Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

ACTION-1: study protocol for a randomised controlled trial on ACT guided heparinization during open abdominal aortic aneurysm repair {1}

Arno M. Wiersema (arno@wiersema.nu)
Dijklander Ziekenhuis https://orcid.org/0000-0001-6045-9022
Liliane C. Roosendaal
Dijklander Ziekenhuis
Mark J.W. Koelemaij
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC
Jan G.P. Tijssen
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC
Susan van Dieren
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC
Jan D. Blankensteijn
Amsterdam UMC - Locatie VUMC: Amsterdam UMC Locatie VUmc
E. Sebastian Debus
Universitätsklinikum Hamburg-Eppendorf: Universitatsklinikum Hamburg-Eppendorf
Saskia Middeldorp
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC
Jan M.M. Heyligers
Tweesteden Hospital Location Saint Elisabeth: Elisabeth-TweeSteden Ziekenhuis
Ymke S. Fokma
Dijklander Hospital: Dijklander Ziekenhuis
Michel M.P.J. Reijnen
Hospital Rijnstate: Ziekenhuis Rijnstate Arnhem
Vincent Jongkind
Amsterdam UMC - Locatie VUMC: Amsterdam UMC Locatie VUmc

Study protocol

Keywords: Abdominal aortic aneurysm, open repair, activated clotting time, heparin, vascular surgery, anticoagulation, RCT

Posted Date: May 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-373186/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background

Heparin is used worldwide for 70 years during all non-cardiac arterial procedures (NCAP) to reduce thrombo-embolic complications (TEC). But heparin also increases blood loss causing possible harm for the patient. Heparin has an unpredictable effect in the individual patient. The Activated Clotting Time (ACT) can measure the effect of heparin. Currently this ACT is not measured during NCAP as standard of care, contrary to during cardiac interventions, open and endovascular. A RCT will evaluate if ACT guided heparinization results in less TEC than the current standard: a single bolus of 5 000 IU of heparin and no measurements at all. A goal ACT of 200-220 seconds should be reached during ACT guided heparinization and this should decrease (mortality caused by) TEC, while not increasing major bleeding complications. This RCT will be executed during open abdominal aortic aneurysm (AAA) surgery, as this is a standardized procedure throughout Europe.

Methods

Seven-hundred-fifty patients, who will undergo open AAA repair of an aneurysm originating below the superior mesenteric artery, will be randomised in 2 treatment arms: 5 000 IU of heparin and no ACT measurements and no additional doses of heparin, or a protocol of

100 IU/kg bolus of heparin and ACT measurements after 5 min., and then every 30 min. Goal ACT is 200-220 sec. If the ACT after 5 min. is < 180 sec. 60 IU/kg will be administered, if the ACT is between 180 and 200 sec. 30 IU/kg. If the ACT is > 220 sec. no extra heparin is given, and the ACT is measured after 30 minutes and then the same protocol is applied. The expected incidence for the combined endpoint of TEC and mortality is 19% for the 5 000 IU group and 11% for the ACT guided group.

Discussion

The ACTION-1 trial is an international RCT during open AAA surgery, designed to show superiority of ACT guided heparinization compared to the current standard of a single bolus of 5 000 IU of heparin. A significant reduction in TEC and mortality, without more major bleeding complications, must be proven with a relevant economic benefit.

Trial registration {2a}

NTR: NL8421

Clinicaltrials.gov: NCT04061798. Date of registration: 20-08-2019.
https://clinicaltrials.gov/ct2/show/NCT04061798?cond=NCT04061798&draw=2&rank=1

EudraCT: 2018-003393-27

Background {6a}

Vascular disease, both occlusive and dilating, is a major contributor to mortality and morbidity. Techniques in both open surgery and endovascular treatments have been refined over the past decades, but at present they are still associated with mortality and high complication rates. (1–8) Since more than 70 years unfractionated heparin (further: heparin) is used by all vascular surgeons worldwide during open and endovascular non-cardiac arterial procedures (NCAP), preventing arterial thrombo-embolic complications (TEC).(9–11) The use of heparin also has a major clinical disadvantage: the prolonged clotting time of blood may increase blood loss, lengthens time needed for adequate hemostasis and may cause an increase in bleeding complications. Bleeding complications may 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, optimal level of coagulation. Another major disadvantage of the use of heparin as a periprocedural prophylactic antithrombotic, is the fact that heparin has an unpredictable effect in individual patients.(12) 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.(13)

In most countries heparin is administered as a standardized bolus in every patient undergoing NCAP. The most often used dosage is 5 000 IU, irrespective of sex, bodyweight, type of procedure or duration of procedure. Interventional radiologists often use a dose of less than 5 000 IU. (9,10)

In all cardiac interventions worldwide, open or endovascular and using cardio-pulmonary bypass or not, the effect of heparin is measured routinely. Many studies have 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.(14,15) This results in better patient related outcomes. Surprisingly vascular surgeons have not adopted this measurement of the ACT during NCAP. This ACT measurement could ensure the individual patient of safe, tailor-made periprocedural anticoagulation.(16–23). This should lead to better results of procedures, with improved patient-related outcomes and less harm for the patient {6b}.

To evaluate the implementation of routine ACT measurements during NCAP, a prospective registry was instituted in 4 major vascular centers in The Netherlands (MANCO, NTR nr. 6973, ClinicalTrials.gov M016-045). All ACT measurements were performed according to a standardized protocol using the same device: Hemostasis Management System Plus (HMS) by Medtronic®, with high-range ACT cartridges (HR-ACT). The percentage of successful measurements was 99% and results were reproducible and comparable between the different hospitals. The validation and standardization of the HMS for ACT measurements are extensively proven in the literature during cardiac interventions. (24,25) Similar studies were performed with other cartridges (low-range ACT) for the HMS and other brands of ACT measurement systems. Results (on file, manuscript in preparation) show that the HMS and the HR-ACT guarantee the most stable, reproducible and comparable results during NCAP. Results of the MANCO study, in more than 700 patients, show that ACT measurements can be introduced safely and adequately

in daily routine in the operation room and angio-suite, both during open and endovascular NCAP. Evaluation of these data resulted in a safe and adequate protocol to ensure the patient of optimal, ACT guided heparinization during NCAP. A goal ACT of 200-220 seconds is considered to be optimal. A systematic review was conducted by our research group, in which only 4 studies could be found that investigated the relation between ACT values and clinical outcomes.(26) Two studies did not find a relationship between ACT value and bleeding complications. (19,23) Saw et al. found that an ACT > 300 seconds was associated with increased combined event rate (death, stroke or MI) in carotid artery stenting. (21) Kasapis et al. found increased bleeding in peripheral endovascular interventions when the ACT was > 250 seconds.(16)

In the MANCO study the effect of the standardized bolus of 5 000 IU was evaluated by measuring the ACT.(27) Results showed that large individual patient variability in the response to heparin was present. The mean baseline ACT in all patients was 129 ± 18 s and the mean ACT 5 minutes after the initial bolus of heparin was 191 ± 36 seconds. After the initial dose of 5 000 IU heparin only 33% and 6% of patients reached an ACT of 200 and 250 seconds, respectively.

