Benefits of laparoscopic versus open aortobifemoral bypass surgery
– focus on the surgical inflammatory reaction, humoral stress response and
health economics

Thesis for the degree of philosophiae doctor (ph.d.)

Anne Helene Krog

Institute of Clinical Medicine
Faculty of Medicine
University of Oslo

Department of Vascular Surgery
Division of Cardiovascular and Pulmonary Diseases
Oslo University Hospital

2017
Contents

1. Preface ................................................................................................................................................. 4
   1.1 Acknowledgements ......................................................................................................................... 4
   1.2 Abbreviations .................................................................................................................................. 6
   1.3 List of papers ....................................................................................................................................... 7
2. Introduction ............................................................................................................................................ 8
3. Background ............................................................................................................................................ 9
   3.1 Atherosclerosis ............................................................................................................................... 9
   3.2 Peripheral arterial disease and aortoiliac occlusive disease ......................................................... 9
   3.3 Open aortic bypass surgery for AIOD ...................................................................................... 13
   3.4 Percutaneous transluminal angioplasty for AIOD ................................................................... 14
   3.5 Laparoscopic aortic surgery ........................................................................................................ 14
   3.6 The acute phase response ........................................................................................................... 17
   3.7 The hormonal stress response .................................................................................................... 19
   3.8 Cost-effectiveness ....................................................................................................................... 20
4. Aims of study ....................................................................................................................................... 22
   4.1 Main aim .......................................................................................................................................... 22
   4.2 Specific aims ..................................................................................................................................... 22
5. Materials and methods ..................................................................................................................... 23
   5.1 Design ........................................................................................................................................... 23
   5.2 Participants ...................................................................................................................................... 25
   5.3 Randomization and blinding ........................................................................................................ 26
   5.4 Intervention .................................................................................................................................... 26
      Open technique ................................................................................................................................. 26
      Laparoscopic technique .................................................................................................................. 27
      Postoperative care .......................................................................................................................... 29
   5.5 Outcomes ....................................................................................................................................... 30
   5.6 Analysis ........................................................................................................................................... 30
      Inflammatory response ...................................................................................................................... 30
      Humoral stress response ............................................................................................................... 31
      Cost-effectiveness .......................................................................................................................... 32
   5.7 Statistical methods ........................................................................................................................ 33
General ........................................................................................................................................... 33
Paper I ............................................................................................................................................... 34
Paper II ........................................................................................................................................... 34
Paper III ........................................................................................................................................ 35
5.8 Ethics ...................................................................................................................................... 35
6. Summary of results .................................................................................................................. 37
  6.1 Paper I .................................................................................................................................. 37
  6.2 Paper II .................................................................................................................................. 39
  6.3 Paper III ................................................................................................................................ 41
7. Discussion ................................................................................................................................. 44
  7.1 Discussion of methodology, strengths and weaknesses .................................................... 44
    Study design, participants and sample size ............................................................................. 44
    Blood sampling and biomarkers ............................................................................................. 45
    Cost-effectiveness measures ................................................................................................. 46
    Statistics ................................................................................................................................. 47
    Ethical issues .......................................................................................................................... 48
  7.2 Discussion of main findings ................................................................................................. 49
    Main Findings ......................................................................................................................... 49
    Recent literature ................................................................................................................... 51
    Clinical implications .............................................................................................................. 54
8. Conclusions ............................................................................................................................... 56
  8.1 Main conclusions ............................................................................................................... 56
  8.2 Concluding remarks and future perspective .................................................................... 56
9. References ............................................................................................................................... 58
10. Papers I-III .............................................................................................................................. 75
1. Preface

1.1 Acknowledgements

These studies were funded and carried out at the Department of Vascular Surgery, Division of Cardiovascular and Pulmonary Diseases, Oslo University Hospital. They are the main organiser of the ongoing multicentre randomized controlled trial, namely, Norwegian Laparoscopic Aortic Surgery Trial (NLAST).

I wish to thank our trial collaborators;

- The Department of Vascular Surgery, Østfold Central Hospital, Kalnes.
- The Department of Vascular Surgery, Sørlandet Hospital HF, Kristiansand.
- Oslo Center for Biostatistics and Epidemiology (OCBE).
- The Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital.

I would like to thank my employer the Institute of Clinical Medicine, University of Oslo, for providing me with a scientific education, financial support and working facilities.

I am grateful to the staff of the Department of Vascular Surgery; doctors, nurses and secretaries, for all their help, friendly encouragement, scientific input and coffee. I also owe the surgical, anaesthetic and laboratory staff gratitude for their positive attitude and facilitation.

My sincere gratitude goes to my main supervisor Syed S.H. Kazmi for providing me the opportunity to be a part of the NLAST project, his scientific guidance, innovative thinking, optimism and moral support.
A very special thank you goes to my university supervisor the late prof. Jørgen J. Jørgensen who always was a personal role model in his scientific expertise, his inspiring teaching and his kind heart. I also wish to thank his successor as my supervisor, prof. Theis Tønnessen for all his help.

I am very grateful for my article collaborators; Mehdi Sahba, Erik Mulder Pettersen, Irene Sandven, Per Medbøe Thorsby, Torbjørn Wisløff and Jon Otto Sundhagen for all their help, insight, knowledge and feedback. Epidemiologist Irene Sandven and health economist Torbjørn Wisløff performed the AUC, GEE and GLM calculations.

I would like to thank my family and friends for their patience and encouragement; especially my loving partner for his continuous support and all the dinners he has prepared. Finally, I am thankful for my clever and supportive friends, my sister for creating fun distractions, my mother for her moral support, insight and academic advice, and my late father for his high goals, strict discipline, love and inspiration.
### 1.2 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AIOD</td>
<td>Aortoiliac occlusive disease</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>IL-8</td>
<td>Interleukin-8</td>
</tr>
<tr>
<td>LABF</td>
<td>Laparoscopic aortobifemoral bypass</td>
</tr>
<tr>
<td>LAS</td>
<td>Laparoscopic aortic surgery</td>
</tr>
<tr>
<td>NLAST</td>
<td>Norwegian Laparoscopic Aortic Surgery Trial</td>
</tr>
<tr>
<td>OABF</td>
<td>Open aortobifemoral bypass</td>
</tr>
<tr>
<td>PAS</td>
<td>Peripheral atherosclerotic disease</td>
</tr>
<tr>
<td>PTA</td>
<td>Percutaneous transluminal angioplasty</td>
</tr>
<tr>
<td>QALYs</td>
<td>Quality adjusted life years</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>TASC-II</td>
<td>Trans-Atlantic Inter-Society Consensus II</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness to pay</td>
</tr>
</tbody>
</table>
1.3 List of papers


2. Introduction

This dissertation deals with some of the many important questions regarding the possible advantages of totally laparoscopic aortobifemoral bypass surgery (LABF) in the treatment of aortoiliac occlusive disease (AIOD). The scientific work performed and presented are three substudies from an ongoing randomized controlled trial, the Norwegian Laparoscopic Aortic Surgery Trial (NLAST), comparing LABF to open aortobifemoral bypass (OABF). The focus in this dissertation will be on the potential benefits from LABF regarding the postoperative inflammatory reaction, the surgical stress response and cost-effectiveness. These are topics that previously have not been examined in a randomized fashion.
3. Background

3.1 Atherosclerosis

Atherosclerosis is a systemic vascular disease. Its aetiology is partly unknown and likely multifactorial.\(^1\) However, we do know that the development of atherosclerosis is linked to a number of risk factors; the most common being smoking, age, gender, heredity, dyslipidaemia, diabetes, hypertension and lifestyle factors like diet and exercise.\(^2\) The pathogenesis begins with an injury of the endothelium. Lipids in the blood enter the vascular wall and causes inflammation attracting lymphocytes, monocytes and mast cells. Monocytes migrate into the vascular wall to remove the lipids, which in turn cause them to transform to foam cells and eventually apoptosis. Extracellular lipids cause cell necrosis and inflammation. Proinflammatory mediators stimulate the migration of smooth muscle cells from the tunica media to the tunica intima. Eventually an atheroma will form with a core of necrotic foam cells and lipids, and a fibrous cap on the luminal side of the vessel wall. Calcification of the plaque increases as calcium is deposited in the vascular wall.\(^1,3\) The plaque protrudes into the vessel lumen and may instigate stenosis and thrombotic occlusions. The arterial stenosis/occlusion can in turn cause multiple clinical manifestations depending on its localisation; for instance cardiac infarction, stroke and intermittent claudication.\(^4\)

3.2 Peripheral arterial disease and aortoiliac occlusive disease

Peripheral arterial disease (PAD) is an atherosclerotic lesion, compromising the blood flow to the extremities. Studies have shown an incidence for PAD between 1-20 % in the general population depending on the age-group examined. The risk of PAD increases with age.\(^2,4\) The Framingham heart study found an incidence for PAD in all age-groups of 7.1 per 1000 per year in men versus 3.6 per 1000 per year in women, with a dramatic increase after the age of 75.\(^2,5\) Some prevalence estimates have shown PAD in approximately 10 % of the population
above 60-70 years of age. However, these estimates differ because of the major influence of ethnicity/heredity, gender and age.\textsuperscript{2} The prevalence of PAD seems to be increasing globally.\textsuperscript{2} One of the studies found that 26\% of the patients with PAD had aortoiliac occlusive disease (AIOD).\textsuperscript{6} AIOD is an atherosclerotic and/or thrombotic lesion in the aortoiliac segment. The long arterial occlusions are demonstrated in angiograms from a patient with AIOD in figure 1. We can see the occlusion in the magnetic resonance angiogram (MRA) (left), and the heavily calcified aortoiliac section in the computed tomography reconstructed angiogram (middle) and computed tomography angiogram (CTA) (right). A normal aorta is depicted in figure 2, CTA (left) and reconstructed CTA images (right) for comparison.

![Figure 1](image)

**Figure 1** Patient with aortoiliac occlusive disease. Magnetic resonance angiogram (left), computed tomography reconstructed angiogram (middle) and computed tomography angiogram (right).  
**Source:** Oslo University Hospital, patient included in the study, printed with permission from the patient.
Figure 2 Patient with normal aorta and iliac arteries. Computed tomography angiogram (left) and computed tomography reconstructed angiogram (right).

Source: Department of Radiology, Oslo University Hospital, printed with permission from the patient.

The Trans-Atlantic Inter-Society Consensus II (TASC-II)\(^4\) has classified these atherosclerotic AIOD lesions into four types based on the extent of the disease (figure 3). The TASC-II consensus rapport recommends primarily endovascular treatment for type A lesions. The choice of treatment for B and C lesions, surgical or endovascular, is open for discussion based on the patients’ comorbidity and suitability. Due to the heavily calcification in TASC-II type D lesions, the consensus document recommends either an open or laparoscopic aortobifemoral bypass.\(^4\)
L. Norgren and W. R. Hiatt *et al.*

Type A lesions

- Unilateral or bilateral stenoses of CIA
- Unilateral or bilateral single short (≤3 cm) stenosis of EIA

Type B lesions:

- Short (≤3 cm) stenosis of infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of internal iliac or CFA

Type C lesions

- Bilateral CIA occlusions
- Bilateral EIA stenoses 3–10 cm long not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
- Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA

Type D lesions

- Infra-renal aortoiliac occlusion
- Diffuse disease involving the aorta and both iliac arteries requiring treatment
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Bilateral occlusions of EIA
- Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery

Figure 3 Classification of aortoiliac occlusive disease from the Trans-Atlantic Inter-Society Consensus II (TASC-II) document.
**Abbreviations:** CIA, common iliac artery; EIA, external iliac artery; CFA, common femoral artery; AAA, abdominal aortic aneurysm.


Patients with AIOD present symptoms like intermittent claudication, Leriche syndrome and/or critical ischemia of the lower limbs. Leriche syndrome encompasses claudication of the buttocks and/or thighs, loss of femoral pulse and erectile dysfunction, whilst critical ischemia is characterized by rest or night pain, ischemic ulcers or gangrene. Both Rutherford and Fontaine have made a classification of symptoms from PAD.

The Fontaine classification is as follows:

- **Stage I** – Asymptomatic.
- **Stage IIa** – Intermittent claudication, with > 200 meters pain free walking distance.
- **Stage IIb** – Intermittent claudication with < 200 meters of pain free walking distance.
- **Stage III** – Rest pain.
- **Stage IV** – Ischemic ulcers or gangrene.

In general clinical practice, a pain free walking distance < 200 meters is usually considered as a treatment criterion. Patients with PAD also have an increased mortality rate and morbidity especially due to cardiovascular and cerebrovascular incidents. However, the main indication for revascularisation is the reduced health-related quality of life (HRQoL). The HRQoL in patients with PAD is significantly impaired.

### 3.3 Open aortic bypass surgery for AIOD

There is a long history of medical treatment for aortic disease. The condition of AIOD was first described by Graham in 1814, but Leriche was the first to mention the possibility of
surgical grafting for the treatment of AIOD and gave name to the combination of symptoms in Leriche syndrome.\textsuperscript{7,17} Later, in 1950, Oudot was the first to successfully replace the distal aorta with a homologous aortic graft, although the graft occluded only half a year later.\textsuperscript{19} Open aortobifemoral bypass (OABF) surgery developed gradually, and by the 1990s, the risk of surgical complications and mortality was declining, and it became standard surgical treatment of AIOD.\textsuperscript{20,21}

3.4 Percutaneous transluminal angioplasty for AIOD

During the last two decades percutaneous transluminal angioplasty (PTA) has revolutionised the treatment of atherosclerotic disease.\textsuperscript{22,23} PTA treatment of AIOD is a safe technique with excellent short-term results, low morbidity and low mortality.\textsuperscript{4,24} Endovascular therapy is overall the most common treatment of choice in TASC-II type A, B and C lesions. Due to increasing experience and expertise even some type D lesions are being treated endovascularly.\textsuperscript{25,26} However, when compared to open surgery it is clearly less invasive,\textsuperscript{27} but far from being complication free.\textsuperscript{28} Additionally, the patency rates have been shown to be lower after endovascular treatment as compared with open surgery, due to early intimal hyperplasia and in-stent thrombosis.\textsuperscript{29,30}

3.5 Laparoscopic aortic surgery

As early as in the 900’s there were reports of physicians trying to examine the bodily cavities and in the 18\textsuperscript{th} century endoscopic instruments started developing.\textsuperscript{31,32} Around the same time in the early 1900’s both Ott, Kelling and Jacobeus used different approaches to investigate the abdominal and thoracic cavities.\textsuperscript{33,34} Over the years many doctors improved the technique, and in 1983 (Lukichev) and in 1985 (Muhe) performed the first laparoscopic cholecystectomies in humans. However, the technique did not become popular and
widely amongst surgeons until P.Mouret in 1987 introduced his method with the use of
trocar. Different approaches have been employed to create abdominal workspace during
laparoscopic surgery. One has experimented with different gases and even with mechanical
lifting devices, but today the CO2-pneumoperitoneum is the most common. Laparoscopy
has now been widely implemented in almost all surgical specialties, and especially in elective
surgery. The laparoscopic technique has been shown to reduce morbidity, mortality and
hospital stay, and increase patient satisfaction and HRQoL compared with open surgery.

