Tampere University

NIINA KHAN

Comorbidity and Prognostic Indicators in Cardiovascular Surgery

Tampere University Dissertations 212

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium Pinni B 1096,
Kanslerinrinne 1, Tampere,
on 24 April 2020, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Finland

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The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-1441-5 (print)
ISBN 978-952-03-1442-2 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-1442-2

PunaMusta Oy – Yliopistopaino
Tampere 2020

"Success is not final. Failure is not fatal. It is the courage to continue that counts."

(Winston Churchill)

ACKNOWLEDGEMENTS

This thesis was carried out at the Vascular Surgical Division of the Department of Surgery / Centre for Vascular Surgery and Interventional Radiology and Heart Hospital at Tampere University Hospital.

Writing this part of the book comes the easiest to me as there are so many to whom I am deeply grateful. I would like to first thank my supervisors Professor Niku Oksala and Professor Jari Laurikka for guiding me throughout this process with expert advice, patience and unwavering support. Niku, your innovative ideas and enthusiasm have been a source of great inspiration and you have always been there to offer both help and encouragement. Jari, you have given me a unique insight into modern cardiothoracic surgery as well as tools for developing my scientific thinking.

I warmly thank all my co-authors. A special thank you to Leo-Pekka Lyytikäinen for his assistance with the more complex statistical testing, Professor Terho Lehtimäki for sharing his expertise on lipidology and Docent Kati Järvelä for her valuable collaboration with articles II and III.

I wish to offer a sincere thank you to the official reviewers of this thesis, Professor Hannu Savolainen and Docent Pekka Jaakkola for constructive criticism and expert advice, which helped to significantly improve the quality of my work.

During my years in surgery I have been entitled to work with and learn from wonderful colleagues. I am grateful to the late Professor Mikael Victorzon for taking a chance in 2011 and hiring a young woman he hadn't previously met to start her surgical residency and all the support offered along the way. I thank Michael Luther and Sebastian Dahlbacka for being such exceptional role models for an aspiring vascular surgeon and having the patience to show me the ropes in the beginning. I thank Professor Juha-Pekka Salenius for the support and guidance at the beginning of my vascular surgical specialisation as well as for encouraging scientific endeavours.

A special heartfelt thank you to my mentor Docent Velipekka Suominen for guiding me in growing into this profession with both valuable advice and compassion. I would also like to thank Velipekka for his work as a co-author and a member of my follow-up group. Furthermore, I would like to thank Docent Jukka Saarinen for acting as a member of the follow-up group. To all my brilliant fellow

vascular surgeons at Tampere University Hospital, it is a great joy and privilege to be able to work with you.

Without family and friends life would be meaningless. I am grateful to my mother-in-law Hillevi for her support. I would like to especially thank my best friends Annukka and Anu for always being there. Though we are not linked by blood, to me you are and will always be sisters. To my parents, Raija and Eero, I owe my deepest gratitude. You have always gone above and beyond for me offering your love, support and encouragement.

I would like to thank my husband Jaska for scientific contributions with the articles as well as taking care of essentially everything at home allowing me to focus on this thesis. But most importantly, thank you for just being you – the love of my life. Finally, I wish to thank my darling sons Samuel and Mikael who have brought such joy and love to my life no words suffice to describe. I dedicate this book to all my boys, you are my everything.

Tampere, January 12th 2020

Niina Khan

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The thesis was financially supported by The Finnish Medical Foundation, the Academy of Finland, the Tampere University Hospital Medical Research Fund, the Finnish Foundation of Cardiovascular Research, the Finnish Cultural Foundation, the Tampere Tuberculosis Foundation, the Emil Aaltonen Foundation, the Yrjö Jahnsson Foundation European Union 7th Framework Program and EU Horizon 2020.

ABSTRACT

The high-risk nature of cardiovascular surgical patients has become accentuated by the concomitant development of surgical techniques and perioperative care as well as the evolution of other non-surgical invasive procedures and conservative treatment, and by the ageing of the population, resulting in increasingly morbid patients being referred for surgery. In order to optimise the postoperative outcomes, it is now increasingly crucial to understand the role of risk factors in and the characteristic complications of cardiovascular surgery. Firstly, the present thesis studies the occurrence, presentation and predisposing factors of three essential complications in cardiac surgery – postoperative atrial fibrillation, late cardiac tamponade and postoperative infections. Secondly, it ascertains and compares the serum lipid profiles of patients treated for abdominal aortic aneurysms, coronary artery disease and peripheral artery disease and investigates the association of serum lipids with long-term survival in abdominal aortic aneurysm patients. The lipid analyses also include more contemporary lipid parameters estimated computationally with a neural network model, the Extended Friedewald Formula.

The patients included in the thesis were treated in the Heart Hospital and the Vascular Surgical Division at Tampere University Hospital between 2001 and 2014. Data was mainly collected from the units' respective databases, Kardio and Vascuset, and from the Tampere University Hospital patient record database. Laboratory values were retrieved from the Fimlab Laboratories Ltd database. The data was analysed retrospectively. A total of 1,356 cardiac surgery, 498 abdominal aortic aneurysm and 280 peripheral artery disease patients were investigated.

The incidences of postoperative atrial fibrillation (51%) and late postoperative tamponade or pretamponade (6.2%) were significantly higher than those reported before. The higher occurrence of atrial fibrillation could be due to factors such as a higher median age, a higher prevalence of previous atrial fibrillation and a greater proportion of valvular procedures in the present study compared to earlier research, as these, along with larger left atrium size and emergency surgery, were found to be independent predisposing factors for the condition. Other potential explanations may be linked to the refined inclusion criteria of the present study or to improved

diagnostics. Late tamponade, in turn, was most common in younger, generally healthier patients typically undergoing valvular surgery. Independent risk factors included single-valve surgery and a higher preoperative haemoglobin level. The role of valve surgery as a risk factor for late tamponade has been previously established and is suspected to be associated with a concurrent need for anticoagulant therapy. Potential explanations for the higher incidence of late tamponade could lie in the increased proportion of valve procedures in the present study or in the postoperative chest tube management protocols.

Ten per cent of the cardiac surgical patients suffered from postoperative infections, and repeated hyperglycaemic episodes were found to be significantly associated with these complications. Increased rates of postoperative stroke and greater short-term mortality were also found in patients with repeated hyperglycaemia episodes, and strict glycaemic control was found to be safe in cardiac surgical patients.

In patients treated invasively for abdominal aortic aneurysms, serum triglycerides and low-density lipoprotein cholesterol were associated with increased and intermediate-density lipoprotein cholesterol derived by the Extended Friedevald Formula with decreased long-term mortality. Furthermore, the latter was discovered to significantly complement risk prediction in patients treated for abdominal aortic aneurysms. The findings concerning traditional lipid parameters concurred with previous evidence. Finally, higher serum apolipoprotein A1 levels appeared to be associated with coronary artery disease requiring surgical treatment rather than invasively treated peripheral artery disease.

TIIVISTELMÄ

Sydän- ja verisuonikirurgisten potilaiden korkean riskin luonnetta on entuudestaan korostanut samanaikainen kirurgisten tekniikoiden ja perioperatiivisen hoidon sekä ei-kirurgisten kajoavien toimenpiteiden ja konservatiivisen hoidon kehitys ja väestön ikääntyminen, minkä johdosta entistä sairaampia potilaita ohjataan kirurgiseen hoitoon. Riskitekijöiden roolin sekä hoitoon liittyvien tyypillisten komplikaatioiden ymmärtäminen onkin nykyään aiempaa tärkeämpää sydän- ja verisuonikirurgiassa leikkaushoidon tulosten optimoimiseksi. Väitöskirjatutkimuksen tavoitteina oli selvittää kolmen keskeisen sydänkirurgiaan liittyvän leikkauksen jälkeisen komplikaation – eteisvärinän, myöhäistamponaatioiden ja infektioiden – esiintyvyyttä, taudinkuvaa ja riskitekijöitä. Lisäksi tutkimuksessa määritettiin ja vertailtiin vatsa-aortan aneurysman tai tukkivan ääreisvaltimosairauden vuoksi kajoavasti hoidettujen sekä sepelvaltimotaudin vuoksi ohitusleikattujen potilaiden seerumin rasvaprofiilit. Edelleen väitöskirjatyössä tutkittiin seerumin rasva-arvojen yhteyttä pitkän aikavälin kuolleisuuteen vatsa-aortan aneurysman vuoksi hoidetuilla potilailla. Analyyseihin sisällytettiin perinteisten rasva-arvojen ohella uudempia laskennallisia, niin kutsutun Extended Friedewald Formula -neuroverkon avulla määritettyjä rasva-arvoja.

Tutkimus kohdistui Tampereen yliopistollisen sairaalan Sydänsairaalassa sekä verisuonikirurgisessa yksikössä vuosien 2001 ja 2014 välillä hoidettuihin potilaisiin. Tiedonkeruu suoritettiin pääosin yksiköiden ylläpitämistä Kardio- ja Vascuset-rekistereistä, Tampereen yliopistollisen keskussairaalan potilastietokannasta sekä Fimlab Laboratoriot Oy:n tietokannasta laboratorioarvojen osalta. Analyysit suoritettiin takautuvasti. Tutkimukseen sisällytettiin yhteensä 1 356 sydänkirurgista sekä 498 vatsa-aortan aneurysman vuoksi ja 280 ääreisvaltimotaudin vuoksi hoidettua potilasta.

Leikkauksen jälkeisen eteisvärinän (51 %) ja myöhäistamponaatioiden (6.2 %) esiintyvyydet olivat selvästi korkeammat kuin tähänastisissa tutkimuksissa. Eteisvärinän aiempaa suurempi esiintyvyys saattaa liittyä tutkimuspopulaation korkeampaan mediaani-ikään, leikkausta edeltävän eteisvärinän yleisyyteen ja läppätoimenpiteiden suurempaan osuuteen edeltäviin tutkimuksiin verrattuna. Näiden tekijöiden todettiin olevan leikkauksen jälkeisen eteisvärinän itsenäisiä

riskitekijöitä vasemman eteisen laajentuman ja päivystyksellisen hoidontarpeen ohella. Myös erot tutkimuksen valintakriteereissä ja aiempaa tarkempi diagnostiikka saattavat selittää korkeita eteisvärinän esiintyvyyslukuja. Myöhäistamponaatioiden puolestaan todettiin olevan yleisempiä nuoremmilla, yleisesti ottaen terveemmillä potilailla, joille tehtiin läppäkirurgisia toimenpiteitä. Korkea leikkausta edeltävä hemoglobiiniarvo ja yhden läpän leikkaus olivat itsenäisiä myöhäistamponaatioiden riskitekijöitä. Myös aiemmissa tutkimuksissa on havaittu myöhäistamponaatioiden liittyvän erityisesti läppäkirurgiaan, minkä on arveltu johtuvan näiden toimenpiteiden jälkihoitoon tavanomaisesti liittyvästä verenohennuslääkityksestä. Väitöskirjatyössä havaitun, aiempaa korkeamman myöhäistamponaatioiden esiintyvyyden taustalla saattaa myös olla läppätoimenpiteiden suurentunut osuus kaikista sydänkirurgisista toimenpiteistä tai yksikön leikkauksen jälkeinen dreenihoitoprotokolla.

Leikkauksen jälkeisiä infektioita ilmeni noin 10 %:lla sydänkirurgisista potilaista, ja toistuvien hyperglykemioiden todettiin liittyvän merkitsevästi infektiokomplikaatioihin. Infektioiden lisäksi toistuvat hyperglykemiajaksot liittyivät leikkauksenjälkeisiin aivohalvauksiin sekä lisääntyneeseen lyhyen aikavälin kuolleisuuteen. Tutkimusyksikössä noudatettuun tiukkaan verensokeritason säätelyyn ei todettu liittyvän merkittäviä haittavaikutuksia.

Seerumin triglyseridit ja LDL-kolesterolitaso olivat merkittäviä pitkän aikavälin kuolleisuuden riskitekijöitä vatsa-aortan aneurysman vuoksi hoidetuilla potilailla, kun taas Extended Friedewald -neuroverkon avulla määritetty IDL-kolesteroli vaikutti olevan merkittävä suojaava tekijä. Lisäksi IDL-kolesterolimäärityksillä pystyttiin täydentämään vatsa-aortan aneurysmien vuoksi hoidettujen potilaiden riskin ennustamista. Lopuksi seerumin korkeampi apolipoproteiini A1-pitoisuus vaikutti olevan yhteydessä ennemmin ohitusleikkausta vaatineeseen sepelvaltimotautiin kuin kajoavasti hoidettuun ääreisvaltimosairauteen.

CONTENTS

ABBREVIATIONS

AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CLTI	chronic limb-threatening ischaemia
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
DM	diabetes mellitus
DSWI	deep sternal wound infection
ECG	electrocardiogram
EFW	Extended Friedewald Formula
EVAR	endovascular aortic repair
HDL-C	high-density lipoprotein cholesterol
ICU	intensive care unit
IDL-C	intermediate-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
LVEF	left ventricular ejection fraction
MINS	myocardial injury after noncardiac surgery
NRI	net reclassification improvement
NYHA	New York Heart Association (Functional Classification)
OR	odds ratio
PAD	peripheral artery/arterial disease
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilsin-kexin type 9
POAF	postoperative atrial fibrillation
PPE	postoperative pericardial effusion
SSI	surgical site infection
TAUH	Tampere University Hospital

TAVI	transcatheter aortic valve implantation
TC	total cholesterol
TG	triglycerides
VHD	valvular heart disease
VLDL-TG	very-low-density lipoprotein triglycerides

ORIGINAL PUBLICATIONS

The present thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Khan, J., Khan, N., Loisa, E., Sutinen, J., Laurikka, J. 2016. Increasing Occurrence of Postoperative Atrial Fibrillation in Contemporary Cardiac Surgery. J Cardiothorac Vasc Anesth 30(5): 1302-1307

II Khan, N. K., Järvelä, K. M., Loisa, E. L., Sutinen, J. A., Laurikka, J. O., Khan, J. A. 2017. Incidence, presentation and risk factors of late postoperative pericardial effusions requiring invasive treatment after cardiac surgery. Interact Cardiovasc Thorac Surg 24(6):835-840

III Järvelä, K. M.*, Khan, N.K.*, Loisa, E. L., Sutinen, J. A., Laurikka, J. O., Khan, J. A. 2018. Hyperglycemic episodes are associated with postoperative infections after cardiac surgery. Scand J Surg 107(2):138-144

IV Khan, N., Lyytikäinen, L.-P.*, Khan, J.*, Seppälä, I., Lehtomäki, A., Kuorilehto, T., Suominen, V., Lehtimäki, T., Oksala, N. 2018. Extended Serum Lipid Profile Predicting Long-Term Survival in Patients Treated for Abdominal Aortic Aneurysms. World J Surg 42(4):1200-1207.

V Khan, N., Khan, J., Lyytikäinen, L.-P., Lehtimäki, T., Laurikka, J., Oksala, N. Serum apolipoprotein A-I concentration differs in coronary and peripheral artery disease. Submitted.

* Equal contributions

1 INTRODUCTION

Despite the fact that cardiovascular mortality has been decreasing since the 1970s, cardiovascular diseases continue to be the cause of significant morbidity and mortality both in Finland and worldwide (Bonow et al. 2002; Herrington et al. 2016; Statistics Finland 2016). According to the 2016 Finnish national statistics, they accounted for 36% of all deaths annually, representing the most significant cause of death in the country (Statistics Finland 2016). It is plausible to state that at least some of these deaths could be prevented. Advances in medical and interventional techniques have enabled the treatment of patients who are older and suffer from a greater variety of comorbidities than before. This, together with the ageing of the population, has led to patients who undergo invasive procedures becoming more and more clinically challenging as well as costly. While technical developments have also improved surgical success rates, cardiovascular surgery is still associated with considerable morbidity and mortality. On the one hand, understanding the influence of risk factors on survival and, on the other, being familiar with the clinical presentation and predisposing factors of postoperative complications are crucial in optimising the postoperative outcomes of cardiovascular surgery. The present dissertation investigates the incidence, clinical picture and risk factors of three significant postoperative complications in cardiothoracic surgery – atrial fibrillation, late cardiac tamponade and infections – in addition to studying the serum lipid profiles of cardiovascular surgical patients as compared within subgroups and the effect of lipids on survival.

2 REVIEW OF THE LITERATURE

2.1 Cardiovascular disease

2.1.1 Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the arteries preceded by endothelial dysfunction, a defect in the normal function of the innermost layer of blood vessels, which is associated with poor nitric oxide production and function (Davignon & Ganz 2004). The atherosclerotic process is initiated by the accumulation of cholesterol in the subendothelial space of blood vessels and its subsequent oxidation, followed by the migration of a subtype of white blood cells, macrophages, into the tissue. These then develop into fat-saturated foam cells, forming early atherosclerotic lesions, i.e. fatty streaks, already during childhood. As the process continues, a fibrous cap forms covering the intimal surface of the developed lesion, after which the atherosclerotic plaque is complete. The stability of an atherosclerotic plaque, in turn, is related to the type of macrophages it contains. Lipids are carried in the bloodstream by carrier proteins, and of these, low-density-lipoprotein cholesterol (LDL-C) particles are essential in the accumulation of cholesterol in the subintimal layer, as they transport cholesterol away from the liver where it is processed and towards peripheral tissues. (Berliner et al. 1995; Bobryshev et al. 2016, McGill et al. 2000)

The main manifestations of atherosclerosis include coronary artery disease (CAD), peripheral artery disease (PAD) and cerebrovascular disease. Atherosclerosis also plays a significant role in the development of other conditions, such as arterial aneurysms and valvular heart disease. It is impossible to estimate the exact prevalence of atherosclerosis due to probable undiagnosed asymptomatic disease, but the prevalence of its clinical manifestations is more clearly defined and shall be discussed in the following sections.

The most significant risk factor of atherosclerosis is dyslipidaemia, particularly elevated LDL-C. Other risk factors include hypertension, diabetes, smoking, male sex, and inflammation, whereas exercise, high-density lipoprotein cholesterol (HDL-

C), and apolipoprotein A1 (ApoA1) are protective against it. (Berliner et al. 1995; Falk 2006) Conservative therapy entails the management of risk factors with a healthy diet and lifestyle and, when needed, lipid-targeting medication, most commonly statins. Risk factor management, in turn, can be divided into preventing the disease from occurring, halting or slowing down the process of an already diagnosed disease, and reducing the impact of the clinical manifestations of the disease – these are referred to as primary, secondary and tertiary prevention, respectively. Surgical or endovascular interventions are often required when treating the manifestations of atherosclerotic disease.

2.1.2 Coronary artery disease

CAD, characterised by the atherosclerotic narrowing or complete obstruction of at least one of the coronary arteries feeding the heart muscle and thus instigating myocardial ischaemia, is the most commonly recognised manifestation of atherosclerotic disease. The incidence of myocardial infarctions in the American population is estimated to be 750,000 annually, with one fifth of the events occurring silently (Mozaffarian et al. 2016). The overall prevalence of CAD has been decreasing, and coronary heart disease brought on by CAD is estimated to affect approximately 6.2% of individuals aged ≥20 years in the American population, with a higher prevalence among men than among women (7.6% vs 5.0%, respectively). (Mozaffarian et al. 2016) Owing to potential undiagnosed asymptomatic disease, however, CAD may be even more frequent. The exact incidence or prevalence of CAD in Finland is unknown, but at the end of 2013 over 180,000 individuals were entitled to reimbursements for medication expenses for chronic CAD and associated dyslipidaemias. The majority (60%) of these patients were male and aged 65 or over. (Kela social insurance institution of Finland: Existing, new, and withdrawn entitlements to reimbursement of drug expenses; Stable coronary disease: Current Care Guidelines 2015)

The aetiology of CAD is strongly multifactorial (Poulter 1999). The Framingham Heart Study initially outlined the significant predisposing factors for CAD in the late 1950s and early 1960s, which are similar to those predisposing to atherosclerosis (Dawber et al. 1957; Oppenheimer, 2010). The traditional risk factors include so called conventional risk factors, namely older age, positive family history of early heart disease and ethnicity, as well as modifiable risk factors, such as high blood cholesterol levels (principally LDL-C), high blood pressure, cigarette smoking,

diabetes, obesity, physical inactivity, metabolic syndrome and mental stress/depression (Cohen et al. 2014; Jousilahti et al. 1999; Mozaffarian et al. 2016; Piepoli et al. 2016; Wilson et al. 1998; Wulsin & Singal 2003). The classic risk factors of CAD as well as the other main cardiovascular diseases focused on in the present thesis are presented in Table 1. More recently, other parameters, such as elevated high-sensitivity C-reactive protein (CRP), lipoprotein(a), homocysteine, small dense LDL-C particles and fibrinogen, have also been determined to be associated with the development of CAD (Boushey et al. 1995; Danesh et al. 2000; Erqou et al. 2009; Kannel et al. 1987; Koenig et al. 1999; Park et al. 2010; Toft-Petersen et al. 2011).

The clinical severity of CAD varies from silent ischaemia to stable angina pectoris and, ultimately, acute coronary syndrome, which is further subclassified as non-ST-elevation acute coronary syndrome, including unstable angina and non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction. (Hamm et al. 2011; Ibanez et al. 2018; Roffi et al. 2016) It should, however, be noted that acute myocardial infarction may also manifest without underlying CAD, with an incidence of approximately 5% (Bainey et al. 2018).

The methods applied in the diagnostics of CAD include symptom history, clinical findings with the help of an electrocardiogram (ECG) and, habitually, exercise stress testing in stable patients. The functional testing of stable patients can also be conducted during coronary angiography with fractional flow reserve testing or by pharmacological stress testing with perfusion scintigraphy. Imaging studies, such as echocardiography, computed tomography angiography (CTA) or magnetic resonance imaging, can also be employed. In suspected acute coronary syndromes, cardiac enzymes such as troponin T (TnT) and myocardial-based creatine (CKMb) are utilised in addition to ECG. Coronary angiography remains the gold standard for CAD diagnosis and is also largely applied for therapeutic interventions. (Amsterdam et al. 2014; Ibanez et al. 2018; Montalescot et al. 2013; Roffi et al. 2016)

Lifestyle amendments and medical therapy for both symptom relief and event prevention are endorsed for all CAD patients. The medical treatment regimen includes nitrates, beta-blockers and calcium channel blockers as well as antiplatelet therapy with low-dose acetosalicylic acid (ASA) or clopidogrel, statins and angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers for patients with concomitant conditions such as heart failure or hypertension. Additionally, an invasive approach is recommended for those suffering from acute coronary syndrome, with an early treatment strategy for high-risk patients. Myocardial revascularisation as an adjunct to optimal medical treatment is also advocated for patients with stable CAD that causes limiting symptoms and/or with

a significant anatomic localisation. (Montalescot et al. 2013) The treatment modality – percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) – should be determined in a multidisciplinary meeting, taking into account the patient's clinical status, including other potential heart pathologies such as valve diseases as well as the angiographic lesion distribution and characteristics. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score is a tool that was developed to assist in clinical decision-making between the surgical and endovascular treatment modalities (Hamm et al. 2011; Ibanez et al. 2018; Montalescot et al. 2013; Roffi et al. 2016).

Table 1. A) Compilation of established risk factors for coronary and peripheral artery disease, aortic valve stenosis and abdominal aortic aneurysm formation

Risk factor	Coronary artery disease	Peripheral artery disease	Aortic valve stenosis	Abdominal aortic aneurysm
Age	**OR 1.06 (1.05–1.06)** per year, n=7,360 (Xu et al. 2017)	**OR 2.14 (2.12–2.15)** per 10 years; n=3.6 million (Savji et al. 2013)	**OR 2.0 (1.7–2.3)** per 10 years; n=953 (Stritzke et al. 2009)	**OR 2.33 (2.30–2.36)** per 10 years; n=3.6 million (Savji et al. 2013)
	HR 1.57 (1.50–1.65) (men), **1.84 (1.73–1.95)** (women); per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR 1.75 (1.54–1.99)** (men), **1.96 (1.69–2.28)** (women) per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR 1.75 (1.71–1.78)** per 10 years; n=1.12 million (Yan et al. 2017)	**HR 2.55 (1.93–3.36)** per 10 years; for surgically treated or ruptured AAA; n=30,412 (Landenhed et al. 2015)
	OR 1.11 (1.08–1.14) per year; patient age ≤45; n=1,635 (Otaki et al. 2015)	**OR 2.00 (1.64–2.44)** per 10 years; n=3,786 (Alzamora et al. 2010)	**OR 2.18 (2.15–2.20**) highest vs lowest quartile; n=5,201 (Stewart et al. 1997)	**OR 1.2 (1.1-1.4)** per 1 year; (men); n=175 (Wanhainen et al. 2005)
			HR 1.11 (1.08–1.14) per year; n=3,243 (Eveborn et al. 2014)	**OR 1.71 (1.61-1.82)** per 7 years; n=114,419 (Lederle et al. 2000a)
Sex	**OR 1.96 (1.70–2.26)** male vs female; n=7,360 (Xu et al. 2017)	**NS** male vs female; n=2,174 (Selvin & Erlinger 2004)	**NS** male vs female; n=953 (Stritzke et al. 2009)	**OR 0.18 (0.07-0.48)** female vs male; n=114,419 (Lederle et al. 2000a)
	OR 2.06 (1.50–2.82) male vs female; patient age ≤45; n=1,635 (Otaki et al. 2015)	**OR 1.62 (1.01–2.59)** male vs female; n=3,786 (Alzamora et al. 2010)	**OR 0.59 (0.49–0.71)** male vs female; n=523 (Ortlepp et al. 2003)	**HR 0.48 (0.37–0.69)** female vs male; n=18,782; (Jahangir et al. 2015)
			HR 0.65 (0.6–0.67) female vs male; n=1.12 million (Yan et al. 2017)	**OR 5.5 (2.3–13.8)** male vs female; n=175 (Wanhainen et al. 2005)
			OR 2.03 (1.7–2.5) male vs female; n=5,201 (Stewart et al. 1997)	**HR 3.41 (2.17–5.36)** male vs female; for surgically treated or ruptured AAA; n=30,412 (Landenhed et al. 2015)
Smoking	**RR 1.65 (1.53–1.78)** active smoking (1/d) vs never smoking; **2.34 (1.96–2.79**) active smoking (20/d) vs never smoking; Meta-analysis of 141 cohort studies (Hackshaw et al. 2018)	**OR 5.09 (2.97–8.72)** active smoking vs not smoking; n=1,592 (Leng et al. 1995)	**OR 1.7 (1.1–2.4)** active smoking vs not smoking; n=953 (Stritzke et al. 2009)	**OR 1.98 (1.86–2.03)** former smoking vs never smoking; **2.75 (2.68–2.82)** active smoking vs not smoking n=3,319,993; (Berger et al. 2013)
	OR 7.03 (5.01–9.9) active or past smoking vs never smoking; end point new ACS; n=1,168 (Čeponienė et al. 2014)	**RR 2.72 (1.13–6.53)** heavy smoking (>25 packyears) vs never smoking; n=1,592; (Price et al. 1999)	**NS** active smoking vs not smoking; n=523 (Ortlepp et al. 2003)	**OR 5.07 (4.13–6.21)** former or active smoking vs not smoking; n=114,419 (Lederle et al. 2000a)
	RR 1.77 (1.49–2.11) (men), **2.14 (1.46–3.14)** (women) active smoking vs not smoking; n=14,786 (Jousilahti et al. 1999)	**HR 3.14 (2.1–4.90)** former smoking vs never smoking; **8.93 (5.02–15.89)** active (<15/d) smoking vs not smoking; **16.95 (10.77–26.67)** active (≥15/d) smoking vs not smoking; only women; n=39,825 (Conen et al. 2011)	**OR 1.35 (1.1–1.7)** active smoking vs never smoking; n=5,201; (Stewart et al. 1997)	**OR 3.5 (2.4–5.1)** former of active smoking vs not smoking; n=22,139 (Svensjö et al. 2011)
	OR 1.61 (1.42–1.84) active smoking (at least 1 cigarette per day for at least 1 year) vs not smoking; n=7,360 (Xu et al. 2017)	**HR 12.89 (8.59–19.34)** active smoking (≥25/d) vs never smoking; **1.39 (1.19–1.76)** former smoking (<20 years ago) vs never smoking; (men); n=44,985 (Joosten et al. 2012)	**HR 1.71 (1.09–2.67)** active smoking vs not smoking; n=3,243 (Eveborn et al. 2014)	**HR 1.91 (1.27–2.87)** former smoking vs never smoking; **5.55 (3.67–8.40)** active smoking vs never smoking; n=18,782 (Jahangir et al. 2015)
	OR 1.37 (1.01–1.84) active smoking vs not smoking; patient age ≤45; n=1,635 (Otaki et al. 2015)	**OR 1.55 (1.53–1.57)** former smoking vs never smoking; **2.26 (2.23–2.29)** active smoking vs never smoking; n=3,319,993 (Berger et al. 2013)		**HR 7.01 (4.63–10.62)** (women) and **3.06 (2.37–3.95)** (men) active smoking (<20 packyears) vs never smoking; **10.97 (7.41–16.26)** (women) and **6.55 (5.36–7.99)** (men) active smoking (≥ 20 packyears) vs never smoking; for AAA events; n=78,146 (Stackelberg et al. 2014)
	HR 1.60 (1.46–1.76) (men), **1.86 (1.66–2.07)** (women) active smoking vs not smoking; n=15,737; (Tunstall-Pedoe et al. 2017)	**HR 3.96 (3.01–5.21)** (men), **7.08 (5.07–9.88)** (women) active smoking vs not smoking; n=15,737 (Tunstall-Pedoe et al. 2017)		**OR 5.18 (1.60–16.84)** active smoking vs not smoking; n=175 (Wanhainen et al. 2005)
	1.66 (1.07–2.58) heavy smoking (>25 packyears) vs never smoking; (adjusted for age & sex); n=1,592; (Price et al. 1999)	**OR 4.1 (3.1–5.4)** active smoking vs never smoking; **1.8 (1.3–2.5)** former smoking vs never smoking; n=7,058 (Eraso et al. 2014)		**HR 5.13 (3.49–7.54)** current or recent smoking vs not smoking; for surgically treated or ruptured AAA; n=30,412 (Landenhed et al. 2015)
Hypertension	**RR 1.11 (1.07–1.16)** (men), **1.11 (1.04–1.18)** (women) per 10 mmHg increase in systolic blood pressure; n=14,786; (Jousilahti et al. 1999)	**HR 2.42** hypertension vs no hypertension; (men); n=44,985 (Joosten et al. 2012)	**NS** hypertension vs no hypertension; n=953 (Stritzke et al. 2009)	**OR 1.24 (1.21–1.28)** hypertension vs no hypertension; n=3,319,993 (Berger et al. 2013)

