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Assessing and minimizing risk of patients with aortic diseases

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Roberta Vaccarino

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on Maj 8th, 2024 at 13.00 at the Kvinnoklinikens aula
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Abstract:

Prophylactic endovascular aneurysm repair (EVAR) of abdominal aortic aneurysm (AAA) aims to avoid aneurysm rupture. However, only patients with sufficient long-term survival get benefit from this avoidance. Therefore, accurate patient selection is crucial.

The aim of the project is to evaluate new methods of assessing and minimizing the risks and thereby improve the selection of patient with the most long-term benefit from prophylactic EVAR.

The specific aims of this thesis were:

- Evaluate if ilio-femoral calcium score measured on preoperative computed tomography is associated with survival after EVAR of varied complexity, with particular focus on cardiovascular events.
- Evaluate if combining ilio-femoral calcium score to the Glasgow Aneurysm Score (GAS) improves the prediction of long-term survival in patients undergoing infrarenal EVAR.
- Investigate if preoperative assessment of long-term survival in patients undergoing infrarenal EVAR can be improved by measuring the ileo-psoas muscle size and visceral adipose tissue on preoperative CT angiography.
- Explore and create a standardized protocol of CO_2-angiography during EVAR in a multicenter setup.
- Evaluate a protocol based on the preferential use of automated CO_2-angiography during fusion-guided IBD implantation.

Conclusions

Low ilio-femoral calcium score may be associated with lower incidence of fatal cardiac events and all-cause long-term mortality after EVAR of varied complexity. The preoperative assessment of the long-term survival of patients undergoing infrarenal EVAR can be done with the clinically based Glasgow Aneurysm Score. This can potentially be refined in low-risk patients by measuring and adding the ilio-femoral calcium score. CT-based assessment of the ileo-psoas muscle size and visceral adipose tissue did not contribute to improve the prediction of long-term survival after EVAR.

A CO_2-EVAR operative protocol was developed and this protocol enabled all involved centers to accomplish EVAR procedures using minimal amounts of iodine contrast. Reduction of intraoperative iodine contrast exposure during IBD implantation is feasible through the predominant use of automated CO_2-angiography. This can be safely done without affecting the technical success or radiation exposure, but this did not have an impact on the postoperative renal function.

Key words: AAA, EVAR, risk assessment, Agatston Calcium Score, Glasgow Aneurysm Score, Sarcopenia, Visceral adipose tissue, CO_2-angiography

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To my beloved family

"There will be obstacles. There will be doubters. There will be mistakes.
But with hard work, there are no limits."
-Michael Phelps-

Table of Contents

Abbreviations

AAA Abdominal Aortic Aneurysm

ACS Agatston Calcium Score

AKI Acute Kidney Injury

ARF Acute Renal Failure

BMI Body Mass Index

CAC Coronary Artery Calcifications

CAD Coronary Artery Diseases

CEUS Contrast-Enhanced Ultrasound

CHA Contralateral Hypogastric Artery

CI Confident Interval

CIN Contrast-Induced Nephropathy

CKD Chronic Kidney Disease

CO_2 Carbon Dioxide

CTA Computed Tomography Angiography

DAP Dose Area Product

DSA Digital Subtraction Angiography

DUS Doppler Ultrasound

ePTFE Expanded Politetrafluoroetilene

ESC European Society of Cardiology

ESVS European Society of Vascular Surgery

EVAR Endovascular Aneurysm Repair

FEVAR Fenestrated Endovascular Aneurysm Repair

FU Follow-up

GAS Glasgow Aneurysm Score

GFR Glomerular Filtration Rate

HR Hazard Ratio
HU Hounsfield Unit
IAA Iliac Artery Aneurysm
IBD Iliac Branch Device
ICM Iodinate Contrast Media
LoRA Lower Renal Artery
NICE National Institute for Health and Care Excellence
PACS Picture Archiving and Communication System
PAD Peripheric Artery Diseases
PET Polyethylene Terephthalate
RFR Renal Function Reserve
ROC Receiver Operating Characteristic
SAT Subcutaneous Adipose Tissue
STROBE Strengthening the Reporting of Observational studies in Epidemiology
TAT Total Adipose Tissue
TPA Total Psoas Area
VAT Visceral Adipose Tissue

List of papers

Paper I

Roberta Vaccarino, Mohammed Abdulrasak, Timothy Resch, Andreas Edsfeldt, Björn Sonesson, Nuno V Dias. Low Ilio-femoral Calcium Score may predict higher survival after EVAR and FEVAR. Ann Vasc Surg. 2020 Oct; 68:283-291.

Paper II

Roberta Vaccarino, Melker Wachtmeister, Jianming Sun, Yan Bornè, Timothy Resch, Björn Sonesson, Nuno V. Dias. Ilio-femoral Calcium Score may assist Glasgow Aneurysm Score prediction of long-term survival of low-risk patients after infrarenal EVAR. Int Angiol. 2022. doi: 10.23736/S0392-9590.22.04883-0.

Paper III

Roberta Vaccarino, Melker Wachtmeister, Angelos Karelis, Elisabet Marinko, Jianming Sun, Timothy Resch, Björn Sonesson, Nuno V. Dias. The role of CT-assessed Sarcopenia and Visceral Adipose Tissue in predicting long-term survival in patients undergoing elective endovascular infrarenal aortic repair. Submitted manuscript.

Paper IV

Andrea Vacirca, Gianluca Faggioli, **Roberta Vaccarino**, Nuno Dias, Martin Austermann, Marco Virgilio Usai, Alexander Oberhuber, Johannes Frederik Schäfers, Theodosios Bisdas, Nikolaos Patelis, Sergio Palermo, Mauro Gargiulo. The optimal operative protocol to accomplish CO_2-EVAR resulting from a prospective interventional multicenter study. J Vasc Surg. 2023 May;77(5):1405-1412.

Paper V

Roberta Vaccarino, Angelos Karelis, Bharti Singh, Elisabet Marinko, Kalliopi-Maria Tasopoulou, Timothy Resch, Björn Sonesson, Nuno V. Dias. The role of Carbon Dioxide Automated Angiography in aorto-iliac branched repair. Submitted manuscript

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What this thesis adds

This thesis contributes to the ongoing research on how to improve assessment of the long-term survival of patient about to undergo prophylactic treatment of AAA. It is crucial to increase the benefit from the repair while avoiding futile operation in high-risk patients. I investigated whether there is a link between postoperative long-term survival and preoperative computed tomography imaging, specifically regarding ilio-femoral calcium score, sarcopenia and visceral adipose tissue.

Moreover, this project aimed to study how to minimize intraoperative risk during EVAR. Particularly, I explored the intraoperative use of automated carbon dioxide angiography in order to decrease the use of contrast media protecting renal function and thereby potentially impacting long-term survival.

Introduction

Abdominal Aortic Aneurysm

Aneurysm is defined as a dilatation of the arterial wall having at least a 50% increase in diameter compared with the expected normal diameter. (1) Ectasia is an intermediary state of enlargement less than 50%. A “true” aneurysm develops from a progressive weakening of the structural elements of the arterial mural layers: intima, media and adventitia. Based on their clinical presentation, aortic aneurysms can be symptomatic or asymptomatic. Their main complication is the rupture of the aneurysmatic wall, this can be contained or free.

Aortic aneurysms are classified on the basis of the site and the extent of the disease. Most of the aneurysms are located in the abdominal aorta (Figure 1). In clinical practice, the threshold to define abdominal aortic aneurysm is a diameter of 30 mm (2), and its shape can be fusiform or saccular.

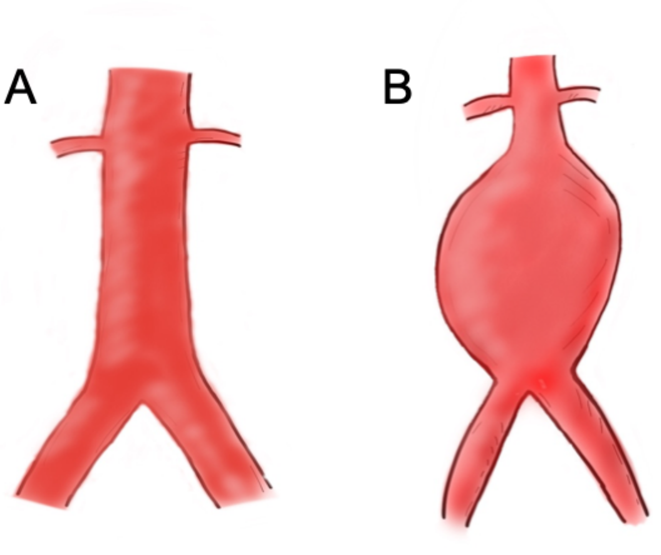


Figure 1: A: Normal aorta; B: Aorta with abdominal aneurysm © Vaccarino 2024

Infrarenal aneurysms are the most common aortic aneurysms. When the aneurysmal wall involves renal or mesenteric arteries and extends up to the level of the diaphragmatic hiatus, abdominal aneurysms are considered complex and they are classified as follows: (3)

- Short neck infrarenal AAA: 4 - 10 mm infrarenal neck
- Juxtarenal AAA: 0 – 4 mm infrarenal neck
- Pararenal AAA: involving at least one of the renal arteries
- Paravisceral AAA: involving renal arteries up to mesenteric superior artery but not the celiac axis.

Iliac Artery Aneurysms

Iliac Artery Aneurysm (IAA) is defined as the dilatation of the common iliac vessel ≥ 18 mm in men and ≥ 15 mm in women. Often, IAA are associated with the simultaneous dilatation of the abdominal aorta (aorto-iliac aneurysm). Internal iliac arteries are considered aneurysmal when their diameter is ≥ 8 mm. (1, 4-6) Based on anatomical features, Reber classifies isolated IAAs into four types: (7)

- Type I: Aneurysm involving common iliac artery
- Type II: Aneurysm involving internal iliac artery
- Type III: Aneurysm involving both common and internal iliac artery
- Type IV: Aneurysm involving common, internal and external iliac artery

Epidemiology

Even if prevalence of AAA increases considerably with age after 65 years, in the last two decades, we observed a decline of both prevalence and incidence of AAA. Swedish Screening Programme and UK National Screening Programme reported a prevalence < 1% in 2020 and 2021.(8) This decrease has been attributed to the improvement of the risk management and, above all, the reduction of smoking habit. (9) Indeed, the association of intensity and duration of smoking is the strongest risk factor for AAA. (10) Moreover, smoking cessation seems to be associated with a reduction of growing rate and aneurysm rupture. (11, 12)

Other important risk factors for the development of AAA include male gender, age, hypertension, positive family history, hypercholesterolemia, central obesity and presence of atherosclerotic occlusive diseases such as coronary diseases. The association between arterial aneurysm and atherosclerotic degeneration has been widely studied and in 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice classified patients with AAA as having an established atherosclerotic cardiovascular disease. Indeed, in order to decrease high risk of cardiovascular events in patient with AAA, intensive risk factors treatment, such as smoking cessation, blood pressure control, statin and antiplatelet therapy, physical exercise and healthy diet, is recommended. (8)

Diagnosis

The majority of non-ruptured AAAs are asymptomatic and, if not identified through a screening program, are accidentally diagnosed during abdominal imaging performed for unrelated condition. If presents, common symptoms are perception of a pulsatile mass in the abdomen, abdominal or back pain, tenderness on palpation and rarely large AAA can cause symptoms related to the local compression. Most AAAs become symptomatic due to complication such a rapid grow or rupture.

Physical examination

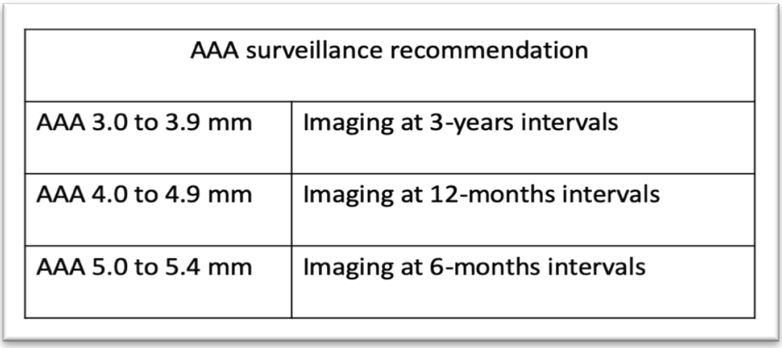
The aorta can be palpated with patient in supine position and relaxed abdominal musculature. The right and left lateral wall of the aorta should be localized to estimate aortic diameter. Auscultation with a stethoscope placed on the middle of the abdomen can determine the presence of a bruit, which is indicative of turbulent blood flow, marker of underlying pathology. The sensitivity of the physical examination depended on AAA size, body habitus of the patient and skills of the clinician.(13, 14) Consequently, abdominal palpation is not a solid method for diagnosis of AAA.

Imaging

Abdominal ultrasonography is the least expensive and least invasive tool used in the diagnosis of AAA. Today, it is the imaging method recommended for the first line detection and management of small AAA.(8, 15) Once the diameter for elective AAA repair has been met on Doppler Ultrasound (DUS), Computer Tomography Angiography (CTA) becomes the most widely employed imaging modality for the immediate preoperative assessment of patients with AAA.

Screening

Reports from UK and Sweden, countries with well-established screening programs, show an important contribution of the screening in decreasing AAA prevalence. (16-19) Early diagnosis reduces the high mortality rate associated with rupture. (16, 20-26) Patients who are diagnosed with AAA are recommended to start cardiovascular risk factor management, smoking cessation, blood pressure control, statin and antiplatelet therapy and lifestyle advices. Moreover, patients with AAA should be invited to imaging surveillance using DUS (Figure 2). (8, 27) Today, ultrasound screening is recommended in population considered “high risk”. (8) The main risk factors for AAA are male gender, age and smoking history. (10, 13). Evidence for screening women remains debatable. (28-31)



AAA surveillance recommendation	
AAA 3.0 to 3.9 mm	Imaging at 3-years intervals
AAA 4.0 to 4.9 mm	Imaging at 12-months intervals
AAA 5.0 to 5.4 mm	Imaging at 6-months intervals

Figure 2: DUS surveillance reccomandation for small AAA

Clinical decision making

The presence of the AAA is associated with the risk of rupture which is mostly related to the aneurysm size. Surgical treatment aims at the prevention of the mortality and morbidity related to the rupture. Before planning prophylactic aneurysm treatment, several parameters must be evaluated like the relationship between risk of rupture, perioperative risk and patient’s life expectancy. Moreover, it is important to consider patients own will. Latest European Society of Vascular Surgery guidelines (ESVS) recommends imaging surveillance and cardiovascular risk factor management for small AAA. (8) The prophylactic treatment should be considered when AAA is ≥ 55 mm in men and ≥ 50 mm in women. Moreover, small AAA showing rapid growth (≥ 10 mm/year) should be considered for remeasurement of the aneurysm diameter as a first measure.

AAA surgical repair

Once the aneurysm reaches the diameter recommended for elective repair and the patient is considered eligible to surgery, repair of AAA is considered the most effective way to prevent rupture. Currently, two surgical techniques are available: open aortic repair and endovascular aortic repair. Endovascular repair should be considered for most patients with suitable anatomy and reasonable life expectancy, while open aortic repair should be preferred for these patients with long life expectancy. (8)

Open Aortic Repair

The procedure is carried out in an operating room under general anaesthesia. The technique consists in the replacement of the aneurysmatic aorta with a prosthetic graft made by Polyethylene Terephthalate (PET) or Expanded Polytetrafluoroethylene (ePTFE). The choice of midline, transperitoneal or retroperitoneal incision is left to the surgeon. (8) After exposure of the vessels, proximal and distal clamps are placed. The aneurysmal segment is replaced with a synthetic graft sutured with a non-resorbable monofilament as close as possible to the renal arteries. Bifurcated graft should be preferred to maintain sufficient main body length and at least one internal iliac artery should be preserved (Figure 3). (32, 33)

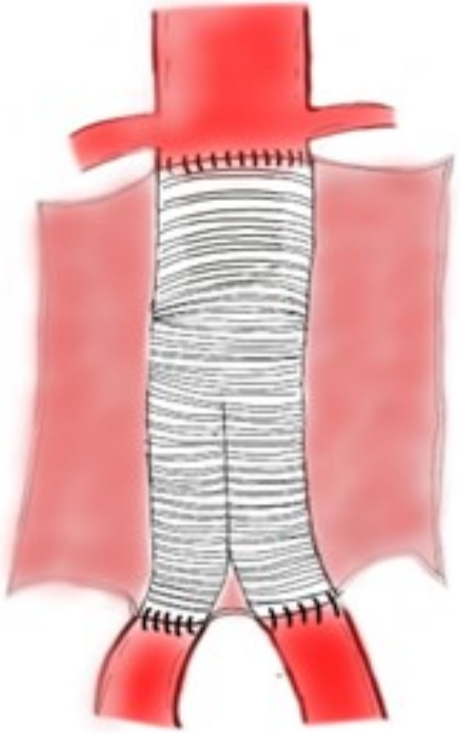


Figure 3: Open aortic repair. Replacement of the aneurysmatic aorta with prosthetic graft. © Vaccarino 2024

EVAR

The procedure is carried out under fluoroscopic guidance and the patient can be under general or local anaesthesia. The endovascular technique consists in excluding the aneurysm from systemic circulation and pressure by sealing the sac from the inside, leaving the aneurysmatic aorta in place. After open or percutaneous access from the patient’s common femoral arteries, guidewires, introducer sheaths, and catheters are introduced into the vessels. The percutaneous access is a much less invasive technique. However, it is crucial to assess calcifications in the femoral arteries, since their presence is the only predictor of percutaneous access failure. (34-36) Once the renal arteries and graft landing zones are identified by an angiography using intraarterial contrast media, the main body of the endograft is introduced and placed under the lowest renal artery. Aneurysm´s sac in then sealed and excluded from systemic circulation by introducing the iliac limbs which extend the main body (figure 4). In complex AAA, when the aneurysm anatomy is not suitable for infrarenal EVAR, Fenestrated Endovascular Aortic Repair (FEVAR) is a common option requiring aortic side branches incorporation using customized fenestrated stent graft based on patient´s specific anatomy.

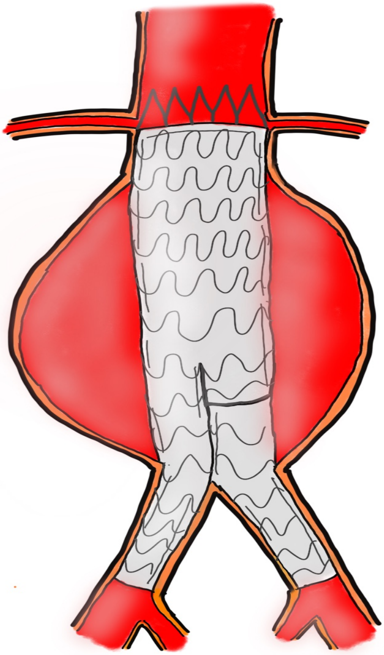


Figure 4: Endovascular aortic repair. Exclusion of the aneurysmatic sac by infrarenal endograft placement. © Vaccarino

EVAR outcome criteria and definitions

The primary outcome criteria for EVAR are preventing aneurysm rupture with consequent death and preventing aneurysm-related death resulting from primary or secondary intervention. (3, 37)

The secondary outcome criteria are preventing complications related to disease progression, avoiding device failure, endoleaks, secondary interventions and disabling complications (stroke, paraplegia, dialysis). (3, 37)

Technical success

Technical success is defined during a time window that goes from the beginning of the surgical procedure until 24 postoperative hours. It requires the uncomplicated positioning and deployment of a patent endoprotesis, without signs of twist, kinks or obstructions, with successful access to the arterial system in absence of type I or III endoleak. (3, 37)

Clinical success

It is the successful deployment of the endoprotesis in absence of death or permanent disabling complications resulting from the treatment. It defined by the following criteria: (3, 37)

- Technical success
- Absence of death
- Absence of rupture
- Absence of disabling complications (paraplegia, stroke, dialysis)
- Absence of type I or III endoleak
- Absence of aneurysm sac expansion > 5 mm
- Absence of device migration > 10 mm
- Maintenance of device integrity

Moreover, assisted primary clinical success is defined by the maintenance of the initially obtained success with additional secondary intervention to accomplish the foretasted targets.

