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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by their Roman numerals (I–V):

I Lieberg J, Pruks L.-L., Kals M, Paapstel K, Aavik A, Kals J. Mortality after elective and ruptured abdominal aortic aneurysm surgical repair: 12-year single-center experience of Estonia. Scandinavian Journal of Surgery 2018;107:152–157.

II Lieberg J, Kadatski K.G., Kals M, Paapstel K, Kals J. Five-year survival after elective open and endovascular aortic aneurysm repair. Scandinavian Journal of Surgery 2022;111:14574969211048707.

III Lieberg J, Wanhainen A, Ottas A, Vähi M, Zilmer M, Soomets U, Björck M, Kals J. Metabolomic profile of abdominal aortic aneurysm. Metabolites 2021;11:555.

IV Rebane E, Tikko H, Tünder E, Lepner U, Helberg A, Pulges A, Vaasna T, Suba S, Lieberg J, Tamm V, Ellervee T, Vasar O. Venous allografts for infrainguinal vascular bypass. Cardiovascular Surgery 1997;5:21–25.

V Kals J, Lieberg J, Kampus P, Zagura M, Eha J, Zilmer M. Prognostic impact of arterial stiffness in patients with symptomatic peripheral arterial disease. European Journal of Vascular and Endovascular Surgery 2014;48:308–315.

Author's contribution:

Papers I–III: Involvement in the study design, collecting clinical data, data analysis, and writing the paper

Paper IV: Collecting clinical data, partial data analysis, and revising the paper

Paper V: Collecting clinical data and revising the paper

ABBREVIATIONS

AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ALI	acute limb ischaemia
BMT	best medical treatment
CI	confidence intervals
CLTI	chronic limb-threatening ischaemia
CTA	computed tomography angiography
CVD	cardiovascular disease
DSA	digital subtraction angiography
eAAA	elective abdominal aortic aneurysm
EVAR	endovascular aneurysm repair
GSV	great saphenous vein
GPR	graft patency rate
HR	hazard ratios
IC	intermittent claudication
IQR	interquartile range
LEAD	lower extremity arterial disease
LSR	limb salvage rate
LysoPC	lysophosphatidylcoline
OSR	open surgical repair
PAD	peripheral artery disease
PC	phosphatidylcholine
PTFE	polytetrafluoroethylene
rAAA	ruptured abdominal aortic aneurysm
ROC	receiver-operating characteristic
SD	standard deviation

1. INTRODUCTION

Abdominal aortic aneurysm (AAA) is a complex pathology with a high mortality rate (around 80%) (Brown et al., 2012) due to its complication, AAA rupture, which is why timely treatment is crucial. AAA prevalence and incidence rates have decreased over the last 20 years, the current prevalence in 65-year-old men is between 1.3% and 3.3%. Owing to the amelioration of intensive care units and introduction of endovascular aneurysm repair (EVAR), in-hospital mortality in elective abdominal aortic aneurysm (eAAA) patients has declined greatly over time and has been reported to be around 1%–3% (Brown et al., 2012; De Martino et al., 2013). Despite remarkable improvements in short-term survival rates after surgical repair of both eAAA and ruptured abdominal aortic aneurysm (rAAA) during the last 50 years, the mid- and long-term survival rates remain relatively constant: the 5-year crude survival rate after eAAA repair is around 70% (Bahia et al., 2015; De Martino et al., 2013; Mani et al., 2009) and after rAAA repair around 40% (Mani et al., 2009).

EVAR has become standard therapy alongside open surgical repair (OSR) for AAA and evidently there has been a change in the demographics of the population treated for AAA as a consequence of EVAR (Wanhainen et al., 2019). Current evidence suggests also significant short-term survival benefit from EVAR versus OSR in elective AAA repair, but this benefit is lost during mid- and long-term follow-up (Becquemin et al., 2011; Greenhalgh et al., 2004; Lederle et al., 2012; Li et al., 2019; Prinssen et al., 2004; Yokoyama et al., 2020). Patients treated by EVAR are more likely to experience aortic complications and reinterventions compared with those treated by OSR (Stather et al., 2013).

The launching of an AAA screening programme has been associated with a significant reduction in AAA-specific mortality in Sweden (Wanhainen et al., 2016a). On the other hand, these programmes, along with the growing use of abdominal imaging for other indications, have led to an increase in the identification of patients with small AAA. Still, the benefit of early diagnosis is limited because most detected AAA are below the currently accepted threshold for elective endovascular or surgical repair. As the management of small AAA remains controversial (Laine et al., 2017), predicting the progression of small AAA is critical in clinical practice. Moreover, diameter of the aneurysm may not be the best criterion for estimating disease activity in translational science studies. Surrogate biomarkers of growth and rupture could give precise indication for elective treatment. New imaging modalities, such as volume measurement, biomechanical analysis, functional and molecular imaging, and circulating biomarkers have the potential to be adopted in clinical practice in the future (Gürtelschmid et al., 2014; Moris et al., 2014; Vega de Cèniga et al., 2009; Wanhainen et al., 2016b). Development of novel high-throughput technologies (e.g. metabolomics) seems to be a good approach for finding new possible biomarkers of AAA.

Peripheral artery disease (PAD) or lower extremity arterial disease (LEAD) is a manifestation of systemic atherosclerosis with a prevalence of 2.7–3% in population aged 45–49 years, increasing up to 18.2 % in persons aged 60–90 years (Kröger et al., 2006; Ouriel 2001; Sigvant et al., 2007). The association of PAD with increased future cardiovascular disease (CVD) events and mortality, and total mortality has been demonstrated in numerous studies (Criqui et al., 1992; Ness et al., 1999). However, PAD patients remain underdiagnosed and -treated with regard to guideline-directed medical therapy. The therapeutic approach to patients with PAD includes two aspects. The first is to address specific symptoms of any localization and the risk related to a specific lesion. The second aspect of management in these patients is related to their increased risk of any CVD event. Regarding PAD patients, surgical revascularization is recommended for those with vocational limiting symptoms or those with lifestyle limiting claudication who have failed medical and exercise therapy, or patients with chronic limb-threatening ischemia (Aboyans et al., 2018).

Possible explanations for the PAD patients' poor prognosis lie in accumulation of classical CVD risk factors and in functional impairment and progression of the disease (Criqui et al., 2008; Leeper et al., 2013). However, the exact mechanisms through which PAD is associated with increased risk are not fully understood. Therefore, identification of novel prognostic markers for PAD may improve understanding of the mechanisms of atherosclerosis, which may ultimately lead to new and better therapies (Cooke et al., 2010). Altered arterial wall properties, such as arterial stiffness, might be one potential cause of poor prognosis in patients with PAD. Increased arterial stiffness is an important independent determinant of CVD events, mortality and total mortality (Mattace-Raso et al., 2006), and plays also an important role in atherosclerosis (Safar 2007). Arterial stiffening may induce arterial remodelling, wall thickening and development of atheroma. Moreover, arterial stiffness may contribute to ulceration and rupture of atherosclerotic plaques (Lovett et al., 2003).

In the present thesis, patients with elective and emergency AAA (Papers I–III) and with symptomatic PAD (Papers IV and V) were studied. AAA and PAD are very serious and complex vascular surgical diseases with significantly increased CVD mortality. Their prevention, timely diagnosis and treatment enable to reduce patients' mortality and to improve their quality of life. In the current thesis we aimed to evaluate the results of surgical and endovascular treatment of patients with AAA and PAD; and to determine the role of functional and biochemical markers (i.e. biomarkers) in pathogenesis and risk prediction in these patients.

2. REVIEW OF THE LITERATURE

2.1. Abdominal aortic aneurysm

Aneurysm, originated from the ancient Greek word, means a dilatation or widening of an artery, most commonly being fusiform in shape. AAA is characterized by structural deterioration of the aortic wall, leading to a permanent and localized aortic dilation. AAA diagnosis is made when the maximum aortic diameter is ≥3 cm, which usually is more than 2 standard deviations above the mean diameter for men (Ellis et al., 1991; Lederle et al., 1988; Lindholt et al., 1999). This definition, based on external ultrasound diameters had a sensitivity of 67% and a specificity of 97% in predicting the need for AAA repair within 10 years (Freiberg et al., 2008). A lower threshold might be more appropriate in women and some Asian populations (Li et al., 2018; Sweeting et al., 2018).

AAA prevalence and incidence rates have decreased over the last 20 years, which has been attributed partially to the decline in smoking (Sampson et al., 2014; Sidloff et al., 2014; Svensjö et al., 2011). Prevalence is negligible before the age of 55–60 years and thereafter prevalence increases steadily with age (Sampson et al., 2014). In 1990, the global prevalence in 75–79-year-old persons was 2,423 per 100,000 population versus 2275 in 2010 (Sampson et al., 2014).The current prevalence in 65-year-old men is 1.7% in the Swedish Screening Programme with an additional 0.5% with an already known AAA (Svensjö et al., 2011), 1.3% in the UK National Screening Programme (Jacomelli et al., 2016a and 2016b) and 3.3% in a Danish screening programme targeting men aged 65–74 years (Grondal et al., 2015).

AAA development and progression is connected with oxidative stress, aortic wall inflammation, elastin and collagen degradation, apoptosis and loss of extracellular matrix, neovascularization, and depletion of smooth muscle cells (Lederle et al., 2002). Aortic dilation and rupture are probably caused by increased turnover and loss of fibrillary collagen and increased expression of collagenase, elastase, and matrix metalloproteinase (Lederle et al., 2002; Wanhainen et al., 2016b). Formation and progression of intraluminal thrombus may be involved in the evolution and possible rupture of AAA.

AAAs are usually clinically silent. Symptoms or signs of an intact AAA, if present, are mainly pain or tenderness on palpation, localised to the AAA or radiating to the back or to the genitals. Symptoms may be related to complications, either by compression of nearby organs (duodenal obstruction, lower limb oedema, ureteral obstruction) or distal embolism. For rupture the signs are usually more dramatic (haemodynamic collapse, pallor, abdominal and/or back pain, abdominal distension, and rarely primary aorto-enteric or arterio-venous fistula) (Wanhainen et al., 2019).

However, most AAAs show discontinuous growth patterns and alternate periods of stability and nongrowth with periods of acute expansion and rupture (Colledge et al., 2019). Besides catastrophic AAA rupture with mortality over 80% (Wanhainen et aö 2019), patients with AAA are more likely suffering from

multivascular manifestations of atherosclerotic disease (Oliver-Williams et al., 2019). This indicates that, besides timely repair of AAA, which is crucial, also monitoring and secondary CVD prevention are important in these patients after AAA diagnosis.

2.1.1. Management of patients with abdominal aortic aneurysm

AAA is mostly an asymptomatic but potentially fatal condition because progressive enlargement of the abdominal aorta is spontaneously evolving towards rupture (Laine et al., 2017). Abdominal ultrasound and duplex ultrasonography are first line imaging tools for detection and management of small AAAs, with high sensitivity and specificity (Lindholt et al., 1999, Long et al., 2012). Computed tomography angiography (CTA) plays a key role in assessing the extent of the disease and in therapeutic decision making and planning. CTA is also the recommended imaging modality for the diagnosis of rupture and is an important tool in follow up after repair (Roy et al., 2008).

Indications for endovascular or open elective repair are based upon a maximum diameter of AAA ≥5.5(male)/≥5.0(female) cm and symptomatic AAA (Wanhainen et al., 2019). An ultrasound based AAA screening programme for 65-year-old men is a highly cost-effective preventive health measure (Wanhainen et al., 2016a). On the other hand, these programmes, along with the growing use of abdominal imaging for other indications, have led to an increase in the identification of patients with small AAA. Still, the benefit of early diagnosis is limited because most detected AAA are below the currently accepted threshold for elective EVAR or OSR. As the management of small AAA remains controversial (Laine et al., 2017), predicting the progression of small AAA is critical in clinical practice. Moreover, diameter of the aneurysm may not be the best criterion for estimating disease activity in translational science studies.

Non-surgical treatment of AAA includes quitting smoking, appropriate management of comorbidities affecting the cardiovascular system, and moderate physical activity, which could limit the expansion rate of AAA (Moll et al., 2011; Wanhainen et al., 2019). Several different classes of drugs have been assessed for their ability to reduce the rate of small aneurysm growth in randomized trials. To date, no class of drug has been shown to be effective, including doxycycline, beta blockers, angiotensin converting enzyme inhibitors, and statins (Bicknell et al., 2016; Kokje et al., 2015; Meijer et al., 2013; Rughani et al., 2012) and other trials are still ongoing. Exercise has not been proven to reduce AAA growth rate, either (Myers et al., 2014). All the observational studies show that current smoking is associated with increased AAA growth rate and smoking cessation is probably associated with an approximately 20% reduction in growth rate, as well as halving the risk of aneurysm rupture (Sweeting et al., 2012). Patients with diabetes also have a lower AAA growth rate than patients without diabetes, which has recently been suggested to

be related to metformin, used to treat type II diabetes (Fujimura et al., 2016; Golledge et al., 2017; Sweeting et al., 2012).

AAA patients have a high risk of future CVD events. A systematic review has demonstrated that for patients with small AAAs, the annual risk of CVD death was 3.0% (95% CI 1.7–4.3) (Bath et al., 2015). The European guidelines on CVD prevention recommend that all patients with symptomatic PAD should use antiplatelet therapy, lipid lowering agents if low density lipoprotein (LDL) cholesterol >2.5mmol/L, and antihypertensives in the case of systolic blood pressure >140 mmHg, unless contraindicated (Aboyans et al., 2018; Graham et al., 2007; Piepoli et al., 2016). More specifically, a study examining the drugs taken by 12,485 UK patients with a recorded diagnosis of AAA showed that the five-year survival rates were significantly improved for those taking statins (68% vs. 42%), antiplatelet therapy (64% vs. 40%), or antihypertensive agents (62% vs. 39%) compared with AAA patients who were not taking these medications (Bahia et al., 2016). Other healthy lifestyle strategies including smoking cessation, exercise, and diet should be as recommended for any patient with CVD, although there is little high quality specific evidence that such strategies are effective for patients with AAA.

2.1.2. Elective and emergency open and endovascular abdominal aortic aneurysm repair

The principle of definite treatment of AAA is removal of the aneurysm sac from circulation by OSR or by EVAR. Owing to the amelioration of intensive care units and introduction of EVAR, in-hospital mortality in elective abdominal aortic aneurysm (eAAA) patients has declined greatly over time and has been reported to be around 1%–3% (Brown et al., 2012; De Martino et al., 2013). Despite remarkable improvements in short-term survival rates after surgical repair of both eAAA and ruptured abdominal aortic aneurysm (rAAA) during the last 50 years, the mid- and long-term survival rates remain relatively constant: the 5-year crude survival rate after eAAA repair is around 70% (Bahia et al., 2015; De Martino et al., 2013; Mani et al., 2009) and after rAAA repair around 40% (Mani et al., 2009). However, the launching of an AAA screening programme has been associated with a significant reduction in AAA-specific mortality in Sweden (Wanhainen et al., 2016a).

Patients should undergo eAAA repair only if the risk of rupture outweights the risks from surgery. The availability of less invasive methods (EVAR) has made it possible to treat patients who are older and/or have more comorbidities. This might explain why there has been a lack of improvement in long-term survival rates (Bahia et al., 2015). Studies have shown that in patients undergoing both eAAA (Beck et al., 2009; Brown et al., 2012; Stather et al., 2013; Thomas et al., 2014) and rAAA (Antoniou et al., 2013; Egorova et al., 2008; Thomas et al., 2014) repair, EVAR yields lower 30-day mortality rates than OSR. The OSR procedure is more strenuous and has quite high operative mortality (4%–10%) (Brown et al., 2012). Therefore, older (De Martino et al.,

2013) patients with more comorbidities (Egorova et al., 2008; Stone et al., 2013; Thomas et al., 2014) are recommended to undergo EVAR if anatomically feasible. On the other hand, significant short-term survival benefit from EVAR versus OSR in elective AAA repair was lost during mid- and long-term follow-up (Becquemin et al., 201; Greenhalgh et al., 2004; Lederle et al., 2012; Li et al., 2019; Prinssen et al., 2004; Yokoyama et al., 2020). EVAR is associated with a higher number of late ruptures (Stather et al., 2013), aneurysm-related mortality (Patel et al., 2016) and reinterventions (Brown et al., 2012; Stather et al., 2013).

Patients treated by EVAR are more likely to experience aortic complications and reinterventions compared with those treated by OSR (Stather et al., 2013). The main complication, endoleak, i.e. presence of flow in the aneurysm sac outside the graft after EVAR, occurs in up to one third of cases (Lal et al., 2015). Besides persistent endoleak repair, reinterventions after EVAR procedures, performed mainly with older-generation devices, are often needed because of stent graft thrombosis or stenosis, infection and late AAA rupture (Wanhainen et al., 2019). However, improvements in the design and delivery of modern stent grafts have reduced the frequency of those adverse events over five years and beyond (Becquemin et al., 2021; Mertens et al., 2011).

Smoking (De Bruin et al., 2014; Stather et al., 2013;), comorbidities (De Martino et al., 2013; Stone et al., 2013), and older age at the time of surgery (Bahia et al., 2015; De Bruin et al., 2014; De Martino et al., 2013; Stather et al., 2013; Stone et al., 2013;) have been found to decrease both in-hospital and 5-year survival rates. Reduced 5-year survival is also associated with the maximal diameter of AAA at the time of repair (Bahia et al., 2015). Improvements in long-term mortality have been linked with preoperative administration of certain drugs such as statins and aspirin (De Martino et al., 2013; Stone et al., 2013) and with perioperative administration of β-blockers. This can be related to the cardioprotective effect of these drugs and hence a decrease in myocardial complications (De Bruin et al., 2014; Stone et al., 2013).

Most patients requiring AAA repair suffer from advanced artherosclerotic disease and other comorbidities related to smoking (Schouten et al., 2008; Vega de Ceniga et al., 2010). To optimise the outcome of AAA repair, risk factor optimisation and medical treatment of the underlying CVD should be continued post-operatively (Eldrup et al., 2012). The BMT includes antihypertensive therapy (i.e. angiotensin converting enzyme inhibitors, beta blocking agents), lipid modifying therapy (i.e. statins), and antiplatelets (De Bruin et al., 2014; Kertai et al., 2004; Parmar et al., 2013; Zhang et al., 2015), although evidence about single drugs may be conflicting (Scali et al., 2015a and 2015b).

In the presented thesis we investigated short- and mid-term all-cause mortality, complications and reinterventions in patients undergoing eAAA and rAAA open and endovascular repair (Papers I and II).

2.1.3. Metabolomics as a novel tool in vascular/aortic diseases

Metabolomics is defined as qualitative and quantitative measurement of low-molecular-weight biomolecules (metabolites). It is a powerful and essential tool to assess the phenotype more functionally and to correlate it with genes, lifestyle, environment, and physiology or pathology (Koh et al., 2018; Menni et al., 2015). The term "metabolites" signifies various endogenous and exogenous compounds of different biochemical classes derived from food, microbiota, biochemical pathways, treatments, etc. Because metabolomics provides a unique insight into the relationships between physiological status, lifestyle, and pathologies, and because it correlates with phenotype of the disease, it is particularly suited for obtaining useful information for personalized approach to treatment. Linked to high prevalence and mortality, vascular diseases are clearly within the scope of this personalized approach. The number of studies involving "omics" sciences and metabolomics in the context of precision/personalized medicine in vascular diseases remains limited (De Tullio et al., 2019; Dona et al., 2016; Shah et al., 2012).

