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TITLE	**E**arly **ver**sus **d**iffered **a**rterial **c**atheterization in critically ill patients with acute circulatory failure. A multicentre, open-label, pragmatic, randomised, non-inferiority controlled trial (EVERDAC trial)
Coordinating investigator	**Dr Grégoire MULLER** Service de Médecine Intensive Réanimation, CHR d'Orléans
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Glossary of terms

AE: adverse event

ANSM: Agence nationale de sécurité du médicament et des produits de santé

BIA: Budget impact analysis

BMI: body mass index

BP: blood pressure

CHR: centre hospitalier régional

CHRU: centre hospitalier régional universitaire

CIC: centre d'investigation clinique

CNIL: Commission nationale informatique et libertés

CPP: Comité de protection des personnes

CRF: case report form

CRICS: clinical research in intensive care and sepsis group

CVC: central venous catheter

DRG: diagnosis related groups

ECMO: Extra-Corporeal Membrane Oxygenation

ENCC: Échelle Nationale des Coûts à Méthodologie Commune (National health costs scale)

FiO_2: fraction of inspired oxygen

FNHDD: French National Hospital Discharge Database

GDPR: General Data Protection Regulation

IAC: indwelling arterial catheter

ICER: incremental cost-effectiveness ratio

ICH: international conference of harmonisation

ICU: intensive care unit

ITT: intention to treat

IV: intravenous

NIBP: non invasive blood pressure

PaO_2: arterial partial pressure of oxygen

$PaCO_2$: arterial partial pressure of carbon dioxide

PEEP: positive end-expiratory pressure

RAE: related adverse event

SAE: serious adverse event

$ScvO_2$: central venous oxygen saturation

SOFA: sequential organ failure assessment

SpO_2: blood oxygen saturation measured by pulse oximetry

UAE: unexpected adverse effect

Summary

TITLE	**E**arly **ver**sus **d**iffered **a**rterial **c**atheterization in critically ill patients with acute circulatory failure. A multicentre, open-label, pragmatic, randomised, non-inferiority controlled trial (EVERDAC trial)
SPONSOR	**CHRU de TOURS**
COORDINATOR INVESTIGATOR	**Dr Grégoire MULLER** Intensive care unit, Centre Hospitalier Régional Orléans
BACKGROUND / RATIONALE	The use of peripheral indwelling arterial catheter (IAC) for haemodynamic monitoring is widespread in the intensive care unit (ICU) and is recommended in patients with shock. It allows continuous monitoring of arterial blood pressure (BP) and facilitates quick blood sampling for laboratory testing while avoiding repeated vascular punctures. However, despite these advantages, there is no evidence that IAC could improve patient's outcome, whereas the burden of morbidity generated is not minor (mainly thrombosis and infectious complications). The preparation and insertion of an IAC also consume resources as well as nurse and physician time. Moreover, the presence of an IAC has been shown to increase the number of blood samplings ordered for laboratory testing, favouring anaemia and red blood cell transfusion in excess during the ICU-stay, and therefore exposing patients to additional risks while generating additional costs. No study has so far shown better patient-centred outcomes with the use of an IAC during ICU-stay. Moreover, one large, propensity score-adjusted, retrospective study even suggests that the use of an IAC might be associated with increased mortality among patients with circulatory failure receiving continuous intravenous vasopressors. There are alternatives to the use of the IAC: 1) Recent studies have repeatedly shown that non-invasive BP (NIBP) measurements by oscillometry reliably detect hypotension (mean BP<65mmHg) and patients responsive to cardiovascular interventions; 2) Arterial blood sampling (for blood gas and lactate analysis) could be avoided by analysis of venous blood drawn from a central venous catheter and peripheral

	pulse oximetry readings (SpO_2) (once again a widely used non-invasive technology). Accordingly, we hypothesize that patients with shock may be managed without any IAC. The aim of the present study is to assess whether a less invasive intervention (i.e., no IAC insertion until felt absolutely needed, according to pre-defined safety criteria) is non-inferior to usual care (i.e., systematic IAC insertion in the early hours of shock) in terms of mortality at day 28.
PRIMARY OBJECTIVE	The objective of the present research is a combination of a one-sided test of non-inferiority and a one-sided test of superiority. A stepped approach will be used to evaluate these hypotheses: a) a less invasive intervention (i.e., no IAC insertion until felt absolutely needed, according to consensual and predefined safety criteria) is non-inferior to usual care (i.e., systematic IAC insertion in the early hours of shock) in terms of mortality at day 28 (non-inferiority margin of 5%). b) a less invasive intervention is not only non-inferior but also superior to usual care in terms of mortality
PRIMARY OUTCOME	All-cause mortality by 28 days after inclusion.
STUDY DESIGN	Multi-centre, pragmatic, randomised, controlled, open, two-parallel-group, non-inferiority clinical trial.
PARTICIPANTS	***Inclusion criteria*** *:* ▪ Age ≥ 18 years the day of inclusion ▪ Existence of an acute circulatory failure defined by the presence of the following items 1 and 2: 1) Persisting hypotension (systolic blood pressure less than 90 mmHg or mean arterial blood pressure less than 65 mmHg) for more than 15 min at ICU admission or within the following 24 hours, **OR** requirement of continuous iv vasopressor treatment (i.e. any dose of norepinephrine / epinephrine) 2) Presence at least one of the following signs of hypoperfusion: alteration of mental status; skin mottling; oliguria defined as a urine output < 0.5 mL/kg body weight for at least one hour; arterial lactate > 2 mmol/L; peripheral venous lactate > 3.2

	mmol/L; $ScvO_2$ <70% ▪ Free express oral and informed consent of the patient or a proxy in case of impossibility for the patient to consent; emergency inclusion possible when legal representatives and patient's family are not available ▪ French health insurance holder ***Non-inclusion criteria:*** ▪ Acute circulatory failure, as defined by items 1 and 2 in inclusion criteria list (cf. supra) present for more than 24 hours ▪ NIBP device fails to display a BP value, or cuff placement impossible ▪ Patient for whom an ECMO therapy (either veno-arterial or venous-venous) is already in place or is to be initiated within the next 6 hours ▪ Patient treated with vasopressor doses of more than 2.5 µg/kg/min of *norepinephrine tartrate* plus epinephrine for at least 2 hours (i.e., for instance, more than 8 mg of *norepinephrine tartrate* in 50 mL at the rate of 66 mL/hour for a patient weighing 70 kg) (*please note that in fact this dosage corresponds to 1.25 µg/kg/min of norepinephrine base*) ▪ Severe traumatic brain injury (i.e., traumatic brain injury with a Glasgow coma scale score of less than 9 before sedation) ▪ Patient previously included in the trial ▪ Body mass index (BMI) above 40 kg/m^2 ▪ Pregnancy ▪ Brain death ▪ Moribund patient ▪ Patient known, at time of inclusion, as being under guardianship, tutorship or curatorship
INTERVENTIONS	Two distinct strategies: 1/ Control group: usual strategy of systematic IAC insertion in the early hours of acute circulatory failure 2/ Experimental group: non-invasive strategy consisting of blood

	pressure monitoring by non-invasive automated cuff measurements in patients with acute circulatory failure, and insertion of an IAC only if predefined severity criteria occur.
SAMPLE SIZE	1010 patients
SETTINGS	11 centres
EXPECTED DURATION OF THE STUDY	Expected duration of enrolment: 36 months Duration of the study for a participant: 90 days Total duration of the study: 39 months
EXPECTED RESULTS	We estimate the number of ICU patients presenting with shock as defined by our inclusion criteria as at least 25,000/year in France. More than 80% of them probably undergo IAC insertion during ICU care. On the one hand, we expect several benefits to these patients with the proposed, less invasive intervention: smaller amount of blood drawn for lab tests, less transfusion, and less IAC-related complications such as catheter-related infections. On the other hand, based on recent data, we hypothesize that hemodynamic and ventilatory parameters can be safely monitored without the need of IAC insertion. As a result, we expect that the less invasive strategy, while not affecting mortality (or marginally improving survival, an effect size difficult to capture with the planned sample size), will decrease morbidity through minimizing the burden of catheter-related side effects. This would translate into significant cost saving at the hospital and national levels.

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1. Background

The insertion of an indwelling arterial catheter (IAC) is a common practice in intensive care units (ICU) patients over the world. In the United States, up to 38% of ICU patients may receive it.(1) A European point-prevalence study performed in 1417 ICUs showed that 44% of ICU patients underwent IAC insertion.(2)

In our department in Orléans, France, 47% of the admitted patients have at least one day with an IAC. Ninety-four per cent (94%) of patients receiving continuous iv vasopressor therapy and 80% of patients placed under invasive mechanical ventilation also receive an IAC during their ICU stay. Large-scale multicentre data regarding the frequency of IAC use in French ICUs are lacking. However, our local practice seems quite close to that of other ICUs in France: In a recent multicentre observational study from our group that focused on volume expansion practice in patients with circulatory failure in 19 French ICUS (including most of the 11 participating centres anticipated for the present project), we observed that 53% of patients were already carrying an IAC at the time they received their first fluid bolus in the ICU. This proportion increased parallel to the number of fluid boluses received to reach 100% in patients receiving more than seven fluid boluses. We also observed that, on average, more than 85% of patients who were receiving continuous iv vasopressor therapy at the time they were administered a fluid bolus, were carrying an IAC at the same time.(3)

The reasons for this widespread use of IAC are that it allows continuous measurements of blood pressure, a key physiological variable that drives organ perfusion, and facilitates blood sampling for laboratory testing while avoiding several vascular punctures.(1,4,5) Therefore, despite the lack of high-level evidence of the benefits it could bring to ICU patients, the IAC insertion is commonly recommended to manage patients with septic shock or other kinds of shock.(6,7)

1.1. IAC use and patients outcome

Despite these supposed benefits and its widespread use, there is no evidence that an IAC could benefit to patients with shock through improved survival or decreased morbidity, discomfort and pain. One observational study even showed, while adjusting for a propensity score to receive or not an IAC, an increased mortality associated with IAC use among patients receiving vasopressors.(8) More recently, in a large cohort of ventilated patients who did not require vasopressor support, Hsu et al showed no difference in day-28 mortality after propensity score matching to receive or not an IAC between patients with and without IAC. Interestingly, when survivors were separately analysed, there were no between-group differences in ICU and hospital length of stay.(9) The authors concluded that randomized controlled trials were mandatory to investigate the impact of IAC use on patients' outcomes.

1.2. Morbidity related to IAC

The use of an IAC is not free of complications. Vascular complications such as thrombosis (from 20% to 60%),(10-12) ischemia, hematoma, pseudo aneurysm are not rare events. Infectious complications and bloodstream infections are also common: the incidence density is close to 11 per 1000 IAC-days for colonization and 1 per 1000 IAC-days for related infection.(12)

Moreover, some authors suggest that the presence of an IAC, since it facilitates blood sampling, may increase the number of unnecessary blood samples drawn, therefore favouring anaemia and red blood cell transfusion during the ICU-stay.(9,13-15)

In addition, one may speculate that the time needed to insert an IAC, during the first golden hours of resuscitation, could delay urgent treatments and procedures (therapeutic prescription such as fluid expansion or antibiotics, nurses work overload, transport to imagery or operating room).

1.3. Related costs

Studies that specifically examined the cost related to IAC use in ICU patients are lacking. However, one can speculate that this cost is high when considering the time and resources needed for IAC insertion (on average 20 min of doctor and 20 min of nurse time)(16) and maintenance, the high number of patients undergoing IAC insertion, the cost associated with catheter-related infections and perhaps undue lab tests and transfusions.(17-23)

1.4. Alternatives to the use of IAC

Alternatives to invasive blood pressure measurements

Intra-arterial catheterization is considered the gold standard for BP monitoring. Indeed it provides accurate measurements, detects instant changes in BP and allows arterial blood sampling. Moreover, BP waveform analysis can, under certain conditions, give information about potential fluid responsiveness.(24,25)

However, non-invasive blood pressure (NIBP) measurements through automated oscillometry and brachial cuff are widely used, even in shocked, unstable patients.(26) It is the first-line monitoring used during pre-hospital care, in the emergency department and often at intensive care unit (ICU) admission, before an intra-arterial catheter can be inserted in optimal conditions.