	OR 1.59 (1.43–1.78) hypertension vs no hypertension; n=7,360; (Xu et al. 2017)	**NS** hypertension vs no hypertension; n=7,058 (Eraso et al. 2014)	**NS** hypertension vs no hypertension; n=523 (Ortlepp et al. 2003)	**OR 1.6 (1.2–2.1)** hypertension vs no hypertension; n=22,139 (Svensjö et al. 2011)
	OR 1.82 (1.28–2.58) hypertension vs no hypertension; end point new ACS; n=1,168 (Čeponienė et al. 2014)	**OR 1.60 (1.58–1.62)** hypertension vs no hypertension; n=3,319,993 (Berger et al. 2013)	**HR 1.71 (1.66–1.76)** hypertension vs no hypertension; n=1.12 million (Yan et al. 2017)	**OR 1.15 (1.03–1.28)** hypertension vs no hypertension; n=114,419 (Lederle et al. 2000a)
	HR 1.23 (1.18–1.29) (men), **1.26 (1.19–1.32)** (women) per 1 SD increase in systolic blood pressure; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR 1.47 (1.33–1.63)** (men), **1.44 (1.28–1.61)** (women) per 1 SD increase in systolic blood pressure; n=15,737 (Tunstall-Pedoe et al. 2017)	**OR 1.23 (1.1–1.4)** hypertension vs no hypertension; n=5,201 (Stewart et al. 1997)	**HR 1.44 (1.04–2.01)** hypertension vs no hypertension; n=18,782 (Jahangir et al. 2015)
	OR 1.40 (1.07–1.84) hypertension vs no hypertension; patient age ≤45; n=1,635 (Otaki et al. 2015)	**NS** hypertension vs no hypertension; n=2,174 (Selvin & Erlinger 2004)	**HR 1.02 (1.00–1.03)** per 1mmHg increase in systolic blood pressure; n=3,243 (Eveborn et al. 2014)	**NS** hypertension vs no hypertension; n=175 (Wanhainen et al. 2005)
Diabetes	**RR 2.00 (1.51–2.61)** (men), **2.29 (1.57–3.35)** (women) diabetes vs no diabetes; n=14,786 (Jousilahti et al. 1999)	**HR 2.38 (95% CI not reported)** type II diabetes vs no diabetes; (men); n=44,985 (Joosten et al. 2012)	**NS** diabetes vs no diabetes; n=953 (Stritzke et al. 2009)	**NS** Diabetes vs no diabetes; n=3,319,993 (Berger et al. 2013)
	OR 2.37 (2.03–2.78) diabetes vs no diabetes; n=7,360 (Xu et al. 2017)	**OR 1.5 (1.0–2.3)** diabetes vs no diabetes; n=7,058 (Eraso et al. 2014)	**NS** diabetes vs no diabetes; n=523 (Ortlepp et al. 2003)	**OR 0.52 (0.45–0.61)** diabetes vs no diabetes; n=114,419 (Lederle et al. 2000a)
	OR 2.39 (1.46–3.93) diabetes vs no diabetes; end point new ACS; n=1,168 (Čeponienė et al. 2014)	**OR 1.77 (1.74–1.79)** diabetes vs no diabetes; n=3,319,993 (Berger et al. 2013)	**HR 1.49 (1.44–1.54)** diabetes vs no diabetes; n=1.12 million (Yan et al. 2017)	**NS** diabetes vs no diabetes; n=18,782 (Jahangir et al. 2015)
	HR 2.26 (1.72–2.96) (men), **3.24 (2.42–4.32)** (women) diabetes vs no diabetes; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR 6.31 (4.08–9.76)** (men), **7.39 (4.55–12.00)** (women) diabetes vs no diabetes; n=15,737 (Tunstall-Pedoe et al. 2017)	**NS** diabetes vs no diabetes; n=5,201 (Stewart et al. 1997)	
	OR 1.67 (1.02–2.73) diabetes vs no diabetes; patient age ≤45; n=1,635 (Otaki et al. 2015)	**OR 2.08 (1.01–4.28)** diabetes vs no diabetes; n=2,174 (Selvin & Erlinger 2004)		

Risk as indicated with OR/HR/RR, (95 % CI for OR/HR/RR)

Table 1. B) Compilation of established risk factors for coronary and peripheral artery disease, aortic valve stenosis and abdominal aortic aneurysm formation

Risk factor	Coronary artery disease	Peripheral artery disease	Aortic valve stenosis	Abdominal aortic aneurysm
TC	**RR 1.34 (1.26–1.43)** (men), **1.21 (1.10–1.33)** (women) per 1 mmol/L increase; n=14,786 (Jousilahti et al. 1999)	**RR 3.0 (1.5–6.1)** highest vs lowest quartile; (men); n=14,916 (Ridker et al. 2001)	**OR 1.57 (1.00–2.46)** per 1-SD increase; n=246 (Gerber et al. 2003)	**OR 1.44 (1.27–1.63)** high cholesterol level vs not; n=114,419 (Lederle et al. 2000a)
	HR 1.30 (1.24–1.36) (men), 1.23 **(1.16–1.29)** (women), per 1 SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR NS** (men), **1.23 (1.07–1.41)** (women) per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**OR 1.2 (1.1–1.3)** per 20 mg/dL increase; n=953 (Stritzke et al. 2009)	**OR 1.4 (1.0–1.9)** hyperlipidaemia vs no hyperlipidaemia; n=22,139 (Svensjö et al. 2011)
	RR 1.86 (1.05–3.28) highest quintile vs lowest quintile; (men); n=492 (Stampfer et al. 1991)	**OR 1.67 (1.01–2.74)** TC ≥6.21 mmol/L vs <6.21mmol/L; n=2,174 (Selvin & Erlinger 2004)	**HR 1.17 (1.14–1.21)** Dyslipidaemia vs no dyslipidaemia; n=1.12 million (Yan et al. 2017)	**OR 1.61** per 1-SD increase; n=8,793 (Weng et al. 2018)
	RR 1.7 (1.4–2.0) highest quartile vs lowest quartile; (men); n=6,352 (Benfante et al. 1994)	**OR 1.55 (1.11–2.18)** Hypercholesterolaemia vs no Hypercholesterolaemia; n=3,786 (Alzamora et al. 2010)	**OR 0.49 (0.40–0.58)** TC >5.2mmol/L and/or medical therapy vs TC ≤5.2mmol/L and no medical therapy; n=523 (Ortlepp et al. 2003)	**OR 1.9 (1.3–2.8)** per 1 mmol/L increase; n=175 (Wanhainen et al. 2005)
HDL-C	**HR 1.15 (1.09–1.20)** (men), **1.20 (1.14–1.27)** (women) per 1-SD decrease; n=15,737 (Tunstall-Pedoe et al. 2017)	**RR 0.5 (0.2–0.9)** highest vs lowest quartile; (men); n= 14,916 (Ridker et al. 2001)	**NS** per 1 mg/dL increase; n=5,201 (Stewart et al. 1997)	**OR 0.11 (0.02–0.69)** per 1 mmol/L increase; n=175 (Wanhainen et al. 2005)
	RR 0.92 (0.89–0.94) (men), **0.91 (0.39–0.64)** (women) per 0.1 mmol/L increase; n=14,786 (Jousilahti et al. 1999)	**HR NS** (men), **1.37 (1.15–1.64)** (women) per 1-SD decrease; n=15,737 (Tunstall-Pedoe et al. 2017)	**NS** per 1-SD increase; n=246 (Gerber et al. 2003)	
	HR 0.71 (0.68–0.75) per 1-SD increase; n=302,430 (Di Angelantonio et al. 2009)			
	RR 0.38 (0.21–0.69) highest vs lowest quintile; (men); n=492 (Stampfer et al. 1991)			
LDL-C	**OR 1.68 (1.51–1.87)** per 1-SD increase; n=188,577; (White et al. 2016)	**RR 2.5 (1.2–4.9)** highest vs lowest quartile; (men); n=14,916 (Ridker et al. 2001)	**OR 1.12 (1.03–1.23)** per 1 mg/dL increase; n=5,201 (Stewart et al. 1997)	**OR 1.55** per 1-SD increase; n=8,793 (Weng et al. 2018)
	HR 1.13 (1.08–1.18) (men), **1.15 (1.09–1.22)** (women) per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**NS** per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**OR 1.60 (1.00–2.57)** per 1-SD increase; n=246 (Gerber et al. 2003)	**OR 2.3 (1.2–4.4)** per 1 mmol/L increase; n=175 (Wanhainen et al. 2005)
	OR 1.30 (1.22–1.39) per 1 mmol/L increase; n=7,360 (Xu et al. 2017)			
Non-HDL-C	**HR 1.36 (1.30–1.43)** (men), **1.31 (1.24–1.38)** (women) per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR 1.14 (1.00–1.28)** (men); **1.37 (1.20–1.56)** (women) per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)		
	HR 1.56 (1.47–1.66) per 1-SD increase; n=302,430 (Di Angelantonio et al. 2009)			
TG	**HR 1.30 (1.23–1.36)** (men), **1.45 (1.36–1.55)** (women) per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR 1.26 (1.12–1.42)** (men), **1.85 (1.58–2.18)** (women) per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**NS** per 1 mg/dL increase; n=5,201 (Stewart et al. 1997)	**OR 1.9 (1.2–3.1)** per 1 mmol/L increase; n=175 (Wanhainen et al. 2005)
		RR 2.9 (1.4-5.8) highest vs lowest quartile; (men); n= 14,916 (Ridker et al. 2001)	**NS** per 1-SD increase; n=246 (Gerber et al. 2003)	
		OR 1.55 (1.10–2.19) TG ≥1.70 vs <1.70 mmol/L; n=3,786 (Alzamora et al. 2010)		
Apo A	**HR 1.18 (1.12–1.25)** (men), **1.27 (1.19–1.35)** (women) for 1-SD decrease; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR 1.20 (1.04–1.39)** (men) **1.28 (1.05–1.54)** (women) per 1-SD decrease; n=15,737 (Tunstall-Pedoe et al. 2017)	**NS** per 1 SD increase; n=246 (Gerber et al. 2003)	**HR 0.85 (0.78–0.92)** per 10 mg/dL increase; for surgically treated or ruptured AAA; n=30,412 (Landenhed et al. 2015)
		NS Highest quartile compared to lowest; (men); n= 14,916 (Ridker et al. 2001)		
Apo B	**HR 1.38 (1.31–1.46)** (men), **1.29 (1.24–1.35)** (women) for 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**HR 1.28 (1.15–1.44)** (men), **1.35 (1.23–1.50)** (women) per 1-SD increase; n=15,737 (Tunstall-Pedoe et al. 2017)	**NS** per 1-SD increase; n=246 (Gerber et al. 2003)	**HR 1.07 (1.00–1.15)** per 10mg/dL increase; for surgically treated or ruptured AAA; n=30,412 (Landenhed et al. 2015)
		RR 3.0 (1.5–6.0) highest vs lowest quartile; (men); n= 14,916 (Ridker et al. 2001)		

Risk as indicated with OR/HR/RR, (95 % CI for OR/HR/RR)

2.1.3 Peripheral artery disease

Peripheral artery disease (PAD) is defined as stenosis or total obstruction of one or more arteries of the extremities, and its main pathophysiological mechanism is atherosclerosis, although other aetiologies, such as embolization, fibromuscular dysplasia or popliteal entrapment, are also encountered (Hiatt et al. 2008). Aside from coronary and extremity arteries, atherosclerosis can naturally develop in the cerebral, renal and mesenteric vascular beds, but the intricacies of these manifestations are beyond the scope of the present thesis. The main risk factors for PAD are similar to those of CAD, with a strong emphasis on the effect of advanced age and cigarette smoking (Berger et al. 2013; Criqui & Aboyans 2015; Eraso et al. 2014; Fowkes et al. 1992) (Table 1). PAD is also closely linked to other manifestations of atherosclerosis, with 38.5% of the patients concomitantly suffering from CAD, 23.0% from cerebrovascular disease and 13.1% from both (Bhatt et al. 2006). PAD can be subclassified according to the clinical state as asymptomatic, claudication or chronic limb-threatening ischaemia (CLTI). The present thesis focuses on PAD in the lower extremities.

The incidence of new cases of lower-limb PAD as defined by an ankle-brachial index (ABI) of < 0.9 and/or symptomatic disease is estimated to be approximately 377 per 100,000 person years and 102 per 100,000 person years when only symptomatic cases in individuals aged 35–79 years are taken into account (Velescu et al. 2016). Furthermore, the prevalence of PAD has been rising steadily, with a 28.7% increase in low-income countries and a 13.1% increase in high-income countries between 2000 and 2010. In 2010 it was estimated that the number of people with PAD exceeded 200 million globally, and in 2014 the age- and sex-standardised prevalence was estimated to be 4.6%. (Eraso et al. 2014; Gerald et al. 2013) The prevalence of symptomatic or more severe disease appears to be higher in men as compared to women, excluding patients aged 85 or over where the prevalence is reversed (Criqui & Aboyans 2015; Diehm et al. 2004). In Finland, PAD was found in 47.7%–23.0% of high-risk primary care patients depending on the method of ankle-brachial index (ABI) measurement (Oksala et al. 2010). Furthermore, in the early 1980s, the prevalence of claudication was estimated to be 2.1% in men and 1.8% in women aged 30–59 years (Reunanen et al. 1982). However, the recent prevalence and incidence of symptomatic PAD in Finland are less defined.

The most relevant diagnostic tool applied when examining PAD patients is the ABI obtained by measuring systolic ankle pressures (in mmHg) from the arteria dorsalis pedis and arteria tibialis posterior and dividing the higher pressure value with

the systolic pressure measured from the ipsilateral brachial artery. Values in the range of 0.90–1.40 are considered normal, and both high and low values indicate atherosclerotic disease and are linked to disease severity and overall long-term prognosis. (Aboyans et al. 2018) Imaging studies are required for treatment planning, and duplex ultrasound (DUS), magnetic resonance angiography (MRA), digital subtraction angiography (DSA) or contrast-enhanced computed tomography imaging (CT) is most commonly applied, with DSA still referred to as the gold standard. (Aboyans et al. 2018)

Medical therapy along with lifestyle management, particularly smoking cessation, are the cornerstones of treatment in PAD. Statins are recommended for all patients and antiplatelet therapy – most commonly acetosalisylic acid (ASA) or clopidogrel – for all symptomatic patients and those who have undergone invasive interventions (Aboyans et al. 2018). Overall, conservative treatment is advocated for claudicants as the first line of treatment, with supervised exercise therapy demonstrating great cost-effectiveness. This is seldom available to patients in Finland. However, unsupervised exercise therapy is also known to be beneficial. In the case of severe life-limiting symptoms and/or failure to respond to conservative therapy, elective invasive treatment is indicated, with the exception of lesions in the crural arteries. In chronic limb-threatening ischaemia (CLTI), urgent invasive treatment is warranted. The Wound, Ischemia and foot Infection (WIfI) classification can be used to estimate ischaemia severity and assess the risk of amputation in CLTI patients. The treatment modality chosen depends on the anatomic lesion distribution along with patient-related factors such as age, medical history and mobility. Acute ischaemia is treated without delay. (Aboyans et al. 2018)

2.1.4 Arterial aneurysms

An aneurysm is defined as a local 1.5-fold or greater increase in vessel diameter compared to the diameter of the adjacent normal vessel (Johnston et al. 1991). The aetiologies behind aneurysm formation include degenerative, inflammatory, infectious, post-dissection, developmental and congenital factors (Cronenwett & Johnston 2010). Arterial aneurysms can be found in various anatomical locations. However, aneurysms requiring vascular surgical intervention are most commonly situated in the abdominal aorta (62.3%), the lower extremities (15.6%) and the thoracic aorta (2.8%) (Lawrence et al. 1999). Abdominal aortic aneurysms (AAA)

therefore represent the most clinically significant group of arterial aneurysms in vascular surgery and are also focused on in the present thesis.

2.1.4.1 Abdominal aortic aneurysms

In practice, the diameter limit for an abdominal aortic dilatation to be considered an aneurysm is 3 cm in adults. The incidence of new AAA diagnoses in Western populations is estimated to be between 0.4 and 0.67 annually, with the higher incidences reported in all-male cohorts (Forsdahl et al. 2009; Lederle et al. 2000b; Vardulaki et al. 1999). The prevalence of AAAs, in turn, is estimated to be up to 2.2%–8.9% in men and roughly 1.3%–2.2% in women over 65 of age, and it increases with age. Recently, an AAA prevalence of 0.4% was ascertained in a cohort of women aged 70 years. (Ashton et al. 2007; Nordon et al. 2011; Scott et al. 2002; Singh et al. 2001; Söderberg et al. 2017; Svensjö et al. 2011)

The pathogenesis of aneurysm formation is, to a great extent, both degenerative and inflammatory, and structural deterioration of the vessel wall is histologically characteristic of AAAs. More specifically, a reduction in smooth muscle cell density in the media layer, the destruction of elastin and collagen in the media and adventitia, and lymphocyte and macrophage invasion can typically be detected in AAAs. (Eagleton 2012; Kuivaniemi et al. 2015; López-Candales et al. 1997). The main risk factors of AAA include higher age, smoking, male sex and degenerative diseases, along with a positive family history and white ethnicity, whereas diabetes and female sex are protective against the development of an AAA. (Forsdahl et al. 2009; Johansen & Koepsell 1986; Larsson et al. 2009; Lederle et al. 2000a; Lederle et al. 1997; Pleumeekers et al. 1995; Scott et al. 2002; Singh et al. 2001; Tang et al. 2016; van Vlijmen-van Keulen et al. 2002; Vardulaki et al. 2000; Wilmink et al. 1999.) Smoking is a particularly potent modifiable predisposing factor, with odds ratios (OR) exceeding 3, and early successful cessation can reduce the risk by approximately one third (Lederle et al. 2000a; Lederle et al. 1997; Pleumeekers et al. 1995; Singh et al. 2001; Tang et al. 2016; Wilmink et al. 1999). (Table 1) With regard to genetic predisposition, approximately 10% of AAAs are familial in nature, and an AAA is discovered in approximately one in five patients with a positive (first degree relative) family history (Johansen & Koepsell 1986; Larsson et al. 2009; Sakalihasan et al. 2014; van Vlijmen-van Keulen et al. 2002). Infections can also predispose to aneurysm formation, although with advances in level of health care and the development of targeted antibiotic regimens, these so-called mycotic aneurysms currently account for less than 1% of all aortic aneurysms and the most common

pathogens have shifted from β-haemolytic group A streptococci, pneumococci, syphilis and Haemophilus influenza to Staphylococci and Salmonella (Brown et al. 1984; Lin & Hsu 2014; Maeda et al. 2011; Oderich et al. 2001; Parkhurst & Decker 1955.; Roberts et al. 2009; Sommerville et al. 1959; Sörelius et al. 2016; Stengel & Wolferth 1923). An association between ApoA1 and ApoB concentrations and AAA formation has also been discovered (Landenhed et al. 2015).

AAAs carry a risk of rupture (RAAA), which increases according to the maximum diameter of the aorta, with diameters below 4 cm associated with a virtually nil rupture risk, diameters between 5 cm and 6 cm with a 3%–15% annual rupture risk, and diameters exceeding 8 cm with a 30%–50% annual rupture risk (Brewster et al. 2003; Filardo et al. 2015; Szilagyi et al. 1966). Rupture, in turn, is associated with a significant mortality rate – as high as 80% in all patients reaching the hospital and 24%–60% in those undergoing a surgical intervention (Basnyat et al. 1999; Verhoeven et al. 2008). Vänni et al. (2016) have discovered a similar mortality rate (79.5%) in Finland. The annual incidence of RAAAs in Finland was estimated to be 6.5/100,000 (Vänni et al. 2016). Furthermore, aneurysm rupture is linked to an atherosclerotic disease burden, with 40% of patients with an unexpected RAAA having a history of cardiovascular disease, most commonly CAD (Vänni et al. 2016). It has additionally been discovered that roughly 10% of male patients undergoing elective CABG are harbouring a previously undiagnosed AAA and it has been suggested that concomitant ultrasound screening for AAA when conducting cardiac echocardiography might help prevent aneurysm ruptures (Monney et al. 2004, Savolainen et al. 2010).

Aneurysms are most often recognised as incidental findings in imaging studies. However, screening for AAAs is now increasingly advocated for men aged 65 and over (Chaikof et al. 2018; Moll et al. 2011; Wanhainen et al. 2019). Screening women for AAAs has not been shown to influence rupture rates or mortality (Chaikof et al. 2018; Moll et al. 2011; Scott et al. 2002; Wanhainen et al. 2019). Furthermore, repeated screening of individuals with a first-degree relative diagnosed with an AAA as well as those suffering from true aneurysms in other locations is recommended, and it should be considered in PAD patients (Ålund et al. 2008; MacSweeney et al. 1993; Moll et al. 2011; Wanhainen et al. 2019).

The general indication for the treatment of an AAA is a diameter of 5.5 cm or greater and/or a growth rate of 1.0 cm or more per year in elective cases but in women, repair may be considered at a smaller threshold of 5.0 cm as females have a tendency to suffer a rupture at smaller aneurysm diameters when compared to males (Chaikof et al. 2018; Forbes et al. 2006; Moll et al. 2011; Wanhainen et al. 2019).

Symptomatic and ruptured aneurysms are treated regardless of size, albeit that small aneurysms (< 4 cm) rarely pose these problems. The choice of treatment method – open or endovascular – is at the discretion of the attending vascular surgeon and depends on the AAA anatomy and the urgency of treatment, along with the age and potential comorbidities of the patient. Thus far, endovascular aortic repair (EVAR) has shown an early survival benefit but inferior long-term survival compared to open surgery in elective cases (Patel et al. 2016; Powell et al. 2017). In the treatment of an RAAA, an endovascular treatment strategy was associated with improved long-term survival, better quality of life and better cost-effectiveness at 3 years when compared to an open treatment strategy, although the benefits were not ascertained in a shorter follow-up of 30 days, and at one year only the quality of life and cost-effectiveness were improved (IMPROVE Trial Investigators, 2015, 2017; Powell et al. 2014). According to the latest European guidelines, open surgical treatment is generally recommended for electively treated patients with a longer life expectancy and, in the case of an RAAA, EVAR for anatomically suitable cases (Wanhainen et al. 2019).

2.1.5 Valvular heart disease

Valvular heart disease (VHD) presents as stenosis, regurgitation or a combination of these and is mostly encountered in the aortic, mitral and tricuspid valves. Isolated right-sided VHD is rare, and most cases of pulmonary valve disease are congenital and associated with other congenital disorders, whereas the aetiologies behind isolated tricuspid regurgitation include degenerative diseases and infective endocarditis – a condition commonly afflicting intravenous drug users – in addition to congenital disorders (Iung et al., 2003, 2007; Iung & Vahanian 2014). VHD can develop due to intrinsic valve pathologies, secondarily to other disorders, such as cardiomyopathies, endocarditis and aortic root dilatation, or iatrogenically after radiation treatment, for instance (Boudoulas et al. 2013; Ong et al. 2013). Owing to a dramatic decrease in rheumatic fever and syphilis in the Western society, along with the simultaneous ageing of the population and the concomitant increasing prevalence of degenerative conditions such as ischaemic heart disease, the aetiology of VHD has changed markedly (Boudoulas et al. 2013). The incidence of VHD was recently ascertained to be 63.9 per 100,000 person-years in the Swedish population (Andell et al. 2017). The prevalence of VHD is estimated to be 0.3%–0.7% in adults aged under 45 and, in contrast, 11.7%–13.3% in those aged 75 or over with an overall age-adjusted prevalence of 2.5% (95% CI 2.2%–2.7%). The prevalence of VHD is

similar in men and women. (Iung & Vahanian 2014; Mozaffarian et al. 2016; Nkomo et al. 2006)

The symptoms of VHD vary from non-existent to severe, often graded with the New York Heart Association (NYHA) Functional Classification, and they include fatigue, dyspnoea, tissue oedema particularly in the lower extremities, palpitations, presyncope and syncope (Criteria Committee of the New York Heart Association 1973). A heart murmur is an essential yet nonspecific finding in the clinical investigation, and either transthoracic or transoesophageal echocardiography is considered the key imaging method in the diagnosis and follow-up of VHD. Other methods, such as CT imaging, cinefluoroscopy, cardiac catheterisation and cardiac magnetic resonance, can also be applied. With regard to laboratory parameters, serum B-type natriuretic peptide reflects the functional impairment brought on by the valve disorder as presented by the NYHA class. (Falk et al. 2017) The treatment strategies differ depending on the type and severity of VHD as well as concomitant conditions (Falk et al. 2017; Nishimura et al., 2017, 2014). Overall, stenotic lesions typically require operative interventions at an earlier stage than regurgitant lesions (Rapaport 1975).

The overall prevalence of aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation is estimated to be 0.4%, 0.5%, 0.1% and 1.7%, respectively (Nkomo et al. 2006). Furthermore, in the Framingham Heart Study, mitral regurgitation was found in approximately one fifth of patients, tricuspid regurgitation in 14.8% of men and 18.4% of women, and aortic regurgitation in 13.0% of men and 8.5% of women in a cohort of patients aged 44 or over (Singh et al. 1999). The most clinically significant types of VHD shall be presented in more detail in the following sections.

2.1.5.1 Aortic stenosis and regurgitation

In a European cohort of VHD patients, aortic stenosis was discovered to be the most prevalent of the single native left-sided VHDs, accounting for 43.1% of the cases, whereas aortic regurgitation was found in 13.3% (Iung et al. 2003). A somewhat differing relative prevalence of VHD was ascertained in an American population-based study (Nkomo et al. 2006). The most common aetiologies behind aortic VHD are degenerative (81.9% in aortic stenosis and 50.3% in aortic regurgitation; Table 1), although rheumatic and endocarditis-associated predisposing factors account for roughly 20% of aortic regurgitation cases (Iung et al. 2003). Additionally, in 15% of aortic regurgitation cases, the aetiology is congenital. The

most common congenital heart anomaly, in turn, is a bicuspid aortic valve, which can be found in 1%–2% of the general population and predisposes to valvular dysfunction as well as aortic dilatation/aneurysm formation and dissection (Borger et al. 2018; Hoffman & Kaplan 2002).

The development of degenerative calcific aortic stenosis is an active inflammatory process which bears great resemblance to atherosclerosis – particularly in regard to the lipid deposition, white blood cell activation and the disruption of the basement membrane. As a distinction, it is associated with prominent mineralisation and a small number of smooth muscle cells. (O'Brien et al. 1996; Olsson et al. 1994; Olsson et al. 1999; Otto et al. 1994.) Furthermore, calcific aortic stenosis is strongly associated with CAD and shares similar risk factors (Mautner & Roberts 1992; Peltier et al. 2003).

Thus far, no intervention has been proven effective in reversing or slowing down the disease process of aortic stenosis (Chan et al. 2010; Cowell et al. 2005; Nishimura et al. 2014; Rossebø et al. 2008), and it remains the most common primary valve disease requiring invasive intervention in the Western population (Falk et al. 2017). Invasive treatment entails valve replacement surgery as well as more contemporary transcatheter procedures – transcatheter aortic valve implantation (TAVI) and balloon aortic valvotomy, the latter applied as a bridge procedure before definitive repair in severe symptomatic stenosis. Overall, invasive intervention is indicated in cases of symptomatic, high-gradient stenoses and severe low-flow, low-gradient stenoses. In asymptomatic stenoses, procedures are indicated in severe stenosis associated with systolic left ventricular dysfunction (left ventricular ejection fraction [LVEF] $< 50\%$) or an abnormal exercise test result. Patients should be evaluated individually for selection for either open surgery or TAVI by a multidisciplinary team, taking into account factors such as surgical risk, previous procedures, possible concomitant conditions requiring surgical intervention and life expectancy. (Falk et al. 2017; Nishimura et al., 2017, 2014.)

In aortic regurgitation, traditional open valve replacement and, in some cases, valvuloplasty are the invasive treatment modalities, and surgery is recommended for all symptomatic patients and those asymptomatic individuals with a resting LVEF of $\leq 50\%$, as well as for patients undergoing procedures of the coronaries, the ascending aorta or other valves. Surgery should also be considered for asymptomatic patients with severe left ventricular dilatation. (Falk et al. 2017; Nishimura et al. 2014.) Medical therapy with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and/or beta-blockers may provide symptom relief for patients unfit for surgery and slow down the process of aortic root dilatation in patients with

a specific Fibrillin-1-associated connective tissue disorder, Marfan's syndrome (Elder et al. 2011; Falk et al. 2017; Forteza et al. 2016; Lacro et al. 2014; Milleron et al. 2015; Zendaoui et al. 2011).

2.1.5.2 Mitral regurgitation and stenosis

Mitral regurgitation accounted for 24.8% of VHD cases in a European study, whereas it was discovered in an American general population cohort to be the most prevalent valve pathology (Iung et al. 2003; Nkomo et al. 2006). As in aortic valve diseases, the majority (61.3%) of mitral regurgitation cases are degenerative in origin. A rheumatic aetiology is found in approximately 14.2% of the cases. The invasive intervention for mitral regurgitation is usually surgical, and the relative frequencies of valve replacement procedures and valvuloplasties in the Euro Heart Survey were 53.5% and 46.5%, respectively. (Iung et al. 2003.) Valve repair is usually favoured over replacement when feasible (Falk et al. 2017). In some cases of primary mitral regurgitation, percutaneous edge-to-edge repair is an option, but it is associated with a higher rate of residual regurgitation (Feldman et al. 2015). Overall, surgery is indicated in acute severe mitral regurgitation, in symptomatic patients suffering from chronic severe primary mitral regurgitation with an LVEF of $> 30\%$, and in asymptomatic patients with clinical features predicting an inferior outcome, such as an LVEF of $\leq 60\%$, left ventricular end-systolic dimension of ≥ 45 mm, atrial fibrillation and a systolic pulmonary pressure of ≥ 50 mmHg (Badhwar et al. 2012; Enriquez-Sarano et al. 1994; Falk et al. 2017; Le Tourneau et al. 2010; Nishimura et al., 2017, 2014; Tribouilloy et al. 1999). Complementary medical treatment with nitrates and diuretics to reduce filling pressures, sodium nitroprusside to reduce afterload and inotropic agents to treat hypertension can be utilised in acute mitral regurgitation (Falk et al. 2017; Nishimura et al. 2014). Additionally, intra-aortic balloon counterpulsation can be applied to support systemic circulation as a bridge procedure until definitive repair can be performed (Falk et al. 2017; Nishimura et al. 2014).