Metabolomic profiling of vascular diseases has become an attractive field of research. Altered lipid metabolism in vascular diseases, particularly atherosclerosis, has been the focus of a number of recent studies (Meikle et al., 2011; Paapstel et al., 2016; Rizza et al., 2014; Shah et al., 2012; Stegemann et al., 2014;). The field of lipidomics allows to survey a wide spectrum of lipid species in body fluids/tissues and provides new insights into the pathogenetic mechanisms of vascular diseases. Among these species, sphingomyelines and phosphatidylcholines have received attention as potential novel independent vascular risk markers (Ganna et al., 2014; Shah et al., 2012; Sigruener et al., 2014).

AAA is mostly an asymptomatic, but potentially fatal condition, because progressive enlargement of the abdominal aorta is spontaneously evolving towards rupture (Lederle et al., 2002). Indications for endovascular or open elective repair are based upon a maximum AAA diameter. An ultrasound-based AAA screening programme for 65-year-old men is a highly cost-effective preventive health measure (Wanhainen et al., 2016a). These programmes, coupled with the growing use of abdominal imaging for other indications, have led to better identification of patients with small AAA. Still, the benefit of early diagnosis is limited, because most detected AAA are below the currently accepted threshold for elective endovascular or surgical repair. Although the management of patients with small AAAs has recently been defined in clinical practice guidelines (Wanhainen et al., 2019), predicting progression of small AAAs in an individual patient is still difficult. The diameter of aneurysm may not be the only criterion for estimating growth, and a better understanding of biological mechanisms could help us to identify the mechanisms of drug therapy for slowing down growth (Golledge et al., 2019).

Surrogate biomarkers for development, growth and rupture could give precise information about how guide proper management of AAA. New imaging

modalities, such as volume measurement, biomechanical analysis, functional and molecular imaging, and circulating biomarkers, have shown a potential to be adopted in clinical practice in the future (Kuivaniemi et al., 2015; Mori et al., 2014; Stather et al., 2014; Wanhainen et al., 2016b). Development of novel high-throughput technologies (e.g. metabolomics) is a possible approach to gain a better understanding of the pathophysiology of AAA and to find new possible biomarkers for AAA. Recently reported metabolomic changes in AAA patients were related to carbohydrate, lipid and amino acid metabolism (Ciborowski et al., 2013; Ciborowski et al., 2011; Ciborowski et al., 2012; Quereshi et al., 2017; Rupèrez et al., 2012). In the current thesis we describe the profile of low molecular weight metabolites (<1 kDa) in AAA patients and explore if low molecular weight metabolites are linked to AAA growth (Paper III).

2.2. Peripheral artery disease

The term „peripheral artery disease" (PAD) is generally used for lower extremity artery disease (also abbreviated as LEAD). This should be clearly distinguished from the term „peripheral arterial disease", which encompasses all arterial diseases other than those of the coronary arteries and the aorta (Aboyans et al., 2018). PAD or LEAD is a manifestation of systemic atherosclerosis with a prevalence of 2.7–3% in population aged 45–49 years, increasing up to 18.2 % in persons aged 60–90 years (Kröger et al., 2006; Ouriel et al., 2001; Sigvant et al., 2007;). Overall, the risk of different localizations of PADs increases with age and with exposure to major CVD risk factors, including smoking, hypertension, dyslipidaemia, diabetes etc. But the exact role of other potential risk factors is still being investigated (Aboyans et al., 2018). When a vascular territory is affected by atherosclerosis, then not only the corresponding organ is threatened (e.g. the leg for PAD and the brain for carotid artery disease), but also the total risk of any CVD event is increased (e.g. coronary events) (Aboyans et al., 2018).

Symptomatic PAD typically has 3 presentations: intermittent claudication (IC), chronic limb-threatening ischaemia (CLTI), and acute limb ischaemia (ALI). IC has been defined as a fatigue, cramping, or other discomfort in the lower extremity muscles due to vascular etiology. It can be reproducibly induced by exercise and relieved with rest (Gerhard-Herman et al., 2017). CLTI is defined as rest pain due to ischaemia that has occured during 2 weeks, non-healing wounds, necrosis, or gangrene in either or both legs due to arterial occlusive disease. The Fontaine stages (Fontaine et al., 1954) and Rutherford categories (Rutherford et al., 1997) are useful in classifying the severity of chronic leg ischaemia: IC and CLI (Table 1). ALI is an acute presentation of severe limb hypoperfusion. It is often defined as having been present for 2 weeks. However, rapid assessment and restoration of perfusion in the affected limb in the ALI patient is often necessary to preserve the limb and sometimes to prevent death. ALI symptoms are characterized by the 6 P's as follows: pain,

pallor, pulselessness, poikilothermia, paresthesia, and paralysis. The status of the affected limb in the patient with ALI can be further characterized as viable, threatened, or nonviable, to help instituute appropriate therapy (Aboyans et al., 2018; Patel et al., 2020).

Table 1. Adapted from Rutherford et al. and Fontaine et al. (Patel et al., 2020)

Fontaine stage		**Rutherford grade**	**Category**	
I	Asymptomatic	0	0	Asymptomatic; no haemodynamically significant disease
IIa	Mild claudication		1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
III	Ischaemic rest pain		3	Severe claudication
IV	Ulceration or gangrene	II	4	Ischaemic rest pain
		III	5	Minor tissue loss; nonhealing ulcer, focal gangrene with diffuse pedal ischaemia
			6	Major tissue loss – extending above TM level

2.2.1. Management of patients with peripheral artery disease

Several modifiable risk factors for developing PAD have been clearly identified, as have the medical therapies and preventative strategies for the prevention and treatment of PAD. However, PAD patients remain underdiagnosed and -treated with regard to guideline-directed medical therapy. Importantly, only 10% of people evaluated at a primary care setting with PAD had classic IC symptoms. Apparently, 40% do not complain of leg pain and 50% have leg symptoms that are atypical of IC (Hirsch et al., 2001; McDermott et al., 2001). Moreover, all asymptomatic patients are at increased risk of CVD events.

The ankle-brachial index (ABI) is a non-invasive tool for the diagnosis and treatment monitoring of PAD. It is also a strong marker of generalized atherosclerosis and describes CVD risk. An ABI $\leq$0.90 is associated on average with a 2- to 3-fold increased risk of total and CVD death. An ABI >1.40 represents arterial stiffening (medial arterial calcification) and is also associated with higher risk of CVD events and mortality (Fowkes et al., 2008; Criqui et al., 2010). After initial diagnosis of PAD, dupplex ultrasound and/or CTA and/or magnetic resonance angiography are indicated for anatomical characterization

of PAD lesions and guidance for optimal revascularization strategy (Koelemay et al., 2001; Menke et al., 2010; Met et al., 2009; Ouwendijk et al., 2008).

The therapeutic approach to patients with PAD includes two aspects. The first is to address specific symptoms of any localization and the risk related to a specific lesion. The second aspect of management in these patients is related to their increased risk of any CVD event. General CVD prevention is of utmost importance and management should be multidisciplinary. BMT includes CVD risk factor management, including the best pharmacological therapy, as well as nonpharmacological measures such as smoking cessation, healthy diet, weight loss and regular physical exercise (Graham et al., 2007; Piepoli et al., 2016). Smoking cessation provides the most noticeable improvement in walking distance when combined with regular exercise, especially when lesions are located below the femoral arteries. In patients with IC, natural history is deteriorated by ongoing tobacco use, with an increased risk of amputation (Piepoli et al., 2016; Juergens et al., 1960). The pharmacological component of medical treatment includes antihypertensive and -diabetic, lipid-lowering and antithrombotic drugs. Several studies have shown that statins significantly improve the CVD prognosis of patients with IC or CLTI (Aung et al., 2007; Westin et al., 2014). Additionally, several meta-analyses have shown considerable improvement in pain-free and maximal walking distance with the use of statins (Aung et al., 2007; Momsen et al., 2009). It is suggested that statins could limit adverse limb events in patients with LEAD (Kumbhani et al., 2014).

In subjects with hypertension, calcium antagonists or angiotensin converting enzyme inhibitors and angiotensin-receptor blockers should be preferred because of their potential in peripheral arterial dilatation. A meta-analysis (Shahin et al., 2013) showed improved maximal and pain-free walking distance when using angiotensin converting enzyme inhibitors versus placebo. In patients with IC, exercise therapy is effective and improves symptoms and quality of life and increases maximal walking distance. Some antihypertensive drugs (e.g. verapamil) (Bagger et al., 1997), statins (Gargiulo et al., 2012; McDermott et al., 2003), antiplatelet agents and prostanoids (prostaglandins I2 and E1) (Robertson et al., 2013) have some favourable effects on walking distance and leg functioning. The drugs mostly used for attenuating leg symptoms and for improving perfusion are naftidrofuryl, pentoxifylline, cilostazol, buflomedil, carnitine and propionyl-L-carnitine (Momsen et al., 2009; Stevens et al., 2012).

2.2.2. Revascularization of patients with peripheral artery disease

Regarding IC patients (Fontaine stage II), revascularization is recommended for those with vocational limiting symptoms or for those with lifestyle limiting claudication who have failed medical and exercise therapy. For CLTI patients (Fontaine stages III and IV) and for patients with acute ischaemia, urgent revascularization is recommended, if possible, to minimize tissue loss in those who are likely to ambulate and live independently. The goal of revascularize-

tion is to restore direct in-line flow to the foot of the affected limb. The anatomical location and extension of arterial lesions has an impact on revascularization options. If revascularization is needed, endovascular therapy is the first choice in the case of short and anatomically suitable lesions.

Isolated aorto-iliac lesions are a common cause of claudication. In the case of short stenosis/ occlusion (<5 cm) of iliac arteries, endovascular therapy gives good long-term patency (>90% over 5 years) with a low risk of complications (Indes et al., 2013). In cases of ilio-femoral lesions, a hybrid procedure is indicated, usually endarterectomy or bypass at the femoral level combined with endovascular therapy of iliac arteries, even with long occlusions. If occlusion extends to the infrarenal aorta, covered endovascular reconstruction of an aortic bifurcation can be considered.

In claudicants, mostly affected by femoro-popliteal lesions over 25 cm, better long-term patency is achieved with surgical bypass, especially when using the great saphenous vein (GSV). No head-to-head trials comparing endovascular therapy and surgery are yet available. In the Zilver-PTX trial, 5-year primary patency with conventional and drug-eluting stents was 43% and 66%, respectively (Dake et al., 2016). The 5-year patency after above-the-knee femoro-popliteal bypass is >80% with GSV and 67% with prosthetic conduits (Klinkert et al., 2004). The challenge of endovascular therapy is the long-term patency and durability of stents in the femoro-popliteal region, where the artery is very mobile. Several new endovascular solutions, such as atherectomy devices, drug-eluting balloons and new stent designs, have been shown to improve long-term patency. Compared with endovascular therapy, open surgery may be associated with longer hospital stays and higher complication rates, but it results in more durable patency.

CLTI is almost never related to isolated aorto-iliac disease, and downstream lesions are often concomitant. In addition to CTA and/or magnetic resonance angiography, complete digital subtraction angiography (DSA) down to the plantar arches is required for proper arterial network assessment and procedure planning (Teraa et al., 2016). Hybrid procedures (e.g. aortoiliac stenting and distal bypass) should be encouraged in a one-step modality when necessary. CLTI is unlikely to be related to isolated superficial femoral artery lesions; usually femoro-popliteal involvement combined with aorto-iliac or below-the-knee disease is found. In up to 40% of cases, inflow treatment is needed (Zeller et al., 2014). The revascularization strategy should be judged on lesion complexity. If endovascular therapy is chosen first, landing zones for potential bypass grafts should be preserved. When bypass surgery is decided, the bypass should be as short as possible, using the saphenous vein.

Extended infra-popliteal artery disease is mainly seen in diabetic patients, often associated with superficial femoral artery lesions (inflow disease). Full-leg DSA down to the plantar arches is mandatory to explore all revascularization options (Teraa et al., 2016). In stenotic lesions and short occlusions, endovascular therapy can be the first choice. In long occlusions of tibial arteries, bypass with an autologous vein ensures superior long-term patency and

leg survival. Altough the optimal graft material for infrainguinal bypass is autogenous GSV (Aboyans et al., 2018; Almasri et al., 2019; Brewster et al., 1981; Callow et al., 1982; Cutler et al., 1976; Geiger et al., 1984; Graham et al., 1981; Leather et al., 1981; Veith et al., 1986), there are many instances when this vein is unavailable or inadequate in quality. Prosthetic grafts have consistently failed to meet the standards of autogenous vein graft patency, particularly when used for infrapopliteal and/or secondary reconstructions (Callow et al., 1982; Evans et al., 1981; McAuley et al., 1984; Thomas et al., 1976; Veith et al., 1986). Operative adjuncts such as vein cuffs, patches and arteriovenous fistulas, which have been proposed to improve the results of prosthetic tibioperoneal-bypass, has not yielded the expected results (Dardik et al., 1991; Siegman 1979; Webb 1995). If the patient has an increased risk for surgery or does not have an autologous vein, endovascular therapy can be attempted. The decision of revascularization should also consider the angiosome concept, targeting the ischaemic tissues. In current thesis we analysed the long-term results of femoropopliteal and femoro-tibial bypasses, using venous allografts, when ipsilateral or contralateral GSV and small saphenous vein were not available in patients with PAD (Paper IV).

2.2.3. Increased cardiovascular disease risk in patients with peripheral artery disease

The association of PAD with increased future CVD events and mortality, and total mortality has been demonstrated in numerous studies (Criqui et al., 1992; Ness et al., 1999). Many studies have shown an increased risk of mortality, CVD mortality and morbidity (myocardial infarction, stroke) in patients with symptomatic or asymptomatic PAD, even after adjustment for conventional risk factors (Criqui et al., 2015). The 1- and 5-year mortality of CLTI have been reported to be as high as 26% and 56%, respectively, regardless of treatment (Wolfe et al., 1997). ABI <0.90 is associated with more than doubling of the 10-year rates of CVD events and mortality, and total mortality (Fowkes et al., 2008). After 5 years, 20% of patients with IC present an myocardial infarction or stroke and mortality is 10–15% (Weitz et al., 1996). Possible explanations for the PAD patients' poor prognosis lie in accumulation of classical CVD risk factors and in functional impairment and progression of the disease (Criqui et al., 2008; Leeper et al., 2013). However, the exact mechanisms through which PAD is associated with increased risk are not fully understood. Therefore, identification of novel prognostic markers for PAD may improve the understanding of the mechanisms of atherosclerosis, which may ultimately lead to new and better therapies (Cooke et al., 2010).

Altered arterial wall properties, such as arterial stiffness, might be one potential cause of poor prognosis in patients with PAD. Increased arterial stiffness is an important independent determinant of CVD events, mortality and total mortality (Mattace-Raso et al., 2006), and play also an important role in atherosclerosis (Safar et al., 2007). Arterial stiffening may induce arterial remodelling,

wall thickening and development of atheroma. Moreover, arterial stiffness may contribute to ulceration and rupture of atherosclerotic plaques (Lovett et al., 2003).

Pulse wave analysis and assessment of brachial and aortic pulse wave velocity are well established methods for measuring arterial stiffness. We have demonstrated increased aortic pulse wave velocity, augmentation index, and decreased small and large artery elasticity in patients with PAD (Kals et al., 2006; Zagura et al., 2011). Large-scale studies have shown that increased aortic pulse wave velocity and augmentation index, and decreased small and large artery elasticity are independent predictors of CVD, CVD events and mortality (Grey et al., 2003; Mattace-Raso et al., 2006). Moreover, lower small artery elasticity and higher augmentation index were associated with ABI (Khaleghi et al., 2007; Wilkins et al., 2012), which is the most powerful indicator in PAD and is linked to survival (Criqui et al., 2008).

Only a few studies have estimated associations between vascular function and prognosis in the setting of PAD. Endothelial dysfunction predicts postoperative (Gokce et al., 2002) and long-term CVD events in PAD patients (Brevetti et al., 2003; Gokce et al., 2003; Huang et al., 2007). The present thesis tested the hypothesis that arterial stiffness is an independent predictor of all-cause and CVD mortality in symptomatic PAD patients after controlling for classic CVD risk factors (Paper V).

2.3. Summary of the literature review

AAA is a potentially fatal aortic pathology, which is why timely treatment by OSR or EVAR is crucial. In-hospital mortality in elective AAA patients has declined greatly over time. Despite remarkable improvements in short-term survival rates after surgical repair of both elective AAA and ruptured AAA during the last 50 years, the mid- and long-term survival rates remain relatively constant. Current evidence suggests also significant short-term survival benefit from EVAR versus OSR in elective AAA repair, but this benefit is lost during mid- and long-term follow-up. Patients treated by EVAR are more likely to experience aortic complications and reinterventions compared with those treated by OSR.

Still, the benefit of early diagnosis is limited, because most detected AAA are below the currently accepted threshold for definite repair. Surrogate biomarkers for development, growth and rupture could give precise information about how guide proper management of AAA. Development of novel high-throughput technologies (e.g. metabolomics) is a possible approach to gain a better understanding of the pathophysiology of AAA and to find new possible biomarkers for AAA.

The therapeutic approach to patients with PAD, a manifestation of systemic atherosclerosis, includes two aspects. The first is to address specific symptoms of any localization and the risk related to a specific lesion. The second aspect of

management in these patients is related to their increased risk of any CVD event. The goal of revascularization is to restore direct in-line flow to the foot of the affected limb. The anatomical location and extension of arterial lesions, graft material has an impact on revascularization options and results (operative mortality, graft patency rate (GPR), limb salvage rate (LSR)).

Possible explanations for the PAD patients' poor prognosis lie in accumulation of classical CVD risk factors and in functional impairment and progression of the disease. However, the exact mechanisms through which PAD is associated with increased risk are not fully understood. Identification of novel prognostic markers for PAD may improve the understanding of the mechanisms of atherosclerosis, which may ultimately lead to new and better therapies.

3. AIMS OF THE THESIS

The two general aims of the present thesis were: 1) to evaluate the results of surgical and endovascular treatment of patients with AAA and with PAD; and 2) to determine the role of functional and biochemical markers in the pathogenesis and in risk prediction in these patients.

Specific aims

1. To assess short- and mid-term mortality rates and mortality predictors in patients undergoing non-ruptured and ruptured AAA repair.
2. To compare short- and mid-term survival in patients with non-ruptured AAA treated by OSR and EVAR; and to assess the rate of complications and reinterventions after the procedures, as well as to evaluate their impact on survival.
3. To describe the profile of low molecular weight metabolites in AAA patients and to explore if low molecular weight metabolites are linked to AAA development and growth.
4. To evaluate operative mortality, secondary (or cumulative) GPR and LSR after infrapopliteal bypass surgery using venous allografts in patients with PAD.
5. To test the hypothesis that arterial stiffness is an independent predictor of all-cause and CVD mortality in patients with PAD.

