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Deferring Arterial Catheterization in Critically Ill Patients with Shock

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ABSTRACT

BACKGROUND

In patients with shock, whether noninvasive blood-pressure monitoring is an effective alternative to the recommended use of an arterial catheter is uncertain.

METHODS

In this multicenter, open-label, noninferiority trial, we randomly assigned patients who had shock and had been admitted to an intensive care unit within the past 24 hours to receive early insertion (<4 hours after randomization) of an arterial catheter (invasive strategy) or to be monitored with an automated brachial cuff (noninvasive strategy). Insertion of an arterial catheter was allowed later in patients assigned to the noninvasive-strategy group who met prespecified safety criteria. The primary outcome was death from any cause at day 28 (noninferiority margin, 5 percentage points). Adverse events of special interest related to the blood-pressure monitoring device that was used were recorded, as was patient-reported pain or discomfort related to the ongoing presence of the device.

RESULTS

A total of 1010 patients underwent randomization; 504 patients assigned to the noninvasive-strategy group and 502 assigned to the invasive-strategy group were included in the analyses. A total of 74 patients (14.7%) in the noninvasive-strategy group and 493 (98.2%) in the invasive-strategy group underwent insertion of an arterial catheter. Death within 28 days occurred in 173 patients (34.3%) in the noninvasive-strategy group and 185 (36.9%) in the invasive-strategy group (adjusted risk difference, -3.2 percentage points; 95% confidence interval, -8.9 to 2.5; $P=0.006$ for noninferiority). Results of per-protocol analyses were similar in the two groups. A total of 66 patients (13.1%) in the noninvasive-strategy group and 45 (9.0%) in the invasive-strategy group had at least 1 day of pain or discomfort related to the ongoing presence of the blood-pressure monitoring device. Hematoma or hemorrhage related to the arterial catheter occurred in 5 patients (1.0%) in the noninvasive-strategy group and 41 patients (8.2%) in the invasive-strategy group.

CONCLUSIONS

Among patients with shock, results for death from any cause at day 28 indicated that management without early arterial catheter insertion was noninferior to early catheter insertion. (Funded by the French Ministry of Health; ClinicalTrials.gov number, NCT03680963.)

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The members of the EVERDAC Trial group, all of whom are members of the CRICS-TRIGGERSEP F-CRIN Network, are listed in the Supplementary Appendix, available at NEJM.org.

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THE USE OF AN ARTERIAL CATHETER IS common in the intensive care unit (ICU)^{1,2} and is recommended for the treatment of patients with shock, although evidence from randomized trials is lacking.^{3,4} The detection of arterial hypotension and response to therapy is of utmost importance in patients with shock. In this context, continuous, real-time, accurate blood-pressure measurements obtained by means of an arterial catheter are presumed to enable earlier detection of hypotensive episodes, prompt initiation of volume expansion, and timely vasopressor dose adjustment, thereby minimizing the duration of undertreatment or overtreatment and potentially influencing the course of organ failure and ultimately survival. However, these assumptions rest on expert opinion and have not been tested in randomized trials. Arterial catheterization also facilitates blood sampling, reducing the need for multiple vascular needle punctures and potentially minimizing patient discomfort.^{1,5,6} Nevertheless, arterial catheterization carries its own risks, including ischemia, hematoma, pseudoaneurysm, and bloodstream infections,⁷⁻⁹ and may also lead to more frequent blood sampling, potentially causing anemia and necessitating transfusion of red cells.¹⁰⁻¹³

Meanwhile, noninvasive blood-pressure monitoring with the use of intermittent, automated oscillometry with a brachial cuff is commonly used, even in patients in unstable condition, and may serve as an alternative to invasive monitoring.^{14,15} However, noninvasive cuff-based monitoring can occasionally yield inaccurate blood-pressure readings that may lead to temporarily inappropriate therapeutic actions, and it may also be associated with issues such as pain or discomfort during cuff inflation,¹⁶ as well as rare injuries to the skin¹⁷ or peripheral nerves.¹⁸ The Early versus Deferred Arterial Catheterization in Critically Ill Patients with Acute Circulatory Failure (EVERDAC) trial was designed to evaluate whether management of shock without early arterial catheterization is noninferior to the practice of early catheter insertion with regard to death from any cause at day 28.

METHODS

TRIAL DESIGN AND OVERSIGHT

The EVERDAC trial was an open-label, investigator-initiated, pragmatic, multicenter, parallel-group,

noninferiority, randomized, controlled trial. It was conducted in ICUs at nine hospitals in France (six university hospitals and three general hospitals) by members of the Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis (CRICS-TRIGGERSEP, a member of the French Clinical Research Infrastructure Network). The protocol (available with the full text of this article at NEJM.org) was approved by a national ethics committee (Comité de Protection des Personnes le de France V) and has been published previously.¹⁹ In accordance with French law, which classifies research such as this trial as involving minimal risk and constraints, patients (or their legally authorized representatives, when applicable) received an information sheet and provided documented explicit oral consent. Consent was later obtained from the patients themselves if they regained the ability to consent. Neither the funder (the French Ministry of Health) nor the trial coordinator (University Hospital of Tours, France) participated in the trial design or execution, data interpretation, or writing of the manuscript. The data collection and analysis were conducted by the authors, who vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The manuscript was drafted by three of the authors, and all the authors reviewed and revised the manuscript, approved the final draft, and agreed to submit it for publication.

