Efficacy and Safety of Ciprofol for General Anesthesia in Transcatheter Aortic Valve Replacement: A Study Protocol for a Randomized Controlled Trial

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Abstract

**Background:** Patients who have gone through transcatheter aortic valve replacement (TAVR) and have experienced a decrease in physical and physiological capabilities are more likely to experience unfavorable cardiovascular reactions, including hypotension during induction of anesthesia. Due to the impaired cardiac function of these patients, maintaining hemodynamic stability during anesthesia induction can be challenging. Ciprofol, a novel anesthetic and a version of propofol, brings about a speedy onset, a brief recovery time, reduced injection pain, and consistent cardiorespiratory functioning. This study aims to investigate the effectiveness and safety of ciprofol in induction and maintaining general anesthesia in patients undergoing TAVR to establish its potential use in clinical practice.

**Methods:**

124 elderly patients aged 65–80 undergoing elective TAVR with general anesthesia will be randomly assigned to two parallel groups in this single-center trial. Patients will be randomly allocated to receive either ciprofol or propofol for induction. The primary outcome is the area under the baseline of the mean arterial pressure (MAP) over the first 15 minutes after induction. Hypotension will be identified as a decrease in MAP below 65 mmHg or more than 20% from the initial value during induction. Secondary outcomes include the incidence of adverse events, such as hypotension, bradycardia, nausea and vomiting, stroke, covert central nervous system injury, myocardial infarction, and acute kidney injury, as well as the cumulative doses of vasoactive drugs, the occurrence and intensity of injection pain, and ScO\(_2\) values less than 55% of the area under the curve (AUC).

**Discussion:** This study will provide valuable information on the effectiveness and safety of ciprofol as a general anesthetic for patients undergoing TAVR.

**Trial registration:** ClinicalTrials.gov (NCT05881291).

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers.
**Title**

Efficacy and Safety of Ciprofol for General Anesthesia in Transcatheter Aortic Valve Replacement: A Study Protocol for a Randomized Controlled Trial

**Trial registration (2a and 2b)**

ClinicalTrials.gov (NCT05881291)

**Protocol version (3)**

Protocol version 2.0

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Introduction

Background and rationale

Aortic stenosis (AS) is a common type of valvular heart illness that is linked to a high mortality rate among older adults [1]. Its prevalence among individuals aged 65 and above ranges from 2% to 7% [2]. Etiologically, calcification of the valves is the leading cause of AS [3]. This medical condition has a mortality rate of 50% within two years after the commencement of initial signs like angina, syncope, or heart failure [4]. Transcatheter aortic valve replacement (TAVR) has become a widely used, minimally invasive option for treating severe aortic stenosis (AS), as demonstrated by prior research [5]. TAVR has proven efficacy in reducing mortality and enhancing quality of life and functional status, especially for individuals with the highest surgical risk or advanced age or multiple comorbidities. Recently, the scope of treatment has expanded to include individuals who are classified as low- and intermediate-risk [6,7].

TAVR poses a challenge to anesthesiologists because many patients have a severe preexisting condition, making them high-risk [8]. According to prior reports, hypotension is a common side effect of general anesthesia induction, occurring in 53% of noncardiac surgeries [9]. For patients undergoing TAVR with declined physical and physiological function, careful anesthesia management is required to prevent hypotension after general anesthesia induction [10]. Furthermore, a brief drop in blood pressure can result in tissue hypoperfusion and its complications, leading to an elevated risk of postoperative morbidity and mortality [9,11–13]. Research has established that general anesthesia induction-related hypotension (GAIH) is a distinct factor in predicting adverse clinical results [11].

It has been determined that age, ASA physical status, preoperative hypertension, type II diabetes mellitus, and the utilization of propofol for induction are independent predictors of GAIH [14,15]. Propofol, commonly used for induction, has several drawbacks, including dilated blood vessels, decreased cardiac output, and a higher risk of hypotension in individuals over 50 [16,17]. The effects of propofol are more pronounced in older people, even with a reduced dosage of 1-1.5mg kg$^{-1}$ [18]. Ciprofol, an analog of propofol [19], offers a quick onset of effects, shortens the recovery time, reduces injection discomfort, and maintains stable cardiorespiratory function [20]. This makes it a potential substitute for TAVR. Consequently, it is expected that it will reduce the risk of GAIH.
This study aims to explore the effectiveness and safety of ciprofol in induction and maintenance general anesthesia in patients undergoing TAVR to establish its potential for use in clinical practice.

