BMJ Open

Opioid-free anaesthesia with dexmedetomidine and lidocaine versus remifentanil-based anaesthesia in cardiac surgery: study protocol of a French randomised, multicentre and single-blinded OFACS trial

Emmanuel Besnier ,[1,2] Mouhamed Djahoum Moussa,[3,4] Caroline Thill,[5] Florian Vallin,[6] Nathalie Donnadieu,[7] Sophie Ruault,[6] Emmanuel Lorne,[8] Vincent Scherrer,[1] Julien Lanoiselée,[3] Thomas Lefebvre,[9] Pierre Sentenac,[8] Osama Abou-Arab[9]

To cite: Besnier E, Moussa MD, Thill C, *et al*. Opioid-free anaesthesia with dexmedetomidine and lidocaine versus remifentanil-based anaesthesia in cardiac surgery: study protocol of a French randomised, multicentre and single-blinded OFACS trial. *BMJ Open* 2024;**14**:e079984. doi:10.1136/bmjopen-2023-079984

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-079984).

Received 17 September 2023
Accepted 08 May 2024

For numbered affiliations see end of article.

Correspondence to
Professor Emmanuel Besnier; emmanuel.besnier@chu-rouen.fr

ABSTRACT

Introduction Intraoperative opioids have been used for decades to reduce negative responses to nociception. However, opioids may have several, and sometimes serious, adverse effects. Cardiac surgery exposes patients to a high risk of postoperative complications, some of which are common to those caused by opioids: acute respiratory failure, postoperative cognitive dysfunction, postoperative ileus (POI) or death. An opioid-free anaesthesia (OFA) strategy, based on the use of dexmedetomidine and lidocaine, may limit these adverse effects, but no randomised trials on this issue have been published in cardiac surgery.

We hypothesised that OFA versus opioid-based anaesthesia (OBA) may reduce the incidence of major opioid-related complications after cardiac surgery.

Methods and analysis Multicentre, randomised, parallel and single-blinded clinical trial in four cardiac surgical centres in France, including 268 patients scheduled for coronary artery bypass grafting under cardiac bypass, with or without aortic valve replacement. Patients will be randomised to either a control OBA protocol using remifentanil or an OFA protocol using dexmedetomidine/lidocaine. The primary composite endpoint is the occurrence of at least one of the following: (1) postoperative cognitive disorder evaluated by the Confusion Assessment Method for the Intensive Care Unit test, (2) POI, (3) acute respiratory distress or (4) death within the first 48 postoperative hours. Secondary endpoints are postoperative pain, morphine consumption, nausea–vomiting, shock, acute kidney injury, atrioventricular block, pneumonia and length of hospital stay.

Ethics and dissemination This trial has been approved by an independent ethics committee (*Comité de Protection des Personnes Ouest III–Angers* on 23 February 2021). Results will be submitted in international journals for peer reviewing.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Opioid Free Anaesthesia for Cardiac Surgery (OFACS) trial is a multicentre, randomised, single-blinded study, guaranteeing robust results.
⇒ Exploration of major complications after cardiac surgery as the main endpoint aims to explore the clinical relevance of the strategy.
⇒ Both short-term and long-term outcomes will be explored.
⇒ The trial is not double blinded, which may induce a bias during data acquisition.
⇒ The trial will not explore the costs associated with both strategies.

Trial registration number NCT04940689, EudraCT 2020-002126-90.

INTRODUCTION

The use of opioid derivatives has been widespread in the perioperative setting for decades. Their administration allows the control of sympathetic response to nociceptive stimuli related to the surgical process, attenuating the intraoperative haemodynamic variations.[1 2] Beyond this beneficial effect, opioids can present significant side effects: digestive disorders, from simple nausea and vomiting to postoperative ileus (POI)[3 4]; respiratory depression through the central inhibition of breath control, with a risk of perioperative hypoxaemia[5]; postoperative cognitive dysfunction (POCD) and delirium[6 7]; hyperalgesia[8 9]; and possible suppressive effects on immunity and adrenal functions, which may favour postoperative infections.[10 11] All of

these complications may hinder prognosis after surgery. Furthermore, in the context of the international 'opioid crisis', strategies limiting opioid administration during and after surgery may be of interest.[12 13] Indeed, thousands of people die every year from opioid overdose, with approximately 25% of them having a medical prescription. More specifically, 2–9% of patients still use opioids several months after surgery, in many cases because of persistent pain, and this could therefore facilitate addiction.[14 15] Limiting intraoperative opioids may therefore be part of a global perioperative opioid reduction programme, aimed at reducing secondary hyperalgesia and ultimately opioid addiction.

Cardiac surgery with cardiopulmonary bypass (CPB) is particularly vulnerable to the above-mentioned complications. Indeed, some of the side effects of this surgery overlap with the adverse effects of opioids. Postoperative pulmonary complications are observed in up to 50% of patients and POCD or delirium in 4–54% according to studies and definitions,[16–18] whereas major gastrointestinal complications are estimated to occur in around 3% of patients, essentially acute pancreatitis and paralytic ileus.[19 20] Nausea and vomiting have been observed in 10–15% of patients.[21] All these data suggest a reasoned use of opioids which can present additive effects and their enhanced cardiac surgery-related side effects. Thus, the use of pharmacological alternatives may be considered in order to avoid their use as much as possible.

Opioid-free anaesthesia (OFA) strategies have emerged to avoid intraoperative opioid use. They are based on a drug combination that blocks the deleterious pathophysiological reactions related to nociception independently of opioid pathways. Among the various eligible drugs, lidocaine and dexmedetomidine may be of interest for this objective. Intravenous administration of lidocaine at doses up to 2 mg/kg/hour allows analgesia through a systemic blockade of peripheral neurons and anti-inflammatory proprieties.[22 23] Its use during non-cardiac major surgeries showed a reduction in postoperative pain, nausea–vomiting, ileus and length of stay.[24 25] Dexmedetomidine is an α_2 agonist with analgesic and sedative proprieties. Several studies showed its ability to reduce postoperative pain, opioid consumption, nausea–vomiting and circulatory failure.[26 27] Dexmedetomidine presented sympatholytic proprieties that may allow control of circulatory status during surgical nociceptive stimulation.[28] Moreover, dexmedetomidine showed beneficial effects in ischaemia–reperfusion experimental models, and several studies have shown significant clinical effects of dexmedetomidine after cardiac surgery, making this drug of high interest in this field.[29–31] Other drugs such as esmolol or magnesium have been used as alternatives to opioids. Nevertheless, we think that their use during cardiac surgery may favour circulatory failure and may interfere with CPB management through interference with cardioplegia drugs, delayed weaning from CPB, etc, suggesting the combination of lidocaine/dexmedetomidine as our first choice.

Preliminary results from retrospective studies with small sample size suggested that an OFA-based strategy is safe in cardiac surgery.[32–34] However, a large randomised trial is expected to explore the clinical benefits of OFA. Thus, we hypothesise that OFA may reduce opioid-related complications, and therefore the current trial was designed in order to compare the effects of OFA and opioid-based anaesthesia (OBA) on the incidence of major opioid-related complications after cardiac surgery.

OBJECTIVES OF THE STUDY

The primary goal is to assess the superiority of the OFA strategy compared with the OBA strategy with a reduction in major opioid-related complications within 48 hours after cardiac surgery.

The secondary goals are to compare the influence of the OFA and OBA strategies on the following postoperative complications: nausea–vomiting, pain, arrhythmia, shock, relative adrenal insufficiency, acute kidney injury, length of stay and mortality.

METHODS AND ANALYSIS

The present protocol was elaborated according to the 2013 Standard Protocol Items: Recommendations for Interventional Trials version 1.3, elaborated on 26 March 2020.

Trial characteristics

We designed a multicentre, randomised and single-blinded clinical trial focusing on elective cardiac surgeries with at least two coronary artery bypass grafts (CABGs). The patients will be randomly assigned to OFA or OBA strategies with an allocation ratio of 1:1. The trial will be conducted in four university and non-university cardiac surgery centres in France from 1 July 2021 until 1 July 2024 for a 36-month recruitment period, with the possibility of extending the inclusion period in the event of incomplete enrolment and on express request to the ethics committee.

Patient selection

Inclusion criteria

- Adult patients 18–75 years old.
- Scheduled for an elective cardiac surgery under CPB, with at least one CABG and implying at least one internal mammary artery as graft. This specific population has been chosen because of the extended dissection of the chest wall and a higher expected pain level compared with other cardiac surgeries. An association with aortic valve replacement is permitted.
- Having signed written consent to participate.
- Affiliated with a social security scheme.

Non-inclusion criteria

- Treatment with opioid-based drugs (including tramadol) within 15 days before surgery.
- Past or ongoing history of drug abuse.