Despite the use of heparin, ATEC occurred in 17 patients (9%). The lowest number of

ATEC and hemorrhagic complications occurred in the group of patients with an ACT

between 200 and 250 seconds. Conclusions: A standardized bolus of 5 000 IU heparin does not lead to adequate and safe heparinization in non-cardiac arterial procedures. Patient response to heparin shows a large individual variability. Therefore, routine ACT measurements are

necessary to ascertain adequate anticoagulation. Further research is needed to

investigate if heparin dosing based on the ACT could result in less arterial thromboembolic

complications, without increasing hemorrhagic complications.

Next step was to design a large international 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 aortic aneurysm (AAA) surgery DSAA classification C: aneurysm originating below the Superior Mesenteric Artery. DSAA being the Dutch Surgical Aneurysm Audit, a Dutch registration that is mandatory for all Dutch vascular surgeons who treat patients with an AAA. (28) In this registry details are stored regarding indication, techniques and periprocedural care. The reason to choose open AAA repair for this RCT, is that this procedure is subject to standardized care in all hospitals around Europe, also by following the 2019 European Society of Vascular Surgery Guidelines on Management of Patients with an AAA. (29)

During a trajectory of 2 years funding was applied for at ZorgOnderzoek Nederland Medische Wetenschappen (ZonMw, https://www.zonmw.nl) in close collaboration with the Dutch Surgical

Association and Dutch Vascular Surgery board. ZonMw's principal commissioners are the Dutch Ministry of Public Health, Welfare and Sport (VWS) and the Netherlands Organization for Scientific Research (NWO). ZonMw also increasingly works on behalf of other parties, such as local authorities, health funds, health care insurers, private companies, and professional associations. After an extensive (international) peer-reviewed process, a grant of 1.6 million euros was granted for the ACTION-1 trial: ACT guided heparinization during open abdominal aortic aneurysm repair.

One of the main demands of ZonMw was to execute a pilot study. Results of this pilot study in 46 patients with open AAA repair resulted in a decrease of TEC from 22% in the 5 000 IU group to 7% in the ACT guided group. No increase in bleeding complications or mortality was detected (no mortality in both groups, E-CABG class 1 bleeding in 39% in the 5000 IU group versus 36% in the ACT guided group). (30,31) In the ACT guided group the use of protamine at the end of surgery was also described in a protocol. (32,33) Because of the limited number of included patients, no statistical significance was reached. This underlines the importance of performing a RCT.

Method/design

This study protocol has been reported in accordance with the Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines.(34)

Study design {8}

The ACTION-1 trial is a multicenter RCT designed to compare the outcomes of ACT guided heparinization to a standardized bolus of 5000 IU of heparin, during open AAA repair.

Patients undergoing open AAA repair, meeting eligibility criteria, will be included in the trial after giving written informed consent.

The following Dutch vascular centers (academic and large community training hospitals){9} are currently, or in upcoming months, participating in the ACTION-1 trial: Dijklander Ziekenhuis Hoorn, Amsterdam UMC location VUmc, Amsterdam UMC location AMC, Rijnstate Ziekenhuis Arnhem, Elisabeth-TweeSteden Ziekenhuis Tilburg, Isala Ziekenhuizen location Zwolle, Medisch Spectrum Twente Enschede, Maasstad Ziekenhuis Rotterdam, Groene Hart Ziekenhuis Gouda, St. Antonius Nieuwegein, Alrijne Ziekenhuis Leiderdorp, LUMC Leiden, Amphia Ziekenhuis Breda, Haaglanden MC Den Haag, Gelre Ziekenhuizen Apeldoorn, Slingeland Ziekenhuis Doetinchem, Catharina Ziekenhuis Eindhoven, Zorggroep Twente location Almelo, UMCG Groningen.

Also, the University Heart Center Hamburg is in preparation for intended participation. A website solely for the ACTION-1 study has been developed: ACTION-1.nl. All participating hospitals, inclusion, information for patients (including lay video) are depicted on this website {9}.

The study will be single blinded: only the patient will be fully blinded. Furthermore, the

Independent Central Adjudication Committee (ICAC) will be blinded for the intervention {17a}. Blinding will follow all legal demands for unblinding in case of patient safety, as deemed as such by attending medical personnel {17b}. Also, the Data Safety Monitoring Board (DSMB) can decide to unblind.

Study objectives {7}

To establish that ACT guided heparinization results in safe and optimal anticoagulation during open AAA repair. The hypothesis is that ACT guided heparinization will result in a decrease of TEC, without a significant increase in bleeding complications when compared to the use of a non-ACT guided standardized bolus of 5 000 IU. The decrease in TEC 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.

Sample size calculation {14}

In the DSAA (2014 to 2016) the rate of serious complications was 29% for all patients. According to the Society for Vascular Surgery AAA 2018 guidelines the incidence of TEC is between 15 and 36%. In our preliminary MANCO trial, the incidence of TEC was 14%. For our power calculation the incidence of TEC is set at 14%. The vast majority of mortality after open AAA repair stems from TEC. A mortality rate of 5% after open AAA repair is derived from DSAA. Hypothesis is that decrease of TEC will result in a lower mortality of 3%. Bleeding complications derived from the literature and from our MANCO trial and ACTION pilot study: 18-39% (scored according to E-CABG classification).(30)

Derived from data from our pilot study and from literature, the hypothesis is that ACT guided heparinization will lower the rate of TEC to 8%. The expected incidence for the combined endpoint of TEC and mortality is therefore set at 19% for the 5 000 IU group and 11% for the ACT guided group. Using a continuity corrected chi- square test with a two-sided alpha of 5%, 337 patients are needed in each group to achieve a power of 80%. Including a drop out of 10%, a total of 750 patients are needed for the combined primary endpoints of TEC and mortality.

In our pilot study no increase in bleeding complications was found for open AAA repair (E-CABG class 1 bleeding was 39% versus 36%). Nevertheless, it is important that excessive bleeding does not occur in the intervention group. Therefore, a non-inferiority calculation was performed. Bleeding complications and TEC are different and have a different impact on patients. Bleeding complications Grade 1 E-CABG have less impact on mortality and quality of life than TEC. The expectation is an improvement in combined TEC and mortality of 8%, the non-inferiority for bleeding complications is set at 11%.

Expecting 32% bleeding complications in the standard group and 33% in the intervention group and a non-inferiority limit of 43% (11% limit difference) with a power of 80% and a one-sided alpha of 5%, 272 patients required in each group. Therefore the 750 patients included are sufficient to also evaluate the non-inferiority for bleeding complications.

Main study parameter/endpoint efficacy {12}

Combined incidence of all 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.