**Objectives (7)**

The primary outcome is the area under the baseline of MAP over the first 15 minutes after induction. Secondary outcomes include the incidence of adverse events, such as hypotension, bradycardia, nausea and vomiting, stroke, covert central nervous system injury, myocardial infarction, and acute kidney injury, as well as the cumulative doses of vasoactive drugs, the occurrence and intensity of injection pain, and ScO\textsubscript{2} values less than 55% of the area under the curve (AUC).

**Trial design (8)**

This single-site, two-arm, randomized, parallel-group clinical trial adheres to the SPIRIT checklist (S1 File). A flowchart of the trial is depicted in Fig. 1.

**Methods: participants, interventions and outcomes**

**Study setting (9)**

This study will be conducted at the Second Affiliated Hospital Zhejiang University School of Medicine in China.

**Eligibility criteria (10)**

**Inclusion criteria**

The following are the requirements for inclusion:

1. Those scheduled for elective TAVR undergoing general anesthesia required tracheal intubation.
2. Procedure time: 1–3 h.
3. Those aged 65 to 80 years.
4. 18 kg/m\textsuperscript{2} ≤ body mass index (BMI) ≤ 30 kg/m\textsuperscript{2}.
5. American Society of Anesthesiologists (ASA) classes to.

**Exclusion criteria**

The following are the criteria for exclusion:

1. Allergies to opioids, propofol, or ingredients in ciprofol have been experienced in the past.
2. History of difficult or expected difficult airway.
3. Previous neurological or psychiatric history: craniocerebral injury, convulsions, epilepsy, intracranial hypertension, cerebral aneurysms, cerebrovascular accidents, schizophrenia, bipolar disorder, long-
term use of psychotropic medications, and cognitive dysfunction.

4. Hemoglobin (HB) is less than 10.0 g/dL (100 g/L).

5. Regular use of antipsychotics or antidepressant drugs.

6. Due to severe dysfunction in the lung, kidney, liver, and heart, it is unsuitable for the study.

7. We will not survey if any other conditions deemed unsuitable exist.

**Withdrawal criteria**

Patients will be taken out of the study if they:

1. Suffer from serious negative consequences.

2. During the investigation, a severe complication or illness necessitates immediate action.

3. Withdraw informed consent.

**Who will take informed consent? {26a}**

Experienced clinicians with training will ask for informed permission from potential participants. If the potential participant meets the criteria and is willing to participate in the trial, they will sign and date the consent forms. Here, they will be provided with a thorough explanation of the purpose of the study and the details of the informed consent form.

**Additional consent provisions for collection and use of participant data and biological specimens {26b}**

No additional analyses have been proposed for participant data or biological specimens.

**Interventions**

**Explanation for the choice of comparators {6b}**

Ciprofol and propofol are both utilized in general anesthesia. However, the efficacy and safety of ciprofol, a novel anesthetic, during TAVR is yet to be determined. Therefore, we will compare the effects of ciprofol and propofol in induction and sustaining general anesthesia in patients undergoing TAVR.

