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ORIGINAL RESEARCH

Remote ischemic preconditioning in non-cardiac surgery (PRINCE): a multinational, double blind, sham-controlled, randomized clinical trial

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Abstract

Remote ischemic preconditioning (RIPC) is a clinical procedure aimed at inducing myocardial protection by causing brief ischemia-reperfusion episodes in an organ remote from the heart. We aim to assess whether RIPC provides myocardial protection in patients undergoing non-cardiac surgery. This study, called remote ischemic PReconditioning In Non-Cardiac surgEry (PRINCE), is a double-blind, multinational randomized clinical trial (1:1 allocation ratio) which plans to enroll 1100 patients. The intervention arm will receive RIPC at the beginning of surgery by inflating a blood pressure cuff around a limb for three cycles of ten minutes (inflated cuff for five minutes followed by deflated cuff for five minutes). In the control group, a blood pressure cuff will be put on a limb, and a sham inflation will be performed. Given a potential interaction of propofol with RIPC, induction and maintenance of anesthesia will be performed without propofol. The primary endpoint of the study is to document a significant reduction in postoperative cardiac troponin values among patients receiving RIPC. Secondary endpoints will be cardiac ischemic events at 30 days and 1 year, mortality at 30 days and 1 year, neurologic events at 30 days and 1 year, acute kidney injury at 7 days, need for intensive care unit admission and length of hospital stay. The trial will provide evidence for the effects of RIPC on cardioprotection and other relevant outcomes in high-cardiac risk patients undergoing non-cardiac surgery. Clinical Trial Registration: NCT02427867.

Keywords

Remote ischemic preconditioning; Non-cardiac surgery; Cardioprotection

1. Introduction

Each year millions of non-cardiac surgical procedures are performed all over the world [1]. Unfortunately, perioperative major cardiovascular events (MACE) still occur frequently and negatively affect long-term survival and quality of life [2–4]. Remote ischemic preconditioning (RIPC) is a clinical procedure aimed at inducing myocardial protection from ischemia-reperfusion injury by causing brief ischemia-reperfusion episodes in an organ or vascular territory remote from the heart before an anticipated myocardial ischemic insult [5].

In translating RIPC from bench to bedside, initial proof of principle and small randomized controlled trials (RCTs) showed a decrease in myocardial biomarkers release following various types of cardiac surgery [6–10]. This reduction in cardiac biomarkers release has been linked to improved survival, as seen in a randomized trial conducted on patients undergoing elective percutaneous coronary intervention [11]. A single center RCT by Thielmann and colleagues [12] also suggested that myocardial protection by RIPC might reduce short-term postoperative mortality after coronary artery bypass graft (CABG). Notably, the beneficial effects of RIPC were observed not only immediately but also long term, as evidenced by a reduced incidence of stroke.

However, no multicenter RCT with adequate power has been conducted to evaluate the cardioprotective role of RIPC in patients scheduled for non-cardiac surgery and with a high preoperative cardiovascular risk. Considering the annual number of non-cardiac surgeries performed worldwide [13], even a modest reduction in the incidence of perioperative MACE may have a considerable impact on the global healthcare system. Accordingly, we designed the remote ischemic PReconditioning In Non-Cardiac surgEry (PRINCE) multinational RCT to assess whether RIPC may reduce postoperative cardiac damage evidenced by the release of troponin in non-cardiac surgery patients at high risk for MACE.

2. Material and methods

2.1 Study design

This is a multinational, randomized, sham-controlled, double-blinded trial with a 1:1 allocation ratio. The study is funded by the Italian Ministry of Health (GR-2016-02363852), registered on clinicaltrials.gov as NCT02427867. The Human Research Ethics Committee of all the participating centers approved the study (Fig. 1).

2.2 Study aim

The aim of our study is to test the hypothesis that RIPC reduces cardiac damage defined by post-operative troponin plasma level in high-risk patients undergoing non-cardiac surgery.

2.3 Participants

We plan to enroll high-risk adult patients scheduled for non-cardiac surgery under general anesthesia. Specifically, age $>$50 years, intermediate- or high-risk non-cardiac surgical procedures under general anesthesia and oral antiplatelet therapy will be considered as inclusion criteria. Instead, exclusion criteria will incorporate unstable or ongoing angina, recent acute myocardial infarction ($<$1 month), peripheral vascular disease affecting upper limbs and cardiac surgery.

Table 1 details the inclusion and exclusion criteria for the study.

