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Prospective randomized double-blind study to evaluate the superiority of Vasopressin versus Norepinephrine in the management of the patient at renal risk undergoing cardiac surgery with cardiopulmonary bypass (NOVACC trial)

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Abstract

Background:

Cardiac surgery-associated acute kidney injury (CS-AKI) affects up to 30% of patients, increasing morbidity and healthcare costs. This condition results from complex factors like ischemia-reperfusion injury and renal hemodynamic changes, often exacerbated by surgical procedures. Norepinephrine, commonly used in cardiac surgeries, may heighten the risk of CS-AKI. In contrast, vasopressin, a noncatecholaminergic agent, shows potential in preserving renal function by favorably affecting renal hemodynamic. Preliminary findings, suggest vasopressin could reduce the incidence of CS-AKI compared to norepinephrine. Additionally, vasopressin is linked to a lower incidence of postoperative atrial fibrillation, another factor contributing to longer hospital stays and higher costs. This study hypothesizes that vasopressin could effectively reduce CS-AKI occurrence and severity by optimizing renal perfusion during cardiac surgeries.

Study design:

The NOVACC trial (NCT05568160) is a multicenter, randomized, double blinded superiority-controlled trial testing the superiority of vasopressin over norepinephrine in patients scheduled for cardiac surgery with cardiopulmonary bypass (CPB). The primary composite end point is the occurrence of acute kidney injury and death. The secondary end points are neurological, cardiologic, digestive, and vasopressor related complications at day 7, day 30, day 90, hospital and intensive care unit lengths of stay, medico-economic costs at day 90.

Conclusion:

The NOVACC trial will assess the effectiveness of vasopressin in cardiac surgery with CPB in reducing acute kidney injury, mortality, and medical costs.

Clinical trial registration:

NCT05568160.

Background

Cardiac surgery-associated acute kidney injury (CS-AKI) is a major complication affecting up to 30% of patients. 1 It is associated with increased morbidity, mortality, and healthcare costs. 1, 2. The multifactorial nature of CS-AKI involves ischemia-reperfusion injury, inflammation, and changes in renal hemodynamics. These are often exacerbated by factors such as cardiopulmonary bypass (CPB), fluid balance, therapeutics, and surgery. 3

Understanding and managing renal hemodynamic changes are crucial in reducing the incidence of CS-AKI. 1, 4 Despite being the main vasopressor used in cardiac surgery, many studies have suggested a harmful effect of norepinephrine on the occurrence of CS-AKI. 5-7 In this context, vasopressin emerges as a potential therapeutic agent. 8, 9

Vasopressin preferentially constricts efferent arterioles over afferent arterioles, thereby potentially improving the glomerular filtration rate and renal blood flow. 8 During cardiac surgery, CPB is associated to renal vasoconstriction with a redistribution of blood flow away from the kidney, which, in combination with hemodilution, can decrease renal oxygen delivery. In this context, the use of norepinephrine can exacerbate this effect by further increasing renal vasoconstriction and decreasing renal oxygen delivery, leading to renal injury and CS-AKI. However, vasopressin does not exacerbate renal vasoconstriction, and it has a unique action on the renal vasculature by maintaining renal perfusion without excessive renal vasoconstriction. The pharmacological profile of vasopressin suggests that it could be more beneficial in preserving renal function during cardiac surgery, and preventing alteration of renal function. 9, 10 In this regard, the VANCS trial has begun to shed light on the beneficial role of vasopressin in cardiac surgery, suggesting that it may reduce the incidence of CS-AKI compared to norepinephrine. 10 However, the VANCS study, being mono-centric with potential biases, has led to discussions about the reproducibility of the results. To date, no study has evaluated the clinical benefits of using vasopressin as the primary vasopressor in a high-risk CS-AKI population to reduce its occurrence. These evidences form a crucial foundation for the current study's hypothesis.

Additionally, since vasopressin is a noncatecholaminergic agent, several studies and a meta-analysis have demonstrated a lower incidence of atrial fibrillation. 11 This issue remains a concern, as with CS-AKI, because atrial fibrillation is associated with longer hospital stays and higher costs. 12

The hypothesis of this study posits that the use of vasopressin for managing arterial hypotension due to vasoplegia during cardiac surgeries can reduce the occurrence and severity of CS-AKI. This hypothesis is underpinned by the premise that optimizing renal perfusion and minimizing renal ischemia are key to preventing AKI. This investigation is anticipated to contribute significantly to the evolving landscape of perioperative management in cardiac surgery, potentially leading to improved patient outcomes in this high-risk group.