**Intervention description {11a}**

Before surgery, all patients will be required to fast for 8 hours. Once they enter the operating room, electrocardiogram (ECG), noninvasive blood pressure (NIBP), cerebral oxygen saturation (ScO₂), peripheral oxygen saturation (SPO₂), and bispectral index (BIS) will be monitored. Two external defibrillator pads (Covidien adult defibrillation electrodes; Medtronic) will be positioned. Before the start, it is necessary to secure arteriovenous and central venous access catheters. Radial artery catheters will be inserted under local infiltration anesthesia with lidocaine, and the arterial sensor will continuously monitor arterial blood pressure. Because patients receiving a CoreValve have a higher risk of heart block, a temporary pacemaker is usually inserted through the internal jugular vein. After 3 minutes of
Preoxygenation, oxygen will be administered to the patient through a face mask at 6 L/min. Then, 0.2 mg/kg ciprofol or 1 mg/kg propofol will be administered for 30 s until the patient loses consciousness. When the eyelash reflex disappears and the BIS value is ≤60, 20–25 µg/kg alfentanil and 0.6 mg/kg rocuronium will be initiated. Intubation of the trachea shall be accomplished two minutes after the administration of rocuronium. Following that, a ventilator will provide mechanical ventilation, delivering a tidal volume of 6–8 mL/kg at a rate of 12–20 breaths/min, with a 1:2 inhalation-to-exhalation ratio, an oxygen flow of 2 L/min, and maintaining an end-expiratory PETCO2 level of 35–45 mmHg. Our DoCare system recorded mean arterial pressure (MAP) with a 30 s sampling period during the anesthetic procedure. The baseline MAP will be defined as the mean MAP during the 5-minute preceding induction.

At first, ciprofol is given at a speed of 0.8 mg kg\(^{-1}\)h\(^{-1}\), and the dosage is adjusted as needed (ranging from 0.25 to 0.5 mg kg\(^{-1}\)h\(^{-1}\) per time), with the maximum infusion rate being 1.5 mg kg\(^{-1}\)h\(^{-1}\). Propofol is given initially at 4.0 mg kg\(^{-1}\)h\(^{-1}\) adjusted as appropriate (1-2 mg kg\(^{-1}\)h\(^{-1}\) per time), with maximum allowed infusion rates of 7.0 mg kg\(^{-1}\)h\(^{-1}\). Alfentanil will be infused at a rate of 20–60 µg kg\(^{-1}\)h\(^{-1}\), with additional doses of 5–10 µg/kg allowed if needed. The administration of the experimental drug will be halted when the surgical procedures end. Rocuronium will be intermittently injected on an as-needed basis. In patients who did not experience complications during the surgery, sugammadex (IV, 2 mg/kg) or atropine (IV, 0.02 mg/kg) plus neostigmine (IV, 0.03 mg/kg) will then be administrated to reverse residual muscle relaxation at the end of surgery. The amount of crystalloids and colloids to be administered (including blood) will be determined by the preoperative hematocrit, intraoperative hemodynamics, and the quantity of blood lost. The patients will receive heparin during the operation to keep their activated clotting time at a minimum of 250 seconds, and protamine will be administered when the operation is finished to reverse the effects of heparin.

The INVOS 5100c surface pads (Covidien, Mansfield, MA) will be applied bilaterally on the forehead in order to monitor the ScO\(_2\) continuously, and the resultant values will undergo statistical analysis. The baseline values will be obtained before anesthesia induction and oxygen administration. The drug doses will be modified based on MAP, HR, and BIS values to keep the BIS value within the range of 40 to 60. To monitor cardiac index (CI), systemic vascular resistance index (SVRI), and stroke volume variation (SVV), the PULSION Medical Systems (Gothenburg, Vastra Gotaland, Sweden) will be utilized. Hemodynamic measurements will be taken at various points during the procedure, including the start, after induction, during rapid ventricular pacing, after the valve has been implanted, and when the process is finished.

Hypotension is diagnosed when the MAP is less than 65 mmHg or decreases by more than 20% from the initial value at the time of induction. A single intravenous injection of norepinephrine bolus of 5 µg is administered to treat intraoperative hypotension. A continuous norepinephrine infusion will be initiated if three or more bolus administrations are required. For heart rates below 50 beats/min, 0.5 mg of atropine is to be given.

Criteria for discontinuing or modifying allocated interventions (11b)
Participants may choose to leave the study without any repercussions at any point. However, the investigator can end a participant's involvement in the study in the event of an urgent medical situation. There is no need for criteria to be established for withdrawal from the study due to any risks.

**Strategies to improve adherence to interventions (11c)**

All sessions will be supervised by the study investigator, and the recordings will be included in an adherence note.

**Relevant concomitant care permitted or prohibited during the trial (11d)**

No regulations will be imposed on concomitant care during the trial.