2.4 Randomization, allocation, and concealment

To allocate subjects and minimize assignment biases, all eligible patients will be randomly assigned at the last feasible moment with a 1:1 allocation according to web-based, computer generated, permuted-block sequences, center-stratified randomization list, to receive either RIPC or a sham on top of the available standard of care. Randomization will be conducted by study personnel who are not involved in manage-

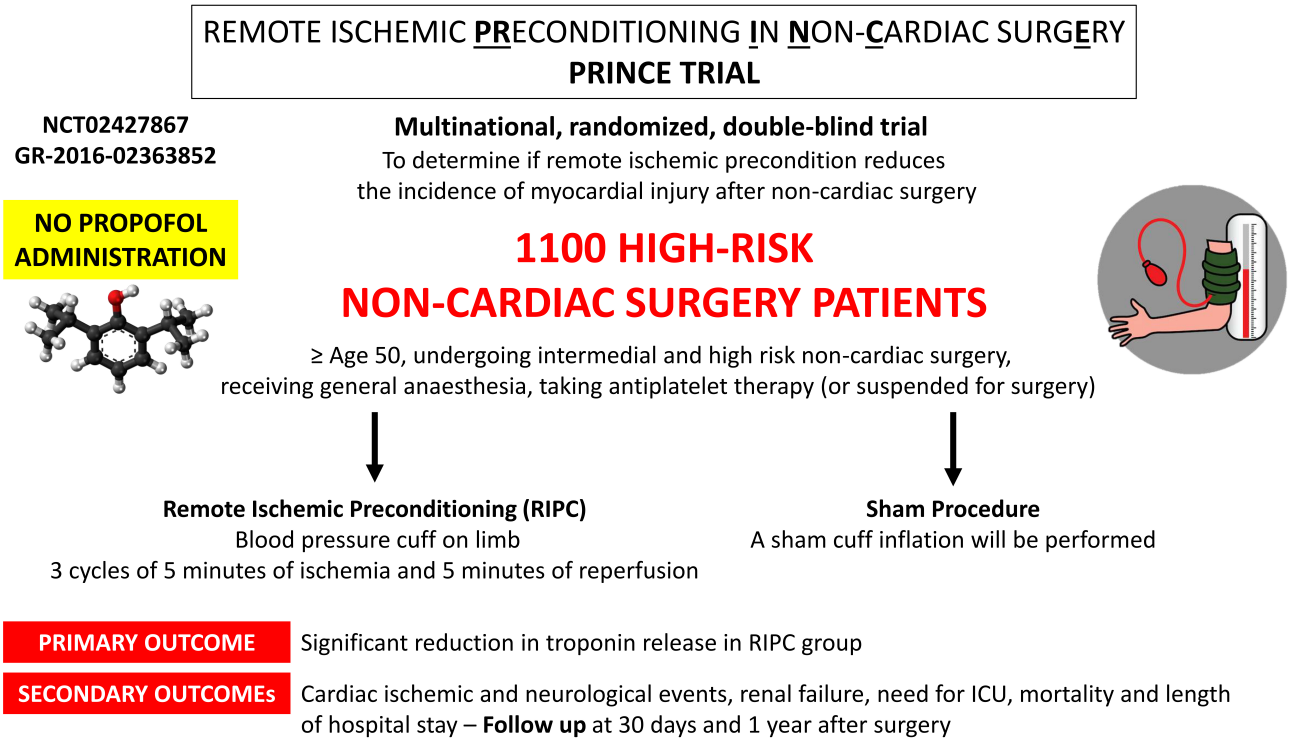

FIGURE 1. Visual abstract. ICU: intensive care unit.

TABLE 1. Inclusion and exclusion criteria.

Inclusion and exclusion criteria
Inclusion Criteria (before randomization, all the criteria must be satisfied)
1. Age >50 years;
2. Intermediate- and high-risk non-cardiac surgery according to 2002 ACC/AHA guidelines [14];
3. Planned to perform an elective general anesthesia;
4. On antiplatelet therapy even if withheld for surgery.
Exclusion Criteria (the patient will be excluded in presence of, at least, one of the following exclusion criteria)
1. Ongoing pregnancy;
2. Planned loco-regional anesthesia with no general anesthesia;
3. Unstable or ongoing angina;
4. Recent (<1 month) acute myocardial infarction;
5. Inclusion in other RCTs within the previous 30 days;
6. Peripheral vascular disease affecting the upper limbs;
7. Cardiac surgery.