Main study parameter/endpoint safety {12}

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.(30,31)

Secondary study parameters/endpoints {12}

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%.(35) 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 hemostatic products, length of hospital (including ICU) stay. 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.

Other study parameters {12}

Preoperative parameters

Patient demographics: sex, smoking history, body length and weight and body mass index, medical history (general, cardiac, pulmonary, diabetes, surgical), medication, all previous vascular interventions. Blood pressure and pulse at outpatient visit, ECG reports. Diameter and anatomical classification of abdominal or iliac aneurysms. Preoperative laboratory results: Hb, leucocytes, sodium, potassium, creatinine, eGFR, platelets. Presence of impaired renal function (eGFR < 40 ml/min).

Peroperative parameters

Epidural analgesia. Surgical approach. Clamping sites at arteries.

Ethical considerations

If patients meet the inclusion criteria, they will be fully informed about the trial and provided with a patient information form and have the opportunity to ask questions. Patients willing to participate will sign the informed consent form. This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki and with the Medical Research

Involving Human Subjects Act (WMO). The medical ethical committee in Amsterdam (2019.732 – NL6675902919) has approved the study protocol, as well as local institutional boards of each participating center. All legal European demands concerning insurances for possible harm from trial participation are met and all separate trial study sites have insurance as legally demanded by Dutch Government for non-trial harm for participating patients {30}.

Safety and quality control

Independent Central Adjudication Committee The ICAC is instituted to decide whether complications are rightfully labelled as TEC in the CRF. Two vascular surgeons and 1 registered Intensive-Care specialist will form this committee, none of them being a member of the ACTION-1 project group.

This committee will gather 30 days after 100, 200, 500 inclusions and 6 weeks after the last inclusion. They are blinded for the intervention and will judge the complication parts of the CRFs of all included patients.

In case of disagreement within this committee, the majority will be decisive. In case this committee decides that they need further clarification on a specific complication, this will be provided by the project group with data from the original electronic patient file of the patient.

Data safety monitoring board {21 a,b}

Despite the fact that this study is labeled as moderate risk, a full DSMB is installed. The DSMB is composed of three independent experts: a vascular surgeon, a cardio-thoracic surgeon and a clinical epidemiologist and biostatistician.

A safety review will be performed by an independent statistician (T. van der Ploeg, PhD) and reviewed by the data safety monitoring committee after the results are available for 100, 200 and 500 patients. This is a safety review, which looks at the combination of several outcomes as opposed to a traditional interim analysis with specified stopping rules.

In case of strong concerns about safety, the safety monitoring committee can advise to stop the study. Furthermore, Serious Adverse Events (SAE) will be reported to the data and safety monitoring committee.

A total of three safety reviews are planned:

- A first interim analysis is planned when approximately 100 subjects have been enrolled. This will provide data sample size calculations, and safety assessments.
- A second interim analysis is planned when approximately 200 subjects have been enrolled. This will provide data sample size calculations, and safety assessments.
- A third interim analysis is planned when approximately 500 subjects have been enrolled. This will provide data sample size calculations, and safety assessments.

Additional ad-hoc interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

Independent personnel who are not directly involved in conducting the study will perform the interim analyses and review of the unblinded outputs.

The DSMB should consider stopping the study if the following conditions are met:

Stopping rule for safety is:

- a difference in all-cause mortality within 30 days after surgery or during the same admission between intervention and control group with P value smaller than 0.05 in disadvantage of the intervention group.
- a difference in life threatening bleeding (E-CABG classification grade 2 or higher: transfusion of 5 or more units of red blood cells or reoperation for bleeding) between intervention and control group with P value smaller than 0.05 in disadvantage of the intervention group.
- a difference in the composite of all-cause mortality or life threatening bleeding (E-CABG classification grade 2 or higher: transfusion of 5 or more units of red blood cells or reoperation for bleeding) between intervention and control group with P value smaller than 0.05 in disadvantage of the intervention group.

Stopping rules for efficacy:

The DSMB should only under exceptional circumstances advise to terminate the trial under overwhelming efficacy of the act guided heparin group over the control group: the DSMB could consider stopping when a difference in incidence of TEC and mortality within 30 days after surgery or during the same admission between intervention and control group with P value smaller than 0.001 occurs, according to Haybittle–Peto boundary.

No further dissemination of interim results should occur, in particular not with individuals involved in treating the study's subjects or assessing clinical data.

While monitoring guidelines have been provided, the DSMB uses all available evidence and its collective judgement to base its recommendation to stop or modify the study.

Adverse, severe adverse events and suspected unexpected serious adverse reactions {22}

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. All adverse events, within 30 days postoperative or in the same admission, reported spontaneously by the subject or observed by the investigator will be recorded.

A SAE is defined as any untoward medical occurrence or effect that results in death, is life threatening (at the time of the event), requires hospitalization or prolongation of existing inpatients' hospitalization,

results in persistent or significant disability or incapacity, or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator. An elective hospital admission will not be considered as a serious adverse event.

All SAE will be reported by the local principal investigator to the sponsor within 24 hours of the study site staff becoming aware of the event. The sponsor will report all the SAE in a line listing, which will be reported once every six months to the medical ethical committee.

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered. Unexpected adverse reactions are suspected unexpected serious adverse reactions (SUSAR) if the following three conditions are met: the event must be serious; and there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose; and the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the Summary of Product Characteristics.

All SUSARs will be reported by the sponsor to the DSMB and to the accredited medical ethical committee via 'Toetsingonline' on the website of the Central Committee on Research involving Human Subjects (CCMO, www.ccmo.nl).

Independent monitoring and extensive quality control including all extensive legal demands for major trials with pharmaceuticals are met by an international acclaimed bureau: Julius Clinical (https://www.juliusclinical.com).

Inclusion criteria {10}

Inclusion criteria are: 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 {10}

Exclusion criteria are: not able to provide written informed consent; previous open or 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 protamine or fish protein.

Recruitment {15}

Patients scheduled to undergo open AAA repair, will be informed about the study by their attending vascular surgeon in outpatient clinic of participating hospitals about the study and the informed consent procedure will be explained. Informed consent will only be obtained by medical personnel who are GCP licensed. Also, a mandatory training by research-staff has to completed and the Site Initiation Visit (SIV) completed {26a}. This SIV is performed by an external, independent trial research organization: Julius Clinical. A total of 750 patients with an abdominal aortic aneurysm requiring open aneurysm repair, will be included in the ACTION-1 study, after signing informed consent (figure 1). An EQ-5D-5L questionnaire is handed out to the patient after receiving informed consent. The patient returns the form by post to the investigators, or bring the form when admitted for surgery, for baseline values. Figure 2 shows the participant timeline {13} and figure 3 shows the study schedule.

Randomization {16 a,b,c}

Randomization will take place just before the start of surgery by one of the researchers of the sponsor, using a computerized program (CASTOR EDC) with a random block size of 2, 4, 6. The randomization will be stratified by participating center.