Most cases of mitral stenosis are rheumatic in origin, although the incidence of rheumatic mitral stenosis has been constantly declining in industrialised countries (Iung et al. 2003; Iung & Vahanian, 2011, 2014). Mitral stenosis can also develop degeneratively, and a potential underlying phenomenon in both stenosis and regurgitation is mitral annulus calcification, a process resembling atherosclerotic calcification and sharing similar risk factors (Abramowitz et al. 2015; Adler et al. 2001; Boon et al. 1997; Kanjanauthai et al. 2010). Invasive treatment is

recommended for symptomatic mitral stenosis patients, and percutaneous mitral commissurotomy is the main intervention, with surgery reserved for those patients who are at a high risk of cardiac complications, who have a low surgical risk and who have contraindications for percutaneous treatment (Falk et al. 2017; Nishimura et al. 2014). Pharmacological therapy with diuretics, beta-blockers, digoxin or heart-rate regulating calcium channel blockers can alleviate the symptoms momentarily (Falk et al. 2017; Nishimura et al. 2014). Additionally, mitral stenosis may predispose to atrial fibrillation and thrombus formation in the left atrium, and in these cases, anticoagulation is required (Falk et al. 2017; Nishimura et al. 2014).

2.1.5.3 Tricuspid valve diseases

Regurgitation is the most common tricuspid valve pathology. Significant tricuspid regurgitation is usually secondary, with a normal leaflet structure, whereas the more infrequent primary regurgitation develops due to a variety of underlying causes, such as infective endocarditis, rheumatic heart disease and congenitally dysplastic valves. (Falk et al. 2017; Lancellotti et al. 2013; Nishimura et al. 2014; Sousa et al. 2012) Overall, invasive treatment for tricuspid regurgitation should be performed before irreversible right ventricular dysfunction develops, and it is primarily surgical, although percutaneous options have also emerged recently and are under investigation in several clinical studies. Surgery is presently indicated in symptomatic patients as well as asymptomatic patients with progressive dilatation of the right ventricle or loss of ventricular function, along with those subjected to left-sided valvular procedures or coronary surgery. As in mitral valve disease, repair is favoured over replacement when feasible. (Falk et al. 2017; Taramasso et al. 2017.) In secondary tricuspid regurgitation, ring annuloplasty is the central point of surgical treatment (Chang et al. 2006; Dreyfus et al. 2005).

2.2 Serum lipids in cardiovascular disease

The conventional serum lipid parameters include total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and serum triglycerides (TG). LDL-C in particular has been recognised as a significant modifiable risk factor in atherosclerotic cardiovascular disease, and lowering it can reduce the incidence of major cardiovascular events and death (Buchwald et al. 1998; Eckel et al. 2014; Mihaylova et al. 2012). It is therefore the central lipoprotein target

of therapy in the primary and secondary prevention of cardiovascular diseases (Catapano et al. 2016; Morris et al. 2014; Stone et al. 2014). Low HDL-C is also independently associated with increased cardiovascular risk, and the threshold levels for men and women are < 1.0 mmol/L and < 1.3 mmol/L, respectively (Chapman et al. 2011; Piepoli et al. 2016). With regard to serum TG, it is suggested that these lipids are not directly atherogenic by themselves but rather a biomarker of cardiovascular risk, owing to their association with atherogenic remnant particles and apolipoprotein CIII (Miller et al. 2011). Specifically, fasting triglyceride concentrations exceeding 1.7 mmol/L are associated with increased risk (Piepoli et al. 2016).

The application of more contemporary lipid parameters – such as apolipoproteins, the core structural and functional constituents of lipoprotein particles, along with lipoprotein subfractions – has been discovered to complement or even improve cardiovascular risk assessment. Particularly apolipoprotein B (ApoB) and its ratio to apolipoprotein A1 (ApoA1), that is, the ApoB/ApoA1 ratio, is possibly one of the strongest risk markers. Additionally, determining non-high-density lipoprotein cholesterol (non-HDL-C) by subtracting HDL-C from TC may provide incremental value. (Catapano et al. 2016; Di Angelantonio et al. 2012; Duschek et al. 2015; Niemi et al. 2009; Oksala et al. 2013; Pencina et al. 2015; Sniderman et al. 2011; Thompson & Danesh 2006; Walldius et al., 2004, 2001; Yusuf et al. 2004.) ApoB is the main apolipoprotein in the proatherogenic lipoproteins VLDL, IDL and LDL and reflects the number of these lipoprotein particles in plasma. As such, it is involved in transferring cholesterol towards the tissues. This may be of use in estimating the atherogenic risk in patients with high concentrations of small dense LDL particles. (Chan 1992; Fisher et al. 2014.) ApoB has even been suggested as a new target for lipid-lowering therapy (Charlton-Menys et al. 2009). ApoA1, in turn, is antiatherogenic, as it transfers excess cholesterol from peripheral tissues to the liver in a process referred to as reverse cholesterol transport, and it is the main apolipoprotein in HDL-C particles (Brufau et al. 2011). Plasma ApoA1 levels below 1.2 g/L in men and 1.4 g/L in women are considered low (Catapano et al. 2016). The Finnish reference values suggested by Fimlab Laboratories Ltd are 1.3–2.2 g/L for ApoA1 and 0.6–1.4 g/L for ApoB in the general population, < 1 g/L in high-risk patients and diabetics, and < 0.8g/L in very high-risk patients (Fimlab laboratories Ltd). An association has also been established between cardiovascular risk and lipoprotein(a), a subclass of lipoprotein consisting of an LDL-particle and a specific apolipoprotein (apolipoprotein[a]) covalently bound to it. However, reliable evidence regarding risk reduction by means of a selective

reduction of lipoprotein(a) is currently lacking. (Nordestgaard et al. 2010; Piepoli et al. 2016.) The latest lipid parameters to pique scientific interest in the field of cardiovascular risk assessment are ceramides, a group of sphingolipids consisting of sphingosine molecules attached to varying fatty acids. Sphingolipids, in turn, are structural components of cell membranes but can be found in the circulation attached to lipoproteins. (Kontush et al. 2013; Larsen & Tennagels 2014; Maggio et al. 2006.) They have been discovered to be associated with major cardiovascular events in a linear fashion in previously healthy individuals, as well as with the 1-year outcome after coronary angiography and with cardiovascular death in both stable CAD patients and those suffering from acute coronary syndromes (Cheng et al. 2015; Havulinna et al. 2016; Laaksonen et al. 2016).

The main lipid parameters associated with the risk of developing CAD are high serum TC and LDL-C, and low HDL-C (Jousilahti et al. 1999; White et al. 2016). TC and HDL-C have a similar association with the risk of PAD, but the extent of the effect exerted by HDL-C may exceed that of TCs (Criqui & Aboyans 2015; Joosten et al. 2012; Meijer et al. 2000; Mowat et al. 1997; Murabito et al. 1997). The ratio of TC to HDL-C has been suggested as potentially the most potent lipid risk factor for developing PAD investigated thus far (Aboyans et al. 2006; Ridker et al. 2001). Serum TG, on the other hand, often shows a univariable association with PAD but fails to persist as an independent risk factor in multivariable analyses (Criqui & Aboyans 2015). Despite the pathophysiological process of atherosclerosis being dependent on the accumulation of cholesterol in the subintimal layer via transport by LDL-C particles, LDL-C does not unequivocally stand out as an independent risk factor for PAD development (Berliner et al. 1995; Ridker et al. 2001). Of the more novel parameters, lipoprotein(a) appears to be associated with PAD (Aboyans et al. 2006; Laschkolnig et al. 2014). Elevated serum TC, LDL-C and TG as well as low HDL-C have also been ascertained as significant lipid risk factors for AAA formation (Forsdahl et al. 2009; Harrison et al. 2018; Lederle et al. 2000a; Tang et al. 2016; Wanhainen et al. 2005; Weng et al. 2018). Along with HDL-C, ApoA1 is negatively associated with AAA formation and growth (Burillo et al. 2015; Landenhed et al. 2015). ApoB, in turn, appears to be a risk factor for the development of an AAA (Landenhed et al. 2015). In aortic valve stenosis, LDL-C and lipoprotein(a) have been suggested as significant risk factors (Stewart et al. 1997). The role of the ApoB/ApoA1 ratio was also recently investigated and found to be associated with a faster haemodynamic progression of aortic stenosis in younger patients (Tastet et al. 2018). When considering the sum of cardiovascular risk associated with various lipid parameters, it would seem plausible to consider these

parameters in relation to each other as lipid profiles in lieu of focusing solely on individual values.

2.2.1 Lipid and lipoprotein measurements and the Extended Friedewald Formula

Lipid analyses should be performed in the resting state, as testing during or within 6 weeks of major physiological stress such as a myocardial infarction renders the measurements unreliable. Traditionally, TC, HDL-C and TG are measured directly from plasma or, more commonly, serum, which typically has an approximately 3% higher concentration of lipids. Venous blood samples are drawn after overnight (i.e. 10–12 h) fasting. Serum is then extracted from the blood by allowing it to clot and centrifuging. If plasma is desired in lieu of serum, blood samples are collected directly into tubes containing ethylenediaminetetraacetic acid, which prevents blood from clotting. In the gold standard method, the Abell-Kendall technique of saponification of cholesterol ester by hydroxide, extraction with petroleum ether, and colour development with acetic anhydride-sulphuric acid (the Liebermann-Burchard test) is subsequently applied to determine or extract cholesterol. The cholesterol concentration can then be measured using spectrophotometry. (Cox & García-Palmieri 1990; Warnick 2000.) The HDL-C concentration is conventionally obtained following the same procedures after first applying reagents such as heparin-manganese, sodium phosphotungstate with magnesium, or dextran sulphate to precipitate the ApoB-containing lipoproteins LDL and VLDL (Cox & García-Palmieri 1990; Warnick 2000). The methods for separating lipoproteins include ultracentrifugation, precipitation, and electrophoresis and quantitative analysis involves sequential ultracentrifugation and precipitation (Cox & García-Palmieri 1990; Warnick 2000). LDL-C, in turn, is traditionally estimated by calculating with the Friedewald formula (in mmol/L): LDL-C = TC – HDL-C – (0.45 x TG) (Friedewald, Levy, & Fredrickson, 1972). This technique for determining LDL-C is limited by its unreliability when serum TG or lipoprotein(a) levels are high (Friedewald et al. 1972; Saeedi et al. 2014). Furthermore, LDL-C estimated with the Friedewald equation does not represent pure LDL-C (Warnick 2000). At present, clinical laboratories mainly apply automated methods, such as enzymatic techniques, for lipid analysis and, in some instances, the Friedewald equation for LDL-C (Warnick 2000).

With regard to apolipoproteins, radioimmunoassays can be used in the direct measurement of ApoA1 and ApoB concentrations and isoelectric focusing in the determination of ApoC and ApoE concentrations (Cox & García-Palmieri 1990). These methods are, however, both arduous and expensive when considering clinical practise. Recently, a technique for computationally estimating apolipoproteins and lipoprotein subfractions was developed and validated for obtaining pure LDL-C, IDL-C, ApoB, ApoA, HDL_2-C-subfraction and VLDL-TG (Niemi et al. 2009). This method, the Extended Friedewald Formula (EFW), is essentially a neural network model that utilises the traditional Friedewald parameters as inputs (Niemi et al. 2009). Instead of producing a specific mathematic formula to calculate new variables, it is able to learn association patterns between input and output values in a fashion resembling the human brain and apply this to new data. In practice, the EFW is a programmed software, a specific multilayer perceptron network, consisting of artificial neurons capable of pattern recognition and prediction. These neurons are organised in three layers each of which has their own function: the input layer, the hidden layer and the output layer. (Niemi et al. 2009)

2.2.2 Pharmacological treatment

The basis of reducing serum-lipid-associated cardiovascular risk is lifestyle management with a healthy vegetable-rich diet and regular aerobic physical activity (Eckel et al. 2014; Stone et al. 2014). However, additional pharmacological therapy is often called for. The most used and investigated group of medications in the primary and secondary prevention of cardiovascular diseases is the serum-cholesterol-targeting 3-hydroxy-3-methylglutaryl-coenzyme A inhibitors, more commonly known as statins. They function via competitively inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme A activity in the liver, thus reducing the intracellular cholesterol concentration and, consequently, increasing the uptake of cholesterol from the blood (Istvan & Deisenhofer 2001). Overall, there is compelling evidence that statins reduce total mortality and the incidence of major cardiovascular events without increasing severe adverse events (Mihaylova et al. 2012; Taylor et al. 2013). For each 1.0mmol/L decrease in serum LDL-C, the risk of cardiovascular mortality and myocardial infarction reduces by 20%–25% (Mihaylova et al. 2012). Statins are also considered to have pleiotropic effects independent of serum lipid levels, but whether or not they have true clinical benefits beyond lipid lowering remains controversial (Oesterle & Liao 2019; Oesterle et al. 2017). Other forms of

lipid-targeting pharmacotherapy include bile acid sequestrants and cholesterol absorption inhibitors such a ezetimibe (Catapano et al. 2016). Particularly promising results in cardiovascular risk reduction have been found in studies with the novel group of proprotein convertase subtilsin-kexin-type 9 (PCSK9) inhibitors (alirocumab, evolocumab) associated with LDL receptor regulation (Abifadel et al. 2003; Bonaca et al. 2018; Navarese et al. 2016; Robinson et al. 2015; Sabatine et al., 2018, 2017, 2015).

Statin therapy is recommended for secondary prevention in patients with clinical atherosclerotic cardiovascular disease, applying a high to moderate intensity, and in primary prevention in adults with an LDL-C concentration of ≥ 4.9 mmol/L to achieve a 50% or greater reduction in LDL-C. Furthermore, with lower LDL-C levels, utilising a risk estimation method such as SCORE when considering the initiation of statin therapy for primary prevention is recommended. (Catapano et al. 2016; Piepoli et al. 2016; Stone et al. 2014.) While the American guideline refrains from providing recommendations on specific LDL-C or non-HDL-C target levels, referring to a lack of evidence regarding comparison between different targets, the European guidelines offer some more precise treatment goals (Catapano et al. 2016; Piepoli et al. 2016; Stone et al. 2014). The recommended target LDL-C level is < 1.8 mmol/L or a reduction of 50% with baseline levels of 1.8–3.5 mmol/L for patients at very high risk (SCORE≥10), < 2.6 mmol/L or a reduction of 50% with baseline levels of 2.6–5.1 mmol/L for patients at high risk (SCORE 5-9), and < 3.0 mmol/L for others (Piepoli et al. 2016).

In patients with acute coronary syndrome, a rapid initiation of high-intensity statin therapy is recommended, with an LDL-C target of < 1.8 mmol/L or a 50% reduction in the LDL-C concentration (Catapano et al. 2016; de Lemos et al. 2004; Ray et al. 2005; Schwartz et al. 2001). Furthermore, brief routine pre-treatment or loading with high-dose statins appears beneficial for CAD patients undergoing percutaneous coronary interventions (Briguori et al. 2009; Catapano et al. 2016; Di Sciascio et al. 2009; Patti et al. 2011). Corresponding recommendations for CABG patients are, however, less well defined. Overall, statin therapy has been shown to stop the disease progression of CAD and reduce calcification in the coronary arteries (Achenbach et al. 2002; Budoff et al. 2000; Callister et al. 1998; Jukema et al. 1995; Pitt et al. 1995; Zhao et al. 1993).

Statins are recommended for all PAD patients, and a serum LDL-C of < 1.8 mmol/L, or a ≥ 50% reduction when the baseline values are in the range of 1.8–3.5 mmol/L, has been suggested as a treatment goal (Aboyans et al. 2018; Aung et al. 2007; Catapano et al. 2016; Piepoli et al. 2016). In addition to reducing cardiovascular

mortality and improving the overall prognosis, statins have been discovered to positively affect walking distance, thus alleviating claudication, and they reduce adverse limb events in PAD as well as the rate of the first peripheral vascular events in patients with and without pre-existing PAD (Aung et al. 2007; Bulbulia et al. 2007; Gargiulo et al. 2012; Kumbhani et al. 2014; McDermott et al. 2003; Westin et al. 2014). With regard to AAAs, statin therapy has been suggested to reduce the growth rate of abdominal aortic aneurysms smaller than 5.5 cm in diameter, although the evidence is regarded as inconclusive at present (Takagi et al. 2012; Wanhainen et al. 2019). Statin treatment has been found to be associated with beneficial perioperative outcomes in AAA patients undergoing invasive interventions (Kertai et al. 2004). However, the data remains limited to retrospective studies and is still inconclusive (Paraskevas et al. 2006). Thus far, no specific lipid targets of treatment for AAA patients have been set, but statin treatment is recommended (Catapano et al. 2016; Chaikof et al. 2018; Moll et al. 2011; Wanhainen et al. 2019).

In contrast to CAD and PAD, in aortic valve stenosis, neither statins nor intensive lipid lowering therapy has been able to slow down the progression of the disease or decrease the rate of aortic-valve-stenosis-related events in prospective RCTs. These medications are therefore not recommended in isolated aortic valve stenosis in the absence of other indications for use (Catapano et al. 2016; Chan et al. 2010; Cowell et al. 2005; Rossebø et al. 2008). The evidence in terms of other valve pathologies remains insufficient (Catapano et al. 2016).

2.3 Treatment strategy in cardiovascular surgery

In Finland, cardiothoracic and vascular surgery were integrated as a single specialty up until 2002, after which they were divided into two separate surgical fields. Despite obvious differences especially in perioperative treatment and anaesthesiologic practises, such as utilising the cardiopulmonary bypass, the fields still share similar operative techniques. Additionally, the patient material is very similar with respect to risk factor profiles and comorbidities, and in this sense the distinction is somewhat arbitrary. While mastering the appropriate surgical techniques and strategies is the cornerstone of surgical care and a prerequisite for high-quality treatment, managing risk factors and optimising perioperative care is equally important in order to achieve the best possible results. The specifics of surgical and endovascular techniques are beyond the scope of the present thesis, and the focus is on risk factors and identifying major complications. However, the main guidelines regarding which

treatment strategies the cardiovascular surgery practices are based on at the study centres are presented briefly in the following section.

2.3.1 Guidelines

Several clinical practice guidelines have been created to assist in evidence-based decision-making in the treatment of cardiovascular diseases and cardiovascular surgery. These guidelines offer the most up-to-date research-based views on recommended treatment strategies along with the level of evidence the recommendations are based on. However, an uncritical following of the guidelines without individually assessing each patient is to be discouraged. Instead, they serve as a valuable reference when optimising patient care and treatment results. Table 2 presents the principal guidelines in use during the study period of the present thesis as well as the newest recommendations.

Table 2. Key clinical practice guidelines in cardiovascular surgery

Subject	Publication year	Name	Reference
CAD	2011	ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation	(Hamm et al. 2011)
	2012	2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease	(Fihn et al. 2012)
	2013	The 2013 ESC guidelines on the management of stable coronary artery disease	(Montalescot et al. 2013)
	2014	2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes	(Amsterdam et al. 2014)
	2016	2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation	(Roffi et al. 2016)
	2016	2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction	(Levine et al. 2016)
	2018	2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation	(Ibanez et al. 2018)
Valvular disease	2014	2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease	(Nishimura et al. 2014)
	2017	2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease	(Nishimura et al. 2017)
	2017	2017 ESC/EACTS Guidelines for the management of valvular heart disease	(Falk et al. 2017)
PAD	2007	Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)	(Norgren et al. 2007)
	2017	2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease	(Gerhard-Herman et al. 2017)
	2017	2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases	(Aboyans et al. 2018)
AAA	2011	Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery	(Moll et al. 2011)
	2018	The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm	(Chaikof et al. 2018)
	2018	European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms	(Wanhainen et al. 2019)

2.4 Postoperative outcomes

The procedural success of surgical treatment can be estimated from different perspectives, applying a variety of parameters referred to in studies as end points. Firstly, survival or mortality can be investigated. The typical subclassifications used are in-hospital mortality or 30-day mortality and long-term mortality in reference to the time scale, as well as disease-specific mortality, cardiovascular mortality and all-cause mortality referring to the cause. Secondly, morbidity in its different variations is habitually studied. The classic end points applied in cardiovascular surgery include myocardial infarction, stroke, limb events such as major amputation or freedom from it, wound healing, walking distance, reinterventions, vessel or graft patency, NYHA class, and possible treatment complications or lack thereof. These solitary events may also be integrated to form composite end points, such as major adverse limb events or major adverse cardiovascular events, although these can cause confusion as the definitions sometimes differ between studies. Thirdly, when the full effects of treatment on the one hand and the possible treatment-related complications on the other on patients' lives are at the focus of interest, the quality of life can be ascertained by, for instance, utilising questionnaires. Finally, from the view point of society, health care costs are an important aspect to consider, and for this, cost-effectiveness analyses are carried out. (Criteria Committee of the New York Heart Association 1973; Diehm et al. 2008; Hicks et al. 2018; Kip et al. 2008; Marsh et al. 2012.) In the following sections, the mortality associated with cardiovascular surgery, along with methods to estimate it, and the major complications of cardiac surgery concentrated on in the present dissertation are presented.

2.4.1 Survival and mortality

During the past four decades, there has been a remarkable overall decline in mortality from cardiovascular diseases (Wilmot et al. 2015). Still, even with advances in primary and secondary prevention as well as surgical and endovascular interventions, these diseases represent the most significant cause of death in the Western world. Furthermore, the mortality from CAD in patients aged under 55, particularly in women, has remained disturbingly stagnant since the 1990s (Wilmot et al. 2015). Consistently with the high-risk nature of cardiovascular diseases, patients undergoing cardiovascular surgical procedures can also be regarded as high-risk patients. A

continuous updating of the knowledge on the postoperative mortality associated with cardiovascular surgery, along with investigating the magnitude of the impact of known risk factors and attempting to identify novel and more potent ones, is a prerequisite for improving survival after cardiovascular surgical treatment.

In 2011, the estimated mortality from CAD was 225/100,000 and 125/100,000 among American men and women, respectively, aged 25 years or over (Wilmot et al. 2015). The overall perioperative mortality in contemporary cardiac surgery, including both CABG and valve procedures, in turn, was reported to be roughly 3.8% in a German study (Rahmanian et al. 2013). In single CABG, the perioperative mortality is approximately 3% and in single-valve surgery less than 5% (Iung et al. 2003; Roques et al. 1999; Thorsteinsson et al. 2016). Advanced age; female sex; PAD/extracardiac arteriopathy; pulmonary hypertension; atrial fibrillation; previous cardiac surgery; serum creatinine; left ventricular ejection fraction; recent myocardial infarction and unstable angina; active endocarditis; emergency operations and procedures other than CABG; as well as postoperative complications, such as the need for dialysis, sepsis, respiratory failure and gastrointestinal complications, have been discovered to independently predict mortality after cardiac surgery (Bhave et al. 2012; Rahmanian et al. 2013; Roques et al. 1999). Additionally, perioperative hyperglycaemia has been determined to be an independent risk factor of mortality after cardiac surgery in both diabetic and non-diabetic patients (Doenst et al. 2005).

PAD is associated with significantly increased morbidity as well as cardiovascular and all-cause mortality (Agnelli et al. 2019). In a Canadian patient cohort, mortality was estimated to be 8.2% annually after the diagnosis of PAD. In reference, the annual mortality after myocardial infarction in the same study was 6.3% and after a stroke 11.3%. (Caro et al. 2005.) ABI values of 0.90 and below and above 1.40, as well as a higher rate of decline in ABI over time, are linked to a worse prognosis. Overall, below-normal ABI values are associated with a 2–3 times higher risk of all-cause and cardiovascular death. It is estimated that an ABI decrease of > 0.15 is significantly and independently associated with increased long-term overall and cardiovascular mortality (RR 2.4 and 2.8, respectively, in a three-year follow-up). (Criqui et al., 2008, 2010; Fowkes et al. 2008.) The perioperative mortality after lower-limb reconstruction surgery has been ascertained to be approximately 2.9% (Welten et al. 2008). Furthermore, the risk of stroke or myocardial infarction associated with PAD corresponds to that associated with CAD, but PAD patients often suffer from inferior risk factor management when compared to CAD patients (Agnelli et al 2019; Baumgartner 2005). The rates of cardiac and limb ischaemic events are particularly increased after lower extremity revascularisation procedures

(Baumgartner et al. 2018). Freedom from major amputation is another relevant factor when discussing the survival of PAD-patients, particularly of those suffering from critical ischaemia. Use of the Wound, Ischemia and foot Infection classification (WIfI) that takes into account a possible wound and infection in addition to the severity of ischaemia in the affected limb is endorsed when predicting the risk of an individual patient. (Aboyans et al. 2018; Mills et al. 2014.)

AAA-related complications were estimated to account for approximately 3.0 deaths per 100,000 in the United States in 2016 (Centers for Disease Control and Prevention 2015). With regard to operative mortality, the 30-day mortality in elective AAA repair is currently assessed to be between 1.2% and 3.2% (Conrad et al. 2007; Greenhalgh et al. 2004; Hertzer et al. 2002; Powell et al. 2017). EVAR appears to offer an early survival benefit over open surgery, with 30-day mortality rates of 1.1%–1.7% and 2.9%–4.7%, respectively (Greenhalgh et al. 2004; Patel et al. 2016; Powell et al. 2017). However, beyond the first three postoperative years, the survival advantage of EVAR disappears, and after eight years, the mortality is greater among patients treated with EVAR as compared to open surgery (Patel et al. 2016; Powell et al. 2017). Furthermore, the overall 5-year survival after elective aneurysm repair still remains between 60% and 70% (Bahia et al. 2015; Karthikesalingam et al. 2013; Powell et al. 2017; Roger et al. 1989). The main causes of death in both short- and long-term follow-up are cardiovascular and pulmonary diseases (Goodney et al. 2010). Factors such as female sex, advanced age, renal insufficiency, congestive heart failure and chronic obstructive pulmonary disease have been discovered to be associated with an inferior prognosis after AAA repair (Beck et al. 2009; Grootenboer et al. 2010; Mureebe et al. 2010; Schlösser et al. 2010). In the treatment of RAAA, an EVAR strategy has shown similar early but significantly lower three-year mortality rates (48% vs 56%) compared to an open surgical strategy (IMPROVE Trial Investigators 2017). Preoperative factors associated with mortality in rupture cases entail older age (> 76 years), elevated creatinine (> 190 μmol/L), cardiac arrest, loss of consciousness, Glasgow Coma Scale score < 15, blood pressure < 90 mmHg, low haemoglobin (< 90 mg/l), and ischaemia detected in an ECG (Chen et al. 1996; Hardman et al. 1996; Robinson et al. 2013; Tambyraja et al. 2007). Additionally, suprarenal aortic clamping has been found to be associated with a worse prognosis (Robinson et al. 2013).

The development of varying degrees of myocardial ischaemia is not rare after surgical treatment, yet previous literature has set the focus mostly on postoperative myocardial infarctions. During the past few years, a more comprehensive end point based on cardiac troponin T levels – myocardial injury after noncardiac surgery

(MINS) – has emerged into the research concerning postoperative survival (Botto et al. 2014). This is of particular importance, as postoperative myocardial ischaemia regardless of the symptomatic status is associated with a poor prognosis and most patients suffering from it are asymptomatic and therefore at a risk of remaining undiagnosed (Devereaux et al. 2011). The incidence of MINS is estimated to be approximately 8.0%–16% depending on the definition, with as few as 6.9%–18% of the patients reporting ischaemic symptoms, and it is independently associated with 30-day mortality after surgery (Botto et al. 2014; Devereaux et al. 2017; Puelacher et al. 2018).

There has been an increasing interest in secondary preventive interventions for cardiovascular surgical patients utilising statins and other lipid-targeted medications as well as direct oral anticoagulants (DOAC). For instance, short-term treatment with 20 mg of atorvastatin per day for one month prior to surgery was discovered to significantly decrease major cardiovascular events after vascular surgery in a six-month follow-up RCT (Durazzo et al. 2004). Another RCT produced similar findings with preoperative fluvastatin therapy (80 mg per day), which was found to be associated with markedly lower rates of postoperative myocardial ischaemia and cardiovascular death after vascular surgery as compared to placebo, without provoking excess adverse events (Schouten et al. 2009). A recent Cochrane review, however, considered the present evidence on the specific effect of preoperative statin treatment on perioperative outcome in vascular surgery to be insufficient, despite the fact that statins are recommended for all PAD patients (Sanders et al. 2013). Other meta-analyses concluded that preoperative statin therapy did not influence perioperative mortality in cardiac or non-cardiac surgery but did reduce the rate of postoperative atrial fibrillation (POAF) and shorten the hospital stay after cardiac surgery, in addition to protecting against myocardial infarction after non-cardiac surgery (Kuhn et al. 2015; Putzu et al. 2018). In addition to the more traditional statins, a novel group of lipid-targeting medication, PCSK9 inhibitors, has become available for clinical practice. PCSK9 inhibitors lower LDL-C levels efficiently by increasing the liver uptake of the lipoprotein via preventing LDL receptor destruction (Chaudhary et al. 2017). In long-term follow-up, these inhibitors have demonstrated an ability to reduce the risk of major cardiovascular events in patients with previously diagnosed atherosclerotic cardiovascular disease and to curb both cardiovascular and major adverse limb events in PAD patients (Bonaca et al. 2018; Sabatine et al., 2018, 2017).

With regard to DOACs, administering 110 mg of dabigatran twice a day was recently discovered to significantly lower the risk of major vascular complications in

patients diagnosed with MINS after non-cardiac surgery, including vascular surgery, thus improving their prognosis in a two-year follow-up. Major vascular complications were defined as vascular mortality, non-fatal myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation or symptomatic venous thromboembolism. Furthermore, the intervention did not increase the composite of life-threatening, major, and critical organ bleeding (Devereaux et al. 2018). Another DOAC, rivaroxaban, with a dosage of 2.5 mg twice daily combined with aspirin 100 mg once per day, in comparison to aspirin alone, was found to decrease the composite end point of cardiovascular death, stroke or myocardial infarction in patients with stable atherosclerotic vascular disease treated conservatively. The intervention also subjected the patients to more major bleeding events, although there was no significant difference when only intracranial and fatal bleeding were considered. (Eikelboom et al. 2017.) The effect of rivaroxaban on outcomes after endovascular or surgical interventions for PAD is also being investigated at present (Capell et al. 2018).