Oscillometric devices measure the amplitude of pressure oscillations in the air-filled arm cuff during gradual deflation. As cuff deflates below systolic BP, blood flows through the reopening brachial artery and induces arterial wall oscillations that increase until the counterpressure exerted by the cuff allows minimal arterial wall tension and maximal arterial volume change. The cuff pressure at this point of maximal oscillation determines the mean BP. Notwithstanding some artefacts, oscillometric mean BP measurement is accurate to a few mmHg.(27) This point is of crucial importance since generally

intensivists pay great attention to the mean BP, as it represents the perfusion pressure of most organs, and mainly rely on it to track response to therapy in shocked patients.(28)

As existing oscillometric devices and algorithms best operate within a certain range of cuff compliance, the cuff size is of paramount importance. Too large cuffs expose to underestimation of BP whereas too small cuffs expose to overestimation.(29) Clinicians should measure the patient's arm circumference and scrupulously follow manufacturer instructions to choose the appropriate cuff size.

With modern oscillometric devices, recent prospective studies have shown that mean and diastolic BP measurements with arm NIBP fulfilled the ISO Standard,(30-32) i.e., reported a mean bias of 5 mmHg or less when compared to the intra-arterial reference, even in hypotensive, unstable ICU patients receiving continuous iv vasopressors. Remarkably, arm NIBP detection of mean BP <65 mmHg was associated with a high area under the receiver operating characteristics curve (AUC_{ROC}) of 0.90-0.98.(30,31,33,34) Moreover, changes in arm NIBP have sufficient accuracy to provide good detection of a significant increase in intra-arterial mean BP, enabling identification of BP responders to urgent therapy (AUC_{ROC} of 0.89-0.98 for a 10% mean BP increase cutoff).(33) In addition, arrhythmia did not alter the performance of the tested devices.(33) It should be noted however that oscillometric NIBP measurements still remain challenging in very obese patients, even when cuff size is optimal.(32,35)
Clinicians sometimes place the cuff around a lower limb(26) when placement at the arm is impossible or contraindicated. NIBP measurements are less accurate if the cuff is placed at the ankle or the thigh rather than at the arm.(30) However, ankle and thigh NIBP still reliably detect hypotensive (mean BP < 65 mmHg) and therapy-responding patients (AUC_{ROC}=0.93 and 0.96, respectively).(30)

Despite these recent data on the accuracy and clinical usefulness of oscillometric BP measurements, staunch defenders of the invasive technique may still argue that the reported accuracy of oscillometry of about 5 mmHg is not sufficient and endangers patients by inducing inappropriate therapeutic decisions. However, it is worth reminding that invasive measurements through fluid-filled measuring systems like those used in all ICUs may suffer of technical imperfections such as over- or under-damping, or imprecise zero levelling.(36) This may well result in inaccuracy of about 5 mmHg, even in optimal conditions (level of pressure transducer, optimal damping coefficient of the measuring system): Invasive radial or femoral artery BP as displayed by ICU monitors may exhibit interval agreement widths of about 5 mmHg for mean and diastolic BP and 10 mmHg for systolic BP when compared to high performance research tools.(37) More importantly, invasive BP is most often measured in the radial artery, and sometimes in the femoral artery. Radial and femoral mean BP values may differ by 5-10 mmHg(38)

because of the pulse-wave reflection phenomenon that amplifies the radial pressure(39) or conversely because of high dosages of vasopressor that constrict the brachial artery thereby dampening the radial pressure. Despite these potential discrepancies between radial and femoral pressures, clinicians often rely on the same pressure thresholds to manage therapy, regardless of whether the IAC is placed in radial or femoral artery. Moreover, current recommendations and guidelines for shock management do not specifically address this issue and often give a unique pressure threshold (mean BP of 65 mmHg), once again without differentiating radial and femoral measurements.(40)

In summary, provided that cuff size is appropriately chosen, arm NIBP measurements have rather good accuracy to estimate intra-arterial pressure. Whether this accuracy is better or worse than with the use of usual invasive ICU equipment (IAC and fluid-filled systems) to estimate the true intra-arterial pressure value (i.e., measured with invasive high-fidelity systems) is not known. However, when compared to the intra-arterial reference measured with usual equipment, NIBP allows the detection of hypotension (mean BP<65 mmHg) and of significant (±10%) changes in mean BP. This holds true in patients with pronounced hypotension, high vasopressor dosages or arrhythmia. However, as the correspondence between intra-arterial and NIBP value is not perfect, and also because optimal thresholds may differ across oscillometric devices, clinicians may choose to favour sensitivity for detecting hypotension (mean intra-arterial BP < 65 mmHg) when interpreting NIBP values. To this end, the 70 mmHg value for NIBP may offer a clinically relevant compromise.(33)

Alternatives for arterial blood gas and arterial lactate measurements and other lab tests

Central venous lines allow the safe infusion of drugs potentially toxic to the peripheral veins, such as vasopressors and hyperosmotic solutions. For these reasons, they are often used when caring for ICU patients,(1,2) and their risk/benefit ratio seems to favour patients' safety when compared to the use of peripheral venous lines.(41)

Venous blood sampling through internal jugular or subclavian central venous catheters has been popularized after the study by Rivers et al in 2001 that suggested that the central venous oxygen saturation ($ScvO_2$) could be a target for therapy in patients with septic shock.(42)

Blood drawn from superior vena cava catheters can be used to estimate arterial blood gases and lactate concentration with variously appreciated accuracy but of potential clinical value.(43-46) As recently reported by our group in a large cohort of ICU patients with circulatory failure, the analysis of central venous blood combined with finger pulse-oximetry readings (SpO_2) provide useful prediction of arterial pH, $PaCO_2$, SaO_2 and lactate concentration.(47) In short, when the estimation of arterial values from

central venous blood analysis predicts values within the normal range, this helps ruling out blood gas or lactate abnormal values with high probability.

In routine practice most of blood drawings for laboratory testing are not followed by any change in therapy or by the application of a new procedure. In a literature review, van Walraven et al. estimated that 30% to 90% of these tests were not indicated.(48) Among them, arterial blood gas and lactate measurements were widely prescribed for reasons not fully evidence-based such as control after changes in ventilator settings, daily (or more frequent) check, or monitoring of the sickest patients for instance.(49-51)

In summary, a number of arterial punctures and arterial blood drawings can be avoided by simply checking SpO_2 and analysing central venous blood. This does not prevent prescribing arterial puncture in some cases, depending on the clinical situation and the clinician's confidence. Of note, central lines may be safely used to sample blood for other purposes than blood gases or lactate monitoring, as safely done for decades in cancer/haematology patients.(52-55)

2. Study objectives

2.1. Primary objective

Our main hypothesis is based on the following observations:

- IAC insertion is time consuming and may delay urgent procedures
- IAC insertion is cost consuming
- IAC may lead to complications (infections, thrombosis) and undue blood samplings and transfusions
- NIBP, with an adapted cuff size, can be used safely and reliably to predict MAP < 65 mmHg
- NIBP can be used to track spontaneous or therapy-induced changes in MAP
- Central venous blood analysis combined with SpO_2 offer clinically useful estimation of arterial lactate, arterial pH, PaO_2, $PaCO_2$ and SaO_2

Therefore, the question arises of whether ICU patients with circulatory failure would not be safely managed without the insertion of an IAC, contrary to what is currently done in common practice.

The objective of the present research is a combination of a one-sided test of non-inferiority and a one-sided test of superiority. A stepped approach will be used to evaluate these hypotheses:
a) a less invasive intervention (i.e., no IAC insertion until felt absolutely needed, according to consensual and predefined safety criteria [see below]) is non-inferior to usual care (i.e., systematic IAC insertion in the early hours of shock) in terms of mortality at day 28 (non-inferiority margin of 5%).
b) a less invasive intervention is not only non-inferior but also superior to usual care in terms of mortality

2.2. Secondary objectives

1. To assess the non-invasive strategy as compared to the invasive usual strategy for the management of patients regarding vasopressor-free days at day 28, organ failure progression, fluid balance, and duration of mechanical ventilation support.
2. To assess the impact of the non-invasive strategy on the number of lab tests ordered, the number of vascular punctures performed, the magnitude of related pain reported by the patients, the evolution of blood haemoglobin level, the number of red cell transfusions administered during the ICU stay, the number of catheter-related infections, and on the direct hospital medical costs of care.
3. To determine the efficiency of the non-invasive strategy when compared to the recommended invasive strategy (ICER: 'Cost/Life day gained at 28 days').
4. To evaluate the budget impact of the generalization of the non-invasive strategy (in case of demonstrated non inferiority) in France from the viewpoint of the French health system on a 5 years' time frame

2.3. Outcome measures

Primary outcome measure

All-cause mortality by 28 days after randomisation

Secondary outcome measures

- To account for the potential bias brought by deaths occurring as the result of life-sustaining treatments withdrawal/withholding, as frequently encountered in ICUS, we will record such events from inclusion to Day 35 (i.e., until one week after the primary time point)(56)
- Cumulative incidence of death from inclusion through Day 90
- Cumulative survival free of IAC insertion, from inclusion through Day 90
- Number of patients who underwent IAC insertion, in both groups
- Evolution of daily Sequential Organ Failure Assessment (SOFA)(57) score during the first seven days
- Daily amount of intravenous fluid given for rapid vascular volume expansion from Day 1 to Day 7
- Daily fluid balance from Day 1 to Day 7
- Duration of mechanical ventilation
- Ventilator-free days from Day 1 to Day 28 (for this purpose patients dying between randomisation and Day 28 will be assigned a 0 value; for survivors at Day 28, all the days free of invasive mechanical ventilation through an endotracheal tube within the 28-day period will be taken into account)
- Proportion of patients treated by renal-replacement therapy between Day 1 and Day 28
- Renal replacement therapy-free days from Day 1 to Day 28 (for this purpose days without renal replacement therapy from Day 1 to Day 28 for survivors at Day 28, and from Day 1 to the date of death for patients dying before Day 28, will be taken into account)
- Proportion of patients treated by vasopressor between Day 1 and Day 28
- Vasopressor therapy-free days from Day 1 to Day 28 (for this purpose days without vasopressor therapy from Day 1 to Day 28 for survivors at Day 28, and from Day 1 to the date of death for patients dying before Day 28, will be taken into account)
- Mean daily blood volume drawn for lab testing during ICU stay
- Number of blood cultures performed during ICU stay
- Number of attempts at arterial puncture during ICU stay
- Evolution of blood haemoglobin level from Day 1 to Day 28
- Evolution of haematocrit from Day 1 to Day 28
- Number of red blood cell packs transfused from Day 1 to Day 28
- Number of transcutaneous arterial and venous puncture for lab tests, arterial catheter insertion and set up of monitor, blood drawing from the arterial catheter or other vascular line through ICU stay and time (min) spent by nurses and physicians (min) on these tasks during the first three days of the

ICU stay (in a random sample representing 10% of the total number of included patients).