Study design and objectives

The NOVACC trial is a multicenter, randomized, double-blinded superiority, controlled trial (Clinical Trials.gov Identifier: NCT05568160) of vasopressin over norepinephrine to treat arterial hypotension due to vasoplegia in cardiac surgery with CPB. The protocol was approved by the Ethics Committee (Comité de Protection des personnes II de France VI) on July 29, 2022, and by the Agence Nationale de Sécurité du Médicament et des Produits de Santé on January 8, 2022. The study design is detailed in Figure 1.

Objectives

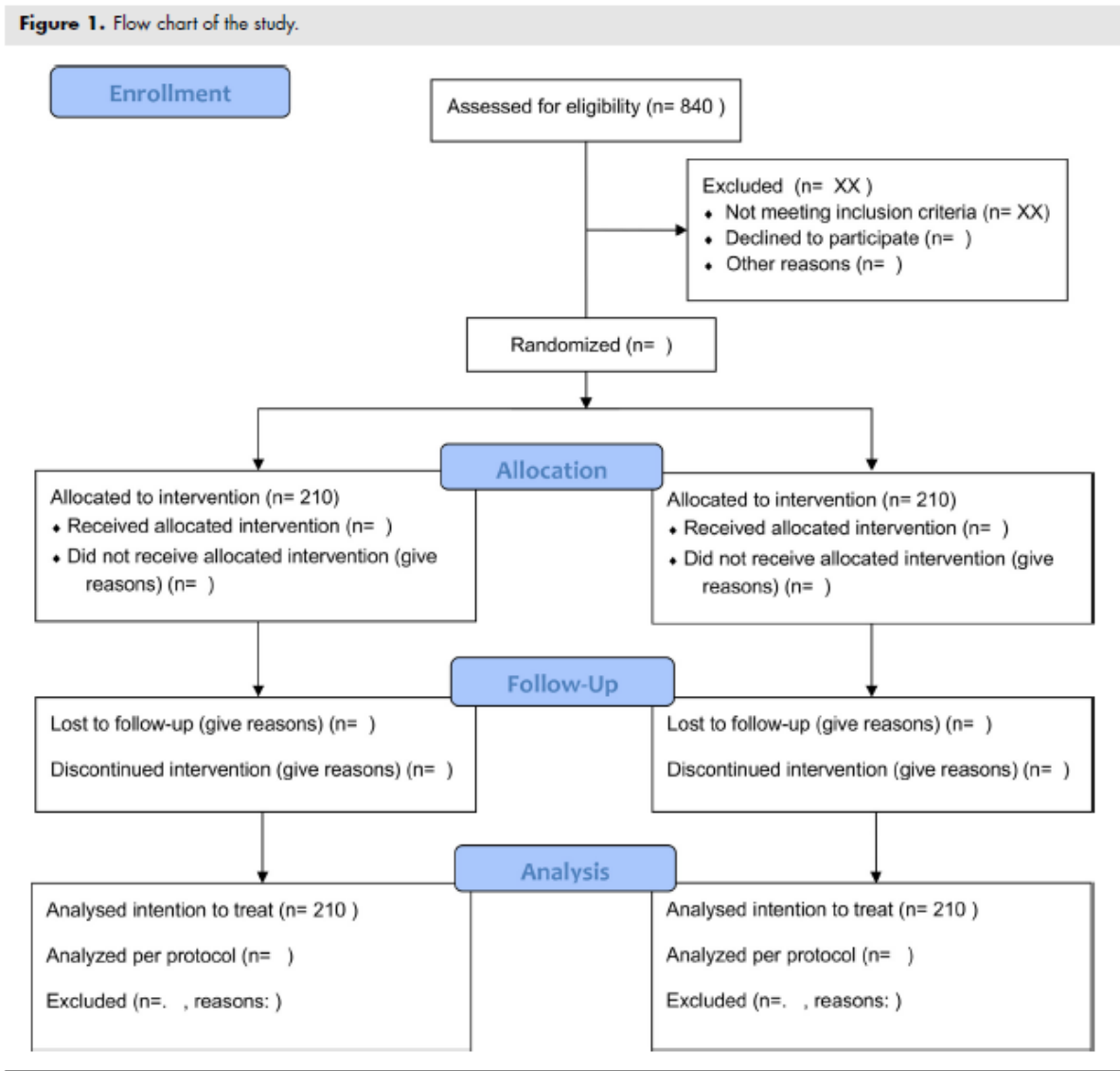
The primary objective is to compare 2 blood pressure optimization strategies—vasopressin versus norepinephrine—on the occurrence of a composite end- point of renal complications and death (MAKE) during the 7 days following cardiac surgery with CPB.