Secondary clinical success is defined as an initially failed treatment corrected with a secondary intervention. (3, 37)

Clinical success can be further defined as:

- 30-day clinical success: within 30 days
- Short-term clinical success: from 30 days to 6 months
- Mid-term clinical success: up to 5 years
- Long term clinical success: beyond 5 years

Procedure-related mortality

Defined as any death that occurs during hospital stay or within 30 days post-operation or as a result of a secondary intervention aimed to treat first intervention complications. (38) Death occurring beyond 30 days is defined late mortality and more correctly short-term mortality (from 30 days up to 6 months), mid-term mortality (up to 5 years) and long-term mortality (beyond 5 years). (3, 37, 38) Patients´ survival is essential for the evaluation of treatment efficiency and it is defined as the length of time between the procedure and the patient's death. (37, 38)

Endoleaks

The endoleak is one of the most common complication following EVAR and it is defined as the persistence of blood flow into the aneurysmatic sac. (37, 39, 40) It is important to identify both presence and origin of endoleaks since they can lead to aneurysm growing and even rupture, requiring sometimes additional intervention. (3, 37, 41) Endoleaks are classified into primary (present at the time of EVAR) and secondary (detected during follow-up). Moreover, by the source of communication between sac and the systemic circulation, endoleaks are classified as follows:

- Type I endoleak: sealing zone failure
  - *Type Ia: failure of proximal sealing zone*
  - *Type Ib: failure of distal sealing zone*
  - *Type Ic: failure of iliac occluder*

- Type II endoleak: retrograde flow from aortic side branches
  - *Type IIa: one vessel visible*
  - *Type IIb: multiple vessel visible*

- Type III endoleak: midgraft failure
  - *Type IIa: separation or poor apposition of modular components*
  - *Type IIb: graft disruption*

- Type IV endoleak: graft porosity

- Undetermined endoleak: visible endoleak with no clear origin

- Endotension: enlargement of the aneurysm sac > 5 mm with no imaging evidence of endoleak

Long-term outcome after EVAR

While, on the one hand, the great development of endovascular techniques had led to a clear decrease of perioperative morbidity and mortality, on the other hand, long-term outcome after EVAR has been challenged. In literature there are great variety of data showing higher risk of death in patients who have undergone AAA repair when compared with general population. (42) The causes are mostly cardiovascular. (43-45) Many factors play a role in affecting long-term outcome after EVAR such as age, female gender, aneurysm diameter and comorbidities, mainly CKD and COPD. (42, 46-51) Patients who have undergone EVAR should be offered postoperative best medical treatment with statins, antiplatelet and blood pressure medications and a dedicated follow-up program to detect possible late complication. (52-55)

Follow-up after EVAR

EVAR is associated with risk of postoperative late complications such as endoleak, aneurysm sac growth, graft infection, graft occlusion and migration. (56-58) Life-long follow-up after the procedure is mandatory to detect late complications and identify possible device failure and disease progression. (8, 59-61)

Different imaging modalities can be used.

DUS examination can be used to measure sac diameter, to verify the absence of endoleaks (62, 63) and assess limb patency and flow. The potential of DUS can be increased by the use of echogenic contrast, Contrast Enhanced Ultrasound (CEUS), and the combination with 3D volume. (64)

CTA is today considered the gold standard in EVAR follow-up since it gives bright assessment of most EVAR complications. Patients who have undergone EVAR are recommended early post-operative imaging (within 30 days) using computed tomography angiography to assess the presence of endoleak, component overlap and sealing zone length. However, the value of frequent CTA during EVAR follow up has been debated considering the risks of malignancy associated with the radiation exposure and the possible renal impairment associated to the use of contrast medium. (65-68) Recent studies showed that intra-operative angiography combined with cone beam CT for completion assessment could possibly replace the early (30 day) post-operative CTA, (69, 70) and simple DUS AAA diameter measurements seems to be an alternative method to follow stable or shrinking AAA in low risk patients after AAA. (71-75)

Preoperative risk assessment

Once the aneurysm diameter reaches the recommended diameter to consider elective repair, other risk factors than aneurysm diameters may influence the decision making since several patients are not considered suitable for surgery and assessment of perioperative risk is necessary. Patients should undergo accurate preoperative evaluation to assess cardiac and pulmonary risk and estimate preoperative kidney function and nutritional status.

CT-based risk-assessment tools

CT-principles

During CT scanning, the x-ray tube rotates around the subject and generate 3D images, while a detector on the opposite side records the beam intensity. The attenuation describes the radiodensity of the object and it is expressed in Hounsfield Units (HU). During spiral or helical scanning, the subject simultaneously moves perpendicular to the plane of rotation of the x-ray tube and detector. Modern CT systems have 16 to 640 slices and multidetector CT systems allow simultaneous acquisition of images from multiple parallel slices, reducing examination time.

CTA is the most widely employed imaging modality for the immediate preoperative assessment of patients with AAA. CTA plays a key role in assessing the extent of the disease and planning the repair. It must include multi-thin slice cuts of 1-3 mm from the neck to the groin, including the whole aorta. Moreover, since it is routinely done for all patients undergoing endovascular treatment, it is ideal to use it as instrument to refine clinical risk assessment through new ways of image postprocessing.

The main drawback of CTA is the potential issues derived from the use of iodinated contrast media (ICM), such as Contrast Induced Nephropathy (CIN) and allergic reactions or issues derived from the exposure to ionizing radiation that may increase risk of malignancy. (65-68)

Agatston Calcium Score

It estimated that about 42% of perioperative death after non-cardiac interventions are attributable to cardiovascular events.(76, 77) Patients with AAA have high risk of cardiovascular events and ESC guidelines defined cardiac risk between 1% and 5% in patients undergoing EVAR.(78) It is easy to understand how the investigation of new simple ways to assess cardiac risk without exposing the patients to further expensive and invasive investigations have been a milestone in modern research. The role of atherosclerosis in AAA development is debated. Either they are or not a casual factor, atherosclerosis and AAA share several common risk factors and calcifications are commonly present into the aneurysmatic arterial wall (figure 5) as well as in other circulatory beds. (79, 80) Moreover, AAA prevalence is higher in patients with Coronary Artery Diseases (CAD) suggesting that CAD is significantly associated with AAA. (81-83) Coronary Artery Calcifications (CAC) are present in most of the patients with CAD.

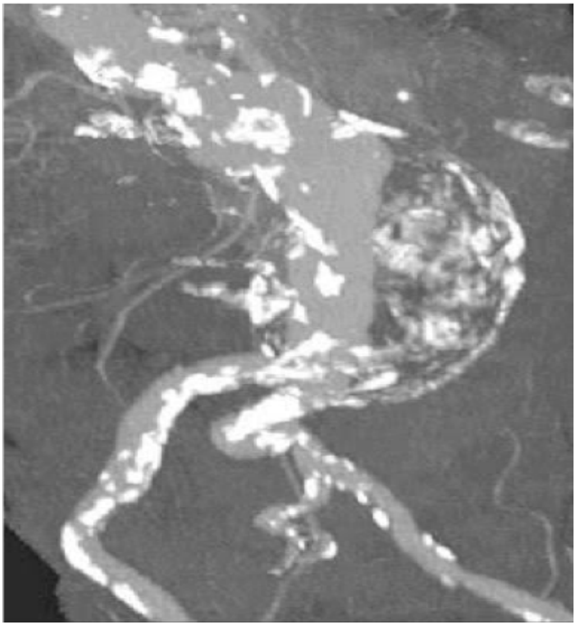


Figure 5: aorto-iliac calcifications

There is a strong association between CAC burden and atherosclerosis. Estimation and quantification of calcifications detected on noncontrast-enhanced CT are generally done by a semi-automated tool, Agatston Calcium Score (ACS). The calculation is made by the weighted sum of calcified lesions with a density above 130 Hounsfield Unit (HU) multiplied by the area of the calcification speck. The score of each calcified speck is then summed to obtain the total ACS. (84)

Agatston score is today a standardized method to quantify CAC and coronary plaque burden and it is one of the most used tools for cardiovascular risk assessment in the population. (85)

The detection and the measurement of vascular calcification assessed by ACS in other circulatory beds as a marker of the degree and severity of the atherosclerotic burden is much less studied. Iliac calcification seems to predict adverse events in patients with Peripheric Artery Diseases (PAD) and aorto-iliac calcifications can potentially predict mid-term mortality in patients undergoing elective EVAR.

Ileo-psoas muscle size: a tool to assess frailty and sarcopenia

Frailty, defined as multi-system decline associated to increased vulnerability to stressors (86), and sarcopenia, defined as loss of muscle function and mass (87), are two complementary conditions that become more prevalent with increasing age. Sarcopenia, assessed by measuring ileo-psoas muscle size, was found to be associated with poor long-term outcome after AAA repair (88). But its role as a predictor of long-term outcome after EVAR is controversial and debated (89, 90). However, despite significant relationship with survival after elective AAA repair, there are not enough evidence and assessment of sarcopenia does not improve sufficiently the survival prediction ability. Currently, assessment of sarcopenia is not recommended to be used as a tool for risk stratification in the decision-making process (8, 88).

Visceral Adipose Tissue (VAT)

Obesity, defined as excessive fat accumulation with Body Mass Index (BMI) > 30 (91), has been reported to be associated with various comorbid conditions such as hypertension, diabetes, stroke and increased risk of developing cardiovascular diseases (92). Obesity is generally considered a potential risk factor for postoperative mortality and morbidity.

BMI, obtained dividing the weight in kilograms by the square of the height in meters, measures weight adjusted for height. Although BMI is used as an indicator of obesity, caution should be taken because BMI is a tool that measures excess of weight rather than excess of fat. Several methods have recently been developed to quantify abdominal adipose tissue. By measuring the cross-sectional distribution of abdominal fat on CT, it is possible to obtain several variables such as visceral adipose tissue area, subcutaneous adipose tissue, total adipose tissue and the ratio of visceral-to-total adipose tissue areas. Different studies have shown association between visceral adipose tissue and poor outcomes after general surgery in cancer patients. (93, 94) Moreover, periaortic adipose tissue has been suggested to play an important role on the aortic aneurysm development. (95) However, its role in predicting long-term survival after EVAR has not been sufficiently investigated. (96).

Clinical-based risk-assessment tools

Preoperative clinical-based scoring systems are risk-assessment tools calculated on preoperative patient´s clinical characteristics. They should be easy to assess and should give a broad and general idea about preoperative patient’s condition. Different scoring systems have been developed to assist clinicians in the prediction of outcomes after aortic surgery.

Glasgow aneurysm score (GAS)

The GAS is a clinical prognostic scoring system developed by A.K Samy in 1994. GAS is calculated by the sum of the age at the time of the repair and the points obtained by preoperative comorbidities such as age, myocardial disease, cerebrovascular disease and renal disease. GAS seems to be a reliable clinical tool to predict operative in-hospital mortality after repair of either intact or ruptured AAA. (97, 98) Moreover, GAS appeared in recent studies to be even a good predictor of 30-days mortality and mid-term survival in patients undergoing elective EVAR for AAA.(99) In addition, as a result of its simplicity, GAS easily can be calculated at bedside, supplying a brief and quick estimation of the preoperative risk.

Assessment, optimization and protection of renal function

Post-operative impairment of kidney function is one of the most frequent complications after EVAR occurring in about 20-30% of patients and progression to chronic kidney diseases is associated with increased morbidity and lower long-term mortality. (100, 101) Post-operative acute kidney injury (AKI) is defined as a rise in serum creatinine ≥ 26 µmol/L or ≥ 50 % within 48 hours of surgery or a fall in urine output to < 0.5 mL/kg/hour for more than six hours after surgery. (102) Main risk factors of developing AKI after EVAR are pre-existing chronic kidney diseases (CKD), renal embolization, catheter manipulation, ischemia, displacing of graft landing zone and the use of iodinated contrast media (ICM) during arteriography. Kidney function should be assessed on all the patients undergoing EVAR and refer to the nephrologist patients with severe renal insufficiency for renal function optimization. (8) Currently, there are no established strategies to prevent AKI after EVAR besides preoperatory hydration. Figure 6 shows a schematic representation of the renal veins and renal arteries anatomy.

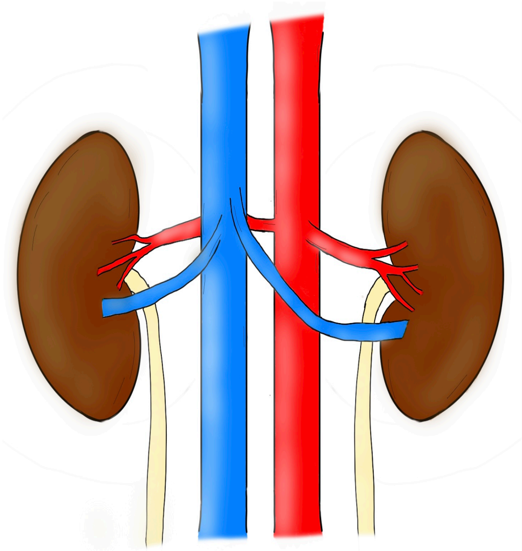


Figure 6: Schematic representation of renal veins and arteries anatomy

Contrast-induced nephropathy (CIN)

CIN is a severe complication of angiographic procedures resulting from the administration of ICM. Contrast media is necessary to enhance the visibility of the vessels during arteriography. ICM is excreted mainly by the kidneys within 24 hours from its administration. CIN is defined as an impairment of the kidney function within 48 - 72 hours after iodine contrast administration, without other clear causes. This impairment was assumed as either ≥ 25% increase in serum creatinine from baseline or a ≥ 44 µmol/L increase in absolute serum creatinine value. (103) CIN is one of the main causes of AKI and even if CIN is commonly a transient and reversible form of AKI, it is associated with prolonged hospital stay and increased risk of morbidity and mortality. (104)

Causes, treatment and preventions strategies:

Risk factors to develop CIN can be patient- or procedure-related.
Main patient-related risk factors are:

- eGFR less than 40 ml/min/1.73 m^2
- Known or suspected acute renal failure
- Diabetes mellitus

Main Procedure-related risk factors are:

- High volume of ICM

- Repeated exposure to ICM within 48-72 hours
- High osmolarity contrast media
- Contemporary use of nephrotoxic drugs.

The mechanism that leads to renal damage by the use of contrast media is not fully understood yet. Determining factors can be hypoxia of the renal medulla due to impact on vasoactive agents, direct toxicity of contrast media and contrast-induced renal tubular cell apoptosis. (105-107)

During its excretion, depending on osmolarity, viscosity and volume, ICM generates osmotic forces into the renal tubules causing water elimination and consequently an increase of intratubular pressure, reducing GFR and contributing to development of acute renal failure (ARF). (108)

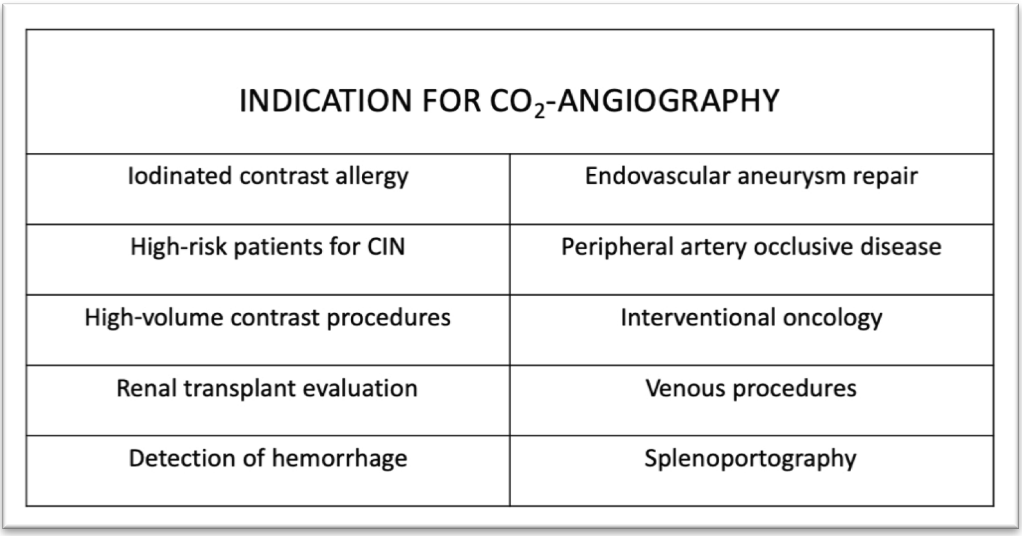
Once diagnosed, CIN treatment is mainly adjuvant, consisting of electrolyte management and fluid administration. Moreover, immediate haemodialysis after ICM exposure does not seem to have benefit in patients with preoperative CKD. (109-111) Limitations of specific treatment options makes CIN prevention crucial, especially in high-risk patients.

Suggested strategies are:

- Volume expansion with normal saline or sodium bicarbonate (112, 113)
- Minimizing the use of nephrotoxic drugs where clinically possible (113)
- Minimizing volume of contrast media (113, 114)

CO_2- angiography – an alternative to conventional ICM- angiography

CO_2 is a natural chemical compound that is found in gas state at room temperature. CO_2 was used for the first time as contrast agent in 1914, when it was used to evaluate abdominal viscera. Its use as intra-arterial agent was developed in 1970 by Hawkins (115, 116). In the following years, CO_2 was mostly used in situations where conventional contrast angiography was contraindicated, such as iodinated contrast allergy or renal failure, but in present days the use of CO_2 as a contrast agent is in continuous development thanks to the many properties of this gas(117). Indications for CO_2-angiography use are listed in figure 7.

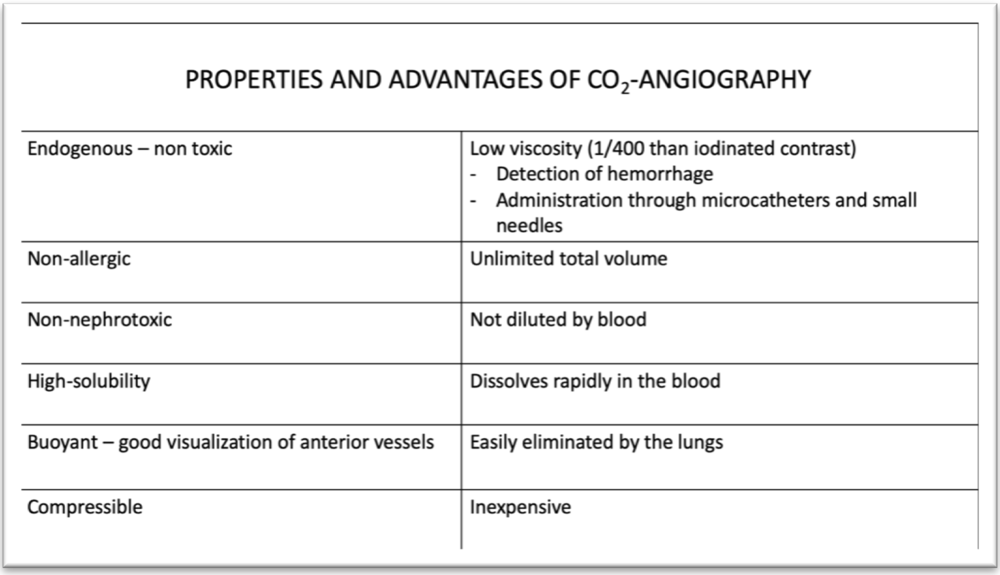


INDICATION FOR CO_2-ANGIOGRAPHY	
Iodinated contrast allergy	Endovascular aneurysm repair
High-risk patients for CIN	Peripheral artery occlusive disease
High-volume contrast procedures	Interventional oncology
Renal transplant evaluation	Venous procedures
Detection of hemorrhage	Splenoportography

Figure 7: Indication for use of CO_2-angiography

Properties and advantages of CO2

CO_2 is a gas with multiple properties that make it an excellent contrast agent not only as an alternative to conventional iodinated contrast. Compared to other contrast agent, it is a natural bioproduct and for this reason CO_2 lacks in toxicity and allergic properties. Moreover, it is not nephrotoxic and consequently its use during angiography reduces risk for CIN (118-122). It is compressible and non-flammable. Its low viscosity makes CO_2 particularly useful for bleeding detection and allows its delivery via very small catheters. Thanks to its buoyancy, CO_2 is great to visualize anterior vessels like mesenteric and celiac ostia. Unlike iodinated contrast, CO_2 does not mix with blood and dissolves within 30 seconds without effecting the pH. When it is administrated intravenously is excreted by the lungs at one pass. It is an inexpensive contrast agent and, thanks to all its properties, there is not a maximum recommended dose. Properties and advantages of CO_2-angiography use are listed in figure 8.