- High-degree intracardiac conduction disorders.
- Bradycardia <50 bpm.
- Severe heart failure with left ventricle ejection fraction <40%.
- Myocardial injury within five preoperative days.
- Shock.
- Oxygen therapy.
- Chronic therapy with non-invasive ventilation.
- Contraindication to one of the trial drugs (dexmedetomidine, lidocaine, dexamethasone, ketamine, remifentanil, morphine, non-steroidal anti-inflammatory drugs).
- Body mass index ≥35 kg/m².
- Chronic adrenal insufficiency or treatment with corticosteroids (≥20 mg of hydrocortisone or equivalents).
- Combined cardiac surgeries (other than aortic valve replacement).
- Acute cerebral disease.
- Liver failure (factor V <50%).
- Cognitive disorders.
- Inability to perform the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) test.
- Pregnant or breastfeeding women.
- Inability to give consent.
- Person deprived of liberty by an administrative or judicial decision or person placed under judicial protection/under guardianship.
- Participation in another experimental trial within the month before inclusion.

Endpoints

The primary endpoint is the occurrence of at least one of the following events within 48 postoperative hours (composite endpoint):

- POI defined as the absence of gas or solid transit or actual bowel occlusion.
- Acute respiratory failure defined as need for oxygen therapy ≥6 L/min and/or need for respiratory support (high-flow nasal cannula, curative non-invasive ventilation, invasive ventilation with a new tracheal intubation) and/or acute respiratory distress and/or inability to wean from invasive ventilation because of hypoxaemia.
- POCD defined as a positive CAM-ICU score or delirium.
- Death.

The secondary endpoints are defined as follows:

- Intraoperative safety concerns
  - Bradycardia requiring atropine administration (atropine will be used if heart rate <35 bpm for at least 120 s, or heart rate <40 bpm with circulatory failure).
  - Arterial hypotension or hypertension, defined as the necessity of any pharmacological treatments (antihypertensive drugs or vasopressors).
- Within 48 postoperative hours
  - Nausea–vomiting.
  - Pain evaluated by a visual analogue scale (VAS) (maximal pain and number of episodes with VAS ≥3/10) and total morphine consumption.
  - De novo atrial or ventricular rhythm disorders.
  - Shock.
  - High-degree cardiac conduction disorders.
  - Maximal troponin plasma level.
  - Acute kidney injury defined by a Kidney Disease Improving Global Outcomes (KDIGO) score ≥1 (increase in creatinine over at least 26.5 µmol/L).[35]
  - Relative adrenal insufficiency at 24 hours (increase in cortisol <250 nmol/L 1 hour after 250 µg tetracosactide intravenous injection).
- Within hospital stay
  - Suspected or confirmed postoperative pneumonia.
  - Duration of invasive mechanical ventilation/intensive care unit (ICU) stay/hospital stay.
- Mortality within 2 months.
- Pain at 3 months, evaluated by VAS and 4-points Neuropathic Pain (DN-4) scales.

Design

Standard anaesthesia and postoperative care in both groups

Anxiolysis may be administrated according to the practices of each centre. Preoperative chronic medication use will be managed as recommended by the French Society of Anesthesiology and Critical Care, and notably β blockers will be maintained on the day of the surgery, whereas calcium channel blockers and ACE inhibitors or equivalent will be stopped at least 24 hours before surgery.

Patients will be monitored according to the current guidelines for cardiac surgery[36]: electrocardioscopy, pulse oximetry, capnography, invasive arterial catheter for blood pressure measurement, jugular or subclavicular central catheter with continuous central venous pressure, rectal or vesical temperature and bispectral index.

After preoxygenation with a 100 FiO_2 to achieve an end-expired oxygen fraction over 90%, general anaesthesia will be induced in both groups by using propofol (target concentration infusion (TCI)—site effect 1–5 µg/mL) or etomidate (0.2–0.5 mg/kg) in association with a neuromuscular blocker (cisatracurium 0.2 mg/kg or atracurium 0.5 mg/kg). Anaesthesia will be maintained using TCI of propofol or volatile anaesthesia to target a bispectral index between 40 and 60, and intermittent or continuous administration of neuromuscular blockers to obtain a train of 4 at 0. In the absence of specific guidelines or recommendations on this topic, the choice of hypnotic and paralysing drugs will be left at the discretion of the anaesthetist according to patient characteristics and local protocols. Patients will receive dexamethasone (0.1 mg/kg) and ketamine (0.2 mg/kg) at the beginning of anaesthesia, followed by a continuous infusion of ketamine (0.2 mg/kg/hour, stopped 45 min before the end of surgery), as recommended by the French guidelines.[37]

In cases of hypotension with a mean arterial pressure ≤65 mm Hg during the off-CPB period, circulatory intervention will be initiated with the use of vasopressors

(ephedrine or phenylephrine or norepinephrine) in combination with fluid administration if required. Because the recommended threshold for mean arterial pressure (MAP) during the CPB period is large (50–80 mm Hg according to European Assocation for Cardio-Thoracic Surgery (EATCS) guidelines[36]), vasopressor use will be left at the discretion of the anaesthetist, with a lower value of 50 mm Hg, and after optimisation of pump flow. In cases of hypertension, antihypertensive drugs will be administrated (nicardipine 1 mg or urapidil 10 mg every 2–5 min to obtain adequate blood pressure). The maximal upper blood pressure level permitted will be determined between the anaesthetic and surgical team, and according to pre-existing protocols if existing.

Antibioprophylaxis will consist of cefazolin 2 g (+1 g every 4 hours and 1 g for CPB priming) or vancomycin 30 mg/kg in case of a history of allergy.

CPB will be carried out according to the recent guidelines and the local practices of each centre.[36]

At the end of surgery, patients will receive analgesia with paracetamol 1 g, nefopam 20 mg and a non-steroidal anti-inflammatory (ketoprofen or diclofenac at the discretion of the clinician).

After surgery, patients will be transferred under invasive mechanical ventilation to cardiac surgical ICU for postoperative care. Extubation will be performed in awakened patients with spontaneous ventilation under pressure support of no more than 10 cmH_2O and positive end-expiratory pressure (PEEP) of no more than 5 cmH_2O. In cases of ventilation for more than 48 hours, extubation will be performed after a successful spontaneous breathing trial (low-pressure ventilation with pressure support of 7–8 cmH_2O and zero PEEP, or T-tube trial; absence of polypnoea, hypoxaemia, agitation, tachycardia or hypertension within 30 min of the trial).[38] Then, oxygen will be administrated if required to obtain SpO_2 between 92% and 96%.

Circulation management (fluid therapy and vasoactive drugs) will be conducted according to each centre practice, with an objective of a mean arterial pressure of at least 65 mm Hg.

Postoperative analgesia within the first 48 hours will be performed using paracetamol 1 g/6 hours (intravenous or oral), nefopam 80 mg/day by continuous infusion, ketoprofen or diclofenac every 8 hours (respectively 100 and 75 mg, or 50 and 50 mg if weight <70 kg) and patient-controlled analgesia based on morphine 1 mg and droperidol 0.05 mg/7 min.

The design of the trial and the specificities of each arm are described below and in online supplemental file 1.

Control group (OBA)

Patients will receive 50 mL of NaCl 0.9% as placebo within 10 min before induction of general anaesthesia.

Remifentanil will be added to standard care using TCI at an effect site concentration of 4 ng/mL for anaesthesia induction, followed by a TCI of 1–10 ng/mL according to the clinical situation. Infusion will be stopped at the end of surgery.

Morphine 0.15 mg/kg will be administrated at the end of surgery along with other analgesics.

Experimental group (OFA)

Dexmedetomidine (0.5 µg/kg) and lidocaine (1.5 mg/kg) will be administrated within 10 min before induction of general anaesthesia, followed by a continuous infusion of lidocaine (2 mg/kg/hour, stopped 45 min before the end of surgery) and dexmedetomidine (1 µg/kg/hour until sternotomy, reduced at 0.5 µg/kg/hour until CPB onset and then stopped). Dexmedetomidine infusion may be reduced in cases of bradycardia or hypertension/hypotension, and even stopped in cases of severe bradycardia (see the 'Safety concerns' section). It also may be increased in cases of tachycardia.

Sample size calculation, statistics and allocation

Sample size calculation

The primary endpoint of this study is a composite endpoint defined by the occurrence of at least one of the four major opioid-related complications within 48 hours after cardiac surgery. The sample size was calculated with respect to Pearson's χ^2 test at a one-sided 0.05 level, to compare the occurrence of complication between the two groups. In a recent French national survey, 50% of patients presented at least one complication among POCD, ileus or respiratory distress (data not published). In order to obtain 80% power for the difference given by the respective composite endpoint probabilities of 35% and 50% in the OFA and OBA arms, respectively, with one-sided type I error of 5% (reduction in complications of at least 30%), 134 patients will have to be included in each group, hence 268 patients overall. The unilateral characteristic of the test is justified by a previous retrospective study from Guinot *et al*, where OFA showed a reduction in postoperative outcomes. These data have been recently confirmed by another cohort study from the same authors.[32 33]

Statistics

The main analysis will be carried out on all randomised patients according to the treatment group drawn at random (intention-to-treat principle).

