ACTION-1: ACT Guided Heparinization During Open Abdominal Aortic Aneurysm Repair, a Randomised Trial.

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Primary Objective: To establish that ACT guided heparinization results in safe and optimal anticoagulation during open AAA repair. We hypothesize that ACT guided heparinization will result in a decrease of thrombo-embolic complications, without a...

Ethical review	Approved WMO
Status	Completed
Health condition type	Aneurysms and artery dissections
Study type	Interventional

Summary

ID

NL-OMON55676

Source
ToetsingOnline

Brief title
ACTION-1

Condition

- Aneurysms and artery dissections

Synonym
abdominal aortic aneurysm, dilated bloodvessel in abdomen

Research involving
Human

Sponsors and support

Primary sponsor: Dijklander Ziekenhuis
Source(s) of monetary or material Support: ZonMW,Academisch Medisch Centrum,Dijklander Ziekenhuis,Medtronic B.V.,Vrije Universiteit Medisch Centrum

Intervention

Keyword: abdominal aortic aneurysm repair, activated clotting time (ACT), heparine, thrombo-embolic events

Outcome measures

Primary outcome

Primary endpoints: Combined incidence of all thrombo-embolic complications (TEC) and all-cause mortality within 30 days or during the same admission in hospital. TEC are any complication as caused by thrombus or embolus perioperatively, including but not exclusively: myocardial infarction, leg ischemia, deep venous thrombosis, colon ischemia, TIA/stroke, graft thrombosis, peroperative thrombus requiring embolectomy or redo of an anastomosis, thrombus or embolus in organs or lower limbs and other peripheral thrombosis. Incidence of bleeding complications according to E-CABG classification, grade 1 and higher: per- or postoperative transfusion of 2 or more units of red blood cells, transfusion of platelets, transfusion of fresh frozen plasma or reoperation for bleeding during hospital stay.

Secondary outcome

Secondary endpoints: Secondary endpoints: complications (non-TEC), within 30 days postoperative or in the same admission, as defined by DSAA and suggested standards for reports on aneurysmal disease: all complications requiring re-operation, longer hospital stay, all other complications. Incidence of kidney injury as defined by RIFLE criteria: rise of serum creatinine > 100% or decrease of eGFR with 50%.32 Allergic reactions. ACT values (in intervention group), total heparin administration, protamine administration. Peroperative

blood loss, blood transfusions either autologous or homologous, other blood products administration, total operative time, aortic clamping time, use of adjunctive haemostatic products, length of hospital (including ICU) stay.
Relation ACT and anti-Xa. Health status as measured with the EQ-5D-5L. Economic and healthcare costs evaluation by IMCQ and IPCQ and addition of out-of-pocket expenses.

Study description

Background summary

Vascular disease, both occlusive and dilating, is a major contributor to mortality and morbidity, also in The Netherlands. Techniques in both open surgery and endovascular treatments have been refined over the past decades, but at present are still associated with mortality and high rates of complications and morbidity. Unfractionated heparin (UFH) is used by all vascular surgeons worldwide during open and endovascular non-cardiac arterial procedures (NCAP) since more than 70 years. UFH is used as a periprocedural prophylactic antithrombotic to reduce the clotting of blood and thereby preventing arterial thrombo-embolic complications, such as myocardial infarction, stroke, bowel-ischemia and peripheral embolic events in extremities. The use of heparin also has a major clinical disadvantage: the prolonged clotting of blood may increase blood loss, lengthens time needed for haemostasis and may cause an increase in bleeding complications. The severity of bleeding complications can be mild such as a hematoma or pain, but may sometimes require blood transfusions or even surgical (re-)exploration in case of extensive and even life-threatening bleeding.
Because of the fine line between thrombosis and bleeding, vascular interventions require precise technique and an accurate level of coagulation. Another major disadvantage of the use of heparin as a periprocedural prophylactic antithrombotic is the fact that heparin has a unpredictable effect in individual patients. The molecular structure of heparin causes a variety of its effect, creating not only a difference in efficacy between different brands, but even between batches of the same brand. The above described characteristics of heparin result in an unpredictable effect as an antithrombotic in the individual patient, possibly being harmful.
In Europe, UK, and in a substantial part of the USA and the rest of the world, heparin is administered as a standardized bolus in every patient undergoing NCAP. Most used dosage is 5.000 IU, irrespective of sex, bodyweight, type of