PATIENTS

Adult patients (≥ 18 years of age) in the ICU were eligible for enrollment within the first 24 hours after ICU admission if they had acute circulatory failure, defined by persistent hypotension (systolic blood pressure < 90 mm Hg or mean arterial blood pressure < 65 mm Hg) for more than 15 minutes or initiation of vasopressor therapy, plus at least one sign of tissue hypoperfusion. Patients were excluded if no blood-pressure value was displayed on a noninvasive blood-pressure device or brachial-cuff placement was impossible. Additional exclusion criteria were the following: receipt of extracorporeal membrane oxygenation, administration of a high dose of intravenous vasopressors (norepinephrine tartrate plus epinephrine at a dose of > 2.5 μg per kilogram of body weight per minute [2 μg of norepinephrine tartrate is equal to 1 μg of norepinephrine base]), severe traumatic brain injury, body-mass index (BMI), the

weight in kilograms divided by the square of the height in meters) greater than 40, pregnancy, and refusal to participate. The exclusion and inclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION

Patients were randomly assigned in a 1:1 ratio to either the noninvasive-strategy group (no early arterial catheterization) or the invasive-strategy group (early arterial catheterization). Randomization was stratified according to center, the need for invasive mechanical ventilation, and vasopressor dose (intravenous norepinephrine tartrate plus epinephrine at a dose of $<0.36 \mu\text{g}$ per kilogram per minute or at a dose of $\geq 0.36 \mu\text{g}$ per kilogram per minute). Randomization was conducted by means of a secure, centralized, Web-based interactive response system, with the use of permutation blocks of varying sizes determined by the statistician.

INTERVENTION

In the noninvasive-strategy group, insertion of an arterial catheter was not permitted until the 28th day after randomization unless at least one of the predefined safety criteria was met. These safety criteria, established by means of the Delphi method¹⁹ involving two rounds of consensus with the anticipated investigators, included the following: the inability of the bedside monitor to display a value for pulse oximetry or noninvasive blood pressure, an absolute need for arterial blood gas measurement after five consecutive failed arterial-puncture attempts, the need for extracorporeal membrane oxygenation therapy, a vasopressor dose greater than $2.5 \mu\text{g}$ per kilogram per minute of norepinephrine tartrate plus epinephrine, or the need for high-risk surgery (as determined by the physician), in which case the arterial catheter had to be removed within 4 hours after the patient's return to the ICU. If the patient had an arterial catheter in place before enrollment, it had to be removed within 1 hour after randomization. The frequency of noninvasive oscillometric blood-pressure measurements was left to the clinician's discretion. None of the centers used fully continuous noninvasive blood-pressure monitoring with specialized devices (such as those using volume clamp or applanation tonometry technology).¹⁵ To minimize the number of arterial needle punctures, blood draws through the central venous catheter,

if available, were recommended. A mobile Web application and a dedicated website were made available to all investigators to help estimate arterial blood gas on the basis of central venous blood values, if desired.²⁰

In the invasive-strategy group, an arterial catheter had to be inserted within 4 hours after randomization (if one was not already in place). The use of noninvasive blood-pressure monitoring was not allowed except during insertion or replacement of the catheter or when the use of an arterial catheter was considered to be futile (e.g., with the administration of norepinephrine tartrate at a dose of $\leq 0.2 \mu\text{g}$ per kilogram per minute, no epinephrine administration, or signs of hypoperfusion for at least 4 hours, or in case of a medical decision to initiate palliative care). In both groups, the arterial catheter had to be removed if its use was considered to be futile.

GENERAL PATIENT CARE

All aspects of care unrelated to management of the arterial catheter were left to the discretion of the clinical teams, who otherwise adhered to international guidelines for the management of patients with shock.²¹ Additional information is provided in Table S2.

OUTCOMES

The primary outcome was death from any cause at day 28. Key secondary outcomes included the evolution, over the first 7 days, of the Sequential Organ Failure Assessment (SOFA) score,²² which grades the number and severity of organ failure (scores range from 0 [no organ failure] to 24 [highest severity of organ or system failure]) among respiratory, hematologic, renal, liver, cardiovascular, and neurologic systems; number of days free from ventilator support, renal replacement therapy, and vasopressor therapy from day 1 to day 28; and the number of infections related to arterial or central venous catheters during the ICU stay.^{23,24} We also recorded adverse events of special interest because of the safety implications they present. Patient-reported pain and discomfort related to the ongoing presence of the blood-pressure monitoring device ó whether an arm cuff or an indwelling arterial catheter ó were evaluated daily with the use of an 11-point numeric scale in patients who were awake and able to communicate, at a time sufficiently distant from any vascular puncture procedure, to

ensure that any acute pain or discomfort from the puncture itself was not captured.²⁵ A complete list of secondary outcomes and adverse events of special interest is provided in Table S3.