PROPERTIES AND ADVANTAGES OF CO_2-ANGIOGRAPHY

Endogenous – non toxic	Low viscosity (1/400 than iodinated contrast) - Detection of hemorrhage - Administration through microcatheters and small needles
Non-allergic	Unlimited total volume
Non-nephrotoxic	Not diluted by blood
High-solubility	Dissolves rapidly in the blood
Buoyant – good visualization of anterior vessels	Easily eliminated by the lungs
Compressible	Inexpensive

Figure 8: Properties and advantages of CO_2-angiography

Contraindications, complications and precautions

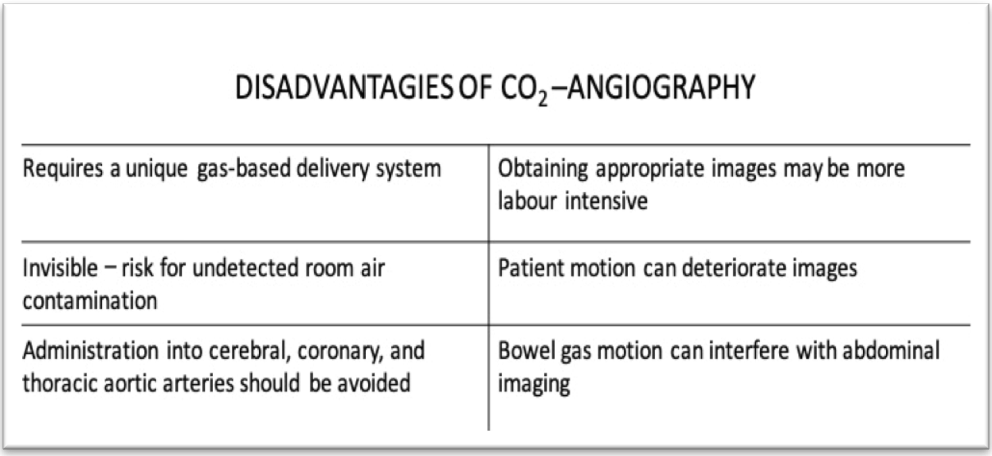
CO_2 is no safe to use on central nervous system due to the risk of causing cerebral air embolism and consequently ischemic seizures, stroke or death. It is recommended to avoid arterial injections above the diaphragm or with patients head in an elevated position.

Since CO_2 is an invisible gas, there is the risk of contamination without detection that may lead to air embolism. It is mandatory to use closed delivery systems a and valves directing gas from CO_2 source toward the patient to prevent air room contamination.

Moreover, due to its buoyancy, CO_2 can dissipate into small vessels leading to gas trapping which may cause potential ischemia. The main symptom of trapping is pain and, if the patient is under general anaesthesia, the diagnosis can be made from the fluoroscopy images since the gas will not dissolve in the canonical 30 seconds. Once trapping phenomenon has occurred, it is recommended to change rapidly patients position to promote gas movement. Because of buoyancy, CO2 use in sensitive vessels such coronaries, cerebral and spinal vessels is not recommended (123-127). Main disadvantages of CO_2-angiography use are listed in figure 9.

Absolute contraindications to the use of CO_2 -angiography are:

- Direct or refluxed administration of CO_2 into the cerebral, cardiac, or thoracic aortic arteries
- Use of arterial CO_2 in known right-to-left shunt
- The concomitant use of intravenous CO_2 injections and nitrous oxide anesthesia



DISADVANTAGIES OF CO_2–ANGIOGRAPHY

Requires a unique gas-based delivery system	Obtaining appropriate images may be more labour intensive
Invisible – risk for undetected room air contamination	Patient motion can deteriorate images
Administration into cerebral, coronary, and thoracic aortic arteries should be avoided	Bowel gas motion can interfere with abdominal imaging

Figure 9: Disadvantages of CO_2-angiography

Aims

The specific aims of this thesis were:

I. Evaluate if ilio-femoral calcium score measured on preoperative computed tomography is associated with survival after EVAR of varying complexity, with particular focus on cardiovascular events.

II. Evaluate if combining ilio-femoral calcium score to the Glasgow Aneurysm Score improves the prediction of long-term survival in patients undergoing infrarenal EVAR.

III. Investigate if preoperative assessment of long-term survival in patients undergoing infrarenal EVAR can be improved by measuring the ileo-psoas muscle size and visceral adipose tissue on preoperative CT angiography.

IV. Analyse different steps during CO_2-EVAR to create a standardized operative protocol for the use of automated CO_2-angiography during this procedure.

V. Evaluate if a protocol based on the preferential use of automated CO_2-angiography during fusion-guided Iliac Branch Device Implantation (IBD) is technically feasible and reduces the risk of postoperative AKI.

Materials and methods

General and specific methods for papers I, II and III

Study population

All patients who underwent EVAR for non-ruptured AAA at the Vascular Centre of Malmö between 2004 and 2012 were identified from hospital records for potential inclusion in studies I, II and III. In study I patients who underwent FEVAR were also included. The study frame began on 2004, when all the CT images at the Vascular Centre of Malmö became digitally available on PACS (Picture Archiving and Communication System). The inclusion period ended on 2012 in order to have a long enough follow-up to study the long-term survival. Retrospective chart review was done to identify preoperative comorbidities and risk factors. Survival data was retrieved from the Swedish population register (Dödsorsaksregistret, Socialstyrelsen). Verification and completing of the information were done from hospital charts if necessary. In order to study the long-term survival, patients who died within 30 days postoperatively were excluded for the mortality analyses.

Imaging and CT-based risk-assessment tools

All patients included in studies I, II and III were examined preoperatively with a spiral CT- scanner (Siemens Sensation 16 to 64, Erlangen, Germany). The image acquisition protocol was: spiral mode, 0.5-sec gantry rotation, collimation 0.6-1.5 pitch, and tube settings 80-120 kVp/20 mAs. A caudocranial scanning direction was selected, covering from the jugulum or diaphragm to the femoral trochanter minor. Scans were registered before and after intravenous iodine contrast injection. Dedicated post processing software applications were used for the CT measurements (iNtuition; TeraRecon, San Mateo, CA and Syngo.via; Siemens Medical Solution Inc. Malvern, PA, USA). The measurements were done by one or two observers. A cross-check was done between the measurements to exclude observer-related errors.

Agatston Calcium Score

In the first study Agatston Calcium Score was calculated on the preoperative non-contrast-enhanced thinnest axial CT reconstructions, from the bifurcation of the aorta to the common femoral arteries bilaterally. The software marked automatically the calcifications as the structures with HU > 130 (Figure 10). Each image was reviewed and only the marked structures that corresponded to the arterial segments of interest were included in the score calculation.

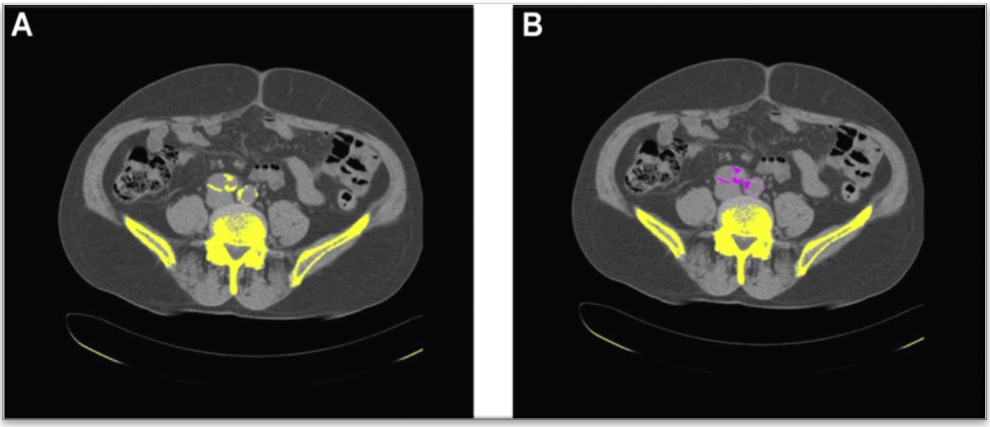


Figure 10: Nonconntrast-enhaanced CT scan. (A) The software has marked all the images with Housfields unit > 130 (yellow color). (B) The user marks the sections corresponding to the lesions to be incluede in the measuring of the calcium score (pink color). This figure was published on Annals of Vascular Surgery, Vol 68, Author Vaccarino et al, “Low ilio-femoral Calcium Score may predict higher survival after EVAR and FEVAR”, P 283-291, © 2020 Elsevier Inc.

Total psoas muscle area and Total psoas muscle area index

Based on previously established methodology (figure 11), in the third study Total Psoas Muscle Area (TPA) was measured on the pre-operative thinnest axial CT reconstructions at the level of the middle of the fourth lumbar vertebra. Total psoas muscle area index was then calculated by dividing TPA by the square of the body height.

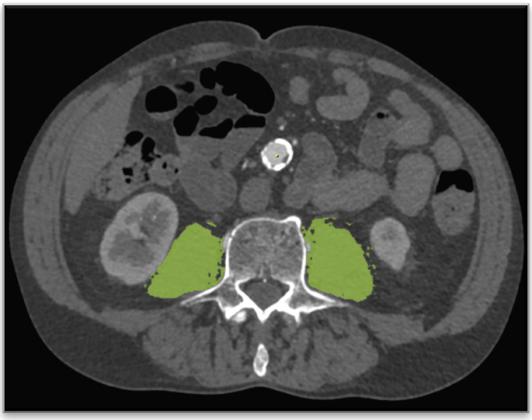


Figure 11: Total psoas muscle coss-sectional area (TPA) measured at the level of the middle of the fourth lumbar vertebra. © 2024 Vaccarino

Visceral adipose tissue

In the third study, abdominal visceral adipose tissue (VAT) volume was measured using a full 3D analysis of visceral fat between the superior margin of the liver and the bottom of the pelvis. The areas of VAT, subcutaneous adipose tissue (SAT) and total adipose tissue (TAT) were evaluated on a single axial slice at the level of the inter-vertebra disk L2-L3 as the cross-sectional area of visceral, subcutaneous and the total adipose tissue, respectively (figure 12). The VAT index was calculated as the ratio between VAT and TAT.

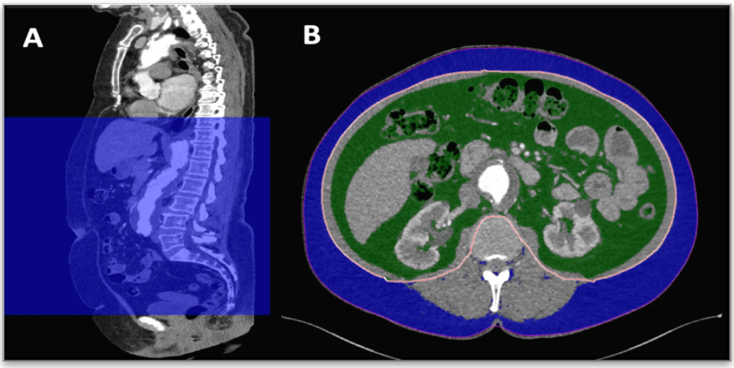


Figure 12: Measurement of abdominal adipose tissue. (A) Volume was measured in a full 3D analysis of visceral adipose tissue between the superior margin of the liver and the bottom of the pelvis. (B) Visceral adipose tissue (VAT) area, Subcutaneous adipose tissue (SAT) anrea and Total adipos tissue area (TAT) measured on an axial reconstruction at the level oof the inter-vertebral disk L2-L3. © 2024 Vaccarino

Clinical-based risk-assessment tools

Glasgow Aneurysm Score

In paper II GAS was calculated by the sum of the age at the time of EVAR and the points obtained by the preoperative comorbidities as follows: age + [7 points for myocardial disease] + [10 points for cerebrovascular disease] + [14 points for renal disease]. Preoperative comorbidities were collected retrospectively from clinical charts. Myocardial disease was assumed based on noted anamnesis in the charts. Renal disease was defined as a history of acute or chronic renal failure and/or creatinine level ≥ 133 µmol/L (≥ 1.5 mg/dL). Cerebrovascular disease was defined as presence of transient ischemic attacks or all types of stroke. (128, 129)

Methods for paper IV

We prospectively enrolled patients undergoing CO_2-EVAR in five different European centers. The study period went from 2019 to 2021. An automated injector was used to perform CO_2-EVAR. In case of difficult visualization of the lowest renal artery (LoRA), a small amount of ICM was injected. LoRA visualization and image quality were analysed at different procedure steps:

- I step: preoperative CO_2-angiography from pigtail placed in the aorta at the level of renal arteries ostia and from the femoral introducer sheath. II step: angiographies from pigtail at 0%, 50%, and 100% of proximal main body deployment. (Figure 13)
- III step: Contralateral Hypogastric Artery (CHA) visualization with CO_2 injection from femoral introducer sheath.
- IV step: completion angiogram from pigtail and femoral introducer sheath.

Evaluation of intraoperative and postoperative CO_2-related adverse events were done. Moreover, to verify the sensitivity of CO_2-angiographies on endoleak diagnosis, comparison was done between the endoleaks detected at final CO_2-angiogram and those detected with DUS/CEUS or CT scan performed before discharge.

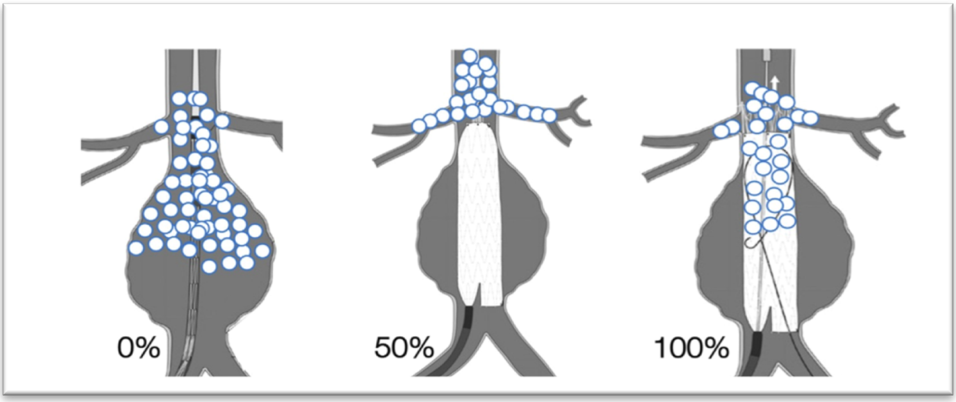


Figure 13: Carbon dioxide (CO2) angiography at 0%, 50% and 100% oof proximal main body deproiment. This figure was published on Journal of Vascular Surgery, Vol 77, Author Varcica et al, “The optimal operative protocol to accomplish CO_2-EVAR resulting from a prospective interventional multicenter study”, P 1405-1412, © 2023 Elsevier Inc.

Methods for paper V

Patients undergoing elective EVAR of AAA including at least one iliac branched device implantation at a single tertiary university centre between May 2013 and August 2019 were screened for inclusion. A cohort of patients in which an intraoperative imaging protocol using predominantly CO_2 was identified. Inclusion required the use of a standardized intraoperative imaging protocol combining fusion imaging, low-frequency pulsed fluoroscopy (3.75 frames/s) and preferential use of automated carbon dioxide angiography (Angiodroid SRL, San Lazzaro di Savena, Italy) for DSA recurring to ICM (Omnipaque; GE Healthcare 140 mg I / ml) whenever image quality was insufficient with CO_2. The completion angiography was universally done with CO_2 and iodine (20 ml at 20 ml / second through a multi-side hole catheter placed suprarenal) (Figure 14). A control group was identified by selecting patients that had undergone similar repairs where a similar intraoperative imaging protocol was used with the exception that CO_2 was injected manually and used only for the initial adjustment of the fusion imaging. After this initial angiography, all digital subtraction angiographies were performed with ICM. Retrospective clinical chart review was done to identify pre- and postoperative comorbidities. A thin slice CTA with non- and contrast-enhanced scans in the arterial phase were performed preoperatively for endograft planning. Postoperatively, a CTA with an extra late scan was done one month postoperatively with a serum creatinine taken within the preceding week.

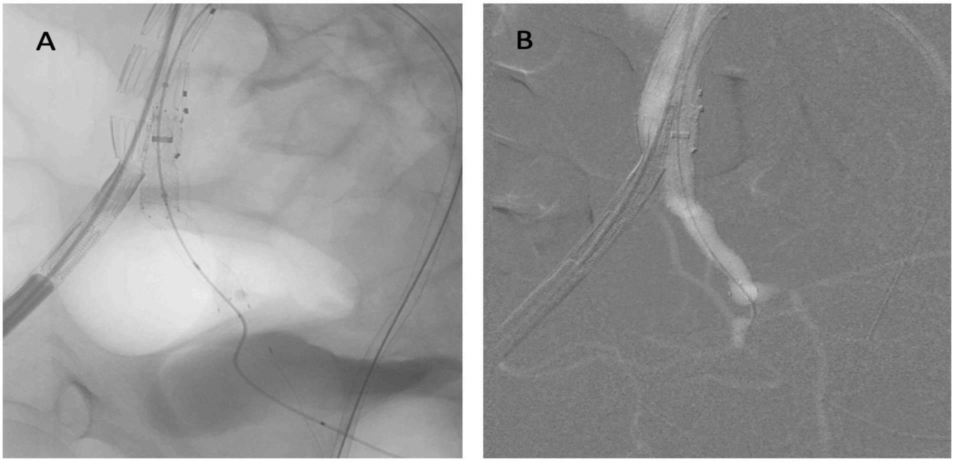


Figure 14: CO_2-angiography during EVAR implantation. A: native image; B: DSA using CO_2 as a contrast agent.

Definitions

Acute Kidney Injury

Post-operative AKI was defined by adapting the National Institute for Health and Care Excellence (NICE) definition. It assumed a rise in serum creatinine ≥ 26 µmol/L or ≥ 50 % within 48 hours of surgery. The original definition also included a fall in urine output to < 0.5 mL/kg/hour for more than six hours after surgery. (102) Given the retrospective nature of our study, this variable could not be reliably collected since hourly urinary output was only measured during the stay in the postoperative recovery unit which was of 6 hours if not evident complications were identified.

Acute Renal Failure

Post-operative ARF was defined as a decrease of eGFR of at least 25% from the baseline. (130)

Contrast Induced Nephropathy

Post-operative CIN was defined a new impairment of the kidney function within 48-72 hours after iodine contrast administration, without other clear cause. This impairment was assumed as either ≥ 25% increase in serum creatinine from baseline or a ≥ 44 µmol/L increase in absolute serum creatinine value. (103)

Statistical analysis

In all the papers the values are presented as median and interquartile range or absolute number and percentage. Continuous variables were compared with Mann-Whitney U test or Student t test, while Chi-squared test was used for categorical variables. Survival rates were estimated using life tables, with standard error in %. Survival analysis comparison was done with a log-rank (Mantel-Cox) test. Univariate and multivariate (Cox) regression analyses were performed for baseline comorbidities. $P < 0.10$ was used for including variables in the multivariate model backward stepwise. Results of Cox analysis are presented as Hazard Ratio (HR) with 95% Confident Interval (CI) per standard deviation. Statistical significance was assumed when $P < 0.05$. In study I and II normal distribution was not assumed. In study I, after dividing Agatston Calcium Score in quartiles, survival analysis comparison was done between the lowest calcium quartile and the 3 highest. In study II Glasgow Aneurysm Score was calculated using the preoperative comorbidities as described above. An optimal cut-off for GAS was estimated based in receiver operating characteristic (ROC) analysis. The population was then divided in high GAS and low GAS by the optimal cut-off and survival analysis comparison was done. IBM SPSS statistics, version 23 and 25 (SPSS Inc, Chicago, IL) was used for data analysis.