ACC: American College of Cardiology; AHA: American Heart Association; RCTs: randomized controlled studies. Cardiac risk stratification for non-cardiac surgical procedures according to the 2002 ACC/AHA guidelines is reported on the ***Supplementary material****.*

ment of operative theatre. As soon as the patient is randomized, study personnel not involved in data sampling will receive an e-mail containing the group allocation details. Patients will be unaware of their group allocation, as they are under general anesthesia at the time. Throughout the trial, study investigators will remain blinded to group allocation. Attending anesthesiologists and operative theatre nurses will not be aware of group allocation, with the notable exception of emergency situations and safety issues, and they will not be involved in any step of data management. In each center, one individual responsible for performing the RIPC procedure will be identified. The unblinded individual will place the blood pressure cuff prior to the induction of general anesthesia. During the procedure, the unblinded staff member will inflate the cuff in all cases. In the control arm, the release valve will remain open, creating a sham procedure. In this way, the operating room staff will not know whether the patient has undergone the RIPC procedure or not. Data collection will be performed by trained personnel

blinded to group allocation.

2.5 Interventions

Patients will be randomized to undergo either RIPC or a sham procedure. A blood pressure cuff will be positioned on a lower or upper limb of each patient. For those in the experimental arm, RIPC will commence immediately after the induction of general anesthesia. This involves three cycles of ischemia, each lasting 5 minutes, achieved by inflating the blood-pressure cuff to 200 mmHg, followed by a 5-minute reperfusion with the cuff deflated. For those patients in the control group, the cuff will be placed around the arm, and a sham cuff inflation will be performed at 0 mmHg pressure following the same time points.

Induction and maintenance of general anesthesia will be performed without the use of propofol in both groups, in line with previous studies suggesting that propofol may interfere with the molecular mechanisms associated with RIPC-induced organ protection [15–18].

All other details of general anesthesia will be at the discretion of the attending anesthesiologist according to local routine practices. Even though no risks to study subjects are expected, the study procedures may be suspended by an attending anesthesiologist if clinically indicated.

2.6 Data collection

The data described below will be recorded at the time of randomization. In cases where multiple measurements are available, the one closest in time to the randomization will be considered.

We will collect data on administrative and demographic data, weight, height, medical history (chronic disease), American Society of Anesthesiologists classification [19], New York Heart Association classification [20] chronic pharmacologic therapy, type of surgery and its urgency level, anesthesia data encompassing drugs used for induction and management.

At 30 days and at 1 year after randomization, follow-up interviews will be performed and will focus on hospital readmissions and survival.

2.7 Outcomes

Data will be collected intraoperatively, throughout the entire postoperative period, at hospital discharge, and then at 30 days and at 1 year after randomization.

The study primary endpoint is to document a reduction in postoperative myocardial injury in patients receiving RIPC when compared with patients not receiving this strategy. Myocardial injury will be considered present when blood levels of cardiac Tn (either T or I) are increased above the 99th percentile upper reference limit [21–23].

Postoperative Troponin increase is associated with a 10% risk of death within 30 days after surgery with most patients (84%) not exhibiting or reporting any symptoms indicative of ischemia [2, 24]. Furthermore, a retrospective cohort study of 750 patients undergoing major non-cardiac surgery indicated a dose response relationship between the post-operative value of cardiac troponin and the incidence of 6-month mortality [25].

Additional tests will be performed as required tailored to the clinical needs of each patient and in accordance with international guidelines and local routine practices.

Secondary Outcomes Measures:

- Myocardial infarction within 30 days from randomization [26];
- Stroke within 30 days from randomization [26–28];
- Acute Kidney Injury according to the Kidney Disease Improving Global Outcomes (KDIGO) classification within 7 days from randomization [2, 29];
- Need for intensive care unit [28];
- Length of hospital stay [28];
- All-cause mortality at 30 days.

Although the incidence of peri-operative stroke in patients undergoing non-cardiac, non-neurologic surgery is low (0.1–1%), this clinical condition is a leading cause of disability, with a devastating social and economic impact [30]. Otherwise, acute kidney injury can occur in this surgical setting with an incidence that can range between 2% and 29%, according to the type of surgery and the pre-operative value of creatinine [31]. Preliminary results coming from trials performed in non-cardiac surgical settings showed a possible beneficial effect of RIPC on neuroprotection and reduction in the incidence of acute kidney injury [32].

Secondary Outcomes Measures at 1 year (which will be reported in a separated manuscript):

- Cardiac ischemic events within 1 year from randomization [26];
- Stroke within 1 year from randomization [26–28];
- All-cause mortality at 1 year.