Dion et al had a goal to improve and make the open aortobifemoral bypass procedure less
invasive for the treatment of AIOD. They developed a new laparoscopic aortic surgery
technique for aortoiliac occlusive disease (AIOD). Dion et al performed the first
laparoscopic assisted aortobifemoral bypass in 1993, and after a series of animal studies,a totally laparoscopic aortobifemoral bypass was performed in 1995. In the years following
the employment of the laparoscopic technique, several cohort studies and systematic
reviews have been published. The technique has been improved and the indication for
surgery has been broadened.

The use of a mini-laparotomy to perform the proximal anastomosis can make the laparoscopic
technique more accessible for vascular surgeons by using a hand-assisted approach, hand-
assisted laparoscopic aortic surgery (HALS). Vascular surgeons have not traditionally had
much laparoscopic experience and there is a lack of simpler procedures to improve the
learning process. The HALS has been proven to be less invasive than the traditional open
median laparotomy, but probably does not carry the same benefits compared with totally
LABF. Robotics has also been introduced as a way to facilitate the laparoscopic aortic
surgery, robot-assisted laparoscopic aortic surgery (RALS). Initially camera-holding
robotic arms were used, but later the state of the art Da Vinci robot has been used to perform the LABF. The combination of a 3-dimensional operation field and robotic arm with a multiple degree of movements facilitates the laparoscopic aortic anastomosis. On the other hand, the cost of such a robot and its maintenance is a major issue for its widespread availability. Recently there has been a development in suture-less techniques, but so far this technique is in its infancy.82,83

In addition to vascular surgeons' reluctance and respect for this technically demanding procedure, there is also the rightful fear of inflicting injury upon the patients. Fourneau et al. have estimated the learning curve of the LABF technique to 25-30 patients.49 In their experience the increased rate of conversions during the learning period did not seem to have a significant effect on morbidity and mortality.50 During the last few years the spectre of laparoscopic vascular procedures has increased, and both celiac compression syndrome,84-86 abdominal aortic aneurysms (AAA),66,87-101 aortomesenteric bypasses102,103 and complications regarding endovascular aneurysm repair (EVAR)104-109 have been treated laparoscopically. In 2002 Coggia et al. presented a simplified technique where the exposure of the aorta was done through a transperitoneal, retrocolic, prerenal approach.110 The results were promising. The first comparative series on LABF compared with OABF for AIOD were published in 2005,111,112 and the method was implemented at several centres.53

We started using the laparoscopic aortic surgery technique at Oslo University Hospital in 2005,113 and have conducted a comparative cohort study from 2005-2011, published in 2015.10 As our results were comparable to others and show an advantage from LABF, we felt safe to continue our practice. However, we still considered the lack of scientific evidence in the form of RCTs a problem for the wide implementation of the technique as a standard. In
2011, we started planning a randomized controlled trial; Norwegian Laparoscopic Aortic Surgery Trial (NLAST). The studies presented in this thesis are a part of the NLAST.

3.6 The acute phase response

The body has physiological regulatory and protective mechanisms against trauma and surgical stress.\textsuperscript{114} Inflammatory and endocrine reactions are a part of this physiological regulatory response.\textsuperscript{115-119} Sometimes after major trauma/surgery the inflammatory response can also have a negative effect and lead to severe complications like systemic inflammatory response syndrome (SIRS).\textsuperscript{120-122} This can in turn cause multiple organ dysfunction syndrome (MODS) and mortality.\textsuperscript{123-125} The quantification of this inflammatory process has been used as a prognostic tool,\textsuperscript{126-128} to predict complications,\textsuperscript{129,130} and as a measurement for the surgical trauma.\textsuperscript{131-133}

Several studies have shown reduced physiological immune response after minimally invasive surgical techniques, particularly when comparing laparoscopic vs open surgery.\textsuperscript{134-142} The inflammatory markers have also been used to measure the level of acute phase response in association with major vascular surgical procedures.\textsuperscript{143-145}

Surgical trauma initiates a cascade of inflammatory markers.\textsuperscript{114,119,146,147} The manipulation and damage of the peritoneum in laparotomy may be one of the causes to the increased inflammatory reaction after open surgery.\textsuperscript{148-150} Although we probably do not fully know the entire process, there are some key modulators (schematically presented in figure 4).
Figure 4 Key modulators in the inflammatory response to tissue damage.

Abbreviations: TNF-α, Tumour necrosis factor–alfa; IL-1, Interleukin-1; IL-6, Interleukin-6; IL-8, Interleukin-8; CRP, C-reactive protein

Tumour necrosis factor–alfa (TNF-α) and Interleukin-1 beta (IL-1β) are the first to be released at the site of tissue damage. They stimulate the production of other cytokines like Interleukin-6 (IL-6) and Interleukin-8 (IL-8). IL-8 activity influences the level of circulating granulocytes, and both IL-6 and IL-8 correlate with the extent of tissue trauma and
ischemia. IL-6 plays a central part of the reaction, and is the primary mediator for C-reactive protein (CRP).

3.7 The hormonal stress response

Bodily harm also initiates a number of endocrine reactions. Corticotropin releasing hormone (CRH) regulates ACTH release, which in turn influence the release of glucocorticoids and mineralocorticoids. Cortisol, adrenocorticotropic hormone (ACTH) and epinephrine increase during and immediately after surgery. Metanephrine is a product of epinephrine. Serum aldosterone level increases during surgical stress as a reaction to: ACTH, low blood pressure and potassium levels.

The endocrine stress hormones have been used as a measurement of graded surgical trauma. They have a rapid release and short half-life time. Some studies have shown that laparoscopic surgery may lead to a decreased hormonal stress response in patients, which in turn is correlated with decreased morbidity and mortality. But so far, the evidence has not been conclusive. It has been suggested that the effect might be different in major surgery. Aortic crossclamping create large hemodynamic changes at the time of crossclamping and declamping. Additionally, both crossclamping and CO₂-pneumopertionue initiates the release of catecholamines. The aortic crossclamping time is longer with the LABF than the OABF. The LABF and the OABF are both major abdominal surgeries with crossclamping of the aorta, and in LABF the pneumoperitoneum is an additional stress factor. This could result in a large hormonal stress response. We consequently found it interesting and relevant to compare the stress response during these two procedures.
3.8 Cost-effectiveness

Introduction of a new treatment requires research on both efficacy and efficiency, and there is an increasing focus on the latter from health providers and the decision makers. In other fields of laparoscopic surgery the results differ in regards to the cost-effectiveness of laparoscopic surgery compared to the open laparotomy. The main driver of costs in laparoscopic surgery is expensive surgical equipment, but shorter hospital stay may outweigh this expense.\textsuperscript{182-187}

The cost-utility is a cost-effectiveness analysis used in health-economics,\textsuperscript{188} and is used to determine the best utilization of funds for the decision-makers.\textsuperscript{181} The main indication for surgical treatment of PAD is impaired health-related quality of life (HRQoL).\textsuperscript{11,13} The LABF for AIOD has already been proven, in different cohort studies, at least as safe as the open approach.\textsuperscript{189} The cost-utility is based on calculation of costs per quality adjusted life years (QALYs) gained. It encompasses both the duration of life, but also the quality of those years, which reflects how most people value health. The QALY is defined as a year of perfect health measured by patient-reported outcomes (PROMs). The cost-utility can be useful to calculate exactly “how much health you can gain” per extra money spent. The incremental cost-effectiveness ratio (ICER) is calculated as the incremental cost (Δcosts) divided by the incremental effect (ΔQALYs), and will give you the cost per QALYs gained. The ICER should be below the level of “willingness to pay”(WTP), see figure 4. A level of WTP can be estimated by how much people are willing to pay for a certain amount of health-gain. Treatments that are clearly both more effective and less expensive than their predecessor are placed in the lower right quadrant (figure 5) and considered “dominant”. “Dominant” interventions are recommandable regardless of the WTP, and should be considered as
replacement for the comparative treatment. On the other end of the scale, treatments that are less effective and more expensive than their comparator, in the upper left quadrant are considered not recommendable. The WTP can be used as a threshold. The ICER should be below this threshold, and can thereby be used as a tool in decision-making. Norway is a country where medical expenses mostly are covered by the government. Although a Norwegian threshold on the price of a QALY has not been set, a recent estimation resulted in a range of € 43,000 to 94,000 per QALY gained.

![Diagram of cost per effect gained. If the new treatment has lower costs and higher effect, it is clearly cost-efficient compared with the existing treatment and is considered “dominant”](image)

Figure 5 Diagram of cost per effect gained. If the new treatment has lower costs and higher effect, it is clearly cost-efficient compared with the existing treatment and is considered “dominant”. 
4. Aims of study

4.1 Main aim

We aimed to compare totally laparoscopic aortobifemoral bypass surgery to the open aortobifemoral bypass in a randomized setting.

4.2 Specific aims

- To compare the immunological acute phase response after laparoscopic vs open aortobifemoral bypass surgery.
- To compare the hormonal stress response during and after laparoscopic vs open aortobifemoral bypass surgery.
- To measure the cost-effectiveness of laparoscopic vs open aortobifemoral bypass surgery.
5. Materials and methods

5.1 Design

Since February 2013, we have been conducting a multicentre randomized controlled trial; NLAST, at the Department of Vascular Surgery, Oslo University Hospital. These substudies were a part of the NLAST. Patients with symptomatic aortoiliac occlusive disease (AIOD), type D lesions, classified according to the TASC-II document were randomized to either LABF or OABF (figure 6).
Figure 6 Flowchart of the Norwegian Laparoscopic Aortic Surgery Trial

**Abbreviations:** AIOD; aortoiliac occlusive disease, TASC-II; Trans-Atlantic Inter-Society Consensus II, LABF; Laparoscopic aortobifemoral bypass, OABF; Open aortobifemoral bypass.
5.2 Participants

Three vascular surgery departments in the South-East region of Norway were involved in this study:

- The Department of Vascular Surgery, Østfold Central Hospital, Kalnes
- The Department of Vascular Surgery, Sørlandet Hospital HF, Kristiansand
- The Department of Vascular Surgery, Aker, Oslo University Hospital, Oslo

Patients with symptomatic AIOD, eligible for aortobifemoral bypass, were offered to participate in the study. Inclusion and exclusion criteria are described in table 1.

Table 1 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient with AIOD, TASC-II type D lesions,(^4) and with symptoms in the form of:</td>
<td>• Eligible for endovascular procedure</td>
</tr>
<tr>
<td>◦ Intermittent claudication, with patient-reported pain-free walking distance &lt; 200 m, and/or</td>
<td>• Chronic Obstructive Pulmonary disease (COPD) ≥ stage IV(^b)</td>
</tr>
<tr>
<td>◦ Chronic critical lower limb ischemia(^a), duration of symptoms &gt; 2 weeks.</td>
<td>• Symptomatic coronary heart disease</td>
</tr>
<tr>
<td></td>
<td>• Chronic heart failure, ejection fraction(EF) &lt; 40%</td>
</tr>
<tr>
<td></td>
<td>• Active cancer disease</td>
</tr>
<tr>
<td></td>
<td>• Hostile abdomen due to previous major abdominal surgery</td>
</tr>
<tr>
<td></td>
<td>• Abdominal aortic aneurysm (AAA) ≥ 3.0 cm(^4)</td>
</tr>
<tr>
<td></td>
<td>• Acute critical limb ischemia, duration of symptoms ≤ 2 weeks</td>
</tr>
</tbody>
</table>

Abbreviations and definitions: AIOD; aortoiliac occlusive disease, COPD; Chronic obstructive pulmonary disease, \(^a\)Chronic critical ischemia was defined as rest pain, ischemic ulcers or gangrene for more than two weeks, \(^b\)COPD was classified according to the GOLD classification.\(^{192}\)

All patients in our vascular department are evaluated by a multidisciplinary team of specialists in interventional radiology and vascular surgery. The interventionalists have improved their
techniques during the last few years and are now able to treat even some TASC D lesions. The first choice of treatment for these patients was an endovascular procedure. Only, if the procedure was unsuccessful or the patient deemed not suitable for endovascular treatment, bypass surgery was offered.

5.3 Randomization and blinding

The patients were enrolled by clinicians and researchers, and randomized to either open or laparoscopic surgery. We used block randomization, with six patients in each block and different sequences for the three participating hospitals. The sequence was random, unknown and was contained in closed, opaque, sequentially numbered envelopes until randomization. Blinding of surgeon and/or participants after randomization was not possible.

5.4 Intervention

The patients underwent aortobifemoral bypass surgery with either a totally laparoscopic or an open approach under general anaesthesia (figure 7). Both techniques begin with the dissection of the common femoral artery. We used bifurcated aortobifemoral silver coated Dacron grafts. If necessary a thromboendarterectomy of the common and/or deep femoral artery was performed to ensure good run-off, before completing the distal anastomosis. Doppler flow was registered through each graft limb.