Ethical consideration

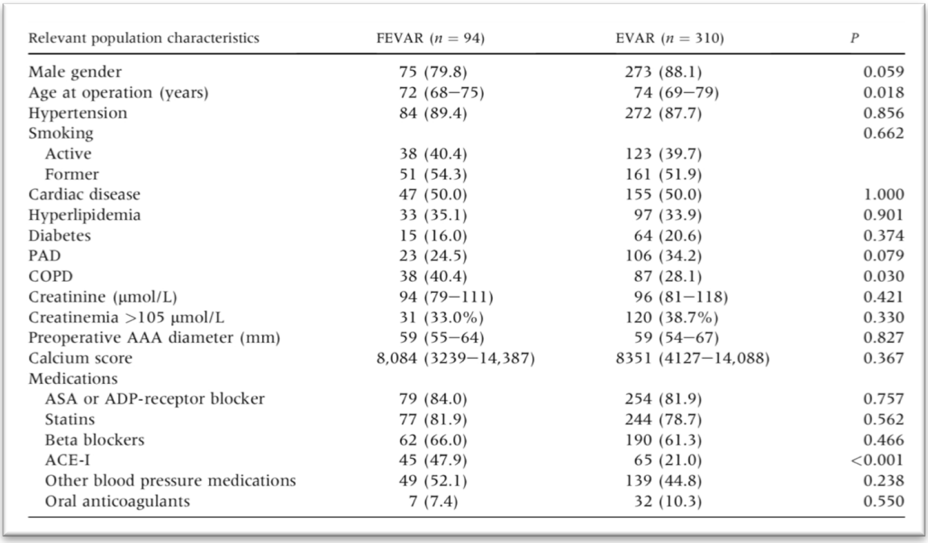
All the projects were ethically approved by the regional ethical committee. The studies were done in accordance with the principles outlined in the declaration of Helsinki for medical research involving human subjects and complied with the STROBE guidelines for cohort studies. Patients included in studies I, II, III and V consented for the procedure but a specific study informed consent was waived due to the retrospective design of the study. Project IV was ethically approved by the initiating centre and locally. Local and national requirements for the written informed consent were followed.

Results

Paper I

Six hundred fifty-one patients who underwent infrarenal EVAR or FEVAR for non-ruptured AAA during the study period were screened for inclusion. Of these, 404 (62.05%) had enough good quality imaging for being included. Three hundred and ten patients (76.73%) underwent EVAR and 94 (23.26%) patients underwent FEVAR. Nine patients (2.2%) died within 30 days postoperatively, while the remaining patients were followed up for a median duration of 6.3 years (4.7 – 8.4). There was no significant difference in overall survival between the included and excluded patients (P = .33). Table 1 shows detailed patient characteristics.

Table 1: Patients characteristics for included patients, by proccedure type. This table was published on Annals of Vascular Surgery, Vol 68, Author Vaccarino et al, “Low ilio-femoral Calcium Score may predict higher survival after EVAR and FEVAR”, P 283-291, © 2020 Elsevier Inc.

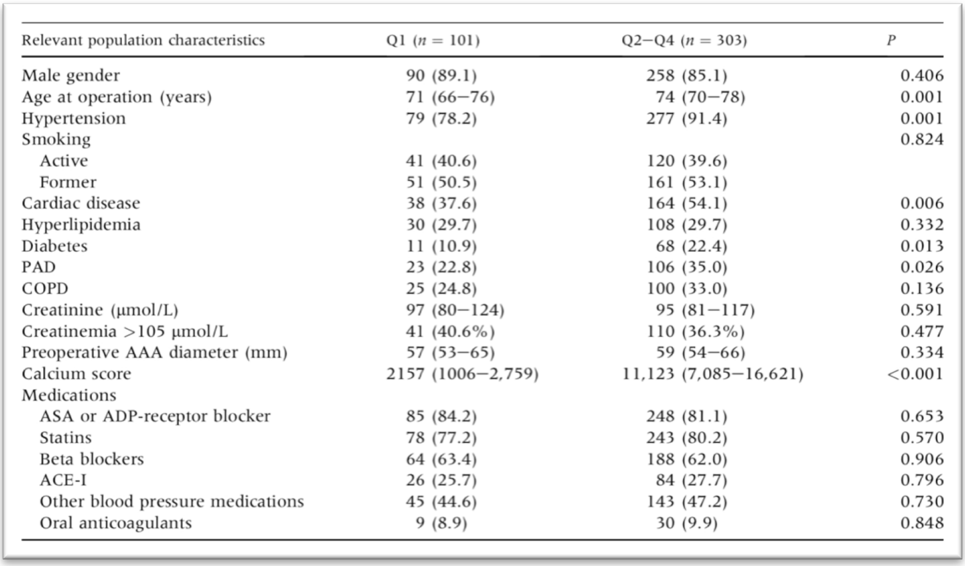


Relevant population characteristics	FEVAR (*n* = 94)	EVAR (*n* = 310)	*P*
Male gender	75 (79.8)	273 (88.1)	0.059
Age at operation (years)	72 (68–75)	74 (69–79)	0.018
Hypertension	84 (89.4)	272 (87.7)	0.856
Smoking			0.662
Active	38 (40.4)	123 (39.7)	
Former	51 (54.3)	161 (51.9)	
Cardiac disease	47 (50.0)	155 (50.0)	1.000
Hyperlipidemia	33 (35.1)	97 (33.9)	0.901
Diabetes	15 (16.0)	64 (20.6)	0.374
PAD	23 (24.5)	106 (34.2)	0.079
COPD	38 (40.4)	87 (28.1)	0.030
Creatinine (μmol/L)	94 (79–111)	96 (81–118)	0.421
Creatinemia >105 μmol/L	31 (33.0%)	120 (38.7%)	0.330
Preoperative AAA diameter (mm)	59 (55–64)	59 (54–67)	0.827
Calcium score	8,084 (3239–14,387)	8351 (4127–14,088)	0.367
Medications			
ASA or ADP-receptor blocker	79 (84.0)	254 (81.9)	0.757
Statins	77 (81.9)	244 (78.7)	0.562
Beta blockers	62 (66.0)	190 (61.3)	0.466
ACE-I	45 (47.9)	65 (21.0)	<0.001
Other blood pressure medications	49 (52.1)	139 (44.8)	0.238
Oral anticoagulants	7 (7.4)	32 (10.3)	0.550

COPD, chronic obstructive pulmonary disease; ASA, acetylsaliccylicc acid; ADP, adesonise diphosphate; ACE, angiootensin-cconverting enzyme

The median calcium score was 8348 (IQR 3830 – 14.179) for all patients, and it did not differ between EVAR and FEVAR patients (8.351 [4127 – 14.088] and 8084 [3239 – 14.387], respectively; P = .367). Calcium score was divided into quartiles. The lowest quartile was compared to the highest three quartiles. Patients in the lower quartile were younger (P = .001), less hypertensive (P = .0001), and had less cardiac disease (P = .006). In a logistic regression model, cardiac disease was the only preoperative characteristic associated with a high calcium score with OR of 1.864 (1.091 - 3.185; P = .023). Table 2 shows the patient characteristics when grouped according to the quartiles.

Table 2: Patients characteristics for included patients, first quartile versus second-fourth quartile. This table was published on Annals of Vascular Surgery, Vol 68, Author Vaccarino et al, “Low ilio-femoral Calcium Score may predict higher survival after EVAR and FEVAR”, P 283-291, © 2020 Elsevier Inc.

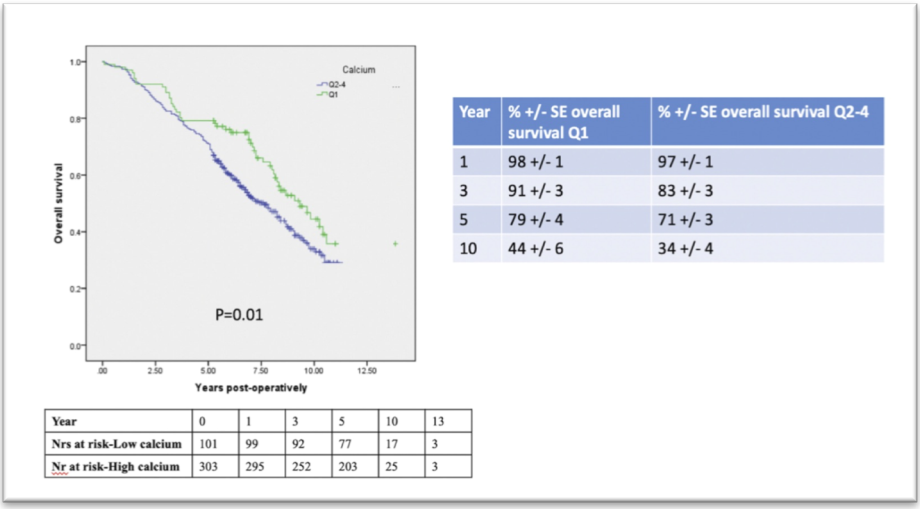


Relevant population characteristics	Q1 (*n* = 101)	Q2–Q4 (*n* = 303)	*P*
Male gender	90 (89.1)	258 (85.1)	0.406
Age at operation (years)	71 (66–76)	74 (70–78)	0.001
Hypertension	79 (78.2)	277 (91.4)	0.001
Smoking			0.824
Active	41 (40.6)	120 (39.6)	
Former	51 (50.5)	161 (53.1)	
Cardiac disease	38 (37.6)	164 (54.1)	0.006
Hyperlipidemia	30 (29.7)	108 (29.7)	0.332
Diabetes	11 (10.9)	68 (22.4)	0.013
PAD	23 (22.8)	106 (35.0)	0.026
COPD	25 (24.8)	100 (33.0)	0.136
Creatinine (μmol/L)	97 (80–124)	95 (81–117)	0.591
Creatinemia >105 μmol/L	41 (40.6%)	110 (36.3%)	0.477
Preoperative AAA diameter (mm)	57 (53–65)	59 (54–66)	0.334
Calcium score	2157 (1006–2,759)	11,123 (7,085–16,621)	<0.001
Medications			
ASA or ADP-receptor blocker	85 (84.2)	248 (81.1)	0.653
Statins	78 (77.2)	243 (80.2)	0.570
Beta blockers	64 (63.4)	188 (62.0)	0.906
ACE-I	26 (25.7)	84 (27.7)	0.796
Other blood pressure medications	45 (44.6)	143 (47.2)	0.730
Oral anticoagulants	9 (8.9)	30 (9.9)	0.848

COPD, chronic obstructive pulmonary disease; ASA, acetylsaliccylicc acid; ADP, adesonise diphosphate; ACE, angiootensin-cconverting enzyme

Survival and regression analysis

Two hundred twenty-two (54.1%) patients died during the study period. Fifty-two (23.4%) deaths were due to cardiac events. Estimated overall survival was 98 ± 1%, 73 ± 2%, and 36 ± 3% at 1, 5, and 10 years, respectively. Survival was not influenced by the type of repair (P = .699). Patients in the first quartile had higher overall survival compared with the ones in the second-fourth quartile (P = .01); Figure 15

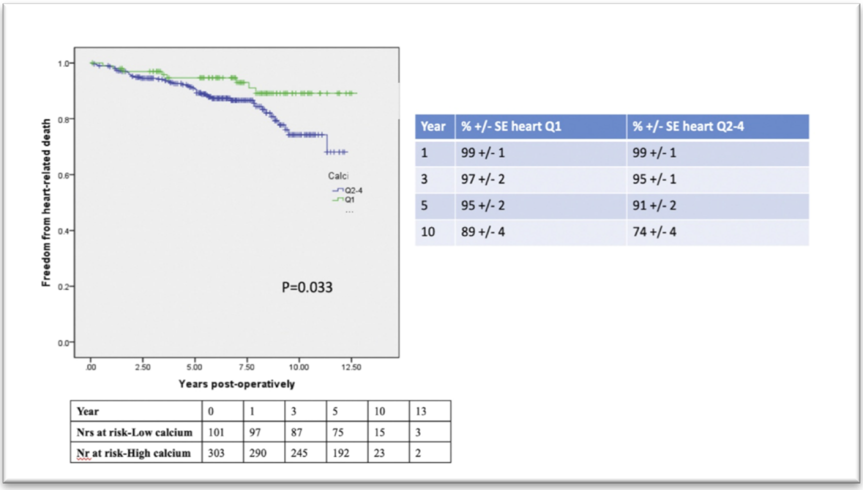


Year	% +/- SE overall survival Q1	% +/- SE overall survival Q2-4
1	98 +/- 1	97 +/- 1
3	91 +/- 3	83 +/- 3
5	79 +/- 4	71 +/- 3
10	44 +/- 6	34 +/- 4

Year	0	1	3	5	10	13
Nrs at risk-Low calcium	101	99	92	77	17	3
Nr at risk-High calcium	303	295	252	203	25	3

Figure 15: Overall survival in the first quartile of calcium score (Q1, green) versus remaining quartiles (Q2-Q4, blue). This figure was published on Annals of Vascular Surgery, Vol 68, Author Vaccarino et al, “Low ilio-femoral Calcium Score may predict higher survival after EVAR and FEVAR”, P 283-291, © 2020 Elsevier Inc.

Cardiac event-free survival was higher for patients in the first quartile compared with the higher quartiles (P = .033); Figure 16



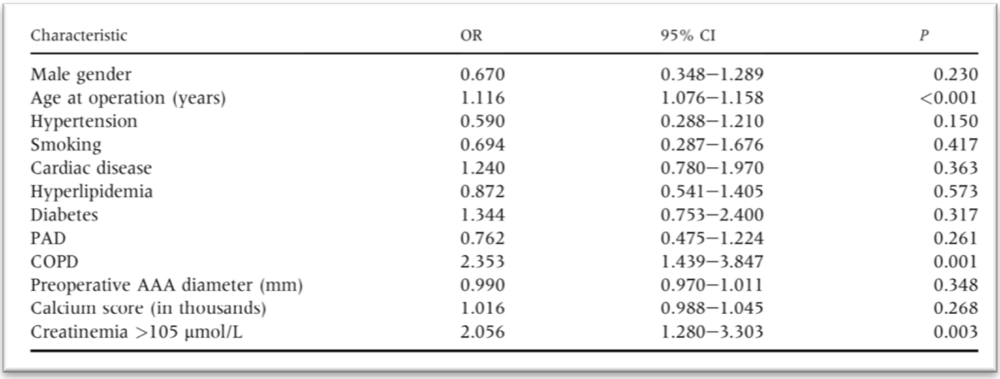
Year	% +/- SE heart Q1	% +/- SE heart Q2-4
1	99 +/- 1	99 +/- 1
3	97 +/- 2	95 +/- 1
5	95 +/- 2	91 +/- 2
10	89 +/- 4	74 +/- 4

Year	0	1	3	5	10	13
Nrs at risk-Low calcium	101	97	87	75	15	3
Nr at risk-High calcium	303	290	245	192	23	2

Figure 16: Overall survival in the first quartile of calcium score (Q1, green) versus remaining quartiles (Q2 – Q4, blue). This figure was published on Annals of Vascular Surgery, Vol 68, Author Vaccarino et al, “Low ilio-femoral Calcium Score may predict higher survival after EVAR and FEVAR”, P 283-291, © 2020 Elsevier Inc.

Calcium score was not associated with survival (OR 1.016 [0.988 - 1.045]; P = .268) nor cardiac event-free survival (OR 1.024 [.986 - 1.063]; P = 0.222) in univariate regression analysis (Tables 3 and 4, respectively).

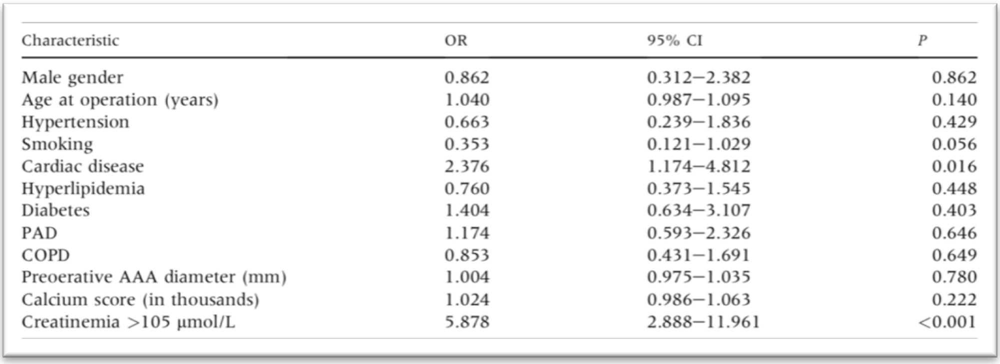
Table 3: OR based on univariate logistic regression, for all-cause mortality. This table was published on Annals of Vascular Surgery, Vol 68, Author Vaccarino et al, “Low ilio-femoral Calcium Score may predict higher survival after EVAR and FEVAR”, P 283-291, © 2020 Elsevier Inc.



Characteristic	OR	95% CI	*P*
Male gender	0.670	0.348−1.289	0.230
Age at operation (years)	1.116	1.076−1.158	<0.001
Hypertension	0.590	0.288−1.210	0.150
Smoking	0.694	0.287−1.676	0.417
Cardiac disease	1.240	0.780−1.970	0.363
Hyperlipidemia	0.872	0.541−1.405	0.573
Diabetes	1.344	0.753−2.400	0.317
PAD	0.762	0.475−1.224	0.261
COPD	2.353	1.439−3.847	0.001
Preoperative AAA diameter (mm)	0.990	0.970−1.011	0.348
Calcium score (in thousands)	1.016	0.988−1.045	0.268
Creatinemia >105 µmol/L	2.056	1.280−3.303	0.003

95% CI, 95% confidence interval, COPD, chronicc obstructive pulmonary disease.

Table 4: OR based on univariate logistic regression, for freedom from cardiac event. This table was published on Annals of Vascular Surgery, Vol 68, Author Vaccarino et al, “Low ilio-femoral Calcium Score may predict higher survival after EVAR and FEVAR”, P 283-291, © 2020 Elsevier Inc.



Characteristic	OR	95% CI	*P*
Male gender	0.862	0.312−2.382	0.862
Age at operation (years)	1.040	0.987−1.095	0.140
Hypertension	0.663	0.239−1.836	0.429
Smoking	0.353	0.121−1.029	0.056
Cardiac disease	2.376	1.174−4.812	0.016
Hyperlipidemia	0.760	0.373−1.545	0.448
Diabetes	1.404	0.634−3.107	0.403
PAD	1.174	0.593−2.326	0.646
COPD	0.853	0.431−1.691	0.649
Preoerative AAA diameter (mm)	1.004	0.975−1.035	0.780
Calcium score (in thousands)	1.024	0.986−1.063	0.222
Creatinemia >105 µmol/L	5.878	2.888−11.961	<0.001

95% CI, 95% confidence interval, COPD, chronicc obstructive pulmonary disease.

Preoperative cardiac disease (P = .016) and renal insufficiency (P < .001) were predictors for cardiac-related events.

Paper II

Five-hundred out of 500 patients who underwent infrarenal EVAR for non-ruptured AAA during the study period were included, Figure 17. There was not difference in survival between included and excluded patients, P = .529.