Patient characteristics will be described using standard parameters: mean, SD, median, IQR and extreme values for quantitative variables and frequencies and percentages for categorical variables.

The proportion of patients experiencing the main outcome and its 95% CI will be estimated in each group and compared by means of Pearson's χ^2 test.

This analysis will be complemented by a comparison using the logistic regression model with the main outcome (patients meeting the primary endpoint within 48 hours after cardiac surgery) as the response and the treatment group (OFA or OBA) and potential factors associated with the response as explanatory variables such as age,

body mass index, Euroscore 2, type of surgery (CABG or combined surgery) and duration of CPB.

The same general approach as outlined above will be used to compare the secondary qualitative outcomes (nausea–vomiting, pain, arrhythmia, shock, relative adrenal insufficiency, acute kidney injury, mortality) and Student's t-test will be used to compare quantitative parameters (length of stay).

No interim analysis will be performed.

Since this is an intention-to-treat analysis, in cases of missing value for the primary endpoint, imputation will be used according to the maximal bias assumption for incomplete observations. Namely, patients will be considered to experience the main outcome in the OFA group, and conversely in the OBA group.

All statistical tests are two sided, with a two-sided 0.05 level required for statistical significance.

Allocation and blinding

Patients who give written informed consent to participate in the study will be randomly assigned to the control (OBA) and experimental (OFA) groups. Inclusion and randomisation will be performed using the Ennov Clinical trial online software (Ennov, France), and a unique and anonymous number will be attributed to each patient. Randomisation will be stratified by centre in a 1:1 ratio using balanced blocks. All data will be collected and anonymised in an electronic case report form on the Ennov Clinical trial platform by a dedicated clinical research technician. Data will be monitored by a clinical research assistant in the presence of the clinical research technician and the main investigator of the site. Data will be stored for 15 years after the end of the trial in a dedicated secure server by the Clinical Research Department of the Rouen University Hospital.

Patients will be blinded to the allocated group and a 50 mL vial of 0.9% NaCl will be administrated before induction of anaesthesia in the OBA group to reinforce the blindness. The anaesthesia team will not be blinded to the allocation, but the postoperative care team in ICU will be blinded.

Safety concerns

In accordance with French regulations, every serious adverse event related to the investigational medicinal products or not, expected or unexpected, will be immediately reported to the sponsor (Clinical Research Department of the Rouen University Hospital) by the investigator, with the exception of those that are identified as not requiring immediate reporting in the protocol. A serious adverse event is defined as one that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, causes significant disability or prolonged incapacity, is a congenital anomaly or birth defect or is a medical event. The investigator will have to complete a 'serious adverse event' form on which will be indicated the date of onset, criterion of seriousness, intensity, treatment dates, causality relationship with the investigational medicinal products and the outcome. The period in which serious adverse events should be reported begins from the date of the authorisation of the study until 48 hours after the end of the anaesthetic of the patient included in the study or without a time limit if it is possibly related to the investigational medicinal product and/or to the clinical trial.

As mentioned in the protocol, the following events will not require immediate reporting: complications associated with cardiac surgery and unrelated to investigational medicinal products will not require immediate reporting but will be collected in the case report form.

Moreover, in order to avoid collection duplication in the case report form, the events POI, acute respiratory failure and POCD will be recorded as the primary endpoint in the case report form but not reported on the 'adverse event' page. In the same way, nausea and vomiting and bradycardia will be recorded as secondary endpoints in the case report form, with the exception of bradycardia meeting one of the following definitions, which will be reported on the adverse event page and subject to immediate reporting: (1) appearance of profound bradycardia in relation to investigational medicinal products (heart rate below 35 bpm lasting more than 120 s or below 40 bpm with haemodynamic repercussions) will be considered as a serious adverse event; (2) episodes of atropine-refractory bradycardia, defined as failure to normalise heart rate (heart rate greater than or equal to 50 bpm), despite at least two administrations of 1 mg atropine.

In the case of profound and severe bradycardia (heart rate below 40 bpm), if there is no response to two doses of 1 mg atropine, the treatment will be stopped prematurely, and an alternative anaesthetic technique used to ensure the surgical procedure.

In addition, serious adverse events will be submitted to the data and safety monitoring board (DSMB). The DSMB is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct.

This is justified in view of the study population at risk of mortality (independently of this trial), the off-label use of anaesthesia drugs in the OFA group and the high rate of complications associated with cardiac surgery. The DSMB will comprise three experts: an anaesthetist, a drug safety expert and a methodologist. The members will meet before the start of the trial, then on a regular basis (after 10% and half of the patients included, at the end of the study after the database lock), and if necessary, at any time at the sponsor's request in the case of a significant event. The DSMB will have to assess the benefit/risk ratio of the trial and to give recommendations on whether the study should be discontinued or not. All serious adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably considered will be considered as suspected serious adverse reactions (SARs). If they are unexpected, they are

qualified as being suspected unexpected SARs and will be notified in a report by the sponsor to EudraVigilance (European pharmacovigilance database) and to the local regulatory agency within the regulatory time periods for reporting: immediate reporting if seriousness criteria are death or life threatening, and reporting within 15 days for other seriousness criteria.

Patient and public involvement

None

ETHICS, DISSEMINATION AND DATA SHARING

The protocol has been approved by an ethics committee (*Comité de Protection des Personnes Ouest III*—No 2020-002126-90 on 9 December 2020) and by the national agency for drugs and health product safety (9 March 2021). In case of substantial modification in the protocol and eligibility of patient outcomes, the protocol will be resubmitted to these institutions. After presentation of the protocol by an investigator, written consent is mandatory for inclusion in this trial, and patients will be able to withdraw their consent at any time by simple request. The information and consent form is presented in online supplemental file 2.

Data generated by this trial will not be publicly available but on reasonable request to the corresponding author (EB, emmanuel.besnier@chu-rouen.fr). In this case, data will be totally deidentified. Requesters should provide a structured and detailed protocol for the proposed study and the reasons for reusing data.

The preparation of manuscripts and presentations at congresses resulting from the Opioid Free Anaesthesia for Cardiac Surgery (OFACS) trial will be carried out by the coordinating investigator or under his authorisation and responsibility. The principal investigators of each site will be cited in the articles, in a position based on their participation in the inclusion process. Other investigators, as well as people who have actively participated in the trial, may be cited in the manuscript according to their actual participation, or in an annexed list of investigators. The methodologist/biostatistician will also be listed among the authors. All publications will follow the 2010 Consolidated Standards of Reporting Trials guidelines.[39]

CONCLUSION AND PERSPECTIVES

To our knowledge, this is the first randomised, blinded trial designed to compare an OFA strategy versus an OBA strategy in cardiac surgery. The interest of OFAs for anaesthesiologists is rising. Nevertheless, the current level of evidence is low given the lack of randomised trials and regarding the recent publication of negative results of the Postoperative and Opioid Free Anaesthesia (POFA) study in non-cardiac surgery.[40] Given the particularity of cardiac surgery and the encouraging initial retrospective publications in this field, the results of this trial could thus rigorously define the place of this strategy in the intraoperative management of cardiac surgery patients.

Author affiliations
[1]Department of Anesthesia and Critical Care, Rouen University Hospital, Rouen, France
[2]U1096, INSERM, Rouen, France
[3]Department of Anesthesiology and Critical Care, Lille University Hospital, Lille, France
[4]ULR 2694-METRICS : évaluation des technologies de santé et des pratiques médicales, Univ.Lille, Lille, France
[5]Department of Biostatistics, Rouen University Hospital, Rouen, France
[6]Research Department, Rouen University Hospital, Rouen, France
[7]Department of Pharmacy, Rouen University Hospital, Rouen, France
[8]Anesthesia and Critical Care Medicine, Clinique du Millenaire, Montpellier, France
[9]Department of Anesthesiology and Critical Care, University Hospital Centre Amiens-Picardie, Amiens, France

Contributors EB contributed to the design of the trial, coordinated the project and wrote the draft. MDM, PS and OA-A are the principal investigators of the centre. CT is responsible for statistics and methodology, and contributed to the study design. FV is responsible for the coordination of the project. ND is responsible for drug distribution and contributed to the study design. SR is responsible for the safety concerns of the trial. EL and VS are coinvestigators of the centre.