procedure or duration of procedure.
In all cardiac interventions, open or endovascular and using cardio-pulmonary bypass or not, the effect of heparin is measured routinely in every patient worldwide. Abundant literature has shown that the activated clotting time (ACT) is the preferred test to measure the effect of heparin and that using this test increases safety of these cardiac interventions. This results in better patient related outcomes. Surprisingly vascular surgeons have not adopted this measurement of the ACT during NCAP.
A study group, Consensus on Arterial Peri-Procedural Anticoagulation (CAPPA), was formed in the Netherlands to create consensus on periprocedural anticoagulation during non-cardiac procedures. After surveys and two published systematic reviews, this group concluded that ACT measurement in NCAP is to be preferred and should be introduced in daily practice. This to ensure the individual patient of safe, tailor-made periprocedural anticoagulation. This should lead to better results of procedures with improved patient related outcomes and less harm for the patient.
In a consortium of 5 large training hospitals (university and teaching hospitals) we initiated a study to evaluate the feasibility and safety of measuring the ACT during NCAP (MANCO, NTR nr. 6973, ClinicalTrials.gov M016-045). The infrastructure of research in these 5 hospitals proved to be effective.
Results of more than 500 patients show that ACT measurements can be introduced safely and adequately in daily routine in the operation room during open and endovascular procedures. Evaluation of these data resulted in a safe and adequate protocol to ensure patient of optimal, ACT guided heparinization during NCAP. A goal ACT of 200-220 seconds is considered to be optimal. Literature from mainly cardiac interventions, indicated that a fixed value of 250-300 seconds is safe. At higher ACT values more bleeding complications were recorded. In our 500+ patients the individual base ACT value was: mean 132 sec (+/- 16).
Next step will be to conduct a large (inter)national multicenter trial to provide level 1 evidence that ACT guided heparinization will result in less thrombo-embolic complications without more bleeding complications than unmonitored heparinization with the use of a standardized bolus. This will be evaluated during open abdominal aneurysm (AAA) surgery DSAA classification C: aneurysm originating below the Superior Mesenteric Artery. DSAA being the Dutch Surgical Aneurysm Audit, a Dutch registration which is mandatory for all Dutch vascular surgeons for treated patients with an AAA. These procedures include standardized care regarding indication, techniques and periprocedural care. The hiatus of sound evidence on periprocedural anticoagulation and heparinization during NCAP has been prioritized by the Dutch Board of Surgery, the Board of Vascular Surgery, and by the Federation of Medical Specialists. These boards have granted their full cooperation, also to expand the already existing infrastructure of this research. The intended study will be used to create an infrastructure and consortium of 20+ major vascular surgical centers in the Netherlands for research. Supported by the Dutch Board of Vascular Surgery and initiated by the already existing collaboration between the mentioned 5 large

hospitals, this will secure implementation of major clinical trials in the near future. Part of the grant from ZonMw will be used for the founding and securing of this infrastructure.

Study objective

Primary Objective: To establish that ACT guided heparinization results in safe and optimal anticoagulation during open AAA repair. We hypothesize that ACT guided heparinization will result in a decrease of thrombo-embolic complications, without a significant increase in bleeding complications when compared to the use of standardized bolus of 5 000 IU. with one ACT-measurement at the end of the procedure. The decrease in thrombo-embolic complications will lead to less mortality and morbidity, lower number of re-operations or better patency, all substantially improving patient*s quality of health, efficiency of medical care and quality of vascular medical care. Results will be implemented in guidelines in the Netherlands and Europe for vascular surgeons and promoted worldwide.

Secondary Objective(s): NA

Study design

(Inter)national multi-centre RCT, reported according to CONSORT 2010 statement. Patients will be blinded for the allocated treatment. Patients will be randomized using a computerized program (CASTOR EDC) with a random block size 2, 4, 6. The randomization will be stratified by participating centre. Analysis will be performed by intention to treat principle. A separate analysis per protocol will also be performed as a sensitivity analysis. Separate evaluation of results and if complications can be labelled as TEC, will be performed by an Independent Central Adjudication Committee. The 3 members of this Committee will be blinded to the allocated treatment.

Intervention

ACT guided heparinisation during open abdominal aortic aneurysm surgery

Study burden and risks

Benefits for participating is that there could be a reduction in thrombo-embolic complications and mortality when the ACT is measured.

Risks could be that the ACT guided heparinization could lead to more bleeding complications. The ACT of 200-220 seconds and the use of protamine is proven to be safe.

Measurements

Extra blood samples will be drawn, under general anaesthetic, from an arterial line in the wrist. This arterial line is part of standard procedure for this type of surgery and is of no extra burden in the ACT guided group.
In total a maximum of 48 ml of extra blood will be drawn. This amount does not cause problems in adults.
In patients in the non-ACT arm, one ACT measurement will be performed just before the end of the surgery (max. 5 ml).

Participation also involves:
- complete 5 short questionnaires; pre-operative, 1 and 4 weeks, 3 and 6 months after surgery.
- complete longer questionnaires; one at 3 months and two at 6 months after surgery.
- patient will be called between 30-35 days (max. duration time 5 minutes), to evaluate complications after discharge.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Inclusion criteria

- Able to speak and read in local language of trial hospital.
- Patients older than 18 years scheduled for elective, open repair of an iliac or abdominal aortic aneurysm distal of the SMA (DSAA segment C).
- Implantation of a tube or bifurcation prosthesis.
- Trans-abdominal or retroperitoneal surgical approach of aneurysm.
- Able and willing to provide written informed consent.

Exclusion criteria

- Not able to provide written informed consent.
- Previous (endovascular) intervention on the abdominal aorta (previous surgery on other parts of
the aorta or iliac arteries is not an exclusion criterion).
- History of coagulation disorders, heparin induced thrombocytopenia (HIT), allergy for heparin or
thrombocyte pathology.
- Impaired renal function with EGFR below 30 ml/min.
- Acute open AAA surgery.
- Hybrid interventions.
- Connective tissue disorders.
- Dual anti-platelet therapy, which cannot be discontinued.
- Life expectancy less than 2 years.
- Inflammatory, mycotic or infected aneurysms.
- Allergy for fish protein or protamine

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active

Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-03-2020
Enrollment:	620
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Heparin-Leo
Generic name:	Heparin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	20-02-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	06-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	22-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	14-07-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2018-003393-27-NL
ClinicalTrials.gov	NCT04061798
CCMO	NL66759.029.19