- Number of arterial and central venous catheter insertion during ICU stay
- Numbers of arterial and central venous catheter-related infections during ICU stay, expressed as the incidence of new cases per 1000 catheter-days, including local and catheter-related bloodstream infections as consensually defined.(58,59)
- Numbers of local infections of arterial and central venous during ICU stay (number of new cases per 1000 catheter-days).
- Numbers of arterial and central venous catheter-related bloodstream infections during ICU stay, (number of new cases per 1000 catheter-days).
- Number of bloodstream infections during ICU stay, catheter-related or not
- Duration of ICU stay
- Duration of hospital stay
- ICU mortality
- Hospital mortality
- Day-90 mortality
- Number of Adverse Events of special interest (Ischemia and/or necrosis of finger(s) or toe(s), documented bowel ischemia, occurrence or worsening of acute renal failure with need of renal replacement therapy, need of tracheal intubation in a patient previously not intubated, Cardiac arrest, nerve injury of upper limb(s), skin lesions at cuff location or at IAC insertion site, arterial thrombosis, hematoma, arterial pseudo aneurysm, haemorrhage at IAC insertion site either during IAC placement or later)

- Incremental Cost-Effectiveness Ratio (ICER): «Cost/Life day gained at 28 days'», from the health system viewpoint, between the non invasive strategy and the recommended invasive strategy: $(Costs_{NIBP}–Costs_{IAC})/(\text{Life expectancy at } D28_{NIBP}–\text{Life expectancy at } D28_{IAC})$
- Budget impact analysis of the generalization of the non-invasive strategy (in case of demonstrated non inferiority) in France from the viewpoint of the French health system on a 5 years' time frame
- Patient-reported pain and discomfort related to the device used for BP monitoring will be assessed using numerical scales in both groups, once a day as soon as the patients are awakened and capable of correctly evaluating their pain and discomfort (cf. APPENDIX 1)

3. Interventions

Once included, the patient will be randomly assigned, for the 28 following days, to one of the following strategies:

a) **"usual care"**: An IAC will be inserted as soon as possible (within the first four hours after randomization)

and will be maintained except in case of IAC futility (as defined below), suspected or proven IAC related infection or thrombosis (at discretion of attending physician) until day 28 or ICU discharge (whichever comes first). After day 28, clinicians may choose to maintain or to remove IAC.

During the intervention period, in case of removal for accidental or other reasons than futility (i.e. IAC infection, IAC dysfunction, unavailability to draw blood), another IAC should be inserted during the next four hours (insertion site at the discretion of the attending physician).

In case of IAC removal for other futility criteria than decision of palliative care, an IAC will be inserted within the four hours of new onset of circulatory failure as defined below:

- Presence of
    - Persisting hypotension (systolic blood pressure less than 90 mmHg or mean arterial blood pressure less than 65 mmHg) for more than 4 hours
    - OR requirement of continuous iv vasopressor treatment (i.e. noradrenaline tartrate at a dose ≥ 0,2 µg/kg/min or any dose of epinephrine) for more than 4 hours
- AND at least one of the following signs of hypoperfusion: alteration of mental status; skin mottling; oliguria defined as a urine output < 0.5 mL/kg body weight for at least one hour; arterial lactate > 2 mmol/L; peripheral venous lactate > 3.2 mmol/L; $ScvO_2$ <70%

b) **"non-invasive care":** No IAC insertion will be allowed during the first 28 days, excepted if predefined safety criteria (indicating absolute need of IAC insertion) are reached (see below): IAC will be inserted within the 4 hours of presence of safety criteria and patient will be managed as if he/she were part of usual care group until day 28 or ICU discharge. Arterial blood draw is allowed via direct arterial puncture as frequently as indicated.

Criteria of IAC futility (one or more criteria defined futility) allowing IAC removal at physician's discretion:

- The patient no longer needs significant vasopressor therapy (i.e. no longer needs norepinephrine tartrate at a dose ≥ 0,2 µg/kg/min or any dose of epinephrine) for more than 4 hours, and exhibits no sign of hypoperfusion (i.e., neither alteration of mental status, skin mottling, oliguria defined as a urine output < 0.5 ml/kg body weight for at least one hour, arterial lactate > 2 mmol/L, peripheral venous lactate > 3.2 mmol/L or $ScvO_2$ <70%)
- Medical decision of palliative care

Safety criteria for IAC insertion for patients initially randomized in the "no-IAC" group:

As undisputable criteria are lacking in the medical literature, criteria were consensually determined (Delphi method) after collecting the opinion of the anticipated investigators (senior ICU physicians) in each centre. After two turns of notation, the following criteria were retained (since the median of notation fell between 7 and 9 on a 9-point scale; extending from score 1 ["do not agree at all"] to score 9 [fully agree]) with low

(instead of strong) agreement between physicians (because the lower limit of notations fell below 4):

- Although the pulse oximetry monitor was working well at inclusion, it can no longer display any reliable SpO_2 value
- Despite NIBP readings were available at inclusion, NIBP now consistently fails to display any reliable BP value
- Absolute need of one arterial blood gas measurement whereas 5 consecutive arterial puncture attempts have failed (*Remember that we encourage the clinicians to preferably rely on SpO_2 readings and on arterial blood gas estimates derived from central venous blood analysis when a superior vena cava line is present*)
- Need of veno-venous or veno-arterial ECMO
- Need of vasopressor dosages of more than 2.5 µg/kg/min of *norepinephrine tartrate* plus epinephrine for at least 2 hours (i.e., for instance, more than 8 mg of *norepinephrine tartrate* in 50 mL at the rate of 66 mL/hour for a patient weighing 70 kg)
- Need of high risk surgery (left at the attending physician discretion) within the next 4 hours; in this case, the indwelling arterial catheter should be withdrawn within the 4 hours after the patient returns in ICU, unless one or several of the above criteria are fulfilled.

3.1. Differences between the usual care and the non-invasive care strategies

Description of blood pressure monitoring among randomisation group

In the "usual care" group, BP will be monitored through the arterial line sensor connected to the usual monitoring device (fluid-filled system). Site of IAC insertion, insertion technique, skin antisepsis and catheter care will be at the discretion of the attending physician, according to local guidelines. Non-invasive BP monitoring is not allowed, except when IAC is considered futile (as defined above) and during IAC insertion or replacement.

In the "non-invasive" group, automated oscillometric monitor will be used to monitor BP. ***The size of the cuff will be adapted according of the arm circumference and manufacturer recommendations***. The dedicated indicator will be placed at the level of the artery. If deemed appropriate according to clinical context, the cuff may be placed at the lower limb.(30)

In both groups, alarm thresholds and interval of BP measurements will be left at the discretion of the attending physician.

Blood sampling technique

In the "usual care" group, blood samples for lab tests will be drawn from the IAC, as many times as

necessary. Blood-drawing through the central venous catheter is forbidden, excepted for $ScvO_2$ measurements.

In the "non-invasive" group, blood-drawing trough the central venous catheter is recommended for usual lab tests. To avoid interruption or bolus on specific continuous therapeutics, we strongly recommend infusing vasopressor agents in a dedicated line of the central venous catheter that should not be the line used for sampling. Regarding the monitoring of ventilation parameters and of the lactate blood level, we encourage the attending intensivists and investigators to rely on SpO_2 (60,61) to assess oxygenation, and on predicted pH, $PaCO_2$, and lactate derived from central venous blood analysis.(47) For this purpose, formula to derive estimates of arterial blood parameters and abacuses giving probabilities of true arterial values below or above given thresholds for each predicted value will be provided to the sites (APPENDIX 2).

Arterial blood gas parameters

We will develop a mobile application to automatically estimate arterial blood gas parameters from central venous parameters and SpO_2 (see APPENDIX 2). As the study is not cluster randomized, the mobile app with the arterial blood parameters calculator will be available for all investigators regardless whether they are in charge of patients randomized in the "invasive" (presence of IAC) or the non-invasive group. To minimize this potential source of bias, we want to emphasise, and this will be clearly reminded in the mobile app, that central venous blood drawing will not be allowed in the "invasive" group, except for $ScvO_2$ measurements.

Modalities of patients' general management

In both group, patients will be managed following international and national guidelines, except for the IAC insertion.

Regarding blood sampling for lab tests, to avoid unnecessary blood spoliation in both arms, we strongly encourage investigators and attending intensivists to properly assess the real need of each lab test ordered. We discourage sampling for routine (daily or more frequent) monitoring or after changes in FiO_2 or PEEP. If blood gas were drawn for suspicion of metabolic or respiratory disorder, only the control after therapeutic intervention will be allowed.

In addition, to decrease blood spoliation during sampling through any vascular catheter (IAC for the invasive group, CVC for the non invasive group), we strongly suggest to apply the following procedure that may help minimizing the discard volume of blood withdrawn before the sampling.(62,63)

After cleaning the catheter hub, draw off 3 mL (for sampling through IAC) or 5 mL (through CVC) of blood (i.e., at least 2 times the catheter's priming volume)(64) with a syringe and waste the syringe. Draw the blood sample through the Vacutainer system. Be sure to sample blood from a line of the catheter not dedicated to continuous vasopressor therapy (to avoid bolus or discontinuous infusion).

For the centres using a closed system for reinfusion, they can continue to use it without discarding blood.

4. Study design

The projected study will be a multi-centre, pragmatic, randomised, controlled, open, two-parallel-group, non-inferiority clinical trial with 1:1 assignment of interventions.

Although blinding is not possible due to the nature of the assessed intervention, the primary endpoint is objective (mortality at day 28). The trial will associate medical, surgical, and mixed ICUs, as well as academic tertiary care hospitals and community hospitals.

We deliberately decided not to perform a cluster-randomized trial. This design is prone to the risk of selection bias. Moreover, there are few centres in the study, which could lead to chance imbalance.

As the need for IAC insertion is rooted in intensivists' mind when caring for patients in shock, there is a real risk that patients assigned to the non-invasive arm will frequently be switched to the invasive arm (with IAC insertion). To prevent this kind of contamination bias, the study scientific committee has set reasonable and consensual safety boundaries that will fix in which circumstances the insertion of an IAC will become an inescapable need (in terms of vasopressor requirement for instance [see the *"3. Interventions"* paragraph]).

In the end, we opted for a classical standard individually randomised trial and worked at limiting group contamination.

4.1. Randomisation

Randomisation will be electronically centralised via a dedicated website.

Randomisation will be stratified on centres, invasive mechanical ventilation (yes or no) and vasopressor dosage, namely < or ≥ 0.18 µg/kg/mn of continuous iv norepinephrine (ie. 0.36 µg/kg/mn of continuous iv norepinephrine tartrate) or of epinephrine or of the sum of both medications dosages at time of enrolment.

The statistician in charge of the project will determine permutation blocks, the size of which will not be known by the investigators.

4.2. Study time points definitions

Patients will be declared enrolled in the study once consent obtained.

