Title page

Norwegian **l**aparoscopic **a**ortic **s**urgery **t**rial (NLAST)
- study protocol of a multicenter prospective randomized controlled trial for total laparoscopic and open aorto-bifemoral bypass for aortoiliac occlusive disease

Final study protocol version dated February 2013.

Author: Syed Sajid Hussain Kazmi

Study protocol

Norwegian **l**aparoscopic **a**ortic **s**urgery **t**rial (NLAST) - study protocol of a multicenter prospective randomized controlled trial for total laparoscopic and open aorto-bifemoral bypass for aortoiliac occlusive disease

Main investigator

S. Sajid H. Kazmi, MD, PhD
Department of Vascular Surgery,
Heart, Lung and Vascular Clinic,
Oslo University Hospital, Aker.
sshkazmi@gmail.com; syekaz@ous-hf.no
Tel: +47 23336658; Jobb: +47 02770
Mobil: +47 92468309

Trail partners

Work in progress (*All vascular surgery departments in the South Eastern Region have been invited to take part in this study*).

Steering Committee

S. Sajid H. Kazmi, MD, PhD, Oslo University Hospital
Jørgen J. Jørgensen, MD, PhD, Oslo University Hospital
J. Otto Sundhagen, MD, Oslo University Hospital
Michael Abdelnoor, MPH,PhD, Oslo University Hospital
Mehdi Sehba, MD, Sykehuset i Østfold, Fredrikstad
Russel Jakobsen, MD, Sykehuset i Vestfold, Tønsberg
Karsten Myhre, MD, Sykehuset i Vestre Viken, Drammen Sykehus
Erik Mulder Pettersen, MD, Sykehuset i Sørlandet, Kristiansand Sykehus
(……..)Akershus Universitetssykehus

CONTENTS

Background

The total prevalence of peripheral arterial disease (PAD) is reported to be in the range of 3% to 10%, increasing to 15% to 20% in the persons over 70 years (1-3). This prevalence and the incidence of PAD are likely to increase because of the aging of Western populations. The clinical presentation of PAD depends upon the severity of atherosclerotic lesion. On the basis of clinical presentation, Rutherford RB et al., has suggested the following classification of the PAD, divided into grades and categories (4):

Grade	*Category*	*Clinical description*
0	0	Asymptomatic
	1	Mild claudication
I	2	Moderate claudication
	3	Severe claudication
II	4	Ischemic rest pain
III	5	Minor tissue loss – ulcus, focal gangrene
	6	Major tissue loss – functional foot no longer salvageable

The delineation between mild, moderate and severe claudication is not specified in Rutherford classification, but is mentioned in the Fontaine classification as 200 meters. Fontaine classification is as follows:

Stage I – Asymptomatic.
Stage IIa – Intermittent claudication after more than 200 meters of pain free walking.
Stage IIb – Intermittent claudication after less than 200 meters of walking.
Stage III – Rest pain.
Stage IV – Ischemic ulcers or gangrene.

The main symptom of atherosclerotic lesions in the aorto-iliac segment is intermittent claudication, and only 1-3% of patients with the disease present with more severe symptoms like critical limb ischemia (5).

Trans-Atlantic Inter-Society Consensus (TASC) II has classified the aorto-iliac occlusive disease (AIOD) lesions into type A-D (5) Figure 1, Table 1. Most of the patients can be treated conservatively, according to the best medical treatment principles (6,7). However,

symptomatic desease may need additional treatment. For TASC II types, A and B lesions, percutaneous transluminal angioplasty (PTA) should be the treatment of choice. Whereas, type C lesions can either be treated with PTA or open surgery. TASC II recommends surgery as the treatment of choice for type D lesions.

Due to the increasing experience within the endovascular techniques and partly, due to the technical advancements, even complex type D lesions, are being tried to be primarily treated endovascularly. However, the reinterventions rate are higher for the PTAs and the long time results of aortobifemoral bypass still remains best for the treatment of PAD (8-11). Also surgery remains as the only treatment option after an unsuccessful endovascular treatment.

Patients with TASC type D lesions and with severe intermittent claudication (defined as <200 meters pain free walking distance) or critical ischemia (defined as >2 weeks symptoms duration) can be treated with an aorto-bifemoral bypass (ABFB), either through median laparotomy or by a totally laparoscopic procedure (5,12).

The feasibility of a totally laparoscopic ABFB has been proven during the last 15 years, by a number of published series (12-15). Although longer operation time, the lesser invasive nature of the totally laparoscopic ABFB seems to have important short term advantages (less post-operative morbidity, shorter hospital stay, faster recovery).

Although, the conservative treatment of PAD, in addition to patients life-style changes may prevent aggravation/ progression of the disease, intermittent claudication and short walking distance (<200 meters) seriously reduce the patients quality of life. Total laparoscopic ABFB may help achieve an even earlier improvement in the quality of life in patients with severe AIOD.