Treatment details {11a}

ACT-guided heparinization

Heparin is given to reach an ACT of 200-220 seconds. At the start of the procedure, before any heparin is given, a baseline ACT measurement is performed. 3-5 minutes before clamping of the aorta, 100 IU/kg bodyweight of heparin is administrated intravenously. If patients weighing more than 150 kg, a maximum heparin dose of 15.000 IU heparin is administered to prevent overdose.

5 minutes after administration of heparin, ACT measurement is performed. If the ACT is below 180 seconds, an additional dose of heparin of 60 IU/kg is administered. If the ACT is between 180 and 200 seconds, an additional dose of heparin of 30 IU/kg is administered, and if the ACT is 200 seconds or longer, no extra heparin is given.

Five minutes after every administration of heparin the ACT is measured. If the ACT is 200 seconds or longer, the next ACT measurement is performed every 30 minutes, until the end of the procedure or until new heparin administration is required (because of ACT < 200 seconds). After each new dose of heparin, an ACT measurement is performed after 5 minutes and the above described protocol of ACT measurements will be repeated. After re-establishing blood flow and removing all clamps, the ACT is measured. Depending on that ACT value near the end of surgery, protamine is given to neutralize the effect of heparin.

If the ACT at closure is between 200 and 250 seconds, 2500 IU protamine should be administered. If the ACT is higher than 250 seconds, 5000 IU protamine should be administered, and if between 180 and 200 seconds, 1000 IU protamine. Five minutes after the administration of protamine, the ACT is measured. The ACT should preferably be below 180 seconds. If the ACT is still more than 200 seconds, protamine

should be administered again using to the above-mentioned protocol. When an additional dose of protamine is required, ACT measurement is performed 5 minutes after that administration.

5000 IU of heparin

A single dose of 5 000 IU of heparin is given 3-5 minutes before clamping of the aorta. No ACT measurements are performed. Only on clarified indications extra doses of heparin or protamine are permitted, at the discretion of the attending vascular surgeon. Deviations from protocol will be clearly stated with reasoning in the operative report.

Patients with additional doses of heparin or protamine outside protocol will not be excluded from the trial. Evaluation will be performed according to intention-to-treat analysis but also a per-protocol analysis will be performed and, if indicated, a sensitivity analysis.

Follow-up and quality of life measurements

Postoperative treatment, blood tests and outpatient clinic visits will be according to local protocols. The patients will be sent 3 kind of surveys; the EQ-5D-5L for quality of life evaluation, after 1 week, 4 weeks, 16 weeks and 23 weeks postoperatively; the iMCQ, for the evaluation of medical consumption, after 23 and 26 weeks postoperatively; and the iPCQ, for the economic evaluation, after 26 weeks postoperatively. These forms can be completed online or at home by the patients and send to the investigators by post. These questionnaires will be included in the CRFs

Data collection and management {18 a,b, 19}

After thirty days, all postoperative variables will be collected into the electronic database. All study parameters are standard care and can be reproduced from electronic patient files. Extensive standard operating procedures (SOP) are present to secure that data is properly scored.

All data will be collected at each participating center using the eCRF in the electronic database Castor EDC. Castor complies with all applicable laws and regulations with regard to ICHG GCP and the General Data Protection Regulation (GDPR). Each participating center will maintain a key list. This key list stays in the local hospital and will not be shared. After completion of the study, all study documents will be stored on site for 25 years.

All participating sites will be monitored by a Clinical Research Associate (CRA) of the sponsor Dijklander ziekenhuis and a selection sites by a monitor of Julius Clinical, a Clinical Research Organization (CRO) {27}.

After completion of the trial, all raw data will be made available for others, following the mandatory policy of ZonMw. No contractual agreements are made that limit any access for other investigators {29}.

Statistical analysis {20 a,b,c}

Descriptive statistics of continuous variables will be presented as means with standard deviations (SD) or medians with inter-quartile ranges (IQR) depending on the distribution of the data.

Categorical data will be presented as proportions and numbers. The statistical efficacy analysis will be conducted according to the intention-to-treat principle. A separate per protocol analysis will be performed additionally as a sensitivity analysis. All analyses will be performed with the latest version of the Statistical Package for Social Sciences (SPSS, SPSS Inc., Armonk, NY, USA).

The analysis of primary efficacy and safety outcomes will be performed on an intention-to-treat basis and in a hierarchical fashion. If statistical analysis shows that there is a statistically significant difference in the primary efficacy endpoint statistical analysis of the primary safety study parameter will be performed. If there is no significant difference between study groups in primary efficacy endpoint, assessment of primary safety endpoint will be considered exploratory.

Primary efficacy study parameter

The primary endpoint is the composite of the incidence of all TEC, including myocardial infarction, leg ischemia, deep venous thrombosis, colon ischemia, stroke, graft thrombosis, thrombo-embolic complications in kidney or spleen and other peripheral thrombosis and all-cause mortality within 30 days after surgery or during the same admission. Also, peroperative thrombosis requiring additional actions peroperatively (i.e., embolectomy, atherectomy or re-do of an anastomosis because of thrombus). The statistical efficacy analysis will be conducted with a chi-square test for proportions. Differences in the incidence of this composite endpoint between the intervention and control group will be expressed as the absolute risk difference with 95% confidence interval.

Primary safety study parameter

Incidence of bleeding complications according to E-CABG classification, grade 1 and higher.(31) For the bleeding complications a non-inferiority test will be used. We test the hypothesis that the difference in bleeding between the intervention group and the control group is below the a priori specified boundary of 11%. This will be tested using a one-sided t test with an alpha of 0.025, with the null hypothesis that the number of bleedings is above the threshold margin and the alternative hypothesis that is below the threshold margin. If the confidence interval for the bleeding complications does not include the non-inferiority limit in the per-protocol analysis and the intention-to-treat analysis non-inferiority for bleeding complications is established.

Secondary study parameter(s)

Secondary endpoints include all complications as defined by DSAA and suggested standards for reports on aneurysmal disease. Health status measured with the EQ-5D-5L questionnaire. Differences in categorical outcomes between the intervention and control group will be expressed as the absolute risk difference with 95% confidence interval. Differences in continuous outcomes will be tested with the

student's t- test in case of a normal distribution or the Mann-Whitney U-test in case the data do not follow the normal distribution. The level of significance is set at a two-sided p-value < 0.05.

Other study parameters

Peroperative blood loss, blood transfusions either autologous or homologous, other blood products administration, total operative time, clamping time, use of adjunctive hemostatic products, length of hospital (including ICU) stay and health status. ACT values measured. Amount of heparin and protamine used. The outcomes of the first 5 patients from all participating hospitals will be analyzed and compared with the outcomes of patients included later. Data on previous heparin protocol will be collected per hospital. Analyses will be conducted to determine whether the previously used heparin protocol affects the outcomes.

