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IN PERSPECTIVE
Educational Papers

Should renin–angiotensin system inhibitors be stopped or not before non-cardiac surgery?

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Evidence before this study

The global annual volume of major surgical procedures is estimated to exceed 300 million, representing ~5% of the world's population, with numbers likely increasing due to an ageing population.[1] Approximately 85% of these are non-cardiac surgeries (NCSs). Perioperative mortality for patients over 45 years of age following NCS is around 2%,[2] with other complications, such as perioperative myocardial injury or infarction (PMIs), occurring much more frequently.[3] Significant efforts have been made to reduce perioperative complications, with optimal drug management being crucial.[4]

Continuation of renin–angiotensin system inhibitor (RASI; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) during the perioperative period is linked to an increased risk of perioperative hypotension, leading to higher use of vasopressors and inotropes. Prolonged intraoperative hypotension may increase the risk of end-organ damage, including kidney injury, myocardial damage, and stroke.[5–7] However, a systematic review of nine studies (five randomized controlled trials and four cohort studies) found that withholding RASI therapy on the morning of NCS did not reduce mortality or major adverse cardiovascular events.[8]

The POISE-3 trial further evaluated 7490 patients undergoing NCS on blood pressure medications and reported no significant difference in major cardiovascular events within 30 days post-surgery between a hypotension-avoidance strategy (withholding RASI before and for 2 days after surgery) and a hypertension-avoidance strategy (13.9 vs. 14%, $P = 0.92$).[9,10] Anaesthesiologists maintained a mean arterial pressure (MAP) of ≥80 mm Hg in the hypotension-avoidance group and ≥60 mm Hg in the hypertension-avoidance group. The minimal difference in blood pressure and heart rate between the groups likely accounts for the similar outcomes.

Study design

The STOP-or-NOT trial (NCT03374449)[11,12] is an investigator-initiated, multicentre, open-label, randomized controlled trial conducted at 40 French hospitals, designed to compare the effect of a strategy of preoperative discontinuation of RASI therapy vs. a strategy of preoperative continuation of RASI therapy on all-cause mortality and post-operative complications after major NCS. The target enrolment for the trial was 2222 patients. The study included patients requiring major NCS, defined as a procedure with an expected duration of more than 2 h from incision and an anticipated post-operative hospital stay of at least 3 days. The enrolled patients were required to have been on RASI therapy for a minimum of 3 months prior to surgery.

Study endpoint

The primary endpoint was a composite of all-cause mortality and major post-operative complications, which included (i) post-operative major cardiovascular events (such as acute myocardial infarction, arterial or venous thrombosis, stroke, acute pulmonary oedema, cardiogenic shock, hypertensive crisis, and cardiac arrhythmias requiring intervention), (ii) sepsis or septic shock, (iii) respiratory failure requiring re-intubation or non-invasive ventilation, (iv) unplanned admission to intensive care, (v) acute kidney injury, (vi) hyperkalaemia, and (vii) surgical complications necessitating reintervention.[11]

Prespecified secondary endpoints included intraoperative hypotension (MAP <60 mm Hg or requiring treatment with vasopressors), all-cause mortality, acute kidney injury, post-operative organ failure assessed by the maximum Sequential Organ Failure Assessment score, length of hospital and intensive care stay, and hospital-free days.

Study patients

At baseline, the mean age of the 2222 patients was 67 years (SD, 10 years); 65% were male, 98% were being treated for hypertension, 9% had chronic kidney disease, 8% had diabetes, and 6% had heart failure. The baseline characteristics of the 2222 patients randomized to a RASI discontinuation strategy ($n = 1115$ patients) or a RASI continuation strategy ($n = 1107$ patients) were comparable between the groups. In both groups, it was recommended that RASI therapy was resumed as soon as possible after surgery. Follow-up was for a median of 28 days [interquartile range (IQR) 28–31 days].

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Principle findings

The rate of all-cause mortality and major post-operative complications at 28 days was 22% (245 of 1115 patients) in the RASI discontinuation group and 22% (247 of 1107 patients) in the RASI continuation group {risk ratio, 1.02 [95% confidence interval (CI), 0.87–1.19]; $P = 0.85$}. The results remained unchanged after adjustment for the stratification factors used during randomization and the baseline characteristics.[12]

The effect of discontinuation vs. continuation of RASIs on the risk of post-operative cardiac and non-cardiac complications was consistent across subgroups. With respect to secondary outcomes, episodes of hypotension during surgery occurred in 41% of patients in the discontinuation group compared with 54% of patients in the continuation group [risk ratio, 1.31 (95% CI, 1.19–1.44)]. However, the median duration of perioperative hypotension was short (6 vs. 9 min, respectively). Similarly, vasopressor support was high in both arms, but in the RASI continuation group, support was more frequent (85 vs. 72%, $P = 0.02$). Acute kidney injury occurred with similar frequency in both groups (11%).

Other study considerations

Adherence to the study instructions was excellent (96.3% of patients had complete adherence). The patients in the RASI continuation group stopped treatment at a median of 0 days (IQR, 0–0 days) before surgery compared with a median of 3 days (IQR, 3–3 days) in the RASI discontinuation group. Patients resumed treatment a median of 1 day post-operatively in both arms.

In perspective

The STOP-or-NOT trial addresses a key dilemma in perioperative medicine: whether to continue or discontinue RASI therapy before NCS. Legrand *et al.*[12] conducted a rigorous randomized trial that revealed no significant difference in post-operative outcomes between the continuation and discontinuation of RASI therapy. Despite the risk of intraoperative hypotension associated with continuation of RASI, the trial demonstrated that neither strategy improved clinical outcomes, underscoring the limited predictive value of perioperative hypotension as a direct surrogate for adverse clinical events. In addition, the study highlights that the incidence of intra- and post-operative hypotension is high, and the incremental attributable risk to continuing RASI therapy is small.

The trial's design, including a pharmacokinetically informed withdrawal timing, is a clear strength, ensuring that the drug effects were fully eliminated when discontinued. The potential limitation of the study is that it may not inform the best perioperative management in all clinical subgroups commonly encountered in clinical practice. The limited enrolment of patients with heart failure (6%), reduced ejection fraction, uncontrolled hypertension, and chronic kidney disease does not allow us to infer the best practices into these populations.

Current NCS clinical practice guidelines vary with respect to recommending withholding RASI therapy or not before major NCS.[4,13] The ESC guidelines on cardiovascular assessment and management of patients undergoing NCS from 2022 suggest that in patients without heart failure, withholding RASI therapy on the day of NCS should be considered to prevent perioperative hypotension (Class IIa, LoE B).[4] However, in patients with stable heart failure, perioperative continuation of RAAS inhibitors may be considered (Class IIb, LoE C). The lack of clinically meaningful differences between the treatment arms in the STOP-or-NOT trial suggests that clinical practice guidelines may need to be revised. Notwithstanding, clinicians may still consider tailoring the perioperative approach. Discontinuation may be appropriate in cases of concern for hypotension, while continuation could be preferred for patients with concerns about stopping their medication or for practical reasons.

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Data availability

No new data were generated or analysed in support of this research.

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