The complete participant flowchart is shown in Fig. 2.

The complete KDIGO classification is reported in the **Supplementary material**.

2.8 Sample size

The study primary endpoint is to document a reduction in post-operative myocardial injury in patients receiving RIPC when compared with patients not receiving this strategy. Myocardial injury is defined as being present when blood levels of cardiac Tn (either T or I) are increased above the 99th percentile upper reference limit [21].

Sample size calculation is based on the rate of patients with post-operative cardiac troponin increase above the 99th percentile upper reference limit. We expect to observe a significant reduction in the number of patients with elevated postoperative cardiac troponin values among patients receiving RIPC. Previously published literature reported an increase in post-operative cardiac troponin in 22% of subjects undergoing non-cardiac surgery [33, 34]. In agreement with previous studies which documented a protective effect of RIPC on cardiac troponin release [27, 35, 36], we expect to observe that in the RIPC group the post-operative cardiac troponin will be increased in 15% of subjects and that this is clinically relevant. Sample-size calculation is based on a two-sided alpha error of 0.05 and 80% power, with continuity correction and a two-tails test, 546 subjects per group will be necessary with a total of 1.092 patients. According to these data, the number of patients planned for our study will be 1100 patients (accounting for the

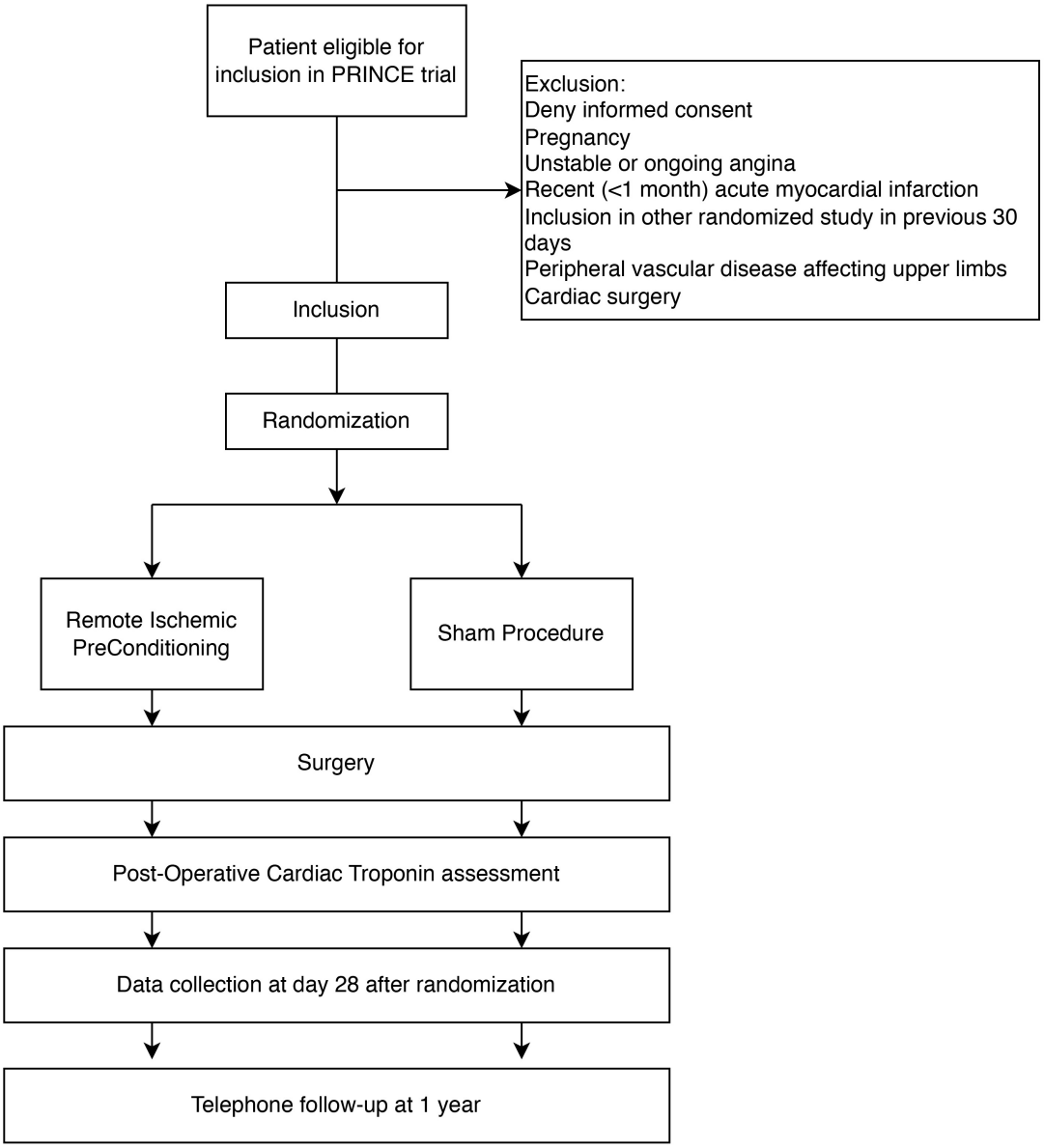

FIGURE 2. Study flowchart. PRINCE: remote ischemic preconditioning in non-cardiac surgery.

planned ad-interim analysis and possible protocol deviations). Sample size was performed with the group sequential design command for a two-sample proportion test using Pearson's chi-square test of STATA (Stata Statistical Software, version 18, College Station, TX, USA).

2.9 Statistical plan

Primary data analysis will adhere to an intention-to-treat (ITT) approach. Additionally, a per-protocol analysis will be performed which will exclude those patients who: (A) did not receive the assigned study procedure or; (B) were later found not to meet the inclusion/exclusion criteria. Statistical analyses will be carried out by an independent statistician who is blinded to group allocation. A web-based case report form will store data which will be analyzed using STATA (Stata Statistical Software, version 18, College Station, TX, USA) without applying imputation for missing data. Baseline and demographic disease characteristics will be summarized using descriptive statistics. We will report categorical variables as absolute numbers and percentages. To compare the two treatment groups, we will use unadjusted univariate analyses utilizing the Fisher exact test or Chi-squares appropriate. Relative risks and 95% confidence intervals will be calculated using the two-by-two table method. Continuous variables will be reported as median and interquartile range (IQR) or mean $\pm$ standard deviation (SD) depending on data distribution. In our study between-group differences will be evaluated using the Wilcoxon signed rank test or the *t* test of Student, in accordance with the Shapiro-Wilk normality test. Logistic regression models, adjusted for baseline values, will be used to estimate the treatment effect (and its 95% confidence intervals) with respect to primary endpoints. Treatment assignment will be forced into the regression model. Statistical significance will be set at the two tailed 0.05 level for hypothesis testing.