Open technique

The procedure was performed using the traditional open approach through a midline laparotomy. The aorta was dissected free, and a retroperitoneal tunnel was made along the iliac vessels bilaterally from the aortic bifurcation to the respective right and left groin wound.
The graft limbs were placed through the retroperitoneal tunnels and carefully placed dorsally to the ureters. The patients received intravenous heparin and the infra renal aorta was clamped just below the renal arteries and with another clamp a few centimetres distally. The proximal end-to-side anastomosis was performed with continuous 3-0 polypropylene sutures. The aortic clamps were removed and the graft limbs were clamped. The distal anastomoses were constructed in an end-to side fashion with continuous 5-0 polypropylene sutures. Inflow and retrograde blood-flow through the arteriotomy was checked and the graft limbs were irrigated with heparin sodium chloride solution before the anastomoses were completed and the blood circulation re-established to the lower limbs. Surgical drains were placed bilaterally, along the anastomosis. The subcutis of the groin was closed with continuous absorbable sutures and the skin was approximated with metal clips. The abdominal graft was covered by suturing the retroperitoneum and an active surgical drain was placed along the anastomosis. The midline abdominal fascia was closed with synthetic monofilament absorbable sutures and skin incision was closed with metal clips.

**Laparoscopic technique**

The surgery was based on a technique described by Coggia et al, using 6 small incisions for the laparoscopic equipment. A 12 mm transumbilical trocar was placed and pneumoperitoneum was created with CO₂-insufflation. A pneumoperitoneum pressure of approximately 12 mmHg was maintained during the procedure. Under direct laparoscopic vision, a long clamp was placed through the right groin wound, dorsal to the right inguinal ligament, along the right iliac vessels, dorsally to the right ureter, until it reached the aortic bifurcation. Then the patient was placed in a right lateral position. The free dissection of the aorta was completed with a transperitoneal, retrocolic, prerenal approach. The infrarenal aorta was dissected free from the renal arteries to the aortic bifurcation, where the retroperitoneal
clamp placed through the right groin wound was visualized. Through a 12 mm trocar the graft was placed in the abdominal cavity and the graft limbs were pulled down with the help of the retroperitoneal clamps along the iliac vessels to the respective right and the left groin wound. Laparoscopic aortic clamps were placed on the infra renal aorta. If necessary, thromboendarterectomy of the aorta at the anastomosis site was performed. In cases of suprarenal aortic clamping, after aortotomy and thromboendarterectomy at the anastomosis site another aorta clamp was placed immediately distal to the renal arteries before the supra renal clamp was removed. The end-to-side proximal anastomosis was performed with two short polypropylene 3-0 sutures. Teflon pledgets were tied at the end of each suture. The assistant held the sutures in traction with the help of atraumatic laparoscopic suture clamps with custom made rubber protection on the clamping jaws. The aortic clamps were removed, graft limbs were clamped and the anastomosis checked for patency. The descending colon was placed back to its position and the patient was again placed in the decubitus position. A wound drain was placed along the anastomosis and CO₂-exsufflation was performed. Distal anastomoses at the common femoral artery were made bilaterally, in an end-to-side fashion with 5.0 polypropylene sutures and flow was re-established to the lower extremities. The fascia was closed with absorbable sutures at the umbilical trocar position. At the rest of the trocar incisions only the skin was approximated with metal clips. Absorbable sutures were used to close the subcutaneous tissue in the groin wounds and metal clips in the skin.
Postoperative care

The patients in the OABF group received epidural analgesia after surgery. Both groups were offered oral and/or intravenous analgesia if necessary. The patients received i.v. low molecular weight heparin as postoperative thrombosis prophylaxis, when the activated partial thromboplastin time (APTT) was below 50 seconds. They were transferred from the intensive care unit (ICU) to the vascular surgery ward when their condition and vital parameters were stable. All doctors with the vascular departments were involved in the postoperative evaluation and care of the patients, and all patients were discharged when they met the following discharge-criteria;

- Able to walk
- Oral intake of food
- Normal urination/defecation
• No untreated ongoing local or systemic complication.

We followed the patients at the out-patient clinic at 1, 3 and 6 months. Additionally, all patients in the NLAST trial will be followed up postoperatively at 1, 2, 5 and 10 years.

5.5 Outcomes

Paper I: Inflammatory response measured by perioperative serum levels of interleukin-6 (IL-6), interleukin-8 (IL-8) and C-reactive protein (CRP).

Paper II: Hormonal stress response measured by perioperative levels of adrenocorticotropic hormone (ACTH), aldosterone, metanephrine and cortisol.

Paper III: Cost-utility based on health-related quality of life (HRQoL), quality adjusted life years (QALYs) and procedure related costs.

5.6 Analysis

Inflammatory response

The inflammatory response was quantified by the serum level of Interleukin-6 (IL-6), Interleukin-8 (IL-8) and C-reactive protein (CRP) at the following six different time points;

1. Before surgery (baseline)
2. After completion of the distal anastomosis and flow to one of the lower limbs was re-established
3. 6 hours after beginning of surgery
4. 12 hours after beginning of surgery
5. 24 hours after beginning of surgery

6. At discharge from hospital

Blood samples were primarily taken from an arterial catheter, or if not possible from a central venous catheter or a peripheral vein. They were centrifuged at 4°C, 3000 r/min, within 1 hour from sampling. 2 ml serum was transferred to polypropylene nunc vials and frozen within 2 hours from sampling at - 80 °C until testing. IL-6 and IL-8 were analysed using a human high sensitivity bead-based multiplex assay (Milliplex MAP kit). Whereas, the serum CRP level was analysed using the immune turbidimetric method.

**Humoral stress response**

Humoral stress response was quantified by perioperative measurements of adrenocorticotropic hormone (ACTH), aldosterone, metanephrine and cortisol. Blood samples were taken before, during and after surgery at the following eight different time points deemed to potentially be moments with large alterations in physiological stress:

1. After anaesthesia and administration of central venous access (baseline)
2. Right after first groin incision
3. Right after the beginning of laparotomy/laparoscopy
4. Immediately before cross clamping of the aorta
5. Immediately after placement of the aortic clamp
6. After reestablishment of flow through the first vascular graft limb
7. Wound closure
8. 24 hours after the beginning of surgery (follow-up)
Blood samples were primarily taken from arterial catheter, and if not possible from central venous catheter. ACTH and metanephrines were analysed from ethylenediaminetetraacetic acid (EDTA) plasma. EDTA tubes were placed on ice before sampling, and centrifuged at 4°C, 3000 turns/min, within 30 minutes. Cortisol and aldosterone were analysed from serum, which had been centrifuged at 4°C, 3000 turns/min and frozen within two hours. Both plasma and serum samples were frozen in polypropylene nunc vials at -80°C until analysis.

Aldosterone was analysed using a chemiluminescent immunoassay (CLIA) (LIAISON Aldosterone assay), on the LIAISON Analyzer (Diasorin Inc, USA). Cortisol was analysed using a competitive luminoimmunoassay (LIA) and ACTH with a non-competitive immunoluminometric assay (ILMA). Both analysed on kits from Siemens on the Immulite 2000 from Siemens Healthcare (Siemens Healthcare, Germany). Metanephrine was analysed using a competitive radioimmunoassay (RIA), on a kit from LDN (Labor Diagnostika Nord GMBH, Germany).

Interleukins and hormone samples were analysed by the Hormone Laboratory at Oslo University Hospital.

**Cost-effectiveness**

We calculated the cost-utility based on HRQoL and costs. We used the EQ-5D-5L questionnaire validated in Norwegian and health-related quality of life (HRQoL) score was estimated based on a value set from the United Kingdom, due to the lack of a Norwegian value set.\(^{193-195}\) HRQoL was measured at the following timepoints:

- Before surgery (baseline)
- 1 month postoperative
- 3 months postoperative
- 6 months postoperative
Costs were measured in terms of cost of surgical equipment, prosthesis and hospital stay. During surgery for the first three open and three laparoscopic patients, all disposable and non-disposable surgical equipment was meticulously registered by a designated nurse. A mean price for the resources used during surgery was calculated for each group based on those six patients. As the procedure is relatively standardized, we considered it to be sufficient to extrapolate the cost of the interventions from these six patients. The cost of postoperative hospital stay was based on national data for price per day in a somatic ward.\textsuperscript{196} We chose a health care sector perspective for the analysis and only resources connected to the surgery and hospital stay were registered.

\textbf{5.7 Statistical methods}

\textbf{General}

Categorical variables were presented as frequencies and continuous variables by the median and interquartile range. Comparisons between the two treatment groups were performed using the Mann-Whitney U test for continuous variables and Fisher’s exact test for categorical variables. Systemic morbidity was defined as all non-fatal complications related to the surgical procedure, excluding complications related to the graft and wound.\textsuperscript{9} Area under the curve (AUC) was used on serial, correlated measurements. AUC is a superior method to distinguish a significant difference between the groups compared to the repeated calculation at single measurement points.\textsuperscript{197}

These studies were substudies in a larger randomized trial and individual power analyses were not conducted on the outcomes.

Level of statistical significance was set at 5 \% (p < 0.05).
We used statistical software from Epi Info (Epi Info™ software, Center for Disease Control and Prevention, Atlanta, USA), IBM SPSS statistics version 22.0 (IBM corporation, New York, USA), MedCalc version 13.1.2 (MedCalc software, Ostend, Belgium), STATA 13.0 (StataCorp LP, College Station, Texas, USA) and Microsoft Office Excel® (Microsoft, Redmond campus, Redmond, USA).

**Paper I**

The three inflammatory markers (CRP, IL-6 and IL-8) were considered as continuous outcomes and measured at four fixed timepoints for all subjects. Mean serum levels and confidence intervals for the inflammatory markers at all timepoints were calculated and presented graphically. Area under the curve (AUC) was calculated for these serial measurements, and differences between the two groups were evaluated by a parametric test.\(^{197}\) All markers were analysed in their logged form due to skewed distribution of data. A multivariate analysis was performed, based on the General Estimated Equations (GEE) model,\(^ {198}\) controlling for confounders or risk factors. Timepoint two and six were not taken at a fixed point in time (reestablishment of flow through graft and discharge from hospital), and was consequently removed from the AUC and GEE analyses to minimize variability and make the models more robust.

**Paper II**

The four markers of operative stress; cortisol, aldosterone, ACTH and metanephrine were considered as continuous outcomes and measured at eight timepoints for all subjects in the two groups. These serial measurements of the stress hormones were presented graphically as the mean value and confidence interval at the different time points. We used a GEE model to
control for confounding factors. All markers were analysed in their logged form due to skewed distribution of data. Since the number of clusters were scarce (30 patients), we considered measures at only three timepoints (i.e. after intubation and establishment of central venous access, immediately before aortic cross clamping, and 24 hours after start of surgery) to meet the conditions for the adequacy of the GEE model. In addition we evaluated change in serum levels from baseline (after intubation and establishment of central venous access) to follow-up (24 hours after start of surgery). Comparison between the two treatment groups was performed using analysis of covariance (ANCOVA). \(^{199}\)

**Paper III**

The EQ-5D-5L questionnaire was used and EQ-5D score was calculated at four timepoints for all subjects in the two groups. We calculated QALYs using AUC. Deceased patients were set to have a quality of life equal to 0. One QALY is defined as one year of perfect health (patient-reported). There were missing values for one patient at 3 and 6 months, we imputed the mean value for the same treatment group at each timepoint. To give a better impression of the uncertainty in the overall estimates of cost-effectiveness, we performed 1000 bootstrap samples and calculated △costs and △QALYs. No discounting of costs or health effects was performed due to the short time horizon of the analyses. A generalized linear model (GLM) was used to analyse differences in QALYs and costs, and control for confounding factors and baseline values.

**5.8 Ethics**

The patients were not exposed to any additional unnecessary harm or strain as a result of their participation. The participants gave an informed, written consent. The trial was approved by
the Regional Committee for Medical and Health Research Ethics (registration number 2012/1367). Ethical standards were in accordance with the Helsinki Declaration of 1975. Establishment of a biological bank was approved by the Norwegian Data Inspectorate. The trial was registered at www.clinicaltrials.gov with the registration number NCT01793662.
6. Summary of results

6.1 Paper I

This was a substudy of a RCT where the first thirty patients with severe aortoiliac occlusive disease (AIOD) eligible for aortobifemoral bypass surgery were randomized to LABF (n=14) or OABF (n=16). The main objective of our study was to measure the inflammatory response to surgery as an indication of surgical invasiveness and prognosis. The inflammatory response was measured by perioperative measurements of serum Interleukin-6 (IL-6), Interleukin-8 (IL-8), and C-reactive protein (CRP) at six different timepoints (figure 8).

- Interleukin-6 was significantly lower after the laparoscopic procedure measured by comparing AUC, and after adjusting for the confounding effect of coronary heart disease (p=0.010).

- The differences in serum levels of IL-8 and CRP did not reach statistical significance; p-values were 0.24 and 0.88, respectively.
Figure 8 Mean serum level of Interleukin-6, Interleukin-8 and CRP during and after LABF vs OABF

Abbreviations and definitions: LABF; Laparoscopic aortobifemoral bypass, OABF; Open aortobifemoral bypass. Lines represent the 95 % confidence interval (CI).

Source: Paper I, Copyright (2016), reprinted with permission from Dove Medical Press Ltd.

Timepoints:

1. Before surgery (baseline)
2. After completion of the distal anastomosis and flow to one of the lower limbs was re-established
3. 6 hours after beginning of surgery
4. 12 hours after beginning of surgery
5. 24 hours after beginning of surgery
6. At discharge from hospital
6.2 Paper II

The main objective of this paper was to measure the stress hormones during surgery and aortic crossclamping in patients undergoing LABF vs OABF as an indicator of surgical stress. We monitored adrenocorticotropic hormone (ACTH), aldosterone, metanephrine and cortisol at eight different timepoints. The population consisted of the same thirty consecutive patients as in paper I, randomized to LABF (n=14) or OABF (n=16).

- During surgery there was an increase in all humoral stress markers in both groups (figure 9).
- All stress markers declined during the aortic crossclamping in both groups.
- LABF generated lower levels of metanephrine (p= 0.05) and higher level of aldosterone (p=0.05) as compared to OABF.
- The analysis of covariance showed increased levels of cortisol and ACTH in open group at 24 hours as compared to the baseline and this difference was statistically significant between the two groups, ( p= 0.016 and p= 0.010 respectively). Cortisol and ACTH returned earlier to baseline serum levels in the LABF group.
- There was significantly less bleeding during LABF, a median of 275 ml vs 1000 ml after OABF (p=0.0285).
- There was a longer anastomosis time, median of 43 minutes (LABF) vs 30 minutes (OABF) (p= 0.0002).
- There was significantly shorter postoperative hospital stay in the LABF group, median 5.0 days vs 9.0 days (p= 0.0010).
- There was no statistical difference in postoperative morbidity or mortality.
Figure 9 Comparing cortisol, aldosterone, ACTH and metanephrine during and after LABF vs OABF.