STATISTICAL ANALYSIS

We anticipated that the noninvasive approach would provide a marginal benefit over the invasive approach, given that systematic arterial catheterization may pose risks to patients in terms of catheter-related infections and excessive blood sampling, whereas the theoretical advantages conferred by invasive monitoring (i.e., accurate and dynamic tracking of blood-pressure changes) have not, to date, shown any benefit to patients in randomized trials.²⁶ On the basis of mortality reported in a large multicenter trial involving patients with shock enrolled early in their ICU stay,²⁷ we hypothesized that death from any cause at day 28 would be 25% in the invasive-strategy group and 22.5% in the noninvasive-strategy group. We calculated that a sample size of 1010 patients would provide the trial with 80% power to show the noninferiority of the noninvasive approach to the invasive approach, with a noninferiority margin of 5 percentage points. We planned a priori a superiority analysis if the hypothesis of noninferiority was verified.

Analyses were conducted in accordance with the statistical analysis plan (available with the protocol),¹⁹ which was amended after blinded review of the data. The risk difference for the primary outcome was estimated with a binomial generalized-estimating-equation model that included an identity link function with adjustment for the stratification variables and the center effect.²⁸ The primary hypotheses were assessed with the use of the stratified Farrington Manning test for differences in proportions.

The analyses were conducted in the intention-to-treat population and in two per-protocol populations (Table S4). Statistical analyses for secondary outcomes, which are described in the statistical analysis plan, were not adjusted for multiplicity; therefore, secondary outcome findings should be interpreted as exploratory. Two-sided 95% confidence intervals were calculated for all estimates. Differences in the medians were estimated with the use of unstratified bootstrapping (10,000 samples with replacement).

No subgroup analyses were prespecified. Two

post hoc subgroup analyses were conducted: one that analyzed the primary outcome (death from any cause at day 28), death from any cause by day 90, and vasopressor-free days according to the type of shock; and one that was restricted to patients who were receiving continuous intravenous vasopressors. Both analyses are described in the Supplementary Appendix.

After reviewing the data, we noted that a substantial proportion of the patients in the noninvasive-strategy group underwent arterial catheter insertion after reaching the predefined safety threshold for the vasopressor dose (2.5 μ g per kilogram per minute of norepinephrine tartrate plus epinephrine). Consequently, we conducted a post hoc safety analysis to assess the proportion of patients who reached this threshold in both groups.

RESULTS

PATIENTS

Of 4183 patients who were assessed for eligibility between November 15, 2018, and November 29, 2022, a total of 1010 underwent randomization (Fig. S1); 506 were assigned to the noninvasive-strategy group and 504 to the invasive-strategy group. The intention-to-treat population included 1006 patients (504 in the noninvasive-strategy group and 502 in the invasive-strategy group (Fig. 1). The characteristics of the patients at randomization are shown in Table 1 and Table S5.

INTERVENTION AND PROTOCOL ADHERENCE

Of the 64 patients (12.7%) in the noninvasive-strategy group who already had an arterial catheter in place at the time of randomization, 31 had their arterial catheters removed according to protocol-specified guidelines (within 1 hour after randomization), 31 had them removed later (within 24 hours after randomization), 1 had the catheter removed between 24 and 48 hours after randomization, and in 1 patient, the arterial catheter was not removed. A total of 74 patients in the noninvasive-strategy group (14.7%) underwent arterial catheterization at a median time of 22 hours (interquartile range, 6 to 141) after randomization; most of these (68 patients) underwent catheterization because they met the prespecified safety criteria. All the patients who did not have an arterial catheter received blood-pressure moni-

