Peri-Operative ISchemic Evaluation-3 Trial

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Perioperative bleeding in the setting of noncardiac surgery is strongly associated with 30-day cardiovascular complications and mortality. Trial evidence suggests that intravenous TXA reduces perioperative bleeding and transfusion in orthopedic...

Ethical review	Approved WMO
Status	Completed
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON48217

Source
ToetsingOnline

Brief title
POISE-3

Condition

- Heart failures
- Joint disorders

Synonym
heart failure, vascular events

Research involving
Human

Sponsors and support

Primary sponsor: Population Health Research Institute
Source(s) of monetary or material Support: Population Health Research Institute;Canada

Intervention

Keyword: Bleeding, Peri-operative bloodpressure, Vascular events

Outcome measures

Primary outcome

The co-primary efficacy outcome for TXA trial is a composite of life-threatening bleeding, major bleeding, and critical organ bleeding at 30 days after randomization.

The co-primary safety outcome for TXA trial is a composite of myocardial infarction, non-hemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism at 30 days after randomization.

The primary outcome for the BP management trial is a composite of vascular death, and non-fatal myocardial infarction, stroke, and cardiac arrest at 30 days after randomization.

Secondary outcome

The secondary outcomes for TXA trial are:

1) a net risk-benefit outcome as a composite of vascular death, and non-fatal life-threatening, major or critical organ bleeding, myocardial infarction, stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism at 30 days after randomization;

2) International Society on Thrombosis and Haemostasis (ISTH) major bleeding;

3) BIMS;

3) MINS;

4) myocardial infarction at 30 days after randomization.

The secondary outcomes for the BP management factorial are:

1) all-cause mortality at 30 days after randomization;

2) MINS;

3) myocardial infarction at 30 days after randomization.

Study description

Background summary

Globally more than 200 million adults undergo major noncardiac surgery annually. Despite the benefits of surgery, a substantial proportion of patients suffer major complications.
The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) study (a large, international, prospective cohort study evaluating complications after noncardiac surgery) showed that among a representative sample of 40,000 adults >=45 years of age undergoing noncardiac surgery, 1.8% died within the first 30 days after surgery (confidential data, not yet published). In the VISION cohort, perioperative bleeding accounted for approximately 25% of the deaths (confidential data, not yet published). There is encouraging but not definitive evidence that tranexamic acid (TXA) may prevent perioperative bleeding in noncardiac surgery. Moreover, TXA is an anti-fibrinolytic drug for which in vivo data shows an association with thrombus formation, and its safety in the prothrombotic noncardiac surgery setting has not been established.
There is evidence suggesting that perioperative hypertension is associated with cardiovascular complications. Despite some variability across practices, routine care is to continue antihypertensive medications in the perioperative setting in patients on chronic therapy. Despite the potential risk of perioperative hypertension, there is also evidence that perioperative hypotension is independently associated with all-cause death and cardiovascular complications at 30 days after noncardiac surgery.
We previously performed two large prophylactic perioperative randomized controlled trials (RCTs) - the PeriOperative ISchemic Evaluation (POISE) and POISE-2 Trials - evaluating the efficacy of metoprolol, clonidine, and aspirin (ASA). POISE and POISE-2 demonstrated the independent association between perioperative bleeding and cardiovascular events. In these trials clinically important hypotension was independently associated with myocardial infarction, stroke, acute kidney injury (AKI), and death.
We will conduct a large international RCT (i.e., POISE-3) of TXA versus placebo, and using a partial factorial design, we will evaluate a hypotension-avoidance strategy versus a hypertension-avoidance strategy, in

patients having noncardiac surgery.

Study objective

Perioperative bleeding in the setting of noncardiac surgery is strongly associated with 30-day cardiovascular complications and mortality. Trial evidence suggests that intravenous TXA reduces perioperative bleeding and transfusion in orthopedic surgery; however, the data are based on small trials, and few non-orthopedic noncardiac surgery patients have been included in perioperative TXA trials. Moreover, the safety of TXA in the noncardiac surgery setting (i.e., the effect on arterial and venous thrombotic events) has not been established. There is the need for a large, adequately powered trial to establish definitive evidence and drive subsequent practice. In particular, to support a more extensive use in noncardiac surgery, a reliable proof of the non-inferiority of TXA compared with placebo in terms of safety, together with a confirmation of its efficacy in different types of noncardiac surgeries, is required.
Although usual care is consistent with a hypertensive avoidance strategy in the noncardiac surgery setting, there is compelling evidence that perioperative hypotension is frequent and is associated with cardiovascular events and mortality. There is no definitive evidence from RCTs to support the adherence to specific perioperative BP targets, nor the adoption of strategies of perioperative management of antihypertensive medications. Moreover, there is no clear evidence that hemodynamics in one of the perioperative phases (i.e. pre-, intra-, or post-surgery) has more impact on outcomes than in other phases. There is the need to compare a hypotensive-avoidance strategy to a hypertensive-avoidance strategy in patients undergoing noncardiac surgery to determine the impact on major cardiovascular complications and death.