Abbreviations and definitions: LABF; Laparoscopic aortobifemoral bypass, OABF; Open aortobifemoral bypass. Boxes represent the interquartile range (IQR), ◦ represent outliers and * represent extreme values.

Source: Paper II, Copyright (2017), reprinted with permission from Taylor and Francis Online.

Timepoints:

1. After anaesthesia and administration of central venous access (baseline)
2. Right after first groin incision
3. Right after the beginning of laparotomy/laparoscopy
4. Immediately before cross clamping of the aorta
5. Immediately after placement of aortic clamp
6. After reestablishment of flow through the first vascular graft limb
7. Wound closure
8. 24 hours after the beginning of surgery
6.3 Paper III

We aimed to perform a cost-utility analysis on LABF vs OABF. The first fifty consecutive patients in the NLAST were randomized to either a totally laparoscopic (n =25) or an open surgical procedure (n=25). One patient in the open group dropped out before surgery, after randomization. The patients in paper I and II are included in the same material.

- We found significantly (p= 0.001) higher increase in quality adjusted life years (QALYs) measured by AUC, after LABF vs OABF during follow-up, with a difference of 0.07 QALYs (figure 10).

Figure 10 Health related quality of life presented as mean EQ-5D-5L score at baseline and during follow-up after LABF vs OABF.

Abbreviations and definitions: LABF; Laparoscopic aortobifemoral bypass, OABF ; Open aortobifemoral bypass, Error bars representing the 95 % confidence interval (CI)

Source: Paper III, Copyright (2017), reprinted with permission from Dove Medical Press Ltd.
- The total costs (surgical equipment, vascular graft and hospital stay) after laparoscopic surgery (€ 9,953) was less than with open surgery (€ 17,260), p= 0.001.

- The laparoscopic group had significantly longer operation time than the open group (221 vs 196 min, p=0.024), but shorter postoperative hospital stay (4.0 vs 7.0 days, p <0.001).

- There was an increased incremental effect (ΔQALYs) and lower costs (Δcosts) after LABF compared with OABF (figure 11A and B).
Figure 11

A: Scatter plot of costs per quality adjusted life years (QALYs) gained comparing totally laparoscopic aortobifemoral bypass with open aortobifemoral bypass.

B: Incremental cost (Δcosts) and incremental effect (ΔQALYs) between LABF and OABF based on bootstrapping.

Abbreviations and definitions: LABF; Laparoscopic aortobifemoral bypass, OABF; Open aortobifemoral bypass, QALYs; quality adjusted life year; €=Euro

Source: Paper III, Copyright (2017), reprinted with permission from Dove Medical Press Ltd.
7. Discussion

7.1 Discussion of methodology, strengths and weaknesses

Study design, participants and sample size

The RCT is the golden standard when it comes to investigating effectiveness of an interventional treatment compared to an existing method. We have previously reported our results from the pilot comparative cohort study conducted from 2005-2011. ¹⁰ We found the LABF technique to be safe, feasible and possibly beneficial. However, this method of comparison carries a risk of selection bias. Randomization seeks to eliminate selection bias, and to make sure confounding factors are evenly distributed. Hence, it was a natural choice to design a RCT to compare the LABF and OABF procedures. However, RCTs also have their limitations; they are quite resourceful, expensive and time consuming. Since an increasing number of patients even with TASC II type D lesions are being treated endovascularly, the inclusion for this RCT has been taking longer time than we anticipated. However, we are determined and aim to include all eligible patients, and our inclusion criteria reflect the clinical world.

Despite our randomization, a bias may have occurred. The population was distributed between three different hospitals and the procedures on more than a dozen surgeons, but with only two of the hospitals and only one vascular consultant performing the laparoscopic surgery. Senior doctors performed and junior doctors assisted in both types of surgery. It is not possible to avoid this bias without centralizing all study patients to one hospital. But this would however not have been acceptable for our partner hospitals, who also conduct vascular surgical training of junior doctors. Additionally, it would not reflect the clinical reality. Bias may also occur as the researchers, staff and patients were not blinded. However, blinding in surgical studies is almost impossible, and was not possible in our type of intervention.
Another problem with the RCT can be the homogeneity of the population, if the inclusion/exclusion criteria are not representative of the clinical world, thus making it difficult to generalize. Generalizability and external validity can also be an issue in small samples. Additionally, all three of these studies are conducted as substudies in the same RCT without any individual calculation of sample size for the outcomes. However, this is not uncommon in studies on secondary outcome or hypothesis generating studies. Also, to the best of our knowledge, these outcomes; inflammatory changes, hormonal stress response and cost utility analysis, have not previously been investigated in a randomized fashion. These outcomes and the randomized comparison of LABF vs OABF makes this trial unique.

**Blood sampling and biomarkers**

Selection of biomarkers, the timing and the number of repeated blood samples were issues both in paper I and II. Examining previous research we found several different blood sample protocols, and none in our specific field of surgery.

We chose IL-6, IL-8 and CRP at these six different timepoints based on previous literature on the acute phase response in both laparoscopic and vascular surgery.\(^{133,143-145,200}\) Although, in retrospect, we could have measured the serum level of CRP for a longer time to be sure to capture the peak. There were also too many repeated correlated timepoints for the regression model, and we had to remove some of the timepoints, however fewer measuring points would have made it difficult to capture the variation over time.

Since we hypothesized that the LABF is minimally invasive compared to the OABF bypass, we aimed to examine the humoral stress response in both procedures at various critical
timepoints during surgery. Previously endocrine stress response has been used in a number of studies as a surrogate to monitor the body’s physiological response to surgery and/or trauma. However, the fact that the blood samples were not taken at fixed timepoints for all patients except for baseline and 24 hours after surgery created a problem for the regression model. On the other hand, we were anticipating specific events to create stressful responses, particularly the aortic cross-clamping. The hormonal changes at this timepoint would not have been captured if we had chosen fixed timepoints for blood sampling.

Catecholamines, especially norepinephrine should not be measured in plasma taken from a peripheral vein due to peripheral production. Blood samples were in a few cases, where the arterial access was not available, taken from a peripheral vein. However, we measured metanephrine, which has a longer half life time and is more evenly distributed in the vascular system. Other reasons to measure metanephrine instead of epinephrine and norepinephrine were the use of artificial norepinephrine during surgery and the interaction with paracetamol during testing.

**Cost-effectiveness measures**

EQ-5D is a generic, patient-friendly questionnaire, frequently used in health economic evaluations. A disease specific tool for PAD might have been better to assess reduced HRQoL due to leg pain, but not to measure difference in HRQoL due to laparoscopy compared with laparotomy. Additionally, so far none of the disease specific questionnaires are validated for the economic analysis.

We chose a follow-up time of 6 months. When comparing HRQoL for laparoscopic vs open procedures the main gain is in the early postoperative period, but some maintain a difference
in HRQoL for up to a year. In our pilot study the main effect on HRQoL was during the first 6 months. As a result we considered 6 months to be sufficient, as there is no indication that the benefits in terms of HRQoL and spared economic costs will be in favour of other than LABF with a longer follow-up time.

At the time being there are no known price per day of hospital stay in our hospital, hence we used national data. This price may be inaccurate for our patients as it is calculated as the mean price for all types of hospital admissions in somatic specialist health care in Norway. In cost-effectiveness analyses there is no limit to the extent of registration of resources, for instance by a micro-cost assessment method. Some studies include in great detail both resources used at the hospital and in the community, e.g. sick-leave, physical therapies etc. We decided to focus mainly on the costs of the procedure and hospital stay, and the HRQoL during the first 6 postoperative months. We know the main gain is retrieved during these months and also the main driver of costs in the laparoscopic group is the surgery itself. However, more details would be interesting and our research group is at the moment working on a micro-cost evaluation, which might shed extra light on this subject.

**Statistics**

A multivariate analysis was used in article I and II, based on the General Estimated Equations (GEE) model. This method was developed by Zeger and Liang controlling for confounders or risk factors. We know that the GEE works best if the number of cluster (patients) is large (N>50), the number of observations in a cluster is small and when the measurements are taken at the same time for all subjects. In our analyses we had to remove timepoints from the model to make it more robust. Despite the amount of measurements, we had almost no missing values in our material.
No individual power calculations were made for these substudies. The sample size and design did not permit any additional analyses to investigate the correlation between our biomarkers and clinical outcome. Multiple testing and repeated correlated measurements in a small sample also affect the certainty of statistical analyses. This of course should be considered whilst drawing conclusions from these studies. In clinical studies one has the risk of both type I and type II error. Falsely rejecting the null hypothesis and deducing there is a difference between the groups, is called a type I error and is common in smaller samples. One overestimates an effect from a new treatment. A type II error is falsely accepting the null hypothesis and status quo, which can occur if the level for statistical significance is set too low. Some results can be clinically relevant, even though they are not statistically significant. There is a risk of a type I error in these substudies. Nonetheless as our investigations are statistically significant in such a small sample, it generates new knowledge and the possibility for new hypotheses.

**Ethical issues**

Patients were informed and had signed a written consent to take part in the NLAST. All the patients willingly sought surgical treatment for their illness. Since there is no certain difference in mortality or morbidity so far in the published literature or in our studies, we find it ethical to continue this randomized trial. The patients did not experience any additional harm or strain as a result of their participation, except for a few additional follow-up visits at our out-patient clinic, the time spent filling out questionnaires and some additional blood samples. However, most patients did not perceive this as strain, rather as an extra service, and the quality of life questionnaires indicate an overall satisfaction.
7.2 Discussion of main findings

Main Findings

In the patients operated with LABF, we found a reduced inflammatory response which in the literature has been proven correlated to reduced morbidity and mortality. Inflammation has been getting more and more attention in the medical community as it seems to be involved in a number of illnesses, reactions and outcomes. Our results are comparable with results from other fields of surgery, where laparoscopy seems to decrease the inflammatory reaction caused by the surgical trauma surgery.\textsuperscript{134-142} Only one non-randomized study has been published regarding the inflammatory response to LABF, and in that study the hand-assisted mini-laparotomy technique was used during completion of the aortic anastomosis.\textsuperscript{210}

The humoral stress response surprisingly increased during LABF, except for metanephrine, but there was an earlier return to preoperative levels compared with the open group. It is possible the cause is the prolonged trauma after open surgery due to the size of incision and the postoperative pain. This is in accordance with research in other fields of surgery.\textsuperscript{133,141} Some find no difference, but others notice this earlier return to baseline.\textsuperscript{166,172,211} The lack of surgical stress response during aortic cross clamping is curious, and may indicate less effect of the prolonged cross-clamping than assumed. On the other hand, the pneumoperitoneum seems to be much more stress inducing than we first thought. In our study there were higher serum levels of cortisol, ACTH and aldosterone in the laparoscopic group during surgery, however, in the GEE model only the difference in aldosterone was statistically significant. A possible cause of increased stress hormones may be the pneumoperitoneum, which is known to initiate an inflammatory and endocrine stress response.\textsuperscript{178,179,212-214} Researchers in one study found a similar cortisol reaction to both laparoscopic surgery and pneumoperitoneum alone, which indicates that the surgical stress
may be mainly attributable to the pneumoperitoneum.\textsuperscript{215} The pneumoperitoneum also causes hypercapnia, reduced venous blood return, reduced cardiac output and reduced renal blood flow.\textsuperscript{38,216,217} Reduced renal blood flow decreases renal function, increases aldosterone and can cause oliguria,\textsuperscript{218,219} and could be the cause of increased serum aldosterone during LABF. Aldosterone release is also inhibited by the administration of saline.\textsuperscript{220} The OABF group in our study had a significant higher blood loss and it is possible that the OABF group as a result have been given more fluid supplements during surgery than the laparoscopic group, consequently resulting in much lower aldosterone in the open group.

The aortic anastomosis time is longer in the laparoscopic group which is associated with an increased stress response.\textsuperscript{177,221,222} There is also a synergic effect combined with the pneumoperitoneum. However, in our study the hormone levels decrease in both groups during aortic crossclamping, and the effect of prolonged aortic anastomosis time in the laparoscopic group does not seem to increase the hormonal stress markers. A possible explanation could be the extent of aortoiliac occlusion. In these patients with TASC-D lesions the haemodynamic changes of aortic crossclamping are naturally minimal.\textsuperscript{177}

We found LABF to be clearly cost-efficient compared to OABF which is comparable to research on other minimally invasive techniques.\textsuperscript{182,205,223-225} The only other economic investigation performed on LABF was a non-randomized comparative cohort which demonstrated decreased costs after LABF compared to OABF.\textsuperscript{112} However, they also removed the patients converted to open surgery from the analysis, and these patients might have been the ones in need of more resources.
We found increased HRQoL and reduced costs which makes the LABF a “dominant intervention” compared to open surgery. It is clearly cost-effective and considered recommendable as a new treatment. In addition, the difference in total costs and HRQoL are very clinically significant. The mean difference in costs was more than € 7,000, which should generate interest amongst leaders of the vascular community. However, the implementation of a technique is also based on local qualifications, politics, geography and patient demography. The effect would probably be best with high volumes of patients due to the learning curve and cost of equipment. The findings of our study should be of interest to health providers, as well as for the patients suffering from AIOD in need of an aortobifemoral bypass.