**Provisions for post-trial care (30)**

Following the trial, all patients will resume their prior standard care.

**Outcomes (12)**

**Primary outcome**

Our primary endpoint is the area under the baseline MAP over the first 15 minutes after induction. During the initial 15 minutes post anesthesia induction, HR, SBP, DBP, and MAP will be monitored every 30 seconds and then at 5-minute intervals after that. The data will be included in the automatically generated anesthetic record, and the observer will record the number of boluses and total dosage of vasoactive medications given.

**Secondary outcomes**

The following are the secondary outcomes:

1. Frequency of hypotension within 15 min after induction of anesthesia.
2. The occurrence of bradycardia within 15 minutes after the start of anesthesia, with bradycardia being defined as a heart rate below 50 beats per minute.
3. The dosage of vasoactive drugs utilized during the initiation phase of general anesthesia and continued throughout the entire anesthesia process.
4. Incidence of reactions to tracheal intubation: If HR and/or MAP increase by 20% or more compared to the baseline, this should be taken as a positive indication of intubation.
5. Incidence and degree of injection pain are measured using a four-point graded scale: 0 = no pain; 1 = verbal complaint of pain; 2 = withdrawal of the arm; 3 = both verbal complaint and withdrawal of the arm.
6. Quality of life and recovery from illness (QoR-15) score (S2 File) on the first day after surgery.
7. The occurrence of nausea and vomiting after surgery.
8. The incidence of postoperative delirium. The CAM Chinese Reversion (CAM-CR) scale [21] will be used to detect postoperative delirium. The CAM-CR scale consists of 11 fundamental CAM items. Each item utilizes patients' symptoms to establish severity levels: 1 for absence, 2 for mild, 3 for moderate, and 4 for severe. To calculate the CAM-CR score, sum up the items and note that the score can range from 11 to 44. A patient with a score of 19 or below will not be diagnosed with delirium, while a score ranging from 20 to 22 suggests a possible presence of delirium, and a score exceeding 22 confirms the diagnosis of delirium.

9. Incidence of stroke and covert central nervous system (CNS) injury [22]:

(a) Ischaemic stroke

Symptoms that appear suddenly and follow a distinct pattern in single or multiple vascular areas of the brain, spinal cord, or retina are necessary to meet the criteria:

- Symptoms that persist for a period of 24 hours or until death, accompanied by evidence of CNS infarction on pathology or neuroimaging, and no other identifiable causes.
- Pathology or neuroimaging results confirm a CNS infarction in the relevant vascular region, with symptoms persisting for less than 24 hours.

(b) Hemorrhagic stroke

The onset of neurological problems or symptoms caused by bleeding within the brain or in the space surrounding it, unrelated to any injury, is known as a hemorrhagic stroke.

(c) Covert CNS injury

Evidence of CNS focal or multifocal ischemia or hemorrhage on neuroimaging or pathology may be seen without acute neurological symptoms that match the location of the lesion or bleeding in this particular situation.

10. Incidence of postoperative myocardial infarction [22]:

(a) In patients with normal baseline creatine kinase-MB (CK-MB)

If the peak CK-MB measured within 48 hours of the procedure is ≥10 times the local laboratory upper limit of normal (ULN) or ≥5 ULN, along with one or more of the following,

- New pathologic Q-waves are present in at least two contiguous leads.
- A new LBBB has been identified.
- Angiographic complications that limit blood flow in a major epicardial vessel or in a branch with a diameter of more than 1.5 mm.
- Imaging has revealed a considerable amount of viable myocardium that has been lost due to the procedure.
(b) In the absence of CK-MB measurements and an average baseline cardiac troponin (cTn)

The cTn (I or T) level measured within 48 h of the procedure rises to ≥70 the local laboratory ULN or ≥35 ULN with one or more of the following:

- New pathologic Q-waves are present in at least two contiguous leads.
- A new LBBB has been identified.
- Angiographic complications that limit blood flow in a major epicardial vessel or in a branch with a diameter of more than 1.5 mm.
- Imaging has revealed a considerable amount of viable myocardium that has been lost due to the procedure.