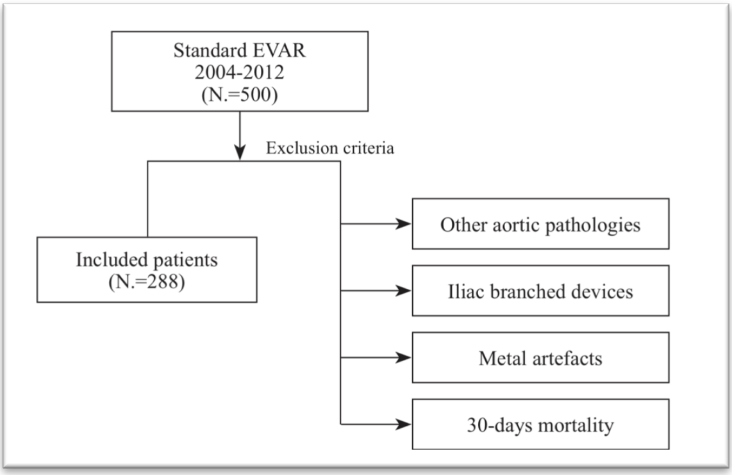
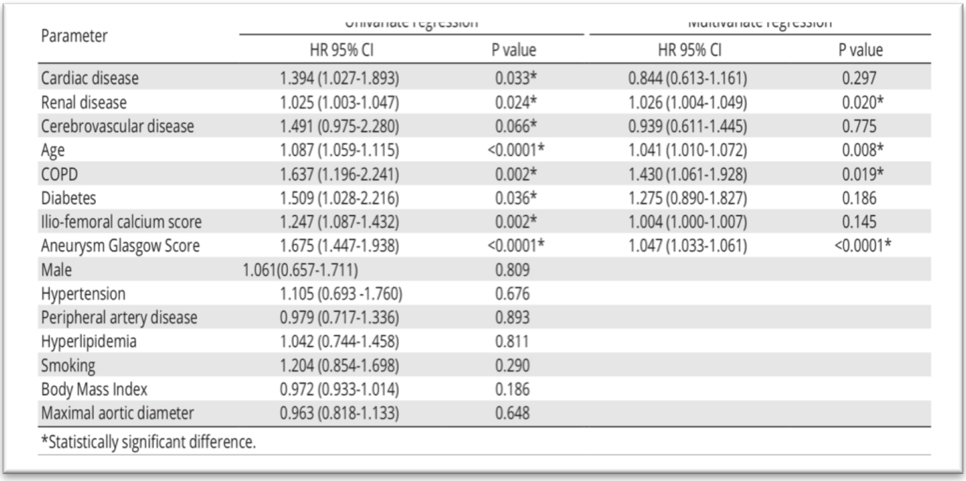


Figure 17 : Flow chart exclusion criteria: All the patients undergoing infrarenal EVAR for non-ruptured AAA between January 2004 and December were screened for inclusion. Patients treated for other aortic pathologies (pseudoaneurysm, aortic ulcerations, dissection), along with treatment for iliac aneurysm with branched devices, were excluded. Patients were also excluded if they did not have adequate preoperative imaging available for review (metal artefact due to hip prothesis or iliac stents). Patients were excluded if they did not survive more than 30 days postoperatively. This figure was published on International Angiology, 2022, August;41(4):285-91,"Ilio-femoral calcium score may assist Glasgow Aneurysm Score prediction of long-term survival of low-risk patients after infrarenal EVAR". DOI:10.23736/S0392-9590.22.048883-0 © 2022 Edizioni Minerva Medica

Patients were followed-up for a median of 7 (4 - 9) years after EVAR. One hundred-eighty-nine of the included patients (65.6%) died during follow-up. Technical success was achieved in 274 patients (95%). Estimated survival was 97±1%, 71±2% and 37±3% at 1, 5 and 10 years, respectively. Age, renal disease, chronic obstructive pulmonary disease, and GAS were independent risk predictors for long term survival. (Table 5)

Table 5: Univariate and multivariate Cox regression analysis for the whole population. Cox regression univariate analysis was performed for baseline comorbidities. Variables with P value <0.10 in the univariate analysis were included in the multivariate model. This table was published on International Angiology, 2022, August;41(4):285-91,“Ilio-femoral calcium score may assist Glasgow Aneurysm Score prediction of long-term survival of low-risk patients after infrarenal EVAR”. DOI:10.23736/S0392-9590.22.048883-0 © 2022 Edizioni Minerva Medica



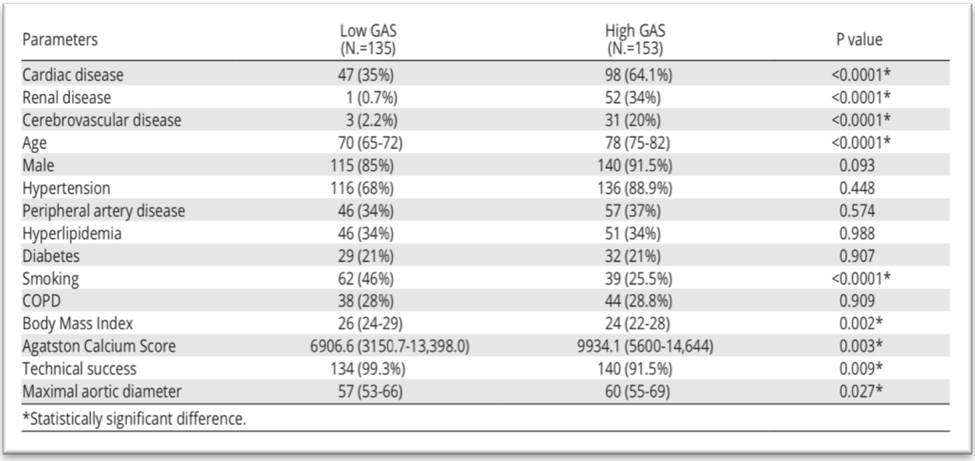
Parameter	Univariate regression		Multivariate regression	
	HR 95% CI	P value	HR 95% CI	P value
Cardiac disease	1.394 (1.027-1.893)	0.033*	0.844 (0.613-1.161)	0.297
Renal disease	1.025 (1.003-1.047)	0.024*	1.026 (1.004-1.049)	0.020*
Cerebrovascular disease	1.491 (0.975-2.280)	0.066*	0.939 (0.611-1.445)	0.775
Age	1.087 (1.059-1.115)	<0.0001*	1.041 (1.010-1.072)	0.008*
COPD	1.637 (1.196-2.241)	0.002*	1.430 (1.061-1.928)	0.019*
Diabetes	1.509 (1.028-2.216)	0.036*	1.275 (0.890-1.827)	0.186
Ilio-femoral calcium score	1.247 (1.087-1.432)	0.002*	1.004 (1.000-1.007)	0.145
Aneurysm Glasgow Score	1.675 (1.447-1.938)	<0.0001*	1.047 (1.033-1.061)	<0.0001*
Male	1.061(0.657-1.711)	0.809		
Hypertension	1.105 (0.693 -1.760)	0.676		
Peripheral artery disease	0.979 (0.717-1.336)	0.893		
Hyperlipidemia	1.042 (0.744-1.458)	0.811		
Smoking	1.204 (0.854-1.698)	0.290		
Body Mass Index	0.972 (0.933-1.014)	0.186		
Maximal aortic diameter	0.963 (0.818-1.133)	0.648		

*Statistically significant difference.

Glasgow Aneurysm Score

GAS median was 80 (73 - 88). The population was divided in two groups based on the optimal cut-off of 80 found with ROC curve (area under the curve 0.732, 62% sensitivity and 24% specificity, P <.0001). One hundred thirty-five patients (46.9 %) had low GAS, and 153 (53.1 %) had high GAS. Patients with high GAS were older and had higher prevalence of cardiac, renal and cerebrovascular disease, as expected from the calculation of the GAS itself. However, patients with high GAS were less often smokers (P < .0001) and had lower body mass index (P = .002). (Table 6)

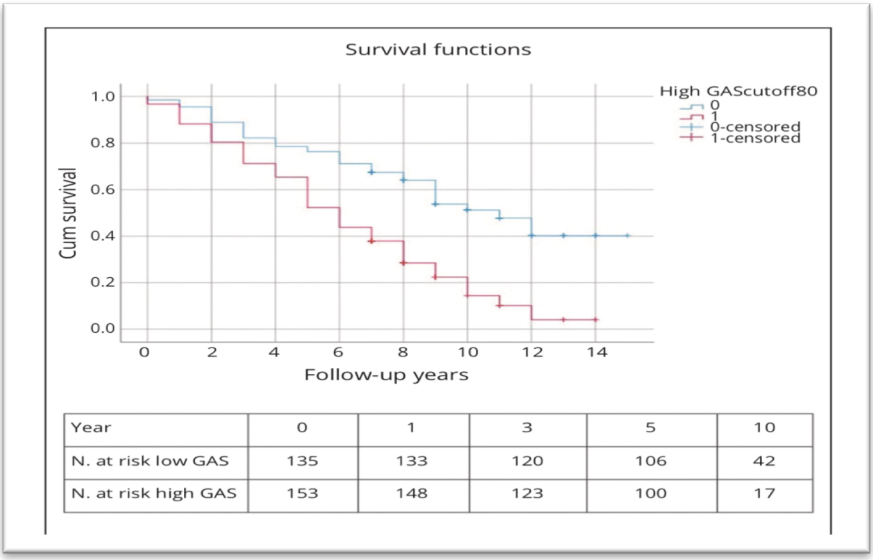
Table 6: Patients characteristics divided by low GAS and High GAS. This table was published on International Angiology, 2022, August;41(4):285-91,“Ilio-femoral calcium score may assist Glasgow Aneurysm Score prediction of long-term survival of low-risk patients after infrarenal EVAR”. DOI:10.23736/S0392-9590.22.048883-0 © 2022 Edizioni Minerva Medica



Parameters	Low GAS (N.=135)	High GAS (N.=153)	P value
Cardiac disease	47 (35%)	98 (64.1%)	<0.0001*
Renal disease	1 (0.7%)	52 (34%)	<0.0001*
Cerebrovascular disease	3 (2.2%)	31 (20%)	<0.0001*
Age	70 (65-72)	78 (75-82)	<0.0001*
Male	115 (85%)	140 (91.5%)	0.093
Hypertension	116 (68%)	136 (88.9%)	0.448
Peripheral artery disease	46 (34%)	57 (37%)	0.574
Hyperlipidemia	46 (34%)	51 (34%)	0.988
Diabetes	29 (21%)	32 (21%)	0.907
Smoking	62 (46%)	39 (25.5%)	<0.0001*
COPD	38 (28%)	44 (28.8%)	0.909
Body Mass Index	26 (24-29)	24 (22-28)	0.002*
Agatston Calcium Score	6906.6 (3150.7-13,398.0)	9934.1 (5600-14,644)	0.003*
Technical success	134 (99.3%)	140 (91.5%)	0.009*
Maximal aortic diameter	57 (53-66)	60 (55-69)	0.027*

*Statistically significant difference.

Patients with high GAS had lower survival (23 ± 3 %) compared to the ones with low GAS (53 ± 4 %) at 10 years postoperatively, P ≤ .0001). Figure 18.

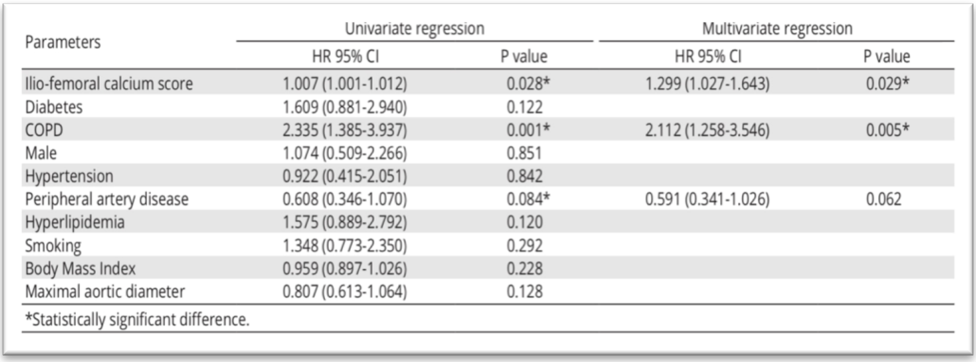


Year	0	1	3	5	10
N. at risk low GAS	135	133	120	106	42
N. at risk high GAS	153	148	123	100	17

Figure 18: Blue line: low GAS; red line: High GAS (P < 0.0001). This figure was published on International Angiology, 2022, August;41(4):285-91,“Ilio-femoral calcium score may assist Glasgow Aneurysm Score prediction of long-term survival of low-risk patients after infrarenal EVAR”. DOI:10.23736/S0392-9590.22.048883-0 © 2022 Edizioni Minerva Medica

GAS was associated with long-term mortality in a univariate regression (HR = 1.675, 95% CI 1.447- 1.938, P ≤ .0001). This retained significance also in a multivariate Cox regression model including the pre-operative comorbidities not used for GAS calculation (HR = 1.047, 95% CI 1.033-1.061, P < .0001), (Table V). In the population of low GAS, ilio-femoral calcium score and COPD were independent risk predictors for long term survival (table 7). While in the population of high GAS, peripheral artery disease and maximal aneurysm diameter were significantly associated with survival in univariate analysis. Significance did not retain in multivariate analysis (Table 8).

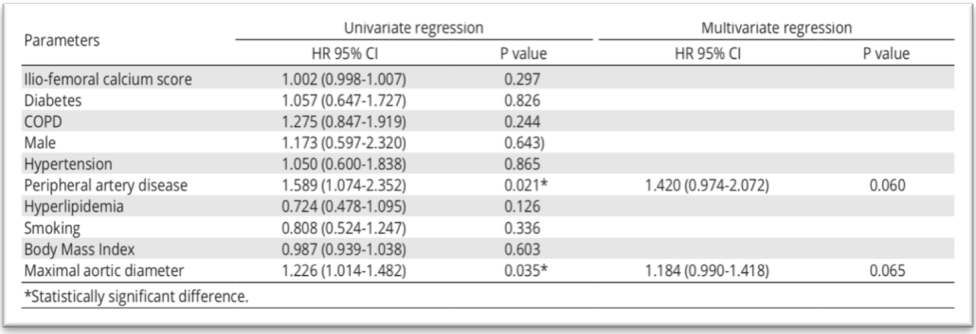
Table 7: Univariate and multivariate Cox regressioon analysis for population with low GAS. This table was published on International Angiology, 2022, August;41(4):285-91, "Ilio-femoral calcium score may assist Glasgow Aneurysm Score prediction of long-term survival of low-risk patients after infrarenal EVAR". DOI:10.23736/S0392-9590.22.048883-0 © 2022 Edizioni Minerva Medica



Parameters	Univariate regression		Multivariate regression	
	HR 95% CI	P value	HR 95% CI	P value
Ilio-femoral calcium score	1.007 (1.001-1.012)	0.028*	1.299 (1.027-1.643)	0.029*
Diabetes	1.609 (0.881-2.940)	0.122		
COPD	2.335 (1.385-3.937)	0.001*	2.112 (1.258-3.546)	0.005*
Male	1.074 (0.509-2.266)	0.851		
Hypertension	0.922 (0.415-2.051)	0.842		
Peripheral artery disease	0.608 (0.346-1.070)	0.084*	0.591 (0.341-1.026)	0.062
Hyperlipidemia	1.575 (0.889-2.792)	0.120		
Smoking	1.348 (0.773-2.350)	0.292		
Body Mass Index	0.959 (0.897-1.026)	0.228		
Maximal aortic diameter	0.807 (0.613-1.064)	0.128		

*Statistically significant difference.

Table 8: Univariate and multivariate Cox regressioon analysis for population with high GAS. This figure was published on International Angiology, 2022, August;41(4):285-91,"Ilio-femoral calcium score may assist Glasgow Aneurysm Score prediction of long-term survival of low-risk patients after infrarenal EVAR". DOI:10.23736/S0392-9590.22.048883-0 © 2022 Edizioni Minerva Medica



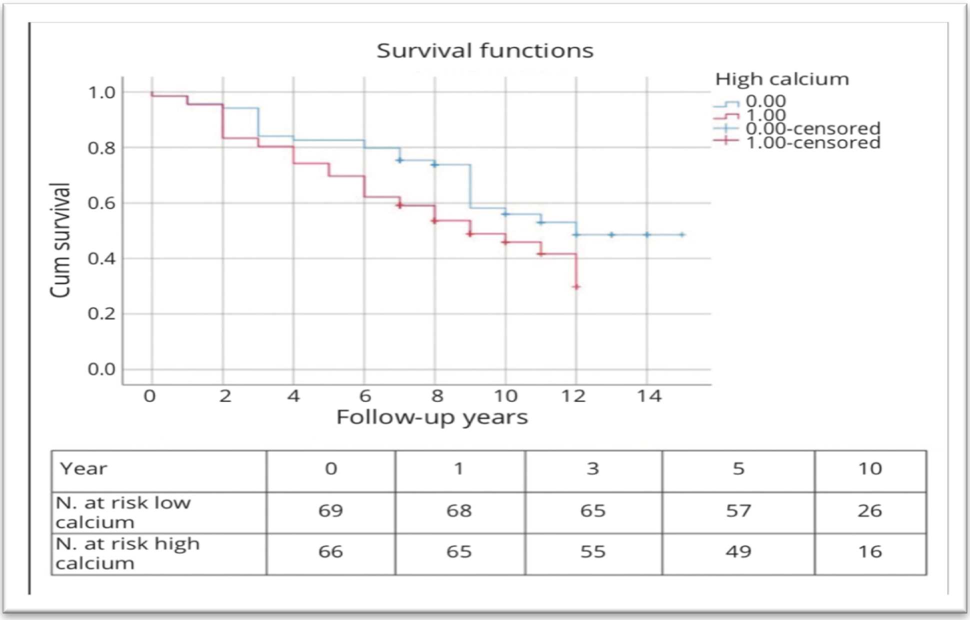
Parameters	Univariate regression		Multivariate regression	
	HR 95% CI	P value	HR 95% CI	P value
Ilio-femoral calcium score	1.002 (0.998-1.007)	0.297		
Diabetes	1.057 (0.647-1.727)	0.826		
COPD	1.275 (0.847-1.919)	0.244		
Male	1.173 (0.597-2.320)	0.643)		
Hypertension	1.050 (0.600-1.838)	0.865		
Peripheral artery disease	1.589 (1.074-2.352)	0.021*	1.420 (0.974-2.072)	0.060
Hyperlipidemia	0.724 (0.478-1.095)	0.126		
Smoking	0.808 (0.524-1.247)	0.336		
Body Mass Index	0.987 (0.939-1.038)	0.603		
Maximal aortic diameter	1.226 (1.014-1.482)	0.035*	1.184 (0.990-1.418)	0.065

*Statistically significant difference.

Ilio-femoral calcium score and GAS

Median ilio-femoral calcium score was 8613.9 (4519.45 - 14264.25). Ilio-femoral calcium score was associated with increased mortality in a univariate regression (P = .002). Significance was not retained in a multivariate Cox regression which included the preoperative comorbidities (P = .145). In the group of low GAS, the ilio-femoral calcium score was lower compared to the group of high GAS (P = .003). There was a positive correlation between GAS and ilio-femoral calcium score (r = .123; P = .037). Ilio-femoral calcium score was significantly associated with mortality in the group with low GAS (HR = 1.007, 95% CI 1.001 - 1.012, P = .028), but not in the group with high GAS (HR = 1.002, 95% CI .998 - 1.007, P = .297). The significance retained in a multivariate Cox regression analysis (HR = 1.299, 95% CI 1.027 - 1.643, P = .029) (Table 7).

Dividing the group of low GAS, into high and low ilio-femoral calcium score according to the median, patients with high calcium had lower survival (74 ± 5%) compared to the ones with low calcium (82 ±. 4%) at 5 years postoperatively, P = .047. (Figure 19).