The total laparoscopic ABFB procedure has been performed for the treatment of AIOD, TASC II type D lesions since 2005, at the Vascular Department, Oslo University Hospital Aker (16). We have overcome the learning curve and the procedure is routinely offered to the suitable patients. The results of our experience with the technique are being compiled. On the basis of published literature and our own experience, naturally, we find it necessary to compare the two procedures in a randomized controlled fashion to confirm the efficacy of one procedure over the other.

Method

This is a prospective multi-centre, non-blinded, randomized control study. Patients with symptomatic AIOD and with TASC II type D lesions in the aortoiliac segment will be randomized for either totally laparoscopic aortobifemoral bypass (ABFB) or open surgery through median laparotomy.

Study aim and objectives

The aim of the study is to compare the surgical and clinical outcomes between the open and total laparoscopic ABFB for the treatment of AIOD, with TASC II type D lesions. Specifically, the study will examine the postoperative complications and the improvement in QoL after the two treatments, and the short, mid- and long-term effects of each treatment. The study will help us to document carefully the efficacy of each treatment modality and perform cost-analyses.

Hypothesis

Our main hypothesis is that the laparoscopic ABFB is a better treatment method than the conventional open ABFB, for the treatment of TASC II type D lesions based on the following criteria:

1- Patients treated with laparoscopic ABFB have fewer post-operative complications as compared to open ABFB.
2- Patients treated with laparoscopic ABFB achieve earlier and better QoL,
3- Patients treated with laparoscopic procedure have less aggressive systemic inflammatory response than open surgery,
4- Patients treated with laparoscopic ABFB have less operative stress, and
5- Laparoscopic ABFB is more cost-effective than open ABFB for the treatment of AIOD, TASC II type D lesions.

Endpoints

The *primary endpoint* of this study is post-operative complications (systemic and local complications).
Secondary endpoints of this study are:

The health related quality of life (QoL), assessed by using bodily pain domain in the Short Form SF– 36 questionnaire, 3 months post-operatively (17).
Changes in serum proinflammatory markers from baseline (IL-6, IL-8, TNFα, suPAR, hs-CRP and CRP) (18),
Operative stress response- defined as serum changes from baseline in catacholamines (adrenalin, noradrenalin), cortisol, aldosterone, insulin, ACTH, etc, (19)
Mean change in walking distance from baseline,
Mean change in ABI from baseline,
Mean change in serum kreatinin, uric acid, GFR, total cholesterol, triglyseride, HDL and LDL,
Cardiovascular and endothelial function biomarkers such as PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa, NO, E-selectin, vascular cell adhision molecule-1 (sVCAM-1), intercellular adhision molecule-1 (sICAM),
Hospital stay and post-operative morbidity.

Other secondary endpoints are procedure related events such as duration of operation, operative blood-loss, conversion to open procedure, re-operations and re-admissions. Furthermore type and amount of analgesics, VAS-pain score, return to per-oral diet, flatus, defecation and return to walking and all-cause mortality, shall also be registered.

Primary, primary assisted patency and secondary patency will be noted. The primary patency is defined as persistent patency without repeat intervention (4). Assisted primary patency is defined as patency achieved with minor reintervention including dilatation or anastomotic revision to prevent graft failure. Secondary patency is defined as patency obtained by restoration after occlusion (4).

Systemic morbidity is defined as non-fatal damage or disease with a health impact that is related to the procedure and involves any organ or tissue other than the peripheral arterial system or the surgical wound (4,13). *Local morbidity* is defined as non-fatal procedure related damage or disease that involves the peripheral vascular system or the surgical wound (4,13).

Data concerning late complications (hernia, re-stenosis, occlusions etc.) occuring after more than four weeks will be collected at the out-patient clinic, 1, 3, 6 and 12 months and at 2, 5 and 10 years, post-operatively.

Power analysis

The first study considered was the study published by Bruls et al. (20). They had 31 systmic and local complications among 150 (20.6%)patients operated with open ABFB and just 5 among 74 patients operated with LABF procedure. A relative risk of 20,6 / 6,8 = 3,0 was calculated for their study. They had a follow-up time period of 24 months and the post operative complications rate ratio (RR) of 0,33 could be calculated for their study population.

The second study considered was our pilot study (in manuscript). In this study 22 sytemic and local complications occurred among 30 patients(73.3%) operated with open ABFB and 11 among 50 patients operated with LABF procedure during a mean follow-up time period of 3,49 years. A relative risk of post-op complications was calculated to be 73 / 22 = 3,02, i.e., almost the same as observed by Bruls et al. And a rate ratio (RR) of 0,30 was calculated for a mean follow-up time period of 3,49 years.

The mean relative risk RR of the two studies was 0,33 + 0,30 / 2 = 0,315 and the mean follow-up time period was 2,0 + 3,4 / 2 = 2,9 years. The mean incidence of systemic and local complications was 20.6%+73.3%=47%

Concidering these figures and a ratio of unexposed divided by exposed (OABF / LABF) of 2, for type I error of 5% and a power of 90% we will need 35 patients in the laparoscopic ABFB group and 70 patients in the open ABFB group for a mean follow-up time period of 2,9 years. Considering also a 20% drop-out, we will need to increase the sample power by a coefficient of 1.2. This means that we would need 42 patients in the LABFB group and 84 patients in the OABFB group, i.e., a total of 126 patients.