(c) In patients with elevated baseline CK-MB (or cTn)

The CK-MB (or cTn) should increase from its most recent preprocedure level by the recommended amount and any new ECG changes.

11. Incidence of acute kidney injury (AKI). Following the Clinical Practice Guideline [23] from Kidney Disease Improving Global Outcomes (KDIGO), the classification and grading of AKI will be performed. As per the guideline, AKI is characterized by any of the following criteria:

- Stage 1: An increase in serum creatinine of ≥1.5-2.0 within seven days compared with baseline and an increase of ≥26.4 mmol/L within 48 hours of the index procedure.
- Stage 2: An increase in serum creatinine of >2.0-3.0 within seven days compared to baseline.
- Stage 3: An increase in serum creatinine of >3.0 within seven days compared with baseline or serum creatinine of ≥354 mmol/L with an acute increase of ≥44 mmol/L.
- Stage 4: AKI that necessitates the use of either temporary or permanent renal replacement therapy.

12. A comparison of two groups with ScO₂ values less than 55% of the area under the curve (AUC).

13. Variations in inflammatory factor levels have occurred before and after surgery: IL-6, TNF-α, systemic immune inflammation index (SII), and platelet count (neutrophil /lymphocyte count).

Participant timeline (13)

The schedule of trial enrollment, allocation, interventions, and assessments is shown in Table 1.

Sample size (14)

The primary objective of this experiment is to measure the area of the MAP baseline curve within 15 min of general anesthesia induction. Previous clinical studies demonstrate that propofol's mean (standard deviation) is −10706.429 (6877.0052). Anesthesia experts agreed that a 33% difference in MAP baseline curve area between the two groups within 15 min of induction is clinically relevant. This must be
statistically significant at a confidence level of 0.05 with an 80% confidence interval. To account for a 5% dropout rate, 124 subjects are required, with 62 in the group receiving a propofol injection and 62 in the group receiving a propofol injection.

Recruitment (15)

Recruitment for the study will be carried out among the inpatients of the Second Affiliated Hospital Zhejiang University School of Medicine, beginning in June 2023 and concluding in June 2024.

Assignment of interventions: allocation

Sequence generation (16a)

An independent investigator will use a computer-generated random number sequence to allocate qualified participants to either the test drug group (ciprofol) or the control group (propofol) in a 1:1 ratio.

Concealment mechanism (16b)

The allocation information will be kept secret through numbered, opaque-sealed envelopes. The envelopes will be stored securely throughout the study and opened by the researchers when the participant arrives in the operating room.

Implementation (16c)

The attending anesthesiologists will receive sequentially numbered opaque envelopes on the day of the surgery, which have been generated per the randomization schedule.

Assignment of interventions: blinding

Who will be blinded (17a)

This study is single-blinded, with only the patients unaware of the details. Conversely, the dosage adjustment between propofol and ciprofol during treatment makes it hard to blind the researchers. However, investigators assessing outcomes and analyzing data will not know which group was assigned what. Researchers not blinded to the study will participate in the drug's allocation, preparation, and administration but not in evaluating the outcomes.

Procedure for unblinding if needed (17b)

The attending anesthesiologists administering study drugs during induction cannot be blinded to ensure the safety of the patients.

Data collection and management

Plans for assessment and collection of outcomes (18a)
During this study, researchers who have received training in obtaining and evaluating outcomes before the research will record all collected information in the appropriate patient case report form (CRF) while maintaining objectivity. This information will remain undisclosed to the public. If a patient withdraws from the study, the reasons for doing so will be noted and the dropout rate will be calculated.

**Baseline features of patients**

Following approval, a researcher working autonomously will gather initial data the day before the operation. All personal information will remain private and will only be used for research. Demographic data will be gathered the day prior to surgery, including gender, age, vital signs, BMI, medical history, family history, smoking and drinking habits, allergies, prior operations and anesthesia, and medications. Additionally, ASA classification, Society of Thoracic Surgeons (STS) risk score, Mini-Mental State Examination (MMSE), and New York Heart Association (NYHA) Functional Classification will be assessed. Tests such as ECG, cardiac computed tomography angiography (CTA), echocardiography, and diffusion-weighted magnetic resonance imaging (DW-MRI) will also be conducted. Lastly, the most recent laboratory values, including hemoglobin (HB), creatinine, serum albumin, blood urea nitrogen (BUN), CK-MB, cardiac troponin T (cTnT), N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), and interleukin 6 (IL-6) will be evaluated.