4. SUBJECTS AND METHODS

4.1. Study population, design and protocol

4.1.1. Patients with elective and emergency abdominal aortic aneurysm repair (Paper I)

The medical records of the AAA patients undergoing OR or EVAR between 1 January 2004 and 31 December 2015 were retrospectively reviewed. We collected and analyzed patient demographics, comorbidities, medications, imaging studies, and pre-, peri-, and postoperative data from archived hospital records on paper and from records stored with the hospital's online system of patients; 30-day, 90-day, 1-year, 2-year, 3-year, 4-year, and 5-year survival data were documented from the national registry. This study was carried out in accordance with the Declaration of Helsinki of the World Medical Association and the Ethics Committee on Human Research of the University of Tartu (Licence No. 262/T-8). All operations were performed at a single institution by fellowship-trained vascular surgeons; the EVAR procedures were performed by interventional teams consisting of a fellowship-trained vascular surgeon and an interventional radiologist. Patients were considered to meet the criteria for surgical treatment if the maximum AAA diameter was ≥5.5 cm for men and ≥5.2 cm for women; if AAA had grown ≥0.5 cm during the last 6 months or the patient had symptomatic or rAAA.

The primary outcome measure of the study was all-cause mortality rates (30-day, 90-day, and 5-year) after OR and EVAR in patients with eAAA and rAAA. The secondary outcome measure was establishment of the factors related to mortality.

4.1.2. Patients with elective open and endovascular abdominal aortic aneurysm repair (Paper II)

The medical records of the non-ruptured AAA patients undergoing OSR or EVAR between 1 January 2011 and 31 December 2019 at Tartu University Hospital, Estonia, were retrospectively reviewed. We gathered survival data (i.e. the time and place of death) from the national Population Registry (Ministry of the Interior Affairs, Republic of Estonia). Additionally, clinical data from the records of AAA patients, and OSR and EVAR procedures, stored within the hospital's online system, was collected and analysed. This study was carried out in accordance with the Declaration of Helsinki of the World Medical Association and the Ethics Committee on Human Research of the University of Tartu (Licence No. 307/T-20).

All operations were performed at a single institution by fellowship-trained vascular surgeons; the EVAR procedures were performed by interventional teams consisting of a fellowship-trained vascular surgeon and an interventional radiologist. Patients were considered to meet the criteria for surgical treatment

if the maximum AAA diameter was ≥5.5 cm for men and ≥5.2 cm for women; if AAA had grown ≥0.5 cm during the past 6 months, or if the patient had symptomatic non-ruptured AAA. EVAR procedures were usually assigned to patients with several comorbidities and high surgical risk, suitable aortic anatomy and advanced age. Patients were treated by EVAR under general anaesthesia, and stent grafts were implanted through the common femoral artery by puncture or through surgical exploration (mainly in the first years). Bifurcated graft devices (W.L. Gore & Associates, Inc., Newark, Delaware, US; Cook, Bloomington, IN, US; Medtronic Inc., Santa Rosa, CA) were used for all EVAR procedures. Patients were treated by OSR under general anaesthesia, and a tube graft or a bifurcated aorto-bi-iliac of aorto-bi-femoral graft was employed if the iliac arteries were occluded or severely stenosed. All EVAR patients were recommended to attend follow-up within 30 days following intervention, then at six months and one year, and henceforth annually over five years. Clinical and radiological follow-up was conducted according to standard practice and included assessment of AAA by either abdominal plain X-ray, computed tomography or magnetic resonance angiography.

The primary outcome measure of the study was time-dependent short- and mid-term all-cause mortality rates with a cut-off of 5 years for follow-up after OSR and EVAR in patients with non-ruptured AAA. The secondary outcome measure was the number of complications and reinterventions following OSR and EVAR procedures and their effect on survival.

4.1.3. Patients with abdominal aortic aneurysm and healthy controls (Paper III)

From 2008, all patients with AAA and age and gender matched healthy controls in Uppsala were invited to donate blood to explore different biomarkers for AAA progression (Wanhainen et al., 2017). In the current study, blood was collected from two groups of patients with previously diagnosed AAA according to its progression: AAA with fast yearly growth rate (mean 3.3 mm; range 1.3–9.4 mm; n=39) and with slow yearly growth rate (0.2 mm; range –2.6–1.1 mm; n=40); as well as from healthy subjects (i.e. with non-aneurysmal aorta (n=79). All aortic measurements in patients and controls were performed, using ultrasound, by registered nurses, specially trained in ultrasonography, or by ultrasound technicians. The maximum anteroposterior diameter of the infra-renal aorta was measured according to the leading-edge-to-leading-edge principle (Gurtelschmid et al., 2014).

The median interval between the infra-renal aortic measurements was 3.8 years (range 1.3–14). The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Research Ethics Review Board of the Uppsala/Örebro region (Dnr 2007/052). Informed consent was given by all participants prior to the investigation.

The following inclusion criteria were used for AAAs; 1) aortic diameter ≥35 mm, 2) follow-up ≥6 months, and 3) ≤5mm shrinkage during follow-up. In

this pilot study, we included 40 patients with the slowest growth and 39 with the fastest growth. Additionally, 79 patients with a normal aorta at screening were selected as controls.

All participants were asked to complete a standardized health questionnaire on smoking habits and medical history. Coronary artery disease was defined as a history of angina pectoris or myocardial infarction; CVD, as a history of stroke or transient ischemic attack; hypertension, as a history of hypertension or current antihypertensive medication; diabetes mellitus, as a history of dietary- or medically-treated diabetes; and renal insufficiency as a history of a clinically relevant renal impairment. Based on the smoking history, three groups were defined: never-smokers, former smokers and active smokers.

4.1.4. Patients with symptomatic peripheral artery disease (Paper IV)

Between January 1978 and December 1993, 1442 reversed vein bypass procedures were performed for infrainguinal disease at the Tartu University Surgical Hospital (current Tartu University Hospital). A subgroup of 107 (7.4%) infrapopliteal bypasses were performed using reversed vein allograft; the group included 95 men and 12 women with a mean age of 64±10 (range 44–87) years. In 99 (92.5%) limbs the diagnosis was atherosclerosis and in eight (7.5%) was Buerger's disease. Major risk factors included smoking (80.2%), heart disease (26.4%), diabetes (8.3%), hypertension (6.5%) and cerebrovascular disease (5.3%). The indication for operation was CLTI: rest pain (54.2%) or gangrene (45.8%). Pre- and intraoperative DSA was used to identify run-off vessels. The absence of autologous vein was a result of previous saphenous vein stripping in 11 patients (10.3%), previous bypass surgery in 44 (41.1%) and poor quality vein in 52 (48.6%) patients.

Alloveins were harvested using a flexible intraluminal vein stripper during varicose vein surgery. Segments of good quality and with suitable diameter were harvested and lengths were sewn end-to-end to increase graft length. The allografts were stored in saline solution containing heparin and antibiotics at 4°C for up to 10 days. From 1988, all donor patients were screened for hepatitis and HIV, and ABO compatibility was acceptable in the majority of cases.

4.1.5. Patients with symptomatic peripheral artery disease and healthy controls (Paper V)

Patients with PAD (with Fontaine stages II–IV) were prospectively recruited from the Department of Vascular Surgery, Tartu University Hospital, Estonia, between October 2, 2002 and May 24, 2010. The primary end point of this cohort study was mortality (all-cause and CVD). The subjects were all male with angiographically proven PAD, i.e. with occlusion or stenosis of the arteries of the lower extremities. Their ABI was less than 0.90 (range 0.1–0.89). The patients' exclusion criteria were the following (based on clinical examination,

ECG and blood tests): any concomitant acute or chronic inflammatory disease, myocardial infarction, coronary revascularization or cerebrovascular events during the past 6 months, earlier revascularization procedures at the lower limb, upper limb occlusive arterial disease, cardiac arrhythmias, or valve pathologies, diabetes mellitus, malignancies and renal failure. Demographic data, supplied with particulars about the risk factors for CVD, were collected on the study entry day when the vascular indices were measured. Smoking status was defined as current or past versus never. This study was carried out in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the Ethics Committee, University of Tartu. Informed written consent was obtained from each participant.

The subjects were studied and the plasma samples were collected after an overnight fast and abstinence from any medications, tobacco, alcohol and tea or coffee. After 15 minutes of rest in a quiet, temperature-controlled room, ABI and blood pressure were measured and pulse wave analysis was performed. All hemodynamic and pulse wave analysis recordings were made in duplicate for each time point. Thereafter, venous blood samples were drawn from the antecubital fossa for biochemical measurements.

The follow-up period ended in August 4, 2011 (mean follow-up, 4.1±2.2 years). The deceased subjects were identified from the mortality records of Estonia and death was confirmed on the basis of death certificates. All other subjects were considered to be alive at the end of the follow-up period. The causes of death were drawn from death certificates using a telephone interview with the subjects' general practioner or relatives, and were coded in accordance with the *International Classification of Disease* (tenth revision). Death due to acute myocardial infarction, nonhaemorrhagic stroke, or exacerbation of heart failure was defined as CVD death.

Of the 123 subjects in whom arterial stiffness parameters were measured, 5 were excluded from analysis because of the poor quality of the recording of arterial stiffness index, leaving 118 subjects. Additionally, we excluded one subject with an unknown cause of death, leaving 117 subjects for analyses. Power calculation was based on the expected 20% difference in PAD survival, according to the small artery elasticity value. Considering this, about 120 subjects had to be included (two sided test, $\beta=0.2$ at $\alpha=0.05$; RR=0.3).

4.2. Methods

4.2.1. Biochemical analysis (Papers I, II and V)

Peripheral venous and arterial blood samples were collected in serum separator tubes for biochemical analysis (Papers I, II and V). The serum levels of glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, (hs)CRP, sodium, potassium, urea, creatinine, hemogram, eGFR (calculated by the Chronic Kidney Disease Epidemiology Collaboration equation), pH, base excess and

lactate were measured in the local clinical laboratory with automated analyzers using standard laboratory methods. Other blood samples were centrifuged within 30 minutes of collection and the serum was pipetted into Eppendorf tubes. The tubes were stored at −70 °C until assayed. Serum oxidized LDL level was measured using an enzyme-linked immunosorbent assay (Merdcodia Oxidized LDL ELISA, Uppsala, Sweden).

4.2.2. Targeted serum metabolite profiling (Paper III)

Peripheral venous blood samples were collected in plain tubes (Plain BD Vacutainer® Tubes) for metabolomic analysis. All samples were centrifuged within 60 minutes of collection and the supernatant was transferred into 1.5 mL Eppendorf tubes. The tubes were frozen at −70 °C until assayed.

Acetonitrile, formic acid, and water (HPLC–grade) were purchased from Sigma-Aldrich (Germany). An Agilent Zorbax Eclipse XDB C18, 3.0×100 mm, 3.5 µm with Pre-Column SecurityGuard, Phenomenex, C18, 4×3 mm was used with the AbsoluteIDQ® p180 kit (Biocrates Life Sciences AG, Innsbruck, Austria) for the targeted analysis of metabolites.

The serum samples were thawed on ice and processed following the steps in the AbsoluteIDQ® p180 kit's user manual. In summary, the serum (10 µl) was pipetted onto a 96-well plate with added internal standards and dried, using nitrogen, following a derivatization process using phenylisothiocyanate. All samples were measured on QTRAP 4500 (ABSciex, USA) coupled to Agilent 1260 series HPLC (USA), using the C18 column and flow injection analysis. The concentrations of the metabolites were calculated in the vendor's software using internal standards' intensities for reference.

The Biocrates commercially available AbsoluteIDQ® p180 kit enables quantification of up to 188 metabolites from different compound classes. The lipids and hexoses were measured by flow injection analysis-mass spectrometry (FIA-MS) and small molecules were measured by liquid chromatography-mass spectrometry (LC-MS). The experimental metabolomics measurement technique is described in detail by patents EP1897014B1 and EP1875401B1 (at https://patents.google.com/patent/EP1897014B1 and https://patents.google.com/patent/EP1875401B1). Briefly, a 96-well based sample preparation device was used to quantitatively analyze the metabolite profile in the samples. This device consists of inserts that have been impregnated with internal standards, and a predefined sample amount was added to the inserts. Next, a phenyl isothiocyanate (PITC) solution was added to derivatize some of the analytes (e.g. amino acids). After the derivatization was completed, the target analytes were extracted with an organic solvent, followed by a dilution step. The obtained extracts were then analyzed with a LC-MS system. Concentrations were calculated using an appropriate mass spectrometry software (LC part) and Biocrates MetIDQ™ software (FIA part), and the data were imported and merged in MetIDQ for further analysis.

The Biocrates AbsoluteIDQ® p180 kit used in this study is standardized and quality controlled by the manufacturer. It has been proven to be a quantitative and reproducible solution for the measurement of various metabolites as demonstrated by an international ring trial (Siskos et al., 2017) thus illustrating the precision and reproducibility of the analysis.

4.2.3. Measurement of arterial stiffness and ankle-brachial pressure index (Paper V)

Peripheral blood pressure was measured from both arms using a validated oscillometric technique (OMRON M4-I; Omron Healthcare Europe BV®, Hoofddorp, The Netherlands). The arterial waveform was measured in the dominant arm by a Cardiovascular Profiling Instrument (HDI/Pulse Wave CR-2000, Hypertension Diagnostics Inc®, Eagan, USA). This method of vascular assessment is based on a modified 2-element Windkessel model that allows calculation of small and large artery elasticity (Duprez et al., 2013).

The augmentation index and central haemodynamics were assessed by systolic pulse wave analysis using a Sphygmocor apparatus (SphygmoCor; AtCor Medical®, Sydney, Australia) (Zagura et al., 2011). Pulse pressure amplification was expressed as the percentage of increase in pulse pressure in the peripheral (brachial) artery relative to central (aortic) pulse pressure, according to the formula: pulse pressure amplification=100×(peripheral pulse pressure-central pulse pressure)/central pulse pressure. Aortic and brachial pulse wave velocities were measured by sequentially recording the ECG-gated carotid and femoral or radial artery waveforms (SphygmoCor; AtCor Medical®, Sydney, Australia) (Zagura et al., 2011). The ABI was measured using the Bidirectional Doppler MD 6® (D. E. Hokanson Inc, Bellevue, WA, USA). The mean of the two blood pressure readings (from the arm whose blood pressure values were higher) and the lower ABI value of the two legs were included in statistical analysis.

4.2.4. Statistical analysis

Survival after AAA repair (Papers I and II)

Data were collected and analysed using the software R (version 3.3.1 (Paper I) and 3.6 (Paper II) for Windows ((R Core Team (2021); R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). All continuous variables were compared with the Mann–Whitney U test except for age where an unpaired t-test was performed to compare the eAAA and rAAA (Paper I) or OSR and EVAR patient groups (Paper II). Continuous variables are described by medians (interquartile range, IQR) except for age (Papers I and II), and haemoglobin (Paper II) value, which are expressed as mean (standard deviation). Categorical data is presented as the number (%) of patients and was analysed using the Chi-square test. The Kaplan–Meier estimate was used to assess the difference in the survival curves

using the log-rank test. Univariate Cox proportional hazard models were used to determine the potential risk factors related to the prognosis of AAA repair. Joint impacts of factors were estimated using the multivariate Cox model, adjusted for gender, and presented as hazard ratios (HR) with 95% confidence intervals (CI) (Paper I). To determine independent risk factors for 5-year survival, multivariate age-adjusted Cox models were estimated. All variables with $p<0.10$ from the univariate model were implemented to the multivariate Cox model to find independent risk factors. The assumption of proportional hazards was assessed based on the scaled Schoenfeld residuals. The results of the Cox models were presented as HRs with the 95% CI (Paper II), $p<0.05$ was considered statistically significant.

Metabolomic profiling of AAA (Paper III)

Data were analysed using the software R, version 3.3.1 for Windows. Continuous variables are expressed as mean or median and standard deviation (SD) or range and categorical data are expressed as the number (%) of patients or healthy subjects. The chi-square test was used to determine an association between categorical variables. To account for the differences in several clinical parameters between the groups, generalized linear models were built where clinical parameters were added as covariates. The Spearman rank correlation was performed to find potential bivariate associations. All p-values from the models were adjusted for multiple comparisons using a Benjamini & Hochberg false rate discovery of 5%. p-values <0.05 were considered statistically significant.

Operative mortality, graft patency and limb salvage rate in PAD patients (Paper IV)

Patients were examined at 3 months, then 6-monthly for 2 years, and thereafter annually. Grafts were evaluated on clinical grounds. Secondary (or cumulative) GPR and LSR were calculated by the cumulative life-table method; Peto's method was used to assess standard error. A paired Student's t-test was used for comparisons and linear regression analysis was used for correlation. Statistical significance was assumed at the 95% confidence level ($p<0.05$)

Arterial stiffness and mortality in PAD patients (Paper V)

Data were collected and analyzed using the software R, version 2.15.2 for Windows. All data were tested for normality of distribution, and log transformation and/or nonparametric tests were used where appropriate. Continuous data are expressed as means ± SD if distributed normally, or otherwise, as medians with the 25% and 75% percentiles. Dichotomous variables are given as prevalence in number and percentage. Relationships of the AS parameters and potential confounders with all-cause and CVD survival were estimated using the chi-square test for categorical variables and the Student`s t-test or the Mann-Whitney test for continuous variables that had a normal or skewed distribution, respectively. Survival was assessed by the Kaplan-Meier curves and was com-

pared by the log-rank test according to the median of the arterial stiffness parameters. For the arterial stiffness parameters, additional adjustments were made for mean arterial pressure and heart rate. To evaluate whether oxidized LDL levels or red blood cells count added to the predictive value of arterial stiffness, the study population was divided into eight groups: patients with small artery elasticity higher than the median and oxidized LDL or red blood cells count lower than the median; those with both small artery elasticity and oxidized LDL or red blood cells count higher than their respective median values; those with both small artery elasticity and oxidized LDL or red blood cells count lower than their respective median values; and those with small artery elasticity lower than the median value and oxidized LDL or red blood cells count higher than the median value. A Cox proportional hazards regression model was then used to control for the confounders identified by univariate analysis (inclusion criteria $p<0.1$). The proportional hazards assumptions were satisfied. Receiver-operating characteristic (ROC) curves were employed to compute the discriminatory power of different sets of prognostificators. Differences in the discriminatory power between the models were estimated by a nonparametric approach to the analysis of the areas under the ROC curves by using the theory of generalized *U* statistics.

5. RESULTS

5.1. Mortality after non-ruptured and ruptured abdominal aortic aneurysm surgical repair (Paper I)

Elective AAA repair (including 50 EVAR procedures) was performed on 228 patients. EVAR was performed from November 2011. All 48 patients with rAAA were treated with OSR. The follow-up period ended September 22, 2016 (mean follow-up 4.2±3.3 years). The baseline characteristics of the eAAA and rAAA patients are presented in Tables 2 and 3. For the eAAA patients, the 30-day, 90-day, and 5-year mortality rates were 0.9%, 2.6%, and 32%, respectively (Figure 1). The 30-day, 90-day, and 5-year mortality rates for the rAAA patients were 22.9%, 33.3%, and 55.1%, respectively (Figure 2). For all observed follow-up periods (overall, 30 days, 90 days, and 1, 2, 3, 4, and 5 years), the eAAA patients showed better survival rate (all p-values <0.002). Comparison of the eAAA patients undergoing OSR and those undergoing EVAR revealed no difference (data not shown, all p-values >0.2). Multiple regression analysis showed that higher preoperative creatinine levels and older age were independently positively associated with higher 5-year mortality rates in patients with eAAA (Table 4). Because only two deaths occured during 30 days after eAAA repair, it was not reasonable to estimate predictors of short-term mortality. For the rAAA patients, independent risk factors for all-cause 30-day mortality were the lowest perioperative haemoglobin levels and the highest lactate levels (Table 5), but 5-year mortality risk factors were not detected.