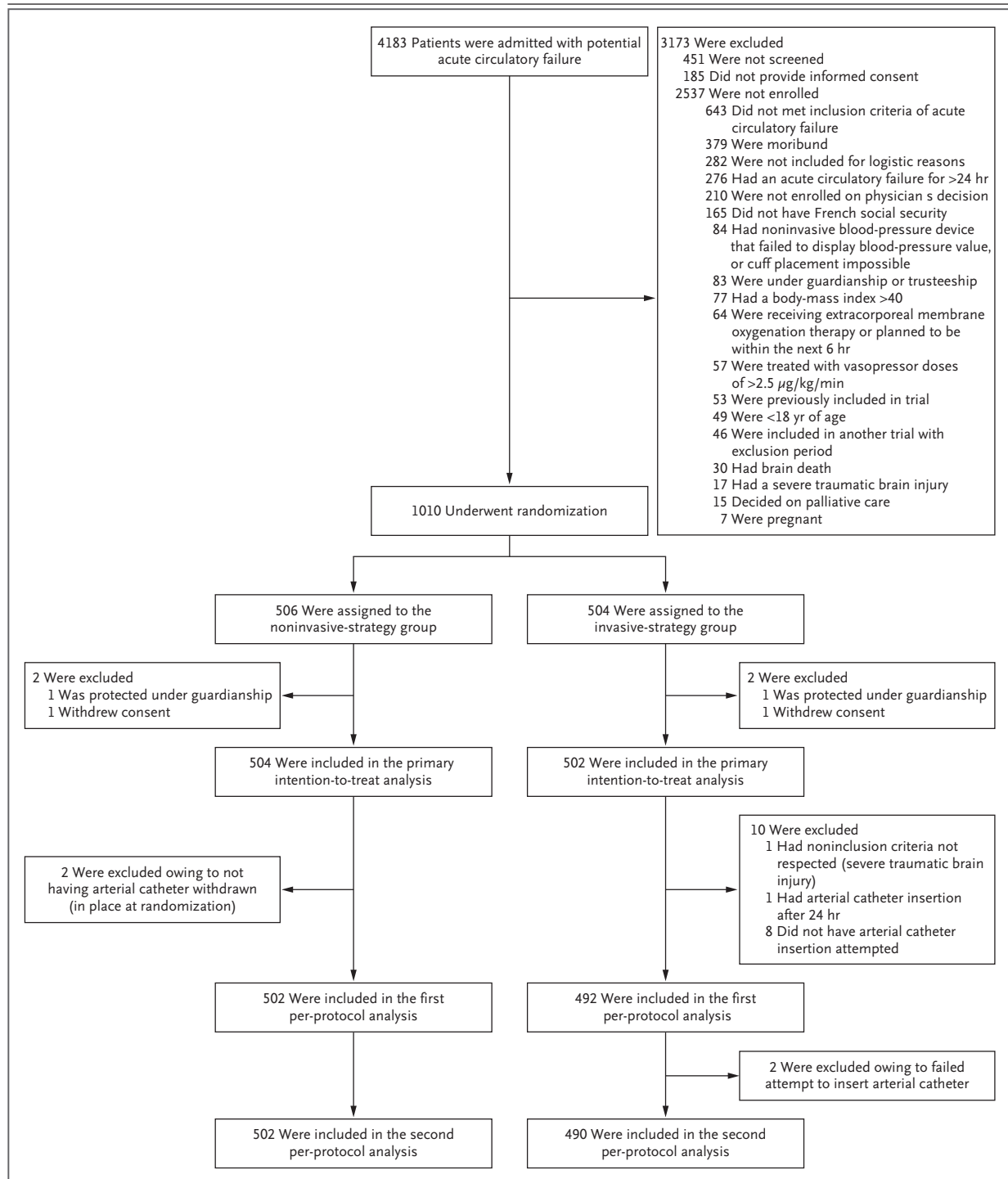


Figure 1. Enrollment, Randomization, Intervention, and Follow-up.

Of 4183 consecutive patients who were admitted to the intensive care unit with low blood pressure or receiving vasopressors on day 1, a total of 451 were inadvertently missed during prospective screening. Of the remaining 3732 patients assessed for eligibility, 210 were excluded at the physician's discretion (specific reasons for exclusion were not recorded).

Table 1. Characteristics of the Patients at the Time of Randomization (Intention-to-Treat Population).*

Characteristic	Noninvasive Strategy (N = 504)	Invasive Strategy (N = 502)
Age yr	66±13	67±12
Sex no. (%)		
Female	173 (34.3)	151 (30.1)
Male	331 (65.7)	351 (69.9)
Body-mass index	27±5	27±6
SAPSII	62±20	63±19
SOFA score	10±4	10±4
Type of admission no. (%)		
Surgical	31 (6.2)	31 (6.2)
Medical	473 (93.8)	471 (93.8)
Source of admission to ICU no. (%)		
Direct admission by ambulance	124 (24.6)	128 (25.5)
Admission after emergency department admission	149 (29.6)	134 (26.7)
Transfer from hospital floor	134 (26.6)	141 (28.1)
Transfer from another hospital	97 (19.2)	99 (19.7)
Cause of acute circulatory failure no. (%)		
Septic shock	260 (51.6)	286 (57.0)
Cardiogenic shock	59 (11.7)	55 (11.0)
Hemorrhagic shock	37 (7.3)	24 (4.8)
Shock after cardiac arrest	54 (10.7)	39 (7.8)
Obstructive shock	3 (0.6)	5 (1.0)
Other shock	91 (18.1)	93 (18.5)
Coexisting condition no. (%)		
Chronic arterial hypertension	239 (47.4)	268 (53.4)
Diabetes	141 (28.0)	132 (26.3)
Atrial fibrillation	84 (16.7)	84 (16.7)
Chronic cardiac insufficiency	32 (6.3)	38 (7.6)
Cirrhosis	45 (8.9)	39 (7.8)
Chronic obstructive pulmonary disease	37 (7.3)	41 (8.2)
Long-term dialysis	11 (2.2)	11 (2.2)
History of acute myocardial infarction	38 (7.5)	32 (6.4)
Active solid-organ cancer	45 (8.9)	47 (9.4)
Active hematologic cancer	29 (5.8)	47 (9.4)
Other causes of immunosuppression	43 (8.5)	54 (10.8)
Invasive mechanical ventilation before randomization no. (%)	337 (66.9)	339 (67.5)

Table 1. (Continued.)

Characteristic	Noninvasive Strategy (N = 504)	Invasive Strategy (N = 502)
Vasopressor therapy at randomization no. (%)	440 (87.3)	452 (90.0)
Including norepinephrine	430 (85.3)	439 (87.5)
Including epinephrine	15 (3.0)	16 (3.2)
Total dose of vasopressor used before randomization in patients receiving vasopressor therapy $\mu\text{g}/\text{kg}/\text{min}$ ^{**}	0.44±0.39	0.41±0.35
Norepinephrine	0.44±0.38	0.40±0.35
Epinephrine	0.37±0.50	0.49±0.52
Vasopressor dose $\geq 0.36 \mu\text{g}/\text{kg}/\text{min}$ no. (%) ^{**}	181 (35.9)	177 (35.3)
Median time between ICU admission and randomization (IQR) hr	5.6 (1.9 to 13.1)	5.4 (2.0 to 14.8)

