Angiotensin inhibitors during the perioperative period: to withdraw or to continue?

Published: 24-06-2020
Last updated: 08-04-2024

The objective of the proposed trial is therefore to determine the effect of continuation versus withdrawal of ACEi and ARB in the perioperative period on postoperative complications, expressed as acute kidney injury, myocardial injury, and quality...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON54753

Source
ToetsingOnline

Brief title
AIPOP (Angiotensin-inhibitors during the perioperative period)

Condition

- Myocardial disorders
- Renal disorders (excl nephropathies)
- Therapeutic procedures and supportive care NEC

Synonym
1. Perioperative acute kidney injury, 2. Perioperative myocardial infarction

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W,Grant van de ZonMW (Goed Gebruik Geneesmiddelen),In kind bijdrage niet-academische centra

Intervention

Keyword: Acute kidney injury, Angiotensine converting enzyme-inhibitors, Angiotensine receptor blockers, Cardiovascular events, Perioperative period

Outcome measures

Primary outcome

The primary outcome for this study is acute kidney injury, defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline as any of the following: - Increase in serum creatinin by >=0.3 mg/dl (>=26.5 µmol/l) within 48 hours; or - Increase in serum creatinin to >=1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or - Urine volume <0.5 ml/kg/h for 6 hours.

Secondary outcome

- Postoperative myocardial injury, defined as an increased level of serum troponin above the clinical cut-off value; - Intraoperative or postoperative hypotension, defined as a mean arterial pressure <65 mmHg for at least 10 minutes from the start of anesthesia until the end of surgery; - Postoperative hypotension, defined as a mean arterial pressure <65 mmHg from the end of surgery up to and including the second postoperative day; - Postoperative clinically diagnosed delirium. - Length of stay in hospital or nursing home; - End-stage renal disease within three months after surgery, defined as renal disease requiring dialysis or organ transplantation; - Major cardiovascular complications (myocardial infarction, coronary revascularization, heart failure, arrhythmia, stroke) within three months after surgery; - All-cause

mortality within three months after surgery; - Quality of life at 4-6 weeks and three months after surgery. - Absenteeism during three months after surgery - Protocol adherence regarding preoperative intake or withdrawal of ACEi/ARB. Amendment due to early discontinuation: - Acute kidney function loss, defined as the change between preoperative and postoperative creatinine and eGFR; - Acute postoperative myocardial injury, defined as an absolute postoperative increase in serum troponin of more than clinical cut-off value as compared to the preoperative value; - Disability at three months after surgery based on the World Health Organization Disability Activity Score (WHODAS)

Study description

Background summary

In The Netherlands alone each year over 1 million patients undergo a surgical procedure under anesthesia. Many of these patients suffer from cardiovascular diseases including hypertension. About one third of older surgical patients chronically use angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for the treatment of hypertension. These drugs lower blood pressure by vasodilation and natriuresis through inhibition of the renin-angiotensin-aldosterone system (RAAS), and have beneficial effects on long-term outcome in patients with hypertension, heart failure and chronic kidney disease. By their effect on blood pressure however, in the perioperative period these drugs may have adverse effects. One of the most common effects of anesthesia and surgery on the cardiovascular system is hypotension, which may occur during anesthesia and in the first postoperative days, especially in patients with cardiovascular disease. Importantly, concurrent use of ACEi or ARB on top of anesthetic side effects blocks the physiologic response from the RAAS to hypotension. As a result, hypotension may persist and contribute to compromised tissue perfusion, leading to poor wound healing, organ failure and death. On the other hand, withdrawal of ACEi and ARB around surgery may increase RAAS activity, blood pressure and systemic vascular resistance, which may in turn impair regional circulation. The kidney and heart are vulnerable to injury resulting from poor tissue perfusion as provoked by perioperative factors including hypotension. Both perioperative acute kidney injury and myocardial injury occur frequently, and are associated with poor prognosis.