2.4.1.1 Risk assessment and scoring systems

A variety of scoring systems have been developed to assist in risk prediction and decision-making in both primary and secondary prevention (Goff et al. 2014; Piepoli et al. 2016). These systems are mainly beyond the scope of the present thesis, but some of the most significant ones assessing postoperative survival shall be briefly presented.

The EuroSCORE scoring systems were created for estimating early postoperative mortality after cardiac surgery in Europe. The first EuroSCORE was presented in 1999, and it entails several pre- and perioperative risk factors. The area under the ROC curve (AUC) was 0.79–0.76. (Nashef et al. 1999.) Initially, there was only an additive score easy to utilise in clinical work, which was, however, prone to underestimating mortality in high-risk patients. Therefore, a more sophisticated but less easily applicable logistic system was presented and has been found to predict mortality more accurately. (Nishida et al. 2006; Roques et al. 2003.) The latest version of the system, EuroSCORE II, was presented in 2011 and is reported to have slightly improved AUC values of 0.79–0.81 (Guida et al. 2014; Nashef et al. 2012). However, it tends to overestimate mortality after isolated CABG and underestimate it in high-risk patients (Guida et al. 2014). Postoperative mortality in cardiac surgery can also be predicted by applying a model presented by Rahmanian et al. (2013) based on pre- and postoperative factors independently associated with mortality: age, PAD,

pulmonary hypertension, atrial fibrillation, emergency surgery, procedure other than CABG, postoperative dialysis, sepsis, respiratory failure and gastrointestinal complication. This model was also found to estimate mortality more accurately than the logistic EuroSCORE (Rahmanian et al. 2013). Furthermore, the Society of Thoracic Surgeons' (STS) cardiac surgery risk models have been developed to assist in risk prediction in cardiac surgery, and other models, such as the age-creatinine-LVEF (ACEF) score and the Cleveland Clinic score, have performed particularly well in elective isolated CABG with AUCs of 0.826 and 0.806, respectively (Higgins et al. 1992; O'Brien et al. 2009; Ranucci et al. 2009; Shahian et al., 2009a, 2009b).

In PAD, the risk assessment tools chiefly focus on predicting the fate of the affected limb. At present, the WIfI classification by the Society for Vascular Surgery is attracting the most interest, and it is recommended for the initial evaluation of patients with CLTI (Aboyans et al. 2018; Mills et al. 2014). In addition to amputation risk, it has also been discovered to predict survival in CLTI patients (Beropoulis et al. 2016; Darling et al. 2017).

For AAA patients, in turn, risk scores such as the British Aneurysm Repair score, the Medicare model, and the Vascular Governance North West model have been created to predict mortality after elective surgery, and these have been verified to perform satisfactorily (Giles et al. 2009; Grant et al. 2011; Grant et al. 2013; Grant et al. 2014). Another risk score, the Vascular Study Group of New England model has been primarily developed to estimate survival after invasive treatment of RAAAs but has also been found applicable in elective cases, where it appears to be the most accurate risk score (Eslami et al. 2018; Robinson et al. 2013). Moreover, this model also takes into account EVAR patients, which is not the case for all risk scores. The Glasgow Aneurysm Score and the Vancouver Score are also suitable risk estimation tools for both elective and emergency treatment (Chen et al. 1996; Samy et al. 1994). Systems such as the Hardman index and the Edinburgh ruptured aneurysm score are selectively for RAAA patients (Hardman et al. 1996; Tambyraja et al. 2007). However, at present, deciding on palliative treatment for RAAA patients based solely on scoring systems is discouraged due to insufficient evidence, accentuating the need for further investigation of risk factors in the future (Wanhainen et al. 2019).

2.4.2 Infections

Postoperative infections are among the most significant complications encountered after surgical procedures, and they vary from less severe to life-threatening

conditions. These can be divided into surgical site infections (SSI), further subclassified as minor and major or superficial, deep and organ/space as well as other infections, such as lung infections, urinary tract infections, sepsis and cannula- or catheter-related infections. The incidence of postoperative infections is estimated to be between 5.0% and 21% in cardiac surgery, and it appears to be on the rise (Horan et al. 1992; Michalopoulos et al. 2006; Mocanu et al. 2015; O'Keefe et al. 2017). At present, respiratory tract infections, urinary tract infections and central-venous-catheter-related infections are the most common ones after cardiac surgery (Michalopoulos et al. 2006; Mocanu et al. 2015; O'Keefe et al. 2017). SSIs, in turn, occur in 3%–4% of the patients when leg harvest site infections are not taken into account (O'Keefe et al. 2017). The occurrence of postoperative infections in vascular surgery differs greatly depending on the type of operation, with the lowest incidences reported for carotid surgery and the highest for infrainguinal procedures (Turtiainen & Hakala 2014). In a Finnish vascular surgical patient cohort, the incidence of surgical site infections after abdominal aortic or lower limb procedures was ascertained to be 27%, with staphylococcus aureus as the most common pathogen (Turtiainen et al. 2010). Overall, the rate of postoperative infections after elective vascular surgery is estimated to be between 3.7% and 6.5% (deFreitas et al. 2011; Vogel et al. 2010).

The independent risk factors of postoperative wound infections include surgical wound class, diabetes and perioperative hyperglycaemia, as well as malnutrition, American Society of Anaesthesiologists (ASA) physical status grouping, duration of surgery, and low postoperative haematocrit concentration (Ata et al. 2010; Garibaldi et al. 1991; Kao & Phatak 2013; Kotagal et al. 2015; Malone et al. 2002). In patients undergoing vascular surgery, advanced age and female sex have been recognised as independent predisposing factors (Vogel et al. 2010). The significant risk factors found to be associated with postoperative infections in cardiac surgery, in turn, encompass a history of immunosuppression, diabetes, elevated BMI, poor cardiac reserve, urgent or emergency surgery, the use of bilateral mammary grafts, the need for blood transfusions of more than five units perioperatively (including the first postoperative day), early development of acute renal failure, and postoperative respiratory failure. Older age and longer operating times (eight versus four hours) were also associated with postoperative infections but not independently. (Balachandran et al. 2016; Fu et al. 2016; Michalopoulos et al. 2006; Orita et al. 1992; Swenne et al. 2004.)

Infectious complications are treated with oral, intravenous or intramuscular antibiotics, depending on the pathogen and the severity of infection, and, in some

cases, surgical debridement is warranted. These complications substantially increase morbidity and mortality as well as the length of the hospital stay and treatment costs (Furnary et al. 1999; Sears et al. 2016). Therefore, an emphasis should be put on trying to prevent them. A great number of vascular and cardiac surgical patients suffer from diabetes, and the physiological stress brought on by a surgical procedure may elevate blood glucose even in those without the condition (Clarke 1970). The predisposing effect of hyperglycaemia on postoperative infections after cardiac surgery is multifactorial and may be mediated by impaired wound healing and leukocyte dysfunction (Baltzis et al. 2014). As hyperglycaemia is treatable with insulin, it can be regarded as one of the most significant modifiable factors in the prevention of postoperative infections in cardiovascular surgery. There is still, however, controversy regarding optimal therapeutic glucose level targets, the timing of treatment and the safety of tight glycaemic control, which may predispose to hypoglycaemia. (Allegranzi, Zayed, et al. 2016.) Hypoglycaemia, in turn, is associated with mortality in a dose-response fashion in critically ill patients (Finfer et al. 2012).

With regard to the prevention of SSIs, the WHO has recently provided evidence-based recommendations concerning all surgical specialties. Preoperatively, enhanced nutritional support for underweight patients, preoperative bathing or showering, intranasal mupirosin 2% ointment for nasal carriers of Staphylococcus aureus particularly in cardiothoracic surgery, the administration of prophylactic antibiotics within two hours prior to the incision when they are indicated, appropriate surgical hand preparation, and surgical site skin preparation with alcohol-chlorhexidine gluconate solutions are recommended. Hair shaving from the surgical area, antimicrobial skin sealants and the discontinuation of immunosuppressive agents are not endorsed. (Allegranzi, Bischoff, et al. 2016.) Furthermore, in perioperative care, an 80% fraction of inspired oxygen administered intraoperatively, maintaining normothermia, the use of intensive protocols for perioperative blood glucose control in both diabetic and non-diabetic patients, maintaining normovolaemia, utilising appropriate wound drapes and protector devices, negative-pressure wound therapy on primarily closed incisions in high-risk cases, and antimicrobial-coated sutures in the prevention of SSIs are recommended(Allegranzi, Zayed, et al. 2016). Continuing prophylactic antibiotics, particularly beyond the first 48 postoperative hours, is generally discouraged. (Allegranzi, Zayed, et al. 2016; Edwards et al. 2006.)

2.4.3 Atrial fibrillation

The most prevalent cardiac arrhythmia presenting after both cardiac and non-cardiac surgery is POAF (Bessissow et al. 2015). Its incidence has been estimated to be between 0.37% and 10% among non-cardiac surgical patients overall, between 5% and 10% among non-cardiac surgical patients treated in an intensive care setting, and up to 60% among cardiothoracic surgical patients (Bhave et al. 2012; Brathwaite & Weissman 1998; Christians et al. 2001; Danelich et al. 2014; Kanji et al. 2012; Maesen et al. 2012; Seguin et al. 2004). The arrhythmia is more frequent after valve surgery than after CABG. More specifically, the incidence of new-onset POAF is 17%–29% in isolated CABG, 20%–49% in single-valve procedures and as high as 31%–60% in combined CABG and valve surgery (Almassi et al. 1997; Filardo et al. 2009; LaPar et al. 2014; Rostagno et al, 2014; Rostagno et al. 2010; Saxena et al. 2012, 2013). Previous studies and their incidence data, however, suffer, to an extent, from a heterogeneity of cohorts as well as inclusion criteria. POAF is mostly found in patients with pre-existing atrial fibrillation, and new cases account for roughly one third of its presentation (Bhave et al. 2012). The peak of onset is typically within the first four postoperative days (Rostagno et al. 2010). In addition to the type of surgery, factors that have been independently associated with the development of POAF include advanced age, COPD, obesity, use of digoxin 2 weeks prior to surgery, a resting pulse rate below 80, high resting systolic blood pressure, atrial size exceeding 40 mm, a preoperative history of AF episodes, P-wave duration of > 110 ms in ECG, and low postoperative cardiac output as well as the use of inotropic agents for longer than 30 minutes after the termination of cardiopulmonary bypass (Almassi et al. 1997; Amar et al. 2004; Aranki et al. 1996; Bhave & Passman 2012; Leitch et al. 1990; Rostagno et al. 2010; Tran et al. 2015; Zacharias et al. 2005). Evidence regarding the impact of sex on POAF occurrence is controversial, potentially due to the small numbers of women in cardiac surgical patient cohorts (Aranki et al. 1996; Rostagno et al. 2010).

In addition to the subjective symptoms that POAF can inflict upon patients, such as impaired physical performance and discomfort, the clinical significance of the complication is related to its effects on postoperative outcome. Firstly, POAF is associated with a significantly increased risk of ischaemic stroke, with a stronger degree of association in noncardiac as opposed to cardiac surgery (Gialdini et al. 2014; Mariscalco et al. 2014). Secondly, POAF is associated with increased postoperative mortality (Bhave et al. 2012; El-Chami et al. 2010; Mariscalco et al. 2014; Villareal et al. 2004). Thirdly, POAF often necessitates the initiation of

anticoagulant therapy which, in turn, may predispose to bleeding complications and often requires follow-up laboratory testing. Finally, POAF increases the length of the hospital stay after surgery as well as treatment costs (Bhave et al. 2012; Mariscalco et al. 2014). POAF may also serve as a marker for high-risk patients. Additionally, atrial fibrillation has been found to recur within two years in the majority of patients who suffer from POAF in the immediate post-operative period but who revert back to sinus rhythm prior to hospital discharge (Lowres et al. 2018). Evidence from meta-analyses supports the prevention of POAF with beta-blockers, sotalol, amiodarone, magnesium, atrial pacing or posterior pericardiotomy in cardiothoracic surgery (Arsenault et al. 2013; Burgess et al. 2006; Crystal et al. 2002; Koniari et al. 2010; Mitchell et al. 2011). Such prophylactic interventions can also shorten hospital stays and reduce treatment costs, and there is a tendency towards lower stroke rates, although they are not statistically significantly associated with postoperative mortality (Arsenault et al. 2013). Furthermore, statin treatment has been discovered to decrease the incidence and duration of POAF in cardiothoracic surgery (Dotani et al. 2000; Liakopoulos et al. 2009; Ozaydin et al. 2007; Patti et al. 2006). When POAF does occur, the treatment entails either rate or rhythm control, depending on the patients' haemodynamic state and symptoms, and with persisting arrhythmia, anticoagulant therapy is warranted, even though the latter may pose challenges with regard to bleeding complications in the immediate postoperative period (Ha et al. 2016; January et al. 2014; Kirchhof et al. 2016; Mitchell et al. 2011). There appears to be no significant difference in the persistence of atrial fibrillation between the rate and rhythm control strategies in 60 days' follow-up (Gillinov et al. 2016).

2.4.4 Cardiac tamponade

The postoperative accumulation of fluid in the pericardial sac, postoperative pericardial effusion (PPE) diagnosed with ultrasound, is not an uncommon finding after open heart surgery, and it is present in up to 84% of all patients. Overall, the incidence discovered in prospective studies is higher than in retrospective studies. (Ashikhmina et al. 2010; Ikäheimo et al. 1988; Pepi et al. 1994; Weitzman et al. 1984). Early effusions are typically caused by postoperative bleeding, whereas late effusions are considered to be mainly associated with postpericardiotomy syndrome, an inflammatory reaction of the pericardium induced by the surgical intervention. (Alraies et al. 2014; Ikäheimo et al. 1988; Ito et al. 1958; Lehto et al. 2015.) Mild to moderate effusions can resolve without active treatment and are usually managed

conservatively with medication and ultrasound surveillance. Steroids, non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine have been applied in the medical treatment of PPE, despite the fact that studies have been unable to demonstrate an unequivocal benefit of these over placebo (D'Cruz et al. 1989; Meurin et al. 2010; Meurin et al., 2015, Tamarappoo et al., 2016, Wilson et al. 1994). Colchicine does, however, appear to prevent early tamponade (Imazio et al. 2011), but a similar statistically significant effect for NSAIDs was not found (Niva et al. 2002). With regard to the surgical technique, posterior pericardial drainage including posterior pericardiotomy and the placement of a chest tube in the posterior pericardium have been found to reduce the incidence of late PPE that requires invasive treatment (Cakalagaoglu et al. 2012; Erdil et al. 2005; Gozdek et al. 2017; Kuralay et al. 1999).

If left untreated, effusions can persist and ultimately progress to cause cardiac tamponade, characterised by circulatory failure, and eventually death. The overall incidence of late postoperative tamponade is roughly 0.8%–2.0%, and it is two to three times as high after valve procedures as after CABG, whereas the less severe PPE is more common following bypass surgery (Kuvin et al. 2002; Meurin et al. 2004; Pepi et al. 1994; Russo et al. 1993). Late cardiac tamponade has also been found to be associated with anticoagulant therapy and female sex (Kuvin et al. 2002; Malouf et al. 1993; Meurin et al. 2004). Furthermore, an association between an early removal of chest tubes and PPE requiring surgical intervention has been recently discovered (Andreasen et al. 2016). Prompt invasive treatment of cardiac tamponade is vital for survival, and it can be performed by means of pericardiocentesis, percutaneous drainage or surgical fenestration. The sometimes varied clinical picture and ultrasound findings can, however, pose diagnostic challenges (Russo et al. 1993). Due to the severity of the condition, identifying high-risk patients as early as possible appears clinically desirable and enables a timely intervention with potentially fewer risks. Furthermore, it has been suggested that the true incidence of late PPEs requiring invasive treatment may be underestimated at present (Meurin et al. 2004).

3 AIMS OF THE STUDY

The aims of the present study were as follows:

1. To define the incidence, presentation and risk factors of postoperative atrial fibrillation in modern-day cardiac surgery patients (I).

2. To ascertain the incidence, clinical picture and predisposing factors of late postoperative cardiac tamponade requiring invasive treatment after cardiac surgery (II).

3. To determine the association of postoperative hyperglycaemia with infections in cardiac surgery (III).

4. To investigate the serum lipid profiles of patients undergoing AAA repair, including contemporary lipid parameters computationally estimated with a neural network model (the Extended Friedewald Formula), and their association with postoperative survival and vascular surgical burden.

5. To define and compare the serum lipid profiles of PAD patients undergoing an intervention and CAD patients treated with CABG, also including computationally estimated (Extended Friedewald Formula) contemporary lipid parameters (V).

4 SUBJECTS, MATERIALS AND METHODS

4.1 Study settings

The individual studies the present thesis is based on were carried out in the Heart Hospital at Tampere University Hospital (TAUH) and in the Vascular Surgical Division of the TAUH Department of Surgery. Studies I–III were conducted in the Heart Hospital, study IV in the Vascular Surgical Division and study V in both units. The research was registry-based and retrospective in nature, thus including no treatment interventions, follow-up visits, laboratory testing or imaging that were not a part of the standard treatment protocol during the study period.

4.2 Study population and data sources

Data was mainly collected from two clinic-specific prospectively constructed databases, Kardio and Vascuset. Additional data was gathered from the TAUH patient record database, including patients treated in the Heart Hospital, and laboratory values from the Fimlab Laboratories Ltd database.

For studies I, II, III and V, data on 1,356 consecutive adult patients undergoing cardiac surgical procedures between January 2013 and December 2014 was collected. All open cardiac surgical interventions were included in the analyses, whereas patients undergoing transcatheter valve procedures along with those subjected to interventions not unequivocally defined as cardiac surgical, such as solely pericardial procedures, were excluded. Additionally, operations where the intended procedure could not be completed (n=5) were left out of the series. The inclusion criteria and final cohorts of each individual study are presented in more detail in the following sections.

4.2.1 Study I

For study I, patients without previous chronic atrial fibrillation and surviving a minimum of five days postoperatively (n=1,164) were selected for analysis. The inclusion criterion was chosen in order to cover the time of the highest postoperative occurrence of POAF based on previous literature. The follow-up for each patient lasted until the end of the index hospitalisation period, ranging up to the 53rd postoperative day.

4.2.2 Study II

Patients who died within the first seven postoperative days were excluded from study II. The analyses were thus restricted only to individuals at an actual risk of developing late pericardial effusions that would require invasive treatment. A total of 1,308 patients formed the final study cohort, and the follow-up lasted for six months.

4.2.3 Study III

For study III, only patients who survived beyond the second postoperative day (n=1,329) were included. The aim was to assess infections in a cohort truly subjected to the complication, while still taking into account possible early cases. As in study II, the patients were followed for six months.

4.2.4 Study IV

Patients undergoing AAA repair in TAUH between March 2001 and September 2014 (n=959) were investigated in study IV, comprising both elective and emergency cases as well as treatment with both open surgery and EVAR. The availability of serum lipid measurements was a prerequisite for inclusion. Due to the retrospective setting, 461 patients had no lipid testing within 10 years of treatment and were therefore excluded. The follow-up lasted until April 2015.

4.2.5 Study V

For study V, CAD patients undergoing isolated CABG (n=218), with lipid measurements available within two years preceding the intervention, were derived from the original pool of 1,356 cardiac surgery patients. Additionally, PAD patients treated with invasive endovascular or open surgical procedures in TAUH between January 2013 and December 2014 and with available lipid measurements within two years prior to treatment (n=280) were included. The nature of the study was comparative and entailed no follow-up.

4.3 Variables/parameters

The variables collected for all of the studies encompassed demographic information, medical history, the urgency of the intervention as well as procedure-related details. Laboratory values relevant to each study were also collected. For the purposes of study I, POAF was defined as the presence of fibrillation in electrocardiographic rhythm monitoring for a minimum duration of 5 minutes, and each case was verified by a cardiologist. All patients were under continuous and recording electrocardiographic rhythm monitoring followed-up by physicians and trained nurses over the entire hospitalisation period. The time of onset, duration and potential recurrence as well as the clinical picture of the arrhythmia were recorded. Additionally, postoperative outcome measures such as reoperations, stroke and infections were documented.

In study II, pericardial effusions were considered significant when measuring over 10 mm in depth and were defined as tamponades if they presented with haemodynamic instability and/or chamber compression in ultrasonography and as pretamponades if increasing accumulation of fluid or subjective symptoms developed without meeting the criteria of tamponade. Furthermore, the effusions were regarded as late when presenting after the seventh postoperative day in distinction to earlier effusions typically brought on by postoperative bleeding. Data on the presentation of late PPEs requiring invasive treatment, potential preceding medical therapy, the largest diameter of the effusion in ultrasonography, the volume of the drained pericardial fluid as well as the need for reinterventions were obtained.

The diagnostic criteria for postoperative infections in study III were clinical signs of infection (i.e. focal symptoms, fever, leucocytosis, elevated CRP) as well as concurrent imaging findings and/or positive microbial cultures. They were classified

as minor and major SSIs, pulmonary infections, cannula- and catheter-related infections, unclear fever or sepsis, and other infections. Minor SSIs, in turn, encompassed superficial sternal and other wound infections, whereas deep sternal wound infections (DSWI), empyema as well as endocarditis constituted major SSIs. Postoperative glucose values and the need for insulin treatment were also recorded in study III. Hyperglycaemia was defined as blood glucose values exceeding 7 mmol/L and hypoglycaemia as glucose values below 4 mmol/L.

For studies IV and V, the EFW parameters were computationally estimated from traditional Friedewald inputs (TC, TG and HDL-C) by applying the EFW formula neural network model developed by Niemi et al. (Niemi et al., 2009). In study IV, data on the vascular surgical burden as represented by repeated invasive vascular interventions was collected. Finally, data on all-cause mortality was retrieved for studies I and IV. The baseline characteristics of study patients are presented in Table 3.

Table 3. Characteristics of study patients

Patient characteristics	All cardiac surgical patients (n=1,356)	CAD (study V) (n=280)	PAD (study V) (n=218)	AAA (study IV) (n=498)
Male	72%	82%	53%	88%
Median age	68 (18–89)	69 (42–89)	74 (45–95)	73 (44–92)
Hypertension	65%	74%	75%	63%
DM	24%	38%	40%	17%
Smoking	14%	18%	32%	25%
Chronic pulmonary disease	11%	12%	20%	21%
Dyslipidaemia/statin use	58% (dyslipidaemia)	78% (statin use)	51% (statin use)	34% (dyslipidaemia)

4.4 Treatment protocols

The guidelines applied in the study centres for the treatment of CAD, valvular heart disease, PAD and AAAs are presented in brief in section 2.3.1. Overall, the indications for intervention and the general treatment strategies in both cardiac and vascular surgical patients adhered to these guidelines, particularly the European ones.

All cardiac surgical patients (studies I–III & V) were in continuous rhythm monitoring postoperatively throughout the hospitalisation period. There was no discontinuation of previous beta blocker therapy before the operation, and it was habitually continued from the second postoperative day in the absence of contraindications such as hypotension, bradyarrhythmia or conduction disturbances.

Furthermore, all patients were given a 20 mmol intravenous infusion of magnesium sulphate in order to prevent postoperative arrhythmias. When POAF did occur, the attending physician (cardiac anaesthetist, cardiothoracic surgeon or cardiologist) decided on the course of treatment. Most commonly, it included two 2.5 mg doses of metoprolol administered intravenously over 30 minutes and a subsequent amiodarone infusion. The dosage of amiodarone was 300 mg during the first hour, followed by 900 mg over the next 23 hours. If POAF persisted after medical treatment, electric cardioversion was carried out.

Routine postoperative ultrasound surveillance was part of the protocol for all patients undergoing cardiac surgery (studies I–III & V). It was habitually performed on the fourth postoperative day as well as three months after surgery. If signs of tamponade or significant PPE were noticed, the finding was corroborated by a cardiologist. The type of invasive treatment chosen for each patient was at the discretion of the attending surgeon. The most common procedures were surgical fenestration of the pericardium through a left-sided parasternal minithoracotomy or a subxiphoid approach and ultrasound-guided percutaneous drainage of the pericardium.

Antibiotic prophylaxis was given to all cardiac surgical patients (studies I–III & V). For this, 3 g of intravenous Cefuroxime was habitually used in patients with no contraindications for its use. When the operation lasted over four hours, an additional dose of 1.5 g was administered. Potential infections were diagnosed according to clinical signs as well as laboratory and imaging findings and treated accordingly. Furthermore, all cardiac surgical patients (studies I–III & V) were postoperatively followed-up in the cardiac intensive care unit (ICU) until the morning of the first postoperative day or longer when required. After this, patients were treated either on a regular or a high-dependency ward. Blood glucose levels were measured from arterial blood samples every four hours while the patients were in the ICU (ABL90 FLEX blood gas analyser; Radiometer Medical ApS, Brønshøj, Denmark). In cases of hyperglycaemia or hypoglycaemia, supplementary samples were analysed applying a hand-held device (FreeStyle Lite; Abbott Diabetes Care Inc, Alameda, CA, USA). An initial bolus dose of insulin to reduce glucose to the goal level of 4–7 mmol/L, succeeded by an insulin infusion was used for the treatment of hyperglycaemia. Hypoglycaemia, in turn, was treated with a glucose infusion.

The criteria for an AAA intervention (study IV) were an aneurysm of at least 50 mm in diameter in women or 55 mm in men, aneurysm growth of 10 mm or more per year or any symptomatic or ruptured aneurysm. The decision on treatment modality was made case by case in a multidisciplinary meeting for elective patients

and by the attending vascular surgeon, usually in collaboration with an interventional radiologist, for emergency cases. In elective patients with multiple comorbidities and a shorter life expectancy as well as haemodynamically stabile emergency/rupture patients, an endovascular approach was usually favoured. The PAD patients in study IV were treated either operatively, endovascularly or with hybrid procedures according to the clinic's standards.

4.5 Statistical methods

Statistical analyses were conducted with SPSS 16.0 and 23.0 statistical software for Windows and R statistical software version 3.2.0. Univariable analyses were performed by applying the Chi-Square test or Fisher's exact test for categorical variables and the Mann-Whitney U test or Kruskal-Wallis H test for non-parametric scale variables. Furthermore, for categorical variables, multivariable analyses were conducted with binary logistic regression. In study IV, survival was analysed with stepwise multivariable Cox Regression analysis. Lipid parameters and glomerular filtration rate values were first subjected to inverse normal transformation to reduce heteroscedasticity. Stepwise regression analysis was executed in forward and backward directions and, otherwise, default criteria for stepAIC function were applied. To clarify, stepAIC, where the AIC stands for Akaike Information Criterion, is a function used in the R statistical software when conducting stepwise regression analysis, and it provides a method for model selection. Furthermore, in study IV, the additive predictive power of the investigated lipid parameters when used in conjunction with other independent risk factors was investigated by calculating continuous net reclassification improvement (NRI). This was conducted by using the R function IDI.INF in the survIDINRI package. A time point of five years and resampling of 1,000 iterations were applied as parameters. Statistical significance was set at $p < 0.05$.

4.6 Ethical considerations

The individual studies were all performed following the ethical principles of the Helsinki Declaration and in compliance with Finnish laws. Informed patient consent was waived, as information was collected solely from pre-existing patient data in the form of patient record databases, study centre registries and the Fimlab Laboratories

Ltd database and patients were not subjected to any interventions, excess laboratory testing, imaging or control visits. Moreover, the study samples were sizeable, and some of the subjects were already deceased at the time of the studies, rendering it impossible to obtain informed consent. Signed approval from the head of the TAUH Science Centre was thus regarded as sufficient, and it was acquired. Data was handled with confidentiality and care. Articles I–IV were published in peer-reviewed journals relevant in the field, and article V has been submitted for review. Furthermore, when concerning findings were noted in study II, measures were promptly taken to update the treatment protocol and, subsequently, a follow-up investigation was initiated.

5 RESULTS

5.1 Cardiac surgical patients (studies I–III & V)

The perioperative and procedural information as well as demographic data are shown in detail in Table 4 for the entire (n=1,356) cardiac surgical patient cohort. The majority of operations were single CABG (40%) and single valve procedures (30%). The indication for the intervention in 19 (1%) cases was endocarditis and an acute Stanford type-A aortic dissection in 18 (1%) cases. Furthermore, 11 operations were redo procedures. The operations (> 99%) were mainly carried out through a standard median sternotomy, and 44 (8%) CABG procedures were performed without perfusion, i.e. off-pump. In on-pump procedures, cold blood cardioplegia was applied for cardioprotection. Prior to the intervention, 759 (56%) patients received statin and 858 (63%) patients beta blocker medication.

The overall combined 30-day and in-hospital mortality among cardiac surgical patients was 5.6 % (95% CI 4.4–6.8%). The corresponding mortality rates in elective, urgent, and emergency cases were (3.1%, 95% confidence interval [CI] 2.0%–4.2%), (5.6%, 95% CI 2.7%–8.5%) and (19.1%, 95% CI 13.2%–25.0%), respectively ($p<0.001$). The stroke rate, in turn, was 1.9% in elective, 3.6% in urgent and 6.4% in emergency procedures, with an overall stroke rate of 2.8% ($p=0.004$). A total of 183 (13%) patients had reoperations during the primary hospitalisation period, mainly due to postoperative bleeding or wound complications. Subsequent to the primary operation, the median duration of hospitalisation was 5 days (range 3–53) in elective, 6 days (range 1–40) in urgent and 8 days (range 3–51) in emergency cases ($p<0.001$). The duration of the hospital stay was one day in one surviving patient due to a swift referral for cardiac transplantation because of low-output syndrome following CABG.

Table 4. Demographic, preoperative and procedural characteristics of cardiac surgical patients. The largest subgroups are presented separately.