**Recent literature**

Some progress has been made in the research field since we started our project in 2011. The last few years several comparative cohorts and even a RCT have been published (table 2).
### Table 2 Comparative studies published on LABF compared to OABF for AIOD from 1993-2016

<table>
<thead>
<tr>
<th>Author and publication year</th>
<th>RCT</th>
<th>Participants (n)</th>
<th>TASC</th>
<th>Operating time (min)</th>
<th>Blood loss (ml)</th>
<th>30-day mortality (n, %)</th>
<th>30-day morbidity (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olind et al 2005</td>
<td>No</td>
<td>22</td>
<td>NR</td>
<td>267</td>
<td>690</td>
<td>1 (4.5%)</td>
<td>NR</td>
</tr>
<tr>
<td>Rouers et al 2005</td>
<td>No</td>
<td>30</td>
<td>NR</td>
<td>231</td>
<td>725</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Tiek et al 2012</td>
<td>Yes</td>
<td>14</td>
<td>C,D</td>
<td>273</td>
<td>725</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bruls et al 2012</td>
<td>No</td>
<td>95</td>
<td>C,D</td>
<td>242</td>
<td>682</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Kazmi et al 2015</td>
<td>No</td>
<td>50</td>
<td>D</td>
<td>265</td>
<td>400</td>
<td>1</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>211</td>
<td></td>
<td>246</td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Abbreviations:** AIOD, Aortoiliac occlusive disease; LABF, laparoscopic aortobifemoral bypass; OABF, open aortobifemoral bypass; RCT, randomized controlled trial; NR, not reported.

**Notes:** This table is made in part from data and calculations from the article co-authored with Helgetveit in 2017. This study reports composite endpoints. Data for 30-day mortality was provided directly from the main author, and not reported in the article. Due to difference in reporting, calculation of total operating time, blood loss and 30-day morbidity was not possible.

Tiek et al. published the first randomized trial on the subject in 2012, unfortunately they had to close the trial prematurely due to ethical reasons. The hospital where the study was initiated got referrals for laparoscopic aortic surgery. As a result, the local ethical medical board deemed it unethical to randomize these patients, even though there was not sufficient evidence to say that laparoscopic surgery was superior to the traditional open approach. They concluded that laparoscopic aortic surgery was safe with decreased morbidity, shorter hospital stay and earlier recovery. However, the premature termination of the study gave a statistical problem; there was a small sample and not enough power of the study to get statistically significant results.
Bruls et al.\textsuperscript{227} conducted a large comparative cohort, with a total of 251 patients treated for AIOD (95 LABF, 156 OABF). It was a retrospective, single-centre cohort. They found a significant difference in adverse events (mortality and complications) during the first 30 days, 6.8 % (N=5) for LABF and 23.7 % (N=37) for OABF, \(p<0.0001\). There was increased operation time, but significantly shorter hospital stay after LABF. One should comment on the relative high rate of conversion, 22 \%, as the surgeons practiced a low threshold for converting into a mini-laparotomy in the left flank. The conversion group experienced more blood loss and longer hospital stay.

Ricco et al.\textsuperscript{92} published a large cohort-study in 2016 indicating that laparoscopic aortic surgery increase the risk of morbidity and mortality in contradiction to most of the published literature.\textsuperscript{189} Due to the non-randomized nature of the study they used propensity score matching to try to diminish bias,\textsuperscript{228} this method has been criticised as it may cause new bias.\textsuperscript{229} Another issue with this article was the grouping of adverse events and the heterogeneity of the population. The study, like so many others, contained both patients with AAA and AIOD, each procedure carrying unique risks of complications. LABF for AAA seems to have a much higher risk of adverse events than for the treatment of AIOD.\textsuperscript{53,66} These two procedures are not comparable and should be examined separately, which makes the conclusions and applicability uncertain.

Lecot et al.\textsuperscript{209} presented their long-term results in 2016. This non-comparative cohort consisted of 87 patients treated with LABF for AIOD. One year primary and secondary patency rates were 96.1\% and 99.4\%, and at 5 years 83.0\% and 97.0\%, respectively. These results are comparable to open surgery. Additionally, they had a low rate of morbidity and mortality.
In our own research group two articles have been published based on the cohort of patients treated with LABF and OABF between 2005 and 2011. \textsuperscript{10} Fifty patients with symptomatic AIOD were treated with totally LABF. In our first article, a comparative cohort, we compared these patients treated with a LABF (N=50) to patients treated with an OABF (N=30) during the same time-period. The main outcome was a composite endpoint of all-cause mortality, systemic morbidity and graft occlusion. We found an 82 % relative reduction of this composite end-point after LABF. The limitations of the study are the small number of patients and the non-randomized design. Kazmi et al. demonstrated later in a non-comparative study, statistically significant higher HRQoL scores after LABF in the same population. \textsuperscript{16} There was an increase in all quality of life domains of Short-Form 36 (SF-36)\textsuperscript{230} during the first six months.

**Clinical implications**

Open surgery has previously been the gold standard. De Vries and Hunink published a large meta-analysis describing good patency results and decreased mortality and morbidity over time. \textsuperscript{20} PTA, with its minimally invasive nature, has since revolutionised the possibilities in treatment for atherosclerotic disease, reducing mortality and morbidity and broadening the indication and accessibility of treatment. \textsuperscript{22} Although there is still a need for comparative research comparing endovascular treatment to LABF, \textsuperscript{231} endovascular therapy for severe aortoiliac occlusive disease cannot maintain the same patency rates as open surgery. \textsuperscript{23,29,30} In this aspect laparoscopic aortobifemoral bypass surgery shows very promising results in combining the reduced mortality and morbidity of minimally invasive procedures with excellent long-term patency rates. \textsuperscript{209}
In the vascular community the implementation and accumulation of evidence for LABF has been slow. This could be because vascular surgeons lack the basic laparoscopic training and the LABF is not an easy procedure, although the learning curve is manageable. The revolution of the endovascular techniques also made the market for the LABF smaller. Today, only patients with TASC type D lesions are candidates for LABF or OABF, and vascular communities argue the need for ensuring surgical training in open aortic procedures. This is true in hospitals with a small patient population. However our patients with severe AIOD are not healthy. They have a number of comorbidities and are high-risk patients when it comes to performing major surgery like the aortobifemoral bypass. Our patients would probably especially benefit of a minimally invasive technique like the LABF. This treatment option should be an opportunity made available, if not at local hospitals, at least by referral to the hospitals with an established practice. We know from the literature that LABF for AIOD seems to be safe, have shorter hospital stay, possibly less morbidity and unaffected mortality compared to OABF. The results of our three studies add to the pool of evidence regarding LABF. The possible benefits of LABF should be taken into consideration when discussing possible treatment opportunities with patients suffering from symptomatic severe AIOD. The LABF should be in the repertoire of possible treatments as it contains unique benefits not achieved by open surgery or endovascular treatment alone.
8. Conclusions

8.1 Main conclusions

- LABF initiates a decreased perioperative inflammatory response compared with open surgery.
- Patients treated with LABF have higher levels of ACTH, aldosterone and cortisol during surgery, lower perioperative levels of metanephrine, but achieve earlier hormonal homeostasis after surgery as compared with OABF.
- Based on the literature decreased inflammatory response and earlier return of stress hormones to baseline level may be correlated to improved outcome.
- LABF generates a higher gain in HRQoL and lower costs compared with OABF, which makes the LABF clearly cost-effective.
- The acute phase response, humoral stress response and cost-effectiveness for LABF vs OABF have previously not been investigated in a randomized setting, which can instigate new hypotheses,
- The possible benefits of LABF should be taken into consideration when discussing possible treatment options for patients suffering from symptomatic AIOD, TASC II type D lesions.

8.2 Concluding remarks and future perspective

It seems that the laparoscopic aortobifemoral bypass surgery have some potential benefits regarding postoperative inflammation, operative stress and cost-effectiveness and should be considered as an alternative to open surgery. The ongoing trial, NLAST, will probably answer some more of the questions regarding mortality and morbidity after LABF for AIOD, as the first RCT including a pre-trial calculation of sample size in this field. Hopefully we will see several randomized trials in the future to increase the level of evidence, and maybe the
technique will be useful in treating other conditions as the number of surgical indications increase. In our vascular department we have gradually expanded the laparoscopic repertoire to include treatment for celiac compression syndrome, management of type-II endoleaks after EVAR and laparoscopic aortomesenteric bypasses. In the future one might also develop a safer laparoscopic technique to better handle the treatment of abdominal aortic aneurysms. Further investigations are necessary and welcomed.
9. References


59


61


10.1097/SHK.0b013e3181d8e687


139. Torres A, Torres K, Paszkowski T, Staśkiewicz GJ, Maciejewski R. Cytokine response in the postoperative period after surgical treatment of benign adnexal masses:
comparison between laparoscopy and laparotomy. Surg Endosc 2007/10/01
2007;21:1841-48

140. Leung KL, Lai PBS, Ho RLK, Meng WCS, Yiu RYC, Lee JFY, et al. Systemic
Cytokine Response After Laparoscopic-Assisted Resection of Rectosigmoid

inflammatory, and stress responses in a randomized comparison of open and
laparoscopic repair of recurrent inguinal hernia. Surg Endosc 2006;20:468-72

142. Sammour T, Kahokehr A, Chan S, Booth RJ, Hill AG. The Humoral Response After
2010;164:28-37

143. Kolvenbach R, Deling O, Schwierz E, Landers B. Reducing the operative trauma in
aortoiliac reconstructions–a prospective study to evaluate the role of video-assisted

144. Swartbol P, Pärsson H, Truedsson L, Sjöholm A, Norgren L. Aortobifemoral surgery
induces complement activation and release of interleukin-6 but not tumour necrosis

145. Swartbol P, Truedsson L, Norgren L. The Inflammatory Response and its
Consequence for the Clinical Outcome Following Aortic Aneurysm Repair. Eur J
Vasc Endovasc Surg 5/1 2001;21:393-400

146. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery.
Surgery 2000;127:117-26

1994;15:74-80

JN. Peritoneal and systemic cytokine response to laparotomy. Br J Surg 1996;83:347-
48

149. Yahara N, Abe T, Morita K, Tangoku A, Oka M. Comparison of interleukin-6,
interleukin-8, and granulocyte colony–stimulating factor production by the peritoneum

peritoneal mesothelial cells produce many cytokines (granulocyte colony-stimulating
factor [CSF], granulocyte-monocyte-CSF, macrophage-CSF, interleukin-1 [IL-1], and
IL-6) and are activated and stimulated to grow by IL-1. Blood Dec 1 1992;80:2835-42

intravenous IL-8 administration in nonhuman primates. The Journal of Immunology


169. Campbell KA, Joseph SP, Whiting MJ, Doogue MP. The half-lives of plasma free metanephrines. *Clin Endocrinol (Oxf)* 2012;76:764-66


70

181. Follesdal A. [Should prioritization in health care programs be based on duty or care ethics or benefit ethics?]. Tidsskr Nor Laegeforen Oct 23 2003;123:2897-8


214. Ozmen MM, Zulfikaroglu B, Col C, Cinel I, Isman FK, Besler TH. Effect of increased abdominal pressure on cytokines (IL1 beta, IL6, TNFalpha), C-reactive protein (CRP), free radicals (NO, MDA), and histology. Surgical laparoscopy endoscopy & percutaneous techniques 2009;19:142-7


228. Rosenbaum PR, Rubin DB. The Central Role of the Propensity Score in Observational Studies for Causal Effects. *Biometrika* 1983;70:41-55


10. Papers I-III
Comparison of the acute-phase response after laparoscopic versus open aortobifemoral bypass surgery: a substudy of a randomized controlled trial

Anne H Krog1,2
Mehdi Sahba3
Erik M Pettersen4
Irene Sandven5
Per M Thorsby1,6
Jørgen J Jørgensen1,2
Jon O Sundhagen2
Syed SS Kazmi2

1Institute of Clinical Medicine, University of Oslo, Department of Vascular Surgery, Division of Cardiovascular and Pulmonary Diseases, Oslo University Hospital, Oslo, 2Department of Vascular Surgery, Østfold Central Hospital, Fredrikstad, 3Department of Vascular Surgery, Sarlandet Hospital HF, Kristiansand, 4Oslo Center for Biostatistics and Epidemiology (OCBE), 5Oslo Center for Bioinformatics and Epidemiology (OCEB), 6Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway

Purpose: Minimally invasive surgical techniques have been shown to reduce the inflammatory response related to a surgical procedure. The main objective of our study was to measure the inflammatory response in patients undergoing a totally laparoscopic versus open aortobifemoral bypass surgery. This is the first randomized trial on subjects in this population.

Patients and methods: This is a substudy of a larger randomized controlled multicenter trial (Norwegian Laparoscopic Aortic Surgery Trial). Thirty consecutive patients with severe aortoiliac occlusive disease eligible for aortobifemoral bypass surgery were randomized to either a totally laparoscopic (n=14) or an open surgical procedure (n=16). The inflammatory response was measured by perioperative monitoring of serum interleukin-6 (IL-6), IL-8, and C-reactive protein (CRP) at six different time points.

Results: The inflammatory reaction caused by the laparoscopic procedure was reduced compared with open surgery. IL-6 was significantly lower after the laparoscopic procedure, measured by comparing area under the curve (AUC), and after adjusting for the confounding effect of coronary heart disease (P=0.010). The differences in serum levels of IL-8 and CRP did not reach statistical significance.

Conclusion: In this substudy of a randomized controlled trial comparing laparoscopic and open aortobifemoral bypass surgeries, we found a decreased perioperative inflammatory response after the laparoscopic procedure measured by comparing AUC for serum IL-6.

Keywords: inflammation, vascular, laparoscopy, surgery, interleukin, C-reactive protein

Introduction

Every surgical trauma initiates a certain extent of inflammatory response, which is a part of our immune system. However, if excessive, this response can be autodestructive and may lead to complications after surgery. The quantification of this inflammatory process can be used as a measurement for surgical trauma, as well as a prognostic tool. Several studies have shown reduced physiological immune response when comparing minimally invasive surgical techniques to the traditional methods. Laparoscopic surgery causes less tissue trauma than open surgery and seems to preserve better immune function. Interleukin-6 (IL-6) is higher after major abdominal surgery and lower after laparoscopic surgery as compared to open surgery. Studies show that patients undergoing laparoscopic aortobifemoral bypass (LABF) surgery have a low postoperative morbidity and mortality. In addition, a recently...
published comparative cohort study showed significantly lower composite end point of all-cause mortality, systemic morbidity, and graft thrombosis after LABF compared with open aortobifemoral bypass (OABF).19

In this randomized study, we aimed to compare the totally LABF with OABF for the treatment of aortoiliac occlusive disease (AIOD) on the basis of postoperative changes in inflammatory mediators. Only one previous trial has measured the acute-phase response in patients undergoing an LABF, but the trial was not randomized and the hand-assisted minilaparotomy approach was used.20

Hypothesis
LABF surgery induces a reduced systemic inflammatory response compared with OABF.