Date and time of randomisation will determine the beginning of the intervention period (Study H0)

4.3. Inclusion and non-inclusion criteria

Inclusion criteria

- Age ≥ 18 years the day of inclusion
- Existence of an acute circulatory failure defined by the presence of the following items 1 and 2:
    1) Persisting hypotension (systolic blood pressure less than 90 mmHg or mean arterial blood pressure less than 65 mmHg) for more than 15 min at ICU admission or within the following

24 hours, **OR** requirement of continuous iv vasopressor treatment (i.e. any dose of norepinephrine / epinephrine)

2) Presence at least one of the following signs of hypoperfusion: alteration of mental status; skin mottling; oliguria defined as a urine output < 0.5 mL/kg body weight for at least one hour; arterial lactate > 2 mmol/L; peripheral venous lactate > 3.2 mmol/L; $ScvO_2$ <70%

- Free express oral and informed consent of the patient or a proxy in case of impossibility for the patient to consent; emergency inclusion possible when legal representatives and patient's family are not available
- French health insurance holder

Non-inclusion criteria

- Acute circulatory failure, as defined by items 1 and 2 in inclusion criteria list (cf. supra) present for more than 24 hours
- NIBP device fails to display a BP value, or cuff placement impossible
- Patient for whom an ECMO therapy (either veno-arterial or venous-venous) is already in place or is to be initiated within the next 6 hours
- Patient treated with vasopressor doses of more than 2.5 µg/kg/min of *norepinephrine tartrate* plus epinephrine for at least 2 hours (i.e., for instance, more than 8 mg of *norepinephrine tartrate* in 50 mL at the rate of 66 mL/hour for a patient weighing 70 kg) (*please note that in fact this dosage corresponds to 1.25 µg/kg/min of norepinephrine base*)
- Severe traumatic brain injury (i.e., traumatic brain injury with a Glasgow coma scale score of less than 9 before sedation)
- Patient previously included in the trial
- Body mass index (BMI) above 40 kg/m^2 (33,35,65)
- Pregnancy
- Brain death
- Moribund patient
- Patient known, at time of inclusion, as being under guardianship, tutorship or curatorship

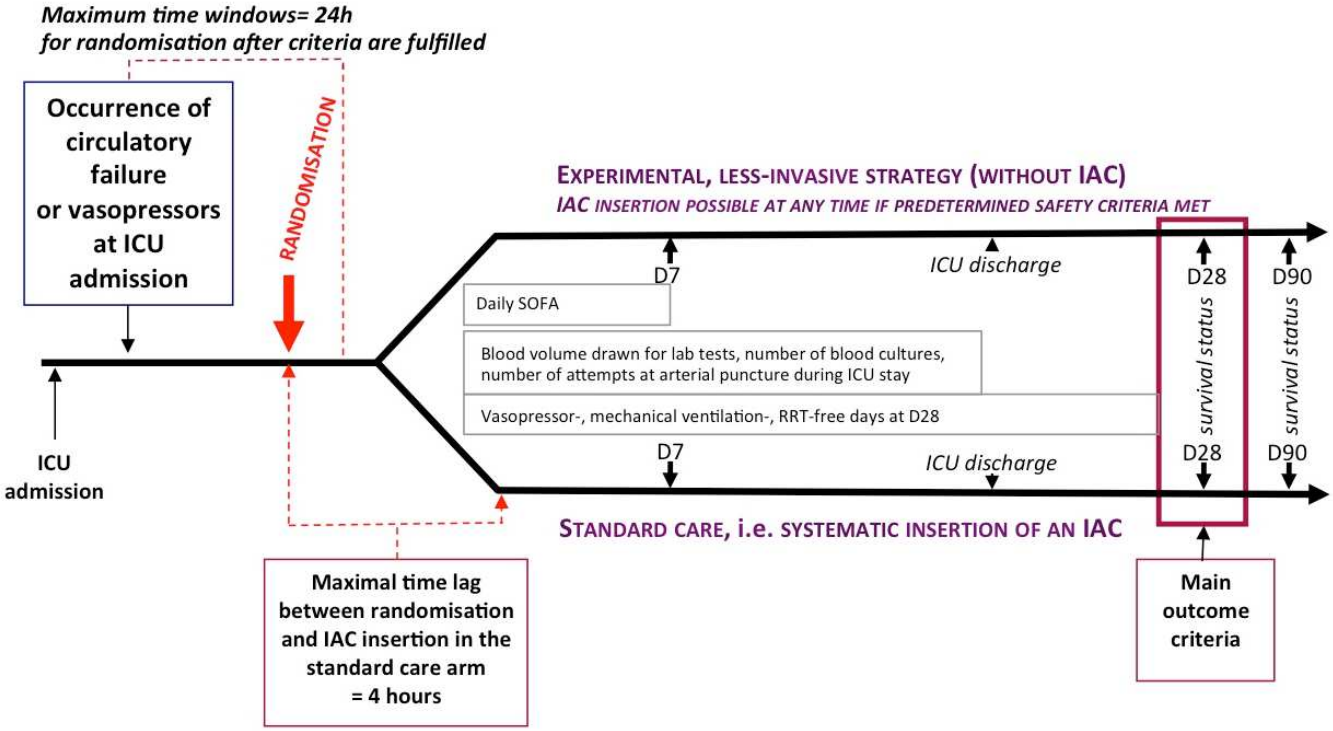
N.B.: Note that a patient already carrying an indwelling arterial catheter can still be randomized in the study provided that all the above criteria are respected. ***If randomised in the "noninvasive group", the catheter should be removed within one hour following randomisation.***

4.4. Exclusion period for subjects inclusion in another study if suitable

No exclusion period after the end of the trial participation.

Patients will be excluded for participation in clinical trial investigating the usefulness of IAC during management of acute circulatory failure, but they will be authorized to participate to other studies.

4.5. Study outline



4.6. Schedules of procedures for each enrolled patient

	Inclusion	**Short-term follow up until D28 or discharge from ICU (whichever comes first)**			***Long-term follow up***
	Study Day 1 starts once patient is randomized	D1, D2, D3	D4, D5, D6, D7	D8 to D28	***D90***
Inclusion/exclusion criteria	X				
Informed consent	X				
Randomisation	X				
Delayed pursuit consent if applicable		X	X	X	X
Clinical assessment (heart rate, blood pressure, SpO_2, pain assessed during transcutaneous vascular puncture[a,e], fluid balance[b])		X	X	X	
Catheter evaluation (IAC insertion, IAC removal, catheter-related infection)		X	X	X	
Laboratory sampling status (blood volume draw, number of attempts at arterial puncture)		X	X	X	
Therapeutic assessment (number of packs of red blood cells transfused)		X	X	X	
Supportive therapy assessment (respiratory status, ventilator settings[c], renal replacement therapy[c], vasopressor support[b])					
Census evaluation (survival status, in ICU, in Hospital)		X	X	X	X
Specific laboratory testing for the study (SOFA)		X	X		
Blood haemoglobin[d]		X	X	X	
Number of arterial and venous punctures for lab tests, arterial catheter insertion and set up of monitor, blood drawings from arterial catheter or other vascular line, through ICU stay[e]		X	X	X	
Microcosting of staff time and equipment used for arterial and venous punctures for lab tests, arterial catheter insertion and set up of monitor, blood drawings from arterial catheter or other vascular line, through ICU stay[e]		X			
Adverse events/Serious adverse events[f]		X	X	X	X
Query on the French National Hospital Discharge Database (at the end of the study)		X	X	X	

[a]: assess by visual or numeric scale for patients able to communicate and by Behavioural Pain Scale(66) otherwise

[b]: fluid balance will be assessed only from D1 to D7

[c]: if applicable

[d]: if available

[e]: on a 10% random sample of study population

[f]: Collection and reporting of adverse events will begin once the informed consent is signed

Patients' follow-up:

Patients will be examined for signs of shock and organ failures throughout their ICU stay, as done in routine practice.

Their deceased/alive status will be recorded at ICU discharge, hospital discharge, by day 28 and by day 90

Lost-to-follow-up

The study centre personnel will make every possible effort to collect the survival status of the enrolled patients at day 28 and day 90 (by consulting electronic hospital records, telephone contact with family practitioner, or with patient him/herself or relatives).

4.7. Measures taken to minimise or avoid bias

Recruitment

All patients admitted in the participating ICUs during the study period will be screened for eligibility. Investigators will make every effort to include all consecutive eligible patients to avoid selection bias. Investigators and study personal at each centre will fill in a screening-log form in which will be recorded included and non included eligible patients' characteristics (age, gender, Simplified Acute Physiology score [SAPS II](67), cause of shock, ICU survival, cause of non inclusion if applicable) to allow assessing the representativeness of the study population and drawing conclusions concerning the generalizability of the results.

Randomisation

Randomisation is mandatory to minimise selection bias.

Stratification

Stratification on centres, invasive mechanical ventilation and vasopressor dosage at time of enrolment is planned to have well balanced groups concerning the general care approach (which could differs between centres).

Definition of safety criteria for IAC insertion in the experimental group

The study scientific committee has set reasonable and consensual safety boundaries that will fix in which circumstances the insertion of an IAC will become an inescapable need. Doing so will contribute to limiting group contamination which would occur if too many patients from the experimental group had an IAC.

Choice of the primary outcome measure

As blinding of investigators and of all ICU staff members is not technically feasible, we chose a "hard" endpoint (Day-28 mortality) to minimise bias.

4.8. Duration of study for each enrolled patient

Patients will be declared included in the study at the time of consent. The intervention period will last 28 days after inclusion. Patients will be followed daily until ICU discharge, until Day 28 for the primary outcome measure (Day 28 mortality), and until Day 90 for mortality (secondary outcome).

The period of follow-up will be extended as needed in case of not resolved serious adverse event.

4.9. Study duration

Duration of the inclusion period: 36 months (given the recruiting capabilities of the participating ICUs)

Duration of each patient's participation: 3 months

Total duration of the study: 39 months

4.10. Rules for interrupting the study

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time for any reason. The Investigator and Sponsor also have the right to withdraw participants from the study. Patients may be removed from the study for the following reasons: (i) Withdrawal of consent: When a subject withdraws consent before completing the study, the reason for withdrawal of consent is to be documented on the CRF and in source documents. (ii) At the request of the Investigator or Sponsor, whether for administrative or other reasons. In case of adverse event, the specific event and any related test and visit will be recorded on the CRF and the intervention may be stopped if judged necessary for safety reasons. In this instance, the patient will be kept for analysis according to the intention-to-treat principle.

When a subject is removed from the study, all observations collected up to the time of termination will be recorded on the CRF along with the reason for termination, and scheduled safety evaluations and Day 28 follow-up examinations will be conducted, if possible. However, in case of pursuit-consent refusal, the data collected will not be used for statistical analysis and the patient will not be included in the final intention-to-treat analysis.

5. Significance

We estimate the number of ICU patients presenting with shock as defined in our inclusion criteria as at least 25,000/year in France. More than 80% of them probably undergo IAC insertion during ICU stay. On the one hand, we expect several benefits to these patients with the proposed, less invasive intervention: smaller amount of blood drawn for lab tests, less transfusion, and less IAC-related complications such as catheter-related infections. On the other hand, based on recent data, we hypothesize that hemodynamic and ventilatory parameters can be safely monitored without IAC insertion. As a result, we expect that the less invasive strategy, while not affecting mortality (or marginally improving survival, an effect size difficult to capture with the planned sample size), will decrease morbidity through minimizing the burden of catheter-related side effects. This would translate into significant cost savings at hospital and national

levels.

6. Sample size and statistical analysis

6.1. Sample size

In a non-inferiority randomised clinical trial, we usually hypothesize *a priori* an equal incidence of the event of interest in the two groups compared. In the present study, our *a priori* hypothesis is different. Indeed, we expect a marginal benefit of the non-invasive approach, because the systematic IAC insertion may harm the patients through catheter-related infections and through blood spoliation. However, even demonstrating that the non-invasive approach is not inferior to the systematic IAC insertion approach could be considered as a positive result (cf., Risk/benefit ratio section).

We therefore assume that the mortality rate at day 28 will be 22.5% in experimental group and 25% in the control group. We set the non-inferiority margin at 5%, power at 80% and alpha risk at 5%. Such hypotheses led us to plan the inclusion of 1010 patients.

6.2. Statistical analysis of clinical outcomes

General principles

The statistical analyses will be performed by the INSERM CIC 1415 unit and supervised by Elsa Tavernier. SAS 9.4 and R 3.3 (or further versions) softwares will be used. A detailed analysis plan will be *a priori* defined. Later modifications must occur before unblinding the database. The statistical analysis will be conducted on the per-protocol and intention to treat (ITT) populations as recommended for non inferiority trials. A statistical report will be written in agreement with the standards as specified in the CONSORT Statement and its extension for non pharmacological interventions and for non inferiority trials (http://www.consort-statement.org/)

Baseline characteristics

Baseline characteristics will be reported per group using descriptive statistics. No statistical test will be performed.

Groups to be compared

The ITT principle will be applied. Nevertheless, patients who would withdrew consent to study participation will be discarded, as required by the French legislation.