The secondary objectives are as follows: the occurrence of a composite endpoint of acute renal failure and death within 90 days, mortality within 90 days, cardiac complications including atrial fibrillation, myocardial ischemia at Day 7, Day 30, and Day 90, digestive complications at Day 7, Day 30, and Day 90, cerebral complications (stroke, confusion) at Day 7, Day 30, and Day 90, complications related to the use of vasopressors (hyponatremia, hypoperfusion of the extremities), the use of rescue norepinephrine, the use of inotropic and vaso- pressor agents from Day 0 to Day 7, the length of stay ICU and hospital and associated costs within 90 days (hospital perspective), the cost-effectiveness at Day 90, expressed in terms of costs per complication (ARF or death) avoided, from a societal perspective, the cost- effectiveness at Day 90, expressed in terms of costs per life-year gained, from a societal perspective, and the cost- utility ratio at Day 90, expressed in terms of costs per healthy life-year gained, from a societal perspective.

Judging criteria

The primary endpoint is defined as a composite com- plication score that comprise the occurrence of a renal complication or death up to 7 days after. Renal compli- cations are defined by the KDIGO definition (stage 1 or higher), and/or the initiation of extra renal replacement therapy. 13 The secondary endpoints are defined as follows: the occurrence of a renal complication (as defined in the primary endpoint), mortality within 90 days, the occurrence of a cardiac complication at 7, 30, and 90 days (arrhythmia requiring treatment (atrial fib- r illation, atrial flutter, ventricular tachycardia, ventricular fibrillation), 14 postoperative myocardial damage (elevation of troponin I or T greater than the 99 percentile of the upper reference limit or greater than 20% of the preoperative value), myocardial infarction defined by an increase in cardiac enzymes (cardiac troponin or high- sensitivity cardiac troponin) plus the appearance of a new Q wave, and/or abnormal kinetics on echocardiography, 15 cardiorespiratory arrest), the occurrence of a digestive complication as listed below at 7, 30, and 90 days (mesenteric ischemia, ischemic colitis diagnosed by imaging (CT scan, endoscopy) or the need for re- operation for a digestive complication following cardiac surgery, 16 the occurrence of a cerebral complication within 7 days (stroke, confusion collected through CAM- ICU), the occurrence of a complication related to the use of the vasopressor agent (hyponatremia ($\text{Na} < 130 \text{ mmol/l-1}$), hypoperfusion of the extremities (cyanosis or necrosis of the extremities), the number of patients requiring rescue norepinephrine, the total dose (mg) of norepinephrine for patients requiring rescue norepinephrine, the Vasoactive Inotropic Score at Day 0, Day 1, Day 2, Day 7 ($\text{VIS} = \text{dopamine dose (mcg kg}^{-1} \text{ min}^{-1}) + \text{dobutamine dose (mcg kg}^{-1} \text{ min}^{-1}) + 100 \times \text{adrenaline dose (mcg kg}^{-1} \text{ min}^{-1}) + 10 \times \text{dose of milrinone (mcg kg}^{-1} \text{ min}^{-1}) + 10,000 \times \text{dose of vasopressin (units/kg/min) + 100} \times \text{dose of norepinephrine (mcg kg}^{-1} \text{ min}^{-1}) + 10 \times \text{dose of phenylephrine (mcg kg}^{-1} \text{ min}^{-1})$), the length of stay in intensive care and hospital (days) at Day 90, the difference in average costs of ICU and hospital stays at Day 90, the incremental

cost-effectiveness ratio at Day 90, expressed in terms of cost per additional complication avoided by the vasopressin strategy compared to the norepinephrine strategy, the incremental cost-effectiveness ratio at Day 90 expressed in terms of cost per additional year of life gained with the vasopressin strategy compared with the norepinephrine strategy, the incremental cost-utility ratio at Day 90, expressed as cost per additional healthy life-year gained (cost/QALY, quality of life questionnaire [EQ-5D®]) 17 with the vasopressin strategy compared to the norepinephrine strategy. Events will be centrally adjudicated by independent experts not in charge of the patients.