	All patients	Only CABG*	Single valve	Multiple valve	CABG* and valve surgery	Aortic surgery**
Number of patients (%)	1356 (100%)	535 (40%)	412 (30%)	73 (5%)	169 (13%)	132 (10%)
Male (%)	973 (72%)	423 (79%)	261 (63%)	47 (64%)	118 (70%)	103 (78%)
Median age (range)	68 (18–89)	68 (40–89)	68 (19–88)	71 (22–85)	74 (42–89)	64 (18–79)
Median BMI (range)	27 (10–61)	27 (17–60)	27 (10–60)	27 (14–45)	27 (17–41)	26 (19–45)
NYHA						
1–2	985 (74%)	345 (66%)	347 (85%)	54 (75%)	126 (75%)	91 (71%)
3–4	343 (26%)	175 (34%)	61 (15%)	18 (25%)	41 (25%)	37 (29%)
Median Euroscore-2 (range)	1.9 (0.5–86.8)	1.8 (0.5–52.6)	1.3 (0.5–49.8)	3.2 (0.6–50.8)	3.0 (0.6–56.4)	3.1 (0.5–86.8)
Urgency (%)						
Elective	934 (69%)	283 (53%)	361 (88%)	58 (79%)	125 (74%)	89 (67%)
Urgent	249 (18%)	158 (30%)	37 (9%)	12 (16%)	29 (17%)	9 (7%)
Emergency	173 (13%)	94 (18%)	14 (3%)	3 (4%)	15 (9%)	34 (26%)
Coronary disease (%)	845 (62%)	535 (100%)	96 (23%)	17 (23%)	166 (98%)	28 (21%)
Diabetes	320 (24%)	179 (34%)	62 (15%)	13 (18%)	48 (28%)	15 (11%)
Dyslipidaemia (%)	790 (58%)	412 (77%)	175 (42%)	28 (38%)	119 (70%)	47 (36%)
Hypertension (%)	881 (65%)	389 (73%)	236 (57%)	36 (49%)	122 (72%)	80 (61%)
LVEF<50% (%)	252 (19%)	121 (23%)	56 (14%)	14 (19%)	43 (25%)	16 (12%)
Chronic lung disease (%)	148 (11%)	58 (11%)	45 (11%)	5 (7%)	21 (12%)	17 (13%)
Active smoker (%)	189 (14%)	94 (18%)	36 (9%)	8 (11%)	22 (13%)	23 (17%)
Preoperative atrial fibrillation						
Paroxysmal	163 (12%)	43 (8%)	61 (15%)	16 (22%)	20 (12%)	17 (13%)
Chronic	156 (12%)	24 (4%)	66 (16%)	33 (45%)	18 (11%)	12 (9%)

* CABG = coronary artery bypass grafting

** Aortic surgery includes aortic root procedures and aortic surgery combined with CABG or valve surgery.

5.2 AAA patients (study IV)

A total of 959 patients were treated for AAAs at TAUH between March 2001 and September 2014. Of these, serum lipid values were available for 498 (52%) patients. The main demographics of these patients are presented in Table 3 in the methods section of the present thesis. Additionally, 206 (41%) patients had a history of CAD,

62 (12%) of previous stroke or transient ischaemic attack (TIA) and 45 (9%) of renal insufficiency. Thirty-seven (7%) patients had previously undergone vascular surgical interventions. Aneurysm rupture was the indication for treatment in 72 (14%) individuals. Slightly over a half of the patients (n=260, 52%) were treated with open surgery and the rest (n=238, 48%) with EVAR. In the study cohort, a history of dyslipidaemia was statistically significantly more common in patients with diabetes compared to non-diabetics (45% versus 31%, p=0.017) and in patients with CAD compared to those free from the disease (44% versus 26%, p<0.001). Patients excluded from the study were somewhat older (median age 75, p=0.003) and had a lower prevalence of diabetes (12%, p=0.032) as well as a higher prevalence of CAD (48%, p=0.048) than the study patients. The median follow-up time was 6.6 (range 0.5–14.0) years.

5.3 PAD and CAD patients (study V)

In study V, 218 CAD patients undergoing CABG and 280 patients treated invasively for lower extremity PAD were included. The demographic information of the PAD patients together with the CAD patients included in study V is presented in Table 3 in the Methods section as well as in Table 5. The indication for treatment in more than half (53.9%) of the PAD patients was CLTI. Of the CAD patients, in turn, 50.9% were operated on for acute coronary syndrome. The interventions for PAD included hybrid or isolated endovascular procedures in 61%, bypass operations in 26%, endarterectomies in 20% and patch angioplasties in 10% of the cases. The median number of bypasses performed in CABG was 3. Overall, CAD patients were more frequently male and somewhat younger, and they had lower rates of smoking and pulmonary diseases and higher rates of statin use than PAD patients. Additionally, urgent or emergency treatment was more common in the CAGB group.

Table 5. Demographic data of CAD and PAD patients in study V. Statistically significant differences are highlighted.

	Coronary bypass surgery patients	Lower extremity artery disease	p-value
Number of patients	218	280	
Male (%)	**82**	**53**	**< 0.001**
Median age (years, range)	**69 (42–89)**	**74 (45–95)**	**< 0.001**
Diabetes (%)	38	40	0.645
Statin use (%)	**79**	**51**	**< 0.001**
Hypertension (%)	74	75	0.771
Smoking (%)	**18**	**32**	**0.001**
Urgent treatment (%)	**51**	**25**	**< 0.001**
Chronic pulmonary disease (%)	**12**	**20**	**0.023**

5.4 Serum lipid profiles (studies IV & V)

Table 6 presents the serum lipid values and EFW estimates for the whole AAA cohort in study IV as well as by demographic subgroup. Women had higher serum HDL-C, EFW-HDL_2 subfraction and EFW-apoA1 levels when compared to men, but they also had elevated TC and TG levels. The median age of women was also higher than that of men (76 versus 73, $p<0.001$). Age under 70 years was linked to a more unfavourable lipid profile in comparison patients aged ≥ 70 years. Active smoking and smoking within 5 years of treatment as well as urgent or emergency surgery were associated with higher serum TC, LDL-C and EFW-LDL-C levels. Patients with a history of dyslipidaemia, diabetes, CAD or stroke had significantly lower concentrations of TC, LDL-C and EFW-LDL-C. In spite of this, both previously diagnosed dyslipidaemia and diabetes were associated with higher serum TG and EFW-VLDL-TG levels, with diabetics additionally displaying lower HDL-C and EFW-HDL_2 concentrations than non-diabetics.

In study V, univariable analyses (Table 7) demonstrated that traditional lipid parameter distributions were similar in the CAD and PAD groups, with the exception of HDL-C concentrations, which were higher in PAD patients. With regard to the more novel parameters, the EFW-HDL_2-subfraction concentrations, EFW-ApoA1 as well as the EFW-ApoB/ApoA1 ratio were significantly more favourable in patients with PAD (Table 7). No other differences in EFW parameters were ascertained between the patient groups. In females, EFW-ApoA1 levels were

significantly higher compared to males (1.56 versus 1.33 g/L, $p<0.001$). A similar finding was discovered in patients aged ≥70 years when compared to younger patients (1.45 versus 1.35 g/L, $p=0.001$). In multivariable analysis (Table 8), older age and smoking were independently associated with a lower likelihood of CAD and, conversely, statin use, male sex and higher EFW-ApoA1 concentrations with a higher likelihood of CAD than of PAD. The serum lipid profiles of AAA, PAD, and CAD patients are presented in Table 9.

Table 6. Serum lipid values and lipid estimates obtained by the extended Friedewald formula in patients treated for abdominal aortic aneurysms. Median values and ranges are shown for all patients and the most important patient subgroups. Statistically significant differences between opposing subgroups (i.e. male vs. female, diabetes vs. no diabetes etc.) are highlighted.

	TC	LDL-C	HDL-C	TG	EFW-VLDL-TG	EFW-LDL-C	EFW-IDL-C	EFW-ApoA1	EFW-ApoB	EFW-HDL_2
All patients n=498	4.50 (2.50–9.10)	2.64 (0.45–6.26)	1.16 (0.68–2.41	1.23 (0.40–4.90)	0.70 (0.12–3.80)	2.78 (1.35–5.96)	0.22 (0.04–0.95)	1.36 (0.99–2.21)	0.94 (0.44–2.04)	0.68 (0.31–1.90)
Male n=438	**4.50 (2.50–8.20)***	2.66 (0.45–5.76)	**1.14 (0.68–2.37)*****	**1.20 (0.40–4.90)****	**0.67 (0.12–3.80)****	2.79 (1.38–5.40)	0.21 (0.08–0.78)	**1.34 (0.99–2.08)*****	0.94 (0.51–1.85)	**0.67 (0.31–1.90)*****
Female n=60	**4.65 (2.50–9.10)***	2.53 (0.49–6.26)	**1.37 (0.79–2.41)*****	**1.53 (0.70–4.90)****	**0.87 (0.22–3.62)****	2.75 (1.35–5.96)	0.23 (0.04–0.95)	**1.53 (1.04–2.21)*****	0.96 (0.44–2.04)	**0.82 (0.38–1.90)*****
Age < 70 years n=176	**4.70 (2.50–8.20)****	**2.87 (0.45–6.26)****	**1.10 (0.68–2.37)****	**1.43 (0.40–4.90 *****	**0.83 (0.17–3.80)*****	**2.96 (1.42–5.96)***	**0.25 (0.09–0.77)*****	1.38 (0.99–2.08)	**1.05 (0.51–1.85)*****	**0.63 (0.31–1.90)*****
Age ≥ 70 years n=322	**4.40 (2.50–9.10)****	**2.53 (0.49–5.89)****	**1.17 (0.68–2.41)****	**1.18 (0.40–4.90)*****	**0.64 (0.12–3.62)*****	**2.71 (1.35–5.40)***	**0.20 (0.04–0.95)*****	1.35 (1.00–2.21)	**0.90 (0.44–2.04)*****	**0.70 (0.34–1.90)*****
Elective n=383	**4.40 (2.50–8.20)***	**2.58 (0.45–5.51)***	1.15 (0.68–2.41)	1.22 (0.40–4.90)	0.69 (0.12–3.80)	**2.74 (1.35–5.40)***	0.21 (0.04–0.78)	1.36 (0.99–2.15)	0.93 (0.44–1.83)	0.68 (0.31–1.90)
Urgent or emergency n=115	**4.70 (2.60–9.10)***	**2.79 (1.06–6.26)***	1.17 (0.68–2.33)	1.28 (0.50–4.90)	0.72 (0.16–3.62)	**2.96 (1.58–5.96)***	0.24 (0.10–0.95)	1.38 (1.00–2.21)	1.00 (0.53–2.04)	0.69 (0.32–1.80)
Open repair n=260	**4.60 (2.50–8.10)****	**2.78 (0.45–5.50)****	**1.14 (0.68–2.37)***	**1.32 (0.40–4.90)***	0.74 (0.12–3.80)	**2.91 (1.35–5.26)****	**0.23 (0.09–0.77)*****	1.37 (1.00–2.21)	**0.98 (0.53–1.85)*****	**0.66 (0.31–1.90)***
Endovascular repair n=238	**4.35 (2.50–9.10)****	**2.45 (0.66–6.26)****	**1.18 (0.68–2.41)***	**1.18 (0.40–4.90)***	0.65 (0.17–3.62)	**2.66 (1.38–5.96)****	**0.20 (0.04–0.95)*****	1.36 (0.99–2.14)	**0.90 (0.44–2.04)*****	**0.70 (0.34–1.90)***
Coronary artery disease n=206	**4.20 (2.50–8.20) *****	**2.35 (1.02–6.26) *****	1.15 (0.70–2.29)	1.22 (0.40–4.40)	0.69 (0.17–3.33)	**2.55 (1.47–5.96) *****	**0.20 (0.09–0.63) *****	**1.35 (1.01–2.09) *****	0.88 (0.51–1.73)	0.68 (0.34–1.80)
Diabetes n=85	**4.10 (2.50–7.00)*****	**2.20 (0.45–5.04)*****	**1.09 (0.69–2.15)****	**1.44 (0.50–4.10)*****	**0.84 (0.24–3.13)*****	**2.43 (1.38–5.06)*****	0.22 (0.10–0.54)	**1.29 (0.99–2.00)***	0.93 (0.53–1.64)	**0.62 (0.31–1.65)****
Hypertension n=312	4.50 (2.50–9.10)	2.58 (0.45–5.89)	1.14 (0.68–2.41)	**1.31 (0.50–4.90) ****	**0.74 (0.18–3.80) ****	2.73 (1.35–5.28)	0.22 (0.04–0.95)	1.35 (0.99–2.20)	0.93 (0.44–2.04)	0.68 (0.31–1.90)
Dyslipidaemia n=167	**4.30 (2.50–9.10) ***	**2.37 (0.45–5.89) *****	1.16 (0.69–2.41)	**1.32 (0.50–4.90) *****	**0.74 (0.20–3.80) *****	**2.58 (1.35–5.40) *****	0.22 (0.09–0.95)	1.38 (1.02–2.15)	0.92 (0.53–2.04)	0.69 (0.31–1.90)
Smoking[1] n=124	**4.70 (2.70–8.10) ****	**2.88 (1.28–5.76) ****	1.16 (0.69–2.41)	1.30 (0.40–4.40)	0.72 (0.17–3.33)	**2.97 (1.65–5.26) ***	**0.24 (0.09–0.77) ***	1.37 (1.03–2.15)	**1.02 (0.51–1.85) ***	0.67 (0.34–1.90)
Pulmonary disease n=103	**4.70 (2.60–9.10) ***	**2.91 (0.87–5.89) ***	1.18 (0.68–2.41)	1.13 (0.40–4.90)	0.62 (0.17–3.62)	**2.94 (1.38–5.26) ***	0.22 (0.08–0.95)	1.39–1.04–2.15)	0.96 (0.51–2.04)	0.70 (0.32–1.90)
Stroke[2] n=62	**4.00 (2.60–8.20) ****	**2.18 (0.49–5.51) *****	1.16 (0.69–2.22)	1.31 (0.60–4.10)	0.73 (0.22–3.13)	**2.39 (1.35–4.92) *****	**0.20 (0.04–0.78) ***	1.33 (0.99–2.09)	**0.88 (0.44–1.83) ***	0.70 (0.31–1.75)

*$p \leq 0.05$, **$p \leq 0.01$, and ***$p \leq 0.001$ (Mann-Whitney U test)

[1]Active smoking or smoking within five years

[2]Previous stroke or transient ischemic attack

Table 7. Serum lipid profiles of patients undergoing isolated coronary artery bypass grafting or invasive treatment for lower extremity artery disease. Statistically significant differences are highlighted.

	Coronary bypass surgery patients	Lower extremity artery disease	p-value
Total cholesterol (mmol/L)	4.2	4.5	0.353
LDL cholesterol (mmol/L)	2.31	2.39	0.772
HDL cholesterol (mmol/L)	**1.18**	**1.27**	**0.006**
Triglycerides (mmol/L)	1.27	1.34	0.824
EFW-VLDL-TG (mmol/L)	0.73	0.76	0.993
EFW-IDL (mmol/L)	0.21	0.21	0.706
EFW-LDL (mmol/L)	2.51	2.60	0.797
EFW-HDL_2 (mmol/L)	**0.69**	**0.77**	**0.004**
EFW-ApoA1 (g/L)	**1.37**	**1.46**	**0.006**
EFW-ApoB (g/L)	0.89	0.91	0.942
EFW-ApoB/ApoA1	**0.66**	**0.61**	**0.032**

Table 8. Multivariable logistic regression analysis including significant preoperative patient characteristics and the serum lipid measurements. The odds ratios have been calculated for having coronary artery disease instead of peripheral artery disease and represent an increase of 0.01 mmol/L for cholesterol and triglycerides and 0.01 g/L for apolipoprotein levels.

	Odds Ratio	p-value
Male gender	**4.01**	**< 0.001**
Age ≥70	**0.51**	**0.005**
Statin use	**3.90**	**< 0.001**
Smoking	**0.26**	**< 0.001**
Chronic pulmonary disease	0.56	0.063
Total cholesterol	0.90	0.389
LDL-cholesterol	1.11	0.343
HDL-cholesterol	0.97	0.835
EFW-VLDL-TG	1.04	0.491
EFW-IDL	1.00	0.931
EFW-LDL	0.97	0.389
EFW-HDL2	1.06	0.209
EFW-ApoA1	**1.11**	**0.044**
EFW-ApoB	1.05	0.522
EFW-ApoB/ApoA1* 0.5-0.7	0.55	0.160
EFW-ApoB/ApoA1* >0.7	0.41	0.207

* Reference value < 0.5

Independent variables are highlighted in boldface.

Table 9. Lipid profiles of abdominal aortic aneurysm, peripheral artery disease and coronary artery disease patients.

	TC	LDL-C	HDL-C	TG	EFW-VLDL-TG	EFW-LDL-C	EFW-IDL-C	EFW-apoA1	EFW-ApoB	EFW-HDL_2
AAA	4.50 (2.50–9.10)	2.64 (0.4–6.26)	1.16 (0.68–2.41)	1.23 (0.40–4.90)	0.70 (0.12–3.80)	2.78 (1.35–5.96)	0.22 (0.04–0.95)	1.36 (0.99–2.21)	0.94 (0.44–2.04)	0.68 (0.31–1.90)
PAD	4.5	2.39	1.27	1.34	0.76	2.60	0.21	1.46	0.91	0.77
CAD	4.2	2.31	1.18	1.27	0.73	2.51	0.21	1.37	0.89	0.69

Median lipid values presented. Unit in apolipoproteins g/L; mmol/L in other lipid values.

5.5 Mortality in AAA patients

Table 10 presents patient survival at different time points for the whole study IV cohort as well as in patient subgroups. At all time points (6 months, 3 years, 5 years and 10 years), age below 70 years was associated with improved survival. At 6 months, EVAR, elective surgery, freedom from diabetes, dyslipidaemia and freedom from renal insufficiency were also linked to lower mortality. Elective surgery continued to be associated with improved survival at 3 years' follow-up. An association of a history of dyslipidaemia with decreased mortality was also found at 5 years. Conversely, pulmonary disease was associated with inferior survival at this time point and continued to do so at the 10-year follow-up. At 10 years, hypertension was also associated with increased mortality. Statistically significant differences in serum lipid values between survivors and non-survivors were discovered only at the 5-year follow-up. Those surviving had lower HDL-C, HDL2 subfraction and apoA1 values compared to non-survivors, with median values of 1.14 (range 0.68–2.29) versus 1.20 (range 0.68–2.41) (p=0.019), 0.66 (range 0.31–1.80) versus 0.72 (range 0.34–1.90) (p=0.016), and 1.35 (range 1.02–2.08) versus 1.40 (range 0.99–2.21) (p=0.022), respectively.

The results of multivariable analysis are presented in Table 11. Older age at the time of treatment, aneurysm rupture, active or previous smoking within 5 years, pulmonary disease and diabetes were associated with increased mortality. In distinction, patients with a history of dyslipidaemia had improved survival. Furthermore, increasing LDL-C and TG levels were associated with a higher mortality rate and, interestingly, EFW-IDL-C with significantly lower mortality. In order to determine the utility of these lipid parameters in risk prediction, continuous NRI was determined. It was discovered that using TG, LDL-C and EFW-IDL-C in addition to the other independent risk factors in the prediction of 5-year mortality provided a continuous NRI of 17.7% (95% CI 2.2–27.7%, p=0.016). TG and LDL-C were then compared to EFW-IDL-C, and it was found that neither the first two combined nor EFW-IDL-C alone had a significant effect on NRI. Including EFW-IDL-C in addition to TG, LDL-C and other independent risk factors produced a continuous NRI of 16.8% (95% CI 1.4–27.3%, p=0.028). A comparable change was not found when including TG and LDL-C with EFW-IDL-C accompanied by other risk factors. Taken together, this provides evidence that EFW-IDL-C is at least as valuable in risk prediction in the study cohort as TG and LDL-C combined. The effect of the number of risk factors on survival at different time points is presented in Figure 1.

Table 10. Survival in patients treated for abdominal aortic aneurysms. The number of surviving patients and patients included in follow-up at different time points are presented separately for all patients and the most important patient subgroups. The patient subgroups and the number of patients included in follow-up are presented separately. Statistically significant differences between opposing subgroups (i.e. elective vs. urgent or emergency, diabetes vs no diabetes, etc.) are highlighted.

	6 months	3 years	5 years	10 years
All patients	455/498 (91.4%)	318/402 (79.1%)	207/312 (66.3%)	39/106 (36.8%)
Male	401/438 (91.6 %)	280/350 (80.0%)	185/273 (67.8 %)	33/89 (37.1 %)
Female	54/60 (90.0%)	38/52 (73.1%)	22/39 (56.4%)	6/17 (35.3%)
Age <70 years	**167/176 (94.9%)***	**124/141 (87.9%)*****	**93/112 (83.0%)*****	**24/39 (61.5%)*****
Age ≥70 years	**288/322 (89.4%)***	**194/261 (74.3%)*****	**114/200 (57.0%)*****	**15/67 (22.4%)*****
Elective	**367/383 (95.8%)*****	**255/306 (83.3%)*****	164/239 (68.6%)	29/83 (34.9%)
Urgent or emergency	**88/115 (76.5%)*****	**63/96 (65.6%)*****	43/73 (58.9%)	10/23 (43.5%)
Open surgery	**226/260 (86.9%)*****	179/225 (79.6%)	127/182 (69.8%)	29/67 (43.3%)
Endovascular repair	**229/238 (96.2%)*****	139/177 (78.5%)	80/130 (61.5%)	10/39 (25.6%)
Coronary artery disease	190/206 (92.2%)	130/169 (76.9%)	91/140 (65.0%)	20/61 (32.8%)
Diabetes	**72/85 (84.7%)***	43/61 (70.5%)	27/45 (60.0%)	5/12 (41.7%)
Hypertension	287/312 (92.0%)	189/243 (77.8%)	122/188 (64.9%)	**16/60 (26.7%)***
Dyslipidaemia	**159/167 (95.2%)***	105/125 (84.0%)	**75/98 (76.5 %)****	16/34 (47.1%)
Smoking[1]	118/124 (95.2%)	81/102 (79.4%)	50/75 (66.7%)	12/28 (42.9%)
Pulmonary disease	92/103 (89.3%)	55/77 (71.4%)	**33/61 (54.1 %)***	**2/15 (13.3%)***
Stroke[2]	53/62 (85.5%)	38/48 (79.2%)	23/39 (59.0%)	3/17 (17.6%)
Renal insufficiency	**72/85 (84.7%)***	43/61 (70.5%)	27/45 (60.0%)	5/12 (41.7%)

*$p \leq 0.05$, **$p \leq 0.01$, and ***$p \leq 0.001$, when compared to controls (chi square test)

[1]Active smoking or smoking within five years

[2]Previous stroke or transient ischemic attack

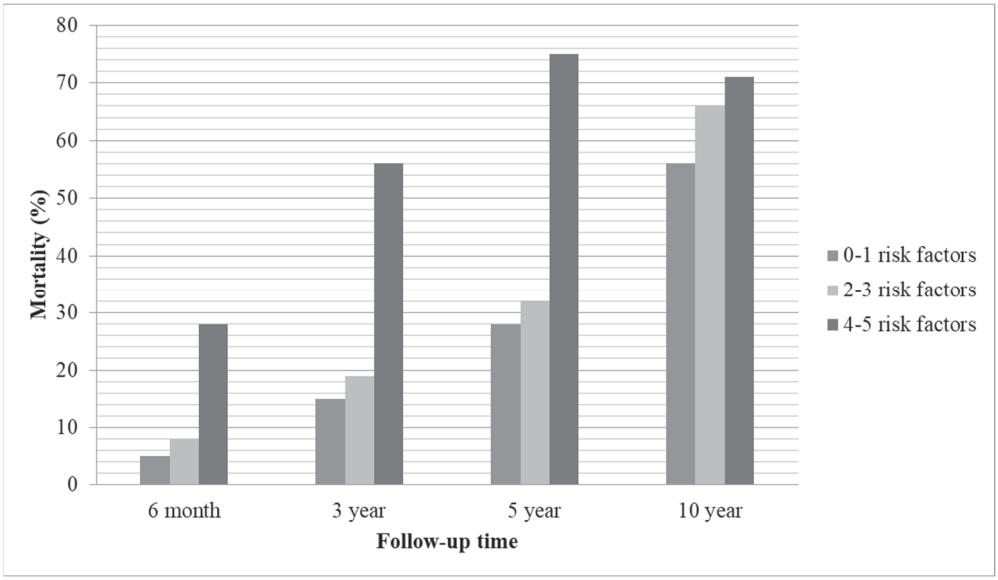
Table 11. Results of stepwise multivariable Cox regression analysis on mortality. In serum lipids, hazard ratios correspond to an increase of one standard deviation. (Factors included in the Cox regression analysis: age, sex, diabetes, hypertension, coronary artery disease, stroke, pulmonary disease, renal insufficiency, previous reconstruction, active smoking or smoking within 5 years, aneurysm rupture, endovascular treatment, TC, LDL-C, HDL-C, TG, EFW-VLDL-TG, EFW-LDL-C, EFW-IDL-C, EFW-ApoA1, EFW-ApoB, EFW-HDL_2, GFR)

	HR	95 % CI	p-value
Age	1.08	1.05–1.10	< 0.001
Aneurysm rupture	2.46	1.68–3.60	< 0.001
Smoking[1]	1.70	1.16–2.49	0.006
Pulmonary disease	1.44	1.03–2.01	0.035
Dyslipidaemia	0.68	0.49–0.95	0.025
TG (SD=0.73mmol/L)	1.84	1.20–2.81	0.005
LDL-C (SD=0.97mmol/L)	1.79	1.18–2.73	0.006
EFW-IDL-C (SD=0.11mmol/L)	0.31	0.19–0.65	< 0.001
Diabetes	1.50	1.01–2.25	0.046
Hypertension	1.30	0.96–1.76	0.090
Stroke[2]	1.39	0.94–2.06	0.094

[1] Active smoking or smoking within five years

[2] Previous stroke or transient ischemic attack

Figure 1. Survival at different time points by the number of present risk factors



5.6 Multiple procedures in AAA patients

Multiple vascular surgical procedures served as a marker of vascular surgical burden. These were required in 89 (17.9%) patients. In multivariable analysis, EVAR was associated with multiple interventions (OR 2.52, 95% CI 1.43–4.55), whereas older age and higher GFR had a reciprocal association (OR 0.96, 95% CI 0.92–0.99, and OR 0.66 for a 1–SD, i.e. 21.05 ml/min increase, 95% CI 0.50–0.86, respectively). No association with the investigated lipid parameters and increased vascular surgical burden was found.

5.7 Postoperative complications

5.7.1 Atrial fibrillation (study I)

After cardiac surgery, 1,316 patients survived a minimum of five days. The demographic information and preoperative and procedural characteristics of all cardiac surgical patients are presented in Table 4. With 152 patients presenting with a history of chronic atrial fibrillation, a total of 1,164 patients formed the final study cohort. The incidence of new-onset POAF in these patients was 51% (n=599). The distribution of POAF according to procedure type is presented in Table 12. Furthermore, 158 patients had previous paroxysmal atrial fibrillation, and 129 (82%, 95% CI 76–88%) of these developed POAF, whereas the incidence in patients with no history of atrial fibrillation was 47% (n=470) ($p<0.001$). The POAF lasted less than 48 hours with no recurrent episodes in 171 patients (29%). In contrast, 428 patients (71%) had prolonged arrhythmia for 48 hours or longer, or recurrent POAF. The time of onset of POAF ranged from 0 to 30 days, and the median time of onset was on the third postoperative day (Figure 2). Patients with POAF had significantly longer hospitalisation periods compared to patients not developing the complication, with a median duration of 6 versus 5 days, respectively ($p<0.001$).

In univariable analyses, older age, previous hypertension and a larger left atrium were associated with developing POAF (Table 13). Moreover, a more severe symptomatic state preoperatively (NYHA 3 or 4 as opposed to NYHA 1 or 2) had a significant association with the arrhythmia. Active smoking, in turn, was protective against POAF in univariable analysis, with an incidence of 39% versus 54 % in smokers and non-smokers, respectively ($p<0.001$). Smokers were, however, also

significantly younger (median age 59 versus 69 years) ($p<0.001$). No sex-related difference in the occurrence of POAF could be ascertained. Furthermore, CAD, diabetes, dyslipidaemia, chronic pulmonary disease, BMI, left ventricular ejection fraction, preoperative serum creatinine level, perioperative cryoablation or preoperative medical therapy with statins or beta blockers had no association with POAF. With regard to other postoperative complications, POAF was not associated with stroke or combined 30-day and in-hospital mortality. Conversely, it was significantly more common in patients with postoperative infections (63% versus 50%, $p=0.008$) as well as those requiring reinterventions (63% versus 50%, $p=0.002$). Although the urgency of the intervention was not associated with POAF when all patients were considered, in the subset of patients undergoing CABG, there was a tendency towards POAF being more frequent in urgent (43%) or emergency (54%) procedures compared to elective (39%) operations ($p=0.058$). Operation type, age, previous atrial fibrillation, left atrium size and emergency surgery were independently associated with the occurrence of POAF in multivariable analysis (Table 14).

Table 12. The distribution of postoperative atrial fibrillation according to the type of procedure in patients without chronic atrial fibrillation and surviving at least five days.

	n	Postoperative atrial Fibrillation (%)	95% confidence interval
All patients	1164	599 (51%)	49%–54%
Only CABG*	500	214 (43%)	38%–47%
Single valve	344	189 (55%)	50%–60%
Multiple valve	38	28 (74%)	59%–88%
CABG* and valve surgery	145	96 (66%)	58%–74%
Aortic surgery**	110	59 (54%)	44%–63%

* CABG = coronary artery bypass grafting

** Aortic surgery includes aortic root procedures and aortic surgery combined with CABG or valve surgery.

Figure 2. Delay of onset in the development of postoperative atrial fibrillation.