Inclusion criteria

1- Patients with AIOD, type D lesion according to TASC II, with severe claudication, defined as less than 200 meters pain-free walking distance or chronic critical ischemia defined as more than 2 weeks of symptoms duration i.e., rest pain and/ or ischemic wound in the lower limb (4, 5).

2- Patients with a previously, unsuccessful endovascular treatment for AIOD (re-occlusion, re-stenosis, evaluated as no longer suitable for a new endovascular procedure).

3- Patients with AIOD and previously unsuccessful axillo-bifemoral or femoro-femoral cross-over bypass, now evaluated to be eligible for open ABFB.

Exclusion criteria

No informed written consent.
Symptomatic coronary artery disease, reduced ejection fraction (< 40%).
Previous multiple major abdominal surgery (e.g., left colon resection, hostile abdomen).
Previous abdominal radiation therapy.
Active cancer.
Abdominal aortic aneurysms >5.0 cm

N.B. Previously performed cholecystectomy, appendectomy or any gynecological procedure are not considered as exclusion criteria.

Participating hospitals

Following hospitals will participate in this study:
Oslo University Hospital HF
Sykehuset i Vestfold HF
Sykehuset i Østfold – Fredrikstad
Besides Akershus University Hospital, Drammen Sykehus and Sørlandet Sykehus are also invited to participate in this trial.

Logistic plan

Since laparoscopic aortic surgery is established and being performed only in Oslo University Hospital, all patients from participating hospitals, randomized to the laparoscopic procedure, will be transferred to Oslo University Hospital, for surgery. *In case, there is any hinder in transferring the patient to Oslo University Hospital, laparoscopic surgical team shall be performing the laparoscopic procedures at the patient's local hospital.* Whereas, the patients randomized for open procedure shall be operated on at the local participating hospital. In order to avoid the impact of initial learning curve on the results of surgery, all operations shall be performed by or assisted by experienced vascular surgeons. Patient's follow-up shall be performed at the hospital of primary referral.

Randomization and data collection

The patients will be informed about the trial and when informed written consent is obtained, randomization will be performed. Randomization will be performed as a permuted block randomization, stratified on every participating centre (23). The randomization list will be transferred to a sequence of sealed envelopes, each containing the name of the next treatment on cards.

Each centre will assign one local coordinator for the collection of data. There will be a regular contact between the coordinators. One research fellow at the Oslo University Hospital will monitor the data of every patient in the study. An internet based data register shall be developed and all information added shall be made anonymous. Access to the data register shall only be provided to a limited number of authorized persons. Daily registration of the treatment data will be done until the patient discharge and at the follow-ups.

Statistical methods

The major outcomes are the total SF36 and its different components. The efficacy analysis of the intervention will be done according to the intention to treat strategy, while another analysis of effectiveness of the intervention will be done according to on treatment strategy.

Change in SF36 components from baseline to 1, 3, 6, 12 and 24 months shall be registered. The ANCOVA method will be used to quantify efficacy and effectiveness, where controlling for baseline and risk factors (24). To study the effect of intervention longitudinally, from baseline to 1, 3, 6, 12 months and 1 year, the General Estimate Equisation (GEE) will be used. Regression model shall be used to control for nuisance and risk factors (25).

Cost-utility analysis

The economic evaluation will be performed as a cost-utility analysis (CUA) where costs and health benefits of the two interventions will be compared. The costs will include relevant resource use, and will be expressed in monetary values, while health effects will be expressed in quality adjusted life-years (QALY). The CUA will be based on a decision analytic model designed as a Markov model to estimate the incremental cost-effectiveness ratio (ICER) of laparascopic surgery compared to open surgery. The thresholdvalue of the ICER for a cost-effective intervention will be defined as Norwegian kroner (NOK) 500 000 per QALY gained, according to guidelines from the Norgwegian Directorate of Health (1).The CUA will be performed from both a societal- and a healthcare perspective with a life-long timehorizon. Costs and health effects will be discounted at annual disount rates of 4% and 2%, respectively (26). Uncertainties in the model will be analysed through sensitivity analysis.

The model will be populated with epidemilogical and clinical data, supplied with data on costs and health effects in terms of health-related quality of life (HrQoL).

Epidemiological data

Data will be obtained from NLAST and published studies on aortoiliac occlusive disease.

Clinical data on laparoscopic vs open surgery

Data will be obtained from NLAST.

Costs

The direct costs related to the patients will be estimated on several different components.