Study population

Inclusion criteria are patient with written and in- formed consent, of legal age, negative pregnancy test for women of childbearing age, scheduled (> 24 h) cardiac surgery with CPB , of any type (myocardial revascularization (coronary bypass), and/or surgical correction of valvulopathy (aortic, mitral, pulmonary, tricuspid), and/or of the ascending aorta and/or removal of intracardiac tumor, and/or closure of a PFO), with at least 3 risk factors for CS-AKI (age > 70 years, combined surgery (more than 2 procedures), common trunk surgery,

pre-operative anemia, chronic respiratory failure, obliterative arterial disease of the lower limbs, diabetes, glomerular filtration $< 60 \text{ mL min}^{-1}$, LVEF $< 40\%$, redo surgery, intra-aortic counter-pulsation balloon, bypass surgery $> 100 \text{ min}$, albuminuria). 1, 6

Non-inclusion criteria are patient not affiliated to or not benefiting from a social security scheme, patient under legal protection (curatorship, guardianship), patient subject to a legal protection measure, patient of full age who is incapable or unable to give consent, patient previously included in this study, patient requiring emergency surgery (less than 24 hours), patients with chronic renal failure on dialysis, patient with a heart transplant, patient for left ventricular assistance device support, patient on ECMO support prior surgery, patients with acute circulatory failure prior surgery (sepsis, hemorrhage), patients with known hypersensitivity to the active substance (argipressin) or to any of the excipients of REVERPLEG®.

Exclusion criteria are as follow: patients not developing persistent arterial hypotension due to vasoplegic syndrome within 12 hours of completion of surgery, defined as persistent mean arterial pressure (MAP) $< 65 \text{ mmHg}$ despite correction of preload and inotropism, with a cardiac index $> 2.2 \text{ l min}^{-1} \text{ m}^{-2}$, and not responding to 30 mg bolus ephedrine, and patient with hemorrhagic shock before receiving vasopressor treatment (study treatment). 10

The preinclusion visit will be carried out by an investigator, and it will take place during the preanesthesia consultation. All participants who meet the inclusion criteria during the study will be asked to participate in the study. The investigating physician will inform the patient about the study and will answer any questions concerning the study's objectives, constraints, foreseeable risks, and expected benefits. He/she will also specify the patient's rights as part of this research and will check the eligibility criteria. Copies of the study information sheet and the consent form are then given to the patient by the investigating physician. The consent form must be signed before any clinical or paraclinical study procedures be performed. A copy of the study information sheet and a copy of the signed consent forms are given to the patient, whereas the original copies are kept by the investigating physician. At the end of the inclusion period or (at the latest) at the end of the research, a copy of each consent form shall be forwarded to the sponsor or its representative; the investigators will be told in a timely manner how these forms should be forwarded.

Number of subjects and Randomization

The number of subject calculations was performed with PASS 11 (NCSS statistical software). Based on multicentric French studies and published studies, the rate of AKI range between 20% and 50%. 2, 5, 6 Because we selected a population treated with vasopressors being at kidney risk, the expected rate of the primary endpoint is evaluated to be 35%. 5, 6 To demonstrate a 15% decrease in the experimental group (minimal difference of clinical interest) with 90% power and a 2-sided alpha threshold of 5%, 410 analysable patients (205 per group) are required. 10 The calculation takes into account the adjustment on the stratification factor. The choice of 90% power was made to take into account the composite nature of the primary endpoint. With a rate of loss of data estimated at 2%, 420 patients will be included. Since, 1 of 2 surgical patients will develop arterial hypotension due to vasoplegia, we plan to include 840 patients in order to randomize 420 patients to have 410 analyzable.