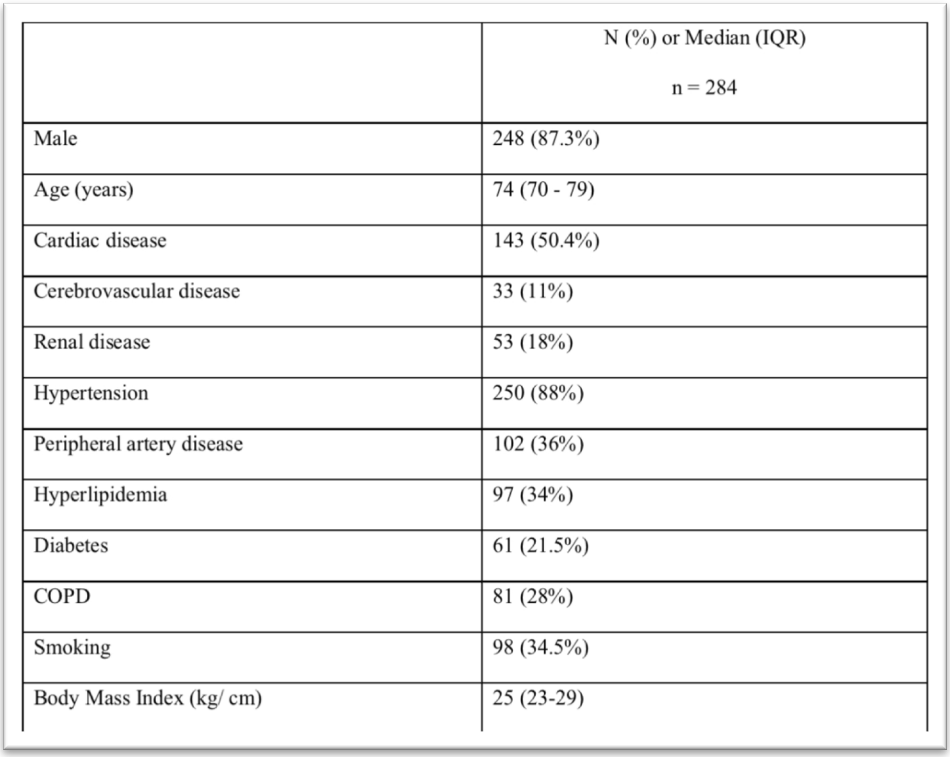
Year	0	1	3	5	10
N. at risk low calcium	69	68	65	57	26
N. at risk high calcium	66	65	55	49	16

Figure 19: Blu line: patients with low calcium in the low GAS group; red line: patients with high calcium in the low GAS group (P = .047). This figure was published on International Angiology, 2022, August;41(4):285-91,“Ilio-femoral calcium score may assist Glasgow Aneurysm Score prediction of long-term survival of low-risk patients after infrarenal EVAR”. DOI:10.23736/S0392-9590.22.048883-0 © 2022 Edizioni Minerva Medica.

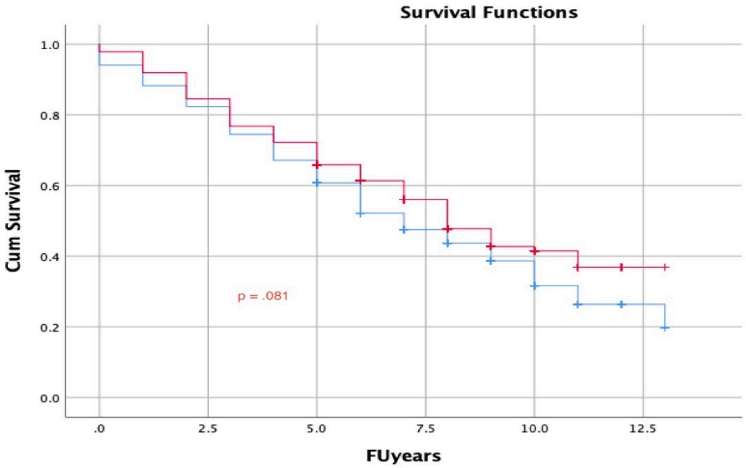
Paper III

Two hundred eighty-four patients out of 500 patients were treated with infrarenal EVAR during the study period could be included in the study. Table 9 shows detailed patient characteristics. There was no difference in the survival between included and excluded patients (P = .081) (Figure 20). Technical success was achieved in 271 of the included patients (95.4 %). Patients were followed-up for a median of 8 (4 - 11) years after EVAR.

Table 9: Patients characteristics.



	N (%) or Median (IQR) n = 284
Male	248 (87.3%)
Age (years)	74 (70 - 79)
Cardiac disease	143 (50.4%)
Cerebrovascular disease	33 (11%)
Renal disease	53 (18%)
Hypertension	250 (88%)
Peripheral artery disease	102 (36%)
Hyperlipidemia	97 (34%)
Diabetes	61 (21.5%)
COPD	81 (28%)
Smoking	98 (34.5%)
Body Mass Index (kg/ cm)	25 (23-29)



Year	1	5	10
Nrs at risk included	278	192	18
Nrs at risk excluded	192	131	21

Figure 20: Kaplan-Meier Survival plot for patients included (red color) and excluded (blue color) in the study (P = .081).

Two hundred twenty-seven (79.9 %) patients died during the study period. Estimated survival was 97 ± 1 %, 71 ± 2 % and 38 ± 3 % at 1, 5 and 10 years, respectively. Age (HR 1.08 (1.05 – 1.1), P = < .001, cardiovascular (HR 1.32 (1.01 – 1.72), P = .041, cerebrovascular (HR 1.75 (1.15 – 2.68), P = .009, renal diseases (HR 1.04 (1.03 – 1.05), P = .002 and COPD (HR 1.95 (1.44 – 2.65), P = < .001 were significantly associated with mortality in a multivariate COX regression.

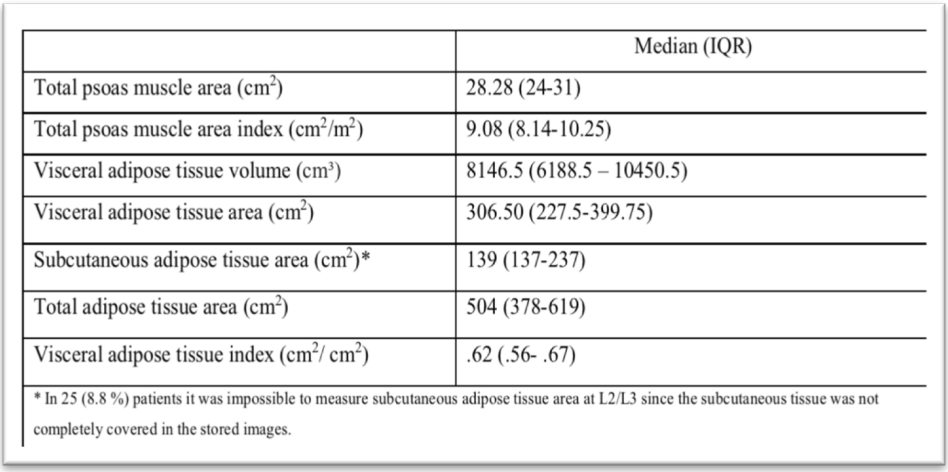
Total Psoas Muscle Area and Total Psoas Muscle Area Index

TPA was 28.28 (24 - 31) cm^2 and TPA index was 9.08 (8.14 - 10.25) cm^2/m^2(table X). TPA was associated with mortality in a univariate (HR = .862 (.748 – .993), P = .040), but not in a multivariate regression model with pre-operative comorbidities (HR = 1.032 (.841 – 1.265, P = .764). No significant association was found between mortality and TPA index in a univariate regression (HR = .886 (.766 - 1.025), P = .103), (table XI).

Visceral Adipose Tissue

VAT volume was 8146.5 (6188.5 – 10450.5) cm^{3} and VAT area was 306.50 (227.5 - 399.75) cm^{2}. SAT area was 193 (137-237) cm^{2}^{2}, TAT area was 504 (378 - 619) cm^{2} and VAT index was .62 (.56-.67). Measurement of SAT area was not possible in 25 (8.8%) patients because the subcutaneous tissue was not completely included in the CT image. The adipose tissue measurements are summarized on table 10.

Table 10: CT-based measuraments

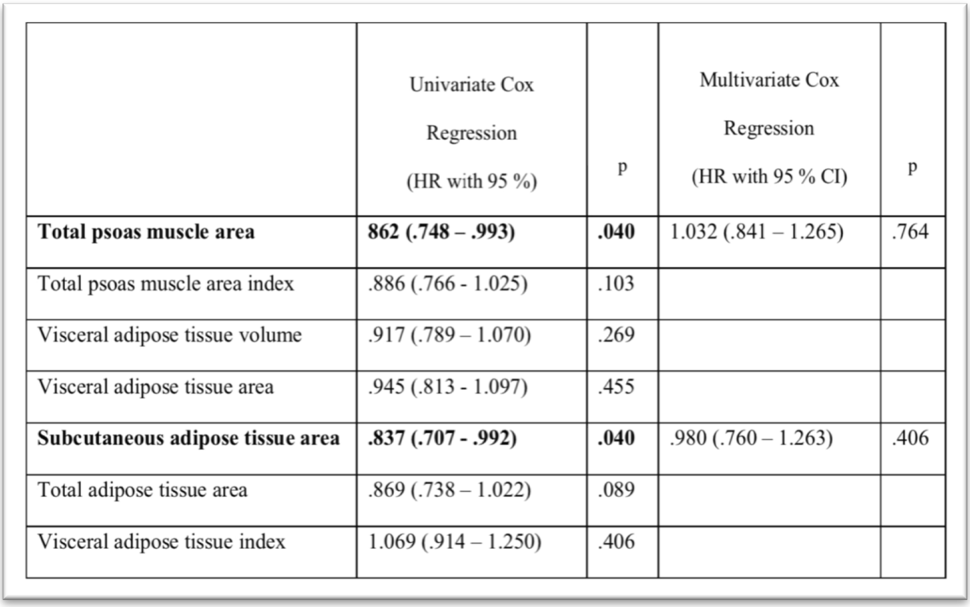


	Median (IQR)
Total psoas muscle area (cm^{2})	28.28 (24-31)
Total psoas muscle area index (cm^{2}/m^{2})	9.08 (8.14-10.25)
Visceral adipose tissue volume (cm^{3})	8146.5 (6188.5 – 10450.5)
Visceral adipose tissue area (cm^{2})	306.50 (227.5-399.75)
Subcutaneous adipose tissue area (cm^{2})*	139 (137-237)
Total adipose tissue area (cm^{2})	504 (378-619)
Visceral adipose tissue index (cm^{2}/ cm^{2})	.62 (.56- .67)

* In 25 (8.8 %) patients it was impossible to measure subcutaneous adipose tissue area at L2/L3 since the subcutaneous tissue was not completely covered in the stored images.

Univariate regressions did not show any association between any of the adiposity measurements and mortality with the exception of subcutaneous area (HR = .837 (.707 - .992), P = .040; however, in a multivariate COX regression, the SAT area loss its significance when the pre-operative comorbidities were included (HR = .980 (.760 – 1.263), P = .875), (table 11).

Table 11: Uni- and multivariate COX regression for CT-based measurements

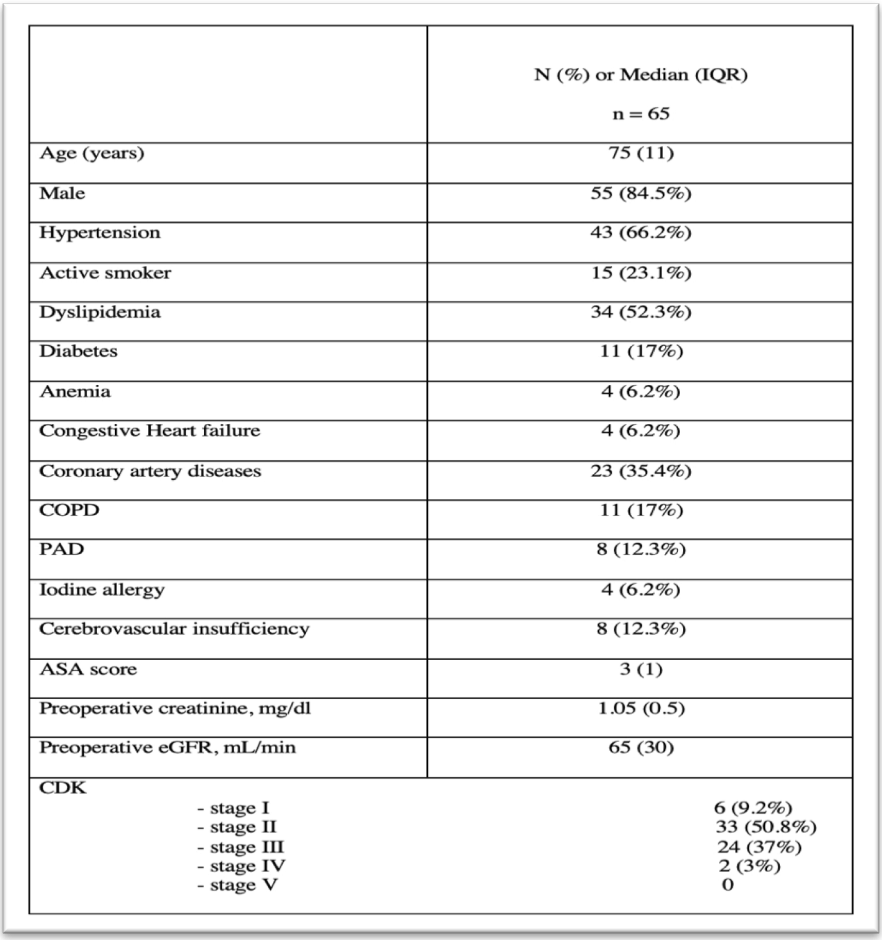


	Univariate Cox Regression (HR with 95 %)	p	Multivariate Cox Regression (HR with 95 % CI)	p
Total psoas muscle area	**862 (.748 – .993)**	**.040**	1.032 (.841 – 1.265)	.764
Total psoas muscle area index	.886 (.766 - 1.025)	.103		
Visceral adipose tissue volume	.917 (.789 – 1.070)	.269		
Visceral adipose tissue area	.945 (.813 - 1.097)	.455		
Subcutaneous adipose tissue area	**.837 (.707 - .992)**	**.040**	.980 (.760 – 1.263)	.406
Total adipose tissue area	.869 (.738 – 1.022)	.089		
Visceral adipose tissue index	1.069 (.914 – 1.250)	.406		

Paper IV

Enrolling period went from 2019 and 2021. Sixty-five patients undergoing CO_2-EVAR were recruited by five different European vascular centers. Twenty-five patients (38.5%) were recruited by the vascular centre of Malmö, 22 (33.8%) by Bologna, 14 (21.5%) by the University hospital of Münster, 2 (3.1%) by Athens and 2 (3.1%) by St. Franziskus Hospital Münster. Patients clinical and anatomical characteristics are reported in table 12 and 13.

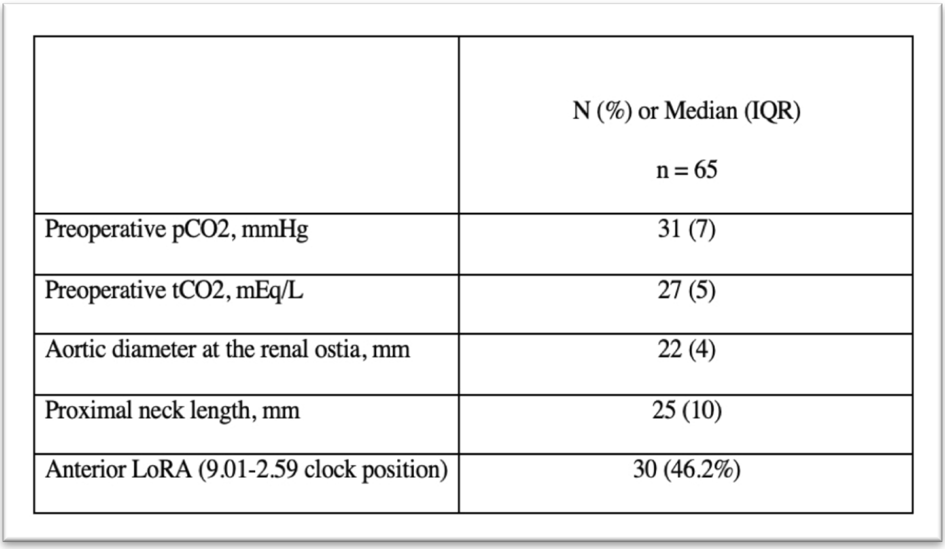
Table 12: Patients clinical characteristics



	N (%) or Median (IQR) n = 65
Age (years)	75 (11)
Male	55 (84.5%)
Hypertension	43 (66.2%)
Active smoker	15 (23.1%)
Dyslipidemia	34 (52.3%)
Diabetes	11 (17%)
Anemia	4 (6.2%)
Congestive Heart failure	4 (6.2%)
Coronary artery diseases	23 (35.4%)
COPD	11 (17%)
PAD	8 (12.3%)
Iodine allergy	4 (6.2%)
Cerebrovascular insufficiency	8 (12.3%)
ASA score	3 (1)
Preoperative creatinine, mg/dl	1.05 (0.5)
Preoperative eGFR, mL/min	65 (30)
CDK	
- stage I	6 (9.2%)
- stage II	33 (50.8%)
- stage III	24 (37%)
- stage IV	2 (3%)
- stage V	0

COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease ;ASA, American Soociety of Anesthesiologist; CKD, chronic kidney disease; eGFR, estimated glomular filtration rate.

Table 13: Patients preoperative characteristics



	N (%) or Median (IQR) n = 65
Preoperative pCO2, mmHg	31 (7)
Preoperative tCO2, mEq/L	27 (5)
Aortic diameter at the renal ostia, mm	22 (4)
Proximal neck length, mm	25 (10)
Anterior LoRA (9.01-2.59 clock position)	30 (46.2%)

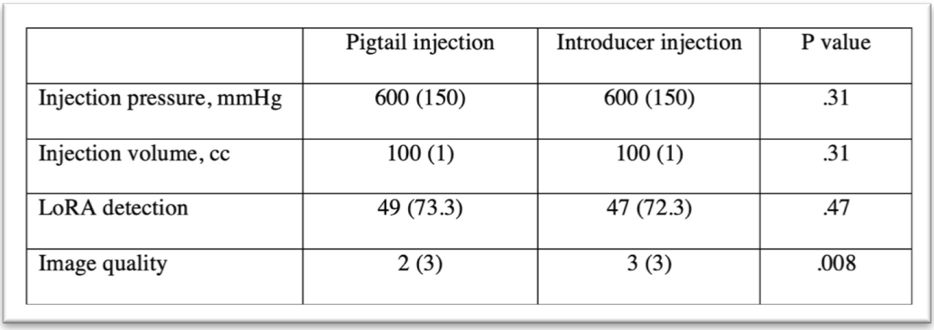
LoRA, lowest renal artery; pCO2, pressure of carbon dioxide; tCO2, total carbon dioxide.

Procedural steps analysis

Step 1*- first preimplant CO_2-injection:*

Significantly better image quality when the angiography was performed from the femoral introducer rather than from the pigtail, P = .008. Table 14.

Table 14: Step 1: comparison between pigtail and introducer injections

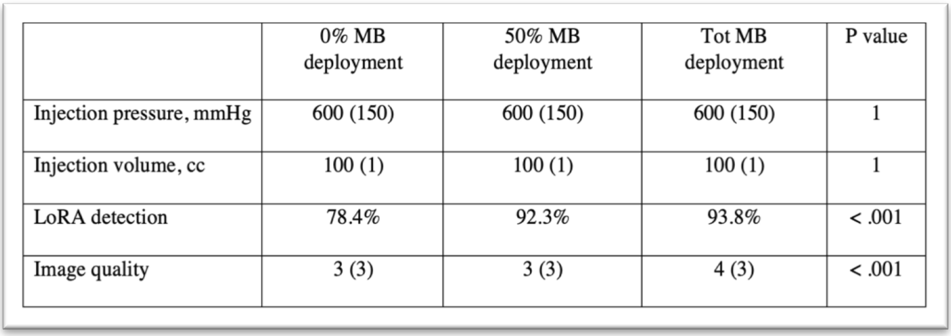


	Pigtail injection	Introducer injection	P value
Injection pressure, mmHg	600 (150)	600 (150)	.31
Injection volume, cc	100 (1)	100 (1)	.31
LoRA detection	49 (73.3)	47 (72.3)	.47
Image quality	2 (3)	3 (3)	.008

LoRA, lowest renal artery

Step 2- *CO_2-angiographies at different main body deployment phases:*
Image quality (P = .001) and LoRA detection (P = .001) were significantly higher at 50% and 100% of proximal main body deployment compared with 0%.
Table 15.