**Assessment of the patient during and after anesthesia.**

During anesthesia, the following will be monitored: vital sign parameters, total dose or infusion rate of anesthetic agents, vasoactive drugs, ScO$_2$, BIS, CI, SVRI, estimated blood loss, urine volume, type and dose of fluids and blood transfusions, duration of surgery and anesthesia, valve type, pre- and post-dilatation times, and contrast dose. The postoperative laboratory, imaging, and electrocardiogram examination results will be preserved. Postoperative vitals, including CAM-CR score and QoR-15, will also be recorded.

**Plans to promote participant retention and complete follow-up {18b}**

The preoperative visit will include a full explanation of the intraoperative procedure and postoperative care. The researchers in charge of follow-up will track patients one day after the operation.

**Data management {19}**

A paper-based questionnaire will be used to collect data, which will remain anonymous. The Second Affiliated Hospital Zhejiang University School of Medicine will securely store the information recorded on paper forms in accordance with data protection procedures. To avoid data entry mistakes, a fixed dual researcher will enter the data and manually review it. The data will be saved in Microsoft Excel spreadsheets.

**Confidentiality {27}**
For the purpose of preserving personal information and contacts, a unique alpha-numeric ID will be given to each patient in order to guarantee privacy.

**Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use (33)**

No biological samples will be taken for this research.

**Statistical methods**

**Statistical methods for primary and secondary outcomes (20a)**

All participants who have been administered the trial/control drug and have had their results documented will be included in the full analysis set (FAS). Conversely, the per-protocol set (PPS) consists of all those who follow the protocol to the letter. Then, efficacy will be analyzed based on FAS and PPS. All participants enrolled in the trial and administered the trial/control drug are included in the safety analysis set.

All analyses will be conducted using SAS EG statistical analysis software, with a version of 8.3 or higher. Continuous variables are represented by means (standard deviations), while categorical variables are described using frequencies and percentages. A $t$-test or non-parametric test will be employed to compare the baseline area of MAP in each group within 15 min after general anesthesia induction. Using the trapezoidal area method, it is necessary to determine the baseline area of MAP for each subject within the first 15 min of administering general anesthesia. The formula for this calculation is provided below:

$$
\sum \left( (S_i - MAP_{baseline}) + (S_{i-1} - MAP_{baseline}) \right) / 2 \times \Delta X
$$

The mean MAP at each i-th minute (i=1,..., 15) is represented by $S_i$, and $\Delta X$ symbolizes the difference in the number of adjacent time seconds. The ANCOVA model will be employed to evaluate the MAP baseline area within 15 min of general anesthesia induction, with the treatment group serving as the fixed effect and the MAP baseline value functioning as the covariate. The adjusted least squares mean, and standard error of each group's change values will be calculated, and the disparity in MAP baseline area between the ciprofol group and the propofol group will be established, along with their 95% confidence interval and associated p-value.

The chi-square test or Fisher's exact test probability method will be used to determine the differences between the two groups in terms of the incidence of hypotension, bradycardia, injection pain, nausea and vomiting, tracheal intubation response rate, postoperative delirium rate, stroke, and occult stroke incidence rate, myocardial infarction incidence rate, AKI incidence rate, and ScO2 below 55% absolute value incidence rate.

**Interim analyses (21b)**
No interim analyses are planned for this study.

**Methods for additional analyses (e.g., subgroup analyses) (20b)**

This study will not include any subgroup analyses.

**Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data (20c)**

Statistical analysis will not include any imputation of missing data.

**Plans to give access to the full protocol, participant-level data and statistical code (31c)**

Upon request, the corresponding author can supply the study protocol and data analysis.

**Oversight and monitoring**

**Composition of the coordinating center and trial steering committee (5d)**

The study research team will be responsible for conducting the trial. The principal investigator is in charge of supervising the trial and making sure that it adheres to the study protocol.