All patients meeting the inclusion criteria are informed before the surgery (see above) and included if they agree to participate in the study. They are definitely included and randomised at the time of the occurrence of the arterial hypotension due to vasoplegia. The treatment allocation algorithm will be established by the statistician of the Research Methodology Support Unit of Dijon. Treatment assignment sequences will be generated in blocks of variable size (4, 6, or 8) stratified on the investigating center.

Intervention

Treatment protocol

Treatment group is *argipressin* (REVERPLEG (argipressin acetate) 40 UI/2 mL): argipressin will be diluted in sodium chloride prior to administration to achieve a concentration of 0.12 UI mL⁻¹. The intravenous infusion is started at 5 mL hr⁻¹, increased in increments of 1 mL hr⁻¹ to reach a maximum target rate of 30 mL hr⁻¹, doses range from 0.01 to 0.06 UI min⁻¹. The dilutions and dosages are those of the VANCS study which is specific to cardiac surgery. 10

Control group

Control group is *norepinephrine* (Norepinephrine Tartrate) 2 mg/mL): norepinephrine will be diluted in sodium chloride before administration to a concentration of 0.05 mg mL⁻¹. The intravenous infusion is started at 5 mL h⁻¹, increased in increments of 1 mL h⁻¹ to reach a maximum target rate of 30 mL h⁻¹, doses range from 4 to 25 µg min⁻¹. Norepinephrine dose is expressed as µg kg⁻¹ min⁻¹. This administration protocol is based on the VANCS study. 10

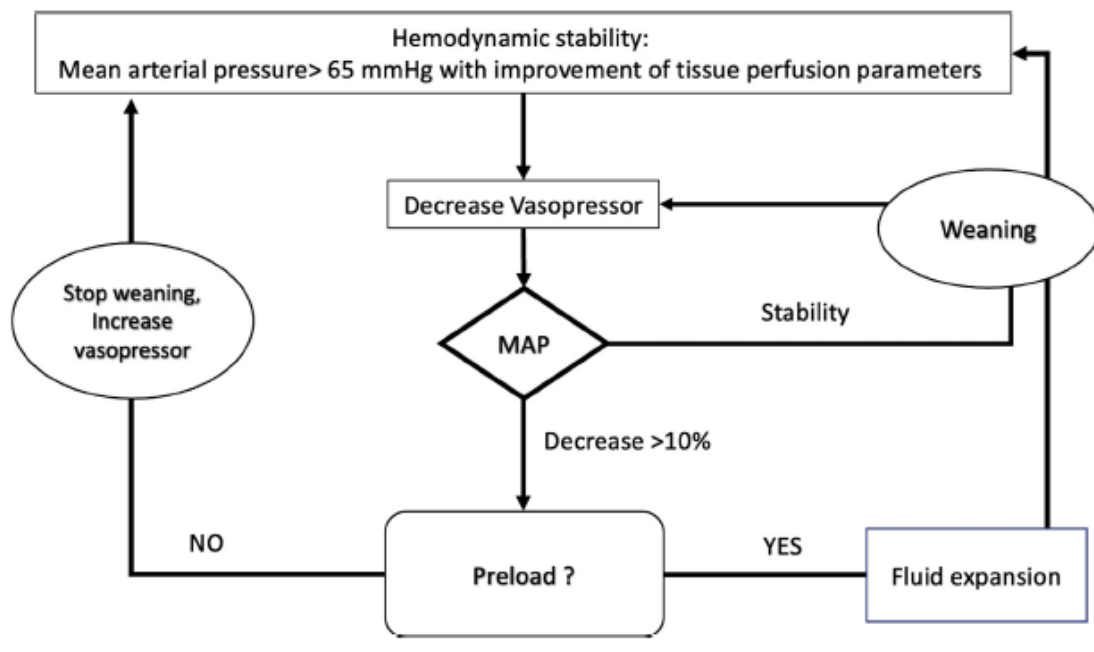
Blood pressure and hemodynamic management

Blood pressure management strategy is standardized as follow. In case of arterial hypotension defined by a MAP < 65 mmHg, the management strategy is based on the following algorithm: eliminate anesthetic agent overdose (BIS > 40), correct preload (fluid expansion) according to the recommended strategy: fluid bolus and cardiac output, rule out a cardiogenic cause (altered preoperative LVEF and decreased cardiac output): if so administer an inotrope (dobutamine, milrinone, levosimendan), ephedrine as an intravenous bolus (3-9 mg) every 5 minutes to a maximum cumulative dose of 30 mg, then study treatment continuously as described if blood pressure does not respond to 30 mg ephedrine cumulatively.