- * Plus minus values are means \pm SD. ICU denotes intensive care unit, and IQR interquartile range. Body-mass index is the weight in kilograms divided by the square of the height in meters. The Simplified Acute Physiology Score, version II (SAPSII),²⁹ calculated during the first 24 hours of ICU admission, rates overall illness severity on a scale of 0 to 163, with higher scores indicating greater severity of illness. In the noninvasive-strategy group, the median SAPSII was 59 (IQR, 47 to 77), with minimum and maximum values of 14 and 116, respectively. In the invasive-strategy group, the median was 63 (IQR, 49 to 77), with minimum and maximum values of 22 and 117.
- The Sequential Organ Failure Assessment (SOFA)²² score was obtained on the day of ICU admission. SOFA scores range from 0 to 24, with higher scores indicating more severe organ failure. In the noninvasive-strategy group, the median SOFA score on day 1 was 10 (IQR, 7 to 12), with minimum and maximum values of 0 and 20, respectively. In the invasive-strategy group, the median was 10 (IQR, 8 to 12), with values ranging from 1 to 19.
- Invasive mechanical ventilation before randomization and vasopressor dose of at least $0.36 \mu\text{g}/\text{kg}/\text{min}$ were randomization stratification factors.
- ^{||} All patients receiving continuous intravenous vasopressor therapy received norepinephrine tartrate (equivalent of twice the dose of norepinephrine base). Among these, 15 patients in the noninvasive-strategy group and 16 patients in the invasive-strategy group received epinephrine, in combination with norepinephrine tartrate or not, at randomization. During the enrollment period, 29 patients in the noninvasive-strategy group and 35 patients in the invasive-strategy group received epinephrine, in combination with norepinephrine tartrate or not. None of the participating centers used any other continuous intravenous vasopressors (e.g., vasopressin, phenylephrine, or angiotensin II).
- ^{**} The dose of vasopressors was calculated as norepinephrine tartrate in micrograms per kilogram of body weight per minute (with $1 \mu\text{g}$ corresponding to $0.5 \mu\text{g}$ of norepinephrine base) plus epinephrine as micrograms per kilogram per minute.
- In the noninvasive-strategy group, 430 patients received norepinephrine and 15 received epinephrine. In the invasive-strategy group, 439 patients received norepinephrine and 16 received epinephrine.

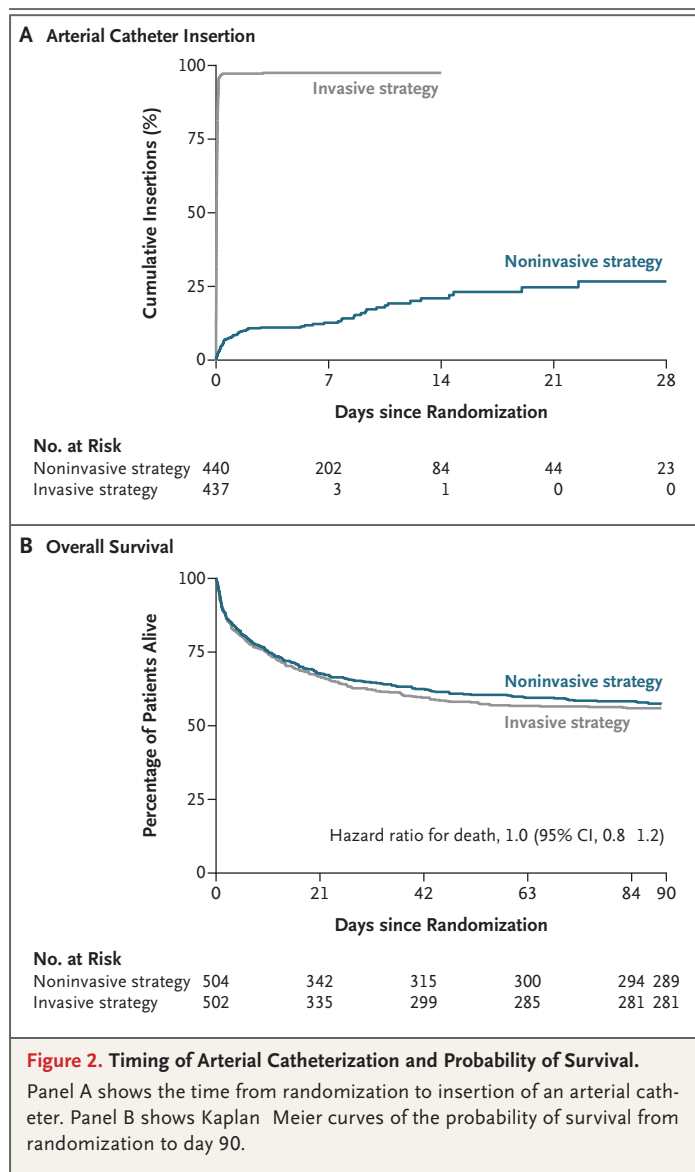
toring by an intermittent, automated oscillometric brachial cuff (Tables S6 and S7).

In the invasive-strategy group, 65 patients (12.9%) already had an arterial catheter in place at the time of randomization. Among the remaining patients, 428 (97.9%) underwent arterial catheter insertion at a median time of 1.0 hours (interquartile range, 0.5 to 1.9) after randomization, including 417 patients (95.4%) who underwent catheterization within 4 hours after randomization. The probability of arterial catheter insertion from randomization to day 28 for both groups is shown in Figure 2A. The number of blood draws obtained by means of the central venous catheter per 1000 ICU days was 215 in the non-

invasive-strategy group and 180 in the invasive-strategy group.