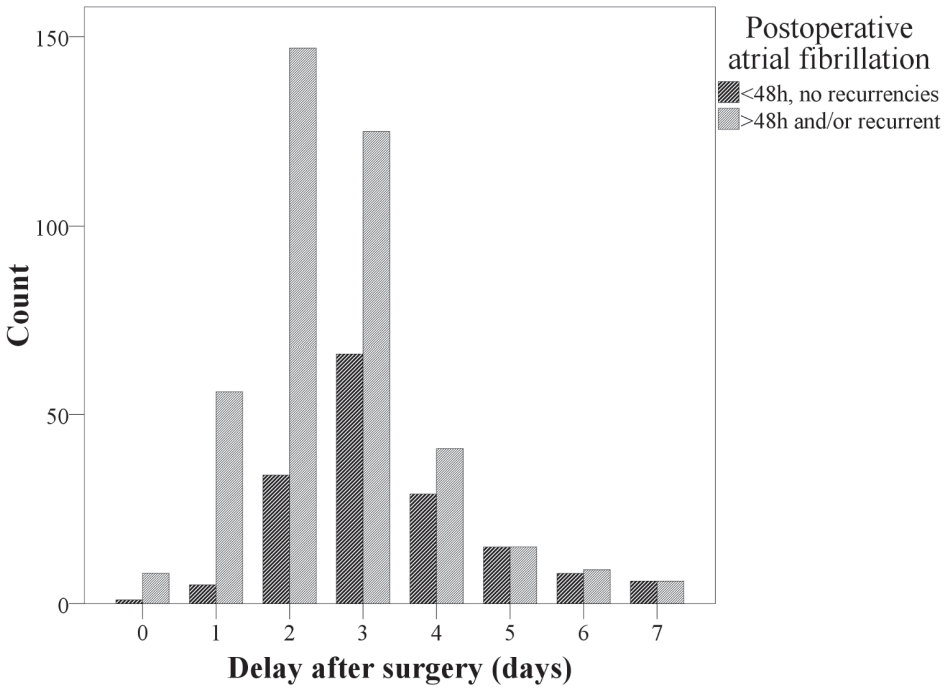


Table 13. The association of patient characteristics and postoperative complications with postoperative atrial fibrillation in univariable analysis. Patients without chronic atrial fibrillation and surviving at least five days postoperatively are included.

		Postoperative atrial fibrillation		
		Yes	No	p
Male sex		71%	73%	0.494
Median age (years)		71	64	< 0.001
Median BMI (kg/m^2)		28	28	0.478
Previous paroxysmal atrial fibrillation		22%	5%	< 0.001
Urgency	Elective	70%	69%	0.777
	Urgent	18%	20%	0.392
	Emergency	12%	11%	0.524
Left atrium size (mm)		42	39	< 0.001
NYHA 3 or 4		29%	24%	0.053
Median Euroscore-2		2.0%	1.5%	< 0.001
Coronary disease		62%	66%	0.181
Diabetes		24%	24%	> 0.999
Dyslipidaemia		60%	59%	0.689
Hypertension		69%	60%	0.001
LVEF < 50%		19%	16%	0.181
Chronic lung disease		10%	11%	0.444
Active smoking		11%	18%	< 0.001
Preoperative β-blocker		64%	59%	0.081
Preoperative statin		57%	49%	0.527
Preoperative serum creatinine (µmol/L)		82	81	0.137
Mortality		3.0%	2.1%	0.343
Stroke		2.2%	3.4%	0.214
Median length of hospitalization (days)		6	5	< 0.001
Reoperations		16%	10%	0.002
Infectious complications		12%	7%	0.008

Table 14. Risk factors for postoperative atrial fibrillation in multivariable analysis.

Risk factor	Odds ratio	95% confidence interval
Male sex	1.34	0.98-1.83
Age[1]		
50–59	1.83	1.00–3.35
60–69	2.96*	1.66–5.29
70–79	5.73*	3.17–10.38
80+	8.49*	4.17–17.28
Previous atrial fibrillation	4.37*	2.77–6.89
Dyslipidaemia	1.02	0.75–1.39
Hypertension	1.15	0.85–1.57
Diabetes	1.18	0.85–1.65
Active smoking	0.82	0.55–1.24
Left atrium >40 mm	1.83*	1.21–2.79
Type of procedure[1]		
Single-valve	2.09*	1.46–2.99
Multiple-valve	3.43*	1.43–8.26
Coronary artery bypass and valve	2.28*	1.46–3.55
Aortic	2.53*	1.53–4.19
Urgency[1]		
Urgent	1.16	0.81–1.67
Emergency	1.75*	1.11–2.76

Baseline groups include patients aged less than 50 years, those undergoing bypass surgery and elective surgery, respectively.

*$p \leq 0.05$

5.7.2 Late tamponade (study II)

The 1,308 patients surviving beyond the first seven postoperative days formed the final study cohort. In this cohort, the combined in-hospital and 30-day mortality was 2.1% (n=28). The number of redo cases was 9 (0.7%). Furthermore, there were 81 (6.2%, 95% CI 4.9%–7.5%) late PPEs requiring invasive treatment, and the median delay from the primary operation to treatment was 11 (range 8–87) days. There were no interventions for late PPEs in patients that had undergone redo operations. Surgical fenestration was chosen for 69 (85%) and percutaneous drainage for 12 (15%) patients. Additionally, eight (9.9%) patients had been started on medical

therapy preceding the invasive treatment. The median maximal thickness of the effusion upon ultrasonography was 25 mm (range 10–0 mm) at the time of the intervention, and the median amount of pericardial fluid drained was 500 ml (range 200–2000 ml). Hemodynamic instability was discovered in 28 (34.6%) and cardiac chamber compression in 44 54.3%) patients. Subjective symptoms, mostly dyspnoea, were present in 46 (56.8%) patients (Figure 3). Eighteen individuals were free from symptoms, haemodynamically stable, and lacked signs of chamber compression but underwent invasive treatment due to significantly increasing pericardial fluid in ultrasound follow-up. A total of 54 (4.1%, 95% CI 3.1%–5.2%) patients were classified as having tamponade and 27 (2.1%; 95% CI 1.3%–2.8%) patients as having pretamponade. A reintervention for recurrent tamponade was required in six (7%) cases. Table 15 displays the incidences of late tamponade and pretamponade by operation type.

A comparison between the preoperative characteristics of patients developing late tamponade or pretamponade and corresponding characteristics in other patients is shown in Table 16. Patients requiring an intervention for late PPEs were younger and generally healthier. Compared to other patients, they were more often undergoing elective procedures, typically presented with a lower median EUROSCORE-II rating and had a smaller prevalence of CAD, impaired left ventricular ejection fraction and preoperative b-blocker medication, as well as higher preoperative median blood haemoglobin and lower preoperative median leukocyte levels. It was found that, in patients developing late tamponade or pretamponade, the aortic cross-clamping (median 103 versus 91 min, p=0.002) as well as perfusion times (median 133 versus 118 min, p=0.001) were significantly longer. Furthermore, patients treated invasively for late PPEs received greater volumes of autologous erythrocytes returned perioperatively through the cell-saving suction system (median volume 1,240 vs 950 ml, p=0.001). Postoperatively, there was no significant difference in the need for non-autologous blood products. Finally, in late tamponade and pretamponade patients, chest drain output was significantly lower compared to other patients (median volume 600 vs 720 ml, p=0.021).

Late tamponade and pretamponade were significantly more prevalent in patients with POAF compared to patients free from the arrhythmia, with incidences of 7.5% and 4.5 % (p=0.028), respectively. However, no associations with postoperative infections, stroke or mortality were discovered. With regard to postoperative laboratory parameters, no significant associations with CRP, creatinine or haemoglobin were ascertained. In contrast, peak median levels of plasma creatine kinase MB isoenzyme (42 versus 34 mg/L, p=0.005) and blood leukocytes (12.4

versus 11.9 x 10^9/L, p=0.045) within the first postoperative week were higher in patients treated invasively for late PPEs. Additionally, the lowest median thrombocyte levels during the first seven postoperative days were lower in these patients (95 versus 109 x 10^9/l, p=0.013). Multivariable analysis found single-valve surgery and high preoperative haemoglobin levels to be independent risk factors of late PPEs that required invasive treatment, whereas age between 60 and 69 years was associated with a lower risk (Table 17).

Figure 3. The dominant signs in patients with subjective symptoms presenting with late tamponade or pretamponade after cardiac surgery.

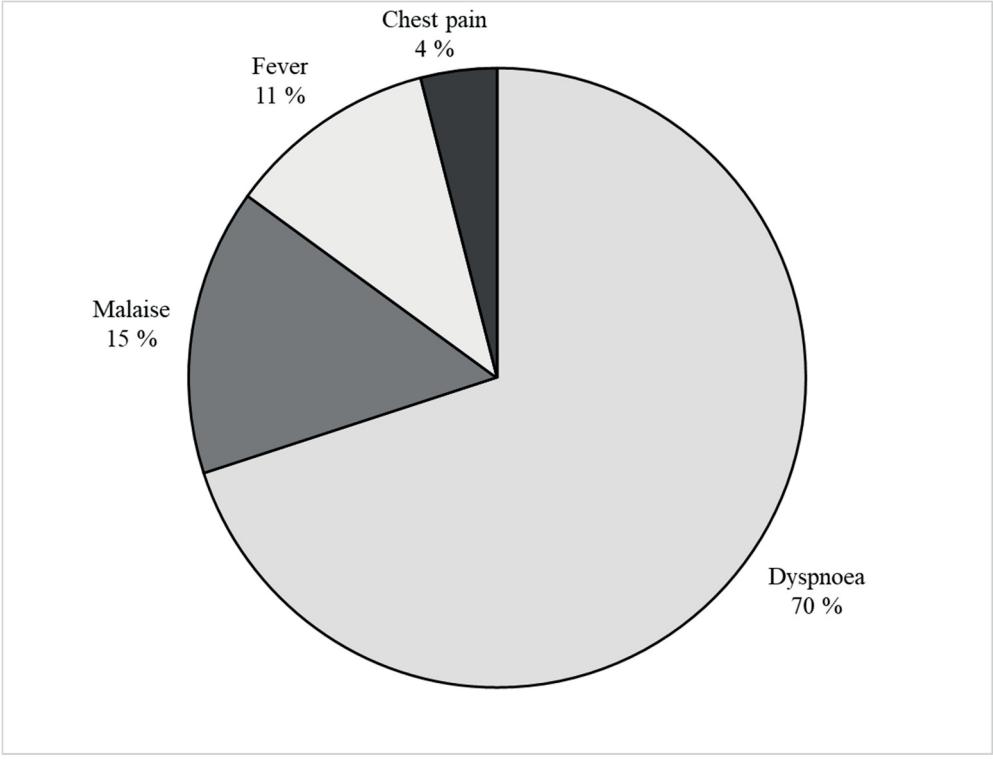


Table 15. The occurrence of late postoperative tamponade or pretamponade within six months after cardiac surgery according to the type of procedure performed.

	Late tamponade	95% Confidence interval	Late pretamponade	95% Confidence interval
CABG*	1.3%	0.4%–2.3%	0%	
Single-valve	6.6%	4.2%–9.0%	3.9%	2.0%–5.8%
Multiple-valve	4.3%	0%–9.2%	5.7%	0.1%–11.3%
CABG* and valve	2.5%	0.1%–4.9%	2.5%	0.1%–4.9%
Aortic** surgery	9.3%	4.0%–14.7%	1.7%	0%–4.1%

* CABG = coronary artery bypass grafting

** Aortic surgery includes aortic root procedures and aortic surgery combined with CABG or valve surgery

Table 16. The associations of preoperative variables and the development of late postoperative tamponade or pretamponade.

	No tamponade	Late tamponade or pretamponade	p-value
Male (%)	882 (71.9%)	61 (75.3%)	0.506
Median age (range)	**68 (19–89)**	**65 (25–85)**	**0.007**
Urgent or emergency surgery (%)	**373 (30.4%)**	**15 (18.5%)**	**0.023**
Median Euroscore-II (range)	**1.85 (0.49–86.83)**	**1.74 (0.50–15.53)**	**0.033**
NYHA 3–4 (%)	297 (26.3%)	16 (21.9%)	0.492
Median BMI (range)	26.8 (10.5–61.3)	27.8 (16.8–43.0)	0.156
Coronary disease (%)	**783 (63.8%)**	**27 (33.3%)**	**<0.001**
LVEF <50% (%)	**232 (18.9%)**	**7 (8.6%)**	**0.017**
Hypertension (%)	801 (65.3%)	46 (56.8%)	0.121
Diabetes (%)	298 (24.3%)	12 (14.8%)	0.052
Dyslipidaemia (%)	725 (59.1%)	41 (50.6%)	0.134
Preoperative atrial fibrillation[1] (%)	285 (23.2%)	24 (29.6%)	0.189
Chronic lung disease (%)	132 (10.8%)	9 (11.1%)	0.854
Active smoking (%)	172 (14.0%)	11 (13.6%)	0.912
Preoperative creatinine µmol/L (range)	83 (34–1,036)	84 (48–206)	0.920
Preoperative haemoglobin g/L	**139 (82–178)**	**143 (104–180)**	**0.025**
Preoperative leukocyte $*10^9$	**6.9 (2.0–112.0)**	**6.4 (4.0–25.0)**	**0.043**
Preoperative statin (%)	697 (56.8%)	39 (48.1%)	0.128
Preoperative β-blocker (%)	**793 (64.6%)**	**37 (45.7%)**	**0.001**

[1]Includes chronic and paroxysmal atrial fibrillation

Table 17. Table 3. Risk factors for late tamponade or pretamponade after cardiac surgery in multivariable analysis. Significant associations are highlighted.

	Odds Ratio	95% Confidence interval
Single-valve[1]	**4.34**	**1.08–17.45**
Multiple-valve[1]	5.17	0.91–29.34
CABG and Valve[1]	2.76	0.65–11.74
Aortic[1]	3.97	0.74–21.20
Urgent or emergency surgery	0.57	0.22–1.48
Euroscore-II	1.01	0.93–1.10
Age 50–59[2]	0.69	0.25–1.87
Age 60–69[2]	**0.31**	**0.10–0.94**
Age 70–79[2]	1.10	0.39–3.13
Age ≥80[2]	0.73	0.17–3.06
Coronary disease	0.71	0.26–1.96
LVEF[3] <50%	0.50	0.16–1.52
Preoperative β-blocker	0.67	0.35–1.27
Preoperative haemoglobin	**1.03**	**1.00–1.05**
Preoperative leukocyte level	0.92	0.78–1.10
Aortic cross-clamping time	1.00	0.99–1.02
Perfusion time	1.00	0.98–1.01
Peak postoperative leukocyte level[4]	1.07	0.98–1.16
Peak postoperative creatine kinase MB[4]	1.00	1.00–1.01
Lowest postoperative thrombocyte level[4]	1.00	0.99–1.01
Volume of returned autologous erythrocytes	1.00	1.00–1.00
Chest tube production	1.00	1.00–1.00

[1] Baseline group isolated coronary artery bypass grafting

[2] Baseline age < 50

[3] Left ventricular ejection fraction

[4] During the first seven postoperative days

5.7.3 Infections (study III)

The incidence of postoperative infections was 9.8% among the 1,329 patients surviving the first two postoperative days. The demographics of this subset of patients according to operation type are presented in Table 18. Cannula- or catheter-related infections (2.6%), major SSIs (2.2%) and lung infections (2.0%) were the most common infection subtypes. These are presented in more detail in Table 19.

Unclear fever or bacteraemia and other infections were found in 0.3% and 0.2% of the patients, respectively. Bacterial cultures were positive in 97 (75%) and blood cultures in 18 (14%) patients with postoperative infections. Figure 4 displays the most prevalent pathogens by infection type. The median time from the index procedure to the manifestation of primary symptoms of a postoperative infection was 6 (range 0–174) days. In major SSIs, the delay was 8 (range 2–174) days, including one prosthetic valve endocarditis presenting within 6 months after the operation, while the delay in minor SSIs was 7 (range 2–26), in lung infections 3 (range 1–10), in unclear fever or bacteraemia 8 (range 4–15), in cannula- or catheter-related infections 6 (range 0–20), in multiple infections 7 (range 3–177), and finally, in other infections 3 (range 2–3) days ($p<0.001$). Readmission after the primary hospitalisation period owing to infectious complications was required in 17 (1.3%) patients.

Urgent or emergency surgery, impaired left ventricular function, age ≥ 70 years and a body mass index (BMI) of ≥ 27 kg/m^2 were associated with increased infection rates. A higher incidence of postoperative SSIs was found in patients with an elevated BMI, whereas cannula- and catheter-related infections were more common in female patients and those aged 70 years or over. Furthermore, pulmonary infections were more prevalent in urgent and emergency procedures compared to elective surgery as well as in patients with a higher new York Heart Association Functional Classification (NYHA) score and inferior left ventricular ejection fraction. Deep SSIs were found in 2.0% of the patients, and they were not statistically significantly associated with the type of operation.

Postoperative infections were also associated with a longer postoperative duration of intubation (median 5.8 versus 4.3 h, $p<0.001$) as well as a longer primary ICU stay (median 1.7 versus 0.9 days, $p<0.001$). Patients with the complication were additionally hospitalised for longer periods (median 11 versus 5 days, $p<0.001$) and had a higher combined in-hospital and 30-day mortality (10.8% versus 2.9%, $p<0.001$) compared to other patients. The mortality rates in different infection subgroups were 20.7% in major SSIs, 15.4% in lung infections, 5.7% in cannula- and catheter-related infections, 10% in patients with multiple infections, and 0% in patients with other infections ($p<0.001$).

Hyperglycaemia (B-gluc >7 mmol/L) was detected in 915 (68.8%) patients. Single hyperglycaemic episodes were found in 388 (29.2%), two episodes in 237 (17.8%) and three or more episodes in 290 (21.8%) patients. Repeated hyperglycaemia was significantly more common in diabetics compared to non-diabetics (53% vs 36%, $p<0.001$). Patients with repeated hyperglycaemic episodes also had a higher median

BMI compared to other patients (27.7 vs 26.3 kg/m2, $p<0.001$). A statistically significant association was found between repeated hyperglycaemia episodes and postoperative infections (12.1% versus 8.2% in patients with single episodes or no hyperglycaemia, $p=0.019$), yet no association with infection subtypes was ascertained (Figure 5). Moreover, repeated hyperglycaemia episodes were associated with postoperative stroke (4.9% vs 1.5%, $p<0.001$) and combined 30-day and in-hospital mortality (6.1% vs 2.1%, $p<0.001$). The median postoperative blood glucose concentration in the whole patient cohort was 6.1 mmol/L (range 4.0–11.6 mmol/L). It was higher in diabetics (6.3 versus 6.1 mmol/L, $p<0.001$) and in patients with postoperative infections (6.3 versus 6.1 mmol/L, $p=0.026$). Additionally, patients with diabetes received higher amounts of insulin compared to other patients (1.9 versus 1.5 IU/h, $p<0.001$). Insulin treatment itself was not statistically significantly associated with later infections. The independent predictors of postoperative infections in cardiac surgery were age ≥ 70 years and repeated hyperglycaemia (Table 20).

Hypoglycaemia (B-gluc <4 mmol/L), in turn, occurred in 101 (7.6%) patients altogether, with 91 (6.8%) patients having one, 9 (0.7%) patients two and one (0.1%) patient three episodes. Sixteen patients (1.2 %) did not receive any insulin, and one of these patients developed hypoglycaemia. An association between hypoglycaemia and the type of procedure performed, postoperative infections, in-hospital mortality, stroke rate, length of hospitalization or postoperative atrial fibrillation could not be found.

Table 18. Demographic data of study (III) patients

	All patients (n=1329)	CABG* only (n=527)	Single-valve (n=410)	Multiple-valve (n=72)	CABG* and valve (n=164)	Aortic** (n=126)
Elective (%)	931 (70%)	281 (53%)	361 (88%)	58 (81%)	124 (76%)	89 (71%)
NYHA 3 or 4 (%)	323 (24%)	168 (32%)	60 (15%)	17 (24%)	37 (23%)	33 (26%)
Median Euroscore-2 (range)	1.8 (0.5–86.8)	1.7 (0.5–52.6)	1.3 (0.5–21.6)	3.1 (0.6–28.6)	2.9 (0.6–56.4)	3.0 (0.5–86.8)
Male (%)	955 (72%)	418 (79%)	260 (63%)	46 (64%)	115 (70%)	99 (72%)
Median age (range)	68 (19–89)	68 (40–89)	68 (19–88)	71 (22–85)	74 (42–87)	63 (28–79)
Median BMI (range)	27 (10–60)	27 (17–60)	27 (10–60)	27 (14–45)	27 (17–41)	26 (19–61)
Median LVEF (range)	59 (19–84)	55 (19–80)	60 (25–84)	60 (28–81)	57 (25–82)	60 (20–80)
Coronary disease (%)	825 (62%)	527 (100%)	95 (23%)	16 (22%)	161 (98%)	26 (21%)
Hypertension (%)	859 (65%)	382 (72%)	234 (57%)	35 (49%)	119 (73%)	75 (60%)
Diabetes (%)	314 (24%)	177 (34%)	61 (15%)	13 (18%)	46 (28%)	15 (12%)
Dyslipidaemia (%)	773 (58%)	407 (77%)	173 (42%)	27 (47%)	115 (70%)	44 (35%)
Chronic lung disease (%)	144 (11%)	57 (11%)	44 (11%)	5 (7%)	21 (13%)	16 (13%)

* CABG = coronary artery bypass grafting

**Includes aortic root, ascending aorta and aortic arch procedures with or without bypass and/or valve surgery.

Table 19. The number of postoperative infections and the most important infection types in all study patients and by patient subgroup. Statistically significant differences between opposing groups and per grouping factor are highlighted.

	N	Any postoperative infection	Major SSI[1]	Minor SSI[1]	Lung infection	Cannula- or catheter-related	Multiple infections
All patients	1329	130 (9.8%)	29 (2.2%)	14 (1.1%)	26 (2.0%)	35 (2.6%)	20 (1.5%)
CABG[2]	527	47 (8.9%)	13 (2.5%)	5 (0.9%)	11 (2.1%)	9 (1.7%)	**6 (1.1%)***
Single-valve	410	36 (8.8%)	8 (2.0%)	4 (1.0%)	3 (0.7%)	14 (3.4%)	**5 (1.2%)***
Multiple-valve	72	9 (12.5%)	0	0	3 (4.2%)	3 (4.2%)	**2 (2.8%)***
CABG[2] and valve	164	26 (15.9%)	5 (3.0%)	4 (2.4%)	5 (3.0%)	5 (3.0%)	**7 (4.3%)***
Aortic	126	11 (8.7%)	3 (2.4%)	1 (0.8%)	4 (3.2%)	3 (2.4%)	**0***
Elective	931	**80 (8.6%)***	19 (2.0%)	8 (0.9%)	**12 (1.3%)****	25 (2.7%)	12 (1.3%)
Urgent or emergency	398	**50 (12.6%)***	10 (2.5%)	6 (1.5%)	**14 (3.5%)****	10 (2.5%)	8 (2.0%)
NYHA[3] 1–2	900	82 (9.1%)	19 (2.1%)	10 (1.1%)	**11 (1.2%)****	26 (2.9%)	11 (1.2%)
NYHA[3] 3–4	323	39 (12.1%)	10 (3.1%)	3 (0.9%)	**12 (3.7%)****	6 (1.9%)	7 (2.2%)
LVEF[4] ≥ 50%	1084	**95 (8.8%)****	**19 (1.8%)***	12 (1.1%)	**15 (1.4%)****	30 (2.8%)	15 (1.4%)
LVEF[4] < 50%	245	**35 (14.3%)****	**10 (4.1%)***	2 (0.8%)	**11 (4.5%)****	5 (2.0%)	5 (2.0%)
Age < 70	715	**58 (8.1%)***	11 (1.5%)	8 (1.1%)	14 (2.0%)	**12 (1.7%)***	9 (1.3%)
Age ≥ 70	614	**72 (11.7%)***	18 (2.9%)	6 (1.0%)	12 (2.0%)	**23 (3.7%)***	11 (1.8%)
BMI[5] < 27	674	**54 (8.0%)***	**8 (1.2%)***	**3 (0.4%)***	9 (1.3%)	18 (2.7%)	14 (2.1%)
BMI[5] ≥ 27	646	**74 (11.5%)***	**20 (3.1%)***	**10 (1.5%)***	17 (2.6%)	17 (2.6%)	6 (0.9%)
Male	955	85 (8.9%)	24 (2.5%)	9 (0.9%)	22 (2.3%)	**14 (1.5%)*****	**10 (1.0%)***
Female	374	45 (12.0%)	5 (1.3%)	5 (1.3%)	4 (1.1%)	**21 (5.6%)*****	**10 (2.7%)***
Diabetes	314	35 (11.1%)	9 (2.9%)	5 (1.6%)	7 (2.2%)	7 (2.2%)	4 (1.3%)
Coronary disease	825	89 (10.8%)	20 (2.4%)	10 (1.2%)	16 (1.9%)	24 (2.9%)	16 (1.9%)
Hypertension	859	86 (10.0%)	17 (2.0%)	11 (1.3%)	16 (1.9%)	24 (2.8%)	14 (1.6%)
Dyslipidaemia	773	75 (9.7%)	18 (2.3%)	11 (1.4%)	14 (1.8%)	23 (3.0%)	**7 (0.9%)***
Chronic lung disease	144	18 (12.5%)	3 (2.1%)	1 (0.7%)	**6 (4.2%)***	2 (1.4%)	**6 (4.2%)****

*p<0.05, **p<0.01, ***p<0.001

[1]Surgical site infection, [2]coronary artery bypass grafting, [3]New York Heart Association Functional Classification, [4]left ventricular ejection fraction, [5]body mass index

Figure 4. Classification and distribution of postoperative infections and the most common pathogens

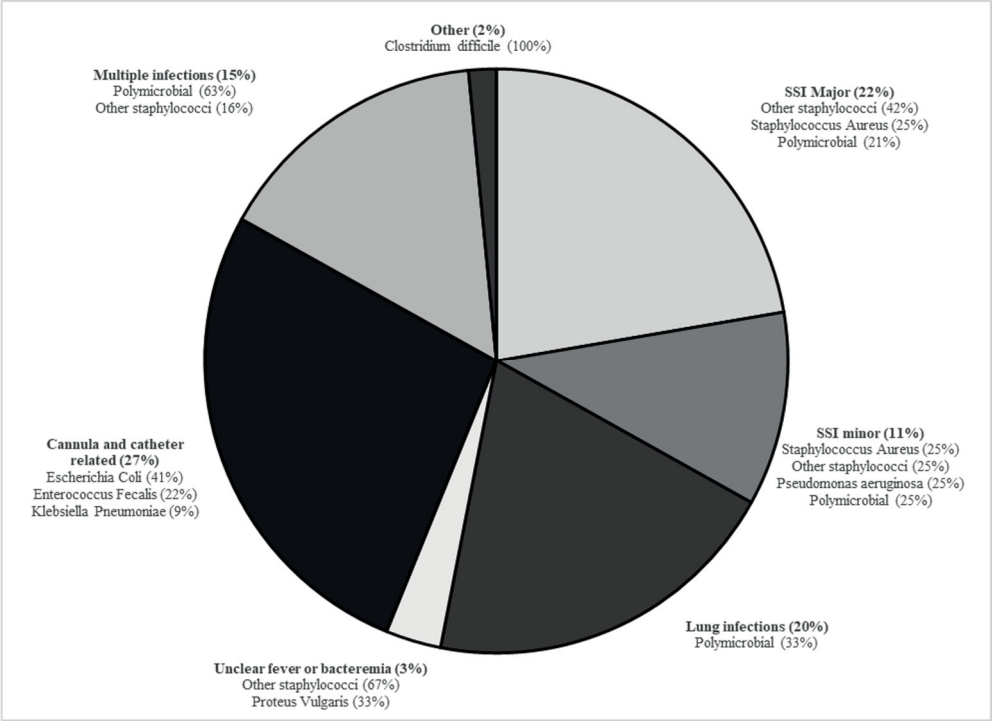


Figure 5. Proportions of patients with infectious complications by the number of hyperglycaemic samples during the first 24 hours after surgery.

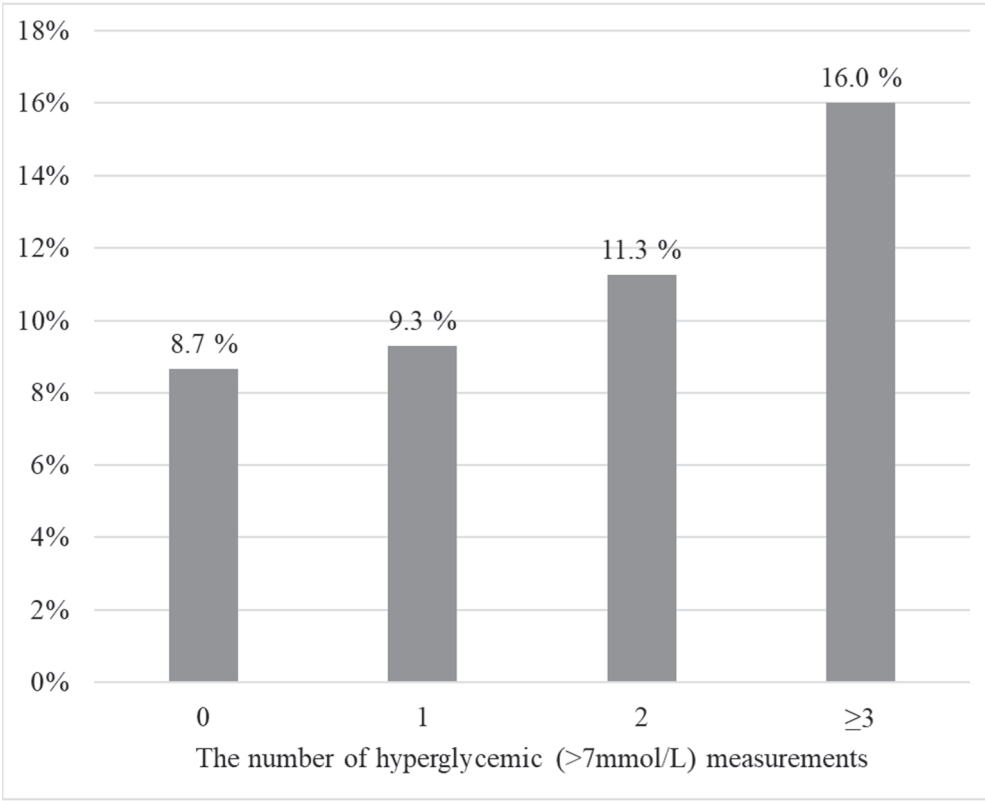


Table 20. Risk factors for postoperative infections in multivariable analysis. Factors associated with postoperative infections in univariable analyses were included. Statistically significant associations are highlighted.

	p	Odds ratio	95% Confidence Interval
Age ≥ 70	**0.017**	**1.57**	**1.09–2.28**
BMI ≥ 27 kg/m^2	0.103	1.37	0.94–1.99
LVEF < 50%	0.051	1.54	1.00–2.38
Urgent/emergency procedure	0.144	1.34	0.91–1.98
Repeated hyperglycemia	**0.031**	**1.51**	**1.04–2.19**

6 DISCUSSION

6.1 Risk factor profiles

Patients treated for an AAA and PAD had a higher median age compared to those undergoing cardiac surgery, including the subgroup of only CAD patients with median ages of 73 (44–92) and 74 (42–89) years versus 68 (18–89) and 69 (42–89) years, respectively (Table 3). The finding is in line with the known risk profiles of patients suffering from these diseases (Criqui & Aboyans 2015; Jang et al. 2013; Savji et al. 2013; Tunstall-Pedoe et al. 2017) (Table 1). The proportion of men in the cardiac surgical (72%) and AAA (88%) cohorts, in turn, was greater compared to the PAD cohort, where the male-to-female ratio was nearly 50:50 (Table 3). A similar finding has been noted in previous research, where male sex unequivocally predisposes to CAD and AAAs but the association with PAD is not as clearly established and, in fact, in patients aged 85 or over, the prevalence in females exceeds the prevalence in males (Alzamora et al. 2010; Criqui & Aboyans 2015; Diehm et al. 2004; Landenhed et al. 2015; Lederle et al. 2000a; Otaki et al. 2015; Selvin & Erlinger 2004; Xu et al. 2017). When considering only CAD patients, it is also possible that non-surgical revascularisation methods were more often chosen for females than for males. This, in turn, could be due to a smaller risk of stroke after PCI compared to CABG especially in women, despite the fact that the concurrent risk of reinterventions is also higher (D'Ascenzo et al. 2014). Furthermore, the proportion of smokers in the present studies was greater in AAA (25%) and PAD patients (32%) compared to all cardiac surgical patients (14%) and CAD patients (18 %), which concurs with preceding evidence (Berger et al. 2013; Criqui & Aboyans 2015; Lederle et al., 2000a; Price et al. 1999; Tunstall-Pedoe et al. 2017) (Tables 1 & 3). Accordingly, the number of individuals with COPD was the highest in the groups with the highest prevalence of smoking. The percentage of diabetics in the AAA cohort (17%) was lower than among CAD (38%) and PAD (40%) patients. This is supported by earlier studies, which have found diabetes to be a significant risk factor for both CAD and PAD. However, when AAA is concerned, diabetes may even serve as a protective factor. (Berger et al. 2013; Jahangir et al. 2015; Jousilahti et al. 1999; Lederle et al. 2000a; Tunstall-Pedoe et al. 2017.) Finally, the rates of arterial hypertension were

similar in all patient groups (Table 3). This is logical, as the impact of hypertension as a risk factor is comparable in CAD, PAD and AAAs (Berger et al. 2013; Jousilahti et al. 1999; Lederle et al. 2000a; Tunstall-Pedoe et al. 2017). Taken together, it can be stated that the risk factor profiles of the cardiovascular surgical patients investigated in the present thesis were comparable those reported in previous literature.