ECONOMIC EVALUATION:

Cost effectiveness analysis (CEA)

General considerations: We hypothesize that ACT guided heparinization could lower the rate of TEC and TEC related mortality to in total 11% and that the quality of life can be increased from 73% to 76%. The economic evaluation of ACT guided heparinization against standard care with a standardized bolus of heparin will be performed as cost-utility analyses and a cost effectiveness analysis from a societal perspective with the costs per quality adjusted life year (QALY) and the costs per prevented complication as the primary economic outcomes. The cost-utility analysis can be used for policy making and composition of a guideline. The cost-effectiveness analysis (CEA) relates to the clinical outcome parameter and may be used for prioritization or bench marking of strategies that enhance surgical patient safety. The CEA and CUA will be based on a time horizon of 6 months. All related complications are within the time horizon of 6 months and patients will be recovered from the surgery. For on-going complications such as leg amputations, colostomy, permanent neurological deficits, dialysis a CEA and CUA with a lifelong time horizon will be made using extrapolation and model-based techniques. For this time horizon discounting of effects and costs will be performed as stated in the most recent guidelines for cost analysis.(36) To account for uncertainties in the lifelong time horizon, a probabilistic sensitivity analysis will be performed.

Incremental cost-effectiveness ratios will be calculated as the difference in costs per QALY gained and as the difference in costs prevented complications. Sampling variability will be accounted for by bias-corrected and accelerated non-parametric bootstrapping. Results will be reported along with their 95% confidence intervals and displayed graphically with cost-effectiveness planes and with cost-effectiveness acceptability curves. One-way and multi-way sensitivity analyses will be done for the unit costs of the most common complications. Some missing data can be expected, if missing data is at random, this will be handled through multiple imputations with predictive mean matching.

Cost analysis

Medical costs, patient costs and productivity losses will be included in the evaluation. The medical costs cover the costs of surgery and related complications, anesthesia, theatre, peri- operative materials, inpatient stay at the ICU and the wards and medications. The patient costs include out-of-the pocket expenses like over-the-counter medication and health care related travel costs. Productivity losses are costs resulting from being absent and decreased productivity during work. Hospital health care utilization will be retrieved from CRFs and hospital information systems. Data on out-of-hospital health care will be gathered with the iMTA Medical Consumption Questionnaire (iMCQ) adjusted to the study setting. The productivity losses will be documented with the iMTA Productivity Cost Questionnaire (iPCQ). Questions on out-of-pocket expenses will be added to these patient questionnaires. Costs will be price indexed based on consumer price indices (CPI).

Costs will be calculated for individual patients as the product sum of the resource use and the respective unit costs. The iMCQ questionnaire will be send 13 and 26 weeks after surgery, the iPCQ only 26 weeks after surgery.

Patient outcome analysis

Patients will be asked to complete the EQ-5D-5L health status questionnaire at baseline, 1 week, 4 weeks, 13 and 26 weeks after surgery. These forms can be completed online or at home by the patients and send to the investigators by post. These questionnaires will be included in the CRFs. The EQ-5D-5L scoring profiles can be converted into a health utility score based on general population based Dutch tariffs.(37) QALYs will be calculated for each patient using linear interpolation between the successive health utility assessments over time.

Publication of data {31a,b,c}

During the informed consent procedure, participants can indicate whether they want to be informed about the results of the study. The results will be shared after, the last patient completed the 6 months surveys. Results will also be published in a peer-reviewed journal and will be described on clinicaltrials.gov.

Persons with substantive contributions to the design, conduct, interpretation, and reporting of this trial will be recognized through the granting of authorship on the final trial report.

Participant level dataset will be shared under pre-defined conditions and contract.

Discussion

The ACTION-1 trial is conducted to investigate if ACT guided heparinization might lead to better (patient related) outcomes than a standardized bolus of 5 000 IU of heparin without measuring its effect. The trial will be executed during open AAA repair in 18 large Dutch Vascular Centers (University and non-University) and 2 major centers in Germany and Denmark.

One of the possible concerns on operational issues might be the inclusion rate. Although the incidence of open AAA repair has declined considerably during the past decades due to the “EVAR first” policy, a stabilization or even small increase in open AAA repair is present. The much-discussed recent NICE Guidelines on AAA treatment and the strong recommendation issued by the Dutch Board of Vascular Surgery to perform EVAR within the applicable IFU, could be contributing factors to the renewed focus on open repair.(38)

Apart from the inclusion issue, some vascular surgeons may experience “cold feet” when their patient is randomized to an arm of the study that is not their preferred heparin regimen. Although our study group has proven convincingly that no evidence is present on either 5 000 IU or ACT guided heparinization, the strong believe and year-long routine of the individual surgeon can be hard to put aside.(26,27) Therefore, it might be anticipated that protocol deviations could occur on this aspect. For example: surgeon not administering a second dose of heparin if ACT is below 200 seconds in the ACT group, or extra gift of heparin outside protocol if the patient is randomized in the 5 000 IU group. The frequency of this reluctance to adhere to the protocol is deemed to be low and equal in both groups. Before the definite participation of each vascular center a 30-minute presentation and discussion was held in which it was underlined that no evidence is present on either heparin regimen. Also, the strong support of the Board of Dutch Vascular Surgeons and the Board of Dutch Medical Specialists, contributes to creating equipoise amongst participating surgeons. To further enhance this feeling, it is emphasized in the protocol that individual surgeons are allowed to deviate from the protocol if this is deemed necessary for patient safety. Furthermore, during all procedures in ACTION-1, one of the trained team members will be present in the operating room during the duration of the entire procedure. The team member will randomize the patient when anesthesia is completed and the team member will perform all ACT measurements, if applicable, to exclude as much as possible any incorrect measurements or inconsistencies regarding ACT measurements. Also, the attending team member will record all variables present in the eCRF. In this manner maximal exclusion of bias can be achieved. During the two years of finetuning the protocol for ACTION-1 and in the process of extensive, repeated international peer-reviewing by the funding agency ZonMw, all possible protocol and operational issues were discussed and, hopefully, anticipated.

Trial status

Medical Ethics Committee and CCMO approval was obtained on 21-st of February 2020 {24}. The current protocol of the ACTION-1 study is version 12, 10-11-2020 {3}. All major protocol modifications and amendments will be submitted to the Medical Ethics Committee, shared with the participating hospitals and published on clinicaltrials.gov. The recruitment of the study began in March 2020. At the current date 61 patients have been included already despite delay in the preparation of participating hospitals due to the corona-crisis. The completion of the study is expected in December 2024, with a 6 moths extension period granted by ZonMw due to corona-crisis.