Funding This trial has been funded by the General Direction for Care Organization under the authority of the French Ministry for Health (Programme Hospitalier de Recherche Clinique Inter-Régional) (grant number API 19-38). Secretariat-drc@chu-rouen.fr

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

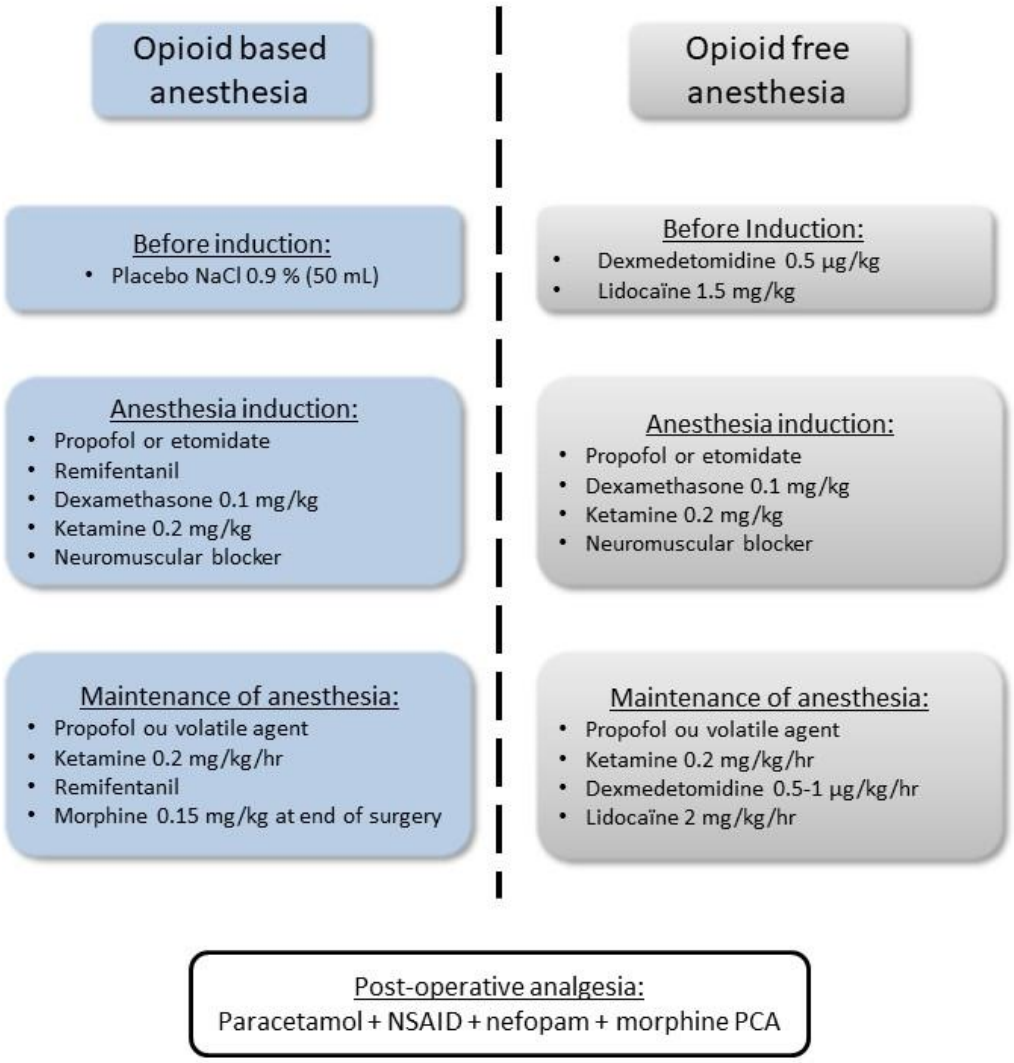
Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Emmanuel Besnier http://orcid.org/0000-0002-0267-0986

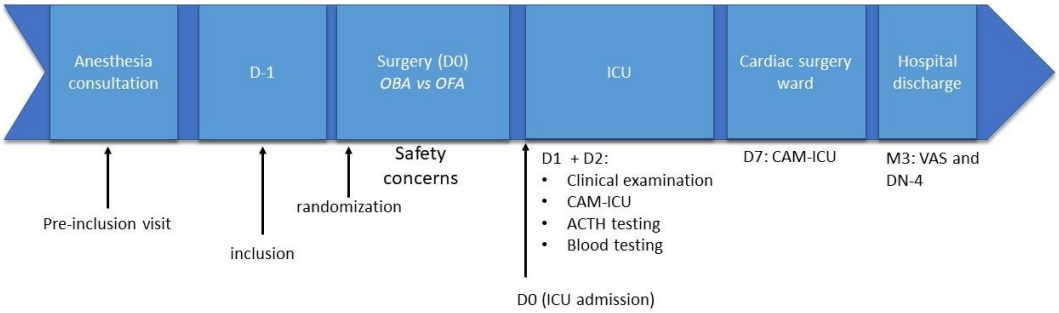
REFERENCES

1 Moffitt EA, Sethna DH. The coronary circulation and myocardial oxygenation in coronary artery disease: effects of anesthesia. *Anesth Analg* 1986;65:395–410.
2 Van Aken H, Meinshausen E, Prien T, *et al*. The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N2O in humans. *Anesthesiology* 1988;68:157–63.
3 Rodriguez-Monguio R, Berkley E, Mendoza E, *et al*. Inpatient administration of opioids and risk for post-operative Ileus in older adults. *J Opioid Manag* 2022;18:317–25.
4 Barletta JF, Asgeirsson T, Senagore AJ. Influence of intravenous opioid dose on postoperative Ileus. *Ann Pharmacother* 2011;45:916–23.

5 Lee LA, Caplan RA, Stephens LS, *et al*. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology* 2015;122:659–65.
6 Wang Y, Sands LP, Vaurio L, *et al*. The effects of postoperative pain and its management on postoperative cognitive dysfunction. *Am J Geriatr Psychiatry* 2007;15:50–9.
7 Yang X, Huang X, Li M, *et al*. Identification of individuals at risk for postoperative cognitive dysfunction (POCD). *Ther Adv Neurol Disord* 2022;15.
8 Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. *Lancet* 2019;393:1558–68.
9 Joly V, Richebe P, Guignard B, *et al*. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005;103:147–55.
10 Sacerdote P, Franchi S, Panerai AE. Non-analgesic effects of opioids: mechanisms and potential clinical relevance of opioid-induced immunodepression. *Curr Pharm Des* 2012;18:6034–42.
11 Donegan D. Opioid induced adrenal insufficiency: what is new? *Curr Opin Endocrinol Diabetes Obes* 2019;26:133–8.
12 Soelberg CD, Brown RE Jr, Du Vivier D, *et al*. The US opioid crisis: current federal and state legal issues. *Anesth Analg* 2017;125:1675–81.
13 Soffin EM, Lee BH, Kumar KK, *et al*. The prescription opioid crisis: role of the anaesthesiologist in reducing opioid use and misuse. *Br J Anaesth* 2019;122:e198–208.
14 Larach DB, Hah JM, Brummett CM. Perioperative opioids, the opioid crisis, and the anesthesiologist. *Anesthesiology* 2022;136:594–608.
15 Brat GA, Agniel D, Beam A, *et al*. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ* 2018;360:j5790.
16 Fischer M-O, Brotons F, Briant AR, *et al*. Postoperative pulmonary complications after cardiac surgery: the VENICE International cohort study. *J Cardiothorac Vasc Anesth* 2022;36:2344–51.
17 Chen H, Mo L, Hu H, *et al*. Risk factors of postoperative delirium after cardiac surgery: a meta-analysis. *J Cardiothorac Surg* 2021;16:113.
18 Bhushan S, Li Y, Huang X, *et al*. Progress of research in postoperative cognitive dysfunction in cardiac surgery patients: a review article. *Int J Surg* 2021;95:106163.
19 Dong G, Liu C, Xu B, *et al*. Postoperative abdominal complications after cardiopulmonary bypass. *J Cardiothorac Surg* 2012;7:108.
20 Marsoner K, Voetsch A, Lierzer C, *et al*. Gastrointestinal complications following on-pump cardiac surgery-a propensity matched analysis. *PLoS One* 2019;14:e0217874.
21 Hijazi EM, Edwan H, Al-Zoubi N, *et al*. Incidence of nausea and vomiting after fast-track anaesthesia for heart surgery. *Braz J Cardiovasc Surg* 2018;33:371–5.
22 Estebe J-P. Intravenous lidocaine. *Best Pract Res Clin Anaesthesiol* 2017;31:513–21.
23 Kaba A, Laurent SR, Detroz BJ, *et al*. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007;106:11–8.
24 Weibel S, Jokinen J, Pace NL, *et al*. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. *Br J Anaesth* 2016;116:770–83.
25 Sun Y, Li T, Wang N, *et al*. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Dis Colon Rectum* 2012;55:1183–94.
26 Jakob SM, Ruokonen E, Grounds RM, *et al*. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012;307:1151–60.
27 Grape S, Kirkham KR, Frauenknecht J, *et al*. Intra-operative analgesia with remifentanil vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis. *Anaesthesia* 2019;74:793–800.
28 Bao N, Tang B. Organ-protective effects and the underlying mechanism of dexmedetomidine. *Mediators Inflamm* 2020;2020:6136105.
29 Gao W, Du L, Li N, *et al*. Dexmedetomidine attenuates myocardial ischemia-reperfusion injury in hyperlipidemic rats by inhibiting inflammation, oxidative stress and NF-KB. *Chem Biol Drug Des* 2023;102:1176–85.
30 Turan A, Duncan A, Leung S, *et al*. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet* 2020;396:177–85.
31 Wang G, Niu J, Li Z, *et al*. The efficacy and safety of dexmedetomidine in cardiac surgery patients: a systematic review and meta-analysis. *PLoS One* 2018;13:e0202620.
32 Guinot P-G, Spitz A, Berthoud V, *et al*. Effect of opioid-free anaesthesia on post-operative period in cardiac surgery: a retrospective matched case-control study. *BMC Anesthesiol* 2019;19:136.
33 Guinot P-G, Andrei S, Durand B, *et al*. Balanced nonopioid general anesthesia with lidocaine is associated with lower postoperative complications compared with balanced opioid general anesthesia with Sufentanil for cardiac surgery with cardiopulmonary bypass: a propensity matched cohort study. *Anesth Analg* 2023;136:965–74.
34 Aguerreche C, Cadier G, Beurton A, *et al*. Feasibility and postoperative opioid sparing effect of an opioid-free anaesthesia in adult cardiac surgery: a retrospective study. *BMC Anesthesiol* 2021;21:166.
35 Kellum JA, Lameire N, KDIGO AKI, *et al*. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary. *Crit Care* 2013;17:204.
36 Wahba A, Milojevic M, Boer C, *et al*. 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. *Br J Anaesth* 2019;123:713–57.
37 Aubrun F, Nouette-Gaulain K, Fletcher D, *et al*. Revision of expert panel's guidelines on postoperative pain management. *Anaesth Crit Care Pain Med* 2019;38:405–11.
38 Quintard H, l'Her E, Pottecher J, *et al*. Intubation and extubation of the ICU patient. *Anaesth Crit Care Pain Med* 2017;36:327–41.
39 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
40 Beloeil H, Garot M, Lebuffe G, *et al*. Balanced opioid-free anesthesia with dexmedetomidine versus balanced anesthesia with remifentanil for major or intermediate noncardiac surgery. *Anesthesiology* 2021;134:541–51.