A. Procedural costs of intervention for laparoscopic and open surgery. The costs will be estimated through microcost analyses, which will follow each individual patient during surgery, and register the actual consumption of resources related to the intervention (lenght of stay, cost of complications, use of personnel, use of medical equipment, medication etc.).
B. Costs of hospitalisations after intervention
C. Costs of out-patient consultations
D. Costs of rehabilitation
E. Costs of prescription medications

There will also be obtained written consent from participants to be able to obtain register data on the individual patients regarding resource utilization of healtcare services.
In the societal perspective indirect costs related of sickness absence will also be included.

Health-related quality of life

Data on HrQoL will be obtained from the generic measurement instruments SF-36 and EQ-5D, and will be collected pre-operatively, and at 1, 3, 6, 12, 24 months post-operatively. Data from the SF-36 questionnaire will be transformed to preference-based utilities that can be used in the CUA, by using SF-6D.

QoL registration

SF-36 (version 2.0) and EQ-5D questionnaire will be filled out by the patients preoperatively and at 1, 3 and 6 months and at 1 and 2 years, post-operatively. All patients included in the NLAST study shall fill the QoL forms and return it by post (prepaid postage envelope) to Dr.

S Sajid H Kazmi, Karavdelingen, Hjerte-, lunge- og karklinikken, Oslo Universitetssykehus HF Postboks 4959 Nydalen, 0424 Oslo.
Every effort shall be made to get the fully answered questionnaire, back from the patient in time.

Pro-inflammatory markers

Blood samples shall be collected from peripheral veins preoperatively and during the follow-up. The samples shall be collected from the central vein as long as the patient is admitted with the hospital for surgery and has an established central line.

Blood samples for inflammatory markers will be collected same day before operation 1, 6, 12 and 24 hours and at 1, 6 and 12 months, postoperatively. Blood samples obtained will be centrifuged immediately at 4°C and serum collected in tubes, will be stored at -70°C until analysed, finally.

Each participating hospital must have a freezer for the storage of blood samples. The freezer must be connected to the hospital´s emergency power supply to avoid any damage of stored blood samples due to increased temperature.

Operative stress-response

Blood samples for catacholamines (adrenalin, noradrenalin), cortisol, aldosterone, insulin, blood sugar, ACTH, etc shall be collected from peripheral veins during the follow-up. The samples shall be collected from the central vein as long as the patient is admitted with the hospital for surgery and has an established central line. The samples shall be collected (i) 5 minutes after intubation, (ii) 2 minutes after operation start, (iii) 2 minutes before abdominal aortic cross-clamping, (iv) 1-2 minutes after aortic cross-clamping, (v) 30-45 minutes after aortic cross-clamping, (vi) 5 minutes before lapaoscopy/ laparotomy completion and at (vii) 24 hours post operatively.

Recruitment

Patients inclusion in this study will start from (…….) 2012 and will continue for a period of 3 years (……. 2015) or until recruitment of 120 patients.

Withdrawal of subjects

Patients may withdraw from the study at any time without prejudice. All subjects will be followed until the conclusion of the study unless the subject requests withdrawal of consent. All applicable activities scheduled for the final visit should be performed at the time of discontinuation. Any adverse experience that is present at the time of discontinuation/ withdrawal should be recorded.

Study approval

The checklists by the Consolidated Standards of Reporting Trials (CONSORT) will be used to design, conduct and reporting for the trial (27). The trial will be registered in the www.clinicaltrial.gov. The trial will be conducted in accordance with the principles of the Declaration of Helsinki and"good clinical practice" guidelines. Authorship will be in accordance with the Vancouver recommendations. An approval shall be applied and obtained from the Regional Ethic Committee in the South Eastern Norway. All patients shall receive oral and written information about the treatment and the study, and informed written consent shall be obtained from the patients for treatment, as well as for inclusion in the study.

Personal, equipment, resources and economy

The clinical research post is funded by the University of Oslo. We will apply for economic support for the purchase of ELISA kits aswell as other biochemical kits, liquid nitrogen transport containers, refrigerators for bio-bank, postage and press expenditures, laboratory sevices, etc., with the South Eastern Health authority.

Surgical procedure

Operations will be performed under general anaesthesia. All patients shall receive epidural analgesia. However, patients with totally laparoscopic ABFB will not recieve epidural analgesia until they complain of post-operative pain. Patients will receive a standard intravenous antibiotic prophylaxis with Cefalotin 2gr, at the start of surgery then repeated, every 3 hours for a total of 4 doses. In patients with penicillin allergy, Dalacin will be administered. All patients will receive a standard bowel preparation the evening before surgery.

Open ABFB

Common femoral artery (CFA) and its tributaries will be approached through a longitudinal incision in the groin bilaterally. Abdominal aorta will be approached through a median laparotomy. Abdominal aorta below the renal arteries will be prepared distally to the aortic bifurcation. Retroperitoneal tunnel along the iliac arteries will be created and a bifurcated graft (Dacron or Silver or PTFE) with a minimum dimension of 14mm x 7mm will be placed along the aorta and its limbs pulled through the tunnels into the respective groins.

