]	17.7 (5.8 to 47.2) [1008]	26.4 (8.9 to 65.6) [1021]	−8.7 (−12.8 to −4.6)
Mean dose rate, μg kg^{-1} min^{-1}			
Median (IQR)	0.12 (0.06 to 0.23)	0.15 (0.08 to 0.26)	−0.03 (−0.04 to −0.02)
Highest dose rate, μg kg^{-1} min^{-1}			
Median (IQR)	0.26 (0.13 to 0.57)	0.32 (0.16 to 0.63)	−0.06 (−0.09 to −0.02)
Metaraminol[b]			
Total dose, mg			
Median (IQR) [No.]	22.0 (9.3 to 60.0) [395]	35.0 (12.7 to 79.8) [420]	−13.0 (−19.5 to −6.5)
Mean dose rate, mg h^{-1}			
Median (IQR)	2.35 (1.44 to 4.25)	2.83 (1.95 to 4.88)	−0.48 (−0.78 to −0.18)
Highest dose rate, mg h^{-1}			
Median (IQR)	4.00 (3.00 to 6.50)	5.00 (3.50 to 7.00)	−1.00 (−1.48 to −0.52)
Terlipressin			
Total dose, U			
Median (IQR) [No.]	2.5 (1.0 to 10.8) [10]	3.3 (1.0 to 6.0) [14]	−0.8 (−8.5 to 6.9)
Time receiving vasopressor with recorded MAP			
≤65 mm Hg[c]			
Median (IQR) h	12 (5 to 25)	6 (2 to 13)	
>65 mm Hg[c]			
Median (IQR) h	12 (5 to 25)	27 (13 to 49)	
Mean MAP while receiving vasopressors, mm Hg[d]			
Median (IQR) [No.]	66.7 (64.5 to 69.8) [1247]	72.6 (69.4 to 76.5) [1267]	−5.9 (−6.4 to −5.5)
Peak MAP while receiving vasopressors, mm Hg[d]			
Median (IQR)	83.0 (75.0 to 92.0)	92.0 (85.0 to 100.0)	−9.0 (−10.4 to −7.6)

Abbreviations: IQR, interquartile range; MAP, mean arterial pressure.

[a] Total number of patients with treatment data recorded until completion of the first treatment episode. In the permissive hypotension group, the proportions of the way in which the first episode ended were 72.8% were free of vasopressors for 24 continuous hours, 11.0% were discharged from ICU prior to being free of vasopressors for 24 continuous hours, and 16.2% died while receiving vasopressors. In the usual care group, the same proportions were 69.0%, 12.3%, and 18.7%, respectively.

[b] See eFigure 6 in Supplement 2.

[c] See eFigure 9 in Supplement 2.

[d] See eFigures 8 and 10 in Supplement 2.

Clinical Management

Patients in the permissive hypotension group had a lower exposure to vasopressors compared with those in the usual care group—median duration 33 hours compared with 38 hours (difference, -5.0; 95% CI, -7.8 to -2.2), mean duration, 46.0 hours compared with 55.9 hours (mean difference, -9.9 hours; 95% CI, -14.3 to -5.5), and median total dose (norepinephrine equivalent), 17.7 mg compared with 26.4 mg (difference, -8.7 mg; 95% CI, -12.8 to -4.6 mg) (**Table 2**; eTable 2 and eFigures 6 and 7 in Supplement 2). Clinical management diverged immediately after randomization (eFigure 8 in Supplement 2), and there was a clear difference in management of vasopressors between the groups (eFigure 9 in Supplement 2). Mean and peak MAP values were lower in the permissive hypotension group (Table 2; and eFigure 10 in Supplement 2). The number of episodes of vasopressors were not significantly different between groups, with 86.8% of patients in the permissive hypotension and 86.3% in the usual care group having a single episode.

Adherence to Protocol

The number of patients with one or more occurrence of nonadherence was 153 (11.3%) (permissive hypotension group). Overall, nonadherence represented 6% of the total time receiving vasopressors. The main reasons for nonadherence were concerns regarding the patient's clinical condition (renal, 36; cardiac, 4; history of chronic hypertension, 2; gastrointestinal, 2; other, 7); and logistical staff-related issues (trial awareness, 54; other clinical priorities, 42; no reason documented, 6).