Table 2. Baseline characteristics of the study population.

Characteristics	**eAAA** (n = 228)	**rAAA** (n = 48)
Age, years (± SD)	71.8 ± 8.6	73.8 ± 8.4
Gender, n (%)		
Male	191 (84)	36 (75)
Comorbidities, n (%)		
Cardiovascular	203 (89)	37 (77)
Pulmonary	30 (13)	10 (21)
Renal	27 (12)	8 (17)
Malignancies	23 (10)	5 (10)
Cerebrovascular	29 (13)	6 (13)
Diabetes	14 (6)	5 (10)
Other	98 (43)	19 (40)
Smoking, n (%)	109 (50)	8 (38)
Maximal diameter of the aneurysm, cm, median (IQR)	6.5 (5.6–7.8)	8.0 (7.0–10.0)

Table 3. Pre- and perioperative markers of the study population.

Pre- and perioperative markers	**eAAA** (n = 228)	**rAAA** (n = 48)
Preoperative biochemical markers, median (IQR)		
Haemoglobin, g/L	141 (129–151)	107 (100–118)
Haematocrit, %	42 (39–45)	34 (30–36)
Platelet count, 10^9/L	204 (168–238)	198 (154–214)
White Blood Cell count, 10^9/L	7.1 (6.0–8.5)	9.8 (8.1–14.4)
P-Glucose, mmol/L	5.8 (5.3–6.5)	9.0 (6.7–11.4)
S-C-reactive protein, mg/L	5.0 (2.0–11.0)	15.0 (3.0–36.0)
P-sodium, mmol/L	140 (138–141)	138 (136–141)
P-potassium, mmol/L	4.5 (4.2–4.8)	4.2 (3.8–4.4)
S-urea, mmol/L	7.3 (5.8–8.8)	8.6 (6.4–10.3)
S-creatinine, µmol/L	90 (76–113)	103 (92–132)
Preoperative blood pressure, median (IQR)		
Systolic blood pressure, mmHg	140 (123–150)	112 (89–143)
Diastolic blood pressure, mmHg	80 (74–88)	70 (54–87)
Perioperative biochemical markers, median (IQR)		
Lowest haemoglobin, g/L	111 (99–123)	84 (72–94)
Lowest haematocrit, %	34 (31–37)	25 (22–28)
Lowest pH	7.3 (7.3–7.3)	7.2 (7.1–7.3)
Lowest base excess, mEq/L	-4.5 (-6.0…-3.0)	-9.2 (-13.2…-6.1)
Highest lactate, mmol/L	1.4 (1.1–1.9)	5.8 (2.3–7.0)

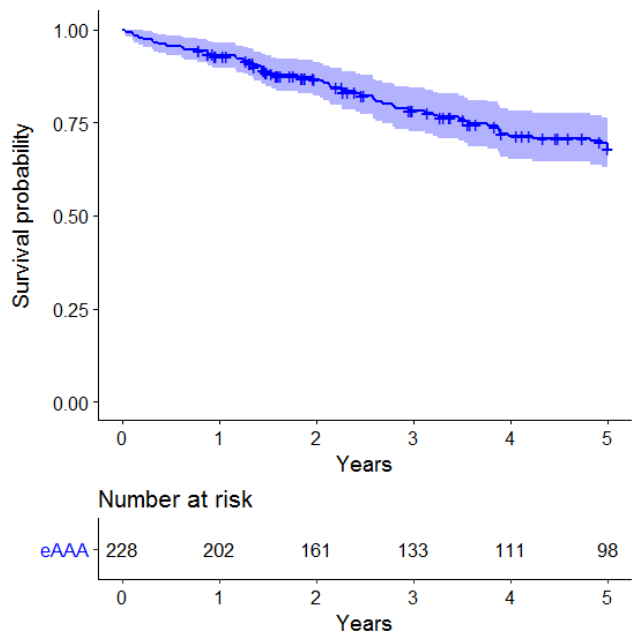

Figure 1. Kaplan-Meier plots showing survival after eAAA repair.

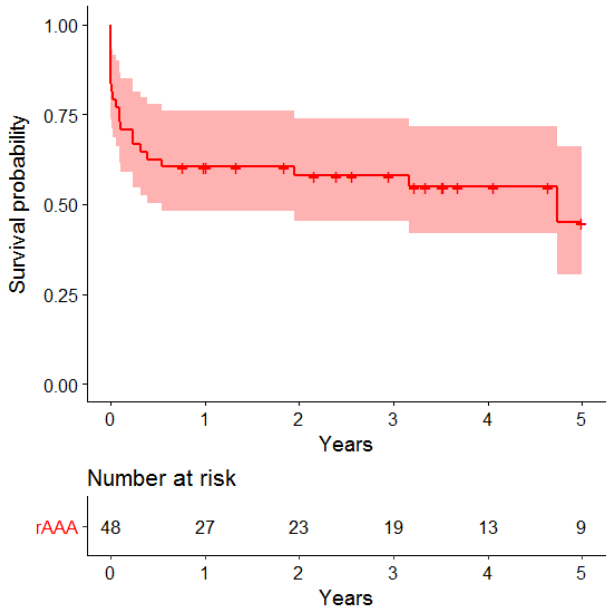

Figure 2. Kaplan-Meier plots showing survival after rAAA repair.

Table 4. Multiple regression analysis of the variables associated with 5-year mortality of eAAA.

Variables	HR (95% CI)	p-value
Preoperative creatinine	1.005 (1.002–1.009)	0.002
Age	1.049 (1.013–1.086)	0.007
Smoking	0.575 (0.323–1.025)	0.061

$R^2 = 0.067$

Table 5. Multiple regression analysis of the variables associated with 30-day mortality of rAAA.

Variables	HR (95% CI)	p-value
Perioperative lowest haemoglobin	0.955 (0.922–0.989)	0.009
Perioperative highest lactate	1.152 (1.004–1.323)	0.044
Age	1.005 (0.923–1.093)	0.916

$R^2 = 0.283$

5.2. Survival, complications and reinterventions after elective open and endovascular abdominal aortic aneurysm repair (Paper II)

A total of 225 non-ruptured AAA patients were treated operatively out of whom 95 (42.2%) with EVAR and 130 (57.8%) with OSR procedures. The follow-up period ended on 1 August 2020 (mean follow-up for all patients was 3.7 ± 2.3 years; for EVAR, 3.6 ± 2.0 and for OSR, 3.8 ± 2.4 years). The baseline characteristics of the EVAR and OSR patients are presented in Tables 6 and 7. Comparison of the patients' baseline characteristics revealed that significantly lower preoperative haemoglobin, haematocrit, platelet and white blood cell values, smaller maximum diameter of AAA and fewer current smokers were associated with the EVAR group. The OSR patients were associated with statistically younger age, lower creatinine and urea levels, and with less renal and cerebrovascular system comorbidities, and with less frequent usage of antithrombotic and heart medications.

For EVAR patients, 30-day, 90-day and 5-year all-cause mortality was 0% (95% CI 0–0%), 1.1% (95% CI 0–3.1%) and 50.0% (95% CI 37.0–60.3%), respectively. Thirty-day, 90-day and 5-year all-cause mortality for OSR patients was 2.3% (95% CI 0–4.9%), 2.3% (95% CI 0–4.9%) and 24.7% (95% CI 14.9–33.4%), respectively (Figure 3). The corresponding values for all elective AAA cases (EVAR and OSR combined) were 1.3% (95% CI 0–2.8%), 1.8% (95% CI 0–3.5%) and 36.8% (95% CI 28.7–44.1%), respectively. The differences in the survival estimates between the OSR and EVAR groups at 30-day and 90-day points were statistically irrelevant (p=0.140, p=0.480, respectively), but OSR patients showed statistically significantly higher 5-year survival (p=0.002).

Endoleaks were detected in 47 cases (49.5%) and arterial/graft thrombosis, in five cases (5.3%) among the EVAR patients. Type II endoleaks were considered a complication only in case the aneurysm was growing more than 5 mm and/or endoleak needed specific reintervention. In total, 25 type II endoleaks were detected on the peri-operative angiogram or on the first follow-up CTA, but only 2 of them were considered a clinically relevant complication. EVAR patients had no significantly higher complication risk compared to OSR patients: a total of 29 postoperative graft related complications were seen in 25 EVAR patients and a total of 22 postoperative complications occurred in 22 OSR patients (26.3% vs 16.9%, p=0.122). All endoleaks, postoperative complications and reinterventions in EVAR and OSR patients are listed in Table 8. Out of the 95 EVAR patients, 10 (10.5%) required reinterventions: two inferior mesenteric artery embolizations (due to type II endoleak), two aortic extender implantations (due to type Ia endoleak), one iliac extender insertion (due to type Ib endoleak), four femoro-femoral cross-over bypasses, and two intra-arterial thrombolyses. One patient required femoro-femoral bypass after the insufficient result of thrombolysis. Fifteen (11.5 %) out of the 130 OSR patients required reinterventions: 6 abdominal wall repairs and debridement (due to dehiscence/

infection of aponeorosis and/or incisional hernias), 5 revascularisations (open thrombectomy or bypass surgery, endovascular angioplasty/stenting), 3 surgical haemostases and one surgical abdominal adhesiolysis. Reintervention rates for the EVAR and OSR groups did not differ statistically (10.5% vs 11.5%, p=0.981).

According to Cox univariate analysis, renal diseases (HR=2.340, 95% CI 1.362–4.020, p=0.002), comorbid malignancies (HR=3.287, 95% CI 1.871–5.775, p<0.001), cerebrovascular diseases (HR=1.939, 95% CI 1.068–3.518, p=0.029), and EVAR *versus* OSR procedure (HR=2.155, 95% CI 1.296–3.584, p=0.003) were significantly associated with poorer 5-year survival. Postoperative graft related complications and reinterventions did not show an increase in 5-year total mortality risk in EVAR patients (p=0.893 and p=0.124, respectively). In OSR patients, postoperative complications, but not reinterventions, increased 5-year mortality risk (p=0.034, p=0.254, respectively).

Multivariate analysis showed that greater aneurysm diameter, EVAR procedure, male gender and cerebrovascular diseases were independently positively associated with 5-year mortality (Table 9). Postoperative complications, as well as reinterventions did not independently increase 5-year total mortality risk in AAA patients.

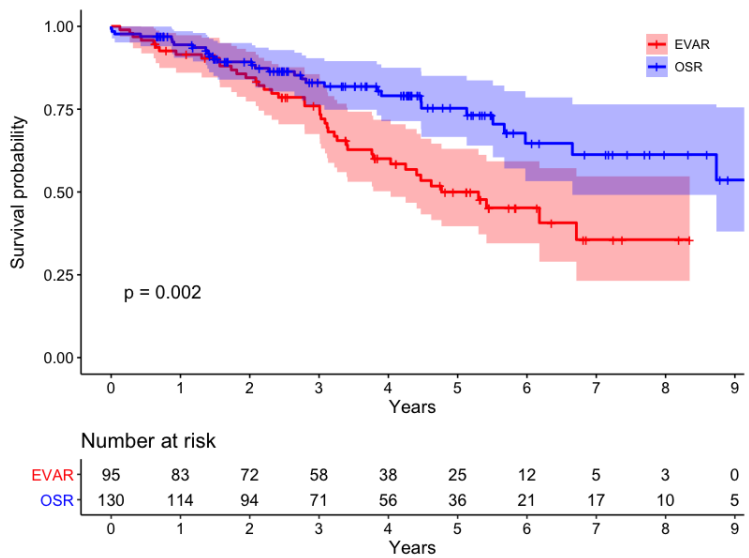

Figure 3. Kaplan-Meier plots showing 5-year survival after OSR and EVAR.

Table 6. Baseline characteristics of the study population

Characteristics	**EVAR** (n = 95)	**OSR** (n = 130)	**p-value**
Age, years (± SD)	77 ± 6.6	69 ± 7.7	< 0.001
Male gender, n (%)	78 (82)	113 (87)	0.419
Comorbidities, n (%)			
Cardiovascular diseases	88 (94)	113 (87)	0.160
Pulmonary diseases	23 (25)	21 (16)	0.169
Renal diseases	23 (25)	16 (12)	0.03
Malignancies	19 (20)	15 (12)	0.110
Cerebrovascular diseases	20 (21)	13 (10)	0.03
Diabetes	14 (15)	20 (15)	1.000
Other diseases	61 (65)	81 (62)	
Medications, n (%)			
Antithrombotic therapy	59 (62.1)	53 (40.8)	0.002
Heart medications	86 (90.5)	101 (77.7)	0.018
Statins	32 (33.7)	45 (34.6)	0.997
Antidiabetic medications	14 (14.7)	19 (14.6)	1.000
Smoking, n (%)	14 (15)	69 (56)	< 0.001
Maximal diameter of aneurysm, cm, median (IQR)	6.0 (5.4–6.8)	6.3 (5.7–7.5)	0.012

Table 7. Preoperative markers of the study population

Preoperative markers	**EVAR** (n = 95)	**OSR** (n = 130)	**p-value**
Biochemical markers			
Haemoglobin (g/L) (SD)	135 ± 16	148 ± 18	< 0.001
Haematocrit (%) (IQR)	41 (38–44)	43 (40–46)	0.001
Platelet count (10^9/L) (IQR)	197 (156–235)	218 (185–251)	0.002
White blood cell count (10^9/L) (IQR)	6.7 (5.8–8.1)	7.4 (6.4–8.7)	0.005
P-Glucose (mmol/L) (IQR)	6.0 (5.5–6.5)	5.8 (5.4–6.5)	0.840
S-C-Reactive protein (mg/L) (IQR)	3.0 (2.0–7.0)	4.0 (1.0–11.0)	0.385
P-Sodium (mmol/L) (IQR)	141 (139–143)	140 (138–142)	0.036
P-Potassium (mmol/L) (IQR)	4.4 (4.1–4.7)	4.3 (4.0–4.5)	0.161
S-Urea (mmol/L) (IQR)	7.3 (6.0–9.2)	6.1 (5.0–8.2)	0.001
S-Creatinine (µmol/L) (IQR)	95 (82–118]	84 (71–103)	0.001
Systolic blood pressure (mmHg) (IQR)	132 (120–146)	134 (124–145)	0.308
Diastolic blood pressure (mmHg) (IQR)	81 (76–89)	80 (76–88)	0.578

Table 8. Endoleaks, complications and reinterventions during 5-year surveillance in elective AAA patients.

	Successful EVARs completed (n=95)		**Open repairs completed** (n=130)	
Endoleak and complication	Number of patients with endoleak and complication	Number of patients with reintervention	Number of patients with complication	Number of patients with reintervention
Endoleak	47			
Type Ia	15	2		
Type Ib	5	1		
Type II	25*	2		
Type III	1			
Endotension	1			
Arterial or graft thrombosis	5**	5	5	5
Incisional hernia, wound dehiscence or infection			8	6
Other (postoperative ileus, bleeding, pneumonia, myocardial infarction)			9	4
In total 79 endoleaks and complications in 70 patients	48 of 95 (50.5 %; 95% CI 40.1–60.9%)	10 of 95 (10.5 %; 95 % CI 5.2–18.5%)	22 of 130 (16.9 %; 95 % CI 10.9–24.5 %)	15 of 130 (11.5 %; 95 % CI 6.6–18.3%)

* Primary type II endoleaks detected on the peri-operative angiogram or on the first follow-up computed tomography angiogram

** 4 patients with arterial/graft thrombosis and concomitant endoleak

Table 9. Multiple regression analysis of the variables associated with 5-year mortality of AAA patients.

Variables	**HR (95% CI)**	**p-value**
Aneurysm diameter	1.218 (1.045–1.421)	0.012
AAA procedure: EVAR	2.184 (1.158–4.120)	0.016
Sex: Male	2.924 (1.157–7.388)	0.023
Cerebrovascular diseases	2.033 (1.078–3.833)	0.028
Age	1.037 (0.995–1.081)	0.085

$R^2 = 0.30$, concordance = 0.68 (se = 0.04)

5.3. Amino acids and (lyso)phosphatidylcholines in patients with abdominal aortic aneurysm (Paper III)

The clinical baseline characteristics of the infra-renal AAA patients and the controls are shown in Table 10.

Table 10. Baseline characteristics of the study population.

Characteristics	**Controls** (n = 79)	**AAA** (n = 79)	**p-value**
Baseline diameter, mm (95% CI)	19 (18–19)	42 (40–43)	<0.001
Age, years	All 65	68 (67–69)	0.01
Male gender	All men	All men	-
Comorbidities,			
Hypertension, % (95% CI)	32.9% (22.7–44.4)	67.5% (56.1–77.6)	<0.001
Coronary artery disease,%(95% CI)	13.9% (7.2–23.6)	50.0% (38.6–61.4)	<0.001
Cerebrovascular disease,%(95% CI)	3.8% (0.8–10.7)	18.8% (10.2–27.3)	0.04
Diabetes mellitus, % (95% CI)	6.3 % (2.1–14.2)	15.0% (8.0–24.7)	0.07
Renal insufficiency, % (95% CI)	0%	10.0% (4.4–18.8)	0.06
Smoking,			
Never smoked, %	41.8 %	16.5%	
Stopped smoking, %	55.7%	65.8%	<0.001
Active smoking, %	2.5%	17.7%	
Medication,			
Aspirin, % (95% CI)	24.1% (15.1–35.0)	58.2% (46.6–69.2)	<0.001
Statins, % (95% CI)	22.8% (14.1–33.6)	51.9% (40.3–63.3)	<0.001

Data is given as mean or percentage (95% CI).

The patients of the AAA group had significantly older age and more comorbidities (hypertension, coronary artery disease, CVD), they were treated more frequently by acetylsalicylic acid (aspirin) and statins, and there were more active smokers and less never-smokers among them, compared with the control group. There were no significant differences in occurrence of diabetes, renal insuffuciency between the study groups. Out of 186 measured low-molecular weight metabolites, the levels of only four amino acids (histidine, asparagine, leucine, isoleucine) and four phosphatidylcholines (PC.ae.C34.3, PC.aa.C34.2, PC.ae.C38.0, lysoPC.a.C18.2) were found to be significantly reduced (p<0.05) after adjustment for confounders (age, smoking status, hypertension, coronary artery disease, CVD, diabetes mellitus, renal insufficiency and medications (aspirin, statins)) between the AAA patients (fast and slow growth rates combined) and the controls (Table 11, Figure 4). There were no significant changes in the metabolites distinguishing the infra-renal AAA patients with slow or fast growth rate from the controls, or distinguishing the patients with low growth rate from those with high growth rate (data not shown). There were multiple significant linear correlations between eight metabolites (Tables 12 and 13). Furthermore, after dividing AAA patients into terciles according to aortic baseline diameter (36/41/47mm), patients in the third tercile (47mm) showde

negative correlation between PC.aa.C34.2 and aortic diameter (r= -0.50, p=0.009); inverse correlation occurred also between His and diabetes (r= -0.45, p=0.02); His (r= -0.48, p=0.01), Leu (r= -0.39, p=0.04), PC.aa.C34.2 (r= -0.43, p=0.03), PC.ae.C34.3 (r= -0.44, p=0.02) and PC.ae.C38.0 (r= -0.39, p=0.04) associated inversely with renal insufficiency; and PC.aa.C34.2 correlated inversely with usage of statins (r= -0.41, p=0.04).