Management of the study treatment is standardized. Study treatment is administered in a blinded fashion using a continuous electric syringe infusion with a start rate of 5 mL h⁻¹ (i.e. a dosage of 0.01 UI min⁻¹ of vasopressin or 4 µg min⁻¹ of norepinephrine). The aim is to achieve a MAP of over 65 mmHg. If the target MAP is still not achieved with a rate of 30 mL h⁻¹, and additional vasopressor support is required, open label norepinephrine (0.1 mg/mL) will be introduced in addition (in both groups), keeping the study treatment at a dosage of 30 mL h⁻¹ for as long as necessary. 10 If the patient improves, the dose will be tapered first by decreasing the rescue norepinephrine (administered in the open-label setting), and only then by decreasing the study treatment. 10

The rules for discontinuing vasopressor treatments are standardized for all patients. In both treatment groups, weaning from the vasopressor is performed by the medical and paramedical team in charge of the patient. The usual procedure for weaning from vasopressor agents is based on hemodynamic, clinical (skin perfusion, mottling, hourly diuresis), and biological (SVO₂, pCO₂ gap, arterial lactates) parameters. 18 Weaning criteria are stability of MAP for more than 1 hour defined by a variation of less than 10%, without worsening of tissue hypoperfusion markers. 19 If there is open-label norepinephrine treatment, this treatment is weaned first. Thereafter, weaning of the study treatment is initiated according to standardized criteria (Figure 2). In the event of discontinuation and the need to resume treatment at a distance, the treatment under study must be resumed if the new administration is carried out within 12 hours of the end of the surgery. Beyond that time, the management strategy will be defined by the physician in charge of the patient according to the usual procedures.

Figure 2. Vasopressor weaning algorithm for both groups.



Other treatments

Discontinuation, continuation, or maintenance of the patient's chronic treatments follow international recommendations. 20-23 Thus, cardiological, nephrological, and diabetic drugs are stopped preoperatively according to these recommendations across all centers. Preoperative fasting is standardized for all patients: 2 hours for clear liquids and 6 hours for solids. 23 The maintenance of peri-operative blood volume is ensured by optimizing preload during/after the surgery by volume expansion (crystalloid) and/or transfusion if necessary. 21 Transfusion is standardized across all centers and follow international recommendations on patient blood management. 24

The conduct of general anesthesia, mechanical ventilation, and CPB are standardized for all patients. Intra and postoperative hemodynamic management is standardized for all patients.

The objectives are as follows: optimization of blood volume (see dedicated paragraph, MAP > 65 mmHg, cardiac index > 2.2 l min⁻¹ m⁻² . 25

The correction of inotropism is ensured by inotrope (dobutamine, milrinone, levosimendan, epinephrine).

On admission to the ICU, each patient receives continuous electrocardiographic monitoring, pulsed oxygen saturation, invasive measurement of arterial and central venous pressure with monitoring of cardiac output. Ventilatory management consists of ventilation in volume-controlled mode with an initial FiO₂ of 50% and then adapted to a SaO₂ target of 95% to 97%. The patient is extubated within the first 6 hours postoperatively in the absence of pulmonary pathology and/or contraindication. Hemodynamic resuscitation in the ICU is standardized and based on MAP ≥65 mmHg, a cardiac index ≥2.2 l min⁻¹ m⁻² , a diuresis ≥0.5 mL kg⁻¹ h⁻¹ , and a lactatemia < 2 mmol l⁻¹ . 18 , 22 , 25 Renal risk management follows the recommendations of expert societies and is based on optimization of blood volume, blood pressure, cardiac out- put, avoidance of nephrotoxic products/drugs. 26 After surgery, all patients will receive baseline intravenous hydration with glucose solution (500 to 1000 mL per day) and electrolytes until the full recovery of feeding. In the ICU, the patient's basic cardiological treatment is reintro- duced progressively from the sixth hour postoperatively, according to the department's usual schedule and inter- national recommendations.

Table 1. Organizational chart of the study (x).