Table 3. Primary and Secondary Mortality Outcomes

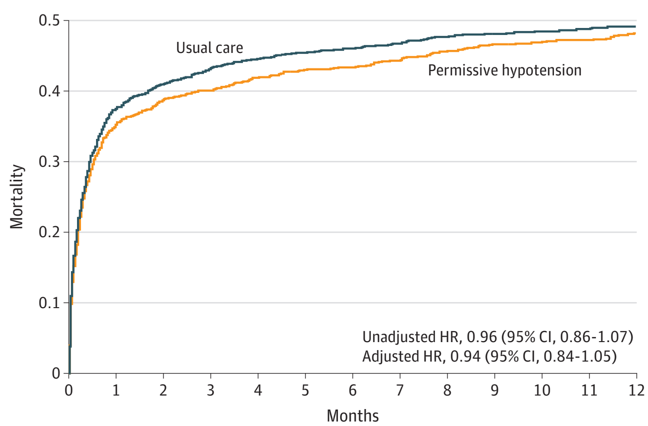
Outcome	No./Total (%) Intervention Group	Usual Care Group	Unadjusted Absolute Difference	*P* Value	Unadjusted Relative Difference (95% CI)	Adjusted Difference (95% CI)[a]
Primary Outcome						
90-d mortality	500/1221 (41.0)	544/1242 (43.8)	−2.85 (−6.75 to 1.05)	.15		
Relative risk					0.93 (0.85 to 1.03)	0.92 (0.83 to 1.01)[b]
Odds ratio					0.89 (0.76 to 1.04)	0.82 (0.68 to 0.98)
Secondary Outcomes						
Discharge mortality						
ICU	362/1212 (29.9)	380/1237 (30.7)	−0.85 (−4.49 to 2.79)	.66		
Relative risk					0.97 (0.86 to 1.10)	0.95 (0.78 to 1.17)[b]
Odds ratio					0.96 (0.81 to 1.14)	0.90 (0.73 to 1.10)
Acute hospital	484/1232 (39.3)	519/1250 (41.5)	−2.23 (−6.09 to 1.63)	.27		
Relative risk					0.95 (0.86 to 1.04)	0.94 (0.85 to 1.03)[b]
Odds ratio					0.91 (0.78 to 1.07)	0.86 (0.71 to 1.03)

Abbreviation: ICU, intensive care unit.

[a] Adjusted for age, sex, comorbidities, prior dependency, vasopressor infusions received at randomization, duration of vasopressor infusion prior to randomization, location prior to admission to ICU and urgency of surgery, Intensive Care National Audit & Research Centre (ICNARC) physiology score, Sepsis-3, and random effect of site. For comparison, the unadjusted OR for the primary outcome is 0.89 (95% CI, 0.76-1.04).

[b] Post hoc analysis.

Figure 2. Kaplan-Meier Survival Curves



No. at risk													
Permissive hypotension	1283	794	743	721	699	667	631	596	545	509	480	442	409
Usual care	1300	772	727	697	677	642	604	569	525	489	459	435	395

All randomized patients are included when calculating survival, excluding 8 patients in the permissive hypotension group and 7 in the usual care group who did not consent to the trial and refused permission for data use. Other surviving patients were censored at the last known date alive or at date of withdrawal or refusal of consent (from whom trial consent was not obtained). The median follow-up time (using the reverse Kaplan-Meier method) was 14.3 months (interquartile range [IQR], 8.8-19.3) for the permissive hypotension group and 14.2 months (IQR, 8.5-19.4) for the usual care group. HR indicates hazard ratio.

Targeting a lower MAP in the permissive hypotension group did not significantly increase the number of hours with MAP values lower than 60 mm Hg (eFigure 9 in Supplement 2).

Cointerventions

During the first episode of vasopressors, there was no clinically important difference in fluid balance, urine output, or the use of pure inotropes. Corticosteroids were administered to 31.6% of patients in the permissive hypotension and 33.9% in the usual care group (eFigure 11 and eTables 3 and 4 in Supplement 2).

Effectiveness

At 90 days, there was no statistically significant difference in all-cause mortality, with 500 deaths (41.0%) among of 1221 patients in the permissive hypotension group compared with 544 (43.8%) among 1242 patients in the usual care group (absolute risk difference, −2.85%, 95% CI, −6.75 to 1.05; *P* = .15). When adjusted for prespecified baseline variables, the odds ratio for 90-day mortality was 0.82 (95% CI, 0.68 to 0.98) compared with an unadjusted odds ratio of 0.89 (95% CI, 0.76 to 1.04) (**Table 3**). For each baseline variable that was used in the adjusted analysis, data were missing for fewer than 0.1% of patients (eTable 1 in Supplement 2). Best- and worst-case sensitivity analyses yielded unadjusted odds ratios of 0.74 (95% CI, 0.63 to 0.87) and 1.08 (0.93 to 1.27), respectively. Adherence-adjusted analysis did not alter the primary results (eTable 5 in Supplement 2).

Mortality at ICU and treating acute care hospital discharge were not significantly different, and there was no significant difference in time to death between groups (adjusted hazard ratio, 0.94; 95% CI, 0.84 to 1.05; **Figure 2**). The mean duration of ICU and treating acute care hospital stay and