6.2 Lipid profiles

6.2.1 AAA patients

The lipid profiles of AAA patients have been previously presented by Wanhainen et al. (2005) as well as Kanaoka et al. (2012). The median lipid values of AAA patients in study IV differ, to some extent, from the values obtained in these previous studies. When compared to the results by Wanhainen et al. (2005), the average TC (4.5 vs 7.3 mmol/L), LDL-C (2.64 vs 4.2 mmol/L) and TG (1.23 vs 2.3 mmol/L) levels were significantly lower in the present study, whereas the HDL-C levels were similar (1.16 vs 1.2 mmol/L). These differences may be due to different rates of statin use. In the study by Wanhainen et al. (2005), it was estimated that only 2.8% of the population were on statin medication. Study IV lacked specific data on lipid-lowering medication at the individual level. However, 34% (n=167) of the patients had a previous diagnosis of dyslipidaemia and, in practice, when the Vascuset database was constructed, patients were mostly labelled as having dyslipidaemia when they had been prescribed medical therapy, most typically statins. It is therefore plausible to assume that the proportion of patients receiving statin therapy in the present study was larger. Additionally, the data collection for the study by Wanhainen et al. (2005) was carried out earlier than for the present study and it is likely that, over the years, the conservative treatment (i.e. dietary interventions, weight control, exercise therapy and lifestyle guidance) of cardiovascular risk factors, including lipids, has significantly improved. A tendency towards lower median serum cholesterol levels over time has been noticed at least in CAD patients (Kannel 1995). Another potential explanation for the differences in lipid values between these studies may be associated with the fact that, in study IV, only patients with available lipid values were included, since lipid measurements were not routinely carried out in the study centre, and these individuals may have been under more careful treatment and surveillance. However,

the only significant difference between the included and excluded patients was that the excluded patients were somewhat older and had a lower prevalence of diabetes and a higher prevalence of CAD.

Kanaoka et al. (2012) reported preoperative lipid values as well as postoperative lipid values at 3 months or after the treatment of an AAA, with the latter being significantly more favourable. The pre- and postoperative values for LDL-C, HDL-C and TG were 3.23 and 2.53 mmol/L, 1.03 and 1.27 mmol/L, and 1.59 and 1.13 mmol/L, respectively. Statin therapy had been prescribed for 38.8% of the study patients, but there was no data on the time of initiation of the treatment, which, in some cases, was only after the operation. Furthermore, the study population was limited to elective patients aged 70 years or younger (n=116). The time frame in which the preoperative lipid values were obtained was not reported. The patients were collected within quite a long time frame, from 1988 to 2011. The LDL-C, HDL-C and TG values in the current study IV were closer to the postoperative than the preoperative values reported by Kanaoka et al. (2012). These differences are most likely also due to similar reasons to the ones mentioned earlier.

Overall, the median serum TC, HDL-C and TG levels in AAA patients in the present study were acceptable, but the LDL-C levels were higher than recommended for patients with PAD (Norgren et al. 2007; Aboyans et al. 2018). For AAA patients, however, no recommendations currently exist for optimal lipid levels (Catapano et al. 2016; Reiner et al. 2011). In study IV, women had higher serum HDL-C and apoA1 levels, yet their TG levels were also higher. Younger patients treated for AAAs tended to have a more unfavourable lipid profile compared to older patients. This could suggest a possible role of serum lipids in the earlier development of an AAA, which would be in line with findings that statin treatment may reduce the growth rate of AAAs smaller than 5.5 cm in diameter, even though evidence on growth reduction is still regarded as inconclusive (Takagi et al. 2012; Wanhainen et al. 2019). Smokers and patients undergoing urgent or emergency surgery also displayed higher TC and LDL-C levels. A history of dyslipidaemia, diabetes, CAD and a previous stroke or TIA was associated with lower TC, LDL-C and EFW-LDL-C levels, most likely owing to concomitant statin therapy.

The apolipoprotein levels in patients treated for AAAs have been previously described by Landenhed et al. (2015). The mean values for apoA1 and apoB were 1.57 g/L (SD 0.282 g/L) and 1.07 g/L (SD 0.261 g/L), respectively. In comparison, in the present study IV, both median EFW-apoA1 (1.36 g/L) and apoB (0.94) levels were somewhat lower.

6.2.2 CAD and PAD patients

Study V included patients undergoing invasive treatment for PAD as well as patients treated with CABG for CAD, essentially representing advanced stages of atherosclerotic disease in both groups. The proportion of patients treated with urgent or emergency surgery in the CAD group is rather high, but a similar change in the ratio of elective and urgent/emergency patients has also been previously reported (Thorsteinsson et al. 2016). This potentially reflects an ongoing trend towards treating elective CAD patients percutaneously. The PAD patients included in study V were comparable to what has been described in earlier studies with respect to their disease presentation and severity (Soden et al. 2017). Statin medication or dyslipidaemia translating into statin use was more prevalent in CAD patients compared to PAD patients. This finding is not optimal, as all CAD and PAD patients, particularly symptomatic ones, should be on statin therapy, but it does reflect the known rates of statin use (Chen et al. 2015; DeCarlo et al. 2017; Kulik et al. 2011; O'Donnell et al. 2017; Stavroulakis et al. 2017). Furthermore, despite differences between the CAD and PAD cohorts in study V with regard to median age, the proportion of males, smoking, the rate of pulmonary disease and dyslipidaemia/statin use, these cohorts quite accurately represent the corresponding real-life patient cohorts and clinical practice, as mentioned earlier.

Overall, the median LDL-C and apoB values of PAD patients undergoing invasive treatment in study V were somewhat higher than the optimal target levels. As PAD is regarded as a high-risk cardiovascular condition, LDL-C levels below 1.8 mmol/L (or a ≥ 50% reduction when baseline values are 1.8–3.5 mmol/L) and/or apoB levels below 0.8 g/L are recommended (Catapano et al. 2016; Aboyans et al. 2018). A similar finding was noticed among CAD patients, who also share the same LDL-C target level (Catapano et al. 2016). When compared to a cohort of CAD patients from the 1990s, the lipid profiles in the present study were markedly more favourable, even though the present study only included patients with advanced disease undergoing CABG: TC 5.79 mmol/L versus 4.2 mmol/L, LDL-C 4.03 mmol/L versus 2.31 mmol/L, HDL-C 0.93 mmol/L versus 1.18 mmol/L, TG 2.13 mmol/L versus 1.27 mmol/L, apoB 1.31 versus 0.89 g/L, and apoA1 1.14 g/L versus 1.37 g/L, respectively (Kannel 1995).

Study V was able to discover some disease-specific differences in lipid values between CAD and PAD patients. Firstly, HDL-C values were higher in PAD despite a lower estimated use of statins, which usually increase HDL-C and apoA1 levels, and the PAD patients' median age was higher, which has been found to be associated

with lower serum HDL-C concentrations (Ferrara et al. 1997; McTaggart & Jones 2008). These differences may at least partly be due to a higher proportion of females in the PAD cohort and did not persist in multivariable analysis. Previously, Fowkes et al. (1992) reported an inverse relationship with PAD and HDL-C levels, whereas Jang et al. (2013) found that CAD patients more often had low HDL-C levels compared to PAD patients in a Korean patient cohort. Secondly, EFW-ApoA1, EFW-ApoB/ApoA1 ratio and EFW-HDL2 differed between the patient cohorts and were more favourable in the PAD group in study V. However, in the multivariable analysis, only EFW-ApoA1 was independently disease-specific, with higher apoA1 levels associating with CAD rather than PAD. An earlier study by Tunstall-Pedoe et al. (2017) found serum TC to be more predictive of CAD than PAD, yet no other significant lipid differences were discovered. ApoA1 was, however, ascertained to be protective against both CAD and PAD (Tunstall-Pedoe et al. 2017). On the basis of the present study, it would be tempting to speculate that apoA1 may be associated with the development and phenotype of atherosclerosis and could be one factor determining whether patients present with CAD or PAD, but the combined evidence thus far is inconclusive.

6.3 Survival in AAA patients

In study IV, aneurysm rupture, advanced age, smoking, pulmonary disease and diabetes were independently associated with increased mortality. Earlier studies have reported comparable findings (Beck et al. 2009; Grootenboer et al. 2010; Mureebe et al. 2010; Schlösser et al. 2010; Thompson et al. 2012). With regard to lipid values, traditional LDL-C (HR 1.79 for a 0.97mmol/L increase, 95% CI 1.18–2.73) and serum TG (HR 1.84 for a 0.73 mmol/L increase, 95% CI 1.20–2.81) were significant predisposing factors for mortality in patients treated for AAAs. LDL-C is a previously well-recognised risk factor for cardiovascular mortality, and it has also been found that a lower LDL-C/HDL-C ratio is associated with reduced mortality in patients treated electively for an AAA (Kanaoka et al. 2012; Mihaylova et al. 2012; Morris et al. 2014). Serum TG in AAA patients, on the other hand, has not been as thoroughly investigated, but a study by Forsdahl et al. (2010) did discover a univariable association with all-cause mortality and TG with median values of 1.67 mmol/L and 1.81 mmol/L in survivors and non-survivors, respectively ($p<0.001$). Additionally, serum TG levels have been ascertained to be significantly linked to all-cause as well as cardiovascular mortality in the general population (Liu et al. 2013).

Factors associated with improved survival in the present study were a history of dyslipidaemia and EFW-IDL-C. The positive effect of previous dyslipidaemia is most likely due to statin use in these patients. As previously mentioned, it is likely that most patients with a diagnosis of dyslipidaemia were on statin therapy. Overall, statin treatment improves postoperative survival and is recommended for all AAA patients (de Bruin et al. 2014; Moll et al. 2011; Wanhainen et al. 2019). Another possible explanation could lie in a more careful follow-up and treatment of comorbidities in patients with dyslipidaemia. The lower mortality associated with EFW-IDL-C is a novel and interesting finding. The RESOLVE trial (Dutheil et al. 2014) found lower baseline concentrations of IDL-C in patients with metabolic syndrome compared to healthy controls, although a direct association between atherosclerosis and IDL-C could not be verified. In contrast, Niemi et al. (2009) discovered EFW-IDL-C to be significantly associated with increased mortality in patients with type I diabetes. The proportion of diabetics in study IV was 17% (n=85), and type I and II diabetics were not analysed separately. However, there were no significant differences in EFW-IDL-C values between patients with and without diabetes. Why EFW-LDL-C did not and traditional LDL-C did reach statistical significance in multivariable analysis remains unclear, but the difference could partly be associated with the fact that LDL-C derived with the traditional Friedewald formula does not represent a pure fraction. Furthermore, the mechanism behind the protective effect of EFW-IDL-C warrants further studies, as it is a part of the same endogenous cholesterol pathway as LDL-C and yet appears to have an opposite effect. Finally, mortality at all time points (6 months, 3 years, 5 years and 10 years) increased substantially with an increasing amount of risk factors, suggesting a cumulative effect.

6.4 Postoperative atrial fibrillation

The overall incidence of POAF after cardiac surgery was 51%, with a higher rate in valve procedures. Compared to previous studies, the incidence rates were 10%–20% higher (Almassi et al. 1997; Filardo et al. 2009; LaPar et al. 2014; Rostagno et al. 2014; Rostagno et al. 2010; Saxena et al., 2012, 2013). There are several possible explanations for this finding. Firstly, the median age of cardiac surgical patients in the present study was 68, which is higher than in most previous studies, and age has been ascertained to be one of one the most significant risk factors for POAF (Amar et al. 2004; Aranki et al. 1996; Leitch et al. 1990; Tran et al. 2015; Zacharias et al.

2005). Secondly, the rate of another central risk factor, a preoperative history of atrial fibrillation, was also higher than rates reported earlier (Mathew et al. 2004; Rostagno et al. 2010; Tran et al. 2015). In study I, preoperative paroxysmal fibrillation was present in 12% and chronic fibrillation in 12% of the patients, whereas the corresponding rates have previously been discovered to be 3% and 9%, respectively (Mathew et al. 2004). Furthermore, the proportion of individuals having any history of atrial fibrillation has been estimated to be 5%–9% (Rostagno et al. 2010; Tran et al. 2015). The increased rate of preoperative atrial fibrillation, in turn, may be due to a true rise in incidence (Martinez et al. 2015). Thirdly, the incidence of POAF is naturally affected by the inclusion criteria of the cohort it is studied in. In some of the earlier studies (Filardo et al. 2009; LaPar et al. 2014; Saxena et al. 2012, 2013), patients who died perioperatively have been included in the analyses, which can have caused bias towards lower incidence rates. It would seem justified to investigate the occurrence of POAF in the population truly at risk of developing the complication – that is, in those surviving a minimum of five days postoperatively, as POAF typically presents within this time frame. There are, however, also studies that have excluded all non-survivors from the analyses but still displayed lower incidences of POAF compared to the present study (Almassi et al. 1997; Rostagno et al. 2010). Fourthly, the high rate of valvular and combined procedures in the present cohort may also have contributed to the POAF incidence, as this tends to be higher after valve surgery than CABG alone (Almassi et al. 1997; LaPar et al. 2014; Mathew et al. 2004). Additionally, only 53% of the CABG procedures were carried out electively, and POAF was more common in urgent and emergency procedures. Finally, the standard treatment protocol in the study centre included continuous postoperative ECG monitoring throughout the hospitalisation period, which can have led to a higher rate of POAF detection (Kaireviciute et al. 2009).

The majority of patients developing POAF had frequent recurrences or a prolonged duration (over 48 hours) of the arrhythmia. The cut-off point for prolonged POAF was set at 48 hours, since treatment with anticoagulants has been recommended for POAF persisting longer than 2 days (Camm et al. 2010). The data set in study I lacked information on the treatment given for and the proportion of patients with persistent atrial fibrillation at hospital discharge. Previous studies have reported an 80% rate of conversion to sinus rhythm within 24 hours as well as a recurrence rate of 24% (Mathew et al. 2004; Soucier et al. 2001). Left-sided intra-atrial cryoablation was conducted intraoperatively for 8 patients undergoing mitral surgery. The rate of POAF did not differ in these patients compared to the rest of the cohort and did not affect the results.

Older age, previous atrial fibrillation, left atrium size and valve or aortic surgery as significant independent risk factors for POAF were in line with earlier literature, whereas the role of emergency surgery has not been as clearly established (Almassi et al. 1997; Amar et al. 2004; LaPar et al. 2014; Mathew et al. 2004; Rostagno et al. 2010; Rostagno et al., 2014; Tran et al. 2015; Zacharias et al. 2005). COPD, on the other hand, has been confirmed as a significant risk factor for POAF in several studies, yet the present study failed to show an association between COPD and POAF (Almassi et al. 1997; Mathew et al. 2004; Zacharias et al. 2005). Moreover, active smoking was more common in patients without POAF compared to those with the arrhythmia (18% versus 11%, $p<0.001$) in univariable analysis, but although there was a tendency towards smoking being protective, multivariable analysis could not demonstrate a statistical difference. This phenomenon noticed in the present study is contradictory to what has been previously reported in the general population but may be due to the fact that smokers were significantly younger compared to non-smokers (Larsson et al. 2016). There was also no association between statin or beta blocker therapy and POAF. The majority of study patients were on these medications preoperatively, and it would be plausible to assume that no differences were observed because most of the patients who would benefit from statins or beta blockers were already receiving them. The postoperative delay in continuing the medications after surgery was not recorded. Earlier continuation could potentially have reduced the incidence of POAF.

Regardless of the high incidence of POAF in the present study, the rate of stroke was not increased. The rates of postoperative infections, in turn, were higher in patients with POAF, but the onset of the arrhythmia in relation to the timing of the infection was not recorded. Some cases of POAF may therefore have been complication-induced, whereas others can have been unrelated to the infection or potentially shared a mutual risk factor.

6.5 Late tamponade and pretamponade requiring invasive treatment

Study II ascertained a significantly higher rate of late PPEs requiring invasive treatment than in previous literature: 6.2% versus 1%–2.6%, respectively (Aksöyek et al. 2005; Bucekova et al. 2012; Meurin et al. 2004; Pepi et al. 1994; Russo et al. 1993). One potential reason behind this could be that the proportion of valve operations compared to CABG procedures in cardiac surgery has increased and the

rate of late tamponade is usually higher after valve surgery (Kuvin et al. 2002; Meurin et al. 2004; Pepi et al. 1994). Another explanation could lie in the duration of chest drainage postoperatively. During the course of the present study, tubes were usually removed on the morning of the first postoperative day. The rationale behind this was the hope to reduce postoperative infectious complications. However, this protocol can have increased the rate of late PPEs requiring invasive treatment, which is a recognised risk of early drain removal (Andreasen et al. 2016). Concurrently with this, the amount of chest tube drainage in the present study was lower in late tamponade and pretamponade patients compared to others. Furthermore, the increased rate of late tamponade and pretamponade could be associated with an increased incidence of POAF (discovered in study I), which is quite consistently treated with anticoagulant therapy. Preoperative anticoagulant usage, in turn, has been found to be linked to increased rates of PPEs, and it is possible that postoperative administration of these medications could have the same effect (Kuvin et al. 2002; Pepi et al. 1994). However, no association between a preoperative history of atrial fibrillation and late tamponade or pretamponade could be verified in study II. A fourth possible cause for the high tamponade and pretamponade incidence is that echocardiography surveillance in cardiac surgical patients is likely to have improved over the years, enabling the earlier and more accurate detection of late PPEs.

According to the univariable analyses, younger, generally healthier patients with a lower rate of CAD and higher preoperative haemoglobin levels were at a greater risk of developing late PPEs requiring invasive treatment. The lower median EuroSCORE-II ratings, lower prevalence of CAD, better left ventricular ejection fraction as well as higher preoperative haemoglobin and lower leukocyte levels could be at least partly attributed to age. Patients with late tamponade or pretamponade also less often underwent urgent or emergency procedures compared to patients free from the complication. This might be explained by the fact that late tamponade and pretamponade were more common in valve surgery patients, whereas urgent or emergency treatment was more common in CABG cases. The effect of age, in turn, may be mediated through variations in the inflammatory processes initiated by the operation. However, in CABG patients, no statistical differences have been found in cytokine levels according to age (Roth-Isigkeit et al. 1998). There was no statistical difference in the incidence of late PPEs requiring invasive treatment between females and males in study II. Previously, Kuvin et al. (2002) have ascertained female sex to be a risk factor for late tamponade. With the proportion of males in the

present study being 72%, it is possible that the study was underpowered to detect possible sex-related differences.

In terms of the perioperative features, tamponade and pretamponade cases had longer median aortic cross-clamping and perfusion times, which may have affected the extent of the systemic inflammatory response. These patients additionally received larger amounts of autologous erythrocytes via the cell-saving suction system compared to others. This could be related to a longer duration of the operations, as suggested by the cross-clamping and perfusion times, operation type and/or increased bleeding and blood loss. The increased cell saver use is, however, somewhat contradictory, as it has been found to be associated with lower systemic levels of proinflammatory markers compared to direct re-transfusion from the suction and cardiopulmonary bypass circuit (Damgaard et al. 2010; Svenmarker & Engström 2003). Moreover, the postoperative creatine kinase MB isoenzyme reaction was more pronounced in patients with late PPEs requiring invasive treatment, reflecting either a greater extent of myocardial injury or the technique of valve operations, such as mitral valve repair where cardiac chambers are opened. The maximum postoperative leukocyte levels were also higher in late tamponade and pretamponade patients. This could be a marker of a more aggressive inflammatory reaction.

The independent risk factors of late PPEs requiring invasive treatment in multivariable analysis were single-valve surgery and a higher preoperative haemoglobin level. The effect of valve surgery concurs with findings in earlier studies, and it is often considered to be associated with anticoagulant therapy (Kuvin et al. 2002; Meurin et al. 2004; Pepi et al. 1994). Multiple-valve procedures did not reach independent statistical significance, potentially due to the small amount of patients in this group. Another possible explanation for the higher incidence of late tamponade and pretamponade in valve surgery compared to CABG may lie in the intended or unintended opening of the left pleura when using the left internal mammary artery as a bypass. In these cases, pericardial fluid is also drained through the pleural drains. In fact, perioperative posterior pericardiotomy has been effectively used to prevent late tamponades (Ali-Hassan-Sayegh et al. 2015; Farsak et al. 2002). With regard to the higher haemoglobin level as a risk factor, the reasons behind this phenomenon remain unclear and merit further research. Age between 60 and 69 years compared to younger patients, in turn, was an independent protective factor. Similarly to preoperative haemoglobin, this is a novel finding, and it might be associated with the immune response.

6.6 Postoperative infections

The overall rate of postoperative infections (9.8%) as well as infection subtypes including deep SSIs (2.05%) was in line with previous evidence (Michalopoulos et al. 2006; Mocanu et al. 2015; O'Keefe et al. 2017). As many as 13% of the patients suffering from infectious complications developed symptoms only after the primary hospitalisation period. The antibiotic prophylaxis protocol applied during the study period entailed a single dose of Cefuroxime in a majority of the patients, which can be regarded as conservative compared to many cardiac surgery programmes. Nevertheless, it was not associated with an increased incidence of infections. Overall, the prophylactic antibiotic practices have varied a great deal and, currently, the WHO advises against continuing prophylactic antibiotics, particularly beyond the first 48 postoperative hours (Allegranzi, Zayed, et al. 2016; Edwards et al. 2006; Gelijns et al. 2014; Lador et al. 2012; Nooyen et al. 1994). Study III found postoperative infections, and major SSIs in particular, to be associated with increased mortality, which concurs with previous evidence (Furnary et al. 1999; Sears et al. 2016).

The preoperative risk factors of postoperative infections in the present study were older age, lower left ventricular ejection fraction, higher BMI and urgent or emergency surgery. Additionally, patients needing ventilator support for a longer time postoperatively had an increased amount of postoperative infections. Earlier studies have found female sex, diabetes, immunosuppression, high BMI, bilateral mammary grafts, poor cardiac reserve, urgent or emergency surgery, the need for blood transfusion of more than five units perioperatively, early development of acute renal failure, and respiratory failure to be independently associated with postoperative infections in cardiac surgery. Older age and longer operation times have also shown an association with infections, albeit mostly not an independent one. (Balachandran et al. 2016; Fu et al. 2016; Michalopoulos et al. 2006; Orita et al. 1992; Swenne et al. 2004). Overall, it can be stated that the risk factors recognised in the present study were well in agreement with the results of earlier studies. However, diabetes was not an independent predisposing factor in the present study. This may be due to the fact that most diabetics in the study cohort were in satisfactory glucose control before the operation.

The median average glucose levels during the first postoperative day in the whole cohort and in patients with infectious complications were 6.1 mmol/L and 6.3 mmol/L, respectively. Repeated hyperglycaemia and a higher average blood glucose level were independently associated with an increased incidence of postoperative infections, stroke and mortality. Single hyperglycaemic episodes, on the other hand,

were not linked to adverse events. In reference to previous literature, Furnary et al. (1999) reported a 3 mmol/L increase in blood glucose to be an independent risk factor of deep SSIs and mortality. Moreover, Omar et al. (2015) found that, in cardiac surgery patients whose postoperative blood glucose levels remained within the target range over 80% of the time regardless of previous diabetes, SSIs were significantly less common. Despite abundant evidence supporting the benefit of strict glycaemic control in cardiac surgery patients, the issue of whether it is more useful in non-diabetics or diabetics remains controversial, and it has even been discouraged in a general surgical cohort of diabetic patients (Buchleitner et al. 2012; Lazar et al. 2004; Ng et al. 2015; Umpierrez et al. 2015). It is still unclear whether hyperglycaemia directly predisposes to infections or whether it rather acts as a marker of other comorbidities or a worse clinical condition potentially subjecting to these complications. Furthermore, there is an ongoing debate regarding the optimal glucose levels for cardiac surgical patients. Some consider possible hypoglycaemia to be a significant risk associated with strict glycaemic control. Such evidence has been found in a cohort of general ICU patients in which strict glycaemic control was associated with hypoglycaemia and increased mortality, although opposite results have also been reported (Finfer et al. 2012). The evidence from mixed ICU cohorts are, however, not generalizable to a cohort consisting solely of cardiac surgery patients. In study III, hypoglycaemia was found in 7.5% of the patients, which is a smaller proportion than in previously reported cohorts (Desai et al. 2012; Lazar et al. 2011). Moreover, hypoglycaemia was not found to be associated with any adverse events. The association of repeated episodes of hyperglycaemia with increased postoperative mortality and stroke incidence in the present study possibly reflects greater overall morbidity in patients with a tendency towards hyperglycaemia. Previously, Doenst et al. (2005) have reported similar findings with high glucose levels independently predicting mortality in both diabetic and non-diabetic patients as well as being associated with a composite of adverse events including stroke.

6.7 Future prospects

The findings presented in the present thesis brought up several significant observations. The incidence of POAF was 10%–20% higher than previously reported, with the independent risk factors being operation type, age, previous atrial fibrillation, left atrium size and emergency surgery. Unfortunately, none of these are modifiable, which raises the question of whether the incidence will only continue to

rise as patients undergoing cardiac surgery are becoming older and suffer from a greater variety of comorbidities than before. Research for preventing postoperative atrial fibrillation may thus be even more important in the future.

The significant rate of late postoperative tamponade and pretamponade requiring invasive treatment in study II was a cause for concern. This was immediately acted upon in the study centre in that chest tube drainage times were lengthened and a follow-up study investigating the effects of this new protocol was commenced. It is also worthwhile to consider if perioperative posterior pericardiotomy should be applied more often, at least in high-risk patients. Repeated hyperglycaemia was significantly associated with an increased incidence of postoperative infections and was also relatively frequent. As contemporary methods aiming at blood glucose control appear suboptimal, improved tools for surveillance and treatment might improve patient outcomes.

The association of EFW-IDL-C with decreased mortality in AAA patients is somewhat contradictory. The finding requires verification and further research into the potential mechanism behind the phenomenon. Overall, AAA patients could benefit from the determination of lipid profiles, also including apolipoproteins and lipoprotein subfractions, in the prediction of survival. These can be easily estimated without added cost by applying the Extended Friedewald Formula neural network model. Furthermore, traditional LDL-C still appears to be a significant risk factor for mortality in patients treated for AAAs. As a previous diagnosis of dyslipidaemia in practice signified statin therapy in the study cohort and it was present in only 34% (n=167) of the study patients, it could be stated that perioperative care was not optimal. A large proportion of current research in AAA patients focuses on the technicalities of treatment and the advantages and disadvantages of treatment modalities. However, one method by which the postoperative prognosis in AAA patients could be easily improved would be to pay more attention to risk factor management, particularly with a more prudent initiation of statin medication.

Study V found a difference in apoA1 levels between CAD and PAD patients. It would be interesting to prospectively study the more novel lipid values including apolipoproteins, apoA1 in particular, in previously healthy cohorts and the risk of developing either CAD, PAD or both over time. Additionally, investigating the effect of these lipid parameters on postoperative outcomes in CAD and PAD cohorts would provide important information. The Extended Friedewald method could also be applied to this type of study in the future. It should also be noted that, regardless of the gradually improving serum lipid profiles over the years, there is still

a need to upgrade the treatment of risk factors in cardiac surgery as well as PAD patients undergoing interventions.

7 STUDY LIMITATIONS

The most significant limitations of the present thesis are related to the retrospective nature of the individual studies it is based on. Despite the fact that information was mostly collected from prospective databases, there were still shortcomings in data, as is often the case in retrospective studies. The retrospective setting did, however, also offer some advantages, such as an acceptable amount of study patients and long-term follow-up data. Additionally, observational studies may depict the true clinical status quo more realistically than prospective controlled trials in which the often strict inclusion and exclusion criteria can rule out a significant segment of the everyday patient material.