Patients and methods
Design
This study is a part of an ongoing multicenter, randomized controlled trial (Norwegian Laparoscopic Aortic Surgery Trial [NLAST]) at the Department of Vascular Surgery, Oslo University Hospital. Patients with severe symptomatic AIOD, classified according to the Trans-Atlantic Inter-Society Consensus (TASC) II as type D lesions, were randomized to either LABF or OABF procedure.21

Participants
Participants were included from three vascular surgery departments in the South-East region of Norway, based on the following inclusion and exclusion criteria.

Inclusion criteria:
- Patient with AIOD, TASC type D lesion,21 and symptoms in the form of
  - intermittent claudication, with walking distance <200 m and/or
  - chronic critical lower limb ischemia with rest pain or ischemic ulcers (duration of symptoms >2 weeks).

Exclusion criteria:
- Eligible for an endovascular procedure
- COPD stage IV or more severe, GOLD classification22
- Symptomatic coronary heart disease
- Chronic heart failure, ejection fraction <40%
- Active cancer disease
- Hostile abdomen, previous major abdominal surgery
- Abdominal aortic aneurysm ≥3.0 cm
- Acute critical limb ischemia (duration of symptoms ≤2 weeks).

Sample size
This was a substudy in a larger randomized trial, and an individual power analysis was not conducted on these outcomes.

Randomization and blinding
The patients were enrolled by clinicians and researchers and were randomized to either open or laparoscopic surgery. We used block randomization, with six patients in each block and different sequences for the three participating hospitals. The sequence was random and was not known by the researchers. It was contained in closed, opaque, sequentially numbered envelopes until randomization. Blinding of surgeon and/or participants after randomization was not possible, but laboratory technicians who analyzed the samples were blinded.

Intervention
All procedures were performed by a team with at least one consultant vascular surgeon. The laparoscopic surgeons were passed the learning curve.19,23 The patients underwent aortobifemoral bypass surgery with either a totally laparoscopic approach in accordance with the technique described by Coggia et al24 or a standard open procedure through a median laparotomy. Aortic clamp was placed just below the renal arteries or just above if suprarenal aortic clamping was necessary. Both procedures were performed under general anesthesia.

Ethics
The project was completely voluntary and participants gave informed, written consent. The trial was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (registration number 2012/1367), and establishment of a biological bank was approved by the Norwegian Data Inspectorate.

Registration
The trial (NLAST) and protocol were registered at www.clinicaltrials.gov with the registration number NCT01793662.

Outcomes
Our primary outcome was inflammation due to surgical trauma measured by detecting serum changes in IL-6, IL-8, and C-reactive protein (CRP).

Biochemical analysis
We chose to measure IL-6, IL-8, and CRP due to their validity in reflecting the level of acute-phase response in major aortic surgery.20,21 The time points were chosen to capture fluctuation over time. IL-6 and IL-8 usually peak during the first 24 hours.
postoperatively, but CRP peaks at a later time. \textsuperscript{10,25,26} Blood samples were taken at the following six different time points:
1. Before surgery
2. After completion of distal anastomosis and flow to one of the lower limbs was reestablished
3. Six hours after beginning of surgery
4. Twelve hours after beginning of surgery
5. Twenty-four hours after beginning of surgery
6. At discharge from hospital.

Blood samples were primarily taken from arterial catheter, or if not possible, from central venous catheter or peripheral vein. Samples were centrifuged at 4°C, 1106 g within 1 hour from sampling. Two milliliters of serum sample was frozen in plastic Nunc vials, within 2 hours from sampling, at –80°C until further analysis.

Procedure for analysis
IL-6 and IL-8 were analyzed at the Hormone Laboratory, Oslo University Hospital, using the MILLIPLEX Map human High Sensitivity T-cell Magnetic Bead Panel (HSTCMAG-28SK, MILLIPLEX\textsuperscript{®} Map Kit; EMD Millipore Corporation, Billerica, MA, USA), while the serum CRP level was analyzed using the immune turbidimetric method performed by an automated machine from ROCHE Module PE Core P800 \& E170 Chemistry Analyzer (Hoffmann-La Roche Ltd., Basel, Switzerland).

Statistics
Categorical variables were summarized as frequencies and continuous variables by the median and interquartile range. Comparisons between the two treatment groups were performed using the Mann–Whitney \(U\)-test for continuous variables and Fisher’s exact test for categorical variables. A graphical presentation of the mean serum levels of the inflammatory markers was plotted in SPSS, including calculation of mean and confidence interval for each time point. The three inflammatory markers (CRP, IL-6, and IL-8) were considered as continuous outcomes and measured at four fixed time points for all the subjects. These serial measurements were analyzed univariately, calculating the area under the curve (AUC).\textsuperscript{27} Differences in AUC between the two groups were evaluated by a parametric test. All markers were analyzed in their logged form due to skewed distribution of data. A multivariate analysis was performed, based on the general estimated equations (GEE) model. In this method, the correlation structure of the data is specified by the investigators at the outset, and the model iterates toward a stable set of estimates to the parameters,\textsuperscript{28} controlling for confounders or risk factors. Time points two and six were not taken at a fixed point in time (reestablishment of flow through graft and discharge from hospital) and were consequently removed from the AUC and GEE analyses to minimize variability and make the models more robust. Statistical significance was set at a 5% level (\(P<0.05\)). We used software from Epi Info (Epi Info\textsuperscript{TM} software; Center for Disease Control and Prevention, Atlanta, GA, USA), IBM SPSS statistics version 22.0 (IBM Corporation, Armonk, NY, USA), MedCalc version 13.1.2 (MedCalc Software, Ostend, Belgium), and Stata 13.0 (StataCorp LP, College Station, TX, USA).

Results
Participant flow and recruitment
Thirty consecutive patients from the participating hospitals were included from February, 2013 to January, 2015 and randomized to either LABF (\(n=14\)) or OABF (\(n=16\)) (Figure 1). The patient baseline characteristics in the two groups are given in Table 1. One patient was converted from laparoscopic to open surgery and was analyzed in the laparoscopic group, as intention to treat. No patients were excluded after randomization or lost to follow-up at the time of analysis. There were no missing values in the inflammation markers. This substudy trial was completed after the inclusion of 30 patients.

Outcomes and estimation
In Figures 2–4, a graphical presentation of the serum levels of IL-6, IL-8, and CRP is given. All the inflammatory
Table 1 Baseline characteristics of patients treated with either totally laparoscopic or open aortobifemoral bypass for severe aortoiliac occlusive disease

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Laparoscopy (N=14)</th>
<th>Open surgery (N=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>59 (7.2)</td>
<td>64 (6.8)</td>
<td>0.1043*</td>
</tr>
<tr>
<td>Female sex, N (%)</td>
<td>7 (50)</td>
<td>9 (56)</td>
<td>0.5095*</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>26.3 (4.2)</td>
<td>24.0 (5.1)</td>
<td>0.2056*</td>
</tr>
<tr>
<td>Current smoker, N (%)</td>
<td>7 (50)</td>
<td>10 (63)</td>
<td>0.1038*</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>10 (71)</td>
<td>11 (69)</td>
<td>1.0000*</td>
</tr>
<tr>
<td>Renal failure, N (%)</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>1.0000*</td>
</tr>
<tr>
<td>COPD, N (%)</td>
<td>4 (29)</td>
<td>3 (19)</td>
<td>0.6746*</td>
</tr>
<tr>
<td>Hyperlipidemia, N (%)</td>
<td>5 (36)</td>
<td>2 (13)</td>
<td>0.2040*</td>
</tr>
<tr>
<td>Diabetes mellitus, N (%)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
<td>0.4667*</td>
</tr>
<tr>
<td>Coronary heart disease, N (%)</td>
<td>2 (14)</td>
<td>5 (31)</td>
<td>0.3992*</td>
</tr>
<tr>
<td>Statin, N (%)</td>
<td>12 (86)</td>
<td>15 (94)</td>
<td>0.5862*</td>
</tr>
<tr>
<td>Acetylsalicylic acid, N (%)</td>
<td>13 (93)</td>
<td>15 (94)</td>
<td>1.0000*</td>
</tr>
<tr>
<td>ASA classification*</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>1.0000*</td>
</tr>
<tr>
<td>ASA class 2, N (%)</td>
<td>14 (100)</td>
<td>15 (94)</td>
<td>0.3992*</td>
</tr>
<tr>
<td>Fontaine classification*</td>
<td>11 (79)</td>
<td>12 (75)</td>
<td>1.0000*</td>
</tr>
<tr>
<td>Critical limb ischemia, N (%)</td>
<td>3 (21)</td>
<td>4 (25)</td>
<td>1.0000*</td>
</tr>
</tbody>
</table>

Notes: *American Society of Anesthesiologists (ASA) classification; *Fontaine classification (classification of symptoms in peripheral atherosclerotic disease); *ABI preoperative

Abbreviations: ABI, ankle brachial index; IQR, interquartile range; SD, standard deviation.

Figure 2 Comparing mean serum level of interleukin-6 (pg/mL) at different time points during and after totally laparoscopic aortobifemoral bypass (LABF) versus open aortobifemoral bypass (OABF).

Notes: Error bars represent the 95% confidence interval (CI). Timepoints: 1, before surgery; 2, after completion of distal anastomosis and flow to one of the lower limbs was reestablished; 3, 6 hours after beginning of surgery; 4, 12 hours after beginning of surgery; 5, 24 hours after beginning of surgery; 6, at discharge from hospital.

Figure 3 Comparing mean serum level of interleukin-8 (pg/mL) at different time points during and after totally laparoscopic aortobifemoral bypass (LABF) versus open aortobifemoral bypass (OABF).

Notes: Error bars represent the 95% confidence interval (CI). Timepoints: 1, before surgery; 2, after completion of distal anastomosis and flow to one of the lower limbs was reestablished; 3, 6 hours after beginning of surgery; 4, 12 hours after beginning of surgery; 5, 24 hours after beginning of surgery; 6, at discharge from hospital.
markers increased after surgery compared with baseline. When comparing the individual time point measurements, serum levels of IL-6 was significantly lower after LABF when compared with OABF at 6, 12, and 24 hours postoperatively (Figure 2). The differences in serum levels of IL-8 and CRP did not reach statistical significance (Figures 3 and 4).

When comparing the summary of the repeated measurements by AUC, mean level of IL-6 was still lower in patients undergoing LABF as compared to OABF (Table 2). No statistically significant difference in the mean level of IL-8 or CRP was found in patients undergoing LABF compared with OABF when comparing AUC (Table 2). After controlling for the confounding effect of coronary heart disease in a final multivariate analysis (Table 3), IL-6 was still significantly lower in the LABF group \((P=0.010)\), and the confounding effect was small \((8.8\%)\). There was no statistically significant difference in IL-8 or CRP.

Operation-related parameters are given in Table 4. Patients treated with a laparoscopic procedure had a longer aortic clamping time when compared with those treated with open surgery, but significantly less bleeding during surgery. There were only two patients with suprarenal aortic clamping, lasting for only 5 minutes (LABF) versus 3 minutes (OABF).

Clinical outcomes are described in Table 5. The patients had significantly shorter hospital stay in the laparoscopic group. There was no statistical difference in postoperative morbidity, and none of the patients died during the study period.

**Discussion**

There was significantly decreased serum levels of IL-6 after LABF compared with OABF, measured by comparing AUC and after controlling for interdependence and the confounding effect of coronary heart disease (CHD; \(P=0.010)\). The differences in serum levels of IL-8 and CRP did not reach statistical significance.

The inflammatory response is an interaction of a number of mediators.\(^2^9\) IL-6 is a key agent in the inflammatory process\(^2^9\) and is higher after major abdominal surgery and lower after laparoscopic surgery when compared with open surgery.\(^2^,\(^1^4^,\(^1^5\)\) The manipulation and damage of the peritoneum in laparotomy may be one of the causes.\(^1^1\) IL-8 activity correlates with IL-6 levels after injury or surgical trauma and influences the level of circulating granulocytes and attracts them to the site of injury.\(^2^,\(^9^,\(^3^2\)\) Both IL-6 and IL-8 correlate with the duration of surgery, blood loss, and extent of tissue trauma, among other things.\(^3^3\) IL-6 induces CRP production.\(^3^4\) CRP in turn binds to phosphocholine on damaged cells and microorganisms, which activates the complement pathway.
with the OABF group (Table 5), and the variation in sampling time point did not allow a comparison.

The serum concentrations of different cytokines may vary according to location of the sampling site. Concentrations in the portal vein are higher after abdominal surgery.\(^36,37\) In this study, the samples were taken primarily from arterial catheter, but in a few cases, they had to be taken from a central venous catheter or peripheral vein. This difference in sampling site could have influenced the serum concentrations of the inflammatory cytokines.

This is a substudy of a randomized trial, which could affect the distribution of known and unknown confounding factors between the two groups, resulting in confounding bias and random effects. There were minor differences in the baseline characteristics, and these factors were deemed as potential confounders. CHD was the most significant

### Table 3

<table>
<thead>
<tr>
<th>Inflammation marker</th>
<th>Coefficient</th>
<th>SE</th>
<th>Z</th>
<th>P-value</th>
<th>Confounding effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>-0.7024</td>
<td>0.2484</td>
<td>-2.83</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Adjusted for CHD</td>
<td>-0.6407</td>
<td>0.2488</td>
<td>-2.58</td>
<td>0.010</td>
<td>8.8%</td>
</tr>
<tr>
<td>IL-8</td>
<td>-0.2695</td>
<td>0.1973</td>
<td>-1.37</td>
<td>0.172</td>
<td></td>
</tr>
<tr>
<td>Adjusted for CHD</td>
<td>-0.2360</td>
<td>0.2005</td>
<td>-1.18</td>
<td>0.237</td>
<td>5.3%</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.0963</td>
<td>0.3739</td>
<td>-0.26</td>
<td>0.797</td>
<td></td>
</tr>
<tr>
<td>Adjusted for CHD</td>
<td>-0.0562</td>
<td>0.3808</td>
<td>-0.15</td>
<td>0.883</td>
<td>41.6%</td>
</tr>
</tbody>
</table>

Note: The confounding effect is quantified using the formula: (Coefficient\(_{crude} - Coefficient\(_{adjusted}\)) / Coefficient\(_{crude}\) × 100.