Table 4. Secondary Outcomes

	Intervention Group	Usual Care	Unadjusted Absolute Difference	P Value	Adjusted Mean Difference (95% CI)
Advanced Respiratory Support[a]					
Receipt, No./total (%)	708/1218 (58.1)	691/1239 (55.8)			
Duration among those receiving support, median (IQR), d	4 (2 to 10)	4 (2 to 10)	0.0 (-0.7 to 0.7)	.64	
Duration among all patients, mean (SD), d	4.5 (8.3)	4.8 (10.0)	−0.3 (−1.1 to 0.4)	.40	−0.3 (−1.0 to 0.4)
Days alive and free of advanced respiratory support to day 28, mean (SD)	15.7 (12.8)	15.1 (13.0)	0.6 (−0.4 to 1.7)	.26	0.9 (0.0 to 1.8)
Renal Support[b]					
Receipt, No./total (%)	302/1218 (24.8)	306/1239 (24.7)			
Duration among those receiving support, median (IQR), d	4 (2 to 7)	4 (2 to 8)	0.0 (-1.1 to 1.1)	.93	
Duration among all patients, mean (SD), d	1.4 (3.6)	1.5 (4.1)	−0.1 (−0.4 to 0.2)	.47	−0.2 (−0.4 to 0.1)
Days alive and free of renal support to day 28, mean (SD)	17.4 (13.2)	16.7 (13.4)	0.6 (−0.4 to 1.7)	.25	0.9 (0.0 to 1.9)
Duration of ICU Stay, Median (IQR) [No. of Patients], d					
Survivors	5.2 (2.9 to 10.5) [850]	5.4 (3.0 to 9.9) [865]	−0.2 (−0.7 to 0.3)	.61	
Nonsurvivors	3.2 (0.9 to 8.1) [632]	2.7 (0.9 to 8.7) [380]	0.5 (−0.4 to 1.4)	.97	
Duration of Acute Hospital Stay, Median (IQR) [No. of Patients], d					
Survivors	18 (10 to 34) [732]	18 (10 to 36) [721]	0 (−2.1 to 2.1)	.27	
Nonsurvivors	6 (1 to 15) [484]	5 (1 to 14.5) [519]	1 (−0.8 to 2.8)	.92	
Cognitive Decline (IQCODE Score) Among Survivors, Mean (SD) [No. of Patients][c]					
At 90 d	2.97 (0.72) [497]	2.99 (0.76) [458]	−0.01 (−0.09 to 0.07)	.80	−0.01 (−0.09 to 0.07)
At 1 y	2.93 (0.81) [254]	2.80 (0.96) [247]	0.13 (−0.00 to 0.25)	.05	0.12 (−0.00 to 0.25)
Health-Related QOL (EQ-5D-5L Utility Score) Among Survivors, Mean (SD) [No. of Patients][d]					
At 90 d	0.677 (0.274) [504]	0.683 (0.272) [464]	−0.006 (−0.038 to 0.026)	.71	−0.000 (−0.031 to 0.031)
At 1 y	0.706 (0.264) [253]	0.716 (0.245) [241]	−0.010 (−0.050 to 0.030)	.62	−0.011 (−0.050 to 0.028)
Safety Monitoring, No/Total (%)					
Any serious adverse event[e]	79/1283 (6.2)	75/1300 (5.8)			

Abbreviations: EQ-5D-5L, European quality of life-5 dimensions 5-level questionnaire; ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, interquartile range.

[a] Defined as receiving 1 or more of the following: invasive mechanical ventilatory support applied via a translaryngeal tube or applied via a tracheostomy; BPAP (bilevel positive airway pressure) applied via a translaryngeal tracheal tube or via a tracheostomy; CPAP (continuous positive airway pressure) via a translaryngeal tracheal tube; extracorporeal respiratory support. Mask or hood CPAP or BPAP and high-flow nasal canula are not considered advanced respiratory support.

[b] Either receiving acute renal replacement therapy (eg, hemodialysis, hemofiltration etc) or renal replacement therapy for chronic renal failure.

[c] Cognitive decline scores on the IQCODE are calculated as the mean of the scores on the 16 items and range from 1 (much improved) to 5 (much worse). No studies have been conducted to establish a minimum clinical important difference (MCID) for critically ill patients aged 65 years or older with vasodilatory hypotension. Patients without completed IQCODE data had missing data imputed.

[d] Utility scale ranges from −0.285 to 1 with lower scores indicating worse health-related QOL. The scale is anchored at 0 (death) and 1 (perfect health). Health utilities were assigned using the EQ-5D-5L value set for England.[25] No studies have been conducted to establish an MCID for critically ill patients aged 65 years or older with vasodilatory hypotension. Patients without completed EQ-5D-5L data had missing data imputed.

[e] See the Methods section for the most serious adverse events.

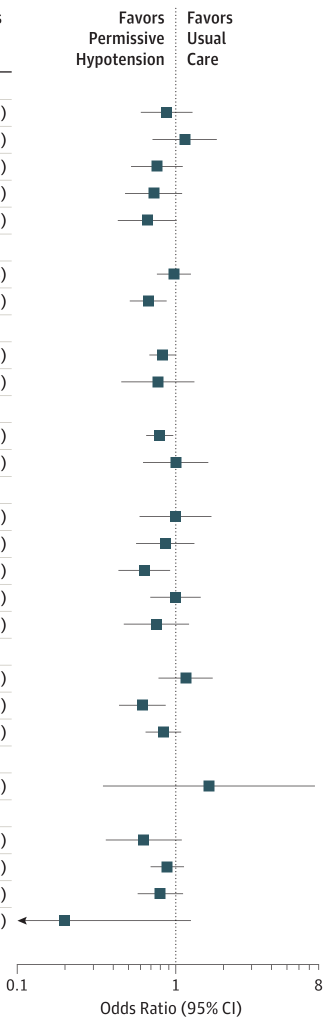
duration and days alive and free from advanced respiratory and renal support to day 28 were not significantly different between groups. Cognitive decline (IQCODE) and health-related QOL (EQ-5D-5L) scores also were not significantly different between groups at 90 days or at 1 year (**Table 4**; and eFigure 12 and eTables 6 and 7 in Supplement 2).