Table 11. Low-molecular weight metabolites in plasma from infra-renal AAA patients and controls*

Metabolites **Amino acids**	**Controls** (n = 79)	**All AAA** (n = 79)	**p-value****	**p-value *****
His	103.0±20.3	86.4±20.1	0.018	<0.001
Asn	53.2±12.2	45.5±10.5	0.018	<0.001
Ile	118.0±38.9	92.3±29.5	0.043	0.001
Leu	227.7±75.1	175.1±55	0.043	0.001
Phosphatidylcholines				
PC.ae.C34.3	5.5±2.1	4.1±1.3	0.018	<0.001
PC.ae.C38.0	2.2±0.7	1.7±0.6	0.046	0.002
LysoPC.a.C18.2	55.5±21.1	43.3±20.8	0.046	0.002
PC.aa.C34.2	334.7±84	286.8±82.8	0.047	0.002

* Only the metabolites that had significantly different levels after adjustment for clinical parameters (age, hypertension, coronary artery and cerebrovascular diseases, renal insufficiency, smoking, diabetes and medications (statins, acetylsalicylic acid)) between healthy subjects and AAA patients are presente in this Table. The concentrations of all metabolites are presented as μM ± standard deviation.

** Benjamini-Hochberg adjusted false discovery rate (FDR) p-value

*** p-value from model

His histidine; Asn asparagine; Leu leucine; Ile isoleucine; PC.ae.C34.3 phosphatidylcholine acyl-alkyl C34:3; PC.aa.C34.2 phosphatidylcholine diacyl C34:2; PC.ae.C38.0 phosphatidylcholine acyl-alkyl C38:0; LysoPC.a.C18.2 lysophosphatidylcholine acyl C18:2

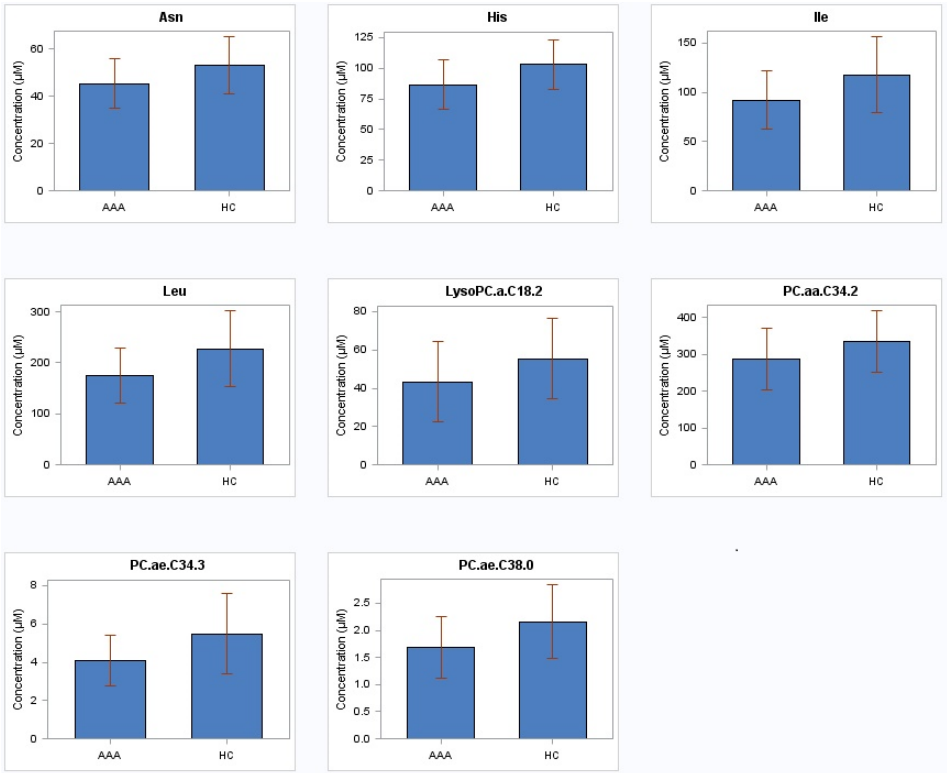

Figure 4. Amino acids and phosphatidylcholines in plasma from 79 patients with AAA and from 79 healthy subjects (HC) with non-aneurysmal aorta. The concentrations of all metabolites are presented as µM ± standard deviation.

Table 12. Correlation matrix of metabolites for AAA patients (with r- and p-values).

	His	**Asn**	**Ile**	**Leu**	**PC.ae. C34.3**	**PC.ae. C38.0**	**LysoPC.a. C18.2**	**PC.aa. 34.2**
His	1.0	0.61 <0.001	0.51 <0.001	0.56 <0.001	0.52 <0.001	0.44 <0.001	0.58 <0.001	0.61 <0.001
Asn	0.61 <0.001	1.0	0.51 <0.001	0.54 <0.001	0.27 0.015	0.23 0.039	0.42 <.001	0.23 0.044
Ile	0.51 <0.001	0.51 <0.001	1.0	0.94 <0.001	0.31 0.006	0.23 0.043	0.47 <0.001	0.42 <0.001
Leu	0.56 <0.001	0.54 <0.001	0.94 <0.001	1.0	0.28 0.011	0.26 0.021	0.39 <0.001	0.39 <0.001
PC.ae. C34.3	0.52 <0.001	0.27 0.015	0.31 0.006	0.28 0.011	1.0	0.53 <0.001	0.63 <0.001	0.77 <0.001
PC.ae. C38.0	0.44 <0.001	0.23 0.039	0.23 0.043	0.26 0.021	0.53 <0.001	1.0	0.44 <0.001	0.58 <0.001
LysoPC.a. C18.2	0.58 <0.001	0.42 <0.001	0.47 <0.001	0.39 <0.001	0.63 <0.001	0.44 <0.001	1.0	0.66 <0.001
PC.aa. C34.2	0.61 <0.001	0.23 0.044	0.42 <0.001	0.39 <0.001	0.77 <0.001	0.58 <0.001	0.66 <0.001	1.0

Table 13. Correlation matrix of metabolites for controls (with r- and p-values).

	His	**Asn**	**Ile**	**Leu**	**PC.ae. C34.3**	**PC.ae. C38.0**	**LysoPC.a. C18.2**	**PC.aa. C34.2**
His	1.0	0.71 <0.001	0.58 <0.001	0.59 <0.001	0.47 <0.001	0.38 <0.001	0.41 <0.001	0.50 <0.001
Asn	0.71 <0.001	1.0	0.41 <0.001	0.37 <0.001	0.45 <0.001	0.29 0.008	0.33 0.003	0.32 0.004
Ile	0.58 <0.001	0.41 <0.001	1.0	0.97 <0.001	0.25 0.03	0.30 0.008	0.19 0.09	0.46 <0.001
Leu	0.59 <0.001	0.37 <0.001	0.97 <0.001	1.0	0.22 0.05	0.28 0.01	0.14 0.23	0.44 <0.001
PC.ae. C34.3	0.47 <0.001	0.45 <0.001	0.25 0.03	0.21 0.05	1.0	0.51 <0.001	0.65 <0.001	0.67 <0.001
PC.ae. C38.0	0.38 <0.001	0.29 0.008	0.30 0.008	0.28 0.014	0.51 <.001	1.0	0.40 <0.001	0.57 <0.001
LysoPC.a. C18.2	0.41 <0.001	0.33 0.003	0.19 0.09	0.14 0.23	0.65 <0.001	0.40 <0.001	1.0	0.57 <0.001
PC.aa. C34.2	0.50 <0.001	0.32 0.004	0.46 <0.001	0.44 <0.001	0.67 <0.001	0.57 <0.001	0.57 <0.001	1.0

5.4. Mortality, graft patency and limb salvage rate after bypass surgery in patients with peripheral artery disease (Paper IV)

There were 66 primary and 41 reoperations (Table 14). Most of the latter were femoro-tibial reconstructions undertaken after autogenous femoro-popliteal of femoro-tibial bypass failure. Thirty-six patients had undergone one and five patients two previous operations. The majority (72.9%) of proximal anastomoses were made at the common femoral artery, the remaining were made at the superficial femoral artery (20.6%) and at the popliteal artery (6.5%). The sites of all distal anastomosis below the knee are presented in Figure 5. All anastomoses were made employing 5/0 or 6/0 Prolene sutures in an end-to-side fashion, the distal anastomosis being performed first. Heparin was given for the first 24 hours after surgery at a dosage of 5000 IU every 4 hours. Oral coumadin therapy was started on the first postoperative day and continued after the patients were discharged from the hospital. Run-off was staged according the the angiographic index. Each patient's tibial artery scored 1, the peroneal artery 0.5. A poor angiographic index, lower than or equal to 1, occurred in 76.0% of the cases (Figure 6).

Table 14. Distribution of 107 infrapopliteal primary operations and reoperations with venous allografts

Procedure	**No. of operations**	
Type of operation	Femoro-popliteal bypass	Femoro-tibial bypass
Primary operation	34 (31.7)	32 (29.9)
Reoperation	6 (5.6)	35 (32.7)
Total	40 (37.3)	67 (62.6)

Values in parentheses are percentages.

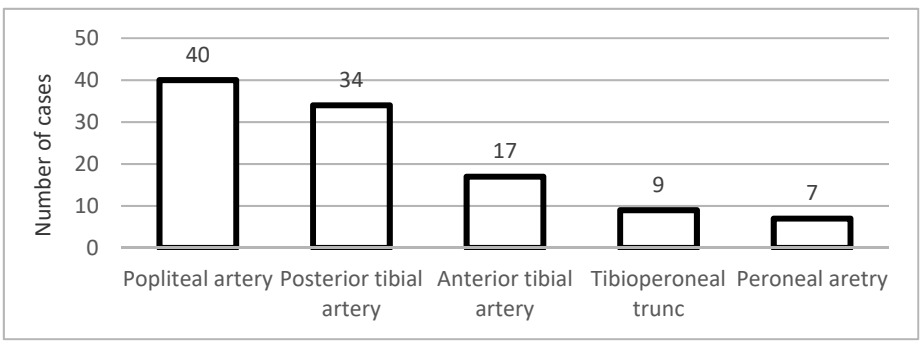

Figure 5. Level of distal anastomosis for 107 operations

Early results of allograft bypass operations are presented in Table 15. Four patients (3.7%) died postoperatively. The causes of death were myocardial infarction (2) and graft infection with haemorrhage (2). Mean follow-up was 64 months.

Late mortality occurred in 12 patients (11.2%), mostly as a result of co-morbitities. Of the 91 surviving patients, six (6.6%) were lost to follow-up. At 30 days, 1, 3 and 5 years after the operation the secondary GPR were 82.9%, 64.5%, 38.2% and 20.6, respectively, and the LSR were 84.3%, 68.4%, 46.1% and 30.6%, respectively (Figure 7). The difference between GPR and LSR remained statistically insignificant.

GPR of infrapopliteal primary and reoperations with venous allografts at 1, 3 and 5 years after the operation was 76.1%, 52.7% and 33.6%, and 41.2%, 19.6% and 9.6%, respectively (Figure 8). The difference between the GPR of the primary and reoperations remained statistically significant ($p<0.05$). The secondary GPR of femoro-popliteal (below the knee) and femoro-tibial bypasses with venous allografts at 1, 3 and 5 years after the operation was 58.8%, 41.1% and 30.2%, and 66.3%, 38.1% and 17.4%, respectively (Figure 9). In this series no statistically significant difference was revealed in the secondary GPR between femoro-popliteal (below the knee) and femoro-tibial allovenous bypass grafts.

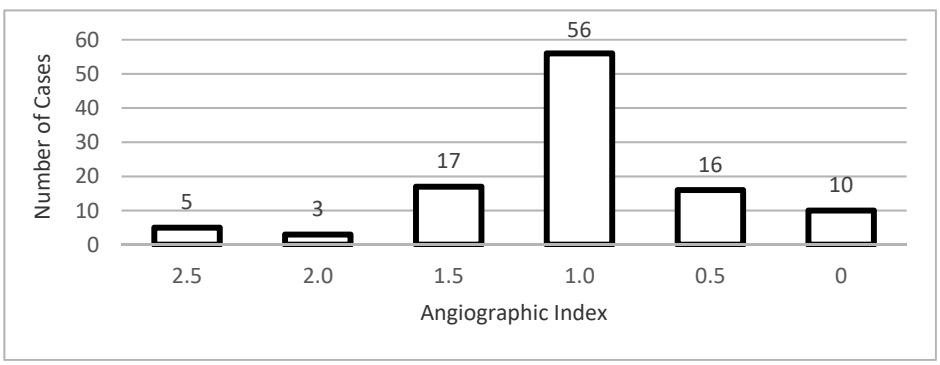

Figure 6. Run-off according to angiographic index in 107 operations

Table 15. Early results (up to 30 days) after infrapopliteal bypass surgery with venous allografts

Procedure	No. of operations	No. of patent grafts	No. of thrombosed grafts	No. of deaths
Primary operation	66	57 (86.4)	7 (10.6)	2 (3.0)
Reoperation	41	28 (68.3)	11 (26.8)	2 (4.9)
Total	107	85 (79.4)	18 (16.8)	4 (3.7)

Values in parentheses are percentages.

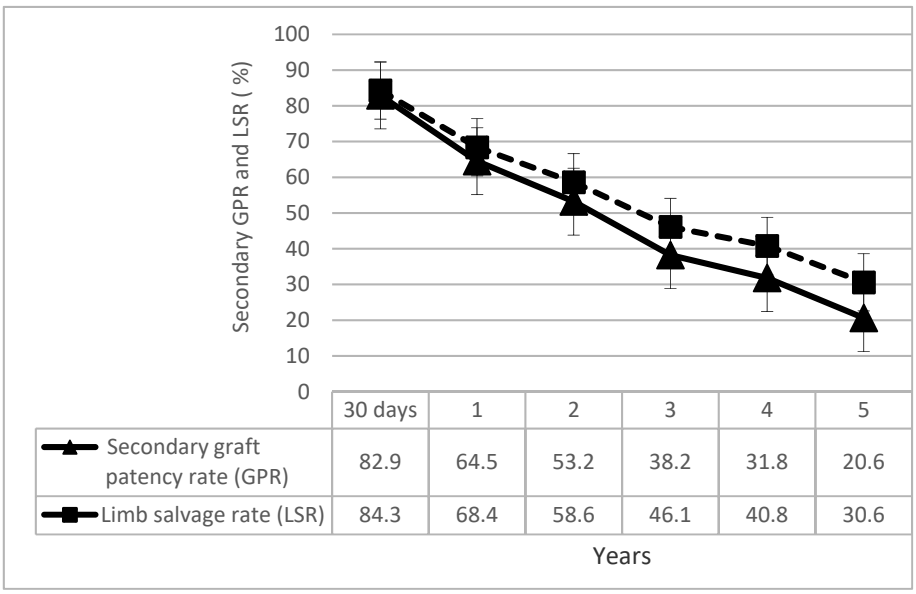

Figure 7. Secondary GPR and LSR for infrapopliteal bypass surgery with venous allografts

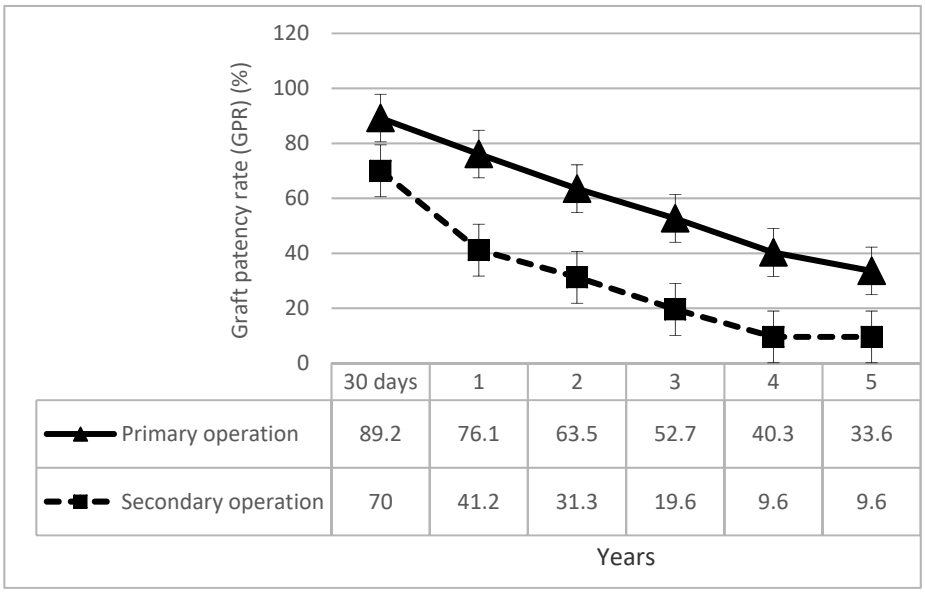

Figure 8. GPR for primary and secondary infrapopliteal bypass surgery with venous allografts

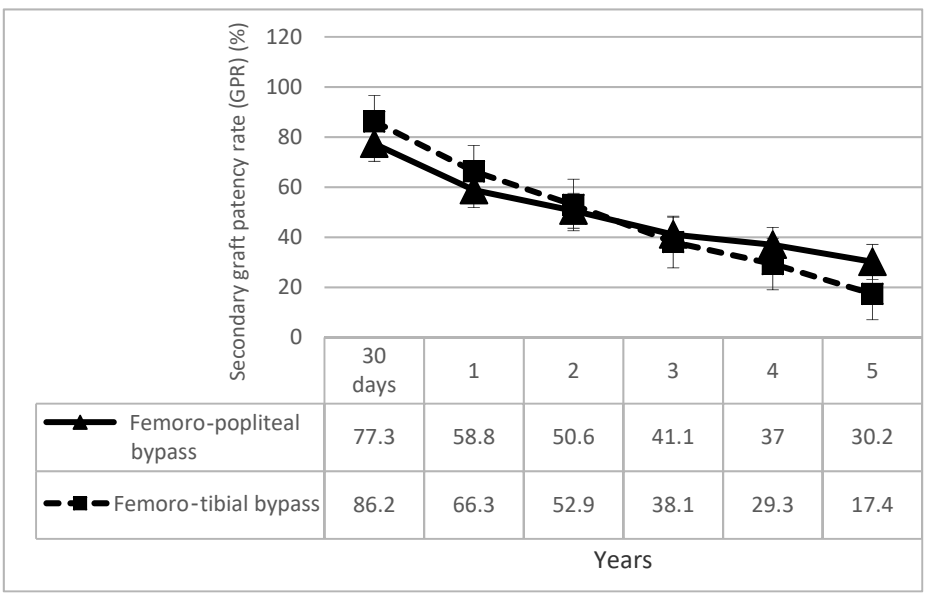

Figure 9. Secondary GPR for femoro-popliteal (below the knee) and femoro-tibial bypass surgery with venous allografts

5.5. Association between arterial elasticity and mortality in patients with symptomatic peripheral artery disease (Paper V)

The 117 patients studied had stage II (n=75), III (n=29), or IV (n=13) of chronic ischaemia as defined by Fontaine. Forty six (39.3 %) patients with arterial hypertension and twenty-three (19.7%) patients with coronary artery disease as the co-morbidity were included in the study. A nonsignificant proportion of the patients used concomitant medications: 46 patients used pentoxifylline; 31 patients, aspirin; 14 patients, statins; 18 patients, angiotensin-converting enzyme inhibitors; 19 patients, calcium channel blockers; 11 patients, angiotensin-receptor blockers; 8 patients, beta-blockers; and 5 patients, diuretics. The mean duration of the follow-up period was 4.1±2.2 years. During that time 32 fatal events occurred; 10 (31.3%) patients sustained a CVD death: 2 (6.3%) died due to acute myocardial infarction, 1 (3.1%) had a fatal ischemic stroke and 7 (21.9%) patients died due to exacerbation of chronic heart failure. The baseline clinical and biochemical characteristics of the survivors and non-survivors are presented in Table 16. As is evident, the non-survivors had lower BMI, haemoglobin and red blood cells count, and higher oxidized LDL values. The non-survivors had also a lower glucose value, however, the glucose level was within a normal range in both groups.