	Screening Anesthesia consultation	Inclusion visit (the d before or the d of the surgery)	Surgery with CEC / Randomization	Vasoplegic shock during surgery or within 12 h of surgery	Follow-up				End of study
	Day -x	Day -1		Day 0	Day 1	Day 2	Day 7	Day 30 - Day 60 (+/-7 d)	Day 90 (+ 15 d)
Clinical examination	x	x							
Patient Information Free, written, and Informed consent	x	x							
Biological check-up		x							
Treatment delivery according to randomization				x	x	x	x	x	x
Post-operative complications: cardiac, renal, and digestive				x	x	x	x	x	x
VIS score				x	x	x			
Neurological complications					x	x	x		
Deaths					x	x	x	x	x
Length of stay in ICU, MCO, and SSR							x	x	x
Serious adverse events				x	x	x	x	x ¹	x ¹
EQ-5D		x			(x) [*]	(x) [*]	x	x	x

* The second collection of the EQ-5D will be done at discharge from the ICU (estimated between D1 and D2 for the majority of patients).

¹ Collection of Serious Adverse Events only if patient is still on treatment or within 7 days of stopping treatment.

Study organization

The coordinating center of the NOVACC trial is the Dijon University Hospital, France. Eight French cardiac surgery centers will participate (Dijon University Hospital, Besançon University Hospital, Nancy University Hospital, Montpellier University Hospital, Amiens

University Hospital, Strasbourg University Hospital, Sauvegarde Clinic, Ramsay Sante, Lyon, France, Institut Arnault Tzanck, Saint Laurent du Var, France). The data management and statistical analyses will be carried out by the biostatistics and clinical research units of the Dijon University Hospital in France. The trial is sponsored by the Dijon University Hospital and is funded by a public grant from the Programme Hospitalier de Recherche Clinique of the French Ministry of Health (PHRCi-2019-093), and a grant from AOP pharma. AOP did not contribute to the study design or to data collection or analyses. The study was registered under the reference NCT05568160 on ClinicalTrials.gov on June 3, 2022. Currently 4 centers are including and the organization of the study is being set up for the remaining investigating centers. The first patient was enrolled in the coordinating center on January 2, 2023.

Data management

Data collected directly during the patient's follow-up will be entered (single-entry) into an electronic case report form (e-CRF) by clinical data manager blinded to treatment allocation on online dedicated website (Table 1). The preconfigured consistency tests will check the quality of the data. If inconsistencies are detected, queries will be sent to the investigator. The data coding will be given on a separate sheet in the e-CRF. Data will be entered initially as the actual numerical value or the actual categorical variable. The data manager will carry out the management of security, quality, and access to the study data. A series of queries will be carried out periodically during the project by a data manager, in conjunction with monitoring visits, in order to validate the consistency of all data. These queries will be repeated iteratively until an error-free database is obtained. At the end of the study, the Clinsight@database (Ennov Clinical) will be frozen by the data manager at Dijon University Medical Center's Clinical Research and Innovation Directorate. Patients will be followed by in-person visits until the end of hospitalization, and on day 30, they will be followed by a phone call on day 90.

Safety evaluation

An independent data safety monitoring board is implemented to review the safety of the trial every 10 patients until the 100th patient then every 100 patients. This review will be based on the description of the adverse events collected (severity, frequency, and consequences), the recruitment status and the results of the safety analyses. The committee will be composed of physicians specialized in cardiac anesthesia and cardiac ICU, a pharmacovigilant and a methodologist/statistician. The safety evaluation parameters are based on the potential adverse events of vasopressor use: digital ischemia; mesenteric/colitis ischemia, myocardial ischemia, hyponatremia, hemodynamic instability despite vasopressor treatment. These parameters are monitored several times a day until the last day of follow-up.

Statistical design

Study and statistical protocol will follow CONSORT guidelines for reporting parallel group randomized trials. 27 A flow chart will describe screened, randomized, and analyzed patients according to the CONSORT figure. The main analysis will be an intention-to-treat analysis,

and it will be completed by a per-protocol analysis taking into account the patients included who have perfectly respected the instructions of the trial protocol. The per protocol analysis will use the same techniques as the intention-to-treat analysis. An interim analysis is planned after half of the patients have been randomized to analyse the safety of the trial.