PRIMARY OUTCOME

Among 1006 patients included in the intention-to-treat analysis, 173 patients (34.3%) in the noninvasive-strategy group and 185 patients (36.9%) in the invasive-strategy group had died by day 28 after randomization (absolute risk difference with adjustment for stratification, -3.2 percentage points; 95% confidence interval [CI], -8.9 to 2.5 ; $P=0.006$ for noninferiority, $P=0.20$ for superiority) (Fig. S2). Similar results were observed in the two prespecified per-protocol analyses.



ization to day 90 are shown in Figure 2B. The median numbers of days free from ventilator therapy, vasopressor treatment, and renal replacement therapy at day 28 were similar in the two groups (Table 2).

Five patients (1.0%) in the noninvasive-strategy group and 41 patients (8.2%) in the invasive-strategy group had a hematoma or hemorrhage at the arterial-catheter insertion site (Table 3). The incidence of arterial catheter-related bloodstream infections per 1000 ICU days was 1 in the noninvasive-strategy group and 3 in the invasive-strategy group (incidence ratio, 0.18; 95% CI, 0.06 to 0.54).

The incidence of arterial puncture attempts for blood sampling (not including punctures for placement of arterial catheters) per 1000 ICU days was 742 in the noninvasive-strategy group and 269 in the invasive-strategy group (incidence ratio, 2.76; 95% CI, 2.41 to 3.16). A total of 66 patients (13.1%) in the noninvasive-strategy group reported serious pain or discomfort related to the ongoing presence of the blood-pressure monitoring device (arm cuff or indwelling arterial catheter) for at least 1 day during the ICU stay, as compared with 45 patients (9.0%) in the invasive-strategy group. Among patients who were able to answer, the corresponding percentages were 22.8% (66 patients) in the noninvasive-strategy group and 15.4% (45 patients) in the invasive-strategy group (Table 3 and Fig. S4). Other secondary outcomes are shown in Table 2 and Figures S5 through S10. Among patients who died within 28 days after randomization, 100 patients (57.8%) in the noninvasive-strategy group and 99 (53.5%) in the invasive-strategy group died after a decision was made to withdraw or withhold life-sustaining treatment (Table S9).

SECONDARY OUTCOMES

The median SOFA score was 10 points (interquartile range, 7 to 12) in the noninvasive-strategy group and 10 points (interquartile range, 8 to 12) in the invasive-strategy group on the day of randomization and decreased over the subsequent 6 days to reach 5 points (interquartile range, 3 to 9) on day 7 in both groups (Fig. S3 and Table S8). By day 90, mortality was 42.7% in the noninvasive group and 44.0% in the invasive group (absolute risk difference adjusted for stratification, -1.7 percentage points; 95% CI, -7.0 to 3.5). Kaplan Meier curves for survival from random-

POST HOC SAFETY AND SUBGROUP ANALYSES

In the noninvasive-strategy group, 65 patients (12.9%) reached the predefined upper limit of vasopressor dose at a median time of 1 day (interquartile range, 1 to 2), including 34 patients who received the dose over a period of at least 2 consecutive hours. In the invasive-strategy group, 72 patients (14.3%) reached the vasopressor-dose threshold at a median time of 1 day (interquartile range, 1 to 2). Among these severely ill patients, 49 of 65 patients (75.4%) in the noninvasive-strategy group and 54 of 72 patients (75.0%) in the invasive-strategy group died by day 28.

Table 2. Secondary Outcomes.

Outcomes	Noninvasive Strategy (N=504)	Invasive Strategy (N=502)	Difference (95% CI)*
Death from any cause at 90 days no. (%)	215 (42.7)	221 (44.0)	-1.7 (-7.0 to 3.5)
Death from any cause in ICU no. (%)	163 (32.3)	169 (33.7)	0.95 (0.77 to 1.18)
Death from any cause in hospital no. (%)	192 (38.1)	197 (39.2)	0.96 (0.79 to 1.17)
Median duration of mechanical ventilation (IQR) days	5.0 (2.0 to 10.0)	5.0 (2.0 to 11.0)	0.0 (-2.0 to 1.0)
Median no. of mechanical-ventilation free days (IQR)	20.0 (0.0 to 27.0)	19.0 (0.0 to 26.0)	1.0 (-10.0 to 2.0)
Vasopressor therapy by day 28 no. (%)	469 (93.1)	487 (97.0)	-4 (-6.6 to -1.3)
Median duration of vasopressor therapy (IQR) days	2.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	-1.0 (-1.0 to 0.0)
Renal replacement therapy by day 28 no. (%)	105 (20.8)	105 (20.9)	-0.1 (-5.1 to 5.0)
Median no. of renal-replacement-therapy free days (IQR)	28.0 (11.0 to 28.0)	28.0 (11.0 to 28.0)	0.0 (-1.0 to 1.0)
Median duration of ICU stay (IQR) days			
Total	6.0 (3.0 to 12.0)	6.5 (3.0 to 13.0)	-1 (-2.0 to 1.0)
Survived to discharge from ICU	6.0 (3.0 to 12.0)	7.0 (4.0 to 13.0)	-1 (-3.0 to -1.0)
Died in ICU	5.0 (2.0 to 12.0)	4.0 (2.0 to 13.0)	1 (-2.0 to 3.0)
Median duration of hospital stay (IQR) days			
Total	12.0 (4.0 to 36.0)	12.0 (5.0 to 25.0)	0 (-2.0 to 2.0)
Survived to discharge from hospital	15.0 (8.0 to 31.5)	16.0 (9.0 to 31.2)	0 (-3.0 to 3.0)
Died in hospital	5.5 (1.0 to 16.2)	6.0 (1.0 to 16.0)	0 (-2.0 to 3.0)
Procedures no. per 1000 ICU days			
Arterial catheters inserted during ICU stay	18	112	0.16 (0.11 to 0.22)
Central venous catheters inserted during ICU stay	45	53	0.84 (0.66 to 1.06)
Blood cultures during ICU stay	203	220	0.92 (0.80 to 1.07)
Blood draws from the venous catheter during ICU stay	215	180	1.19 (0.83 to 1.71)
Attempts at arterial puncture for blood sampling during ICU stay	742	269	2.76 (2.41 to 3.16)
Red-cell packs transfused from randomization to day 28	31	33	0.95 (0.55 to 1.62)
Arterial catheter related bloodstream infections during ICU stay**	0.6	2.7	0.18 (0.06 to 0.54)
Central venous catheter related bloodstream infections during ICU stay	1.6	2.9	0.59 (0.29 to 1.18)