Because patients are ICU patients, it is expected to have no lost-to-follow-up patient. We moreover plan to collect the place of birth, such that we will be able to collect the vital status asking to the city halls. If there are several lost-to follow-up patients, we will use multiple imputation.

The per protocol population will be defined during the blind review.

Statistical analysis of the primary outcome

The between-group difference (experimental group minus usual care group) in rates of day-28 mortality will be estimated based on the 2-sided 95% Confidence Interval (CI). The upper boundary of the 95% CI will be compared with the non inferiority margin of 5%. If non-inferiority is demonstrated, the upper bound of the 95%CI will be compared to 0: if it is lower than 0, then a superiority conclusion will be drawn.(68)

As a sensitivity analysis, we will perform a multivariate logistic regression, to estimate the odds ratio adjusted on the stratification variables.(69)

Statistical analysis of secondary clinical outcomes

- Day-90 mortality: the between-group difference in rates of day-90 mortality will be estimated based on the 2-sided 95% CI.
- Number of patients who underwent IAC insertion, in both groups.

No statistical test will be performed for this outcome, which would be nonsense.

In the usual care group, the proportion of patients who underwent IAC is a measure of adherence. In the experimental group, the proportion of patients who underwent IAC is of relevance as it reflects the limits of the non-invasive approach.

- The effect of intervention on changes over time of the SOFA score, the blood haemoglobin level, haematocrit, mean daily blood volume drawn for lab testing, mean daily amount of intravenous fluids given for rapid vascular volume expansion, mean daily fluid balance, daily maximum pain and associated 95%CI will be estimated using mixed linear models, after data transformation if necessary.
- Duration of mechanical ventilation will be analysed using a competing risk approach, with death as competing risk.
- The effect of intervention on proportion of patients treated by renal-replacement therapy or by vasopressor, proportions of patients with arterial and central venous catheter-related infections or bloodstream infections and associated 95%CI will be estimated using the competing risk approach, with death as competing risk.
- The effect of intervention on number of blood cultures performed, number of attempts at arterial puncture, number of red blood cell packs transfused, number of arterial and central venous catheter insertion and associated 95%CI will be estimated using negative binomial models with duration of ICU stays as offset variable.
- Two-sided 95% CIs of median differences of free-days (Ventilator-free days, renal replacement therapy-free days, vasopressor therapy-free days) will be estimated.
- Duration of ICU and hospital stay: 2-sided 95% CIs of median differences will be estimated.

- The effect of intervention on ICU and hospital mortality and 95% CI will be estimated using competing-risk model with ICU and hospital discharge alive as competing events with death during the stay.

6.3. Statistical analysis of medico-economic outcomes

General principles

Cost-effectiveness analyses will be performed by the Medico-Economic Evaluation Unit of Tours University Hospital and supervised by Solène Brunet-Houdard. They will be based on the effectiveness results obtained by the INSERM CIC 1415 and follow standard recommendations for health-economic analyses (HAS).

Medico-economic objectives

Medico-economic evaluation comprises three secondary objectives:

- To assess the impact of the non-invasive strategy on the direct hospital medical costs of care
- To determine the efficiency of the non-invasive strategy when compared to the recommended invasive strategy (ICER: 'Cost/Life day gained at 28 days')
- To evaluate the budget impact of the generalization of the non-invasive strategy (in case of demonstrated non inferiority) in France from the viewpoint of the French health system on a 5 years' time frame

Therefore, medico-economic criteria are:

- Nurse and physician time (min) spent for arterial and venous puncture for lab tests, arterial catheter insertion and set up of monitor, blood drawings from arterial catheter or other vascular line through ICU stay (in a random sample representing 10% of the total number of included patients)
- Incremental Cost-Effectiveness Ratio (ICER): «Cost/Life day gained at 28 days'», from the health system viewpoint, between the non invasive strategy and the recommended invasive strategy: $(Costs_{NIBP}–Costs_{IAC})/(\text{Life expectancy at } D28_{NIBP}–\text{Life expectancy at } D28_{IAC})$
- Budget impact analysis (BIA) of the generalization of the non-invasive strategy (in case of demonstrated non inferiority) in France from the viewpoint of the French health system on a 5 years' time frame

Cost study and cost-effectiveness analysis

The cost-effectiveness study will last 28 days and will take into account two viewpoints (Health insurance and hospital). The ITT principle will be applied.

Only the direct medical costs related to the hospitalization will be retained. Indeed, patients will be treated almost exclusively in hospitals during this time horizon. The direct link between one hospitalization and the strategy will be checked. Consumed resources will be collected during and at the end of the study:

1) A microcosting will be performed to count and time resources used in ICU for some specific steps from randomisation through day 28:
    a. preparation and insertion of an IAC and set up of monitor
    b. NIBP measurement by oscillometry
    c. arterial and venous blood sampling
    d. peripheral pulse oximetry readings (SpO_2)
    e. transfusion (number of packed red blood cell transfused)
    f. dressing changes

Staff resources (physician, nurse…) will be reported and timed separately. The equipment used for these steps will also be collected. The microcosting will be carried out in each centre on a sample of randomly selected patients (10%) and data will be collected in the Case report Form (CRF). Data from microcosting will allow us to present the results from the health institutions viewpoint.

2) A query of the hospital databases (FNHDD) will take place at the end of the study to collect actual billing data for health insurance (DRG and supplements). This step will include all patients stay data from randomisation to day 28. The coding practices for DRG will be evaluated to take into account the heterogeneity of each centre. A specific attention will be paid to comorbidity (associated diagnosis) that can affect the grouping function and possibly modify the DRG. The hospitalization data, and particularly the activity data, will be analysed to compare patterns of patient's care and comorbidity. Because of the continuous evolution of the DRG classification, hospital stays will be reallocated in the latest classification to keep consistency of data. Data from hospital databases will be used to present results from the health insurance viewpoint.

The valuation of consumed resources during hospitalization will be done from the FNHDD, the national health costs scale (ENCC), public wage grid and public prices of resources measured by microcosting.
Discounting will be applied to costs from the ENCC data to bring them forward to the current year.

Nurse and physician time (min) spent for arterial puncture, arterial catheter insertion and set up of monitor will be compared between both groups.

The overall costs will be computed by multiplying the numbered resources (from the economic data collection) by their respective costs (from the medical service valuation).
Firstly, economic data will be used to describe the population (descriptive analysis). A comparison of economic data (DRG and new hospitalisations) from both groups will be carried out.

The ICER «Cost/ Life day gained at 28 days'» was chosen to rely on the primary judgment criterion. As usual, it will be evaluated on the same timeframe for costs and effectiveness. It will be computed and presented in a cost-effectiveness plan.

A cost-effectiveness acceptability curve will be drawn from a bootstrap simulation to show the probability that the studied strategy is cost-effective for a ceiling ratio. This ratio is determined as the maximum cost that decision makers are willing to pay for one gained life day at 28 days.

According to the "HAS" guide for economic evaluation, sensitivity analysis will be led to evaluate the sturdiness of the results. It will allow us to take into account the uncertainty of surrounding various parameters of the evaluation. The variables challenged in the sensitivity analysis will be costs and results (especially the nursing and physician time and the equipment used).
The uncertainty of the ICER will be assessed using one-way deterministic sensitivity analyses (use of Tornado diagram to present the results).

Budget Impact Analysis

Only if the non-inferiority of the non-invasive strategy is demonstrated, the BIA will determine the financial impact (potential savings) of the wider use of the non-invasive strategy for all eligible patients in France. The budget impact will be analysed from the viewpoint of the health system (Hospital and Health Insurance) over a 5-years' time frame. No discounting will be applied to the BIA data, in accordance with HAS recommendations.
The BIA will consist in multiplying the average annual cost per patient over 5 years by the number of eligible patients, taking into account a penetration rate. We will estimate the financial impact of the non-invasive strategy considering the current and future target populations (such data will be collected from the literature and expert opinions).

Excel®, SAS 9.4, STATA 15 and TreeAge Pro® softwares will be used for all medico-economic analyses.

7. Feasibility

The feasibility of the proposed study is based on (i) the ability of involved ICUs and investigators to recruit patients, (ii) their expertise in the field of shock resuscitation, (iii) their experience regarding inclusion in and conduct of interventional studies in the field of resuscitation, (iv) logistical support provided by the CRICS group and (v) the involvement of the CIC and the UEME-CHU Tours for the methodological, statistical expertise, and database management.

7.1. Recruitment capacities of the participating ICUs

Overall, the 11 involved ICUs admit over 9000 patients a year (http://www.crics.fr/), and we estimate that patients with shock represent 15-20% of these admissions. This yields a minimum of 4050 to 5400 potentially eligible patients over 3 years, among which 19-25% will have to be enrolled to reach the predetermined sample size. On average, each participating ICU will admit 10-14 potentially eligible patients per month. Therefore, the required mean inclusion rate of 2.6 patients/month in each centre appears realistic.

7.2. Expertise of ICUs and investigators in the field of shock resuscitation

A number of recent publications of the investigators are in the field of shock management.

7.3. Centres' skills in clinical interventional research

All the participating ICUs are members of the Clinical Research in Intensive Care and Sepsis (CRICS) group. CRICS is a group of ICUs of which the objective is to develop and professionalise clinical research in critically ill patients (http://www.crics.fr/). CRICS group and his partners have participated in numerous pharmaceutical and academic trials, and have demonstrated their ability to meet their commitments in terms of recruitment.

8. Risk/Benefit ratio

Patients included in this study are very sick patients who are exposed to numerous complications and risks independent of the study arm.

Excepted for the use of an IAC, patients' care will be managed as usual in both arms, according to national and international guidelines and to local operational standard procedures. Whether the risk/benefit balance is favourable in one arm compared to the other is in fact the very question addressed in this study. Every effort will be made by investigators and caregivers to minimise risks in both arms. However, our main hypothesis based on published data is that the systematic IAC insertion may harm the patients through catheter-related infections and through blood spoliation, whereas positive impact on patient-centred outcomes has never been documented. Hence, by minimising IAC-related morbidity, the interventional, less invasive strategy (no systematic IAC) might well also result in a slight but positive effect on survival. As this positive effect is expected to be marginal and might be difficult to capture in a study of reasonable sample size, we chose to design the study as a non-inferiority trial with the mortality as the primary outcome measure, and secondarily test for superiority if non inferiority is demonstrated. Secondary outcome measures will aim at assessing the IAC-related morbidity and costs.

The scientific committee decided to present the study as a study that brings minimal risk (in the meaning of

the French Law)[a,b] to patients and a possible benefit in the intervention arm as compared to usual care, resulting in a potentially favourable risk/benefit balance.

9. Ethical and regulatory considerations

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Research Involving Human Subjects.

The study will be conducted in accordance with the present protocol. With the exclusion of emergency situations necessitating taking specific therapeutic actions, the investigator or investigators undertake to observe the protocol in all respects, in particular as regards obtaining consent and the notification and follow-up of serious adverse events.

The study protocol will be submitted to the Ethics Committee (Comité de Protection des Personnes). Data recorded in this study will be participant to computer processing by INSERM CIC-P 1415 – University Hospital Centre of Tours, and these data collected during the trial will be processed in accordance with the requirements of the CNIL (within the framework of the Reference methodology (MR-001) and the General Data Protection Regulation (2016/679- GDPR)).

We intend to present the study as a study exposing enrolled patients to minimal risks and possibly resulting in a favourable benefit/risk ratio for at least one group of patients. If such benefit/risk ratio and study qualification are approved by the CPP, the study protocol will be transmitted to the ANSM for information. Furthermore, if the CPP recognises that the study exposes the patients to minimal risks, we will ask, as allowed by the French Law, to have the possibility to include the patients without prior consent if patient is not able to consent and if relatives or legal representatives are not present. Thereafter, information will be given to the patient and he/she will be asked to give a delayed pursuit-consent if he/she has regained sufficient capacities.