An independent safety committee, composed by clinical scientists and epidemiologists, will conduct one ad-interim analyses at 50% (n = 550) of enrolled patients to test for the difference in the primary outcome rates between study groups,

to check for potential safety issues as well as assess early efficacy. The efficacy stopping rule would require a low p value ($p < 0.0031$). All research team will be blinded to the interim analysis results. Data evaluation at the interim analysis will be based on the alpha spending function concept, according to Lan and De Mets' and will employ O'Brien-Fleming Z-test boundaries [37], which are very conservative early in the trial. The study will be stopped for efficacy ($p < 0.0031$ after enrolling 50% of patients).

Planned subgroup analyses will be performed according to the type of surgery (vascular surgery, cancer patients), the site of cuff inflation (upper or lower limb), cardiac comorbidities (myocardial infarction and atrial fibrillation), previous neurologic events and hypnotic drugs used for anesthesia induction.

2.10 Monitoring

Independent monitor verifies adherence to data collection and trial procedures, according to the trial protocol and the Good Clinical Practice (GCP) guidelines. Prior to the Covid-19 pandemic, this monitoring was conducted on-site. However, due to the pandemic, the monitoring process has been adapted to a remote format.

2.11 Ethical considerations

There are no major ethical issues concerning the handling of trial data. All the data will be stored in an electronic database with strict anonymity. Each patient will be assigned a unique numeric code, ensuring complete anonymization of their data.

2.12 Study initiation, timing, participating centers

All participating centers obtained Ethical Committee approval before study initiation. We did not set an a priori limit on the number of centers participating in the study.

2.13 Trial status

The trial is ongoing. We expect to complete the recruitment by October 2024. We regularly provide updates about the trial via the department account: @SRAnesthesiaICU.

3. Discussion

In 1986, Murry described the beneficial effects of ischemic preconditioning in an animal experimental model. Multiple anginal episodes before myocardial infarction reduced myocardial cell death after coronary occlusion [38]. Subsequent scientific evidence suggested that cycles of ischemia/reperfusion of non-vital tissues (*e.g.*, limbs) could condition also distal tissues, reducing the negative effects of stressful stimuli such as surgery [4]. Specifically, in cardiac surgery, several RCTs have demonstrated that RIPC is linked to improved prognosis, perioperative myocardial protection, and a significant reduction in the incidence of acute kidney injury and the need for renal replacement therapy [12, 39].