**Composition of the data monitoring committee, its role, and reporting structure (21a)**

The principal investigator will conduct regular reviews of the data and trial progress every three weeks; this study has no data monitoring committee.

**Adverse event reporting and harms (22)**

Assessing safety during anesthesia will involve tracking vital signs and noting any adverse events (AEs) or serious adverse events (SAEs). Any undesirable medical event for a patient, regardless of its connection to the research protocol, is referred to as an adverse event. Further information on evaluating and reporting AEs and SAEs can be found in the S3 File.

**Frequency and plans for auditing trial conduct (23)**

Annually, the research office and ethics committee of the department will audit the study, while the principal investigator will assess the accuracy of the data and the trial's progression every three weeks.

**Plans for communicating important protocol amendments to relevant parties (e.g., trail participants, ethical committees) (25)**

The principal investigator is in charge of any protocol modifications and their implementation. The necessary modifications must be approved by the ethics committee before they can be applied. The principal investigator is responsible for communicating the changes to the protocol and ensuring that all study personnel are properly trained in regard to the amendments.
Dissemination plans

All participants will be required to give written consent before any protocol-specified procedures or assessments are conducted. The findings of the study will be shared at relevant conferences and published in international peer-reviewed journals.

Discussion

Between 4.2 and 5.6 million adults in the US have a clinically significant form of valve disease [24], with the number of individuals aged 65 and older in 2010 being 40 million. However, this number is expected to increase to 55 million by 2020 and 72 million by 2030 [25]. Patients with cardiac dysfunction may experience varying degrees of severity, and anesthetics can reduce the activity of the heart muscle and cause vasodilation, making them susceptible to hypotension during anesthesia induction [26]. Persistent MAP below 80 mmHg for more than 10 minutes or MAP below 70 mmHg for a shorter period slightly increases the chance of end-organ damage [27]. Research demonstrated that MAP below 55 mmHg can lead to cardiac complications and AKI [28]. Intraoperative hypotension with MAP below 55 mmHg in geriatric patients is a risk factor for delirium [29], resulting in decreased activities of daily living and postoperative mortality [30]. When selecting anesthetics, anesthesiologists should evaluate their effectiveness and safety in light of the significance and impact of hemodynamic changes on complications and prognosis.

Propofol, which is commonly used in clinical settings, has the advantage of rapid induction and recovery. Nonetheless, it has a strong effect on the myocardium, causing a drop in blood pressure and significant changes in circulation [31]. Moreover, it has a notable injection pain [32]. Etomidate, a hypnotic agent used for anesthesia induction, has been traditionally viewed to be superior to propofol [33]. However, etomidate can cause various adverse effects, including inhibition of adrenal cortical function, nausea and vomiting, injection pain, and myoclonic movement [34,35]. Thus, anesthetic agents with quick onset, short recovery time, and a stable cardiovascular profile are required.

Ciprofol is a novel sedative/anesthetic and an analog of propofol [19]. Its rapid onset and recovery, high potency, and low injection pain make it a safe drug for those with preoperative hemodynamic instability [36]. A study that was recently conducted on 90 elderly patients undergoing major noncardiac surgery revealed that general anesthesia can be induced with no Serious Adverse Events (SAEs) when ciprofol 0.2–0.4 mg kg$^{-1}$ is administered [37]. Furthermore, according to K. Qin et al. [38], ciprofol is a safe and effective anesthetic for kidney transplantation, with a more sedative effect than propofol. Given the advantages of ciprofol, it could be a more suitable choice for the induction and maintenance of anesthesia for TAVR.

This study is the first to compare the hemodynamic effects of ciprofol and propofol during anesthesia induction in patients undergoing TAVR. Thus, the study aims to compare the efficacy and safety of
Ciprofol for the induction and maintenance of general anesthesia in patients undergoing TAVR to provide new clinical practice data.

**Limitations**

This study has several limitations, as follows. First, ethical considerations have excluded those requiring more meticulous hemodynamic stabilization. Second, to avoid any bias and ensure the safety of the patients, those with a BMI greater than 30 have been excluded from the study.