Opioid-Free Anesthesia and Opioid-Based Anesthesia protocols. NSAID: Non Steroidal Anti Inflammatory Drug (ketoprofen 100 mg and (or 50 mg if weight < 70 kg) or diclofenac 75 mg (or 50 mg weight < 70 kg)). PCA: patient controlled analgesia.



Design of the trial

INFORMATION NOTE FOR PATIENTS PARTICIPATING IN THE RESEARCH

Title of the research involving a human being**: Opioid Free Anesthesia in cardiac surgery – OFACS study**

N° EUDRACT: 2020-002126-90

Coordinating Investigator:
Pr Emmanuel Besnier
Department of Anesthesia and Intensive Care
Rouen University Hospital
1, rue de Germont, 76031 ROUEN Cedex
Tél. : 02 32 88 82 83, Fax : 02 32 88 83 26

Sponsor:
Rouen University Hospital
Clinical research department
1, rue de Germont, 76031 ROUEN Cedex
Tél. : 02 32 88 82 65, Fax : 02 32 88 82 87

Authorization from the ethics committee CPP OUEST II – ANGERS on the 5th February 2021

Authorization from the national agency for security of drugs and medical products (ANSM) on the 9th march 2021.

Madam, Miss, Sir,

Your physician, Professor/Doctor _____, is inviting you to take part in a research protocol entitled “Opioid-free anesthesia in cardiac surgery - OFACS study”, sponsored by Rouen University Hospital.

The aim of this information note is to explain as openly and clearly as possible all the different aspects of this clinical trial, so that you can decide whether or not to take part.

Rational for this trial

Your physician has asked you to take part in this study because you are about to undergo cardiac surgery involving coronary artery bypass grafting.
General anesthesia is essential for cardiac surgery, and for several decades has been based on a combination of hypnotics, major opioids and muscle blockers. Among these, opioids help to limit the pain signal during surgery, so as to limit reactions on the cardiovascular system. Although you are not conscious during the procedure, and therefore cannot feel the pain directly, over-stimulation of the nerve fibers conveying pain can lead to damaging cardiac and vascular reactions during the operation. Despite the beneficial effects of opioids on pain control, these drugs have potentially harmful post-operative side-effects: respiratory depression, which can lead to oxygenation failure, slowed digestive transit, cognitive disorders and even increased pain after surgery (hyperalgesia).
The use of a strategy aimed at reducing the need for opioids, or even doing without it, could therefore be beneficial after major cardiac surgery. To this end, several drugs exist and are commonly used in anesthesia:

- intravenous lidocaine, used to reduce pain after certain types of painful surgery

- dexmedetomidine, which controls the cardiovascular effects of the pain signal and has already been shown to have a beneficial effect on cognition after cardiac surgery.

Thus, the use of a general anesthesia without opioids could be beneficial in cardiac surgery patients on complications attributable to these drugs.

Objective of the trial

The aim of this trial is to evaluate the impact of an opioid-free anesthesia strategy on certain major complications after cardiac surgery, compared with a traditional strategy involving opioids
.

Design of the trial

The trial is taking place in four hospitals in France, and we plan to include 268 patients over a total period of 3 years. Inclusion will take place during the pre-anesthetic visit. Each patient will then be medically monitored for 7 days, including follow-up visits with a physician. Information on the patient's state of health at discharge, or at a maximum of 45 days after inclusion, will be collected from the medical record. A telephone call will be made at 90 days post-inclusion to ask about your post-operative state of health.

Patients undergoing coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass are eligible to participate in this trial. Affiliation to a social and health insurance plan is required to participate in this trial.

Patients with contraindications to drugs used in this trial, chronic treatment with opioids, morbid obesity, cardiac conduction disorders, severe heart failure, prior oxygen therapy or respiratory pressure support, recent coronary suffering or shock cannot take part in this trial. Pregnant or breast-feeding women, or persons deprived of their liberty, are also ineligible. If you have just taken part in a clinical trial involving an innovative drug or procedure, you will not be able to take part in this new clinical trial within 1 month of the end of your participation in the previous trial. You will also not be able to participate in another trial at the same time.

This trial randomly selects the type of anesthetic strategy prior to surgery:
- opioid free anesthesia combining dexmedetomidine and lidocaine,
or
- opioid based anesthesia using remifentanil and morphine.

You will not be informed of the strategy chosen for your care, but your physician will be, to ensure the safety of your care. The rest of the treatment is carried out in the usual way, including other anasthetic treatments and post-operative pain management, in accordance with current guidelines. Morphine can be used in the event of severe pain after surgery, whatever the anesthetic strategy chosen.

Physicians will collect and record some of your health data for the purpose of the trial: post-operative cardiac, respiratory and digestive complications, pain, use of certain medications, duration of respiratory support, length of stay, routine laboratory tests, etc. …

A functional blood test will also be carried out outside the usual care to check for adrenal gland function. This involves checking the adrenal glands' ability to produce cortisol in response to a low-dose of the natural hormone adrenocorticotropin). To this end, 3 additional blood samples (12 mL total) will be taken at 30-minute intervals after the administration of 250 µg of adrenocorticotropin,

using the same sampling catheter used for the usual care. This test will be performed 24 hours after the end of your surgery.

Each patient in the study will be followed up until discharge from hospital, and by telephone at 90 days after inclusion.

	Anesthesia medical consultation	D0 (pre-anesthesia visit) Inclusion V1	D1 (day of surgery) V2	D2 (24 hours after surgery) V3	D3 (48 after surgery) V4	D7 V5	D45 * (or day of the hospital discharge)	D90 +/- 5 days Phone call
Patient information	✓							
Obtaining of consent		✓						
Blood tests	✓			✓	✓			
Blood pregnancy test		✓						
Validation of inclusion and non-inclusion criteria		✓						
Randomization			✓					
Adrenocorticotropin stimulation test				✓				
Pain evaluation			✓	✓	✓	✓		✓
Troponin				✓	✓			
Cognition evaluation				✓	✓	✓		
Duration of respiratory support			✓	✓	✓	✓	✓*	
Duration of vasopressor support			✓	✓	✓	✓	✓*	
Digestive transit				✓	✓			
Acute kidney failure				✓	✓			
Pulmonary complications				✓	✓		✓*	
Total length of hospital stays							✓*	
Mortality							✓*	

Expected beneficial effects

The expected benefits are a reduction in the major complications associated with the use of opioids: less respiratory failure, digestive ileus and cognitive impairment.

Expected risks

The foreseeable risks are complications specific to the study drugs.