The number of serious adverse events was not significantly different between groups with 79 patients (6.2%) having a serious adverse event in the permissive hypotension compared to 75 (5.8%) in the usual care group (Table 4 and eTable 8 in Supplement 2). The most commonly reported serious adverse events were severe acute renal failure (permissive hypotension, 41; usual care, 33), supraventricular cardiac arrhythmia (permissive hypotension, 12; usual care, 13), ventricular cardiac arrhythmia (permissive hypotension, 12; usual care, 5), myocardial injury (permissive hypotension, 8; usual care, 12), mesenteric ischemia (permissive hypotension, 8; usual care, 12), and cardiac arrest (permissive hypotension, 11; usual care, 10).

The tests for interaction were not statistically significant for the subgroups defined by age, chronic heart failure, atherosclerotic disease, predicted risk of death, sepsis status, or vasopressor dose (**Figure 3**). However, for the chronic hypertension subgroup, the difference in 90-day mortality observed between the

Figure 3. Subgroup Analyses of the Primary Outcome

Subgroup	90-d Mortality, No./Total (%) Permissive Hypotension	Usual Care	Post Hoc Analysis Relative Risk (95% CI)[a]	*P* Value for Interaction[b]	Planned Analysis Odds Ratio (95% CI)[a]	*P* Value for Interaction[c]
Age (quintiles), y						
65-69[d]	108/289 (37.4)	124/304 (40.8)	0.93 (0.78-1.13)		0.87 (0.60-1.27)	
70-72	62/194 (32.0)	70/224 (31.3)	1.06 (0.83-1.35)		1.13 (0.71-1.81)	
73-77	127/304 (41.8)	121/274 (44.2)	0.89 (0.73-1.08)	.13	0.76 (0.52-1.11)	.11[e]
78-82	115/243 (47.3)	111/219 (50.7)	0.90 (0.77-1.06)		0.72 (0.48-1.10)	
>82	88/191 (46.1)	118/221 (53.4)	0.84 (0.69-1.02)		0.66 (0.43-1.01)	
Chronic hypertension						
No	286/661 (43.3)	291/671 (43.4)	0.98 (0.88-1.11)	.12	0.97 (0.76-1.24)	.047
Yes	214/560 (38.2)	253/571 (44.3)	0.84 (0.71-0.99)		0.67 (0.51-0.88)	
Chronic heart failure						
No	431/1085 (39.7)	467/1104 (42.3)	0.92 (0.83-1.02)	.69	0.82 (0.68-1.00)	.81
Yes	69/136 (50.7)	77/137 (56.2)	0.88 (0.72-1.08)		0.77 (0.45-1.31)	
Atherosclerotic disease						
No	424/1047 (40.5)	458/1062 (43.1)	0.90 (0.82-1.00)	.34	0.79 (0.65-0.96)	.38
Yes	76/174 (43.7)	86/180 (47.8)	0.99 (0.82-1.21)		1.00 (0.62-1.60)	
Predicted risk of death (quintiles)						
<0.11	33/238 (13.9)	34/252 (13.5)	1.01 (0.67-1.53)		0.99 (0.59-1.68)	
0.11-0.24	55/240 (22.9)	63/250 (25.2)	0.90 (0.69-1.18)		0.86 (0.56-1.31)	
0.24-0.42	79/234 (33.8)	114/257 (44.4)	0.76 (0.60-0.97)	.88	0.63 (0.43-0.92)	.69[f]
0.42-0.68	135/259 (52.1)	124/231 (53.7)	1.00 (0.84-1.19)		0.99 (0.69-1.43)	
>0.68	195/242 (80.6)	209/248 (84.3)	0.94 (0.87-1.02)		0.75 (0.47-1.21)	
Sepsis-3						
No sepsis	124/263 (47.1)	117/275 (42.5)	1.04 (0.85-1.26)		1.15 (0.77-1.71)	
Sepsis	112/364 (30.8)	138/368 (37.5)	0.77 (0.63-0.95)	.07	0.62 (0.44-0.86)	.06
Septic shock	262/589 (44.5)	289/595 (48.6)	0.94 (0.84-1.04)		0.83 (0.64-1.08)	
Infusion at randomization[g]						
None	7/15 (46.7)	9/22 (40.9)	1.20 (0.70-2.05)		1.61 (0.35-7.54)	
Norepinephrine, μg/kg/min						
<0.1	44/142 (31.0)	57/148 (38.5)	0.77 (0.57-1.03)	.45	0.63 (0.36-1.09)	.36
≥0.1	308/648 (47.5)	324/653 (49.6)	0.96 (0.86-1.06)		0.88 (0.69-1.13)	
Metaraminol	131/385 (34.0)	139/387 (35.9)	0.89 (0.73-1.09)		0.80 (0.57-1.11)	
Other/combination	5/15 (33.3)	8/13 (61.5)	0.61 (0.28-1.31)		0.20 (0.03-1.25)	



[a] Adjusted for age, sex, comorbidities, prior dependency, vasopressor infusions received at randomization, duration of vasopressor infusion prior to randomization, location prior to admission to intensive care unit (ICU) or urgency of surgery, Intensive Care National Audit & Research Centre physiology score, Sepsis-3, and random effect of site.

[b] *P* value for test of interactions of risk ratio in adjusted generalized estimating equation (GEE) Poisson regression model.

[c] *P* value for test of interactions in the odds ratio (OR) in adjusted multilevel logistic regression model.