CHRU de Tours, the sponsor of this study, will take out an insurance policy covering third party liability as required by the French Law.

In accordance to the French Law, this research will be registered in the European EudraCT database or in the ANSM *"Recherches et collections biologiques (RCB)"* registry depending on the qualification the CPP gives to the research.

This research will be registered on the web site http://clinicaltrials.gov/ before the inclusion of the first patient.

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[a] Loi n° 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (1) (JORF n°0056 du 6 mars 2012 page 4138)

[b] Arrêté du 3 mai 2017 fixant la liste des recherches mentionnées au 2° de l'article L. 1121-1 du code de la santé publique (JORF n°0107 du 6 mai 2017 texte n°30)

Règlement (UE) 2016/679 (RGPD),

Any substantial modification, i.e. any modification of a nature likely to have a significant impact on the safety of the people involved, the conditions of validity and the results of the study, on the quality and safety of the studied strategies, on interpretation of the scientific documents which provide support for the study or the methods for conducting it, is the subject of a written amendment to be submitted to the sponsor; prior to implementing it, the latter must obtain approval from the ethics committee.

Non-substantial modifications, i.e. those not having a significant impact on any aspect of the study whatsoever, are communicated to the ethics committee for information purposes.

Any amendments to the protocol must be made known to all the investigators participating in the study. The investigators undertake to comply with the contents.

Any amendment modifying the management of patients or the benefits, risks or constraints of the study is the subject of a new Patient Information and Informed Consent form which must be completed and collected according to the same procedure as used for the previous one.

10. Access rights

10.1. Access to data

The sponsor is responsible for obtaining the agreement of all the parties involved in the study in order to guarantee direct access in all the sites where the study is being conducted to source data, source documents and reports, so that he can control their quality and audit them.

The investigators will make available to the people with a right of access to these documents under the legislative and regulatory provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Act) the documents and individual data strictly necessary for monitoring, carrying out quality control and auditing the research.

The Promoter, through its data protection officer, will ensure the compliance of the data processing in accordance with the provisions of Regulation (EU) 2016/679 (GDPR) and its transposition into French law (revision of files and civil liberties).

10.2. Source data

Any original document or object helping to prove the existence or accuracy of a piece of information or fact recorded during the study is defined as a source document.

10.3. Confidentiality of data

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Code), people with direct access to source data will take all necessary precautions to ensure the confidentiality of information related to the study and people taking part in them, particularly as regard

their identity and the results obtained. These people, like the investigators themselves, are subject to professional secrecy.

During the study or when it is over, the information collected on the people taking part in it and forwarded to the sponsor by the investigators (or any other specialized staff member involved) will be coded in respect of confidentiality rules. Under no circumstances may the names or addresses of the people concerned appear in it.

For coding subjects the first letter of the first name and first letter of the last name of the subject will be recorded, accompanied by a code showing the order of inclusion of the subject.

The sponsor will ensure that each person taking part in the study has given his agreement in writing for access to only the individual data that are strictly necessary for quality control of the study.

11. Quality Control and Insurance

11.1. Instructions for collecting data

All the information required by the protocol will be entered in an electronic case report forms and an explanation will be provided for each piece of information which is missing.

The data must be collected as and when they are obtained, and transcribed into these forms in a clear and legible manner. Incorrect data must be clearly crossed out and the new data copied in beside the crossed-out information, with the initials, date and possibly a reason, by the investigator or authorised person who has made the correction.

11.2. Monitoring of the study

The study will be monitored by a clinical research technician. He/she will be responsible for:

- The logistics of and monitoring the study,
- Producing reports concerning its state of progress,
- Verifying that the case report forms are updated (request for additional information, corrections, etc.),
- Sending samples,
- Transmitting SAEs to the sponsor.

He/she will work in accordance with the standard operating procedures, in cooperation with the clinical research associates appointed by the sponsor.

11.3. Quality control

A clinical research associate appointed by the sponsor will regularly visit each study centre during the process of setting up the study, one or more times during the study depending on the frequency of inclusions, and at the end of the study. During these visits, the following aspects will be reviewed:

- informed consent
- compliance with the study protocol and the procedures set out in it
- the quality of the data collected in the case report form: its accuracy, missing data, consistency of the data with the source documents (medical records, appointment diaries, the originals of laboratory results etc.)

Quality control will be performed according to the monitoring plan defined for this study and then, a monitoring report will be written.

11.4. Data management

Data management will be performed by the INSERM CIC-P 1415. An electronic Case Report Form (eCRF) will be developed using the Clinsight® software. eCRF management will be managed in agreement with the INSERM CIC-P 1415 Standardized Operating Procedures (SOP). CRA in charge of the study will be formed to the e-CRF and in charge of the physicians' formation. Data will be entered in investigating centres through a secure web site, monitored by CRAs and queries will be edited by data-managers, in agreement with an *a priori* specified data-management plan.

A blind review will be done prior locking the data-base. The data-base will be locked in agreement with the INSERM CIC-P 1415 SOPs and data will be extracted in a SAS format or other, according to statistical requirements. Raw data will be stored in a XML format.

The query of the hospital databases (FNHDD) will take place at the end of the study. This step will include all patients stay data from randomization to day 28. The data will be requested by UEME and the main investigator from the medical information department of each centre.

The link between the patient's identity and their study code will be made in each centre to preserve confidentiality. UEME will not have access to the patient's identity.

11.5. Audit and inspection

An audit may be performed at any time by people appointed by the sponsor who are independent of those responsible for the study. The aim of an audit is to ensure the good quality of the study, that its results are valid and that the law and regulations in force are being observed.

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study.

The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study.

12. Storage of documents and data concerning the study

The following documents relating to this study are archived in accordance with Good Clinical Practice:

By the investigating doctors:

- For a period of 15 years following the end of the study

- The protocol and any amendments to the protocol
- The case record forms
- The source files of participants who signed a consent form
- All other documents and letters relating to the study

- For a period of 30 years following the end of the study

- The original copies of informed consent forms signed by participants

The investigator is responsible for all these documents for the regulation period of archiving.

By the sponsor:

- For a period of 15 years following the end of the study

- The protocol and any amendments to the protocol
- The originals of the case record files
- All other documents and letters relating to the study

- For a period of 30 years following the end of the study

- A copy of the informed consent forms signed by the participants
- Documents relating to serious adverse events

The sponsor is responsible for all these documents for the regulation period of archiving.

No removal or destruction may be carried out without the sponsor's agreement. At the end of the regulation archiving period, the sponsor will be consulted regarding destruction. All the data, all the documents and reports could be subject to audit or inspection.

13. Rules relating to publication

13.1. Scientific communication

Analysis of the data provided by the study centres will be performed by INSERM CIC-P 1415 Tours and the UEME, Tours. This analysis will result in a written report that will be submitted to the sponsor, who, in turn, shall transmit it to the ethics committee and the relevant authority.

Any written or oral communication of the results of the study must have been previously agreed by the coordinating investigator and, if necessary, by any committee constituted for the study.

Publication of the main results will mention the name of the sponsor, all the investigators who recruited or monitored patients in the study, the methodologists, biostatisticians, economists and data managers who took part in the study, the members of the committee or committees set up for the study and the source of

finance. The international rules for writing and publication (Vancouver Agreement, February 2006) will be taken into account.

Primary publication ranking rule will be the following:

- First author: one investigator from the CHR of Orléans, the initiator of the project
- Second author: Investigator from highest recruiter site
- Third author: Investigator from second highest recruiter site
- Other authors up to the number of authors authorized by the targeted journal: depending both on recruitment and scientific involvement in the project
- Places of methodologist and economist: to be determined
- Senior (last) author: one investigator from the CHR of Orléans

13.2. Communication of the results to patients

In accordance with the law n° 2002-303 of 4th March 2002, patients will be informed, at their request, of the overall results of the study.

13.3. Ceding data

The collection and management of data will be carried out by CHR of Orléans. The conditions for ceding all or part of the database of the study will be decided by the sponsor of the study and will be the subject of a written contract.

14. Costs and payments

14.1. Study costs

There will be no additional costs to subjects as part of this study. The only additional study costs above what is considered to be standard hospital care. Subjects and their insurers or third party payers will not be billed for research related services. All research related services will be paid for by the sponsor.

14.2. Study payments

Research subjects will receive no payments or other remuneration for their participation in the study.

15. Evaluation of security

As this research is involving person with minimal risk (non-invasive blood pressure), all serious adverse event, in accordance with regulations in force, have to be reported by the investigator according with each procedure in place for reporting adverse event related to care in the institution. According to the article L1123-10 of the French Public Health Code, in this low risk study (as defined by the article L1121-1), SAEs are not to be declared within 24 hours but are to be collected and registered in the source documents and

study CRF.

The following AEs will be considered SAEs of special interest and are to be recorded in source documents and study CRF, whatever their relation to the study procedures and whatever the study arm the patient is assigned to:

- Ischemia and/or necrosis of finger(s) or toe(s)
- Documented bowel ischemia
- Occurrence or worsening of acute renal failure with need of renal replacement therapy (while there was no need of renal replacement therapy before this event)
- Need of tracheal intubation in a patient previously not intubated
- Cardiac arrest
- Death of any cause

Each adverse event, serious or not, related or not to the study procedure have to be recorded in source documents and study CRF.

For safety purpose, the ***following AEs that could potentially be related to the BP measuring method used, will be systematically collected in source documents and study CRF*** (not to be declared in real time):

- nerve injury of upper limb(s)
- skin lesions at cuff location or at IAC insertion site
- arterial thrombosis
- hematoma
- arterial pseudo aneurysm
- haemorrhage at IAC insertion site either during IAC placement or later

16. Committees

16.1. Scientific committee

It is composed of members of the scientific committee of the CRICS group and wrote the protocol.

16.2. Data Safety Monitoring Board

For this research that brings minimal risks (in the meaning of the French Law), we do not plan to set up an independent Data Safety and Monitoring Board.

17. Budget Evaluation

17.1. Budget of the study

The study budget will be coordinated by the sponsor, the university hospital centre of Tours. A financial convention will be signed between each participating centre and the sponsor.

17.2. Compensation for participants

No compensation for participants is planned.

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19. APPENDIX 1

In both groups, once the patient alert and capable, we will assess his/her pain and discomfort related to the BP measuring device in place.

Whatever the group the patient is assigned to, he/she will rate, once a day, his/her pain and discomfort using the following 11-point numerical scales.

- Does the presence of the BP measuring device (catheter or cuff) cause you some discomfort?
  To be rated from 0 (no discomfort at all) to 10 (very important and permanent discomfort).

- Does the presence of the BP measuring device (catheter or cuff) cause you some pain, either continuous of intermittent, at the site of measurement (location of catheter or of cuff)?
  To be rated from 0 (not painful at all) to 10 (highest pain ever experienced).

- Does the presence of the BP measuring device (catheter or cuff) cause you some pain, either continuous of intermittent, that extends beyond the site of measurement and spreads over the entire limb?
  To be rated from 0 (not painful at all) to 10 (highest pain ever experienced).

- Does the presence of the BP measuring device (catheter or cuff) cause you some numbness in the hand (or in the foot; depending upon location of the BP measuring device)?
  To be rated from 0 (no numbness at all) to 10 (highest numbness ever experienced).

20. APPENDIX 2

The following pages provide diagrams to help estimate true values of arterial blood gases (pH, $PaCO_2$, SaO_2) and lactate, using central venous blood analysis, SpO_2, and, only for pH, clinical characteristics.

Functions used to calculate these estimates were derived and validated in a large cohort of ICU patients (Boulain et al, Br J Anaesth 2016 117 :341–9).

In each diagram, the user will find upper and lower red and blue lines that delineate, for each predicted value, thresholds above which (for upper lines) or below which (for lower lines) the true arterial value is very unlikely to be, i.e., the threshold closest to the predicted value yielding a negative likelihood ratio with upper 95% confidence interval boundary below 0.1 (for redlines) or below 0.05 (for blue lines).