Intravenous heparin will be given as a thrombosis prophylaxis before aortic cross-clamping. Aortotomy will be performed at the cranial part of infra-renal aorta and after required thromendarterectomy proximal end-to-side anastomosis will be constructed with a 3-0 non-absorbable synthetic monofilament (prolene or premilene) and continuous sutures. Aortic cross-clamping will be removed. Thereafter, common femoral artery and its branches will be clamped bilaterally. Thrombendarterectomy will be performed if necessary and distal anastomosis will be constructed end-to-side with a 5-0 prolene or premilene continuous suture and circulation to the lower limb will be re-established. If required the infra-inguinal procedure will be combined with a further distal vascular reconstruction.

Retroperitonium will be closed and the midline fascia closed with continuous monofilament sutures and skin with metal clips. Groin incisions will be closed in two layers by continuous synthetic absorbable sutures and skin with metal clips.

Laparoscopic ABFB

CFA will be approached bilaterally, in the same manner as with the open surgery group, mentioned earlier. A partial retroperitoneal tunnel will be generated digitally along the right external iliac artery. 12mm trocars will be placed into the abdominal cavity through the umbilicus Figure 2. Trocars, 2, 3, 4 and 5 will be placed while patient is still in the dorsal decubitus position. If patient does not have any peritoneal adherences in the right pelvic fossa, then the full Trendelenberg position will be attained and the retroperitoneal tunnel along the right iliac artery will be completed under direct vision and dorsal to the right ureter. The non-traumatic forcep will be left in place until used later. Patient will be turned towards the right side by tilting the operation table to its maximum right side tilt position. The approach to the aorta will be transperitoneal, retro-colic and pre-renal. The left colon descendens and sigmoideum will be mobilized towards the midline from the splenic to sigmoideum flexure and mobilized towards the midline. Left gonadal vein shall be followed to the left renal vein and infra-renal aorta will be free dissected at this level. Rest of the infra-renal aorta will be free dissected towards the bifurcation distally. Inferior mesenteric artery and the right and left

iliac arteries will be identified. In order to keep small bowel, colon descendens and omentum away from the operation field, a fan-retractor will be placed at position 6. The forcep can be at this stage seen in the retroperitoneal space along the right iliac artery.

The vascular graft will be prepared for the proximal anastomosis and will be placed in the abdomen and the right graft limbs will be retracted through the retroperitoneal tunnel into the right groin. A similar retroperitoneal tunnel will be generated along the left iliac arteries and left graft limb will also be pulled towards the respective groin.

Intravenous heparin will be given as thrombosis prophylaxis and a proximal and a distal aortic clamp shall be placed through the epigastrium and the hypogastrium. Infra-renal aorta will be clamped and aortotomy will be performed. If necessary, thromendarterectomy will be performed. Proximal end-to-side anastomosis will be generated by the technique introduced by Coggia et al. (12). After completion of the anastomosis aorta clamps will be removed. A drain will be placed along the proximal anastomosis and peritoneum and left colon will be placed back to its normal position by removing fan-retractor and tilting the patient back to dorsal decubitus position. Exsufflation of CO_2 will be done and the fascia at the trocar incision places will be closed with absorbable sutures and skin with metal clips. The distal anastomosis in the groin will be performed as described above under open surgery technique.

Details about the operative data (operation time, peroperative bleeding, aorta clamping time, autotransfusion, SAG/plasma/thrombocytes transfusion, etc.) will be noted in an own form and transferred to the database.

Post-operative management

Patients will be observed with a post-operative observation section or an intensive care unit, before being transferred to the general ward. In case of no on-going bleeding, operation drains will be removed on the first post-operative day. Bladder catheter will be removed already on 1 post-operative ay, if the patient is evaluated not to be requiring epidural analgesia. The patients will be encouraged to stand and walk as soon as the epidural analgesia is stopped. If the patients have bowel movements (auscultation of bowel sounds) they can start taking oral fluids and solid food.

The patients can be *discharged* from the hospital when they fulfil the following *criteria*:

1) Drink and eat solid food,

2) Pass stool
3) Can walk by themselves and
4) Have no on-going systemic infection, which needs intra-venous antibiotics

An independent physician will decide when the patients can be discharged. Delay in discharge due to social reasons will be noted.

Follow-up will be carried out at the out patient department at 4 weeks, 3, 6 and 12 months, post-operatively and at 2, 5 and 10 years.

Colour duplex ultra-sound will be performed within 3 months postoperatively.

Discussion

Although laparoscopic ABFB for the treatment of AIOD has been introduced as early as in 1993, the adaptation of the laparoscopic aortic surgery by the vascular surgeons had been slow (28). The laparoscopic technique has been increasingly incorporated by the other specialties like, gastrointestinal, gynecology and urology.