[d] Three patients in the usual care group were identified after randomization to be younger than 65 years and are included in this subgroup.

[e] Test of continuous linear interaction with age: adjusted OR, 0.82 (95% CI, 0.69-0.99) at age 75 years (mean value), interaction OR, 0.90 (95% CI, 0.78-1.02) per 5-year increase in age.

[f] Test of continuous linear interaction with predicted log odds of acute hospital mortality: adjusted OR, 0.82 (95% CI, 0.68 to 0.99) at predicted log odds of −0.64 (mean value) (predicted risk of 35%), interaction OR, 0.97 (95% CI, 0.84-1.12) per increase of 1 in predicted log odds.

[g] Norepinephrine equivalent doses were calculated according to the method described in Khanna et al,[18] using the following conversion factors: epinephrine μg/kg/min (× 1), dopamine μg/kg/min (/150), phenylephrine μg/kg/min (× 0.1), and vasopressin U min −1 (× 2.5).

permissive hypotension (38.2%) and usual care group (44.3%) was more pronounced (adjusted odds ratio, 0.67; 95% CI, 0.49-0.85) than for patients without chronic hypertension (43.3% vs 43.4%; adjusted odds ratio, 0.97; 95% CI, 0.73-1.21; test of interaction, $P = .047$, not adjusted for multiple testing). Secondary outcomes for patients with and without chronic hypertension are detailed in eTable 9 in Supplement 2.

Post Hoc Analyses

Adjustment of the primary outcome model for the effect of site (only) resulted in an absolute risk difference of −2.82% (95% CI, −7.00 to 1.36), consistent with the primary effect estimate. In addition to the prespecified subgroup analyses of the primary outcome (adjusted odds ratios), adjusted relative risks were also calculated. The relative risks for 90-day mortality were consistent with the odds ratios. In patients with chronic hypertension, the adjusted relative risk was 0.84 (95% CI, 0.71 to 0.99) and in patients without chronic hypertension, the adjusted Sepsis-3 was 0.98 (95% CI, 0.88 to 1.11); test of interaction, $P = .12$, not adjusted for multiple testing (Figure 3). Mortality at 28 and 60 days can also be found in eTable 10 in Supplement 2.

Discussion

In this multicenter, pragmatic, randomized clinical trial, among patients aged 65 years or older, receiving vasopressors for vasodilatory hypotension, permissive hypotension compared with usual care did not result in a statistically significantly reduction in mortality at 90 days. The absolute reduction in 90-day mortality associated with permissive hypotension was 2.9% with 95% CI, from a 6.8% reduction to a 1.1% increase.

This trial has several strengths. First, it was set in a representative sample of 65 ICUs in NHS hospitals across the UK. Second, site set-up was rapid, and the trial recruited 2600 patients in 21 months with recruitment being 24 hours a day, 7 days a week. Sites embedded the trial within routine clinical care due to a simple intervention delivered by bedside nurses; a use of "research without prior consent" model; nesting of the trial within routinely collected data (reducing burden); and the increasing maturity of the UK Critical Care Clinical Research Network, funding and enabling trained research nurses to deliver such trials. Third, both cognitive decline and quality of life among survivors were assessed—important outcomes valued by patients.[26,27] Fourth, the usual care comparator avoided risk of artificially increasing harm in the control group. Fifth, the population was enriched by enrolling older patients considered to have a greater chance of benefiting from the intervention. Sixth, careful sensitivity analyses were conducted, including different approaches to handling missing data.

The confidence intervals for the absolute risk difference, as well as for the adjusted analyses, indicate that minimizing exposure to vasopressors in older patients with vasodilatory hypotension was unlikely to be harmful and might have been beneficial. Usual care, which allowed expert clinicians to adjust vasopressors on many parameters (eg, patient characteristics and markers of tissue perfusion), did not outperform use of a single parameter, MAP, to systematically minimize exposure to vasopressors. While the results of the adjusted analysis might suggest that minimizing exposure to vasopressors in older patients with vasodilatory hypotension may be beneficial, the survival analysis and post hoc analyses using alternative approaches to adjustment support the primary analysis.

The results suggest that there may be no harm associated with permissive hypotension and the corresponding significant reductions in exposure to vasopressors, but the study interpretation must be limited because this was not designed as a noninferiority trial. In contrast to the SEPSISPAM trial,[11] the use of renal replacement therapy was not increased in patients with chronic hypertension randomized to a lower MAP target group. The suggestion of a greater benefit associated with permissive hypotension in patients with chronic hypertension, compared with those without, should be interpreted with caution. Significant subgroup comparisons with no adjustment for multiple testing alongside a nonsignificant primary analysis must be deemed exploratory. Although this suggests that it may be safe to tolerate lower MAP, even in patients with chronic hypertension, further research is required to better understand the interaction between this chronic comorbidity and vasopressors. In future studies, consideration should be given to the fact that blood pressure may vary considerably among patients identified as chronically hypertensive and that patients identified as being normotensive may experience unrecognized severe hypertension. In addition, patients who experience chronic hypertension are also at risk of other comorbidities potentially rendering them more vulnerable to vasopressor-induced adverse effects.