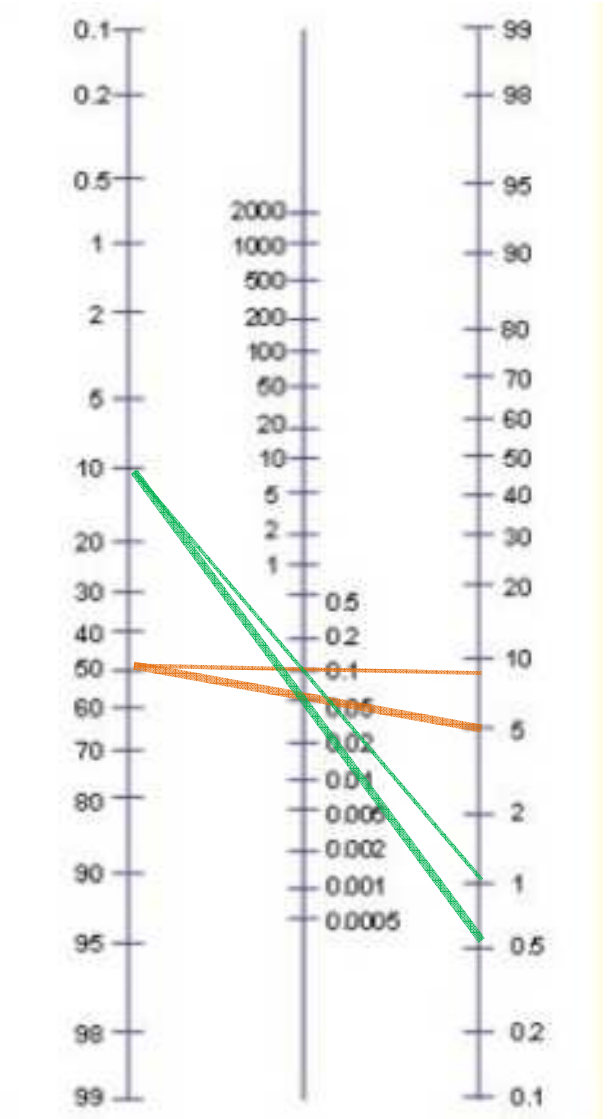
To help the user it is worth reminding how to interpret likelihood ratios, and particularly that their clinical value will depend upon the clinical context, i.e., whether and how much an arterial value is likely to be abnormal. For instance, a COPD patient with encephalopathy and flapping tremor is likely to have abnormally high $PaCO_2$, whereas a patient without past medical history presenting open femoral fractures and haemorrhagic shock is likely to have normal or decreased $PaCO_2$.

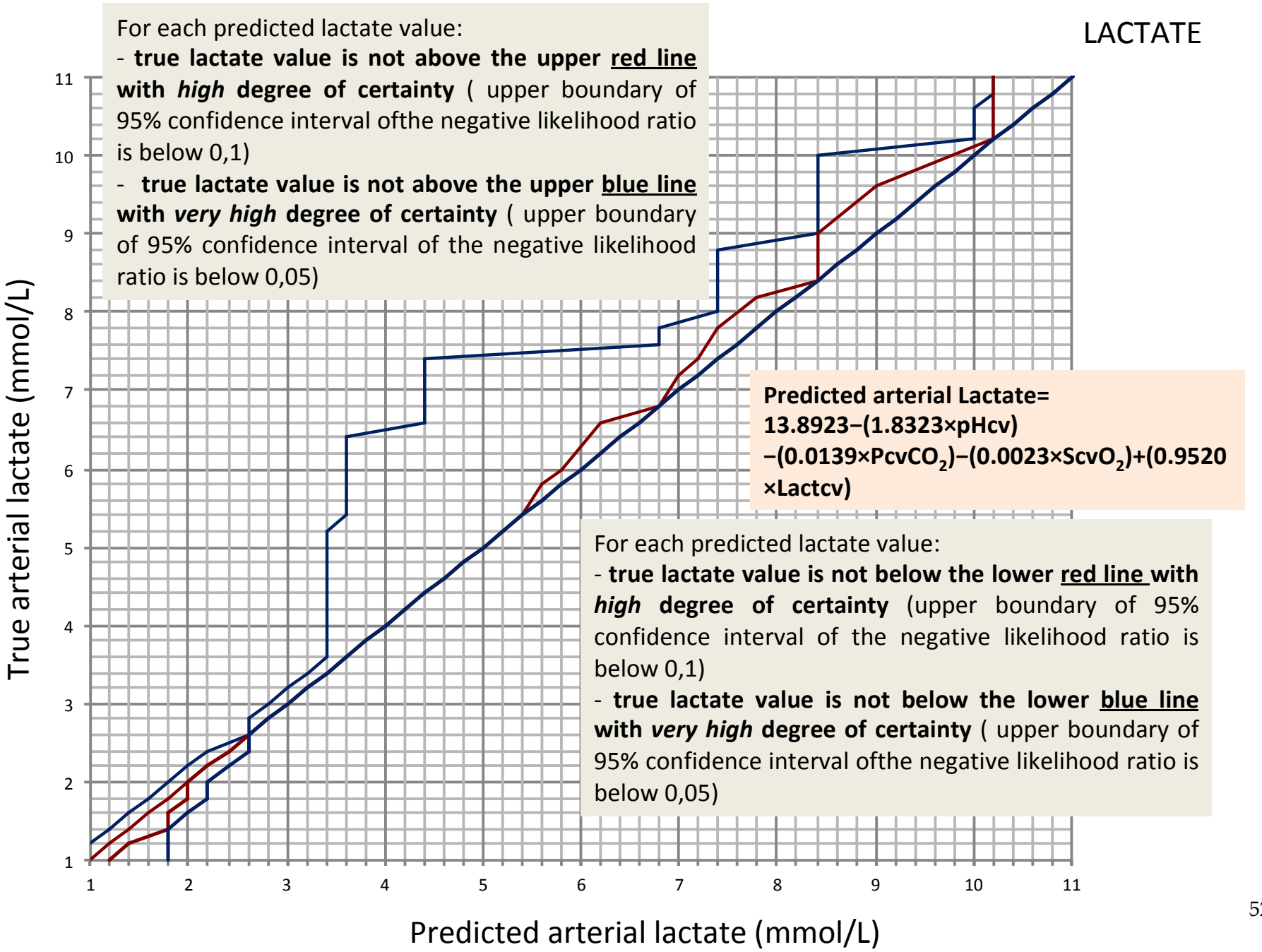
For a pre-test probability of 50% (no idea what the true value could be), a negative likelihood ratio of 0.1 or below results in a post-test probability of 8% or less (thin orange line on Fagan's diagram as shown on right side of this page).

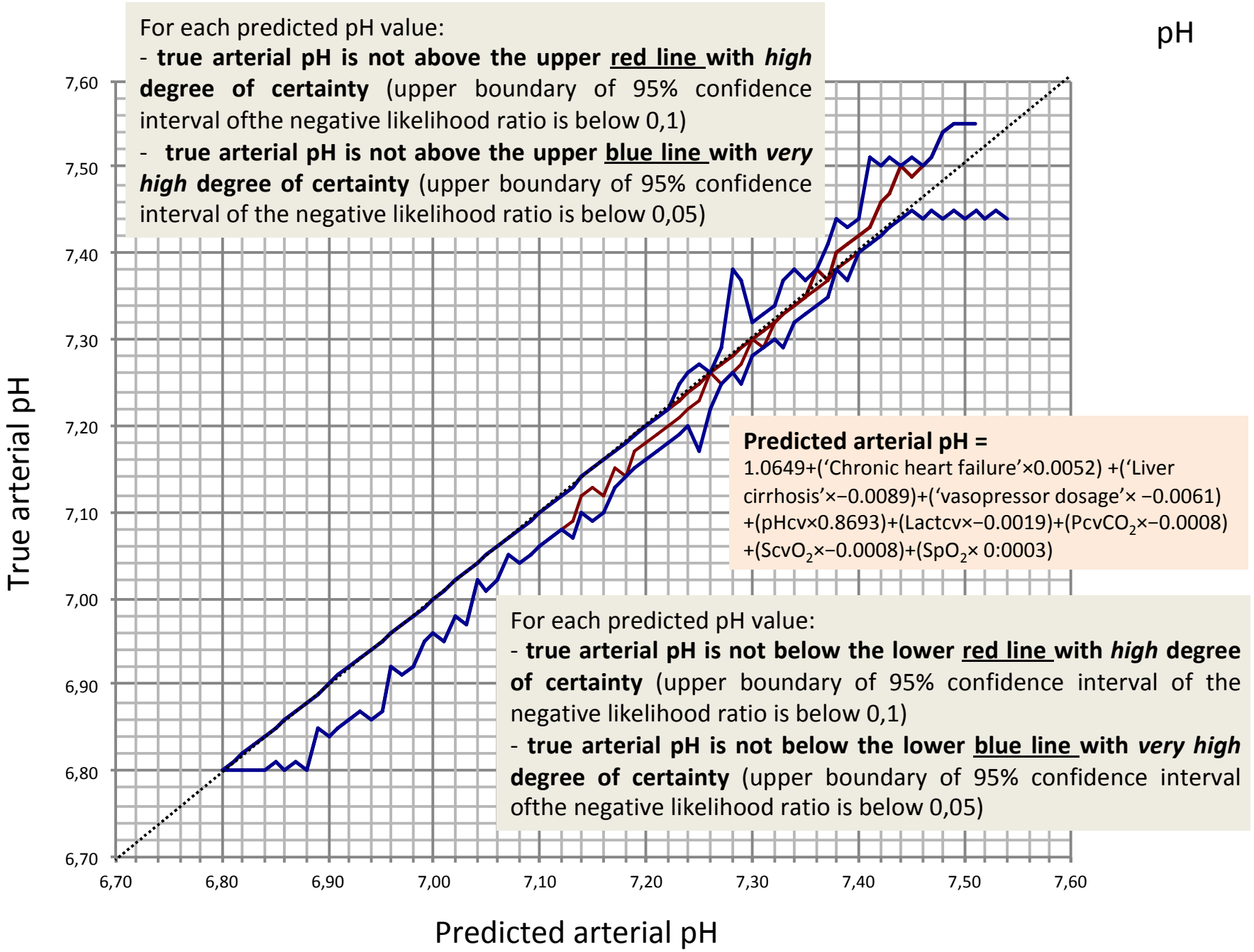
For a pre-test probability of 50%, a negative likelihood ratio of 0.05 or below results in a post-test probability of 5% or less (thick orange line).