**Trial status**

The current protocol is version 2.0 and was issued on April 12, 2023. Participants for this study were first recruited on June 30, 2023, and the recruitment process is projected to finish by June 2024.
Table 1
Schedule of patient enrolment, study interventions and outcome assessment

<table>
<thead>
<tr>
<th>Study period</th>
<th>Time point</th>
<th>Enrollment</th>
<th>Allocation</th>
<th>Intervention</th>
<th>POD1</th>
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<td></td>
<td>Preoperative visit</td>
<td>Allocation</td>
<td>During induction until 15 min after induction</td>
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</tbody>
</table>

**Enrollment**

- Eligibility screen X
- Informed consent X
- Demographic data X
- MMSE X

**Allocation**

<table>
<thead>
<tr>
<th>Study period</th>
<th>Time point</th>
<th>Enrollment</th>
<th>Allocation</th>
<th>Intervention</th>
<th>POD1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Preoperative visit</td>
<td>Allocation</td>
<td>During induction until 15 min after induction</td>
<td></td>
</tr>
</tbody>
</table>

**Interventions**

- Propofol X
- Ciprofol X
- Surgery and anesthesia date X

**Assessments**

- BIS/ScO$_2$ X
- SBP/DBP/MAP X
- HR/CI/SVRI/SVV X
- CAM-CR X
- QoR-15 X

**Abbreviations**

- **AS**: Aortic stenosis
- **TAVR**: Transcatheter aortic valve replacement

**MMSE**: Mini-Mental State Examination; **POD**: postoperative day; **BIS**: bispectral index; **ScO$_2$**: cerebral oxygen saturation; **SBP**: systolic blood pressure; **DBP**: diastolic blood pressure; **MAP**: mean blood pressure; **HR**: heart rate; **CI**: cardiac index; **SVRI**: systemic vascular resistance index; **SVV**: Stroke volume variation; **CAM-CR**: the CAM Chinese Reversion; **QoR-15**: Quality of Recovery-15.
Transcatheter aortic valve replacement

BMI
Body mass index

HB
Hemoglobin

ECG
Electrocardiogram

NIBP
Noninvasive blood pressure

ScO$_2$
Cerebral oxygen saturation

SPO$_2$
Peripheral oxygen saturation

BIS
Bispectral index

MAP
Mean arterial pressure

PETCO$_2$
End expiratory carbon dioxide partial pressure

CI
Cardiac index

SVRI
Systemic vascular resistance index

SVV
Stroke volume variation

RVP
Rapid ventricular pacing

QoR-15
Quality of life and recovery from illness

CAM-CR
CAM Chinese Reversion

CNS
Central nervous system

CK-MB
Creatine Kinase-MB

LBBB
Left bundle branch block

cTn
Cardiac troponin

AKI
Acute kidney injury

AUC
Area under the curve

SII
Systemic immune inflammation index

MMSE
Minimental state examination

CTA
Cardiac computed tomography angiography

DW-MRI
Diffusion-weighted magnetic resonance imaging

NT-pro-BNP
N-terminal pro-B-type natriuretic peptide

IL-6
Interleukin 6

AEs
Adverse events

SAEs
serious adverse events

POD
Postoperative day.

Declarations

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Authors’ contributions

MY, TTN, SGW, TL, YYY, GL, QG, and TTW designed the study and provided input for the study’s structure and statistical analysis. TTN drafted the protocol. All authors read and approved the final protocol.

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Availability of data and materials

If necessary, the corresponding author can be contacted for further information or data.

Ethics approval and consent to participate

The Ethics Committee of the Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China, approved the study protocol (reference number 20230371) on April 12, 2023. Written informed consent must be obtained from each patient before being enrolled in the trial. The trial is registered on clinicaltrials.gov (NCT 05881291).

Consent for publication

All authors have read the final manuscript, approved it, and have given their consent for the publication of the protocol paper.

Competing interests

The authors declare no competing interests.

References


**Figures**

**Figure 1**

Flow diagram outlining the enrollment and randomization study procedures.

**Supplementary Files**

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