Limitations

This trial has several limitations. First, the intervention was not blinded, but the risk of bias was minimized through central randomization, to try to ensure concealment of group assignment, and use of a primary outcome not subject to observer bias. Second, the 90-day mortality in the usual care group was higher than anticipated using data derived from the Case Mix Programme, plausibly because trial eligibility hinged on clinical teams' assessment that vasopressors would be required for at least 6 hours. Third, nonconsent and withdrawals were slightly higher than anticipated in the sample-size calculation. Fourth, in this pragmatic trial, no mechanistic data were collected, and attributable mortality was not adjudicated. Other trials comparing permissive hypotension with usual care are ongoing and may shed light on the effect of vasopressors on surrogate end points (NCT03431181).

Conclusions

Among patients age 65 years or older receiving vasopressors for vasodilatory hypotension, permissive hypotension compared with usual care did not result in a statistically significant reduction in mortality at 90 days. However, the confidence interval around the point estimate for the primary outcome should be considered when interpreting the clinical importance of the study.

ARTICLE INFORMATION

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Author Affiliations: Université de Sherbrooke, Sherbrooke, Quebec, Canada (Lamontagne); Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada (Lamontagne); Clinical Trials Unit, Intensive Care National Audit & Research Centre, London, United Kingdom (Richards-Belle, Thomas, Harrison, Darnell, Hudson, Saull, Rowan, Mouncey); London School of Hygiene and Tropical Medicine, Department of Health Services Research and Policy, London, United Kingdom (Sadique, Grieve, Mason); Critical Care, Poole Hospital NHS Foundation Trust, Poole, Dorset, United Kingdom (Camsooksai); Division of Anaesthetics, Pain Medicine and Intensive Care, Imperial College London, London, United Kingdom (Gordon); Intensive Care Unit, Imperial College Healthcare NHS Trust, St Mary's Hospital, Paddington, London, United Kingdom (Gordon); Patient representative, United Kingdom (Henry, Whitman); Kadoorie Centre for Critical Care Research and Education, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom (Young).

Author Contributions: Ms Thomas and Dr Harrison had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Lamontagne, Harrison, Sadique, Grieve, Gordon, Henry, Young, Rowan, Mouncey.

Acquisition, analysis, or interpretation of data: Lamontagne, Richards-Belle, Thomas, Harrison, Sadique, Grieve, Camsooksai, Darnell, Gordon, Hudson, Mason, Saull, Whitman, Young, Rowan, Mouncey.
Drafting of the manuscript: Lamontagne, Richards-Belle, Thomas, Harrison, Sadique, Grieve, Darnell, Henry, Whitman, Young, Rowan, Mouncey.
Critical revision of the manuscript for important intellectual content: Lamontagne, Richards-Belle, Harrison, Camsooksai, Darnell, Gordon, Hudson, Mason, Saull, Young, Rowan, Mouncey.
Statistical analysis: Lamontagne, Thomas, Harrison, Sadique, Grieve, Mason, Rowan.
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Administrative, technical, or material support: Lamontagne, Richards-Belle, Camsooksai, Darnell, Gordon, Henry, Hudson, Saull, Young, Rowan, Mouncey.
Supervision: Lamontagne, Harrison, Young, Rowan, Mouncey.

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Group Information: *Chief investigator and coinvestigators:* Paul Mouncey, MSc (chief investigator); François Lamontagne, MD (lead clinical investigator); Julie Camsooksai, BSc; Anthony Gordon, MD; Richard Grieve, PhD; David Harrison, PhD; Doreen Henry, MSc; Kathryn Rowan, PhD; Zia Sadique, PhD; Chris Whitman, BSc; and Duncan Young, DM.

Trial Steering Committee: Tim Walsh, MD (chair, independent); Ben Creagh-Brown, PhD (independent); Tom Lawton, MSc (independent); Theresa Melody, RN (independent), Natalie Pattison, PhD (independent); Donna Reid (independent), François Lamontagne, MD (nonindependent), and Paul Mouncey, MSc (nonindependent).

Data Monitoring and Ethics Committee: John Norrie, MSc (chair); Andreas Laupacis, MD; Danny McAuley, MD.

Trial Management Group: Paul Mouncey, MSc, François Lamontagne, MD, Alvin Richards-Belle, BSc; Julie Camsooksai, BSc; Robert Darnell, BA; Anthony Gordon, MD; Richard Grieve, PhD; David Harrison, PhD; Doreen Henry, MSc; Kathryn Rowan, PhD; Zia Sadique, PhD; Michelle Saull, BSc; Karen Thomas, MSc; Chris Whitman, BSc; Duncan Young, DM; and previous members, Nicholas Hudson, BA, and Akshay Patel, MSc.