Abbreviations

AAA = Abdominal aortic aneurysm

ACT = Activated Clotting Time

CCMO = Central Committee on Research involving Human Subjects

CRA = Clinical Research Associate

CRO = Clinical Research Organization

CRF = Case Report Form

DSAA classification C = Aneurysm originating below the Superior Mesenteric Artery

eGFR = estimated Glomerular Filtration Rate

EPF = Electronic Patient File

GCP = Good Clinical Practice

GDPR = General Data Protection Regulation

HIT = Heparin Induced Thrombocytopenia

HMS = Hemostasis Management System

HR-ACT = high-range ACT cartridges

ICAC = Independent Central Adjudication Committee

iMCQ = iMTA Medical Consumption Questionnaire

iPCQ = iMTA Productivity Cost Questionnaire

IU = International Units

NCAP = Non-cardiac arterial procedures

RCT = Randomised controlled trial

RIFLE = Risk, Injury, Failure, Loss, End stage renal disease. Criteria for classifying the severity of acute kidney injury

SAE = Serious Adverse Event

SIV = Site Initiation Visit

SPC = Summary of Product Characteristics

SUSAR = Suspected Unexpected Serious Adverse Reaction

TEC = thrombo-embolic complications

TIA = Transient ischemic attack

WMO = Medical Research Involving Human Subjects Act

Declarations

Ethics approval and consent to participate:

Medical Ethics Committee and CCMO approval was obtained on 21-st of February 2020

Consent for publication:

We are willing to provide a model consent form on request.

Availability of data and materials

Participant level dataset will be shared under pre-defined conditions and contract.

Competing interests:

No financial or other competing interests are present for principal investigators for the overall trial and for each study site.

Funding:

Financial: ZonMw grant: 848043004

In-kind: Medtronic[â] for contribution for Hemostasis Management System Plus devices

In-kind: Dijklander ZH, Amsterdam UMCs: personnel

Authors' contributions:

Design, protocol development, application grant ZonMw: AW, MR, JB, MK, SM, SvD, JT, VJ

Finetuning protocol, different aspects: LR, YF, ED and JH

All authors read and approved the final manuscript.

Acknowledgements:

Not appliclable.

References

1. Burgers LT, Vahl AC, Severens JL, Wiersema AM, Cuypers PWM, Verhagen HJM, et al. Cost-effectiveness of Elective Endovascular Aneurysm Repair Versus Open Surgical Repair of Abdominal Aortic Aneurysms. Eur J Vasc Endovasc Surg. 2016 Jul 1;52(1):29–40.
2. Behrendt CA, Sedrakyan A, Rieß HC, Heidemann F, Kölbel T, Petersen J, et al. Short-term and long-term results of endovascular and open repair of abdominal aortic aneurysms in Germany. J Vasc Surg [Internet]. 2017 Dec 1 [cited 2020 Apr 3];66(6):1704-1711.e3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28780975
3. Behrendt CA, Rieß HC, Schwaneberg T, Larena-Avellaneda A, Kölbel T, Tsilimparis N, et al. Incidence, Predictors, and Outcomes of Colonic Ischaemia in Abdominal Aortic Aneurysm Repair. Eur J Vasc Endovasc Surg [Internet]. 2018 Oct 1 [cited 2020 Apr 3];56(4):507–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30037737
4. Deery SE, O'Donnell TFX, Bodewes TCF, Dalebout BA, Pothof AB, Shean KE, et al. Early reintervention after open and endovascular abdominal aortic aneurysm repair is associated with high mortality. J Vasc Surg. 2018 Feb 1;67(2):433-440.e1.
5. Trenner M, Haller B, Storck M, Reutersberg B, Kallmayer MA, Eckstein HH. Trends in Patient Safety of Intact Abdominal Aortic Aneurysm Repair: German Registry Data on 36,594 Procedures. Eur J Vasc Endovasc Surg [Internet]. 2017 May 1 [cited 2020 Apr 3];53(5):641–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28110907
6. Hynes CF, Endicott KM, Iranmanesh S, Amdur RL, Macsata R. Reoperation rates after open and endovascular abdominal aortic aneurysm repairs. J Vasc Surg [Internet]. 2017 May 1 [cited 2020 Apr 3];65(5):1323–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28073669
7. Prinssen M, Verhoeven ELG, Buth J, Cuypers PWM, Van Sambeek MRHM, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med [Internet]. 2004 Oct 14 [cited 2020 Apr 3];351(16):1607–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15483279
8. Lo RC, Bensley RP, Hamdan AD, Wyers M, Adams JE, Schermerhorn ML. Gender differences in abdominal aortic aneurysm presentation, repair, and mortality in the Vascular Study Group of New England. J Vasc Surg [Internet]. 2013 May [cited 2020 Apr 3];57(5):1261-1268.e5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23384493
9. Wiersema A, Bruijninckx C, Reijnen M, Vos J, Van Delden O, Vahl A, et al. Perioperative prophylactic antithrombotic strategies in vascular surgery: current practice in the Netherlands. J Cardiovasc Surg (Torino) [Internet]. 2015 Feb [cited 2020 Apr 3];56(1):119–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23337406
10. Wiersema AM, Jongkind V, Bruijninckx CMA, Reijnen MMPJ, Vos JA, Van Delden OM, et al. Prophylactic perioperative anti-thrombotics in open and endovascular abdominal aortic aneurysm

(AAA) surgery: A systematic review [Internet]. Vol. 44, European Journal of Vascular and Endovascular Surgery. 2012 [cited 2020 Apr 3]. p. 359–67. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22831869

11. Hirsh J. Erratum: Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety (Chest (1998) 114 (495S)). Vol. 115, Chest. American College of Chest Physicians; 1999. p. 1760.
12. Finley A, Greenberg C. Heparin sensitivity and resistance: Management during cardiopulmonary bypass. Vol. 116, Anesthesia and Analgesia. 2013. p. 1210–22.
13. Arsenault KA, Paikin JS, Hirsh J, Dale B, Whitlock RP, Teoh K, et al. Subtle differences in commercial heparins can have serious consequences for cardiopulmonary bypass patients: A randomized controlled trial. J Thorac Cardiovasc Surg [Internet]. 2012 Oct [cited 2020 Apr 3];144(4):944-950.e3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22743176
14. Nath FC, Muller DW, Rosenschein U, Ellis SG, Topol EJ. Heparin monitoring during coronary intervention: activated clotting time versus activated partial thromboplastin time. Can J Cardiol [Internet]. 1993 Nov [cited 2020 Apr 3];9(9):797–801. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8281479
15. Chew DP, Bhatt DL, Lincoff AM, Moliterno DJ, Brener SJ, Wolski KE, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: Aggregate results from 6 randomized, controlled trials. Circulation. 2001 Feb 20;103(7):961–6.
16. Kasapis C, Gurm HS, Chetcuti SJ, Munir K, Luciano A, Smith D, et al. Defining the optimal degree of heparin anticoagulation for peripheral vascular interventions insight from a large, regional, multicenter registry. Circ Cardiovasc Interv [Internet]. 2010 Dec [cited 2020 Apr 3];3(6):593–601. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21062999
17. Veerhoek D, Groepenhoff F, van der Sluijs MGJM, de Wever JWB, Blankensteijn JD, Vonk ABA, et al. Individual Differences in Heparin Sensitivity and Their Effect on Heparin Anticoagulation During Arterial Vascular Surgery. Eur J Vasc Endovasc Surg. 2017 Oct 1;54(4):534–41.
18. Coyne TJ, Wallace MC, Benedict C. Peri-operative anticoagulant effects of heparinization for carotid endarterectomy. Aust N Z J Surg [Internet]. 1994 Oct [cited 2020 Apr 3];64(10):679–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7945064
19. Poisik A, Heyer EJ, Solomon RA, Quest DO, Adams DC, Baldasserini CM, et al. Safety and efficacy of fixed-dose heparin in carotid endarterectomy. Neurosurgery [Internet]. 1999 Sep [cited 2020 Apr 3];45(3):434–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10493364
20. De Sousa AA, Dellaretti MA, Faglioni W, Carvalho GTC. Monitoring of activated coagulation time in carotid endarterectomy. Surg Neurol [Internet]. 2005 [cited 2020 Apr 3];64(SUPPL. 1):S6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15967231
21. Saw J, Bajzer C, Casserly IP, Exaire E, Haery C, Sachar R, et al. Evaluating the Optimal Activated Clotting Time During Carotid Artery Stenting. Am J Cardiol [Internet]. 2006 Jun 1 [cited 2020 Apr 3];97(11):1657–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16728233