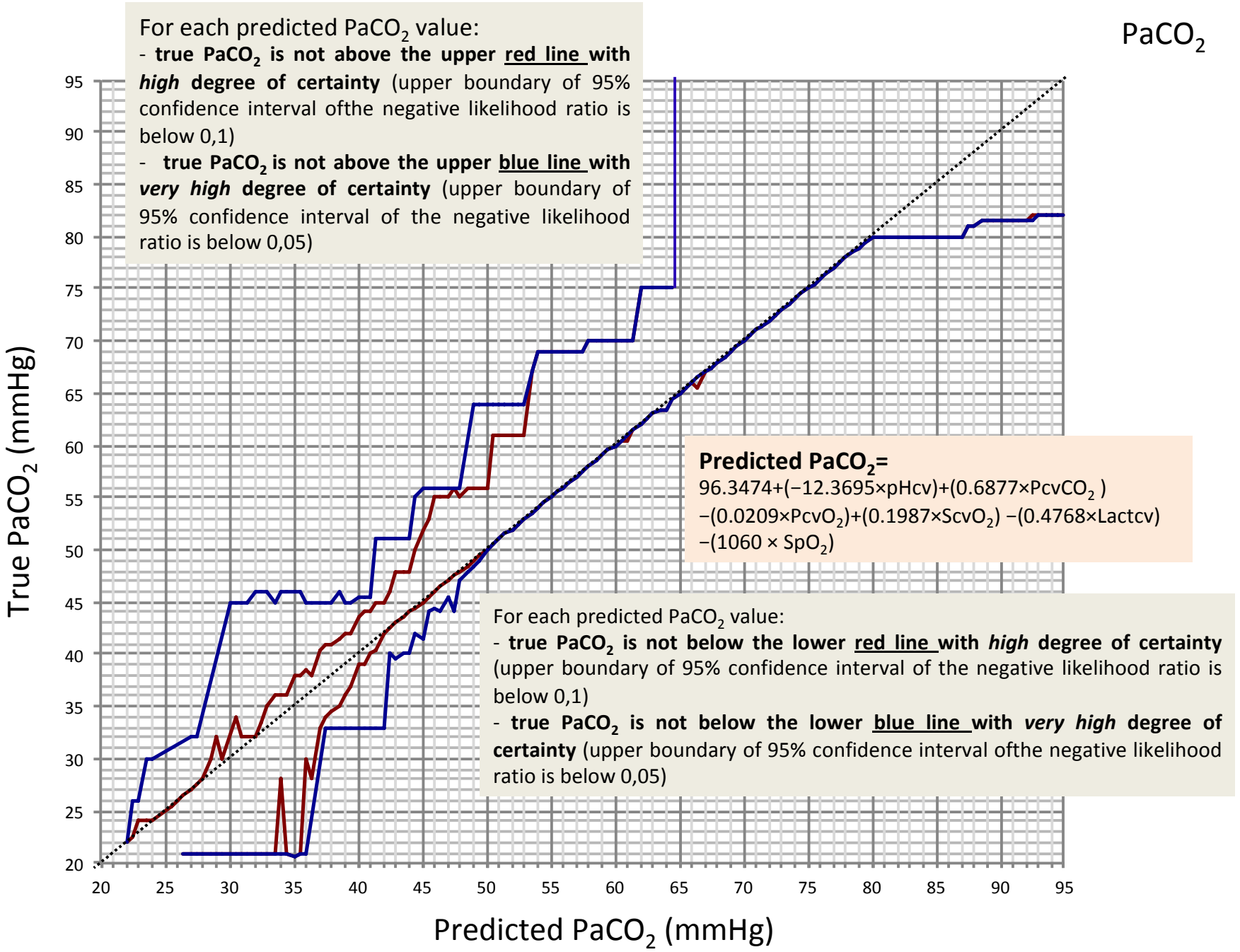
If the *a priori* probability of observing a normal true arterial value is deemed rather low (say pre-test probability of 10%), the post-test probability will be very low (1% or 0.5%) for a negative likelihood ratio of 0.1 or of 0.05 (thin and thick green lines, respectively)

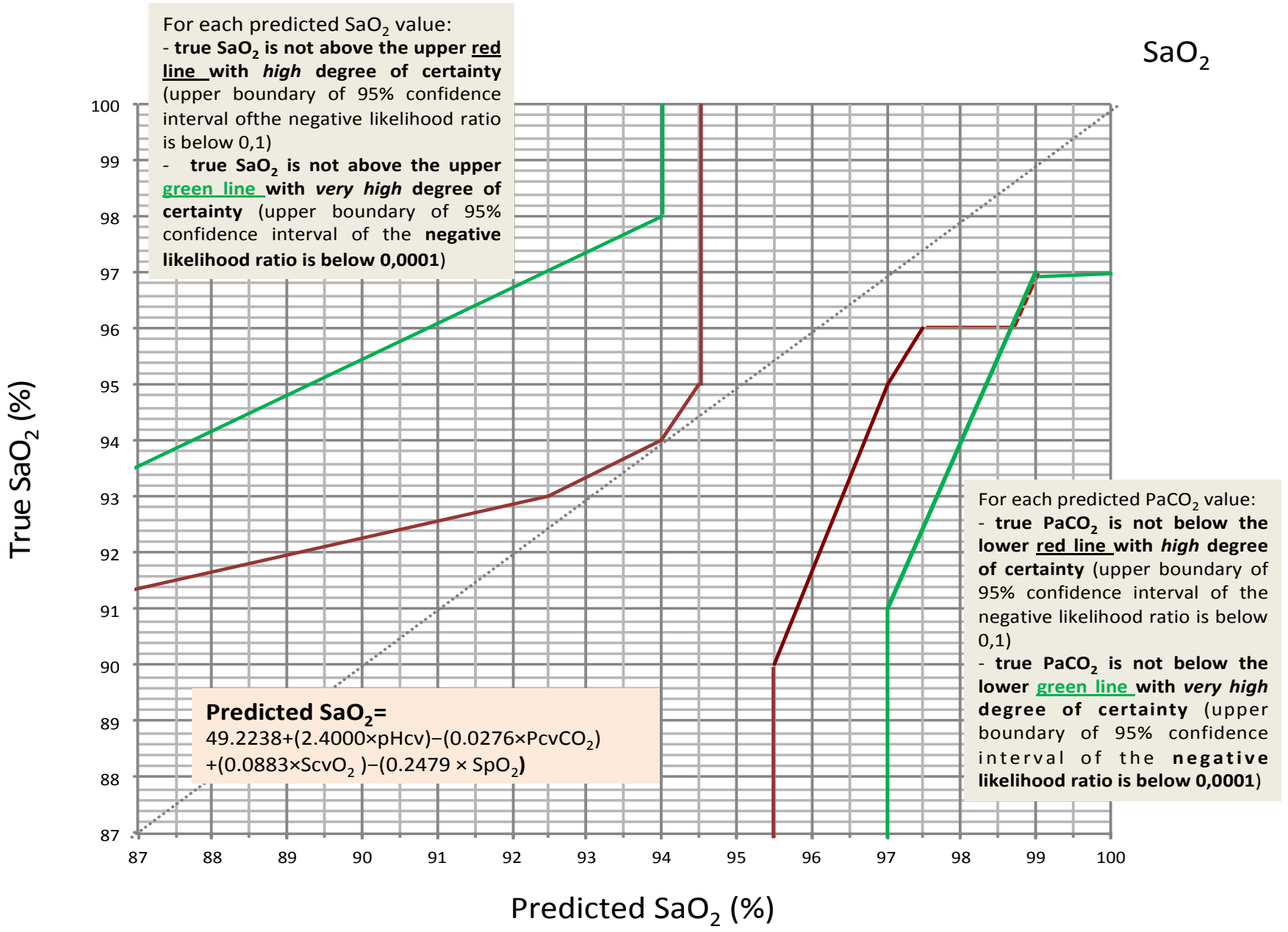
Remember, diagrams and likelihood ratios given in the following pages should always be interpreted according to the clinical context.




LACTATE
For each predicted lactate value:
- **true lactate value is not above the upper red line with *high* degree of certainty** (upper boundary of 95% confidence interval ofthe negative likelihood ratio is below 0,1)
- **true lactate value is not above the upper blue line with *very high* degree of certainty** (upper boundary of 95% confidence interval of the negative likelihood ratio is below 0,05)
Predicted arterial Lactate= 13.8923−(1.8323×pHcv) −(0.0139×PcvCO2)−(0.0023×ScvO2)+(0.9520 ×Lactcv)
For each predicted lactate value:
- **true lactate value is not below the lower red line with *high* degree of certainty** (upper boundary of 95% confidence interval of the negative likelihood ratio is below 0,1)
- **true lactate value is not below the lower blue line with *very high* degree of certainty** (upper boundary of 95% confidence interval ofthe negative likelihood ratio is below 0,05)
True arterial lactate (mmol/L)
Predicted arterial lactate (mmol/L)
1
2
3
4
5
6
7
8
9
10
11


pH
For each predicted pH value:
- **true arterial pH is not above the upper red line with *high* degree of certainty** (upper boundary of 95% confidence interval ofthe negative likelihood ratio is below 0,1)
- **true arterial pH is not above the upper blue line with *very high* degree of certainty** (upper boundary of 95% confidence interval of the negative likelihood ratio is below 0,05)
Predicted arterial pH =
1.0649+('Chronic heart failure'×0.0052) +('Liver cirrhosis'×−0.0089)+('vasopressor dosage'× −0.0061) +(pHcv×0.8693)+(Lactcv×−0.0019)+($PcvCO_2$×−0.0008) +($ScvO_2$×−0.0008)+(SpO_2× 0:0003)
For each predicted pH value:
- **true arterial pH is not below the lower red line with *high* degree of certainty** (upper boundary of 95% confidence interval of the negative likelihood ratio is below 0,1)
- **true arterial pH is not below the lower blue line with *very high* degree of certainty** (upper boundary of 95% confidence interval ofthe negative likelihood ratio is below 0,05)
True arterial pH
7,60
7,50
7,40
7,30
7,20
7,10
7,00
6,90
6,80
6,70
6,70
6,80
6,90
7,00
7,10
7,20
7,30
7,40
7,50
7,60
Predicted arterial pH


For each predicted $PaCO_2$ value:
- **true $PaCO_2$ is not above the upper red line with *high* degree of certainty** (upper boundary of 95% confidence interval ofthe negative likelihood ratio is below 0,1)
- **true $PaCO_2$ is not above the upper blue line with *very high* degree of certainty** (upper boundary of 95% confidence interval of the negative likelihood ratio is below 0,05)
$PaCO_2$
Predicted $PaCO_2$=
$96.3474+(-12.3695\times pHcv)+(0.6877\times PcvCO_2)-(0.0209\times PcvO_2)+(0.1987\times ScvO_2)-(0.4768\times Lactcv)-(1060\times SpO_2)$
For each predicted $PaCO_2$ value:
- **true $PaCO_2$ is not below the lower red line with *high* degree of certainty** (upper boundary of 95% confidence interval of the negative likelihood ratio is below 0,1)
- **true $PaCO_2$ is not below the lower blue line with *very high* degree of certainty** (upper boundary of 95% confidence interval ofthe negative likelihood ratio is below 0,05)
True $PaCO_2$ (mmHg)
Predicted $PaCO_2$ (mmHg)
20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95


For each predicted SaO_2 value:
- **true SaO_2 is not above the upper red line with *high* degree of certainty** (upper boundary of 95% confidence interval ofthe negative likelihood ratio is below 0,1)
- **true SaO_2 is not above the upper green line with *very high* degree of certainty** (upper boundary of 95% confidence interval of the **negative likelihood ratio is below 0,0001**)
SaO_2
Predicted SaO_2=
$49.2238+(2.4000\times pHcv)-(0.0276\times PcvCO_2)+(0.0883\times ScvO_2)-(0.2479\times SpO_2)$
For each predicted $PaCO_2$ value:
- **true $PaCO_2$ is not below the lower red line with *high* degree of certainty** (upper boundary of 95% confidence interval of the negative likelihood ratio is below 0,1)
- **true $PaCO_2$ is not below the lower green line with *very high* degree of certainty** (upper boundary of 95% confidence interval of the **negative likelihood ratio is below 0,0001**)
True SaO_2 (%)
100
99
98
97
96
95
94
93
92
91
90
89
88
87
87
88
89
90
91
92
93
94
95
96
97
98
99
100
Predicted SaO_2 (%)

Predicting SaO_2 from SpO_2 only

From a safety point of view, compared to the prediction of SaO_2 from predicted SaO_2 (see previous page), predicting SaO_2 from SpO_2 in a given patient only gives limited information:

- For SpO_2 values ≥ 98%, one can deduce that the **true SaO_2 is not below the lower green line (i.e., 91%) with *very high* degree of certainty** (upper boundary of 95% confidence interval of the negative likelihood ratio is below 0,0001)

- For other values of SpO_2, SaO_2 is not predictable with sufficient confidence