Participating UK sites: *Addenbrookes Hospital:* (Petra Polgarova, MSc; Peter Featherstone, MBBCh; and Sofia Teixeira, RN); *Aintree University Hospital:* (Colette Jones-Criddle, DipHE; Ben Morton, MBChB; Ian Turner-Bone, DipHE; and Laura Wilding, DipHE); *Altnagelvin Hospital:* (Gail Quigley, PGDip; Noel Hemmings, FCARCSI; Adrian Donnelly, FFICM; and Aidan Campbell, FCAI); *Antrim Area Hospital*: (Emma McKay, BSc; Paul Johnston, FFARCSI; Orla O'Neill, BSc; and Emma Totten, FCARCSI); *Arrowe Park Hospital* (Nadine Weeks, BSc; Paul Jeanrenaud, MBChB; Cathy Jones, BSc; Reni Jacob, Dip; and Ron Mathew Jacob, MBBS.); *Basingstoke and North Hampshire Hospital:* (Maria Alpuerto, BSn; Antony Ashton, MRCP; Denise Griffin, RGN; and McDonald Mupudzi, BSc); *Blackpool Victoria Hospital* (Jason Cuppitt, MBChB; Emma Stoddard, DipHE; Gemma Brown, BSc; and Jazmine McCooey, FdA); *Bristol Royal Infirmary:* (Lisa Grimmer, RN; Jeremy Bewley, FFICM; Katie Sweet, RN; and Chloe Searles, RN); *Broomfield Hospital:* (Rebecca Keskeys, BSc; Jayachandran Radhakrishnan, DipHE; Fiona McNeela, BSc; and Sue Smolen MSc); *Charing Cross Hospital:* (Laura Curran, BN; David Antcliffe, PhD; Roceld Rojo, BSn; and Kim Zantua, BSn); *Countess of Chester Hospital;* (Helen Robertson, BSc; Lyndsay Cheater, MBChB; Maria Faulkner, BSc; and Laura Parry, PGDip); *Darent Valley Hospital:* (Phillipa Wakefield, BN; Zakaulla Belagodu, MBBS; Danielle Vosper, BSc; Carmel Stuart, BA; and Binu Ravindran, MBBS); *Darlington Memorial Hospital:* (Amanda Cowton, BSc; James Limb, BMBS; and Julie O'Brien. RGN); *Derriford Hospital:* (Rosalyn Squires, BSc; Sam Waddy, MA; Esme Elloway, BSc; and Helen McMillan, PGDip); *Dorset County Hospital:* (Sarah Williams, MSc; Andrew Ball, FFICM; Patricia Williams, AdvDip; Sharon Hiscox, Dip; and Sarah Horton, BA); *Glangwili General Hospital:* (Ulla Chappell, PhD: Igor Otahal, PhD; Peter Havalda, MD; and Samantha Coetzee, PGDip); *Gloucestershire Royal Hospital:* (Kelly Matthews, DipHE; Andrew Foo, MBBS; Izzy King, BSc; and Kirsty Manns, BSc); *Hammersmith Hospital:* (Sonia Sousa Arias, BSn; Stephen Brett, MD; Leilani Cabreros, BSc; and Rhoda Rosal, BSc); *Ipswich Hospital:* (Stephanie Bell, Dip; Kate Turner, MBBS; Vanessa Rivers, BA; and Susan Brixey, BA); *James Cook University Hospital:* (Lindsay Garcia, MSc; Judith Wright, FFICM; Keith Hugill, BSc; Susan Mortimer, FFICM; and Nicola Cree, FFICM); *King's College Hospital:* (Fiona Bartley, BSc; Philip Hopkins, PhD; Su Jeffreys, PGCert; Harriet Noble, MSc; and Clare Finney, BSc); *Leicester Royal Infirmary:* (Louise Houslip, MSc; Neil Flint, MBChB; Dawn Hales, MSc; Prematie Andreou, BSc; and Iain McLaren, MBChB); *Lister Hospital:* (Carina Cruz, MRes; Sunil Jamadarkhana, FFICM; Naomi Brice, BSc; Katie Goodyer, RN); *Manchester Royal Infirmary:* (Richard Clark, DipHE; Jonathan Bannard-Smith, MBChB; Emma Connaughton, BSc; and Abigail Williams, BSc); *Medway Maritime Hospital:* (Amanda Cameron, DipHE; Rahuldeb Sarkar, MPH; Vongayi Ogbeide, MSc; and Mary Everett); *Morriston Hospital:* (Ceri Battle, PhD; Milercy Oliveros, MD; Tracy Owen, MSc; and Sharon Storton, DipHE); *Musgrove Park Hospital:* (Patricia Doble, BSc; Richard Innes, MBBCh; Joanne Hutter, DipHE; and Stephen Harris, MBChB.); *Norfolk and Norwich Hospital:* (Georgina Randell, RGN; Stephen Hutchinson, FFICM; Deirdre Fottrell-Gould, RGN; and Lisa Hudig, BSc); *North Devon District Hospital:* (Tracey Shanley, BSc; Guy Rousseau, MBChB; Max Coupe King, MBBS; and Nicolas Stafford, MBBS); *Northampton General Hospital:* (Joy Grewcock, MSc; Jonathan Wilkinson, MBChB; Kathryn Hall, Dip; and Lorraine Campey, BA); *Northern General Hospital, Sheffield:* (Joanne Pons, BSc; Gary Mills, PhD; Sarah Bird, BSc; and Joshua Cooper, BSc); *Peterborough City Hospital:* (Alan Pope, BSc; Matthew Davies, MBChB; Coralie Carle, BMBS; and Nicola Butterworth-Cowin, BSc); *Pinderfields Hospital:* (Loran Davies, BSc, Alastair Rose, FRCA; Sarah Buckley, BSc; Lucy Brooks, MBChB; and Sarah Smith, MSc); *Poole Hospital:* (Julie Camsooksai, BSc; Henrik Reschreiter, DrMed; Sarah Patch, BSc; and Sarah Jenkins, BSc); *Princess Royal University Hospital, Farnborough;* (Olivia Rowe, BSc; Tom Williams, MBBS; Emma Clarey, BSc; and Jane Wilson, BSc); *Queen Elizabeth Hospital, Gateshead:* (Jenny Ritzema, MSc; Vanessa Linnett, MBBS; and Amanda Sanderson, DipHE); *Queen Alexandra Hospital:* (Steve Rose, BN; David Pogson, MSc; Zoe Daly, BSc; and Aimi Collins, BSc) *Queen Elizabeth Hospital, Woolwich:* (Amy Collins, BSc; Ashraf Roshdy, PhD; Ahmed Zaki, MD; Estefania Treus, BSc; Yvonna Marasigan, RN); *Queens Medical Centre:* (Lucy Ryan, MSc; Daniel Harvey, BMBS; Megan Meredith, BSc; and Louise Hughes, BSc); *Royal Berkshire Hospital:* (Nicola Jacques, MSc; Andrew Walden, PhD; Parminder Bhuie, DipN; and Aoife Dowling, BSc); *Royal Cornwall Hospital:* (Sarah Bean, BSc; Jonathan Paddle, MSc; and Karen Burt, RGN); *Royal Blackburn Hospital:* (Caroline Aherne, Dip; Justin Roberts, MBChB; and Rebecca Crosby, MBChB); *Royal Devon and Exeter Hospital:* (Carole Boulanger, MSc; Charly Gibson, MBChB; and Sinead Kelly PGCert); *Royal Glamorgan Hospital:* (Ceri Lynch, FFICM; Bethan Gibson, FFICM; Lisa Roche, BSc; Keri Turner; and Kelly Thomas, BSc); *Royal Gwent Hospital:* (Gemma Hodkinson, MA; Tamas Szakmany, PhD; and Una Gunter, RN); *Royal Liverpool University Hospital:* (Samantha Hendry, BSc; Ingeborg Welters, PhD; Karen Williams, RGN; and Victoria Waugh BA); *Royal Oldham Hospital:* (Ian Angus, DipHE; Redmond Tully, MBBS; Karen Hallett, BSc; and Susan Dermody, AdvDip); *Royal Preston Hospital:* (Mark Verlander, MBA; Shondipon Laha, MA; Alexandra Williams, MSc; and Donna Doyle); *Royal Stoke Hospital:* (David Cartlidge, MSc; Moses Chikungwa, MBChB; Minnie Gellamucho, BSc; and Ruth Salt RGN); *Royal Victoria Infirmary:* (Patricia Piercy, BSc; Ian Clement, DPhil; Leigh Dunn, BSc; Carmen Bradshaw, BSc; and Abigail Harrison, BSc); *Russells Hall Hospital:* (Davinder Kaur, BSc; Mike Reay, MBBS; Vikram Anumakonda, MBBS; Rachel Collins, DipHE; Angela Watts, BSc; and Julie Matthews); *Salford Royal Hospital:* (Alexandra Larkin, MSc; Paul Ferris, MBChB; Kathryn Cawley, MRes; and Joy Dearden, BSc); *Southmead Hospital:* (Beverley Faulkner, *MA,* Matt Thomas, MBChB; Kati Hayes, BSc; and Ruth Worner, RGN); *St Mary's Hospital, London:* (Dorota Banach, BSc; Anthony Gordon, MD; John Adams, BSc; and Maie Templeton, MSc); *St Thomas' Hospital:* (Aneta Bociek, BSc; Marlies Ostermann, PhD; Simon Sparkes, MBBS; Ruth Wan. MRes; and Andrea Kelly, BSc); *Torbay Hospital:* (Joanne Holman, BSc; Thomas Clark, MBChB; and Alison Cornwell, DipHE); *Tunbridge Wells Hospital:* (Ilona Cassar, BSc; David Golden, MBBS; Joanne Jones, BSc; and Miriam Davey, BSc); *University Hospital Coventry:*