22. Goldhammer JE, Zimmerman D. Pro: Activated Clotting Time Should Be Monitored During Heparinization For Vascular Surgery [Internet]. Vol. 32, Journal of Cardiothoracic and Vascular Anesthesia. W.B. Saunders; 2018 [cited 2020 Apr 3]. p. 1494–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28943189
23. Dieplinger B, Egger M, Luft C, Hinterreiter F, Pernerstorfer T, Haltmayer M, et al. Comparison between activated clotting time and anti-activated factor X activity for the monitoring of unfractionated heparin therapy in patients with aortic aneurysm undergoing an endovascular procedure. J Vasc Surg. 2018 Aug 1;68(2):400–7.
24. Lee JM, Park EY, Kim KM, Won JC, Jung TK, Lee SK. Comparison of activated clotting times measured using the Hemochron Jr. Signature and Medtronic ACT Plus during cardiopulmonary bypass with acute normovolemic haemodilution. J Int Med Res. 2018 Feb 1;46(2):873–82.
25. Chia S, Van Cott EM, Raffel OC, Jang IK. Comparison of activated clotting times obtained using Hemochron and Medtronic analysers in patients receiving anti-thrombin therapy during cardiac catheterisation. Thromb Haemost. 2009 Mar;101(3):535–40.
26. Doganer O, Wiersema AM, Scholtes V, Blankensteijn JD, Yeung KK, Jongkind V. No Concluding Evidence on Optimal Activated Clotting Time for Non-cardiac Arterial Procedures [Internet]. Vol. 59, European Journal of Vascular and Endovascular Surgery. W.B. Saunders Ltd; 2020 [cited 2020 Apr 3]. p. 137–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31699657
27. Doganer O, Jongkind V, Blankensteijn JD, Yeung KK, Wiersema AM. A Standardized Bolus of 5 000 IU of Heparin Does not Lead to Adequate Heparinization during Non-cardiac Arterial Procedures. Ann Vasc Surg [Internet]. 2020 [cited 2020 Dec 1];0(0):1–7. Available from: https://doi.org/10.1016/j.avsg.2020.07.035
28. Dutch surgical aneurysm audit. [Internet]. [cited 2020 Apr 3]. Available from: https://dica.nl/dsaa/home
29. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg [Internet]. 2018;(2018). Available from: https://linkinghub.elsevier.com/retrieve/pii/S1078588418306981
30. Biancari F, Ruggieri VG, Perrotti A, Svenarud P, Dalén M, Onorati F, et al. European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG registry): Study Protocol for a Prospective Clinical Registry and Proposal of Classification of Postoperative Complications. J Cardiothorac Surg. 2015 Jun 30;10(1).
31. Brascia D, Reichart D, Onorati F, Perrotti A, Ruggieri VG, Bounader K, et al. Validation of Bleeding Classifications in Coronary Artery Bypass Grafting. Am J Cardiol [Internet]. 2017 Mar 1 [cited 2020 Apr 3];119(5):727–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28024656
32. Mazzalai F, Piatto G, Toniato A, Lorenzetti R, Baracchini C, Ballotta E. Using protamine can significantly reduce the incidence of bleeding complications after carotid endarterectomy without

increasing the risk of ischemic cerebral events. World J Surg [Internet]. 2014 May [cited 2020 Apr 3];38(5):1227–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24276985

33. Yamamoto S, Sakakura K, Taniguchi Y, Yamamoto K, Wada H, Momomura SI, et al. Safety of reversing anticoagulation by protamine following elective transfemoral percutaneous coronary intervention in the drug-eluting stent era. Int Heart J [Internet]. 2018 May 1 [cited 2020 Apr 3];59(3):482–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29743410
34. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ [Internet]. 2013 [cited 2021 Apr 29];346. Available from: https://pubmed.ncbi.nlm.nih.gov/23303884/
35. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, workgroup the A. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care [Internet]. 2004 [cited 2019 Mar 29];8(4):R204. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC522841/
36. Swan Tan S, Bouwmans-Frijters CAM, Hakkaart-van Roijen L. Handleiding voor kostenonderzoek: methoden en referentieprijzen voor economische evaluaties in de gezondheidszorg. Tijdschr voor gezondheidswetenschappen. 2012 Sep 11;90(6):367–72.
37. Versteegh M, M. Vermeulen K, M. A. A. Evers S, de Wit GA, Prenger R, A. Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. Value Heal. 2016 Jun 1;19(4):343–52.
38. Abdominal aortic aneurysm: diagnosis and management NICE guideline [Internet]. 2020 [cited 2020 Dec 1]. Available from: www.nice.org.uk/guidance/ng156

Appendices

{32}: Model consent form and other related documentation given to participants and authorized surrogates. Patients and physicians can find information about the ACTION trial also on ACTION-1.nl. All participating hospitals, inclusion, information for patients (including lay video) are depicted on this website.

{33}: No biological specimens are stored.