Study design

The POISE-3 Trial is an international RCT of 10,000 patients with, or at risk, or cardiovascular disease who are randomized to TXA or placebo given intraoperatively. Patients, health care providers, data collectors, outcome adjudicators, and investigators (e.g., Steering Committee Members) will all be blind to allocation to TXA or placebo. The POISE-3 Trial will utilize a partial 2x2 factorial design to randomize patients taking >=1 antihypertensive therapy to perioperative (i.e., pre-, intra-, and post-operative phase) hypotension-avoidance strategy vs. hypertension-avoidance strategy. Outcomes adjudicators will be blind to treatment allocation for the partial factorial.

Intervention

1. Tranexamic acid or placebo
Within 20 minutes preceding the anticipated skin incision, patients will receive intravenous TXA or placebo (0.9% normal saline) at a loading dose of 1g

over 10 minutes, with a second 1g bolus given at the end of surgery when closing the wound.

2. Perioperative blood pressure management strategies
The perioperative BP management strategies will have three components, (i.e., preoperative, intraoperative and postoperative for the first 2 days after the day of surgery). The intervention is a perioperative BP management strategy aimed at avoiding hypotension. The control group is a perioperative BP management strategy aimed at avoiding hypertension (usual care). For the preoperative BP management component, the antihypertensive medications taken by the patients enrolled in the trial will be either their own medications, or provided by the hospital pharmacy as per each centre*s routine practice. For the postoperative BP management phase, the hospital pharmacy at each center will provide the patient*s medications as per routine practice.

Study burden and risks

Perioperative TXA may increase the risk of seizure. TXA has been shown to be a predictor for postoperative seizure in patients undergoing cardiac surgery, independently of other possible contributing factors, like ischemia, embolic phenomena, drugs, and hypoglycemia. High doses of TXA play a role in increasing the risk, and thus preoperative renal dysfunction can promote the occurrence of these events (being the drug elimination mostly renal). High doses of TXA are usually implemented in cardiac surgery (from 50 mg/kg to more than 100 mg/kg). In the recent ATACAS study postoperative seizures occurred in 15 patients (0.7%) in the TXA and in 2 patients (0.1%) in the placebo group (relative risk, 7.60; 95% CI, 1.80-68.70t). No difference was found between the higher (100 mg/kg) and the lower dose (50 mg/kg), but both doses were in fact higher than the dose that will be used in POISE-3.
In the POISE-3 trial, we will exclude patients with poor renal function (eGFR <30 ml/min) and patients with a history of seizure disorder. Further, we will use a standardized dose of TXA (1 g after anesthesia induction and 1 g at the end of surgery), which corresponds to a maximum cumulative dose of 40 mg/kg in a 50 kg patient. Any postoperative seizure will be recorded.

Patients will be administered blood pressure medication that they are already taking chronically; the decision to administer or withhold the medication will be advised by the trial. The patients own physician will have prescribed these chronic medications. Thus, patients are expected to be stable under these chronic medications both in terms of tolerance and BP control.
The trial intervention group is aimed at avoiding hypotension. However, clinically significant hypertension will also be minimized because patients with elevated SBP >130 mm Hg in the intervention group will be instructed to take certain antihypertensive medications as per Appendix III. Moreover, further management will be left at the discretion of the attending physician, including choice of additional therapy, if indicated.
The trial control group is aimed at avoiding hypertension. Should clinically

important hypotension occur physicians are encouraged to manage this, but choice of corrective therapy will be left at the discretion of treating physician.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Undergoing noncardiac surgery;
2. >= 45 years of age;
3. Expected to require at least an overnight hospital admission after surgery;
4. Provide written informed consent to participate in the POISE-3 Trial, AND
5. Fulfill >=1 of the following 6 criteria (A-F):
A. NT-proBNP >=200 ng/L
B. History of coronary artery disease

C. History of peripheral arterial disease
D. History of stroke
E. Undergoing major vascular surgery; OR
F. Any 3 of 9 risk criteria
i. Undergoing major surgery;
ii. History of congestive heart failure;
iii. History of a transient ischemic attack;
iv. Diabetes and currently taking an oral hypoglycemic agent or insulin;
v. Age >70 years;
vi. History of hypertension;
vii. Serum creatinine > 175 µmol/L (> 2.0 mg/dl);
viii. History of smoking within 2 years of surgery;
ix. Undergoing emergent/urgent surgery.

Exclusion criteria

1. Planned use of systemic TXA during surgery;
2. Hypersensitivity or known allergy to TXA;
3. Creatinine clearance <30 mL/min (Modification of Diet in Renal Disease [MDRD]);
4. History of seizure disorder;
5. Patients with recent stroke, myocardial infarction, acute arterial thrombosis or venous thromboembolism (<1 month);
6. Patients with subarachnoid hemorrhage within the past 30 days;
7. Patients undergoing cranial neurosurgery;
8. Previously enrolled in POISE-3 Trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-11-2019
Enrollment:	400
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cyklokapron
Generic name:	Tranexamic Acid
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-07-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-07-2019
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-08-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-08-2019
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-01-2020

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	08-05-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-05-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-11-2021
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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
EudraCT	EUCTR2018-000539-29-NL
ClinicalTrials.gov	NCT03505723
CCMO	NL67432.075.19

Study results

Date completed:	01-08-2022
Results posted:	30-12-2024

Summary results
Trial ended prematurely

First publication
02-04-2022