(Thomas Billyard, BMBS; Geraldine Ward, MA; Laura Wild, BSc; Pamela Bremmer, BSc; and Christopher Bassford, PhD); *University Hospital Lewisham:* (Rosaleeta Reece-Anthony, BSc; Waqas Khaliq, PhD; Jayson Clarke, MBChB; and Babita Gurung, BSc); *University Hospital of North Tees:* (Michele Clark, MA; Farooq Brohi, MBBS; and Tracey Oldfield, MSc); *Warwick Hospital:* (Sophie Mason, RGN; Ben Attwood, MBBChir; Camilla Stagg, RGN; and Penny Parsons, *BSc*); *William Harvey Hospital:* (Carl Boswell, RGN; Neil Anthony Richardson, FFICM; Tracy Hazelton; Natasha Schumacher, BSc; and Nicholas Dalmon, BSc); *Worthing Hospital:* (Jenny Lord, BSc; David Helm, FFICM; Charalice Ramiro, BSc; and Jordi Margalef, BSc); *Yeovil District Hospital:* (Liliana Silva, RGN; Agnieszka Kubisz-Pudelko, PhD; Alison Lewis, RGN; and Johnyta Panakal RGN); York Hospital: (Danielle Wilcock, Jonathan Redman MBChB, Joseph Carter MBChB, Kate Howard MSc).

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