The technically demanding nature of the procedure, besides the general conception of causing complications during the learning curve phase, has been the most importent reasons of this slow development. Since its introduction in the early 90s, the technique has gradually evolved and also special instruments for laparoscopic aortic surgery have been developed. During the later decade the feasibility of the laparoscopic technique (12-15) has been addressed in a number of publications. Although the technique is technically demanding its learning curve has shown not to be longer than the other advanced laparoscopic abdominal and pelvic procedures (29). Besides, the mortality and morbidity in the early series of totally laparoscopic ABFB are same as with the open ABFB. Less pulmonary complications as well as less post-operative incisional hernia have been observed in the publications concerning laparoscopic ABFB. Most of the studies on open ABFB are retrospectively, and morbidity data reported in such studies is of obvious reasons, often under-estimated (11).

Since AIOD is a progressive disease and it is recommended to perform distal anastomoses at the femoral arteries instead of iliac arteries (30). A significant number of reinterventions have

been observed in cases where iliac arteries have been used for distal anastomosis during a bifurcation graft procedures (30). Therefore the patients included in this trial shall be recieving ABFB.

The main goal of the laparoscopic aortic surgery is to combine the excellent and durable results observed with the open conventional ABFB with the advantages of a lesser invasive laparoscopic procedure. There is need for a multicentre randomized trial to demonstrate the potential advantages of the laparoscopic ABFB.

Visit frequency

Activities to be performed at each post-randomization visit are as followed:

Screening/ visit 1

Prior to study entry the following screening procedures will be performed:
- Obtain written informed consent prior to any study related procedures
- Review inclusion and exclusion criteria to establish eligibility
- Medical history
- Social history (education, profession, job, marital status)
- Preoperative extensive examination, comprising of
    Full physical examination
    Demographic details height, weight, smoking, alkohol
    ECG, eccocardiography (dobutamin stress test in patients with suspected coronary heart disease)
- Lab tests
    Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL and LDL, PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa,
    CRP, hsCRP
- Visual analogue pain scale (VAS) score
- Ankle brachial index
- Pain free walking distance
- Record medications
- Preoperative SF-36 and EQ-5D questionaire
- Schedule next visit within 4 weeks

Baseline and randomization / visit 2 (within 1 month f day 0)

Following baseline procedures will be perfomed at visit 2:

- Review inclusion and exclusion criteria
- Medical history
- Confirm SF36 and EQ-5D questionaire for baseline are completely answered by patient
- Randomize subject

Day of surgery

- Blood samples for proinflammatory markers (shall be sentrifuged immidiately and serum obtained shall be stored at -70°C)

  Blood samples shall be taken before surgery and repeated at 1, 6 and 12 hours after surgery
- Blood samples for stress markers (shall be sentrifuged immidiately and serum obtained shall be stored at -70°C).

  Blood samples shall be taken from the central venous catheter at (i) 5 minutes after intubation, (ii) 2 minutes after operation start, (iii) 2 minutes before abdominal aortic cross-clamping, (iv) 1-2 minutes after aortic cross-clamping, (v) 30-45 minutes after aortic cross-clamping, (vi) 5 minutes before lapaoscopy/ laparotomy completion and at (vii) 24 hours post operatively.
- Register operations data (operation time, aorta cross clamping time, per operative bleeding, per operative analgesia etc)
- Post op VAS score

Post-op day

- VAS scale
- Lab tests

  Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL and LDL, CRP, leucocytes
- 24 hour blood samples for inflammatory markers
- 24 hour blood samples for stress markers
- Remove drains if no longer necessary
- Mobilize patient to walking if no epidural analgesia
- Peroral fluid and solid food if bowel sounds are audible
- Weight
- Peripheral circulation (pulse and doppler)
- Type and quantity of analgesia

- Any local or systemic complication

Discharge criteria

1) drink and eat solid food,
2) pass stool
3) can walk by themselves and
4) have no ongoing systemic infection, which needs intra-venous antibiotics

Besides on discharge the following activities shall be performed:

- Ankle brachial index
- Sick leave duration
- Repeat Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL , CRP, leucocytes
- Weight
- VAS score

1 month post operative follow-up/ visit 3

- VAS score
- SF36 and EQ-5D
- Blood samples for inflammatory markers
- Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL, LDL, CRP, leucocytes
- PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa, NO, E-selectin, vascular cell adhision molecule-1 (sVCAM-1), intercellular adhision molecule-1 (sICAM).PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa
- Sick leave duration
- Any complication
- Ankle brachial index
- Pain free walking distance
- Any complication, local or systemic
- Schedule next visit and duplex scan

3 months post operative follow-up/ visit 4

- duplex scan
- SF36 and EQ-5D
- Blood samples for inflammatory markers

- Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL, LDL, CRP, leucocytes
- PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa, NO, E-selectin, vascular cell adhision molecule-1 (sVCAM-1), intercellular adhision molecule-1 (sICAM).
- VAS score
- Ankle brachial index
- Pain free walking distance
- Any local or systemic complication
- Schedule next visit

6 months post operative follow-up/ visit 5

- SF36 and EQ-5D
- Blood samples for inflammatory markers
- Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL, LDL, CRP, leucocytes
- PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa, NO, E-selectin, vascular cell adhision molecule-1 (sVCAM-1), intercellular adhision molecule-1 (sICAM).
- VAS score
- Ankle brachial index
- Pain free walking distance
- Any local or systemic complication
- Schedule next visit