Analysis strategy

For the description of the characteristics of the population, quantitative variables will be described by the mean \pm standard deviation and the median (25th-75th). Qualitative variables will be described by their number (%). The characteristics of the 2 groups will be compared using the usual univariate tests (chi-2 test or Fisher's exact test for qualitative variables, Student's or Wilcoxon's test for quantitative variables), depending on the conditions of application. The main criteria analysis will be performed using a logistic regression adjusted on the stratification factor (centre). In a second step, a multivariate logistic regression adjusted on baseline characteristics appearing unbalanced between the groups will be performed. Quantitative variables will be compared between the 2 arms using multivariate linear regression adjusted for the stratification factor or the Wilcoxon test depending on the distribution of the variables. Categorical variables will be compared between the 2 arms using logistic regression adjusted on the stratification factor. The evolution of the VIS score will be compared between the 2 arms using a repeated measures analysis of variance (time, treatment) with adjustment on the stratification factor or a Friedman ANOVA according to the distribution of the scores. Concerning mortality, an estimation of the probability of survival will be performed by the Kaplan Meier method and the estimation of the effect of the vasopressin vs. control strategy by a Cox model adjusted on the stratification factor used for the randomization and after verification of the conditions of application (proportionality of the risks). A subgroup analysis will be performed. The interaction between pre-existing factors (glomerular filtration rate, chronic renal failure, alteration of left ventricular function, type of surgery [CABG vs. non-CABG], transfusion) and the effect of treatment on the occurrence of complications will be tested. If significant at the 5% level, the effect of treatment on the occurrence of complications will be analysed by logistic regression, adjusted for the stratification factor of randomisation in each subgroup.

Medico-economic analysis

The population included in the medico-economic analysis will be the intention-to-treat, complemented by an intra-protocol analysis. The comparative analysis of the costs of stays at D90 between the 2 strategies will be evaluated on the basis of a production cost analysis, according to HAS recommendations. The cost distributions will be compared between the 2 arms using an ANOVA adjusted for the stratification factor of the randomisation. The significance level is set at 0.05. Deterministic sensitivity analyses taking into account variations that may impact the costs of the strategies will be considered. This comparative analysis does not take into account the cost of vasopressin treatment in the vasopressin arm. It only looks at the change in hospital costs due to a change in length of stay and rehospitalization between the 2 strategies. The cost-effectiveness analysis at D90 will be performed comparing the 2 strategies in terms of both costs and benefits: the occurrence of a complication (i.e. the occurrence of AKI or death) within 90 days of the vasoplegic syndrome on the one hand; survival time within 90 days of the vasoplegic syndrome, on the other hand. The methodology adopted complies with French "Haute Autorité Santé" guidelines. 28

The analyses will be carried out in blinded manner by the team of the Methodological Research Support Unit of the Dijon University Hospital under the responsibility of a Soudry-Faure for the statistical analysis and AL Soilly for the medico-economic analysis in collaboration with PG Guinot. The significance level is set at 0.05 for all final analyses. For the interim analysis: an alpha risk of 0.0001 is used for the analysis of the primary endpoint (according to the method proposed by Peto-Haybittle in order not to modify the significance level of the final primary analysis). The statistical analysis will be performed using SAS software version 9.4 (NC, Cary) and R.

Conflict of Interest

Pierre-Grégoire Guinot received fees for lectures from Abbott, Medtronic, Aguetant, AOP Pharma, Edwards, and Vygon. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRedit authorship contribution statement

Pierre-Grégoire Guinot: Writing –original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

Olivier Desebbe: Writing –original draft, Investigation.

Guillaume Besch: Writing –original draft, Investigation.

Philippe Guerci: Writing –original draft, Investigation

Philippe Gaudard: Writing –original draft, Investigation.

Diane Lena: Investigation.

Paul Michel Mertes: Data curation.

Osama Abou-Arab: Data curation.

Belaid Bouhemad: Conceptualization.

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Participating sites and NOVACC investigators in France CHU de Dijon, Dijon, France, CHU de Besançon, Besançon, France, Clinique la Sauvegarde, Lyon, France, CHU de Nancy, Nancy, France, CHU de Montpellier, Montpellier, France, CHU d'Amiens, Amiens, France, Institut Arnault Tzanck, Saint Laurent du Var, France.

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