The available evidence on this topic suggests that perioperative continuation of ACEi/ARB is associated with an increased incidence of intra- and postoperative hypotension, but that perioperative withdrawal may be associated with an increased incidence of perioperative hypertension. A recent meta-analysis showed that hypotension occurs in 28% of patients who use ACEi/ARB, and that patients who withheld their ACEi/ARB medication on the morning of surgery had significantly lower risk of intraoperative hypotension (23% versus 30%; OR 0.63; 95% CI, 0.47-0.85). Importantly, there is a strong association between intraoperative hypotension and kidney injury, myocardial injury, and death. Patients who suffer from perioperative hypotension have a two- to five-fold higher risk of postoperative acute kidney injury, a two- to four-fold higher risk of myocardial injury, and a two-fold higher risk of death.

Hence, perioperative withdrawal of ACEi/ARB medication may prevent postoperative complications and improve patient outcomes through the prevention of perioperative hypotension. There is scarce evidence of a beneficial effect of ACEi/ARB withdrawal on patient outcomes. However, these findings are from cohort studies that likely were biased by residual confounding, and from randomized studies that were too small to show any difference. Therefore, it is still unknown whether these drugs should be continued or withdrawn before and shortly after surgery. This is reflected in the fact that current guidelines on this topic are discordant: the American guidelines advise to continue ACEi and ARB in the perioperative period, while the European and Canadian guidelines advise to withdraw these drugs before surgery. As a consequence, policy varies between hospitals and even between anesthesiologists.

Study objective

The objective of the proposed trial is therefore to determine the effect of continuation versus withdrawal of ACEi and ARB in the perioperative period on postoperative complications, expressed as acute kidney injury, myocardial injury, and quality of life.

Study design

A pragmatic, multicenter randomized clinical trial.

Intervention

Withdrawal of ACEi/ARB in the perioperative period, i.e. from 24 hours before surgery until 24-48 hours after surgery. The ACEi/ARB medication is resumed on the second or third day after surgery as soon as the clinical condition allows on judgment of the attending physician. In patients who use ACEi/ARB medication in a combination pill together with a diuretic, this combination pill will be

withdrawn, hence including the diuretic.
This intervention will be compared to perioperative continuation of ACEi/ARB.

Study burden and risks

The burden of participating in this study, consisting of filling out some short questionnaires and a medication diary, and some blood draws, is considered low. Also the risks of participating is considered low. At this moment it is not clear which strategy should be applied, and both strategies are used in current clinical practice, depending on the hospital and/or anesthesiologist.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Chronic angiotensin-converting enzyme inhibitors and angiotensin receptor blockers use for the treatment of hypertension. Patients who use a com-bination pill with a diuretic are eligible as well;
- Scheduled for elective intermediate to high risk noncardiac surgery, defined according to the European Society of Cardiology / European Society of Anesthesiology guidelines on noncardiac surgery under general or regional (spinal, epidural) anesthesia,
- Expected postoperative length of stay of at least one postoperative night

Exclusion criteria

- Severe chronic kidney disease, defined as eGFR<30 ml/min/1.73 m2 - Angiotensin converting enzyme-inhibitors (ACEi)/Agiotensin receptor blockers (ARB) use for the treatment of chronic systolic heart failure, defined as left ventricular ejection fraction <=40%. Patients in whom the ejection fraction currently has improved to >40% as a result of heart failure treatment (e.g. ACEi/ARB use or chronic resynchronization therapy (CRT)) are also excluded - ACEi/ARB use within one year after ST-elevated myocardial infarction, according to the fourth universal definition of myocardial infarction (20,21) - Transplant surgery - ACEi/ARB use in a combination pill together with a drug other than a diuretic, including calcium channel blockers, beta-blockers and neprilysin inhibitorsUse of drugs acting on the renin-angiotensin-aldosterone system other than ACEi/ARB, e.g. aliskiren. - Patients who are not able to manage their medication themselves, e.g. patients who use a medication box or pill dispenser including the *Baxterrol*. - Urgent (<48 hours of diagnosis) or emergency surgery - Nephrectomy (partial or complete, no matter the cause) - Pheochromocytoma surgery - Carotid surgery, including endarterectomy and carotid bypass surgery

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-09-2020
Enrollment:	334
Type:	Actual

Ethics review

Approved WMO Date:	24-06-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	09-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-08-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04506372
CCMO	NL72045.041.20