12 months post operative follow-up/ visit 6

- SF36 and EQ-5D
- Blood samples for inflammatory markers (last samples)
- Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL, LDL, CRP, leucocytes
- PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa, NO, E-selectin, vascular cell adhision molecule-1 (sVCAM-1), intercellular adhision molecule-1 (sICAM).
- VAS score (last values)
- Ankle brachial index
- Pain free walking distance
- Any local or systemic complication
- Schedule next visit

2 years post operative follow-up/ visit 7

- SF36 and EQ-5D (last values)
- Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL, LDL, CRP, leucocytes
- PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa, NO, E-selectin, vascular cell adhision molecule-1 (sVCAM-1), intercellular adhision molecule-1 (sICAM).
- Ankle brachial index
- Pain free walking distance
- Any local or systemic complication
- Schedule next visit

5 years post operative follow-up/ visit 8

- Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL, LDL, CRP, leucocytes
- PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa, NO, E-selectin, vascular cell adhision molecule-1 (sVCAM-1), intercellular adhision molecule-1 (sICAM).
- Ankle brachial index
- Pain free walking distance
- Any local or systemic complication
- Schedule next visit

10 years post operative follow-up/ visit 9

- Hb, fasting plasma glucose, serum kreatinin, uric acid, GFR, total cholestrol, HDL, LDL, CRP, leucocytes
- PAI-I Fibrinogen, Homocysteine, Apo-A, Apo-B and Lpa, NO, E-selectin, vascular cell adhision molecule-1 (sVCAM-1), intercellular adhision molecule-1 (sICAM).
- Ankle brachial index
- Pain free walking distance
- Any local or systemic complication

End of study

Chief investigators responsibilities

i- Is the main surgeon for the laparoscopic surgery of the patiets in this trial.
ii- to ensure collaboration between the steering committee members representing the participatig hospitals.
iii- to ensure, with the help of the steering committe member from each participating hospital, that all patients candidate for aortobifemoral bypass are concidered for the NLAST trial and that the willing patients are randomized.
iv- will ensure that tha data registery is promt and according to the schedulle and protocol instructions.
v- is also the main research supervisor of the research candidate/ s.
vi- has the responsibility along with other identified individuals for the manuscript/s.

Steering Committee´s responsibilities

It is the responsibility of the steering comittee to insure that the NLAST research trial is conducted according to the principles lead down in the Declaration of Helsinki and ”good clinical practice” guidelines.

The members in the Committee shall arrange occasional meetings every 3 months during the inclusion period (3 years). Questions and concerns about the progress of the study, data collection, data quality, treatment safety issues, shall be discussed in the meetings and dealed properly.

Depending upon the rate of patient inclusion in the study, if necessary the inclusion time may be shortened or prolonged.

Responsibilities of the participating hospitals

The participating hospitals in the NLAST study have the following responsibilities:
1 Patient inclusion according to the inclusion and exclusion criteria written in this protocol (See under inclusion/ exclusion criteria).
2 Provide the eligible patients, NLAST-study information form and obtain informed written consent.
3 Take contact with the NLAST study, main organizing center at”Karavdelingen, Hjerte-, lunge, karklinikken, Oslo Universitetssykehus HF, Aker, Telefon 02770 or Cell number 92468309” for randomization of the patient.

4 Register all the relevent study related data, for example, family and social history, history of previous diseases, history of present disease, allergies, smoking, drug history, weight, hight, findings with local and systemic examinations, ankel-brachial index, pain free walking distance, VAS pain scale etc.

5 Register operation related data for example, operation time, aorta cross-clamping time, peroperative bleeding, concomitant operations, per operative complications etc.

6 Shall make own local aggreement with the laboratory sevices department to collect NLAST study related blood samples at the right time (see above mentioned details for blood samples).

7 Each participating hospital shall provide own freezing box (-80°C) for storage of the blood samples. Blood samples shall be transported periodically to the"Central Biobank" at the Oslo University Hospital (OUH).

8 Patients operated locally with the OABF as well as the patients randomized to LABF and operated at the OUH, shall be followed up with the out patient department, 1, 3, 6 and 12 months and there after yearly with the out patient department with each participating hospital.

9 All the blood samples (abuve mentions under visit section) as well as the information about the complications as well as reinterventions and mortality shall be registered.

10 Copy of all the treatment documents and history of the patients in the NLAST study shall be provided (per post) to the central NLAST study register at the OUH.

Publication plan

All study participents give full authority to the principal investigator for primary presentation/ or primary publication of the results. Name of co-authors from participating hospitals and their contribution in the design, conduction of study, collection of data and manuscript generation shall be pre-defined. The authors shall fully meet the criteria for authership/ contributorship defined by the Vancouer recommendations. No other publication is allowed before the primary publication. Any subsiquent presentation or publication by a study participant must be approved by the principal investigator and make reference to the primary publication.