- Dexmedetomidine exposes the patient to the risk of decreased or accelerated heart rate, which is resolved in the vast majority of cases by dose reduction or administration of a heart rate stimulating drug (atropine). Exceptionally, cases of transient blockade of electrical activity at high doses have been described, which resolved spontaneously. Intraoperative hypertension may occur, treatable by dose reduction and antihypertensive medication. These effects are short-lived and resolve by the end

of surgery at the latest. Similarly, dexmedetomidine may cause variations in blood glucose levels, diabetes insipidus (excessive production of urine while blood glucose levels remain unchanged), hallucinations, reduced respiratory rate and nausea or vomiting. These effects disappear when treatment is stopped, which will be the case in this study before you wake up in the intensive care unit. It is therefore unlikely that you will experience these effects. Dexmedetomidine is also widely used in anesthesia and intensive care for patient comfort.

- Lidocaine is not associated with any expected excess risk at the doses used in this study. Side effects have been described in the event of overdosage (nervousness, agitation, headaches and other neurological signs; acceleration or reduction of respiratory and cardiac rhythm, cardiac rhythm disorders). Lidocaine at the doses proposed in this study is commonly used in anesthesia for digestive surgery and has not been associated with overdose.

- Remifentanil is a powerful opioid used daily in anesthesia. Its side effects are those typical of opioids: irregular heartbeat, decrease in heart rate, resolvable in the vast majority of cases by dose reduction or administration of atropine, even transient block of electrical activity at high doses, arterial hypotension and decrease in respiratory rate, cough, nausea and vomiting after surgery. These effects are rapidly reversible when treatment is stopped before you wake up. It is therefore unlikely that you will experience these effects.

Medical alternatives

If you decide not to take part in this trial, or if you voluntarily or on the decision of the physician interrupt your participation, you will be offered the reference treatment usual in your case corresponding to the anesthetic strategy with opioids (remifentanil + morphine or sufentanil).

You are free to interrupt your participation at any time. You will then be able to discuss the most appropriate treatment for your personal situation with your physician.

What are your rights?

Your physician must provide you with all the necessary explanations concerning this trial. If you wish to withdraw your consent at any time, for whatever reason, you will continue to benefit from medical monitoring and care.

In accordance with the provisions of the French Data Protection Act and the European General Data Protection Regulation Act of May 25, 2018, you have the following rights at any times:

- **A right of access**
You have a right to information about your personal data collected, processed or, where applicable, transmitted to third parties (Article 15 of the general data protection regulation European law).
- **A right of rectification**
You have the right to request the correction of incorrect personal data concerning you (Articles 16 and 19).
- **A right to deletion**
You have the right to request the deletion of personal data concerning you. For example, if this data is no longer necessary for the purposes for which it was collected (Articles 17 and 19).
- **A right to restrict processing**
Under certain conditions, you have the right to request a processing limitation. In this case, your data may only be stored but not used for the processing, except with your consent (Articles 18 and 19).
- **A right to oppose processing**

You have the right to oppose to the processing of your personal data at any time (Article 21). Processing will then be stopped by the sponsor on the date on which you notify.
However, all data previously collected to the opposition, erasure request or limitation request may be processed if necessary.

These rights may be obtained from the physician who is treating you as part of the trial, and who is aware of your identity.

Your medical data collected for the study will be pseudonymized, i.e. you will be identified by a code number for the purposes of the research, with no mention of your full name. This data will be kept for 25 years by the trial sponsor.

Your participation in this research is voluntary and you are under no obligation to take part. This will in no way affect your relationship with the physician treating you or with the medical team. If, during the course of the trial, new information becomes available that could modify the interest of the trial, the physician in charge of the trial will inform you of this and will ensure that you wish to continue to take part.
You may stop participating in this protocol at any time. The investigating physician in charge of this trial may also decide to remove you from the trial if he or she deems it necessary, in particular for your well-being.
Your participation will not entail any additional costs for you.
Moreover, if you wish, you may be informed of the results obtained at the end of the trial.

Once you have read this information note, do not hesitate to ask your physician any questions you may have. After a period of reflection, if you agree to take part, you must complete and sign the consent form. A copy of the complete document will be given to you.

We thank you for your cooperation.

Further information about this clinical trial can be obtained from the physician who suggested you take part,

Dr/Pr _____
Adress _____
_____
_____
Téléphone : _____

Or

Medical coordinator Pr Emmanuel Besnier Département d'Anesthésie-Réanimation Hôpital Charles Nicolle CHU de Rouen 1, rue de Germont, 76031 ROUEN Cedex Tél. : 02 32 88 82 83, Fax : 02 32 88 83 26	**Sponsor** Hôpital Charles Nicolle - CHU de Rouen Direction à la Recherche Clinique et à l'Innovation Maison de la Recherche Clinique 1, rue de Germont, 76031 ROUEN Cedex

CONSENT FORM FOR
TO THE PATIENT TAKING PART IN THE TRIAL
OPIOID FREE ANESTHESIA IN CARDIAC SURGERY
OFACS TRIAL – 2019/0399/HP

Sponsor: CHU de Rouen
Medical coordinator: Pr Emmanuel BESNIER

I the undersigned _____ (Surname, first name) certify that I have read and understood the information note concerning the clinical trial entitled "Opioid-free anesthesia in cardiac surgery - OFACS trial".

I had the opportunity to ask any questions I felt would help me understand the information memorandum, and to receive clear, precise answers from Professor/Doctor _____, who also explained to me the nature, objectives, expected benefits, duration of the clinical trial and its follow-up, potential risks and constraints associated with my participation in this trial.

I understand that I am free to accept or refuse to participate in this trial.

I am aware of the possibility of interrupting my participation at any time without having to justify my decision. Naturally, this will not affect the quality of subsequent care I receive. I will then inform the investigator. I have been assured that the decisions that are necessary for my health will be taken at all times, in accordance with the current state of medical knowledge.

My consent does not relieve the investigator and the sponsor of the trial of their responsibilities towards me and I retain all my rights guaranteed by law.

I have been informed that this trial has been approved by an ethics committee (CPP OUEST II - ANGERS on 05/02/2021) and authorized by the ANSM on 09/03/2021, and has been declared to the National Committee for Information Technologies and Freedom (CNIL).

The sponsor of the trial, Rouen University Hospital, has taken out civil liability insurance in the event of damage.

I have been informed that the pseudonymized data recorded as part of this trial may be processed by or on behalf of the sponsor. I have noted that I have a right of access, information, opposition, rectification of personal data concerning me as well as a right to the limitation of processing as provided for by the CNIL (provisions of the Data Protection Act of January 6, 1978 as amended) and the European General Data Protection Regulation Act

The processing of data concerning me rests on a legal basis of a mission of public interest, so data already collected cannot be deleted. I am aware that my data will be kept for 25 years by the trial sponsor.

I may exercise these rights at any time by contacting the physician investigating my case and/or the trial sponsor, the entity responsible for data processing. I have noted that I have the right to lodge a complaint with the CNIL if I consider that the processing of my personal data has been carried out in violation of my rights. My personal data are confidential.

I am aware that the data recorded in the course of this trial may, under conditions ensuring confidentiality and a sufficient level of security, be transmitted to the French health authorities or to any other partner of the sponsor in France.

My attention has been drawn to the fact that the data recorded in the course of this trial may be used in subsequent research for scientific purposes only.

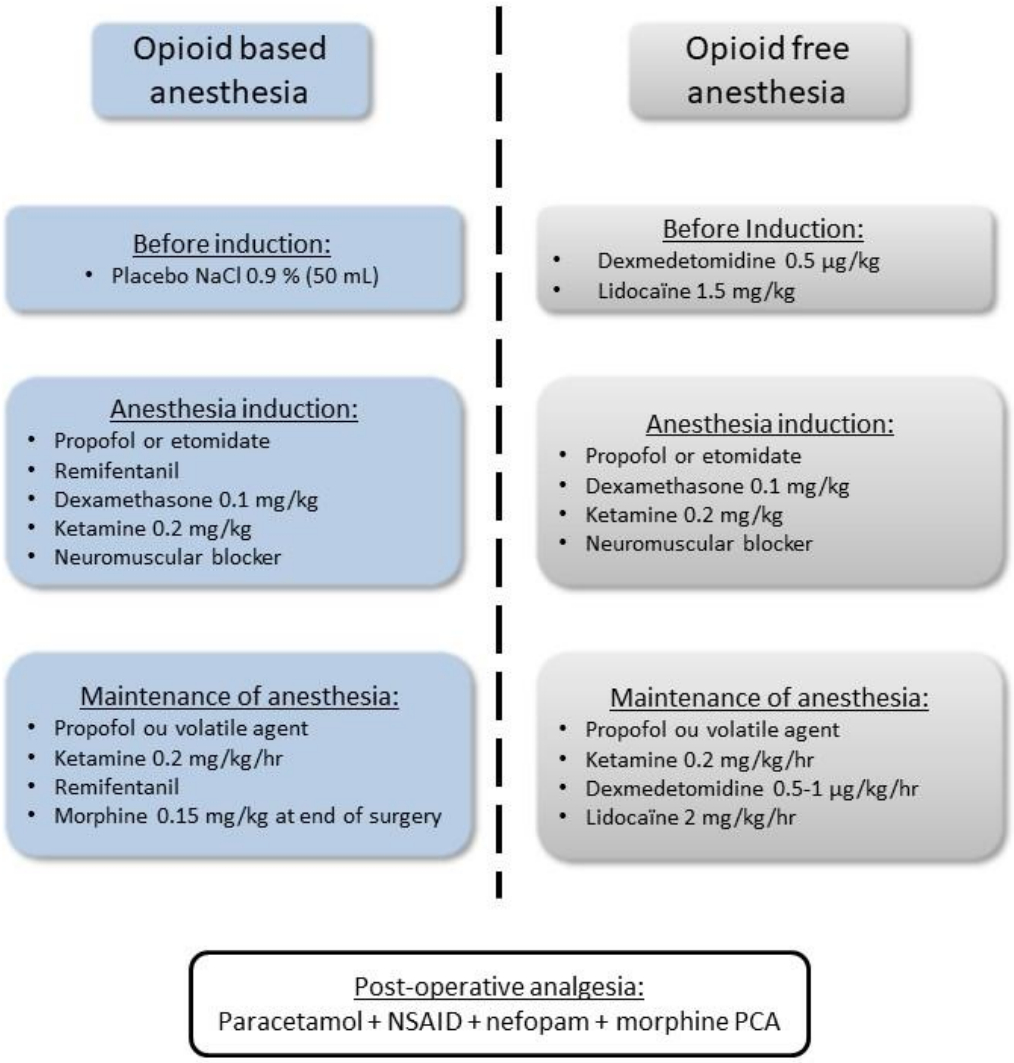
I have noted that my medical file will be consulted by the promoter's trial staff, who are bound by professional secrecy, and that the persons collaborating in this research or mandated by the sponsor, as well as any representative of the Health Authorities, may have access to the information in strictest confidence.