Abbreviations: SE, standard error; CHD, coronary heart disease.

### Table 4

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Laparoscopy (N=14)</th>
<th>Open surgery (N=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (minutes), median (IQR)</td>
<td>216 (195–235)</td>
<td>202 (169–230)</td>
<td>0.2600</td>
</tr>
<tr>
<td>Blood loss during surgery (mL), median (IQR)</td>
<td>275 (150–600)</td>
<td>1,000 (575–1,150)</td>
<td>0.0300</td>
</tr>
<tr>
<td>Suprarenal clamping, N (%)</td>
<td>1 (7.1)</td>
<td>1 (6.3)</td>
<td>0.9200</td>
</tr>
<tr>
<td>Aortic clamping time (minutes),(^c) median (IQR)</td>
<td>43 (41–52)</td>
<td>30 (20–38)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Notes: Statistics: *Mann–Whitney U-test; \(^a\)Fisher’s exact t-test; \(^b\)aortic clamping time defined as: time from cross-clamping of the aorta above the proximal anastomosis until the clamp is moved to the proximal end of the graft.

Abbreviation: IQR, interquartile range.

### Table 5

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Laparoscopy</th>
<th>Open surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay in hospital (days), median (IQR)</td>
<td>5.0 (4.0–6.0)</td>
<td>9.0 (6.5–11.0)</td>
<td>0.001(^a)</td>
</tr>
<tr>
<td>Thirty-day mortality, N</td>
<td>0</td>
<td>0</td>
<td>(\neq)</td>
</tr>
<tr>
<td>Thirty-day systemic morbidity,(^c) N (%)</td>
<td>1 (7)</td>
<td>4 (25)</td>
<td>0.210(^b)</td>
</tr>
</tbody>
</table>

Notes: Statistics: *Mann–Whitney U-test; \(^a\)Fisher’s exact test; and \(^c\)systemic morbidity is defined as systemic complications including systemic infection, ileus, sepsis, acute respiratory distress syndrome, multiple organ failure, renal failure, myocardial infarction, and/or cerebral infarction/hemorrhage. Not including local morbidity defined as local wound infection, lymphatic discharge from wound, simple urinary tract infections, pneumonia, or graft occlusion.

Abbreviation: IQR, interquartile range.

and phagocytosis.\(^3,15\) These reactions to surgical trauma are reflected in our patients, who showed an increase in the serum levels of all three inflammatory markers in both groups after surgery (Figures 2–4).

Timing of blood samples is essential for the detection of serial changes in the serum levels of inflammatory markers. In our study population, we did not take any blood samples between 24 hours postoperatively and the discharge of the patient. Watt et al found in their new systematic review from 2015 that serum levels of CRP peak after 24 hours postoperatively. Additional blood samples for CRP in the postoperative period could have been helpful in detecting the serum changes more efficiently.\(^3\)

Proinflammatory markers were analyzed at the time of discharge for all the patients. However, the patients were discharged much earlier in the LABF group when compared
confounder, and we investigated the confounding effect of CHD in our final multivariate model. The confounding effect on IL-6 was minor (Table 3). We know that the GEE model works best if the number of clusters (patients) is large (>50), the number of observations in a cluster is small, and the measurements are taken at the same time for all the subjects.22 Hence, time points four and six had to be removed from the GEE model.

All the inflammatory markers point in the same direction, indicating less inflammatory response after laparoscopic surgery. However, the population of patients in each group was small, and our participants were included from three different hospitals, which may also have influenced the results. The generalizability and external validity of such a small study are questionable, but we have no indication that there was any population bias. The multiplicity of analyses compared to the number of participants could be problematic, and larger trials with patient inclusion based on power analysis may be an aim for further research.

However, randomization and lack of missing values add to the strength of this study. The repeated measurements are significant to capture the serum peak levels, and the statistical analysis comparing AUC is superior to comparing the difference in repeated correlated measurements.22 Also, to the authors’ knowledge, this is the first randomized trial on this subject.

An understanding of the inflammatory response to surgery is important to clinicians in the treatment and prevention of complications.34 Different therapeutic regimes have been suggested to balance the reaction between proinflammatory response and immunosuppression and restore immune homeostasis. Nevertheless, reducing the initial trauma has proven to be the most logical strategy.39,40 Our results indicate that LABF is a less invasive technique than OABF.

Conclusion
In this substudy of a randomized controlled trial comparing LABF and OABF surgeries, we found a decreased perioperative inflammatory response, measured by comparing AUC for serum IL-6. An adequately powered randomized trial could be an aim for further research.

Acknowledgments
We thank all the participating hospitals and staff for all their help, especially the biochemical laboratories of the local hospitals in Kristiansand, Fredrikstad, and Oslo, who provided help in collecting and storing the blood samples, and the Hormone Laboratory, Oslo University Hospital, who analyzed all the samples.

Disclosure
The authors report no conflicts of interest in this work.

References


Paper III
Cost-utility analysis comparing laparoscopic vs open aortobifemoral bypass surgery

Anne Helene Krog¹,²
Mehdi Sahba³
Erik M Pettersen⁴
Torbjørn Wisløff⁵,⁶
Jon O Sundhagen²
Syed SH Kazmi²

¹Institute of Clinical Medicine, Faculty of Medicine, University of Oslo,
²Department of Vascular Surgery, Division of Cardiovascular and Pulmonary Diseases, Oslo University Hospital, Oslo,
³Department of Vascular Surgery, Østfold Central Hospital, Kalnes,
⁴Department of Vascular Surgery, Sørlandet Hospital Hf, Kristiansand,
⁵Department of Health Management and Health Economics, University of Oslo,
⁶Norwegian Institute of Public Health, Oslo, Norway

Objectives: Laparoscopic aortobifemoral bypass has become an established treatment option for symptomatic aortoiliac obstructive disease at dedicated centers. Minimally invasive surgical techniques like laparoscopic surgery have often been shown to reduce expenses and increase patients’ health-related quality of life. The main objective of our study was to measure quality-adjusted life years (QALYs) and costs after totally laparoscopic and open aortobifemoral bypass.

Patients and methods: This was a within trial analysis in a larger ongoing randomized controlled prospective multicenter trial, Norwegian Laparoscopic Aortic Surgery Trial. Fifty consecutive patients suffering from symptomatic aortoiliac occlusive disease suitable for aortobifemoral bypass surgery were randomized to either totally laparoscopic (n=25) or open surgical procedure (n=25). One patient dropped out of the study before surgery. We measured health-related quality of life using the EuroQol (EQ-5D-5L) questionnaire at 4 different time points, before surgery and for 6 months during follow-up. We calculated the QALYs gained by using the area under the curve for both groups. Costs were calculated based on prices for surgical equipment, vascular prosthesis and hospital stay.

Results: We found a significantly higher increase in QALYs after laparoscopic vs open aortobifemoral bypass surgery, with a difference of 0.07 QALYs (p=0.001) in favor of laparoscopic aortobifemoral bypass. The total cost of surgery, equipment and hospital stay after laparoscopic surgery (9,953 €) was less than open surgery (17,260 €), (p=0.001).

Conclusion: Laparoscopic aortobifemoral bypass seems to be cost-effective compared with open surgery, due to an increase in QALYs and lower procedure-related costs.

Keywords: laparoscopy, aortobifemoral bypass, cost-utility, quality-adjusted life years, QALYs, EQ-5D, health-related quality of life, HRQoL, cost-effectiveness

Introduction
In patients with peripheral arterial disease (PAD), a significantly impaired health-related quality of life (HRQoL), due to reduction in walking ability and limb pain, has been reported.¹⁻⁵ In patients with aortoiliac occlusive disease (AIOD), which is a manifestation of PAD, blood flow to the lower extremities can be improved with the help of either a totally laparoscopic or an open aortobifemoral bypass. The laparoscopic aortobifemoral bypass (LABF) has become an established treatment option for symptomatic AIOD at many dedicated centers.⁶⁻¹¹ At Oslo University Hospital, we introduced the laparoscopic technique in 2005,¹²⁻¹⁴ and since February 2013, we have been conducting a randomized controlled trial,¹⁵,¹⁶ to compare the early morbidity after the two treatment methods.
Previous experiences with minimally invasive surgical techniques have been shown to improve HRQoL and reduce procedure-related expenses.\textsuperscript{17–21} The investigation concerning the relative effectiveness and safety of a new procedure compared with a standard procedure is of importance. Especially, for the health service providers, the cost-effectiveness of any treatment is important in decision making.\textsuperscript{22} Similar to many other national health providers, the Norwegian government is increasingly focused on the cost-effectiveness of our health services, resulting in new national guidelines that describe that any new method has to be assessed for cost-effectiveness.\textsuperscript{23,24} Since we are conducting a study on a new treatment method, laparoscopic aortic surgery, it was relevant to perform a health economic evaluation.\textsuperscript{25} Rouers et al, performed a calculation of mean cost in LABF vs open aortobifemoral bypass surgery (OABF), and found decreased costs per patient in the laparoscopic group.\textsuperscript{26} However, the study was not randomized and they excluded the patients who were converted from laparoscopic to open surgery. No other known economical evaluations of LABF have been performed to this date.

The main objective of our study was to perform a cost–utility analysis by calculating QALYs and costs after totally laparoscopic vs open aortobifemoral bypass procedure.

**Patients and methods**

**Design**

Since February 2013, we have been conducting a multicenter randomized controlled trial, Norwegian Laparoscopic Aortic Surgery Trial (NLAST), at the Department of Vascular Surgery, Oslo University Hospital. This project is a substudy of the NLAST,\textsuperscript{15,16} where patients with AIOD classified according to the Trans-Atlantic Inter-Society Consensus II (TASC-II) as type D lesions are randomized to either LABF or OABF.\textsuperscript{27} Inclusion and exclusion were based on the following criteria.

**Inclusion criteria**

- Patient with AIOD, TASC-II type D lesions,\textsuperscript{27} and with symptoms in the form of:
  - intermittent claudication, with patient-reported, pain-free walking distance <200 m, and/or
  - chronic critical lower limb ischemia with rest pain, ischemic ulcers or gangrene, duration of symptoms >2 weeks.

**Exclusion criteria**

- Eligible for endovascular procedure
- Chronic obstructive pulmonary disease (COPD) ≥ stage IV, GOLD classification\textsuperscript{28}
- Symptomatic coronary heart disease
- Chronic heart failure, ejection fraction <40%
- Active cancer disease
- Hostile abdomen
- Abdominal aortic aneurysm ≥3.0 cm\textsuperscript{27}
- Acute critical limb ischemia, duration of symptoms ≤2 weeks

**Participants**

Three vascular surgery departments in the south-eastern region of Norway participated in the study.

**Intervention**

The patients underwent aortobifemoral bypass through a totally laparoscopic transperitoneal, retrocolic, prerenal approach described by Coggia et al\textsuperscript{29} or a traditional open technique through a midline laparotomy.

**Outcomes and perspective**

The main objectives of our study were to measure QALYs and costs after totally laparoscopic vs open aortobifemoral bypass procedure in order to assess the cost-effectiveness. Based on our cohort study, we expected a gain in HRQoL during the first 6 months and similar results in the 2 groups thereafter.\textsuperscript{13,14} The patients answered the EuroQol EQ-5D-5L questionnaire at 4 different time points; before surgery (baseline), and at 1, 3 and 6 months postoperatively.\textsuperscript{30,31} The costs included in this study are the cost of surgical equipment, prosthesis and the costs related to the hospital stay. We registered exact resource use during surgery for the first 3 open and 3 laparoscopic patients. This included all disposable and non-disposable surgical equipment. We then calculated a mean price for the resources during surgery for each group based on those 6 patients. As the 2 procedures are relatively standardized, we considered it to be sufficient to extrapolate from these 6 patients. The cost of hospital stay was calculated based on national data for price per day in a somatic ward.\textsuperscript{32} Costs included were only those that incurred during the hospital stay. We chose a health care sector perspective for the analysis.

**Randomization and blinding**

The patients were randomized to either LABF or OABF. We used block randomization and closed opaque envelopes. The sequence was random and unknown to the researchers.
Blinding of researchers, surgeons and/or participants was not considered possible.

Analysis and statistics
The EQ-5D-5L questionnaire validated in Norwegian language, was completed at all 4 time points and HRQoL was estimated based on a value set from the UK, due to the lack of any available Norwegian value set. Since these are repeated correlated measurements, we calculated QALYs using area under the curve (AUC) for both groups. Deceased patients were set to have a quality of life equal to 0 after death. One QALY was defined as 1 year of perfect health (reported by patients). Systemic morbidity was defined as all non-fatal complications related to the surgical procedure, excluding complications related to the graft and wound. No discounting of costs or health effects was performed due to the short time horizon of the analyses. Categorical variables were summarized as frequencies and continuous variables by the median and interquartile range. Comparisons between the two treatment groups were performed by using the Mann-Whitney U-test for continuous variables, and Fisher’s exact test for categorical variables. A generalized linear model with gamma family and log link function was used to analyze differences in QALYs and costs. The results were controlled for confounding factors and baseline values, including baseline EQ-5D-5L score. There were missing values for 1 patient at 3 and 6 months, we imputed the mean value for the same treatment group at each time point. To give an impression of uncertainty in the overall estimates of cost-effectiveness, we performed 1000 bootstrap samples and presented incremental cost (Δcosts) and incremental effect (ΔQALYs) between LABF and OABF. This cost-utility is a within trial analysis of a larger ongoing randomized trial, NLAST; therefore, an individual power analysis was not conducted for this sub-study. Statistical significance was set at a 5% level (p<0.05).

The software used for statistical analyses were Epi Info (Epi Info™ software, Centers for Disease Control and Prevention, Atlanta, GA, USA), IBM SPSS statistics version 22.0 (IBM corporation, Armonk, NY, USA) and Microsoft Office Excel® (Microsoft, Redmond campus, Redmond, WA, USA).

Ethics
The project was voluntary and participants gave an informed, written consent. The trial was approved by the Regional Committee for Medical and Health Research Ethics (REC, region south-east of Norway, registration number 2012/1367). The trial was registered at www.clinicaltrials.gov, with the registration number NCT01793662.