* For secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

The value shown is the difference in percentages.

The value shown is a hazard ratio.

The value shown is a difference in median values.

The value shown is an incidence ratio.

|| Values do not include arterial punctures for placement of arterial catheters. When punctures for placement of arterial catheters were included, the analysis yielded 760 attempts at arterial puncture in the noninvasive-strategy group and 380 attempts at arterial puncture in the invasive-strategy group (incidence rate ratio, 2.00; 95% CI, 1.78 to 2.24).

** The raw number of arterial catheter related bloodstream infections was 3 in 3 patients in the noninvasive-strategy group and 14 in 13 patients in the invasive-strategy group.

The raw number of central venous catheter related bloodstream infections was 8 in 8 patients in the noninvasive-strategy group and 15 in 11 patients in the invasive-strategy group.

Table 3. Adverse Events of Special Interest and Assessment of Pain and Discomfort.

Variable	Noninvasive Strategy (N = 504)	Invasive Strategy (N = 502)	Difference (95% CI)*	P Value*
Adverse event of special interest no. (%)				
Ischemia or necrosis of fingers or toes	2 (0.4)	7 (1.4)		0.18
Documented bowel ischemia	6 (1.2)	6 (1.2)		>0.99
Occurrence or worsening of acute renal failure with need of renal replacement therapy	105 (20.8)	105 (20.9)		0.97
Need for tracheal intubation in a patient not previously intubated	39 (7.7)	51 (10.2)		0.22
Cardiac arrest	29 (5.8)	37 (7.4)		0.36
Upper-limb nerve injury	1 (0.2)	0		>0.99
Skin damage at cuff location or at arterial catheter insertion site	7 (1.4)	5 (1.0)		0.78
Arterial thrombosis	2 (0.4)	3 (0.6)		>0.99
Hematoma or hemorrhage at arterial catheter insertion site either during insertion or later	5 (1.0)	41 (8.2)		<0.001
Arterial pseudoaneurysm	0	0	0	
Pain and discomfort				
ICU days per 1000 with pain or discomfort (or both) related to the blood-pressure monitoring device in place no.				
Entire trial population	42	22	1.94 (1.20 to 3.15)	0.07
Among patients able to answer	130	67	1.91 (1.38 to 2.64)	
At least 1 day with pain or discomfort (or both) related to the blood-pressure monitoring device in place during ICU stay				
Total population no. (%)	66 (13.1)	45 (9.0)	4.1 (0.3 to 8.0)	0.05
Patients able to answer no./total no. (%)	66/289 (22.8)	45/293 (15.4)	7.5 (0.0 to 13.9)	0.02

* For secondary outcomes, the widths of the confidence intervals and the P values have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

Questions were focused on the discomfort and pain associated with having the device in situ (i.e., the ongoing presence of the blood-pressure monitoring device, whether an arm cuff or an indwelling arterial catheter). The assessment was not conducted during or immediately after any transcutaneous vascular puncture (arterial or venous).

Among patients able to self-assess, 4.5% (13 patients) of those in the noninvasive-strategy group and 9.6% (28 patients) of those in the invasive-strategy group were not interviewed.

Post hoc subgroup analyses according to the type of shock the patient had at the time of randomization and according to whether patients were receiving vasopressor therapy are described in Figure S11 and Table S10.

DISCUSSION

This multicenter randomized trial showed that, with regard to death from any cause at day 28, a strategy of delaying arterial catheterization in

favor of noninvasive blood-pressure monitoring with automated oscillometry was noninferior to early invasive blood-pressure monitoring in patients with shock. The noninvasive strategy avoided the insertion of an arterial catheter in 85% of the patients assigned to that group. These findings suggest that noninvasive blood-pressure monitoring can safely and effectively replace invasive monitoring for most patients with shock, thus mitigating the risks associated with the use of an arterial catheter.