Table 15: Step 2: comparison between injections at 0%, 50%, and 100% of proximal main body deployment



	0% MB deployment	50% MB deployment	Tot MB deployment	P value
Injection pressure, mmHg	600 (150)	600 (150)	600 (150)	1
Injection volume, cc	100 (1)	100 (1)	100 (1)	1
LoRA detection	78.4%	92.3%	93.8%	< .001
Image quality	3 (3)	3 (3)	4 (3)	< .001

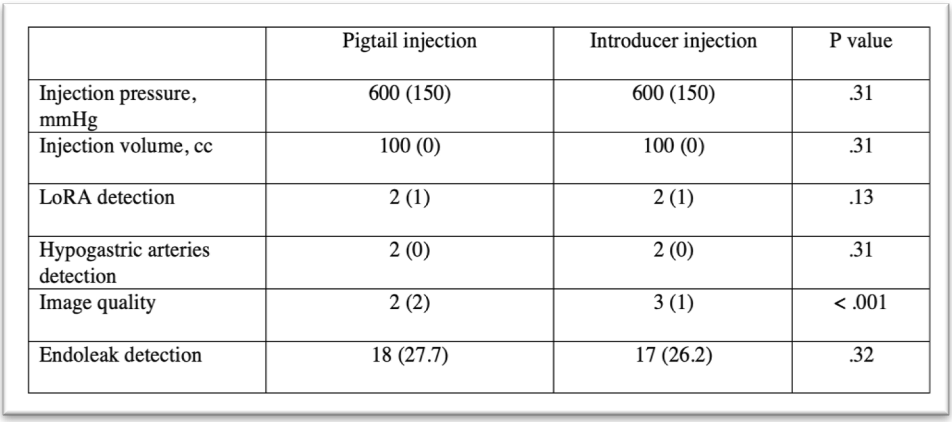
LoRA, lowest renal artery; MB, main body

Furthermore, the LoRA visualization was better at 50% and at 100% of main body deployment compared with the first angiography from pigtail in step 1. Moreover, the quality of the image was higher at 50% and at 100% of proximal main body deployment compared with the first angiography from pigtail in step 1.

Step *3- CO_2-injection performed from the contralateral femoral introducer sheath:* The contralateral hypogastric artery was correctly visualized in 61 (93.8%) of 65 cases.

Step 4*- CO_2-final angiogram performed from pigtail and from introducer sheath*: The image quality was significantly better from the femoral introducer compared with the injection from pigtail, P = .001. Table 16.

Table 16: Step 4 (final angiogram): comparison between pigtail and introducer injections

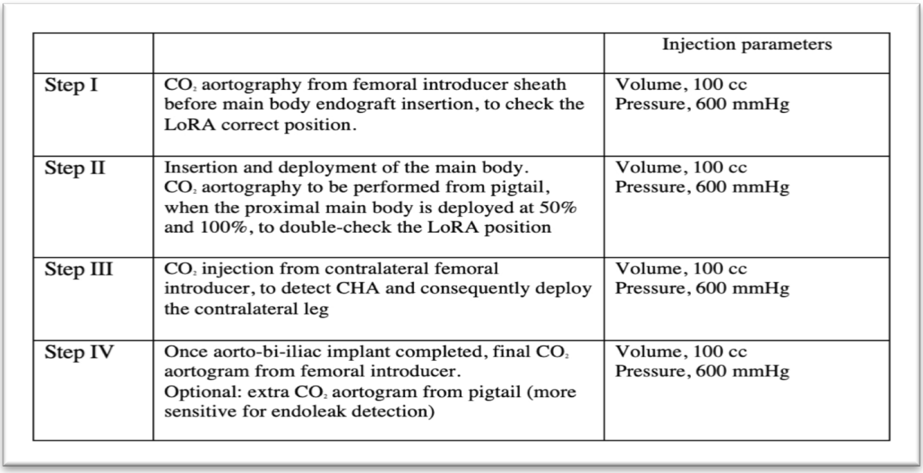


	Pigtail injection	Introducer injection	P value
Injection pressure, mmHg	600 (150)	600 (150)	.31
Injection volume, cc	100 (0)	100 (0)	.31
LoRA detection	2 (1)	2 (1)	.13
Hypogastric arteries detection	2 (0)	2 (0)	.31
Image quality	2 (2)	3 (1)	< .001
Endoleak detection	18 (27.7)	17 (26.2)	.32

All types of endoleaks, and in particular, type II endoleaks, were detected significantly more often with completion CO_2 injected from pigtail compared with the pre-discharge imaging DUS/CEUS/CT scan. The intraoperative (7.7%) and post-operative (12.5%) adverse events (pain, vomiting, diarrhea) were all transient and clinically mild.

The standard CO_2-EVAR procedure protocol with automated injector could be summarized in table 17.

Table 17: Standard protocol for CO_2-angiography for endovascular aortic repair



		Injection parameters
Step I	CO_2 aortography from femoral introducer sheath before main body endograft insertion, to check the LoRA correct position.	Volume, 100 cc Pressure, 600 mmHg
Step II	Insertion and deployment of the main body. CO_2 aortography to be performed from pigtail, when the proximal main body is deployed at 50% and 100%, to double-check the LoRA position	Volume, 100 cc Pressure, 600 mmHg
Step III	CO_2 injection from contralateral femoral introducer, to detect CHA and consequently deploy the contralateral leg	Volume, 100 cc Pressure, 600 mmHg
Step IV	Once aorto-bi-iliac implant completed, final CO_2 aortogram from femoral introducer. Optional: extra CO_2 aortogram from pigtail (more sensitive for endoleak detection)	Volume, 100 cc Pressure, 600 mmHg

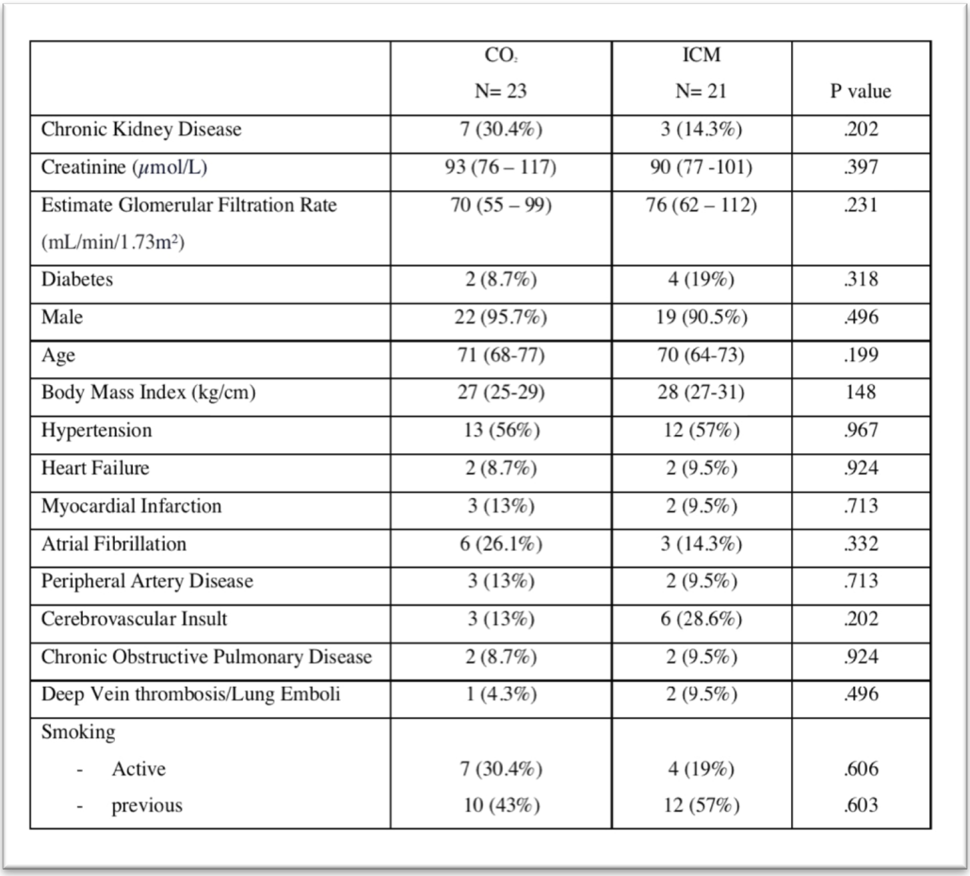
CHA, Contralateral hypogastric artery; LoRA, lowest renal artery.

General anesthesia is recommended to reduce intraoperative gastrointestinal side effects. All CO_2 injections should be performed in DSA modality with patient in apnea

Paper V

Forty-four patients were included in the study. Twenty-three patients in the CO_2 group and 21 in the ICM group. Patients characteristics are detailed in table 18.

Table 18: Patients characteristics divided by groups



	CO_2 N= 23	ICM N= 21	P value
Chronic Kidney Disease	7 (30.4%)	3 (14.3%)	.202
Creatinine (μmol/L)	93 (76 – 117)	90 (77 -101)	.397
Estimate Glomerular Filtration Rate (mL/min/1.73m²)	70 (55 – 99)	76 (62 – 112)	.231
Diabetes	2 (8.7%)	4 (19%)	.318
Male	22 (95.7%)	19 (90.5%)	.496
Age	71 (68-77)	70 (64-73)	.199
Body Mass Index (kg/cm)	27 (25-29)	28 (27-31)	148
Hypertension	13 (56%)	12 (57%)	.967
Heart Failure	2 (8.7%)	2 (9.5%)	.924
Myocardial Infarction	3 (13%)	2 (9.5%)	.713
Atrial Fibrillation	6 (26.1%)	3 (14.3%)	.332
Peripheral Artery Disease	3 (13%)	2 (9.5%)	.713
Cerebrovascular Insult	3 (13%)	6 (28.6%)	.202
Chronic Obstructive Pulmonary Disease	2 (8.7%)	2 (9.5%)	.924
Deep Vein thrombosis/Lung Emboli	1 (4.3%)	2 (9.5%)	.496
Smoking			
- Active	7 (30.4%)	4 (19%)	.606
- previous	10 (43%)	12 (57%)	.603

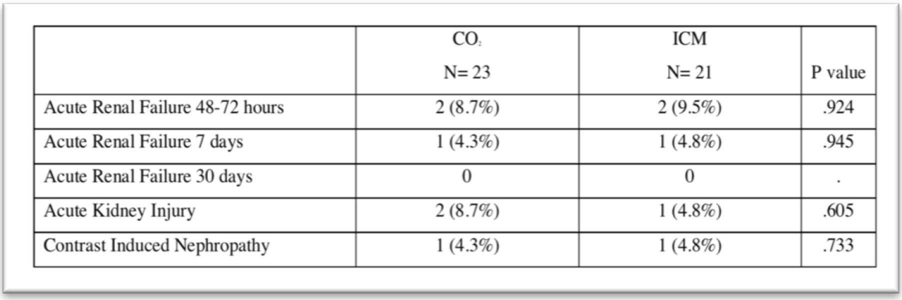
Less ICM volume was used intraoperatively in the CO_2 compared to the ICM groups (55 (IQR 41 – 78) ml vs 113 (IQR 54 – 150) ml, p = .012). This led, consequently, to a lower exposure to iodine (8.2 (IQR 7.1-10.9) g vs 15.8 (IQR 7.6-21) g, p = .015 respectively). There were no differences in technical success, clinical success, procedure time, fluoroscopy time and DAP in the two groups (table 19). There were no adverse events that could be related to the intraoperative use of CO_2.

Table 19: Intraoperative characteristics divided by groups

	CO_2 N = 23	ICM N = 21	P value
Aortic diameter (mm)	52 (42 – 59)	56 (41 – 60)	.496
Right common iliac diameter (mm)	26 (21 – 35)	30 (26 – 40)	.177
Left common iliac diameter (mm)	22 (16 – 24)	22 (19 – 27)	.315
Unilateral Iliac Branched Device	14 (60%)	14 (66%)	.444
Bilateral Iliac Branched Device	9 (40%)	7 (34%)	.444
Iodine Contrast Media Volume (ml)	**55 (41–78)**	**113 (54-150)**	**.012**
Iodine Exposure (grams)	**8.2 (7.1-10.9)**	**15.8 (7.6-21)**	**.015**
Technical Success	22 (95.6%)	21 (100%)	.334
Dose Area Product (Gy.cm²)	71.43 (33.47-144.63)	73.70 (26.02 – 180.16)	.787
Procedure Time (minutes)	169 (131 – 242)	188 (138 -214)	.747
Fluoroscopy Time (minutes)	53 (30-69)	53 (28-70)	.934
Polar renal artery embolization	3 (13%)	1 (4.8%)	.340

There was no difference renal function assessment between the groups, despite the higher number of accessory renal arteries embolized in the CO_2 group (table 20).

Table 20: Postoperative renal function



	CO_2 N= 23	ICM N= 21	P value
Acute Renal Failure 48-72 hours	2 (8.7%)	2 (9.5%)	.924
Acute Renal Failure 7 days	1 (4.3%)	1 (4.8%)	.945
Acute Renal Failure 30 days	0	0	.
Acute Kidney Injury	2 (8.7%)	1 (4.8%)	.605
Contrast Induced Nephropathy	1 (4.3%)	1 (4.8%)	.733

Patients were followed-up for a median of 7 (4 - 7) years after IBD implantation. Fifteen (34.1 %) patients died during the study period, 9 (39 %) patients died in the cohort group and 6 (28.6 %) patients died in the control group. No difference in survival between the cohort and the control group (p = .206).

Discussion

This thesis aimed to explore different modalities of preoperative risk assessment in order to better predict survival for patients treated for aortic diseases supporting surgeons in the clinical decision-making when offering endovascular aortic repair. Furthermore, this thesis also explored an intraoperative technique to protect patients from the procedure-related risks of renal function impairment derived from the exposure to ICM. Specifically, we studied the use of CO_2 as contrast agent to decrease ICM exposure during EVAR and IBD implantation.

CT-based and clinical-based risk-assessment tools

In the first three studies I focused on risk assessment and patients' selection exploring how novel CT-based risk-assessment tools, measured on preoperative CTA, can predict postoperative overall survival and cardiac-related mortality after EVAR.

Patients with AAA have high risk of developing cardiovascular events (HR 2.9) and high risk of cardiovascular death (HR 2.2). (131) EVAR impacted significantly on the AAA repair outcomes, since it can be performed at a remarkably low cardiovascular risk, in local anaesthesia and with minimal demand for critical care. However, late survival following EVAR remains challenging and influenced by many factors. (42, 47, 132)

The intent of studies I and II was to explore the impact of ilio-femoral calcifications on cardiac-related and overall survival after endovascular treatment of AAA.
Appropriate evaluation of ilio-femoral calcifications and access site selection is crucial when planning endovascular procedures in order to shorten procedure time and decrease access site complications such as hematoma, infection, lymphoceles and nerve injury. (34-36) Given the well-known association between femoral atherosclerosis, CAC and poor outcomes after EVAR (133), my initial hypothesis was that ilio-femoral calcification assessment might potentially play a role in preoperative evaluation, not only to quantify access calcifications to avoid complications, but even in risk stratification of patients with aortic diseases. Moreover, studies show an association between calcification of the thoracic and abdominal aorta with impaired survival in patients with aortic diseases undergoing surgery. (134)
The first study showed an association, albeit modest, between low ilio-femoral calcium score and both overall survival and cardiac-free survival. The association

between low-ilio-femoral calcium score and survival did not retain when calcium score was put in a model together with preoperative comorbidities. (135) This was a non-surprising result since, in this study, ilio-femoral calcifications were measured on already high-risk population with several simultaneous comorbidities and risk factors that may have been confounders. Perhaps, the results might suggest that rather than the presence of calcifications, their absence may be the predictive prognostic factor in this population.

Given the abovementioned results, I further investigated the combination of the predicting effect of ilio-femoral calcifications to Glasgow Aneurysm Score, a well-established clinical based risk score. The second study showed a significant association between GAS and survival. (129) As above mentioned, late survival following EVAR is influenced by many factors, mainly age, cardiovascular, cerebrovascular and renal diseases. (42, 47, 132) GAS is a clinical prognostic tool calculated by a scoring system based on the presence of those comorbidities that have been widely independently associated with poor outcome after EVAR. It is therefore not surprising that the concomitance of these comorbidities has a negative prognostic significance on long-term survival. In the study, patients with high values of GAS had less than half lower post-operative survival when compared to patients with low values of GAS. Moreover, this association was strengthened in low-risk patients when combining GAS with ilio-femoral calcium score. Patients with high ilio-femoral calcium score had significantly lower survival compared with the ones with low values. These results enhance the first study hypothesis that ilio-femoral calcifications might have an association with survival and is perhaps an indicator of the presence of the atherosclerotic burden which has not yet become clinically evident.

The aim of study III was to study two more CT-based tools, TPA and VAT, and their impact on long-term survival after EVAR.

Frailty, defined as a multisystem general decay, is undoubtedly a condition associated with decrease resistance to stressors causing vulnerability and consequently poor outcomes in general population and in vascular patients. (136-140) Less studied and less certain are the tools used to define the degree of frailty. It was assumed that frailty condition was associated with progressive loss of skeletal muscle mass and function, thus to sarcopenia, and for this reason, different methods to assess sarcopenia and central muscle mass were developed in the last decade in order to find a standardized tool to define the degree of frailty. (90, 141-143). But their association to post-operative survival and their role in clinical decision making is controversial and debated.

In the III study I explored the role of ileo-psoas muscle size, assessed by the measurement of TPA on preoperative CTA on patients undergoing standard EVAR and long-term survival. No significant association was found between low TPA and poor outcomes after EVAR. In my study, CT-derived psoas muscle measurement did not appear to improve survival prediction.

Certainly, the vastness of non-standardized methods used to assess ileo-psoas muscle size measurement can explain the huge controversy of results in the literature. However, it is important to mention that an essential limitation of the method used in this study is the attempt to define a vast and complex syndrome, such as frailty, from the sole measurement of the ileo-psoas muscle size. Moreover, very frail patients are usually not selected for elective repair but offered best medical treatment. This may have led to a risk of bias in the selection of the study population.

The last CT-based risk assessment tool that was explored in this thesis was VAT and its role as a predictor of long-term survival after EVAR.

Obesity is generally considered a potential risk factor for postoperative mortality and morbidity. Therefore, it was hypothesized that obesity could play a role in the assessment of long-term survival of patients undergoing EVAR. Obesity is commonly defined ad an excessive fat accumulation with BMI > 30 (91) but caution should be taken because BMI is a tool that measures excess of weight rather than excess of fat. By measuring the cross-sectional distribution of abdominal adipose tissue on preoperative CTA, this project aimed to study a more accurate method to quantify abdominal fat. However, no association was found between abdominal adipose tissue and survival after EVAR in this study. Instead, SAT seems to be associated with better outcome after EVAR, even if this associations was not independent from other comorbidity in a multivariate regression. However, it is important to mention that the measurement of SAT was not possible in 25 patients because the subcutaneous tissue was not completely included within the CT image. I had to exclude those patients where it would have been probably most interesting to assess the SAT, since it is assumed that they were the ones with larger adiposity. Lastly, no correlation was found between low ileo-psoas muscle size and adiposity contrary to the recently reported association between obesity and frailty syndrome. (144)

One of the main limitations of studies I, II and. III is their retrospective design. This may have led in the first place to a not precise accuracy of the definitions of comorbidities and risk factors. For instance, the definition of former and active smoking was not accurate. Active smoking should be defined as regular cigarette smoking with duration >6 months at the time of examination. Former smoking should be defined as a history of smoking for longer than 6 months and no current smoking. (145) This information was very fragmented and not precise in the hospital records.