The overall results of the research will be communicated to me directly, on my request.

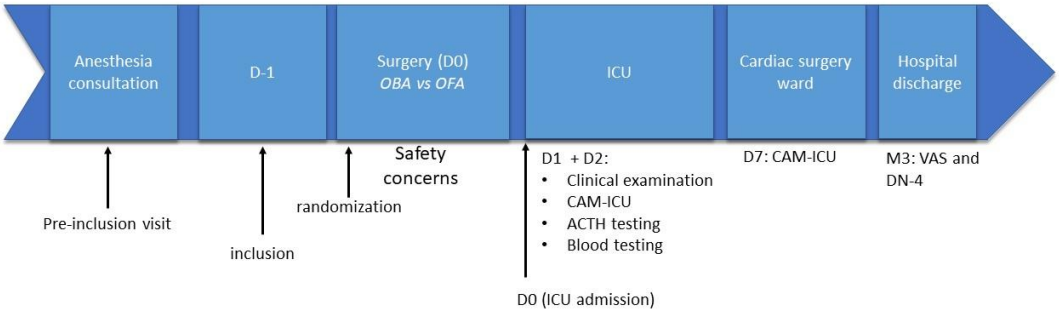
I may at any time request further information from the Professor/Doctor _____ (tel.: _____) who suggested that I take part in this trial.

Given sufficient time to consider my decision, I freely and voluntarily agree to take part in the OFACS trial and I do not object to the processing of my personal data.

The |__|__| |__|__| 2 0 |__|__|	The |__|__| |__|__| 2 0 |__|__|
Trial participant	**Physician**
Name and Surname Signature	Name and Surname Signature



Opioid-Free Anesthesia and Opioid-Based Anesthesia protocols. NSAID: Non Steroidal Anti Inflammatory Drug (ketoprofen 100 mg and (or 50 mg if weight < 70 kg) or diclofenac 75 mg (or 50 mg weight < 70 kg)). PCA: patient controlled analgesia.



Design of the trial

INFORMATION NOTE FOR PATIENTS PARTICIPATING IN THE RESEARCH

Title of the research involving a human being**: Opioid Free Anesthesia in cardiac surgery – OFACS study**

N° EUDRACT: 2020-002126-90

Coordinating Investigator:
Pr Emmanuel Besnier
Department of Anesthesia and Intensive Care
Rouen University Hospital
1, rue de Germont, 76031 ROUEN Cedex
Tél. : 02 32 88 82 83, Fax : 02 32 88 83 26

Sponsor:
Rouen University Hospital
Clinical research department
1, rue de Germont, 76031 ROUEN Cedex
Tél. : 02 32 88 82 65, Fax : 02 32 88 82 87

Authorization from the ethics committee CPP OUEST II – ANGERS on the 5th February 2021

Authorization from the national agency for security of drugs and medical products (ANSM) on the 9th march 2021.

Madam, Miss, Sir,

Your physician, Professor/Doctor _____, is inviting you to take part in a research protocol entitled “Opioid-free anesthesia in cardiac surgery - OFACS study”, sponsored by Rouen University Hospital.

The aim of this information note is to explain as openly and clearly as possible all the different aspects of this clinical trial, so that you can decide whether or not to take part.

Rational for this trial

Your physician has asked you to take part in this study because you are about to undergo cardiac surgery involving coronary artery bypass grafting.
General anesthesia is essential for cardiac surgery, and for several decades has been based on a combination of hypnotics, major opioids and muscle blockers. Among these, opioids help to limit the pain signal during surgery, so as to limit reactions on the cardiovascular system. Although you are not conscious during the procedure, and therefore cannot feel the pain directly, over-stimulation of the nerve fibers conveying pain can lead to damaging cardiac and vascular reactions during the operation. Despite the beneficial effects of opioids on pain control, these drugs have potentially harmful post-operative side-effects: respiratory depression, which can lead to oxygenation failure, slowed digestive transit, cognitive disorders and even increased pain after surgery (hyperalgesia).
The use of a strategy aimed at reducing the need for opioids, or even doing without it, could therefore be beneficial after major cardiac surgery. To this end, several drugs exist and are commonly used in anesthesia:

- intravenous lidocaine, used to reduce pain after certain types of painful surgery

- dexmedetomidine, which controls the cardiovascular effects of the pain signal and has already been shown to have a beneficial effect on cognition after cardiac surgery.

Thus, the use of a general anesthesia without opioids could be beneficial in cardiac surgery patients on complications attributable to these drugs.

Objective of the trial

The aim of this trial is to evaluate the impact of an opioid-free anesthesia strategy on certain major complications after cardiac surgery, compared with a traditional strategy involving opioids
.

Design of the trial

The trial is taking place in four hospitals in France, and we plan to include 268 patients over a total period of 3 years. Inclusion will take place during the pre-anesthetic visit. Each patient will then be medically monitored for 7 days, including follow-up visits with a physician. Information on the patient's state of health at discharge, or at a maximum of 45 days after inclusion, will be collected from the medical record. A telephone call will be made at 90 days post-inclusion to ask about your post-operative state of health.

Patients undergoing coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass are eligible to participate in this trial. Affiliation to a social and health insurance plan is required to participate in this trial.

Patients with contraindications to drugs used in this trial, chronic treatment with opioids, morbid obesity, cardiac conduction disorders, severe heart failure, prior oxygen therapy or respiratory pressure support, recent coronary suffering or shock cannot take part in this trial. Pregnant or breast-feeding women, or persons deprived of their liberty, are also ineligible. If you have just taken part in a clinical trial involving an innovative drug or procedure, you will not be able to take part in this new clinical trial within 1 month of the end of your participation in the previous trial. You will also not be able to participate in another trial at the same time.

This trial randomly selects the type of anesthetic strategy prior to surgery:
- opioid free anesthesia combining dexmedetomidine and lidocaine,
or
- opioid based anesthesia using remifentanil and morphine.

You will not be informed of the strategy chosen for your care, but your physician will be, to ensure the safety of your care. The rest of the treatment is carried out in the usual way, including other anasthetic treatments and post-operative pain management, in accordance with current guidelines. Morphine can be used in the event of severe pain after surgery, whatever the anesthetic strategy chosen.

Physicians will collect and record some of your health data for the purpose of the trial: post-operative cardiac, respiratory and digestive complications, pain, use of certain medications, duration of respiratory support, length of stay, routine laboratory tests, etc. …

A functional blood test will also be carried out outside the usual care to check for adrenal gland function. This involves checking the adrenal glands' ability to produce cortisol in response to a low-dose of the natural hormone adrenocorticotropin). To this end, 3 additional blood samples (12 mL total) will be taken at 30-minute intervals after the administration of 250 µg of adrenocorticotropin,

using the same sampling catheter used for the usual care. This test will be performed 24 hours after the end of your surgery.

Each patient in the study will be followed up until discharge from hospital, and by telephone at 90 days after inclusion.