The arterial stiffness parameters for the survivors and non-survivors are presented in Table 17. In univariate analysis, lower small artery elasticity and peripheral pulse pressure, and higher augmentation index were associated with increased all-cause mortality. The large artery elasticity, brachial and aortic pulse wave velocity, augmentation pressure and central pulse pressure for the study groups were comparable. Lower pulse pressure amplification showed a trend for association with higher all-cause mortality (p=0.08). As the Kaplan-Meier survival curves demonstrate (Figure 10), the incidence of all-cause (left) and CVD (right) deaths during follow-up was higher in PAD patients with small artery elasticity below the median value than in those with small artery elasticity above the median value. In log-rank test, all-cause, but not CVD, mortality was related to augmentation index corrected for a heart rate of 75 beats/min (p=0.04; p=0.89, respectively). Oxidized LDL was related to CVD mortality (p=0.01), but remained of borderline significance for all-cause mortality (p=0.08). Conversely, when the population was divided according to the median value of large artery elasticity, brachial and aortic pulse wave velocity and augmentation index, all-cause survival probability was not associated with arterial stiffness (p=0.19, p=0.89, p=0.73, p=0.24, respectively). The variables that met the entry criterion (p=0.1 in univariate analysis) were included in the Cox proportional hazard model: BMI, peripheral systolic blood pressure, glucose, haemoglobin, red blood cells count, oxidized LDL, small artery elasticity, augmentation index, peripheral pulse pressure and pulse pressure ampli-

fication. The independent significant predictors of all-cause and CVD mortality were small artery elasticity and red blood cells count (Table 18).

The results of an additional Kaplan-Meier analysis for the four subgroups of PAD patients, divided according to the median values of small artery elasticity and oxidized LDL or red blood cells count, are shown in Figure 11. The analysis revealed that oxidized LDL and red blood cells count improved slightly the prognostic value of small artery elasticity, which was confirmed by Cox analysis. Compared with patients with small artery elasticity above the median value and oxidized LDL below the median value, those with both small artery elasticity and oxidized LDL above the median value showed a 1.8-fold increase in the all-cause mortality risk (95% CI, 0.45–7.32; p=0.41). Also, patients with both small artery elasticity and oxidized LDL below the median value showed a 2.7-fold increase in the risk (95% CI, 0.59–11.99; p=0.20). The highest risk for future all-cause mortality was observed in patients with small artery elasticity below the median value and oxidized LDL above the median value (RR 4.6; 95% CI, 1.33–15.86; p=0.02). Compared with patients with both small artery elasticity and red blood cells count above the median value, those with small artery elasticity above the median value and red blood cells count below the median value had a 1.9-fold increase in the risk (95% CI, 0.48–7.7; p=0.36). Patients with small artery elasticity below the median value and red blood cells above the median value had a 4.1-fold increase in the risk (95% CI, 1.13–14.89; p=0.03). The highest risk for future all-cause mortality was observed in patients with both small artery elasticity and red blood cells count below the median value (RR 4.6; 95% CI, 1.3–16.0; p=0.02).

The area under the ROC curve (Figure 12) was 0.70 for the model on the basis of age, BMI, smoking, total cholesterol, HDL-C, glucose, mean arterial pressure, heart rate and ABI. When small artery elasticity and oxidized LDL were added to this model, the discriminatory power improved up to 0.82 (p=0.006).

Table 16. Clinical and Biochemical Characteristics of the Study Population.

Characteristics	**Survivors** (n=85)	**Non-survivors** (n=32)	**p-value**
Age (years)	61.8 ± 8.1	62.9 ± 6.5	0.43
Body mass index (kg/m^2)	25.2 ± 4.1	23 ± 2.9	0.001
Coronary heart disease, n (%)	17 (20)	6 (19)	1.0
Hypertension, n (%)	31 (36)	15 (47)	0.42
Smoking (past+current), n (%)	83 (98)	31 (97)	1.0
Peripheral systolic blood pressure (mmHg)	141 (128–158)	135 (128–142	0.08
Peripheral diastolic blood pressure (mmHg)	78 (73–84)	80 (74–83)	0.62
Central systolic blood pressure (mmHg)	129 (119–142)	126 (121–133)	0.35
Central diastolic blood pressure (mmHg)	79 (75–85)	80 (75–85)	0.65
Mean arterial pressure (mmHg)	99 (93–109)	98 (92–106)	0.53
Heart rate (beats per minute)	66 (59–72)	67(61–74)	0.79
Ankle-brachial index	0.5 (0.3–0.6)	0.4 (0.1–0.5)	0.17
Total cholesterol (mmol/L)	5.9 ± 1.2	5.9 ± 1.1	0.92
HDL-cholesterol (mmol/L)	1.3 (1–1.4)	1.3 (1.1–1.4)	0.31
LDL-cholesterol (mmol/L)	4.2 ± 1.1	4 ± 1.2	0.36
Triglycerides (mmol/L)	1.6 (1.3–2.1)	1.4 (1.2–1.7)	0.16
Glucose (mmol/L)	5.5 (4.9–5.9)	5 (4.8–5.4)	0.009
hsCRP (mg/L)	2.9 (1.1–7.7)	4.6 (2–7.7)	0.16
Creatinine (mmol/L)	78 (68–85)	72 (64–82)	0.25
eGFR (ml/min/1.73m^2)	97 (85–111)	100 (88–116)	0.61
Haemoglobin (g/L)	149.5±14.9	141.4±16.7	0.02
Red blood cells count (x 10^{12}/L)	4.9 (4.5–5.1)	4.7 (4–4.9)	0.009
Oxidized LDL (U/L)*	78 (57–111)	128 (95–177)	0.001

Values are means (±SD), medians (with 25% and 75% percentiles) or prevalence (%).
* values are available for 113 patients.

Table 17. Arterial Stiffness Parameters of the Study Population.

Characteristics	Survivors (n=85)	Non-survivors (n=32)	p-value
Large artery elasticity index (mL/mmHg*10)	12.1 (8.8–15.6)	12.4 (10–15.1)	0.73
Small artery elasticity index (mL/mmHg*100)	2.9 (2.3–3.8)	2.1 (1.8–2.8)	<0.001
Augmentation index (%)	32 (26–39)	38 (31–41)	0.03
Augmentation index@75 (%)	28.1±8.5	31.7±7.2	0.03
Aortic pulse wave velocity (m/s)	10±2.5	10.2±2.1	0.78
Brachial pulse wave velocity (m/s)	8.8±1.4	8.7±1	0.77
Augmentation pressure (mmHg)	16.5±6.9	17.7±5.5	0.31
Peripheral pulse pressure (mmHg)	61 (53–70)	58 (51–62)	0.04
Central pulse pressure (mmHg)	50 (43–57)	47 (42–52)	0.20
Pulse pressure amplification	23 (16–30)	20 (13–24)	0.08

Values are means (±SD), medians (with 25% and 75% percentiles) or prevalence (%).

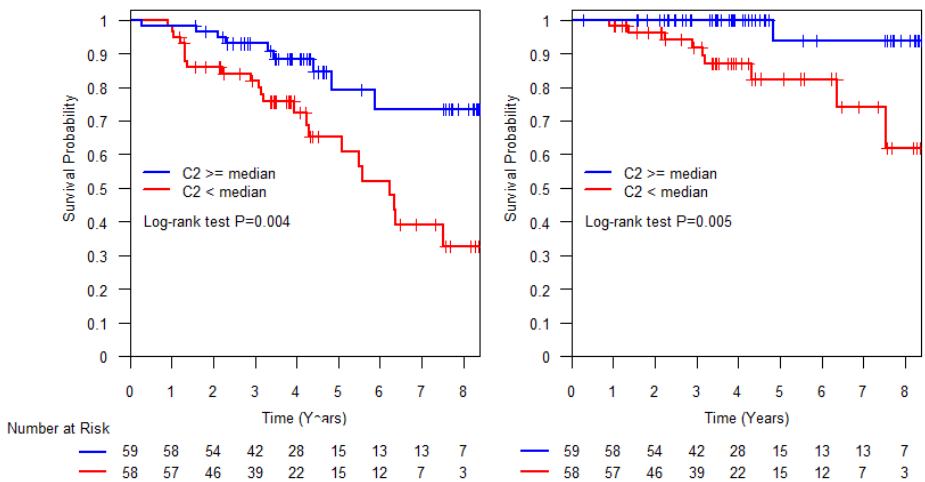

Figure 10. Kaplan-Meier plots showing the relationship between survival and small artery elasticity higher than median values and lower than median values. Left, analysis including all deaths, survival curves differ in the median value of small artery elasticity. Right, analysis including deaths from CVD, survival curves differ in the median value of small artery elasticity.

Table 18. Independent Predictors of All-Cause and CVD Mortality.

Characteristics	RR	95% CI	p-value
All-Cause Mortality			
Small artery elasticity above median (mL/mmHg*100)	0.37	0.17–0.81	0.01
Red blood cells count (x 10^{12}/L)	0.52	0.29–0.92	0.03
CVD Mortality			
Small artery elasticity above median (mL/mmHg*100)	0.11	0.01–0.86	0.04
Red blood cells count (x 10^{12}/L)	0.34	0.13–0.91	0.03

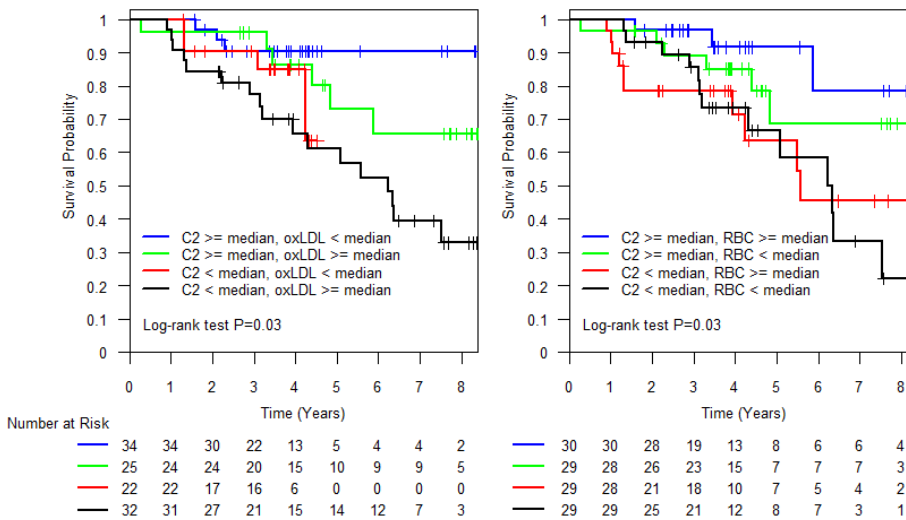

Figure 11. Left, Kaplan-Meier survival curves for the subgroup of patients showing higher or lower than the median values of small artery elasticity (C2) and oxidized LDL (oxLDL). A combination of lower than median C2 and higher than median oxLDL is associated with the highest risk for future all-cause mortality. Right, Kaplan-Meier survival curves for the subgroup of patients showing higher or lower than the median values of C2 and red blood cells (RBC) count. Patients with C2 below the median value and RBC count above the median value had a significantly increased risk for future all-cause mortality. The highest risk was observed in patients with both C2 and RBC count below the median value.

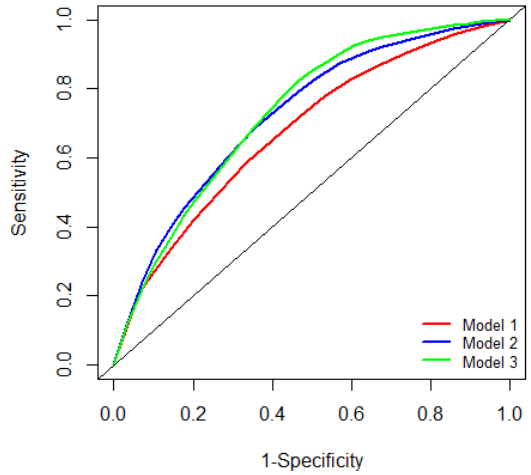

Figure 12. ROC analysis of the conventional risk factors (age,BMI,smoking,total cholesterol, HDL-C,glucose,mean arterial pressure,heart rate,ABI), small artery elasticity and a combination of small artery elasticity and oxidized LDL. The area under the ROC curve for 4.1-year mortality is the lowest for only the conventional risk factors (0.70, 95% CI:0.60–0.80 (model 1)), followed by a combination of the conventional risk factors with small artery elasticity (0.78,95%CI:0.68–0.87 (model 2)), and the highest for a combination of the conventional risk factors with small artery elasticity and oxidized LDL (0.82,95%CI):0.73–0.92 (model 3)). Model 1 vs Model 2 (p=0.03); Model 1 vs Model 3 (p=0.006); Model 2 vs Model 3 (p=0.14).

6. DISCUSSION

6.1. All cause-mortality after elective and emergency surgical repair of abdominal aortic aneurysm (Paper I)

This study is the first to evaluate short- and mid/long-term all-cause mortality, as well as the factors that may influence prognosis, after surgical repair of eAAA and rAAA in Estonia. All patients operated at Tartu University Hospital account for more than half of the AAA operations performed in Estonia. With some limitations, the results could be generalised for the whole of the country.

Our short- and mid/long-term results are in good agreement with previous data from different countries. Reports from Sweden, England and USA show 30-day or in-hospital mortality of 0.9–2.6% after eAAA repair (Karthikesalingam et al., 2016a; Wanhainen et al., 2016a). Short-term (30-day or in-hospital) mortality rate in range of 25–65.9% after rAAA have been reported from several countries in Europe, USA, Canada and Asia (Karthikesalingam et al., 2014; Karthikesalingam et al., 2016b; Raats et al., 2014; Van Beek et al., 2014). However, different discharge policies between hospitals and countries may be the cause of variations in in-hospital mortality rates. Several studies from Europe, USA, Australia and Asia have demonstrated 3–5-year survival rates of 70–80% in eAAA (Bahia et al., 2015; De Martino et al., 2013; Mani et al., 2009; Moll et al., 2011) and 38.6–46.3% in rAAA (Karthikesalingam et al., 2016b; Mani et al., 2009;). Timely repair of the abdominal aorta prevents its rupture and will hence reduce aneurysm-related mortality. Less-invasive EVAR is associated with lower short- and long-term mortality in AAA patients (Edwards et al., 2014). Yet previous studies did not find improvement in long-term outcomes in rAAA (Sweeting et al., 2015) or eAAA (Patel et al., 2016) patients treated with EVAR. With the improvement in intensive care, many patients with rAAA do survive the early postoperative period but fail to fully recover. This is evidenced by the fact that for these patients mortality is high already 90 days after surgery (Karthikesalingam et al., 2016b; Mani et al., 2009).

In our study rAAA mortality at 90 days and at 5 years was 33.3% and 55.1%, respectively. Similar results were obtained in Sweden where the 90-day mortality of rAAA was 33.4% and 5-year mortality was 53.7 (Karthikesalingam et al., 2016b). These results are significantly better than those obtained in England (44% and 61.4 % respectively). Poor outcome in England versus Sweden is partially related to the more extensive use of EVAR and the larger proportion of patients managed in teaching hospitals in Sweden. In both countries, EVAR resulted in better outcomes than OSR. Still, all rAAA patients in our study were treated by OSR and the caseload of our hospital as a teaching hospital is small.

Our study demonstrated that higher mid-term mortality for eAAA patients was associated with preoperative higher creatinine value and older age, while smoking was an almost significant factor. Older age has been associated with

poorer survival rates (Bahia et al., 2015; De Blic et al., 2014; De Marino et al., 2013; Stone et al., 2013) and smokers have been found to have a significantly higher risk of AAA (Lederle et al., 1997; Stackelberg et al., 2014;) and ruptures (Brown et al., 1999). Higher prevalence of acute kidney injury after rAAA repair has previously been demonstrated in patients with elevated preoperative serum creatinine (Ambler et al., 2015).

AAA is more prevalent among men than women, but women have a higher risk of ruptures. In our study 12 (25%) of the 48 patients who had a ruptured AAA were women. Our results showed a trend (data not shown) for the female gender to be a risk factor for eAAA patients undergoing OSR. Previous research also shows that 5-year survival rates are lower for women compared with men in both eAAA and rAAA patient groups (Mani et al., 2009). Women are also more sensitive to the risk effects caused by smoking (Stackelberg et al., 2014).

The finding of the current study that perioperative lower hemoglobin level and higher lactate level were independent determinants of rAAA mortality was quite expected, as hemorrhagic shock is a significant contributor to prognosis. Patients of vascular surgery patients often experience cardiovascular problems during surgery. The fact that beta-blockers have been found to reduce the cardiac mortality of vascular patients casts doubt on catecholamine use during surgery. AAA repair is related to increased perioperative plasma catecholamine levels (Thompson et al., 1999), which may potentiate the negative effect of noradrenaline administered during surgery.

The limitations of this study are its retrospective nature and the bias resulting from the co-variables that can be both confounders and causal intermediates. Because it is a single-center study the case load was relatively small. During the study period the proportion of EVAR was very low. Regrettably, there is no available data about aneurysm-related mortality and other death causes, either.

It is well known that early diagnosis and timely repair of AAA will lead to favourable outcome. Our analysis revealed the factors responsible for total mortality of eAAA and rAAA cases in Estonia. The knowledge of the mortality related factors could be a useful pre- or perioperative indicator for identifying high-risk patients.