Results
Participant flow and recruitment
Fifty consecutive patients from the participating hospitals were included from February 2013 to February 2016. They were randomized to either LABF (n=25) or OABF (n=25). The participant flow is described in Figure 1. The baseline characteristics of the patients in the two groups are given in Table 1. One laparoscopic procedure was converted from laparoscopic to open surgery due to bleeding. The patient was analyzed in the laparoscopic group, in accordance with the “intention-to-treat” principle. No patients were excluded after randomization. One patient dropped out after randomization and another did not wish to complete the follow-up program. One patient in the open group died of an acute myocardial infarction on the second postoperative day. This within trial analysis was completed after the inclusion of 50 patients.

Outcomes and estimation
Operative data and postoperative results are described in Table 2. Operation time was significantly longer in the

Figure 1 Flow chart of patient population with AIOD TASC-II type D lesion treated with either totally LABF or OABF. Notes: *Patient dropped out after randomization; he was randomized to open surgery.
Abbreviations: AIOD, aortoiliac occlusive disease; LABF, laparoscopic aortobifemoral bypass; OABF, open aortobifemoral bypass; TASC, Trans-Atlantic Inter-Society Consensus.
LABF group, but they had shorter postoperative hospital stay than the open group, 4.0 vs 7.0 days, \( p < 0.001 \). There was no statistically significant difference between the two groups in terms of morbidity and mortality; however, there seem to be a tendency toward less total morbidity after LABF, \( p = 0.058 \).

HRQoL-scores based on EQ-5D-5L for the two groups, at baseline and during follow-up are presented in Figure 2. HRQoL is higher during follow-up in the laparoscopic group at all survey time points. Although, there is a small difference in HRQoL at baseline, this difference was not statistically significant. At the single time point measurements; only the difference at 1 month is statistically significant. AUC was calculated for these repeated correlated measurements of HRQoL in both groups. Total QALYs gained were calculated by AUC as HRQoL multiplied by follow-up time. The LABF group had a significantly higher gain in QALYs, with a difference of 0.07 QALYs, \( p = 0.001 \). The costs of resources (hospital stay, surgical equipment and vascular prosthesis) are presented in Table 3. The operative equipment was more expensive in the LABF group. However, the total cost per patient is much less in the LABF group compared with the OABF group, 9,953 € vs 17,260 €, \( p = 0.001 \) (Table 4). The higher gain in QALYs and lower costs are also demonstrated in a scatter plot showing costs and QALYs for each patient (Figure 3A). The open group has more extreme values, both with regard to costs and HRQoL. The uncertainty surrounding the mean estimates of incremental costs and QALYs, based on bootstrapping, are demonstrated in Figure 3B. The Figure 3B shows a high probability that LABF is both more effective and less costly than OABF.

We used a generalized linear model to control for possible confounding effects. The difference in QALYs was still significantly in favor of laparoscopy after controlling

### Table 1 Baseline characteristics of patients treated with either totally laparoscopic or open aortobifemoral bypass for AIOD

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Laparoscopy, ( N=25 )</th>
<th>Open surgery, ( N=24 )</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>62.0 (58.0–66.0)</td>
<td>66.0 (58.5–70.0)</td>
<td>0.170 ( ^a )</td>
</tr>
<tr>
<td>Female gender N (%)</td>
<td>15 (60.0)</td>
<td>14 (58.3)</td>
<td>1.000 ( ^a )</td>
</tr>
<tr>
<td>Current smoker N (%)</td>
<td>12 (48.0)</td>
<td>15 (62.5)</td>
<td>0.393 ( ^a )</td>
</tr>
<tr>
<td>Hypertension (HT) N (%)</td>
<td>19 (76.0)</td>
<td>17 (70.8)</td>
<td>0.466 ( ^a )</td>
</tr>
<tr>
<td>COPD N (%)</td>
<td>4 (16.0)</td>
<td>6 (25.0)</td>
<td>0.335 ( ^a )</td>
</tr>
<tr>
<td>Diabetes mellitus (DM) N (%)</td>
<td>1 (4.0)</td>
<td>0 (0)</td>
<td>0.510 ( ^a )</td>
</tr>
<tr>
<td>Coronary heart disease (CHD) N (%)</td>
<td>2 (8.0)</td>
<td>7 (29.2)</td>
<td>0.060 ( ^a )</td>
</tr>
<tr>
<td>ASA classification, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA class 2.</td>
<td>0 (0)</td>
<td>1 (4.2)</td>
<td></td>
</tr>
<tr>
<td>ASA class 3.</td>
<td>25 (100.0)</td>
<td>22 (91.7)</td>
<td></td>
</tr>
<tr>
<td>ASA class 4.</td>
<td>0 (0)</td>
<td>1 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Fontaine classification, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fontaine class 2b.</td>
<td>19 (76.0)</td>
<td>19 (79.2)</td>
<td></td>
</tr>
<tr>
<td>Fontaine class 3.</td>
<td>5 (20.0)</td>
<td>5 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Fontaine class 4.</td>
<td>1 (4.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L score, median (IQR)</td>
<td>0.58 (0.46–0.73)</td>
<td>0.48 (0.39–0.61)</td>
<td>0.157 ( ^a )</td>
</tr>
</tbody>
</table>

**Notes:** \( ^a \)Mann–Whitney U-test, \( ^b \)Fisher’s exact test, \( ^c \)statistical testing not appropriate. Fontaine classification: a classification of symptoms in peripheral atherosclerotic disease.

**Abbreviation:** IQR, interquartile range; AIOD, aortoiliac occlusive disease; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists classification.

### Table 2 Operative and postoperative characteristics of patients treated with either totally laparoscopic or open aortobifemoral bypass for AIOD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Laparoscopy, ( N=25 )</th>
<th>Open surgery, ( N=24 )</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (minutes), median (IQR)</td>
<td>221 (203–248)</td>
<td>196 (160–230)</td>
<td>0.024 ( ^a )</td>
</tr>
<tr>
<td>Postoperative stay in hospital (days), median (IQR)</td>
<td>4.0 (3.0–5.0)</td>
<td>7.0 (6.0–9.0)</td>
<td>0.000 ( ^a )</td>
</tr>
<tr>
<td>Thirty-day hospital readmission, N (%)</td>
<td>2 (8.0)</td>
<td>4 (16.7)</td>
<td>0.314 ( ^a )</td>
</tr>
<tr>
<td>Thirty-day mortality, N (%)</td>
<td>0 (0)</td>
<td>1 (4.2)</td>
<td>0.490 ( ^a )</td>
</tr>
<tr>
<td>Thirty-day systemic morbidity, N (%)</td>
<td>2 (8.0)</td>
<td>6 (25.0)</td>
<td>0.111 ( ^a )</td>
</tr>
<tr>
<td>Thirty-day total morbidity (systemic and local), N (%)</td>
<td>7 (28.0)</td>
<td>13 (54.2)</td>
<td>0.058 ( ^a )</td>
</tr>
</tbody>
</table>

**Notes:** \( ^a \)Mann-Whitney U-test, \( ^b \)Fisher’s exact test, \( ^c \)systemic morbidity was defined as all non-fatal complications related to the surgical procedure, excluding complications related to the graft and wound, \( ^d \)local morbidity was defined as complications related to the graft and wound.

**Abbreviation:** IQR, interquartile range; AIOD, aortoiliac occlusive disease.
We found significantly higher gain in QALYs and lower costs after laparoscopic vs open aortobifemoral bypass surgery. This gain maintained its statistical significance even after controlling the results for baseline differences in HRQoL and other confounding variables.

Discussion

Summary

EQ-5D is the most commonly used quality of life questionnaire in health economic evaluations, and it is easy and highly tolerated by patients.36,37 Another tool might detect smaller differences, but as long as the results are unambiguous in favor of laparoscopy, this would likely not influence our conclusions.36 We chose a generic quality of life questionnaire to capture the differences between the two groups. A disease specific tool could have been better to assess symptoms and deterioration in HRQoL due to PAD, but would not necessarily capture the differences comparing laparoscopy with laparotomy, which was our main objective.38 Additionally, neither of the disease-specific questionnaires are validated for the economic analysis25 nor made available in the Norwegian language. Although we used a UK tariff for valuing EQ-5D, we do not think the results would have been altered if a Norwegian value set had been available.

HRQoL is the primary indication of treatment and main benefit in revascularization surgery in patients with PAD.2,3 Some have argued the lack of “hard data”, like morbidity and mortality, in these cost-utility evaluations and have also uttered concerns about the use of QALYs and its role in decision making.22,39,40 However, there are no known differences in

Table 3 Resources and estimation of cost per patient comparing totally LABF with OABF

<table>
<thead>
<tr>
<th>Resources</th>
<th>Laparoscopy, unit cost (€)</th>
<th>Open surgery, unit cost (€)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 day of postoperative hospital stay</td>
<td>1,726</td>
<td>1,726</td>
<td>SAMDATA 2014, Norwegian Health Directorate (Huseby et al)25</td>
</tr>
<tr>
<td>Surgical equipment</td>
<td>1,457</td>
<td>516</td>
<td>Estimated mean price of all surgical equipment (disposable and non-disposable) from 3 LABF and 3 OABF. (price based on 2014)</td>
</tr>
<tr>
<td>Vascular prosthesis</td>
<td>419</td>
<td>419</td>
<td>Manufacturer (price based on 2014)</td>
</tr>
</tbody>
</table>

Table 4 Comparing mean total costs in Euro (€) and quality-adjusted life years (QALYs) after LABF vs OABF

<table>
<thead>
<tr>
<th></th>
<th>LABF</th>
<th>OABF</th>
<th>Direct estimate</th>
<th>Regression estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total cost per patient (€)</td>
<td>9,953</td>
<td>17,260</td>
<td>−7,307</td>
<td>−7,429</td>
</tr>
<tr>
<td>QALYs</td>
<td>0.45</td>
<td>0.38</td>
<td>0.067</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Notes: aMann–Whitney U-test.

Abbreviations: LABF, laparoscopic aortobifemoral bypass; OABF, open aortobifemoral bypass; QALY, quality-adjusted life years.
The incremental cost-effectiveness ratio (ICER) can be defined as a price per effect (health) gained. The level of willingness to pay for a treatment can be used as a threshold. The ICER should be below this threshold, and thereby can be used as a tool in decision making. Norway is a country where hospital expenses are fully covered by the government. There are no strict requirements, for the time being, for the reporting of HRQoL in health technology assessment processes in Norway, but the focus is increasing. Although a threshold on the price of a QALY has not been set, a recent attempt of estimating the threshold empirically for Norway, resulted in a range of €43,000 to 94,000 per QALY gained.41 Interventions resulting in increased health and decreased resource use, as is the case of LABF in our study, are in health economics regarded as “dominant”.42 In easier terms; “one saves money and provide a better result”. By definition, these dominant interventions are below the suggested or estimated thresholds, and should be considered as replacement for the comparative treatment.42 Based on these assumptions and the result of our study, one may suggest that the patients with symptomatic AIOD TASC II type D lesions should be offered a LABF instead of an OABF procedure.

We have followed the patients in this study for only 6 months. In other patient groups, it has been shown that the benefits of laparoscopic surgery are mostly gained during the first year,38,43,44 In our pilot study, the main effect on HRQoL was during the first 6 months.14 Even if the difference between the 2 groups would later during follow-up decrease, there is no indication that the benefits in terms of HRQoL and spared economic costs will be in favor of other than LABF. There also seem to be no negative long-term effects of LABF for AIOD.7 Given the assumption of laparoscopy being a dominant intervention at 6 months, which was also confirmed by our analyses, we found no reason to include longer term considerations in the analysis.

We have, in our study, found the main cause of costs is the hospital stay, which is significantly shorter after laparoscopic surgery, mean 4.0 vs 7.0 days. All doctors with the vascular departments were involved in the postoperative evaluation and care of the patients, and all patients were discharged when they met the following discharge-criteria; able to walk, oral intake of food, normal urination/defecation and no untreated ongoing local or systemic complication. We have no indication of any protocol-driven resources.

We used national data for cost per day in hospital.32 This number is calculated as a mean for all types of admissions in somatic specialist health care in Norway, and may not apply for our patients and wards. We know that laparoscopic morbidity or mortality between LABF and OABF for AIOD to this day.9,11 Hence, a cost-utility is an appropriate tool for comparing two procedures, combining the patient-reported quality of life with an economic perspective.

The implementation of laparoscopic aortic surgery, has been slow.11 However, gradually there has been published evidence that the LABF combines the benefits of a minimally invasive technique with the excellent long-term patency rates of OABF for the treatment of AIOD.7,13 In the present study, we have demonstrated higher postoperative HRQoL combined with lower costs after LABF compared with OABF. This is an important finding and should be of interest to health providers, as well as for the patients suffering from AIOD in need of an aortobifemoral bypass.
equipment is expensive, there is more use of disposable equipment and also the operation time is longer. However, the total length of stay in hospital is significantly lower in the LABF group. This might outweigh any increased equipment costs and operation time costs. An opportunity cost evaluation and a micro cost analysis would be useful to assess the costs of the procedure and hospital stay even more specifically.

Generalizability and external validity are of importance when combining an economic evaluation with a clinical trial. We aimed to include all patients eligible for surgery and our inclusion/exclusion criteria reflect the clinical world. Multiple testing and repeated measurements on a small population can weaken the statistical analysis. This influences the strength of the conclusion. However, our results are strong and highly significant. We are the first to investigate these outcomes in a randomized setting, and this might affect decision makers. Further research is necessary to investigate the validity of the results and possible clinical implications.

Conclusion
LABF leads to an increase in QALYs gained and lower treatment costs, and seems to be cost-effective compared with open surgery.

Acknowledgments
We are thankful to all participating hospitals and staff for their help. Especially, we are very thankful to the late Professor Jørgen J. Jørgensen MD, PhD, for all his help and guidance.

Author contributions
Conception and design: AHK, SSHK, TW, JOS. Data collection: AHK, MS, EMP, SSHK. Analysis and interpretation: AHK, TW. Statistical analysis: TW, AHK. Writing the article: AHK, SSHK, TW. Critical revision of the article: AHK, SSHK, TW, EMP, MS, JOS. Final approval of the article: AHK, SSHK, TW, EMP, MS, JOS. Overall responsibility: AHK, SSHK. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

References