	Anesthesia medical consultation	D0 (pre-anesthesia visit) Inclusion V1	D1 (day of surgery) V2	D2 (24 hours after surgery) V3	D3 (48 after surgery) V4	D7 V5	D45 * (or day of the hospital discharge)	D90 +/- 5 days Phone call
Patient information	✓							
Obtaining of consent		✓						
Blood tests	✓			✓	✓			
Blood pregnancy test		✓						
Validation of inclusion and non-inclusion criteria		✓						
Randomization			✓					
Adrenocorticotropin stimulation test				✓				
Pain evaluation			✓	✓	✓	✓		✓
Troponin				✓	✓			
Cognition evaluation				✓	✓	✓		
Duration of respiratory support			✓	✓	✓	✓	✓*	
Duration of vasopressor support			✓	✓	✓	✓	✓*	
Digestive transit				✓	✓			
Acute kidney failure				✓	✓			
Pulmonary complications				✓	✓		✓*	
Total length of hospital stays							✓*	
Mortality							✓*	

Expected beneficial effects

The expected benefits are a reduction in the major complications associated with the use of opioids: less respiratory failure, digestive ileus and cognitive impairment.

Expected risks

The foreseeable risks are complications specific to the study drugs.

- Dexmedetomidine exposes the patient to the risk of decreased or accelerated heart rate, which is resolved in the vast majority of cases by dose reduction or administration of a heart rate stimulating drug (atropine). Exceptionally, cases of transient blockade of electrical activity at high doses have been described, which resolved spontaneously. Intraoperative hypertension may occur, treatable by dose reduction and antihypertensive medication. These effects are short-lived and resolve by the end

of surgery at the latest. Similarly, dexmedetomidine may cause variations in blood glucose levels, diabetes insipidus (excessive production of urine while blood glucose levels remain unchanged), hallucinations, reduced respiratory rate and nausea or vomiting. These effects disappear when treatment is stopped, which will be the case in this study before you wake up in the intensive care unit. It is therefore unlikely that you will experience these effects. Dexmedetomidine is also widely used in anesthesia and intensive care for patient comfort.

- Lidocaine is not associated with any expected excess risk at the doses used in this study. Side effects have been described in the event of overdosage (nervousness, agitation, headaches and other neurological signs; acceleration or reduction of respiratory and cardiac rhythm, cardiac rhythm disorders). Lidocaine at the doses proposed in this study is commonly used in anesthesia for digestive surgery and has not been associated with overdose.

- Remifentanil is a powerful opioid used daily in anesthesia. Its side effects are those typical of opioids: irregular heartbeat, decrease in heart rate, resolvable in the vast majority of cases by dose reduction or administration of atropine, even transient block of electrical activity at high doses, arterial hypotension and decrease in respiratory rate, cough, nausea and vomiting after surgery. These effects are rapidly reversible when treatment is stopped before you wake up. It is therefore unlikely that you will experience these effects.

Medical alternatives

If you decide not to take part in this trial, or if you voluntarily or on the decision of the physician interrupt your participation, you will be offered the reference treatment usual in your case corresponding to the anesthetic strategy with opioids (remifentanil + morphine or sufentanil).

You are free to interrupt your participation at any time. You will then be able to discuss the most appropriate treatment for your personal situation with your physician.

What are your rights?

Your physician must provide you with all the necessary explanations concerning this trial. If you wish to withdraw your consent at any time, for whatever reason, you will continue to benefit from medical monitoring and care.

In accordance with the provisions of the French Data Protection Act and the European General Data Protection Regulation Act of May 25, 2018, you have the following rights at any times:

- **A right of access**
You have a right to information about your personal data collected, processed or, where applicable, transmitted to third parties (Article 15 of the general data protection regulation European law).
- **A right of rectification**
You have the right to request the correction of incorrect personal data concerning you (Articles 16 and 19).
- **A right to deletion**
You have the right to request the deletion of personal data concerning you. For example, if this data is no longer necessary for the purposes for which it was collected (Articles 17 and 19).
- **A right to restrict processing**
Under certain conditions, you have the right to request a processing limitation. In this case, your data may only be stored but not used for the processing, except with your consent (Articles 18 and 19).
- **A right to oppose processing**

You have the right to oppose to the processing of your personal data at any time (Article 21). Processing will then be stopped by the sponsor on the date on which you notify.
However, all data previously collected to the opposition, erasure request or limitation request may be processed if necessary.

These rights may be obtained from the physician who is treating you as part of the trial, and who is aware of your identity.

Your medical data collected for the study will be pseudonymized, i.e. you will be identified by a code number for the purposes of the research, with no mention of your full name. This data will be kept for 25 years by the trial sponsor.

Your participation in this research is voluntary and you are under no obligation to take part. This will in no way affect your relationship with the physician treating you or with the medical team. If, during the course of the trial, new information becomes available that could modify the interest of the trial, the physician in charge of the trial will inform you of this and will ensure that you wish to continue to take part.
You may stop participating in this protocol at any time. The investigating physician in charge of this trial may also decide to remove you from the trial if he or she deems it necessary, in particular for your well-being.
Your participation will not entail any additional costs for you.
Moreover, if you wish, you may be informed of the results obtained at the end of the trial.

Once you have read this information note, do not hesitate to ask your physician any questions you may have. After a period of reflection, if you agree to take part, you must complete and sign the consent form. A copy of the complete document will be given to you.

We thank you for your cooperation.

Further information about this clinical trial can be obtained from the physician who suggested you take part,

Dr/Pr _____
Adress _____
_____
_____
Téléphone : _____

Or

Medical coordinator Pr Emmanuel Besnier Département d'Anesthésie-Réanimation Hôpital Charles Nicolle CHU de Rouen 1, rue de Germont, 76031 ROUEN Cedex Tél. : 02 32 88 82 83, Fax : 02 32 88 83 26	**Sponsor** Hôpital Charles Nicolle - CHU de Rouen Direction à la Recherche Clinique et à l'Innovation Maison de la Recherche Clinique 1, rue de Germont, 76031 ROUEN Cedex

CONSENT FORM FOR
TO THE PATIENT TAKING PART IN THE TRIAL
OPIOID FREE ANESTHESIA IN CARDIAC SURGERY
OFACS TRIAL – 2019/0399/HP

Sponsor: CHU de Rouen
Medical coordinator: Pr Emmanuel BESNIER

I the undersigned _____ (Surname, first name) certify that I have read and understood the information note concerning the clinical trial entitled "Opioid-free anesthesia in cardiac surgery - OFACS trial".

I had the opportunity to ask any questions I felt would help me understand the information memorandum, and to receive clear, precise answers from Professor/Doctor _____, who also explained to me the nature, objectives, expected benefits, duration of the clinical trial and its follow-up, potential risks and constraints associated with my participation in this trial.

I understand that I am free to accept or refuse to participate in this trial.

I am aware of the possibility of interrupting my participation at any time without having to justify my decision. Naturally, this will not affect the quality of subsequent care I receive. I will then inform the investigator. I have been assured that the decisions that are necessary for my health will be taken at all times, in accordance with the current state of medical knowledge.

My consent does not relieve the investigator and the sponsor of the trial of their responsibilities towards me and I retain all my rights guaranteed by law.

I have been informed that this trial has been approved by an ethics committee (CPP OUEST II - ANGERS on 05/02/2021) and authorized by the ANSM on 09/03/2021, and has been declared to the National Committee for Information Technologies and Freedom (CNIL).

The sponsor of the trial, Rouen University Hospital, has taken out civil liability insurance in the event of damage.

I have been informed that the pseudonymized data recorded as part of this trial may be processed by or on behalf of the sponsor. I have noted that I have a right of access, information, opposition, rectification of personal data concerning me as well as a right to the limitation of processing as provided for by the CNIL (provisions of the Data Protection Act of January 6, 1978 as amended) and the European General Data Protection Regulation Act

The processing of data concerning me rests on a legal basis of a mission of public interest, so data already collected cannot be deleted. I am aware that my data will be kept for 25 years by the trial sponsor.

I may exercise these rights at any time by contacting the physician investigating my case and/or the trial sponsor, the entity responsible for data processing. I have noted that I have the right to lodge a complaint with the CNIL if I consider that the processing of my personal data has been carried out in violation of my rights. My personal data are confidential.

I am aware that the data recorded in the course of this trial may, under conditions ensuring confidentiality and a sufficient level of security, be transmitted to the French health authorities or to any other partner of the sponsor in France.

My attention has been drawn to the fact that the data recorded in the course of this trial may be used in subsequent research for scientific purposes only.

I have noted that my medical file will be consulted by the promoter's trial staff, who are bound by professional secrecy, and that the persons collaborating in this research or mandated by the sponsor, as well as any representative of the Health Authorities, may have access to the information in strictest confidence.

The overall results of the research will be communicated to me directly, on my request.

I may at any time request further information from the Professor/Doctor _____ (tel.: _____) who suggested that I take part in this trial.

Given sufficient time to consider my decision, I freely and voluntarily agree to take part in the OFACS trial and I do not object to the processing of my personal data.

The |__|__| |__|__| 2 0 |__|__|	The |__|__| |__|__| 2 0 |__|__|
Trial participant	**Physician**
Name and Surname Signature	Name and Surname Signature