Figures

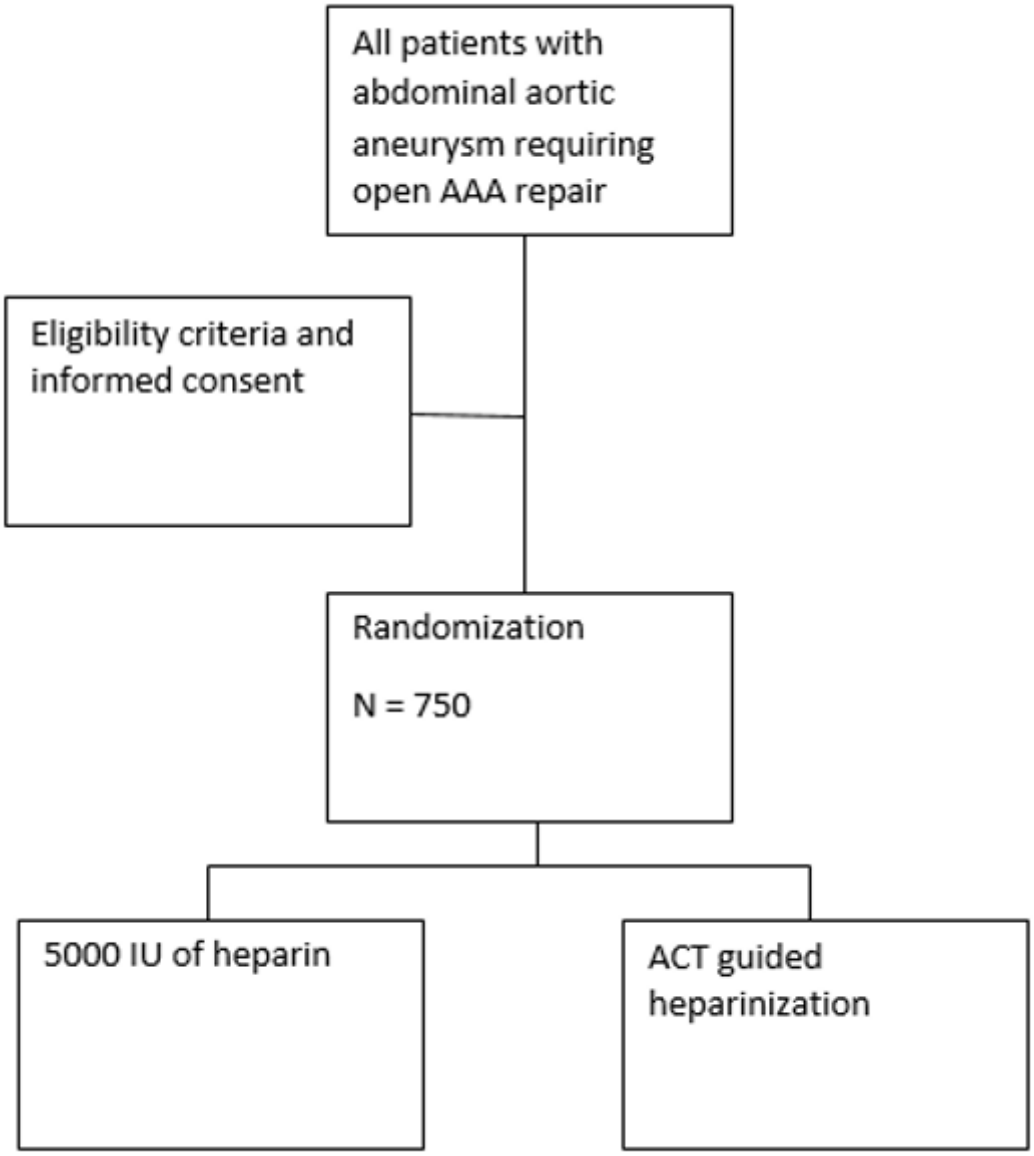

Figure 1

Recruitment

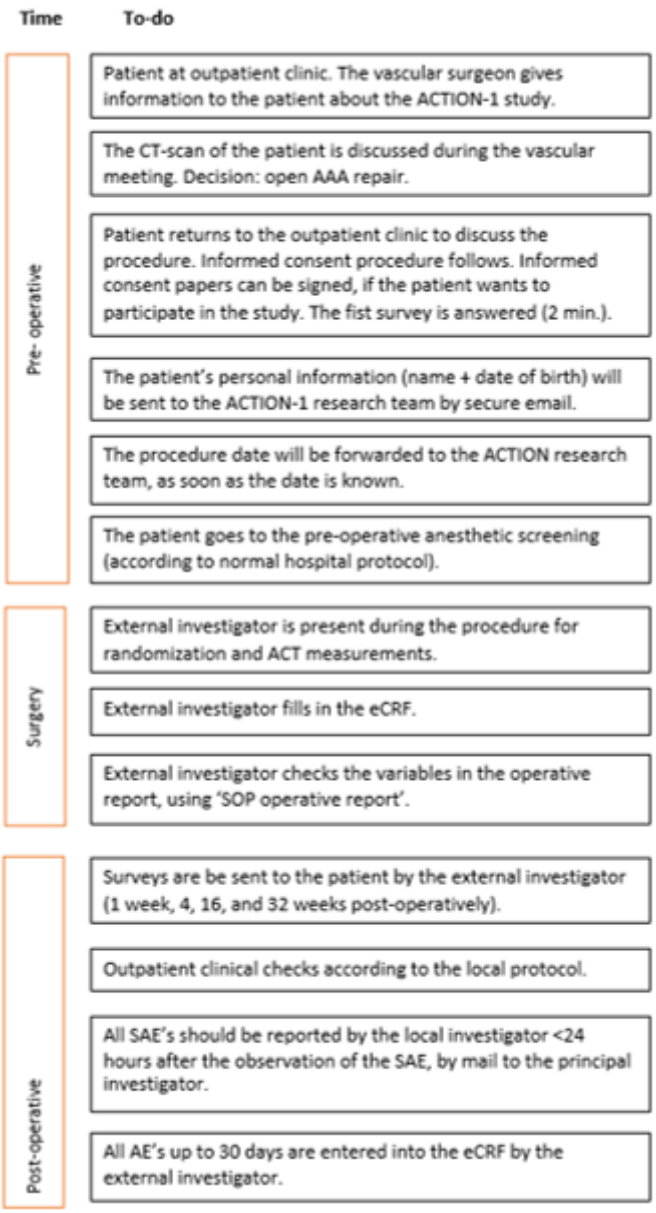

Figure 2

Participant timeline

Study schedule							
Period	Screening & enrollment	intervention	Follow-up				
	... - day 0	0	7 days	28 days	30 days	3 months	6 months
Eligibility	X						
Informed consent	X						
1st survey	X						
Randomisation		X					
Collect baseline variables		X					
Intervention 5000IU		X					
Intervention ACT guided heparinisation		X					
2nd survey			X				
3rd survey				X			
Collect all outcome variables					X		
4th survey						X	
5th survey							X
Reporting of Serious Adverse Events		X					
End of follow-up							X

Figure 3

Schedule of enrollment, interventions and assessment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- EthicalapprovaldocumentEnglishsummaryincluded.df.pdf
- Originalfundingdocumentation.pdf
- Englishtranslationoforiginalfundingdocumentation.docx
- SPIRITchecklist.docx