These promising results were confirmed in a subsequent meta-analysis, including 55 RCTs [40]. Surprisingly, in 2015 two large RCTs, enrolling overall more than 3000 patients who underwent heart surgery, found no clinical advantages associated with RIPC [41, 42]. Such neutral results might have been ascribed to the propofol-based anesthetic regimen. Citing the editorial by Rossaint, we could state that propofol anesthesia and RIPC had an unfortunate relationship [43]. Indeed, all the large multicentric RCTs, performed in the setting of cardiac surgery and including patients treated with propofol, were not able to demonstrate any significant positive effect of RIPC [41, 42]. Conversely, studies have shown different results when an anesthetic plan excluding propofol was used. Laboratory investigations have suggested that the loss of cardioprotection by RIPC during propofol anesthesia could depend on the inhibition of the release of humoral factors. Bunte *et al.* [15] developed an animal experimental model, taking plasma from rats treated with RIPC under pentobarbital or propofol and transferring the two types of solution to naïve hearts before global ischemia. In the first case, a strong infarct size reduction was observed, whereas no such effect was seen under plasma from RIPC treated rats that received propofol anesthesia.

On the contrary, in the context of non-cardiac surgery, the role of RIPC still requires further clarification. A recent meta-analysis [44] identified 18 RCTs (**Supplementary Tables 1,2,3**) evaluating the role of RIPC in non-cardiac surgery, the largest one enrolling 570 patients [27]. The use of a blood cuff (inflated and deflated for 5 minutes over three cycles) was the most common method for administering RIPC. This meta-analysis examined the effect of RIPC on four outcomes: mortality, incidence of acute kidney injury, myocardial infarction, and myocardial injury. Although there was a trend towards reduced event rates in the RIPC group for all these outcomes, these findings were not statistically significant. While this study does not provide definitive clinical conclusions, it highlights the lack of large, adequately powered trials focusing on significant clinical outcomes that could definitively determine the role of RIPC in non-cardiac surgery. Furthermore, both cardiac and non-cardiac surgical interventions can induce a state of stress in which the application of RIPC may confer beneficial effects. However, certain conditions specific to the cardiac surgery setting, such as extracorporeal circulation, may influence the mechanisms of RIPC differently compared to non-cardiac surgical procedures. In recent years, several small RCTs showed a potential benefit of RIPC application in different non-cardiac surgical settings [45–56]. These results need to be confirmed by a large multicentric, international RCT.

4. Conclusions

To our knowledge, PRINCE will be the largest trial on RIPC performed in the setting of non-cardiac surgery. The PRINCE trial will give clear and definitive information about the role of RIPC in non-cardiac surgery. Among its strengths are a large sample size, which is adequately powered to identify outcome and its international multinational conduction. It is also possible that in a multicenter, international trial operational heterogeneity and patient diversity could reduce the magnitude of the study treatment effect. The anesthesia regimen in this trial will deliberately avoid the use of propofol,

thereby eliminating the risk that this hypnotic agent might inhibit the cardioprotection induced by RIPC. Additionally, a 1-year follow-up evaluation will provide robust data on the potential long-term effects of RIPC on survival and on cardiac ischemic and neurological events.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

MaG, GaL, AK, CB, RB, GiL, AZ and RL—contributed to the study conception or design and have directly assessed and verified the data reported in the manuscript. CL, AR, NR, HAMG, MM, GoG, MiG, LKT, SB, MK, FM, LW, AR, SE, GF, LB, FL, IS, FG, EL, FC, MS, EC, AS, LS, VS, NB, GiG, MI, CN, RDC, MP, ST, VA, FM, FC, AY, VL, FL and TB—contributed acquisition, analysis, or interpretation of data. All the authors contributed to editorial changes in the manuscript. All the authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been approved by the Human Research Ethics Committee at IRCCS San Raffaele Scientific Institute, Milan, Italy (43/OSR 34/INT) and by each participating center. Prior to randomization, all patients are required to provide informed consent, ensuring their understanding and agreement to participate in the study.

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FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni is serving as the editor-in-chief of this journal. We declare that Giovanni Landoni had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to AJ.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1865315894992748544/attachment/Supplementary%20material.docx.

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