6.2. Mid-term results after elective open and endovascular abdominal aortic aneurysm repair (Paper II)

This study is the first to compare the 30-day and 5-year all-cause mortality of OSR and EVAR procedures in non-ruptured AAA patients and the incidence of postoperative complications and reinterventions associated with open and endovascular aortic surgery in Estonia. The first EVAR at our centre was performed in 2011 and this study includes all EVAR procedures performed since the introduction of endovascular aortic procedures at Tartu University Hospital (service area is mainly Southern Estonia). The second centre in Estonia where

EVAR procedures are performed is the North Estonia Medical Centre in Tallinn (service area is mainly Northern Estonia).

We found non-significant differences in 30-day post-operative all-cause mortality rates after OSR and EVAR procedures (2.3% *vs* 0%, respectively). However, at 5 years the OSR patients' survival was significantly better compared to EVAR patients' survival (81.5% *vs* 58.9%, respectively). Our better mid-term results after OSR versus EVAR are similar to previous data from different countries. EVAR has been shown to be less invasive than OSR and 30-day all-cause mortality rates are significantly lower for EVAR compared to OSR (1.6% vs. 4.8%, respectively). Despite this short-term benefit, studies have failed to show long-term benefit from EVAR versus OSR after 2 years (Bonfill et al., 2019; Wang et al., 2018). In a recent meta-analysis comparing 151,092 EVAR and 148,692 OSR patients, EVAR was associated with higher long-term all-cause mortality, and higher rates of reintervention and secondary rupture (Li et al., 2019). Another meta-analysis revealed significantly lower 30-day mortality for EVAR compared to OSR (1.2% *vs* 3.3%, respectively), but similar 5-year mortality for both EVAR and OSR (Bulder et al., 2019). In our previous analysis of AAA repair, conducted between 2004 and 2015, we enrolled 228 elective AAA patients of whom 50 (22%) were treated by EVAR; 30-day all-cause mortality rate was 0.9% and the 5-year all-cause mortality rate was 32% in all elective cases (Paper I). In the current study, we included all EVAR procedures performed at our centre (up to 2019); the 5-year mortality rate for all elective AAA cases was 36.8%, which remained almost constant. Also, the low 30-day mortality rate for OSR patients indicates the high quality of the patient selection process, as well as sufficient surgical skills and postoperative care at our centre, despite the relatively small case load.

According to our data, the number of graft and surgery related complications and reinterventions needed after the primary procedure does not seem to have a negative effect on total mortality following EVAR and OSR in multiple regression analysis. This confirms the findings of previous studies that EVAR provides effective protection against AAA rupture (Movsisyan et al., 2020; Väärämäki et al., 2019). Our study showed significantly increased mortality in the EVAR group 5 years after the procedure, compared with OSR, and the 5-year overall survival of EVAR patients was somewhat lower than the data reported by others (Becquemin et al., 2021; Väärämäki et al., 2019; Movsisyan et al., 2020). Although the EVAR procedure is an independent risk factor for 5-year mortality, we cannot ignore the imbalance in the baseline characteristics between the EVAR and OSR groups. Significantly higher mean age and a greater proportion of renal and cerebrovascular comorbidities among EVAR patients may influence not only the choice of treatment modality, but also prognosis. Moreover, higher CVD mortality in East Europe has been reported recently (Movsisyan et al., 2020). A meta-analysis indicates a significant reduction in mortality risk among AAA patients receiving statin therapy compared with non-users (Risum et al., 2021). Yet only one third of the AAA patients treated by EVAR at our centre received statins, which is lower than the

proportion reported in the above analysis. In our centre's practice, younger patients (<70 years of age) without a significant surgical risk were primarily offered OSR, while those with significant comorbidities were treated by EVAR regardless of age.

The number of endoleaks and graft related complications in EVAR patients was relatively high in the present cohort compared with other long-term studies (Patel et al., 2016; Väärämäki et al., 2019). This could indicate the patients' compliance with the surveillance protocol and the availability of systematic follow-up data for analysis. At the same time, a minority of patients (10.5%) in whom graft related complications were detected required reintervention, and only half of the reinterventions were performed due to treatment of endoleak. The reintervention rate was quite similar (Andersen et al., 2018; Greenhalgh et al., 2004) or even lower than that reported by others (Becquemin et al., 2011; Salata et al., 2019). Moreover, there was no need for conversion to open repair. Nor were there secondary sac ruptures diagnosed during lifetime and almost all complications could be treated by the endovascular technique. In our study the reintervention rate for graft limb thrombosis was 5.3%, which is comparable to previous reports where post-EVAR reintervention due to limb occlusion or kinking occurred in 1.4–8% of patients (Bastos et al., 2012; Mantas et al., 2015). Complications and a number of reinterventions after the primary procedure did not increase mortality following EVAR treatment in our study. The devices used in earlier trials were mainly first- or second-generation EVAR devices. It is possible that currently used newer devices and advanced techniques may provide improved long-term outcomes; in this regard, only systemic short-term results are so far available.

Based on our results, postoperative complications after OSR occurred in 16.9% of the patients and thrombosis after OSR occurred in 5 (3.8%) patients, which is acceptable considering the results from other centres. Following open aortic surgery with a bifurcated prosthesis, limb occlusion develops in 1–5% (Biancari et al., 2002; Conrad et al., 2007), leading to acute or chronic limb ischaemia. It has previously been established that patients with aneurysmal disease have higher incidence of incisional hernias after surgical aneurysm repair (11–37%) compared with other patients undergoing abdominal surgery (Nicolajsen et al., 2020). We found incisional hernias and/or dechisceses/infection of aponeurosis in 8 patients (6.2%) of whom 6 (4.6%) needed surgical repair. Postoperative complications and reinterventions were shown not to independently increase 5-year total mortality risk in AAA patients.

In a meta-analysis of survival after elective AAA repair, based on 36 studies including 107,814 patients, the 5-year survival rate was 69% (Bahia et al., 2015), which is comparable to our results (survival was 72% for all elective AAA cases). Our findings that mid-term survival after AAA repair is independently affected by AAA size, male gender and comorbidities are supported by other studies and by a recent guideline (Goodney et al., 2010; Wang et al., 2018; Wanhainen et al., 2019).

The limitations of this study are its retrospective nature and non-randomized design. Because it is a single-centre study, the case load was relatively small. Such sample size may have affected multivariate analysis with the tested number of confounders. Regrettably, data about aneurysm-related mortality and other causes of death was not available. Since the majority of deaths occurred outside hospitals and autopsies are rarely performed in Estonia, we were unable to establish the cause of death. The recent European Vascular Surgery AAA guideline (Wanhainen et al., 2019) also underlines that the risk of late aneurysm-related death is difficult to assess due to inconsistencies in the registration of the cause of death and the lack of adequate long-term cohorts. Our study demonstrated significantly lower mortality in the OSR group 5 years after the procedure in comparison with EVAR. However, the EVAR procedure was performed only to older patients who were too frail for OSR, which could be a selection bias.

In conclusion, 30-day mortality rates for EVAR and OSR after elective AAA repair in our study were similar. Diminished EVAR survival at 5 years is probably related to the poorer population. Still, the EVAR population was not associated with more complications and reinterventions compared to OSR patients. Aggressive follow-up after EVAR enables to timely intervene in aortic complications and thus prevent late AAA sac ruptures and reduce AAA-related mortality.

6.3. Metabolomic profiling of abdominal aortic aneurysm (Paper III)

This study demonstrated several metabolomic shifts in male patients with infrarenal AAA compared to the aortic healthy controls. The main novel observation was that the patients with AAA had decreased levels of four amino acids and four phosphatidylcholines after adjustment for the potential confounders. Since no differences were identified between patients with slow and fast growing AAAs, the discussion will focus on the difference between patients with AAA and healthy controls.

Relevant data about metabolomic alterations in AAA patients has been sufficiently investigated in few articles (Ciborowski et al., 2013; Ciborowski et al., 2011; Ciborowski et al., 2012; Quereshi et al., 2017; Rupèrez et al., 2012). There are some reports on the metabolomic profile of patients with thoracic aortic disease. The analyses made by Doppler et al., demonstrated a general increase in the aortic tissue's total sphingomyelin levels in bicuspid aortic valve-associated thoracic aortic aneurysms and in tricuspid aortic valve-associated aortic dissections compared to controls (Doppler et al., 2017). It was demonstrated that sphingomyelins C16:0, C24:0 and C16:1 and hydroxysphingomyelin C22:1 carried a significant cardiovascular burden and their elevated levels were associated with the risk of myocardial infarction (Floegel et al., 2018). In this study, one lysophosphatidylcoline (LysoPC) and three

phosphatidylcholines (PC), but no sphingomyelin plasma levels, were significantly decreased in the AAA patients compared to the healthy controls. We used a Biocrates AbsoluteIDQ® p180 kit, which does not enable to separate isomers of lipids, thus for a deeper understanding of the role of complex lipids in AAA pathogenesis, further specific, well-focused standardized lipidomics studies are needed (Bowden et al., 2017). Recently, it was also reported that sphingolipids and LysoPCs were significantly reduced in patients with acute aortic dissection (Zhou et al., 2019). An active sphingomyelinase-ceramide pathway, characterised by increased levels of ceramides and metabolisation of sphingomyelins (e.g. by oxidized LDL-induced sphingomyelinase activity), leads to reduced levels of sphingomyelins (Bienias et al., 2016). This pathway has pro-atherogenic, pro-oxidative, and pro-inflammatory activity, resulting in premature vascular ageing and cardiovascular events (Edsfeldt et al., 2016).

AAA and atherosclerosis have some similar pathophysiological processes, such as chronic inflammation, vascular smooth muscle cell apoptosis, extracellular matrix degradation, and thrombosis (Hou et al., 2021; Toghill et al., 2017). Although the two diseases share common risk factors, there is no proof that there exists causal relationship between atherosclerosis and AAA. The risk factors of atherosclerosis, i.e. increasing age, male gender, smoking, hypertension and dyslipidaemia, are positively correlated with AAA (Hou et al., 2021; Toghill et al., 2017; Wanhainen et al., 2005). High plasma lipoprotein a level is a risk factor for AAA (Kotani et al., 2017), as lipoprotein a carries monocyte chemoattractant protein 1 and oxidized phospholipids, causing therefore chronic inflammation, oxidative stress and injury of the arterial wall (Hou et al., 2021). According to a clinical study, increased levels of arachidonic acid were related to AAA incidence and progression, and AAA patients with elevated arachidonic acid levels were more likely to require surgical repair (Lindholt et al., 2018). Moreover, a previous clinical study reported that proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibitors, primary indicated for treatment of hyperlipidaemia, also reduce the risk of AAA (Klarin et al., 2018).

In this study, lysoPC.a.C18.2, PC.ae.C34.3, PC.aa.C34.2 and PC.ae.C38.0 were significantly decreased in the patients with AAA. This is consistent with a previous investigation of more than 3,600 individuals from three population-based studies, which demonstrated that lysoPC.a.C18.2 were inversely associated with body mass index, markers of inflammation and subclinical CVD, and moderately improved risk reclassification beyond traditional risk factors (Ganna et al., 2014). LysoPCs species, described further as being associated also with higher HDL-cholesterol and total cholesterol and lower BMI, mostly derive from PCs. Higher levels of pro-inflammatory and pro-atherogenic LysoPCs were noted during the oxidative modification of LDL-cholesterol that accompanies their conversion to atherogenic particles. However, as they are produced by the phospholipase A2-like activity of Paraoxanase 1, LysoPCs contribute to inhibition of macrophage biosynthesis and consequently reduce cellular cholesterol accumulation and atherogenesis (Rozenberg et al., 2003).

Recent reports have suggested a protective effect of LysoPCs on cardiovascular risk. In a study of type 2 diabetes, LysoPC 18:2 was found to be inversely associated with incident diabetes and impaired glucose tolerance (Wang-Sattler et al., 2012). Decreased levels of LysoPCs were also found in patients with aortic dissection (Zhou et al., 2019). Ciborowski et al., described lower LysoPCs concentrations in the plasma of patients with AAA compared to controls, with a clear trend for a decrease with increasing aneurysm size (Ciborowski et al., 2012). The authors suggested that the possible cause of the decrease in the amount of LysoPCs in the plasma of AAA patients, depending on aneurysm size, is their accumulation in intraluminal thrombus. A previous report showed an increased activity of PLA2 in the serum of AAA patients (Colledge et al., 2011). As the eicosanoids and lysophospholipids are highly important signalling molecules, the results of this study support Cibrowski's hypothesis that increased activity of phospholipase A2 could be a response of the AAA patients' organism in order to augment the low level of lysophospholipids in their plasma. The finding of our study also indicates that AAA patients with lower PCs and LysoPCs may be exposed to vessel wall aneurysmal degeneration and increased risk of atherosclerotic CVD.

In this study, patients with AAA were characterized by reduced levels of four amino acids. Histidine, an indispensable amino acid, is important for regulation of blood pH and for synthesis of haemoglobin, as well as responsible for general growth and natural repair processes. An important metabolic fate of histidine is to be a precursor for glutamic acid (Colledge et al., 2011). Therefore, reduced histidine level may occur in AAA patients due to reasons associated with the metabolic route of glutamic acid. Glutamic acid is a biosynthetic donor of proline, which is a proteinogenic amino acid that is needed in large quantities for biosynthesis of collagen (e.g. in aortic wall) (Devlin 2010). We hypothezise that lower histidine levels, and hence also decreased glutamic acid levels, express enhanced proline utilization to substitute for the amount of degraded collagen during aneurysm formation.

The level of asparagine was lower than expected among AAA patients. An explanation of this reduction may be the decreased activity of plasma aspartic aminotransferase in patients with AAA (Gacko et al., 2005). Lower level of aspartic aminotransferase with increased utilization of glutamic acid in the proline route is associated with the next metabolic shift: the level of aspartate may be reduced due to decreased transfer of the amino group from glutamic acid to oxaloacetate. Asparagine synthetase capability to use aspartate is therefore limited for asparagine production (Pavlova et al., 2018), and as a result, the level of asparagine declines.

Recent research supports the notion that, in fact, elevations in essential branched-chain amino acids (e.g. leucine, isoleucine) contribute causally to insulin resistance and these changes can predict development of diabetes (Wang et al., 2017). Conversely, insulin increases oxidation of whole-body branched-chain amino acids, and inflammatory cytokines can double the whole-body oxidation of branched-chain amino acids and their decrease (Holecek et al.,

1997). In this study, decreased levels of leucine and isoleucine in the AAA patients provide further evidence of the inflammatory pathway in the pathogenesis of AAA. Lower branched-chain amino acids levels may also lead to activation of beta-oxidation, which increases utilization of phosphatidylcolines, as supported by our finding about the reduced levels of lysoPC.a.C18.2, PC.ae.C34.3, PC.aa.C34.2, and PC.ae.C38.0.

This pilot study requires validation, and the sample size used was relatively small. We used plasma instead of aortic tissue for single time point sampling, for obvious reasons in the endovascular era, and also because we wanted to compare patients with slow growth and fast growth. Metabolomic shifts depend on the difference between the rates of low molecular metabolite biosynthesis and their transition from the tissue into the blood, as well as between the rates of their uptake and elimination from the blood. By focusing on the tissue, one can exclude certain system-driven aspects in disease pathogenesis. Nevertheless, diseased aortic wall may produce systemic disease specific metabolic alterations that are reflected in plasma samples. Also the approach of targeted metabolomics, which we opted for to find all analysed metabolites, limited the results; therefore, associations between other metabolite classes might have been missed.

This study identified multiple differences in the plasma metabolomics of AAA patients compared to aorta-healthy controls. Assessment of the levels of different low-molecular metabolites allows to improve the current understanding of the pathogenesis of AAA, with metabolites serving as potential biomarkers in the future.

6.4. Revascularization of patients with chronic limb-threatening ischaemia (Paper IV)

All patients with CLTI should receive BMT with a correction of risk factors (smoking, hypertension, diabetes etc). In those with diabetes, proper antiglycaemic therapy is particularly important for improved limb-related outcomes, including lower rates of major amputation and improved patency after infrapopliteal revascularization (Singh et al., 2014; Takahara et al., 2010). Adequate wound care must be started immediately, as well as the use of adapted footwear, pain control and treatment of concomitant infection. Revascularization should be attempted as much as possible (Dominguez et al., 2015; Lumsden et al., 2009; Manzi et al., 2011; Norgren et al., 2007).

The autologous vein is the conduit of choice for infrainguinal revascularization (Aboyans et al., 2018; Almasri et al., 2019). Published patency rates vary from 52% to 88% over 5 years for infrageniculate femoro-popliteal bypass (Brewster et al., 1981; Cranley et al., 1981; Donaldson et al., 1980; Kent et al., 1989; LiCalzi et al., 1982) and from 37% to 85% for femoro-tibial bypasses (Barry et al., 1985; Szilagyi et al., 1979; Taylor et al., 1987). At Tartu

University Hospital, 5-year patency rates are 67% for autogenous vein femoro-popliteal bypass and 58% for femoro-tibial bypass (unpublished data). Vein allografts were first used in 1978 at Tartu Hospital because of lack of autologous vein (107 in the present series) and non-availability of polytetrafluoroethylene (PTFE) grafts or human umbilical vein grafts. Salvage of the lower extremity after failure of a previous revascularization and absence of a suitable autogenous material is one of the biggest challenges that the vascular surgeon has to face.

By using the human umbilical vein, a 3-year patency rate of 34% for femoro-popliteal bypass grafts and 25% for femoro-tibial bypass grafts was reported (Weisel et al., 1981). Other authors (Jarret and Mahood 1994) reported a 45% patency at 5 years for femoro-popliteal bypasses. Quinones-Baldrich et al., (Quinones-Baldrich et al., 1992) reported a primary 5-year patency of 45% for femoro-popliteal below-knee bypasses using PTFE grafts and a 22% patency for femoro-tibial bypasses at 3 years. Other authors (Pevec et al., 1992) found primary patency rate of 27% for PTFE grafts at 5 years for femoro-popliteal bypasses in the infragenicular position.

The use of venous allografts for lower-extremity revascularization in larger clinical series was first reported by Ochsner et al., (Ochsner et al., 1971) and Tice and Zerbino (Tice and Zerbino 1972) in the early 1970s. In the early series, fresh allovenous transplants were used (Vermassen et al., 1992), while in the most recent series, grafts cryopreserved with dimethylsulphoxide were employed (De Leersnijder et al., 1992; Ochsner et al., 1971; Ochsner et al., 1984; Tice and Zerbino 1972; Walker et al., 1993). In this study alloveins preserved at 4°C in a saline solution, containing heparin and antibiotics for up to 10 days, while others have used alloveins preserved in such conditions for up to 6 months (De Leersnijder et al., 1992). Previous reports on the use of vascular allografts revealed a high incidence of aneurysmal dilatation. Shah et al., (Shah et al., 1993) reported aneurysmal incidence with cryopreserved saphenous vein bypass allografts in three cases (7%). According to the experience of the authors of the present study, aneurysmal dilatation occurred only in four cases (3.7%), all of whom required corrective surgery.