Another potential risk for bias might have been the anatomy of ilio-femoral vessels. However, no patient was considered unsuitable for EVAR due to calcified access, and this thanks to the intraoperative adjunctive manoeuvres such as percutaneous transluminal angioplasty and endoconduits and “pave and crack technique”. (146)

This certainty influenced the intraoperative results, but not the long-term. Unfortunately, the study design lacks in detailed assessment of anatomical characteristics of ilio-femoral vessels and possible intraoperative adjunctive manoeuvres.

Moreover, the potential use of CT-assessed tools for risk stratification was observed only on patients who already were selected for EVAR and consequently already considered fit for this type of repair leading then to a potential risk for bias selection.

Yet another limitation to mention is the exclusion of a large number of patients because of unsuitable CT images. However, survival did not differ between included and excluded patients in any of the studies.

Another important aspect to mention is the potential error using different generation of CT scanners during the time frame of the projects. Furthermore, there may have been some inaccuracy using post-processing software for calculating calcium score, ilio-psoas area and visceral adiposity. In particular, the method to calculate Agatston Calcium Score was initially validated on ECG-gated 3 mm non-contrast CT slices, while we used both 3- and 5-mm slides leading to a risk of underestimating calcium score in our cohort. However, there have been reports showing small differences between different generations of spiral CT scanners. (147-149) Moreover, potential errors using software dedicated for the assessment of the coronary calcium score should be avoided since studies showed that these errors were mostly due to the presence of ICM. In our cohort of patients, calcium score was calculated strictly only on non-contrast-enhanced CT. (149)

In contrast, in the third study, the majority of the preoperative CT images used to assess ileo-psoas muscle size were contrast-enhanced CT scan. This could have influenced the results, since studies suggest that CT attenuation of muscle can be potentially influenced by intravenous contrast and the timing of the image acquisition after contrast injection. (150)

Minimizing intraoperative risk protecting renal function

EVAR patients carry high risk to develop post-operative renal diseases. (151) CIN is a well-known complication related to the ICM use. The incidence of CIN is related to pre-existing comorbidities, mostly CKD. Moreover, even the administration way is considered a risk factor since it has been demonstrated that there is higher risk of developing CIN after intraarterial injection. Lastly, an important risk factor to develop CIN is related to ICM volume. (118, 152-154) During EVAR procedure, of these three variables, only ICM volume can be controlled intraoperatively.

The second part of the thesis wanted to focus on minimizing the exposure to ICM during EVAR and IBD implantation, replacing it partially or completely with CO_2, in order to decrease the risk of CIN aiming to impact on long-term survival.

While, on the one hand, there are numerous studies that have shown that CO_2 is an efficient non-nephrotoxic alternative to ICM, (6) on the other hand, it is necessary to investigate whether its use is safe during endovascular procedures. There is still concern about the correct visualization of the LoRA, important anatomical marker necessary for the correct positioning of the endograft, (11, 12) and even about its capacity to detect endoleaks. (155-157)

We analyzed the various procedural moments during CO_2-EVAR and we found that the best LoRA visualization and the best image quality was obtained in second step with the main body placed into the aorta and at 50% and 100% of the proximal deployment compared to the image obtained in first step from pigtail or introducer sheath. Probably the presence of the endograft into the aortic and iliac artery lumen prevents the gas from diffusing into the lower limb therefore leading to a greater concentration in correspondence with the renal vessels. Furthermore, it is important to mention that the insertion of the endograft towards the landing zone might lead to distortion of the aorta, thus invalidating the angiographic image obtained in the first step. Perhaps, it would be better to consider having the main body in place already during the acquisition of the first angiogram.

CO_2 buoyancy makes this gas particularly suitable for anterior vessels visualization. Controversially, this characteristic makes difficult to visualize the vessels that originate slightly posterior such as native renal arteries. (121, 158, 159) This issue can be solved in different ways. Placing the patient in a lateral supine position would lead to an anteriorization of the target vessel, thus making it better visible but this is not always possible during intervention. Moreover, the visualization could be improved by exploiting the buoyancy property placing a catheter into the renal artery. Alternatively, the ICM could be used exclusively in this phase, then continuing to preferentially use CO_2. This would decrease anyway the total amount of ICM.

Moreover, we found a high sensitivity of CO_2-angiography in the detection of type II endoleak in the final angiogram when compared with pre-discharge DUS, CEUS and CT. But it is important to mention that the majority of type II endoleaks seen intraoperative tend to spontaneous thrombose, (160) and this might explain the discrepancy between intraoperative CO_2-angiogram and the pre-discharge imaging. Different studies explored the capacity of CO_2-angiography in detecting endoleaks compared to conventional ICM-angiography and the results are controversial. (155-157) However, seems that CO_2-angiography have good sensitivity in endoleak detection and in particular in type II endoleak, which, thanks to the low viscosity of the gas, are displayed more quickly and this could contribute to shortening the time to radiations exposure for both patient and staff. (161)

Due to the growing concern about risks related to radiation exposure, optimization and safety during endovascular procedures is mandatory. The use of CO_2-angiography has been associated with an increased exposure to radiation compared to the more standard ICM-angiography. (162) Contrary to what we might expect, in the fifth study, during IBD implantation, we demonstrated a reduction of the DAP in the CO_2 group. This result was due to the use of a dedicated digital subtraction CO_2 program with 2 frames/s, as opposed to the canonical 6 frames/s. The use of this program did not influence technical success and image quality. Furthermore, the use of an automated injector allowed operators distancing from the radiation source during image acquisition, contrary to when manual injection is used. Moreover, the automated injector guarantees even a less abrupt injection of the gas, probably contributing to decrease the CO_2 side effects.

The fifth study showed that CO_2 can be used as a safe contrast agent even during standard IBD implantation, lessening the potential risk for CIN, (119, 120, 163) without negatively affecting the technical success or radiation exposure.

However, the study could not demonstrate a difference in the incidence of postoperative renal injury. The potential reasons to explain this result are many. Mostly, the little number of the patients has probably affected the already low incidence of postoperative renal damage. Furthermore, optimized imaging protocol and use of fusion imaging has contributed to decrease the total amount of ICM in booth groups, as demonstrated in previous studies. (164) Moreover, patients with normal baseline eGFR could still have post-operative renal impairment, even if not clinically detected thanks to the Renal Function Reserve (RFR), capacity of the kidneys to keep an adequate filtration even after a serious loss of cell. (165)

One of the main limitations of studies IV and V is the small number of included patients. This may have impacted negatively on the statistical power of our analysis. Nevertheless, the small size of the population influenced even the choice of not using the propensity score matching to address bias selection in study V.

Additionally, results of study IV are based on subjective evaluations of different surgeons operating in different centers, this might have let to inaccuracy, therefore interobserver agreement was necessary.

Yet, another limitation is the not precise accuracy of the definitions of comorbidities and risk factors due to the retrospective design of study V. In particular, an important variable whose precision was limited is AKI. Indeed, AKI definition needed to be adapted to the retrospective design thus excluding hourly urinary output since this information was not reported in hospital charts. Indeed, hourly urinary output was only measured during the stay in the postoperative recovery unit which was less of 6 hours if not evident complications were identified and then dismissed very shortly after patients discharge.

Conclusions

I. Low ilio-femoral calcium score may be associated with lower incidence of fatal cardiac events and all-cause long-term mortality after endovascular repair of AAA of varying complexity.

II. The preoperative assessment of the long-term survival of patients undergoing infrarenal EVAR can be done with the clinically based Glasgow Aneurysm Score to a certain degree. This long-term assessment can potentially be refined in low-risk patients by measuring the ilio-femoral calcium score on preoperative CT.

III. CT-based assessment of the ileo-psoas muscle size and visceral adipose tissue did not contribute to improve the prediction of long-term survival after EVAR.

IV. Preimplant CO_2 -angiography should be performed from femoral introducer sheath; the partial deployment of the proximal main body creates an impediment to gas flow, which improves the image quality and the detection of the lowest renal artery with CO_2 -angiography performed from pigtail. The use of CO_2 as a contrast agent is safe, in terms of intraoperative and postoperative complications, which were all transient and clinically mild. This CO_2-EVAR operative protocol enabled all involved centres to accomplish EVAR procedures using minimal iodine injections.

V. Reduction of intraoperative ICM exposure during IBD implantation is feasible through the predominant use of automated CO_2-angiography. This can be safely done without negatively affecting the technical success or radiation exposure. The immediate postoperative renal damage was low already when a modern intraoperative imaging protocol with ICM was used and was not significantly reduced further by the use of CO_2.

Future perspectives

Operative risk assessment and optimization of patients undergoing vascular surgery procedure for AAA remains a huge field of study. Cardiac complications cause around 42% of perioperative deaths and the risk of complications increases in the presence of other comorbidities.

My future research ambition is to keep the focus on finding improvements that will lead to better patients' selection, reduction of intraoperative complications and improvement of outcomes. In the last years we have been witnessing an incredible progress of endovascular minimally invasive techniques which will allow treatment for an ever-increasing number of older patients with greater number of comorbidities. This leads to the need of developing more effective tools for greater accuracy in preoperative risk assessment and a greater attention in minimizing procedure-related risks.

The CT-based risk assessment tools explored in this thesis have proven to be very abstractive for the preoperative patients' selection, as they are incapable of synthesizing and representing much larger and more complex syndromes such as cardiovascular diseases or frailty. These results do not alter the fact that preoperative CT, which all patients must undergo in any case, can be a great source of important information in preoperative risk assessment, perhaps with the help of new technologies such as Photon-Counting Detector CT, that might increase definition and maybe help in studying new tools for body composition evaluation.

Moreover, the use of intraoperative CO_2 as contrast agent during EVAR and IBD implantation has proven to be safe and future perspectives are promising in the investigation of its role during much complex procedures with greater risk of intraoperative renal damage such as B/FEVAR. Indeed, these procedures are characterized by the need of renal artery catheterization and selective injections, where perhaps direct ICM injection is even more nephrotoxic.

Populärvetenskaplig sammanfattning

Avhandlingen studerar resultaten av olika utvecklingar som skett vid endovaskulär behandling av aortaaneurysm med fokus på preoperativ riskbedömning och intraoperativ minimering av risker.

Aorta sjukdomar drabbar omkring 9–15/100.000 personer per år i södra Sverige, bukaortaaneurysm (AAA) är den vanligaste. AAA är starkt förknippat med ökad mortalitet, framförallt kardiovaskulärt, som eskalerar med ökande storlek av aneurysmet. Större AAA är också associerat med en ökad risk av ruptur med död som följd. Detta föranleder reparation av AAA i förebyggande syfte när de är >55mm. Endovaskulär aneurysm reparation (EVAR) är förstahandsmetoden för AAA-reparation. Denna behandling förhindrar emellertid endast AAA-relaterad dödlighet på grund av en eventuell bristning utan effekt på den ökade kardiovaskulära risken som dessa patienter har. Av denna anledning är det avgörande att välja patienter med tillräcklig livslängd, vilket gör att de kan dra nytta av den profylaktiska aortareparationen. Det är också viktigt att minimera de risker som finns vid operation som kan äventyra patienternas långsiktiga hälsa och överlevnad, såsom njurskador.

I delarbete I och II utvärderas användningen av ett nytt bearbetningssätt av datortomografibilder för att bedöma åderförkalkningsbörda i bäckenkärl. Denna standardiserade metod har utvecklats och studerats av andra i kranskärl där det gått att se att ett högt calcium score är förknappat med sämre långtidsöverlevnad. I delarbete I och II, använde vi metoden på de datortomografier som redan hade utförts inför aortaoperationerna men inom den delen av kärlträdet som hade avbildats och som oftast visar förkalkningar i bäckenkärl. I den första studien kunde vi se att avsaknad av kalk var relaterat till ett bättre utfall efter operationerna, medan den andra studien visade att calciumscore ytterligare kunde förbättra utvärderingen av utfallet hos de som hade bedömts som låg risk med en annan score baserat på enbart kliniska variabler (Glasgow Aneurysm Score).

I delarbete III användes två andra metoder av datortomografibildbearbetning för att se om långtidsöverlevnad bättre kunde förutsägas efter aortakirurgi. Även om andra studier tydde på att den ena metoden kunde ha betydelse, kunde vi inte visa detta hos någondera av metoderna. Detta trots att vi hade följt patienterna länge och hade inkluderat patienter som hade genomgått behandling för aneurysm med mindre komplex anatomi. Denna studie finns i manuskriptform.

I studie IV studeras användning av koldioxid som kontrastmedel under endovaskulär reparation av enkla infrarenala bukaortaaneurysm. Detta eftersom den klassiska jod kontrasten är känd för att kunna vara nefrotoxisk. Njurskador efter aortakirurgi, även om dessa är transitoriska, är relaterade till en sämre överlevnad på lång sikt. Studien utfördes som ett prospektivt multicenterregister. Den visade att koldioxid kunde användas på ett säkert satt och bilderna som man fick hade god kvalitet. Denna studie publicerades i Journal of Vascular Surgery, som har näst högst Impat Factor inom kärlkirurgiska tidskrifter.

I studie V analyseras om användning av koldioxid under mera komplexa endovaskulära aortareparationer leder till mindre påverkan på njurfunktionen än jodkontrast. För att avgränsa komplexitet selekterades endast patienter som opererades med grafter som hade tillgreningar till mindre bäckenkärl (till lilla bäckenet) och där det inte genomfördes direkta ingrepp på njurartärer. Det valdes en grupp av konsekutiva patienter som behandlats med koldioxid och en kontrollgrupp som bestod av motsvarande antal patienter som hade opererats under den föregående perioden med användning av jodkontrast. Inga skillnader kunde ses i njurfunktionen även om användning av jodkontrast hade minskat avsevärt när koldioxid hade använts primärt. Detta berodde med all sannolikhet på kombinationen av det begränsade antal patienter som inkluderades och den låga incidens av påverkan på njurfunktionen även när jodkontrast användes i ett annars redan optimerat operationsprotokoll.

Sammanfattningsvis utforskar detta avhandlingsprojekt hur olika pre- och intraoperativa bildbaserade tekniska utvecklingar kan appliceras i preoperativ bedömning och intraoperativ optimering av patienter som genomgår endovaskulär aortakirurgi.

Compendio

Questa tesi esplora l’utilizzo di alcune nuove tecniche applicate nella valutazione preoperatoria e nell'ottimizzazione intraoperatoria dei pazienti sottoposti a chirurgia endovascolare per il trattamento dell’aneurisma aortico.

Grazie ad un miglioramento della gestione del rischio cardiovascolare, un migliore controllo della pressione arteriosa, dell´ uso di statine e antiaggreganti e della diminuzione del fumo, la prevalenza e i tassi di incidenza degli aneurismi aortici sono diminuiti negli ultimi 20 anni. L’aneurisma dell’aorta addominale viene riscontrato in circa 1-1.7% della popolazione maschile sopra i 65 anni. Questa patologia è fortemente associata ad un alto rischio di mortalità, principalmente di tipo cardiovascolare, che aumenta con l'aumentare delle dimensioni dell'aneurisma. L’aumento delle dimensioni è inoltre associato ad un elevato rischio di rottura della sacca aneurismatica con conseguente sanguinamento e morte. Per tale motivo, è consigliata la valutazione di un intervento chirurgico quando l’aneurisma raggiunge le dimensioni di 55 mm negli uomini e 50 mm nelle donne.

Sono state sviluppate diverse tecniche chirurgiche per il trattamento dell’aneurisma aortico addominale, ma la riparazione endovascolare (EVAR) è certamente il metodo meno invasivo e correlato ad un rischio intraoperatorio inferiore rispetto alla chirurgia tradizionale a cielo aperto. Le linee guida internazionali raccomandato di valutare la riparazione endovascolare per i casi di rottura e per la maggior parte degli interventi in elezione nel caso in cui i pazienti abbiano un’anatomia adeguata e una ragionevole aspettativa di vita, mentre la riparazione aortica a cielo aperto dovrebbe essere preferita per quei pazienti con una lunga aspettativa di vita.

Il trattamento endovascolare prevede l’esclusione della sacca aneurismatica dalla circolazione sistemica tramite il posizionamento di una endoprotesi grazie all’utilizzo di introduttori e cateteri attraverso le arterie periferiche. Tuttavia, questo trattamento previene esclusivamente la mortalità correlata ad un’eventuale rottura dell’aneurisma, senza alcun effetto sull’aumento del rischio cardiovascolare ampiamente dimostrato in questi pazienti.

Per tale motivo, è di fondamentale importanza una corretta selezione di pazienti con sufficiente aspettativa di vita, consentendo loro di beneficiare dell’intervento. Inoltre, è importante ridurre i rischi legati all'intervento chirurgico che possono mettere a repentaglio la salute e la sopravvivenza a lungo termine dei pazienti, ad esempio i danni ai reni conseguenti all’esposizione al mezzo di contrasto necessario per pianificare ed eseguire l’intervento.

Nel primo e nel secondo studio viene analizzato l'utilizzo di un metodo di elaborazione delle immagini TC preoperatorie dei pazienti candidati a EVAR per valutare la quantità di aterosclerosi nei vasi pelvici attraverso il calcolo di Agatston Calcium Score (ACS). Questo è oggi un metodo ben sviluppato e standardizzato per valutare la malattia coronarica, dove è stata dimostrata una sopravvivenza inferiore in quei pazienti con elevato punteggio di ACS.

Il primo studio ha dimostrato che una minore presenza di calcificazioni ilio-femorali è correlata ad una migliore sopravvivenza postoperatoria nei pazienti sottoposti a EVAR, mentre il secondo studio ha dimostrato che il punteggio di ACS ottenuto può essere utilizzato in associazione al già noto Glasgow Aneurysm Score per migliorarne ulteriormente il valore predittivo postoperatorio nei pazienti considerati a basso rischio.

Nel terzo studio sono stati valutati altri due metodi di elaborazione delle immagini TC preoperatorie per misurare le dimensioni del muscolo ileo-psoas e quantificare la presenza di grasso viscerale addominale. Lo studio non ha dimostrato un’associazione tra la sopravvivenza postoperatoria dei pazienti sottoposti ad EVAR e le ridotte dimensioni del muscolo ileo-psoas o una maggiore presenza di grasso viscerale addominale.

Il quarto e il quinto studio sono dedicati alla valutazione dell'anidride carbonica come mezzo di contrasto alternativo durante la riparazione endovascolare degli aneurismi dell'aorta addominale semplici e complessi. Il mezzo di contrasto iodato, comunemente utilizzato durante le indagini TC pre- e postoperatorie e durante l’intervento endovascolare, è noto per essere nefrotossico. Il danno renale dopo un intervento chirurgico all’aorta, anche se transitorio, è correlato a una minore sopravvivenza a lungo termine.

Il quarto studio è stato condotto come registro prospettico multicentrico e ha dimostrato che l’anidride carbonica può essere utilizzata in modo sicuro durante la riparazione di semplici aneurismi infrarenali senza incidere negativamente sulla riuscita dello stesso, e soprattutto senza recare danni al paziente. Questo studio è stato pubblicato sul Journal of Vascular Surgery, rivista che ha il secondo Impact Factor più alto tra quelle di chirurgia vascolare.

Il quinto studio analizza l’utilizzo dell’anidride carbonica come mezzo di contrasto durante le riparazioni aortiche endovascolari più complesse e se questo porta ad un impatto minore sulla funzionalità renale rispetto al mezzo di contrasto iodato. Non è stata osservata alcuna differenza nella funzionalità renale postoperatoria sebbene la quantitá del mezzo di contrasto iodato fosse significativamente ridotto. Questo risultato è molto probabilmente dovuto alla combinazione del numero limitato di pazienti inclusi nello studio, alla bassa incidenza di impatto sulla funzionalità renale e all’utilizzo di un protocollo chirurgico già ottimizzato.

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