All information obtained as a result of the study will be regarded confidentially.

References

1 Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation 1985;71(3):510-551.

2 Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. Circulation 1995;91(5):1472-1479.

3 Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 2004;110(6):738-743.

4 Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S and Jones DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997 Sep;26(3):517-38.

5 Nordgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45(Suppl. S):S5e67. et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).

6 Department of Health. National Service Framework for Coronary Heart Disease. 2000; London.

7 Hankey GJ, Norman PE and Eikelboom JW. Medical treatment of peripheral arterial disease. JAMA 2006;295(5):547-553.(review)

8 Kashyap VS, Pavko ML, Bena JF, Sarac TP, O'Hara PJ, Lyden SP, and Daniel G. Clair, MD. The management of severe aortoiliac occlusive disease: Endovascular therapy rivals open reconstruction. J Vasc Surg 2008;48:1451-57.

9 Tae-Hoon Kim, Young-Guk Ko, Ung Kim, Jung-Sun Kim, Donghoon Choi, Myeong-Ki Hong, Yangsoo Jang and Won-Heum Shim. Outcomes of endovascular treatment of chronic total occlusion of the infrarenal aorta. J Vasc Surg 2011;53:1542-9.

10 Raffaele Pulli, Walter Dorigo, Aaron Fargion, Alessandro Alessi Innocenti, Giovanni Pratesi, MD, John Marek, and Carlo Pratesi. Early and long-term comparison of endovascular treatment of iliac artery occlusions and stenosis. J Vasc Surg 2011;53:92-8.

11 De Vries S, Hunink M. Results of aortic bifurcation grafts for aortoiliac occlusive disease. J Vasc Surg 1997;26:558-569.

12 Coggia M, Javerliat I, Di Centa I, Colacchio G, Leschi JP, Kitzis M et al. Total laparoscopic bypass for aortoiliac occlusive lesion: 93-case experience. J Vasc Surg 2004;40:899e906.

13 Cau J, Ricco JB, Marchand C, Lecis A, Habbibbeh H, Guillau M et al. Total laparoscopic aortic repair for occlusive and aneurismal disease: first 95 cases. J Vasc Surg 2006;31:567-574.

14 Dion YM, Griselli F, Douville Y and Langis P. Early and mid-term results of totally laparoscopic surgery for aortoiliac disease. Lessons Learned. Surg Laparosc Endosc Percutan Tech 2004;14(6):328-334.

15 Kolvenbach R, Puerschel A, Fajer S, Lin J, Wassiljew S, Schierz E and Pinter L. Total laparoscopic aortic surgery versus minimal access techniques: review of more than 600 patients. Vascular 2006;14(4):186-92.

16 Kazmi SSH, Sundhagen JO, Flørenes TL, Kroese AJ, Jørgensen JJ. Laparoskopisk aortakirurgi. Tidsskr Nor Lægeforen 2007;127(11):1518-20.

17 Ware JE, Gandek B and the IQOLA project group. The SF-36 health survey: Development and use in mental health research and IQOLA Project. Int J Ment Health 1994;23(2):49-73.

18 Kolvenbach R, Deling O, Schwierz E and landers B. Reducing the operative trauma in aortoiliac reconstructions – a prospective study to evaluate the role of video-assisted vascular surgery. Eur J Vasc Endovasc Surg 1998;15:483-488.

19 Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000;85:109-17.

20 Bruls S, Quaniers J, Tromme P, Lavigne JP, Van Damme H, Defraigne JO. Comparison of laparoscopic and open aortobifemoral bypass in the treatment of aortoiliac disease. Results of a contemporary series (2003-2009). Acta Chir Belg. 2012;112(1):51-8.

21 Pocock SJ. Clinical trials. A practical approach. John Wiley & sons. 1983.

22 Vickers AJ, ALTman DG. Analysing controlled trials with baseline and follow-up measurements. BMJ 2001;323:1123-4.

23 Zeger and Liang. Longitudinal analysis for discrete and continuous outcomes. Biometrics 1986;42:121-30.

24 http://www.helsedirektoratet.no/Om/hoyringar/Documents/samfunnsokonomiske-analyser-i-helsesektoren/horingsutgave.pdf

25 Moher D, Schulz K, Altman DG, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. The Lancet April 2001;357:1191-4.

26 Dion YM, Katkhouda N, Rouleau C et al. laparoscopy-assisted aotobifemoral bypass. Surg Laparosc Endosc. 1993;3:425-429.

27 Fourneau I, Lerut P, Sabbe T, Hauthoofd S, Daenens K and Nevelsteen A. The learning curve of totally laparoscopic aortobifemoral bypass for occlusive disease. How many cases and how safe? Eur J Vasc Endovasc Surg 2008;35:723-729.

28 Brewster DC. Direct reconstruction for aortoiliac occlusive disease. Rutherford Vascular Surgery vol.1, 6the Edition, 2005;1106-36.