Invasive blood-pressure monitoring is the standard,³⁰ and noninvasive measurements performed in individual patients often show imperfect accuracy. However, studies have shown that modern noninvasive, oscillometric monitoring devices may accurately detect low mean arterial pressure (a critical determinant of tissue perfusion), its variations induced by therapeutic interventions, and systolic hypertension, even in patients who are treated with vasopressors and those with cardiac arrhythmias.³¹⁻³³ Our findings suggest that in real-world practice, the accuracy and precision of noninvasive readings of blood pressure (which we did not assess) may have been sufficient to adjust treatments for shock. However, one could speculate that potentially inaccurate noninvasive readings might have led to unnecessary escalation in vasopressor doses, for example. Nevertheless, mortality among patients who received the predefined upper limit of vasopressor dose was not higher in the noninvasive-strategy group than in the invasive-strategy group, which makes this hypothesis unlikely. Similarly, the possibility that insufficient vasopressor doses were administered owing to inaccurate readings, which could lead to more frequent organ failure, was also not supported by the data.

Another explanation for our findings could be that the accuracy of blood-pressure measurements may not be the most critical factor affecting patient outcomes. Management protocols that target outcomes other than precise blood-pressure levels may be more important. Within a wide range of mean arterial-pressure measurements, outcomes may predominantly depend on other variables, such as elevated blood-lactate levels,³⁴ urine output, or prolonged capillary refill times.³⁵ This explanation is suggested by two large randomized, controlled trials involving patients who had septic

shock³⁶ or vasoplegic shock³⁷ that showed no meaningful difference in mortality between two different mean arterial pressure levels.

Continuous arterial blood-pressure monitoring provides valuable insights into the pathophysiology of shock. Invasively measured pulse pressure can serve as a surrogate for stroke volume³⁸; its changes during passive leg raising,^{39,40} for example, can help in the assessment of a patient's response to volume expansion. Precise diastolic and systolic arterial-pressure measurements that are obtained from invasive monitoring — unlike noninvasive measurements, in which these values are estimated by the proprietary algorithms embedded into the oscillometric devices¹⁵ — can inform about arterial tone and thus indicate vasoplegia or excessive vasoconstriction.⁴¹ In addition, the continuous nature of invasive blood-pressure monitoring allows for the early detection and prompt treatment of blood-pressure changes (both decreases and increases). However, the full range of information provided by the arterial catheter is seldom used in real-life practice.^{42,43} This underutilization may partly explain why in our trial the invasive strategy did not lead to reduced vasopressor use, a more favorable evolution of organ failures, or improved survival outcomes. Of note, even if our assumption that investigators did not fully exploit all the advantages of invasive monitoring is incorrect — and that they indeed used all the available information — our data still do not show any improvement in survival or other clinical benefits.

We found no randomized trials and only two observational studies with which to compare our results.^{10,44} Our findings are consistent with the similar mortality reported in patients with and those without an arterial catheter in the two large cohorts of critically ill patients in those studies. However, we could not replicate the observed increased mortality associated with arterial catheter use in patients receiving vasopressors in one observational study⁴⁴ — a finding that was absent in our trial in both patients who were receiving vasopressors at the time of randomization and those who received vasopressor therapy at any time during the first 28 days after randomization. This lack of concordance may be attributed to residual confounding in the observational study,⁴⁴ to the limited power of our trial, or to both.

Finally, our findings suggest that, given the noninferiority of the noninvasive approach with respect to death at day 28, arterial catheterization need not be the default option when caring for patients in shock—thus challenging current guidelines. Further studies are warranted to explore the relative importance (from the perspectives of caregivers and patients) of arterial catheter-related complications (e.g., infections and hematomas), as compared with pain and discomfort associated with the use of an automated brachial cuff. Such findings could inform how best to use cuff-monitored blood-pressure measurements (in particular, to determine the appropriate measurement frequency on the basis of perceived or documented illness severity) and clarify how frequently blood sampling is necessary in various clinical contexts.

Our trial has several limitations. First, the trial was not conducted in a blinded manner, which may have introduced bias in the assessment of several secondary outcomes. Second, the evaluation of pain and discomfort may not be complete, because only a very limited number of patients were awake and capable of self-assessment, and we did not include assessment for pain specifically associated with transcutaneous vascular punctures. Third, patients in the noninvasive-strategy group underwent arterial puncture attempts more frequently, a factor that suggests that the guideline to preferentially use the central venous catheter for blood draws—especially for blood gas analyses—may not have been followed as anticipated. Fourth, we did not record the workload and satisfaction levels of health care workers. In the ICU, an arterial catheter is often preferred as a convenience for health care workers (chiefly by simplifying blood sampling),²⁶ and we recognize that this preference may act as a barrier to changing practices. Fully capitalizing on a noninvasive approach in the future will probably depend on more judicious use of blood sampling. Fifth, although the enrolled population was representative of patients typically admitted to highly resourced ICUs for shock (Table S11), our trial included few trauma and postsurgical patients and no patient with a BMI higher than 40, a factor that limits the generalizability of our results to these specific populations. Sixth, a substantial number of potentially eli-

gible patients were either not screened or were screened but not included for reasons that were not documented, which could introduce selection bias. However, the trial population still represented a wide range of severity in both groups (Table 1).

Among critically ill patients with shock, deferring the insertion of an arterial catheter was noninferior to an early insertion strategy with regard to death from any cause at day 28.

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