The present secondary GPR of 64% at 1 year is comparable to that reported by Shah et al., (Shah et al., 1993) and De Leersnijder and colleagues (De Leersnijder et al., 1992) and better than those reported by others (De Leersnijder et al., 1992; Harris et al., 1993; Ochsner et al., 1971; Shah et al., 1993; Walker et al., 1993). However, the late results (21% graft patency rate at 5-years) are worse than those reported by others (De Leersnijder et al., 1992; Ochsner et al., 1984). The difference may be partly explained by the fact that all the present patients had been operated on for rest pain or gangrene, and 63% had femoro-tibial bypasses. In the De Leersnijder's series, 59% of patients had claudication and only 19% had femoro-tibial bypasses. De Leersnijder also reported aneurysmal degeneration of grafts in 15 cases (15%), 60% of whom required surgical correction.

Recent systematic review and meta-analysis demonstrated that CLTI patients with infrapopliteal disease had higher patency rates of GSV graft at 1 and 2 years (primary: 87%, 78%; secondary: 94%, 87%, respectively) compared with all other interventions (Almasri et al., 2019). Prosthetic bypass outcomes were notably inferior to vein bypass in terms of amputation and patency outcomes, especially for below knee targets at 2 years and beyond. Drug-eluting stents demonstrated improved patency over bare-metal stents in infrapopliteal arteries (primary patency: 73% vs 50% at 1 year), and was at least comparable to balloon angioplasty (66% primary patency). Survival, major amputation, and amputation-free survival at 2 years were broadly similar between endovascular interventions and vein bypass, with prosthetic bypass having higher rates of limb loss (Almasri et al., 2019).

Results of this study, conducted over 20 years ago, indicates that vein allografts offer no apparent benefits versus PTFE graft or human umbilical vein in CLTI patients. Since vein allografts have a tendency for aneurysm formation, they should not be used for IC patients, although their better handling properties undoubtedly facilitate distal anastomosis in tibial and pedal arteries. Nonetheless, in circumstances where venous surgery for varicose veins provides a rich harvest for allografts, and where PTFE graft or human umbilical vein is unavailable, the venous allograft is a useful conduit for limb salvage. We have shown also that the use of in situ venous allograft for the treatment of synthetic graft infection in the aorto-femoral segment has led to favourable short- and long-term results (Aavik et al., 2008). Furthermore, one of our recent studies was aimed at comparing the effect of different preservation solutions on the morphology of saphenous veins during long-term cold storage. Demonstrating good retention of endothelial nitric oxide synthase staining throughout the study period (35 days), isotonic saline with heparin and antibiotic seems to have the best potential to retain vein wall functionality, despite its relatively poor morphological preservation (Aavik et al., 2019).

To date, only one randomized trial, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, has directly compared endovascular therapy with open surgery in CLTI patients (Adam et al., 2005). At 2 years there was no significant difference between endovascular therapy and surgery regarding amputation-free survival. In survivors after 2 years, bypass surgery was associated with improved survival (on average 7 months, $p=0.02$) and amputation-free survival (6 months, $p=0.06$) (Bradbury et al., 2010). These data are challenged by more recent endovascular therapy techniques. The results of two ongoing randomized controlled trials, BASIL-2 and Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischaemia (BESTCLI), are awaited (Menard et al., 2014; Popplewell et al., 2016). In each anatomical region, both revascularization options should be individually discussed (Aboyans et al., 2018).

6.5. Prognostic impact of arterial stiffness in patients with peripheral artery disease (Paper V)

This study is the first to evaluate the prognostic impact of arterial stiffness in patients with symptomatic PAD. The main novel finding is that there exists a direct independent relationship between small artery elasticity and all-cause and CVD mortality in a cohort of symptomatic patients with PAD. Our results indicate that decreased elastic properties of the small muscular arteries is an independent predictor of all-cause and CVD mortality in patients with symptomatic PAD.

Our results are in good agreement with previous data. Wan et al., demonstrated that the probability of CVD event or CVD death in patients with coronary artery disease increased with a decrease in small artery elasticity (Wan et al., 2014). A prospective analysis of participants who were initially free from symptomatic CVD demonstrated that small artery elasticity provided predictive information about myocardial infarction, coronary heart death, angina, heart failure, stroke, and PAD (Duprez et al., 2011). Lower small artery elasticity was incrementally associated with incidence of hypertension among normotensive adults free from CVD (Peralta et al., 2010) and CVD events, regardless of age (Grey et al., 2003). Both small artery elasticity and large artery elasticity were associated with subclinical coronary atherosclerosis in a multi-ethnic middle-aged cohort free from CVD (Panaich et al., 2012).

Although patients with PAD are at an increased CVD risk compared with age-matched controls, only a few studies have been conducted to demonstrate associations between vascular function and outcome in PAD patients. Impaired brachial artery endothelial function independently predicts postoperative (Gokce et al., 2002) and long-term CVD events (Gokce et al., 2003; Huang et al., 2007), as well as adds to the prognostic value of ABI in PAD patients (Brevetti et al., 2003). Increased arterial stiffness has been reported in patients with PAD compared with age-matched controls (Kals et al., 2006; Zagura et al., 2011), and there is a link between increased arterial stiffness and atherosclerotic complications (Mattace-Raso et al., 2006). However, there are no data about association between arterial stiffness and outcome in PAD patients. Our main novel finding that lower SAE predicts all-cause and CVD mortality in PAD patients after adjustment for potential confounders, emphasizes the pathophysiological link between arterial stiffness and clinical outcome in patients with systemic atherosclerosis.

Several mechanisms can account for the association between increased arterial stiffness and worse outcome in patients with PAD. Arterial stiffness may favour fatal cardio- and cerebrovascular events through acceleration of atherosclerosis and increase in central pulse pressure (Kampus et al., 2011). Elevated pulse pressure may also induce arterial remodelling by increasing wall thickness, and promote development of plaques (Safar et al., 2007). Higher pulse pressure is independently associated with arterial plaque ulceration in patients with symptomatic carotid stenosis, supporting the hypothesis that

cyclical haemodynamic forces are important determinants of plaque rupture (Lovett et al., 2003). Elevated central blood pressure and thromboembolism, subsequent to plaque rupture due to stiff arteries, may explain the association between increased arterial stiffness and poor outcome in patients with atherosclerosis.

Wilkins et al., demonstrated that decreased small artery elasticity was significantly associated with lower ABI values in apparently healthy persons, while large artery elasticity was less strongly associated with ABI (Wilkins et al., 2012). The ABI correlated also with small artery elasticity in patients with PAD, but its association with large artery elasticity was only a borderline case (Duprez et al., 2001). Although PAD is primarily a disease of the large muscular arteries, the observation that prognosis was associated with small artery elasticity, which represents the oscillatory or reflective component of the small muscular arteries and arterioles, indicates a specific link between changes in the distal vascular bed, and global and CVD mortality risk. The delivery of the blood flow into the lower extremities depends not only on severity of atherosclerosis, but also on the regulatory mechanisms that govern the microcirculatory blood flow, including modulation of vasodilatory and vasoconstrictor activity in the skeletal muscles. In the advanced stages of PAD, microvascular abnormalities become more prominent, representing inadequate compensatory collateral circulation, and may contribute to the symptomatology of the disease (Cooke et al., 2008). Stiffening of the small arteries alters the magnitude and timing of reflected waves and increases central BP and the left ventricle afterload. Thus, a decrease of small artery elasticity, rather than changes in the mechanical properties of the large muscular arteries supplying the lower extremity, exert a stronger impact on the association of vascular dysfunction with severity and outcome in patients with PAD.

Abnormal large artery stiffness is associated with major CVD end points, including heart disease, stroke, and chronic kidney disease. However, we failed to find association of large artery elasticity and aortic pulse wave velocity, i.e. the gold standard measure of arterial stiffness, with PAD patients' prognosis. Nor did the recent PARTAGE Study find significant association between aortic pulse wave velocity and total mortality or major CVD events, while only lower pulse pressure amplification was associated with poor prognosis in very old persons (Benetos et al., 2012). Brand et al., showed that aortic pulse wave velocity was markedly attenuated in patients with advanced PAD and an index of the central pulse pressure/aortic pulse wave analysis mismatch predicted better the presence of critical limb ischaemia compared with alternative vascular indices (Brand et al., 2013). We demonstrated that red blood cells count itself predicts all-cause and CVD mortality, and red blood cells count as well as oxidized LDL adds to the predictive value of small artery elasticity in determining the risk for all-cause mortality in patients with PAD. Previous studies have shown that oxidized LDL is a predictor of all-cause mortality (Linna et al., 2013) and improves the reclassification capacity of Framingham-derived risk

functions (Gòmes et al., 2014). Anaemia is also a common and independent prognostic factor for mortality in CVD patients (Groenveld et al., 2008).

There are several limitations to the present study. First, the study examined male subjects with established atherosclerosis and the findings may not be generally applicable. Second, a limitation of this study is the potential confounding effect of smoking and medications on arterial stiffness. Third, measures of central haemodynamics, arterial stiffness and Windkessel-derived arterial elasticity indices may be subject to substantial under- or overestimation in patients with PAD due to luminal stenosis in various arterial segments (Brand et al., 2013). Fourth, the cause of death was obtained from death certificates using a telephone interview with the patients' general practioners or relatives. A recent systematic review emphasizes the need to improve global methodologies of mortality measurement, because of years-long discrepancies between clinical and postmortem diagnosis (Pagidipati et al., 2013). Finally, a potential limitation of the study is also the small number of subjects.

This study provides the first evidence, obtained from an observational study, that decreased small artery elasticity is an independent predictor of all-cause and CVD mortality in patients with symptomatic PAD. This finding supports further the relevance of arterial dysfunction in progression of CVD and suggests that symptomatic PAD patients with stiffer arteries are at an increased risk for all-cause and CVD mortality. Noninvasive arterial phenotype testing might improve prediction of prognosis and have clinical utility for management of patients with systemic atherosclerosis.

7. CONCLUSIONS

1. In patients with eAAA, 30-day, 90-day, and 5-year all-cause mortality rates were 0.9%, 2.6%, and 32%, respectively. The main predictors of 5-year mortality in eAAA patients were preoperative creatinine value and age. In patients with rAAA, 30-day, 90-day, and 5-year all-cause mortality rates were 22.9%, 33.3%, and 55.1%, respectively. The risk factors for 30-day mortality in rAAA were perioperative haemoglobin and lactate levels. According to this study, the all-cause mortality rates of eAAA and rAAA repair at our hospital were comparable to those at other centres worldwide.
2. 30-day mortality, and complication and reintervention rates for EVAR and OSR after elective AAA repair were similar. Although the EVAR procedure is an independent risk factor for 5-year mortality, higher age and greater proportion of comorbidities among EVAR patients may influence not only the choice of treatment modality, but also prognosis. Multivariate analysis showed that greater aneurysm diameter, EVAR procedure, male gender and cerebrovascular diseases were independently positively associated with 5-year mortality. Postoperative complications, as well as reinterventions did not independently increase 5-year total mortality risk in AAA patients.
3. The levels of only four amino acids (histidine, asparagine, leucine, isoleucine) and four phosphatidylcholines (PC.ae.C34.3, PC.aa.C34.2, PC.ae.C38.0, lysoPC.a.C18.2) were found to be significantly lower after adjustment for confounders among the AAA patients compared with the controls. There were no differences in the metabolites distinguishing the AAA patients with slow or fast growth from the controls, or distinguishing the patients with slow growth from those with fast growth. The current study detected novel significant alterations in amino acids and phosphatidylcholines metabolism associated with AAA occurrence, but no associations were found with AAA growth rate. Therefore, assessment of the levels of different low-molecular metabolites allows to improve the current understanding of the pathogenesis of AAA, with metabolites serving as potential biomarkers in the future.
4. The rate of operative mortality in PAD patients was 3.7%, the secondary GPR for all infrapopliteal bypass operations was 82.9%, 38.2% and 20.6% at 30 days, 3 and 5 years, respectively, the LSR being 84.3%, 46.1% and 30.6%, respectively. Yet the clinical results for more than 20 years suggest that venous allografts may still occupy an alternative position in lower-limb bypass surgery in the absence of appropriate autoveins, cadaveric venous allografts or other biologic/prosthetic grafts.
5. Small artery elasticity above the median was independently associated with decreased all-cause and CVD mortality in PAD patients. This finding further supports the relevance of arterial dysfunction in progression of CVD and suggests that symptomatic PAD patients with reduced small artery elasticity continue to be at an increased risk for all-cause and CVD mortality.

SUMMARY IN ESTONIAN

Kirurgilise ravi tulemused ja biomarkerite seos haiguse patogeneesi ning riskiga kõhuaordi aneurüsmi ja alajäseme arterite haigusega patsientidel

Kõhuaordi aneurüsm (AAA) on aordi raske haigus, mille eluohtlik tüsistus – rebend – põhjustab suremust üle 80%. Seetõttu on haiguse õigeaegne diagnoosimine ja ravi väga olulised. Haiguse levimus ja esinemissagedus on langenud viimase 20 aastaga, tänapäeval on haiguse levimus 65-aastasel meestel vahemikus 1.3–3.3%. Intensiivravi areng ja mitteinvasiivsete meetodite (aordi endovaskulaarne stentproteseerimine, EVAR) kasutuselevõtt on vähendanud haiglasisest postoperatiivset suremust plaanilises aordikirurgias, tänaseks on see vahemikus 1%–3%. Vaatamata postoperatiivse suremuse vähenemisele lisaks plaanilisele ka erakorralises aordikirurgias viimase 50 aasta jooksul on pikemaaegsem elulemus püsinud suhteliselt muutumatuna: 5-aasta elulemusmäär plaanilises aordikirurgias on 70% ja erakorralises aordikirurgias 40%.

EVAR rakendamine on saanud aordi aneurüsmi standardraviviisiks avatud kirurgia (OSR) kõrval. See võimaldab ravida sobiva aordi anatoomia korral kõrgema riskiga haigeid (vanemad, enam kaasuvaid haiguseid jne). Vaatamata EVARi operatsioonijärgsele väiksemale suremusele plaanilises aordikirurgias võrreldes OSRga kaob see positiivne tulem keskmisel ja pikemal vaatlusperioodil. EVAR patsientidel esineb rohkem hiliseid aordi tüsistusi (endolekked, tromboosid jne), mistõttu vajavad nad enam ka kordusinterventsioone.

AAA sõelprogrammid on kulutõhusad ja vähendavad AAA aordist tingitud suremust. Nende programmide tulemusena diagnoositakse ka rohkem väiksemaid, kuid operatiivsele ravile veel mittekuuluvaid AAA. Tänasel päeval pole aga aordi diameetri kõrval ühtegi teist teadupõhist kliinilist parameetrit, mille alusel saaks AAA progresseerumise riski hinnata. Seetõttu on biomarkerid, mis annaksid täpsemat infot AAA tekke ja progresseerumise kohta väga vajalikud planeerimaks õigeaegset ravi. Üks võimalus otsida uusi AAA biomarkereid on madalmolekulaarsete metaboliitide hindamine, st. metaboloomika.

Alajäseme arterite haigus (PAD) on süsteemse ateroskleroosi ilming, mille levimus on ligikaudu 3% vanusegrupis 45–49 eluaastat ja tõustes umbes 18% vanusegrupis 60–90 eluaastat. Kogu maailmas on PAD haiged aladiagnoositud ja- ravitud ning nende südame ja veresoonkonna haigustest tingitud risk on väga kõrge. PAD ravi eesmärkideks on vähendada jäsemega seotud kaebuseid ja jäset säilitada ning alandada üldist südame ja veresoonkonna haiguste riski. Lisaks klassikalistele riskifaktoritele, mis põhjustavad haiguse teket ja progresseerumist, on veel mitmeid uurimata tahke haigusriski hindamisel. Suurenenud arterite jäikus võib olla üks kehva prognoosi põhjuseks neil haigetel. On teada, et suurenenud arterite jäikus on seotud südame- ja veresoonkonna haiguste riskiga ning mõjutab ka ateroskleroosi arengut, põhjustades veresoone naastude haavandust ja rebenemist. Käesolevas töös hindasime kirurgilise ja endo-

vaskulaarse ravi tulemusi AAA ja PAD haigetel ning uurisime funktsionaalsete ja biokeemiliste markerite rolli haiguse patogeneesis ja riskis.

Uuringualusteks olid AAA haiged, kellele teostati plaaniline ja erakorraline AAA resektsioonproteseerimine Tartu Ülikooli Kliinikumi Kirurgiakliiniku veresoontekirurgia osakonnas. Metaboloomilise analüüsi jaoks koguti uuritavad (AAA haiged ja terved vabatahtlikud) Uppsala Ülikoolihaigast Rootsis. Alajäseme arterite haigusega patsiendid viibisid ravil Tartu Ülikooli Kliinikumi Kirurgiakliiniku veresoontekirurgia osakonnas.

Leidsime, et plaanilise aordikirurgia (OSR ja EVAR) 30-, 90-päeva ja 5-aasta kogusuremuse määrad olid vastavalt 0.9%, 2.6% ja 32%. Rebenenud AAA (OSR) haigetel olid 30-, 90-päeva ja 5-aasta kogusuremuse määrad vastavalt 22.9%, 33.3% ja 55.1%. Need tulemusnäitajad on head ja võrdväärsed maailma teiste keskuste tulemustega. Leidsime samuti, et 30-päeva suremus, tüsistused ja kordusinterventsioonid plaanilise EVAR ja OSR korral olid võrdsed. Kuigi EVAR oli 5-aasta suremuse sõltumatu riskifaktor, võib arvata, et kõrgem vanus ja rohkem kaasuvaid haiguseid EVAR haigetel võisid mõjutada mitte ainult raviviisi valikut, vaid ka prognoosi. Postoperatiivsed tüsistused ja kordusinterventsioonid ei mõjutanud kummaski grupis AAA haigete 5-aasta suremust.

Metaboloomiline analüüs näitas, et neli aminohapet ja neli fosfatidüülkoliini olid AAA haigetel tervetega võrreldes statistiliselt oluliselt madalamas kontsentratsioonis peale kohandamist mõjuteguritele. Ei esinenud ainsatki metaboliiti, mis oleks eristunud kiire ja aeglase kasvuga AAA haigetel, ega ka metaboliite, mille abil eristada kiire ja aeglase kasvuga AAA patsiente tervetest inimestest. Uuringul leitud AAA esinemisega seotud metaboliidid avardavad senist teadmist AAA patogeneesist ja on ühtlasi aluseks edasistele biomarkerite avastamise uurimistöödele.

PAD haigete postoperatiivne suremus rekonstruktiivsetel operatsioonidel alloveeniga infrapopliteaalses segmendis oli 3.7%, transplantaadi sekundaarne (kumulatiivne) läbitavus oli 30. päeval, 3. ja 5. aastal vastavalt 82.9%, 38.2% ja 20.6%. Jäseme säilimise määr oli 30. päeval, 3. ja 5. aastal vastavalt 84.3%, 46.1% ja 30.6%. Selle varasema kliinilise töö tulemused on aktuaalsed tänini ja viitavad, et alloveenid on edukalt kasutatavad transplantaadid muude alternatiivide puudumisel. Leidsime samuti, et PAD haigetel oli üldise ning südame ja veresoonkonna haiguste suremuse risk sõltumatult seotud langenud väikeste arterite elastsusega. See tulemus toetab laiemat arusaama, et arterite funktsionaalsed omadused on olulise tähtsusega PAD progressioonis ja nende mõõtmine võiks olla oluline.

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