The individual studies were conducted in a single-centre fashion, and it is therefore important to bear in mind that the results may not be generalisable to other cardiothoracic or vascular surgical units. With regards to PPEs, it would have been interesting to study and report on patients with conservatively managed late manifestations of the complication as well. Moreover, obtaining pericardial fluid and/or tissue samples for analysis could also have offered further information on the mechanisms of late tamponade and pretamponade. As some of the studied complications and outcomes were relatively infrequent, the statistical power for subgroup analyses was limited. Additionally, in studies II and III, some of the investigated complications manifested after the primary hospitalisation period and a small portion of these may have been treated at other hospitals, though referral to the study centre was encouraged.

The main disadvantage in study III was the heterogeneity of the study population, limiting the statistical power, as well as the descriptive nature of the study. Furthermore, a control group with a different glucose treatment strategy for hyperglycaemia would have been valuable for analysing the effects of strict glycaemic control. The study cohort was, nevertheless, relatively large and representative of all cardiac surgical patients, and the incidence of all postoperative infections, not solely SSIs, was determined.

Missing lipid values and the varying time interval between lipid measurements and the intervention for an AAA were the most significant limitations of study IV. Nevertheless, it is still plausible to propose that the study provided a good overall

estimate of the lipid profiles. Utilising lipid measurements further away from the index procedure may also have avoided potential systematic error, since it is known that physiologic stress temporarily alters lipid values. Another weakness of study IV was that information on the type and dosage of lipid-lowering medications and treatment compliance was not available. Despite this, it appeared that most patients with previously diagnosed dyslipidaemia were on statin or other lipid-lowering medications, as they had a significantly improved prognosis compared to patients without the diagnosis.

In study V, possible concomitant CAD or PAD were not taken into account. However, lipid measurements were obtained within 2 years prior to the index procedure that was carried out due to the disease relevant/symptomatic at the time. In addition, the baseline characteristics of PAD and CAD patients differed from each other, but the potential impact of these differences was taken into account in the multivariable analyses. Obtaining lipid measurements from a matched cohort without CAD or PAD for comparison would also have provided additional information. On the whole, the results presented in the thesis are interesting and add to previous information, as long as they are interpreted in the appropriate context.

8 CONCLUSIONS

The findings of the present thesis support the following conclusions:

1. The incidence of POAF is 51%, which is as much as 10%–20% higher than previously reported, and it is prolonged or recurrent in most patients. The most significant predisposing factors are the type of surgery (particularly valvular procedures), advanced age and previous atrial fibrillation.

2. Late PPEs that require invasive treatment are present in 6.2% of cardiac surgical patients and, overall, they affect younger and healthier patients and those undergoing valve surgery.

3. Infectious complications develop in roughly 10% of cardiac surgery patients. Repeated hyperglycaemic episodes are associated with postoperative infections as well as stroke and mortality. A protocol of strict glycaemic control is not associated with increased rates of hypoglycaemia-associated adverse events.

4. Extended-Friedewald-derived lipid parameters complement risk prediction in patients treated for an AAA. An unfavourable lipid profile is associated with the treatment of an AAA earlier in life and with inferior long-term survival.

5. CAD patients treated with CABG and PAD patients undergoing invasive procedures appear to differ from each other in their lipid profiles, with higher serum apoA1 levels obtained from CAD patients.

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ORIGINAL PUBLICATIONS

PUBLICATION I

Increasing Occurrence of Postoperative Atrial Fibrillation in Contemporary Cardiac Surgery

Khan, J., Khan, N., Loisa, E., Sutinen, J., Laurikka, J.

Journal of Cardiothoracic and Vascular Anesthesia, 30 (5): 1302-1307
doi: 10.1053/j.jvca.2016.02.013.

Increasing Occurrence of Postoperative Atrial Fibrillation in Contemporary Cardiac Surgery

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Objective: **Patients referred for cardiac surgery are increasingly older, with a higher prevalence of significant comorbidities and undergoing more extensive surgery. The aim of the study was to ascertain the incidence and presentation of postoperative atrial fibrillation in contemporary patients.**

Design: **A prospective single-center study.**

Setting: **A tertiary academic center.**

Participants: **Between January 2013 and December 2014, 1,356 consecutive patients (72% male, median age 68), including urgent and emergency cases, were analyzed. Preoperative paroxysmal atrial fibrillation was present in 163 (12%) and chronic in 156 (12%) patients.**

Interventions: **No interventions.**

Measurements and Main Results: **Of the 1,164 patients without chronic atrial fibrillation and surviving at least 5 days, 599 (51%) developed postoperative atrial fibrillation, 43% after bypass, 55% after single valve, 74% after multiple valve, 66% after combined bypass and valve, and 54% after aortic procedures, $p < 0.001$, respectively. In 29%, the duration of postoperative atrial fibrillation was less than 48 hours and did not recur, whereas in 71% the arrhythmia persisted for at least 48 hours or recurred during hospitalization. Patients with postoperative atrial fibrillation were significantly older, had a higher prevalence of previous atrial fibrillation and hypertension, larger left atrium, and required longer hospitalization with increased rates of reoperations and infectious complications.**

Conclusions: **The authors report high, 10% to 20% greater than previously described, occurrence of postoperative atrial fibrillation in contemporary patients undergoing cardiac surgery. Most patients with postoperative atrial fibrillation experienced prolonged duration or recurrence of the arrhythmia. The type of surgery, advanced age, and previous atrial fibrillation were the most important risk factors.**

KEY WORDS: cardiac surgery, coronary artery bypass grafting, valve surgery, atrial fibrillation, complication, incidence

THE MOST COMMON complication following cardiac surgery is atrial fibrillation. The incidence of new-onset atrial fibrillation after cardiac surgery is reported to be 17% to 29% after isolated coronary artery bypass grafting, 20% to 49% after single-valve operations, and 31% to 60% after combined coronary artery bypass and valve procedures.[1-6] Besides the type of surgery, important risk factors for postoperative atrial fibrillation include advanced age, prior atrial fibrillation, male gender, obesity, left atrial dilatation and chronic obstructive pulmonary disease, while statin and beta-blocker therapy prior to cardiac surgery reduce the risk for postoperative atrial fibrillation.[7-13] The development of postoperative atrial fibrillation may be symptomatic and/or induce hemodynamic instability, and often requires therapeutic interventions, such as pharmacologic heart rate control and medical or electrical cardioversion, and has been associated with longer hospitalization and increased risk for stroke and mortality.[14-17]

Most studies reported the incidence of postoperative atrial fibrillation according to registry data or in selected patient cohorts, eg, after coronary artery bypass grafting, mostly excluding patients with a history of previous atrial arrhythmias, while some authors excluded only patients with chronic atrial fibrillation. Also, previous studies infrequently reported the duration or recurrence of postoperative atrial fibrillation beyond its first onset. Furthermore, patients referred for cardiac surgery at present are increasingly older, with various comorbidities and complex cardiac conditions undergoing more extensive surgery, which might increase the occurrence of postoperative complications such as atrial fibrillation.

The aim of the present study was to ascertain the incidence and presentation of postoperative atrial fibrillation in patients undergoing cardiac surgery at a single tertiary referral center. Furthermore, the authors sought to describe the prevalence of previous atrial arrhythmias and to identify risk factors for developing postoperative atrial fibrillation and associations with other complications in this patient cohort.

METHODS

This study was an analysis of patients who underwent cardiac surgery between January 2013 and December 2014 in Heart Hospital, Tampere University Hospital, Tampere, Finland, a tertiary academic clinic. Altogether, 1,356 consecutive patients were collected prospectively in an institutional registry and re-reviewed case by case for this study. All adult cardiac surgery, including off-pump coronary bypass procedures, were included in the analysis, and the study cohort comprised elective, urgent, and emergency cases. No isolated procedures aimed at treating atrial fibrillation, such as the Cox-Maze procedure, were performed during the study period, but concomitant left-sided intra-atrial cryoablation was performed in 8 patients undergoing mitral surgery, and these patients were included in the series. In addition, 18 left atrial appendage closures or amputations were performed, 5 of which in patients who underwent simultaneous cryo-ablation. Transcatheter valve procedures and surgical operations not unambiguously cardiac in nature, such as descending aortic aneurysm reconstructions, or surgery involving only the pericardium, such as fenestrations for pericardial fluid accumulations or surgery for tumors invading the pericardium, were not included in the series. Also, 5 operations ended early for various reasons, such as unexpected porcelain aorta, were not included. When the same patient underwent surgery more than once during the study period, the succeeding operation was classified as a

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1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2016.02.013

complication-related reoperation when unplanned and performed during the same hospitalization or as a separate case and included in the series if performed during a separate hospital treatment period.

Preoperative patient demographics and medical history including previous arrhythmias, perioperative and procedural details, and the postoperative clinical course including relevant laboratory parameters were recorded. Previous atrial fibrillation was classified as either paroxysmal or chronic. Postoperatively, all patients were on continuous electrocardiographic rhythm monitoring in which heart rate and rhythm regularity were followed continuously by an automated system and by the nursing staff until referral to secondary care or discharge from the hospital. A minimum duration of 5 minutes was required for the diagnosis of atrial fibrillation and each suspected case was confirmed by a cardiologist. The incidence, delay of onset, duration, and recurrence of postoperative atrial fibrillation, as previously described, as well as other complications, the need for reoperations, and mortalities, were recorded.[18] Pre-existing β-blocker medication was continued until and including the morning of the day of surgery and usually was resumed on the second postoperative day if no hypotension, bradyarrhythmias or conduction disturbances were present. The patients received a 20-mmoL infusion of magnesium sulfate postoperatively, and no other specific measures to systematically prevent postoperative atrial fibrillation were utilized during the study period. When detected, the treatment of postoperative atrial fibrillation was subject to the discretion of the attending physician but usually consisted of administering two 2.5-mg doses of metoprolol intravenously over 30 minutes, followed by an infusion of amiodarone, first 300 mg over 1 hour and then 900 mg over the next 23 hours, after which electric cardioversion was performed if sinus rhythm was not achieved. The incidence of postoperative atrial fibrillation was analyzed in patients without chronic atrial fibrillation and surviving at least 5 days postoperatively. The occurrence and risk factors for developing postoperative atrial fibrillation and its distribution between patient subgroups were analyzed using statistical methods.

This study was performed according to the Helsinki Declaration, and Institutional Review Board approval was obtained. Statistical testing was done using SPSS 16.0 statistical software by using the chi square test and Fisher's exact test to compare proportions in categorical data and the Mann-Whitney U test and the Kruskal-Wallis H test to compare the differences in medians between groups. Multivariable analysis was performed using binary logistic regression analysis and establishing the odds ratios with 95% confidence intervals. Major comorbidities, previously established risk factors, and variables associated with postoperative atrial fibrillation in univariable analysis, except those that were suspected of being caused by or presenting after atrial fibrillation, were included in the multivariable analysis. All p values ≤ 0.05 were considered statistically significant.

RESULTS

The demographic, preoperative, and procedural characteristics of patients are presented in Table 1. The majority of operations (1,350, >99%) were performed through standard median sternotomy. Cardioprotection was established by cold blood cardioplegia. Of coronary artery bypass grafting surgeries, 44 of 535 (8%) were performed off-pump. Eleven

Table 1. Demographic, Preoperative, and Procedural Characteristics of Study Patients

	All Patients	Only CABG	Single Valve	Multiple Valve	CABG and Valve Surgery	Aortic Surgery*
Number of patients (%)	1,356 (100%)	535 (40%)	412 (30%)	73 (5%)	169 (13%)	132 (10%)
Male (%)	973 (72%)	423 (79%)	261 (63%)	47 (64%)	118 (70%)	103 (78%)
Median age (range)	68 (18-89)	68 (40-89)	68 (19-88)	71 (22-85)	74 (42-89)	64 (18-79)
Median BMI (range)	27 (10-61)	27 (17-60)	27 (10-60)	27 (14-45)	27 (17-41)	26 (19-45)
NYHA						
1-2	985 (74%)	345 (66%)	347 (85%)	54 (75%)	126 (75%)	91 (71%)
3-4	343 (26%)	175 (34%)	61 (15%)	18 (25%)	41 (25%)	37 (29%)
Median Euroscore-2 (range)	1.9 (0.5-86.8)	1.8 (0.5-52.6)	1.3 (0.5-49.8)	3.2 (0.6-50.8)	3.0 (0.6-56.4)	3.1 (0.5-86.8)
Urgency (%)						
Elective	934 (69%)	283 (53%)	361 (88%)	58 (79%)	125 (74%)	89 (67%)
Urgent	249 (18%)	158 (30%)	37 (9%)	12 (16%)	29 (17%)	9 (7%)
Emergency	173 (13%)	94 (18%)	14 (3%)	3 (4%)	15 (9%)	34 (26%)
Coronary disease (%)	845 (62%)	535 (100%)	96 (23%)	17 (23%)	166 (98%)	28 (21%)
Diabetes (%)	320 (24%)	179 (34%)	62 (15%)	13 (18%)	48 (28%)	15 (11%)
Dyslipidemia (%)	790 (58%)	412 (77%)	175 (42%)	28 (38%)	119 (70%)	47 (36%)
Hypertension (%)	881 (65%)	389 (73%)	236 (57%)	36 (49%)	122 (72%)	80 (61%)
LVEF <50% (%)	252 (19%)	121 (23%)	56 (14%)	14 (19%)	43 (25%)	16 (12%)
Chronic lung disease (%)	148 (11%)	58 (11%)	45 (11%)	5 (7%)	21 (12%)	17 (13%)
Active smoker (%)	189 (14%)	94 (18%)	36 (9%)	8 (11%)	22 (13%)	23 (17%)
Preoperative atrial fibrillation						
Paroxysmal (%)	163 (12%)	43 (8%)	61 (15%)	16 (22%)	20 (12%)	17 (13%)
Chronic (%)	156 (12%)	24 (4%)	66 (16%)	33 (45%)	18 (11%)	12 (9%)

NOTE. Largest patient subgroups are presented separately.

Abbreviation: BMI, body mass index; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

*Aortic surgery includes aortic root procedures and aortic surgery combined with CABG or valve surgery.

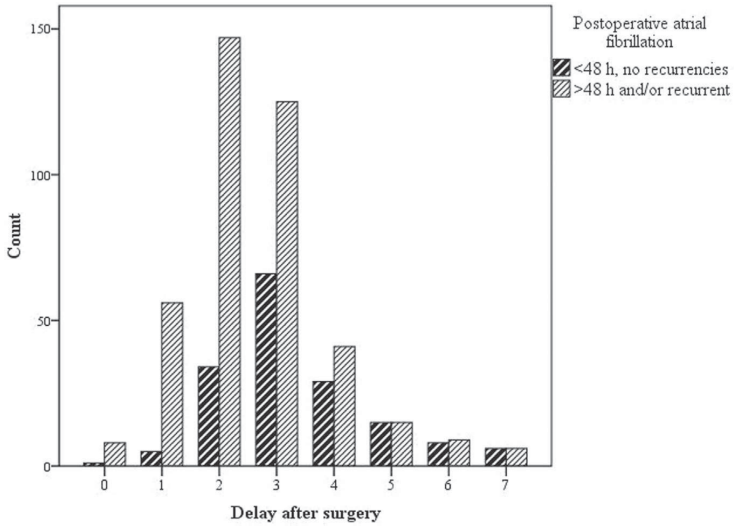

Fig 1. Delay of onset in the development of postoperative atrial fibrillation.

(1%) were redo-operations. The series included 19 (1%) operations for endocarditis and 18 (1%) for acute Stanford type-A aortic dissections. Preoperatively, 858 (63%) patients were on β-blocker therapy, and 759 (56%) patients were on statin therapy. The combined in-hospital and 30-day mortality in the series was 29 out of 934 (3.1%, 95% confidence interval [CI] 2.0-4.2%) in elective, 14 out of 249 (5.6%, 95% CI 2.7-8.5%) in urgent, and 33 out of 173 (19.1%, 95% CI 13.2-25.0%) in emergency cases, respectively, $p < 0.001$, with an overall mortality of 76 out of 1,356 (5.6%, 95% CI 4.4-6.8%). The median length of hospitalization following the primary operation in surviving patients before referral to secondary care or discharge from the hospital was 5 days (range 3-53 days) in elective, 6 days (range 1-40) in urgent, and 8 days (range 3-51 days) in emergency cases, respectively, $p < 0.001$. The surviving patient with only 1 postoperative day of hospitalization was referred for cardiac transplantation due to low-output-syndrome after bypass surgery. Reoperations for various complications, eg, postoperative bleeding or wound complications, during the same hospitalization were required in 183 (13%) patients. The rate of stroke was 2.8%; 1.9% in elective, 3.6% in urgent, and 6.4% in emergency cases, respectively, $p = 0.004$. The occurrence of infectious complications, such as mediastinitis, pulmonary, urinary, wound or cannula-site infections, was 9.8% in this series.

Altogether, 1,316 patients survived at least 5 days postoperatively, and of these, 152 had chronic atrial fibrillation. Of the remaining 1,164 patients, 599 (51%, 95% CI 49-54%) developed postoperative atrial fibrillation. In 171 (29%, 95% CI 25-32%) patients, the duration of postoperative atrial fibrillation was less than 48 hours and did not recur, while in 428 (71%, 95% CI 68-75%) patients, the arrhythmia persisted for at least 48 hours or recurred during hospitalization. The median onset of postoperative atrial fibrillation was 3 days (range 0-30 days) (Fig 1). In patients with a history of paroxysmal atrial fibrillation, 129 out of 158 (82%, 95% CI 76-88%) developed postoperative atrial fibrillation in comparison to 470 out of 1,006 (47%, 95% CI 44-50%) in other patients, $p < 0.001$. The duration of hospitalization was significantly longer in patients with postoperative atrial fibrillation than in other patients, 6 *v* 5 days, $p < 0.001$.

The results of the univariable analysis is presented in Table 2. Patients who developed postoperative atrial fibrillation were significantly older and had more hypertension and a larger left atrium than other patients. Postoperative atrial fibrillation tended to be more common in patients with New York Heart Association 3 or 4 than in patients with New York Heart Association 1 or 2 grade symptoms. The distribution of postoperative atrial fibrillation according to the type of the procedure performed is presented in Table 3. Altogether five patients without chronic atrial fibrillation who survived at least 5 days, 4 undergoing single-valve and 1 undergoing multiple-valve surgery, had simultaneous cryoablation. Of these, 3 (60%) developed postoperative atrial fibrillation, a rate similar to that of other patients undergoing valve surgery. Active smoking until surgery was associated with a lower occurrence of postoperative atrial fibrillation, 39% *v* 54% in non-smokers, $p < 0.001$; however, these patients also were younger, 59 *v* 69 years, respectively, $p < 0.001$. In contrast, gender, coronary disease, diabetes, dyslipidemia, chronic lung disease, body mass index, left ventricular ejection fraction, preoperative serum creatinine concentration, or the use of statins or β-blockers preoperatively were not associated with the development of postoperative atrial fibrillation. Also, the development of postoperative atrial fibrillation was not associated with postoperative stroke or combined in-hospital and 30-day mortality but was significantly more common in patients requiring reoperations, 94 out of 149 (63%) *v* 505 out of 1,015 (50%), $p = 0.002$, and in patients who developed

Table 2. The Association of Patient Characteristics and Postoperative Complications With Postoperative Atrial Fibrillation in Univariable Analysis

	Postoperative Atrial Fibrillation		
	Yes	No	p Value
Male sex	71%	73%	0.494
Median age (years)	71	64	<0.001
Median BMI (kg/m^2)	28	28	0.478
Previous paroxysmal atrial fibrillation	22%	5%	<0.001
Urgency			
Elective	70%	69%	0.777
Urgent	18%	20%	0.392
Emergency	12%	11%	0.524
Left atrium size (mm)	42	39	<0.001
NYHA 3 or 4	29%	24%	0.053
Median Euroscore-2	2.0%	1.5%	<0.001
Coronary disease	62%	66%	0.181
Diabetes	24%	24%	>0.999
Dyslipidemia	60%	59%	0.689
Hypertension	69%	60%	0.001
LVEF <50%	19%	16%	0.181
Chronic lung disease	10%	11%	0.444
Active smoking	11%	18%	<0.001
Preoperative β-blocker	64%	59%	0.081
Preoperative statin	57%	49%	0.527
Preoperative serum creatinine (μmol/L)	82	81	0.137
Mortality	3.0%	2.1%	0.343
Stroke	2.2%	3.4%	0.214
Median length of hospitalization (days)	6	5	<0.001
Reoperations	16%	10%	0.002
Infectious complications	12%	7%	0.008

NOTE. Patients without chronic atrial fibrillation and surviving at least 5 days postoperatively are included.

Abbreviation: BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

infectious complications, 71 out of 112 (63%) *v* 528 out of 1,052 (50%), p = 0.008. The urgency of the operation was not significantly associated with the occurrence of postoperative atrial fibrillation in all patients. Urgent and emergency surgeries were more frequent in patients requiring coronary artery bypass procedures than in other patients, and in this patient group,

Table 3. The Distribution of Postoperative Atrial Fibrillation According to the Type of Procedure in Patients Without Chronic Atrial Fibrillation and Surviving at Least 5 Days

	n	Postoperative Atrial Fibrillation (%)	95% Confidence Interval
All patients	1,164	599 (51%)	49-54%
Only CABG	500	214 (43%)	38-47%
Single valve	344	189 (55%)	50-60%
Multiple valve	38	28 (74%)	59-88%
CABG* and valve surgery	145	96 (66%)	58-74%
Aortic surgery*	110	59 (54%)	44-63%

Abbreviation: CABG, coronary artery bypass grafting.

*Aortic surgery includes aortic root procedures and aortic surgery combined with CABG or valve surgery.

Table 4. Risk Factors for Postoperative Atrial Fibrillation in Multivariable Analysis

Risk Factor	Odds Ratio	95% Confidence Interval
Male sex	1.34	0.98-1.83
Age*		
50-59	1.83	1.00-3.35
60-69	2.96†	1.66-5.29
70-79	5.73†	3.17-10.38
80+	8.49†	4.17-17.28
Previous atrial fibrillation	4.37†	2.77-6.89
Dyslipidemia	1.02	0.75-1.39
Hypertension	1.15	0.85-1.57
Diabetes	1.18	0.85-1.65
Active smoking	0.82	0.55-1.24
Left atrium >40mm	1.833†	1.205-2.79
Type of procedure*		
Single valve	2.09†	1.46-2.99
Multiple valve	3.43†	1.43-8.26
Coronary artery bypass and valve	2.28†	1.46-3.55
Aortic	2.53†	1.53-4.19
Urgency*		
Urgent	1.16	0.81-1.67
Emergency	1.75†	1.11-2.76

*Baseline groups include patients aged less than 50 years and those undergoing bypass surgery and elective surgery, respectively.

†p ≤ 0.05

postoperative atrial fibrillation tended to be more common after urgent (43%) or emergency (54%) surgery when compared to elective (39%) cases, p = 0.058. In multivariable analysis (Table 4), the type of procedure, age, previous atrial fibrillation, left atrium size, and emergency surgery were statistically significant independent predictors of postoperative atrial fibrillation.

DISCUSSION

In this study, the authors sought to ascertain the incidence of and risk factors for postoperative atrial fibrillation as well as its associations with other complications after cardiac surgery in contemporary patients. At present, patients referred for cardiac surgery are increasingly older with a higher prevalence of significant co-morbidities including prior arrhythmias. Postoperative atrial fibrillation is the most common complication after cardiac surgery and associated with higher mortality, stroke, and longer hospitalization. The most important known risk factors for postoperative atrial fibrillation include old age and previous atrial fibrillation. The median age in the authors' study, including all adult cardiac surgery performed at their clinic, was 68 years, which was somewhat higher than in most previous studies. Similarly, 24% of the authors' patients presented with a history of atrial fibrillation, chronic in 12% and paroxysmal in 12%, a significantly higher percentage than described earlier. For example, Mathew et al reported that the prevalence of chronic atrial fibrillation was only 3% and that of paroxysmal atrial fibrillation 9%, while Tran et al reported a prevalence of 9% of any type of atrial fibrillation.[11,19] While the rate of preoperative atrial fibrillation may have been underestimated previously, its incidence also has been rising.[20]

When reporting the incidence of postoperative atrial fibrillation, some authors[1,2,4,5] have included patients with perioperative deaths while others[3,6] have excluded all non-survivors. As patients not surviving the operation cannot develop postoperative complications, the authors believe that the incidence of postoperative atrial fibrillation should be reported in patients actually at risk for the complication and have included patients surviving at least five days, as most cases of atrial fibrillation present by this time.

As expected, the authors reported a higher incidence of postoperative atrial fibrillation than in earlier literature. Furthermore, the majority of their patients experiencing postoperative atrial fibrillation had frequent recurrence or prolonged duration of the arrhythmia during hospitalization. A cut-off point of 48 hours was chosen because anticoagulation therapy has been suggested in patients with postoperative atrial fibrillation persisting longer than 48 hours.[18] Unfortunately, the type of treatment given for and the number of patients with atrial fibrillation during hospital discharge was not recorded. In earlier reports, the conversion rate of postoperative atrial fibrillation to sinus rhythm within 24 hours was 80%, and a recurrence rate of 43% has been reported.[19,21] However, despite the high occurrence of postoperative atrial fibrillation, the rate of stroke in the series was standard. A small number of patients in the authors' series underwent simultaneous cryoablation; however, the rate of postoperative atrial fibrillation in these patients was similar to that of other patients and did not affect the results.

In addition to older age and higher prevalence of prior arrhythmias, the increased rate of postoperative atrial fibrillation was explained partly by a high rate of valvular and combined procedures in this study. Furthermore, only 53% of bypass procedures were elective, and the rate of postoperative atrial fibrillation tended to be higher in urgent and emergency cases in these patients. Also, continuous ECG monitoring throughout the treatment period, a standard practice in the authors' clinic, may have led to a greater rate of arrhythmia detection.[22] The authors found no association with the use of statins or β-blockers and postoperative atrial fibrillation in this study but reported a high prevalence of the aforementioned medications preoperatively, which could imply no differences were observed because most patients who would benefit from concurrent treatment were already receiving the medications. Patients receiving and not receiving the medications probably were not otherwise comparable, and the authors did not record the delay after which these medications were resumed after surgery. It was possible that earlier continuation would have reduced the incidence of atrial fibrillation. Conduction disturbances that may postpone the continuation of β-blockers are typical after valve surgery, after which the risk of atrial fibrillation was greater.

The rates of reoperations and infectious complications were higher in patients who developed postoperative atrial fibrillation. However, whether atrial fibrillation occurred before or after the aforementioned complication was not recorded, and it was therefore possible that in some cases the onset of postoperative atrial fibrillation was complication-induced, while in other cases the two complications were unrelated or shared a mutual risk factor. Active smoking was associated with lower occurrence of postoperative atrial fibrillation in the present study, probably because these patients were significantly younger. Smoking has been associated with increased risk of atrial fibrillation in the general population.[23]

The authors' study had several limitations, the most important of which was that the authors reported single-center results that may not apply for all cardiac surgery programs and that information on some factors that may have affected the incidence of postoperative atrial fibrillation, such as medications, was imperfect. The greatest strength of the current study was that the authors had a relatively large patient cohort of consecutive patients of whom none was excluded patients, as in most previous studies.

In conclusion, the authors report a high occurrence of postoperative atrial fibrillation in contemporary patients undergoing cardiac surgery. The prevalence of previous atrial fibrillation was similarly high. The majority of patients developing postoperative atrial fibrillation experienced prolonged duration or recurrence of the arrhythmia. The type of procedure, older age, and previous atrial fibrillation were the most important risk factors.

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PUBLICATION II

Incidence, presentation and risk factors of late postoperative pericardial effusions requiring invasive treatment after cardiac surgery

Khan, N., Järvelä, K., Loisa, E., Sutinen, J., Laurikka, J., Khan, J.

Interactive CardioVascular and Thoracic Surgery, 24 (6): 835-840
doi: 10.1093/icvts/ivx011.

INCIDENCE, PRESENTATION AND RISK FACTORS OF LATE POSTOPERATIVE PERICARDIAL EFFUSIONS REQUIRING INVASIVE TREATMENT AFTER CARDIAC SURGERY

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Word count: 4,246

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ABSTRACT

Objectives: Occurrence and risk factors of late postoperative pericardial effusions requiring invasive treatment, i.e. pretamponade and tamponade, following cardiac surgery are incompletely described in current literature. The purpose of this study was to define the incidence and presentation of late pretamponade and tamponade as well as outline significant predisposing factors.

Methods: A cohort of 1,356 consecutive cardiac surgery patients treated in a tertiary academic centre between January 2013 and December 2014 was followed-up for six months after surgery. Pericardial effusion was considered late when presenting after the seventh postoperative day. The incidence, timing, and risk-factors of, as well as symptoms and clinical findings associated with late pretamponade and tamponade in patients surviving at least seven days was analysed.

Results: Of 1308 patients included in the analysis, 81 (6.2%) underwent invasive treatment for late postoperative pericardial effusion, 27 (2.1%) for pretamponade and 54 (4.1%) for tamponade, respectively, with a median delay of 11 (range 8-87) days after the primary operation. Haemodynamic instability was present in 34.6%, signs of cardiac chamber compression in 54.3%, and subjective symptoms, mostly dyspnoea, in 56.8% of patients, respectively. Treated patients were younger, had lower Euroscore-II rating, less coronary disease, better cardiac function, higher preoperative haemoglobin values, and had mostly undergone elective surgery involving cardiac valves. In multivariable analysis, independent risk factors were single valve surgery and high preoperative haemoglobin level, while age 60-69 was associated with lower risk.

Conclusions: Younger, generally healthier patients undergoing valve surgery are at greatest risk for developing late tamponade or pretamponade.

Keywords: cardiac surgery; cardiac tamponade; complication; coronary artery bypass grafting; incidence; valve surgery

INTRODUCTION

Postoperative pericardial effusion (PPE) is a common finding after cardiac surgery. Most effusions are small, asymptomatic, and inconsequential, with reported rates up to 84% of patients in prospective studies and significantly less in retrospective studies. [1-4] The effusion tends to reach its maximum size by the tenth postoperative day after which it typically resolves spontaneously [4]. PPE can, however, persist or progress and ultimately proceed to cause life-threatening cardiac tamponade [5]. Persisting PPE has been found in approximately one fifth of cardiac surgery patients at postoperative day 20 and the incidence of late cardiac tamponade is estimated to be between 1% and 2.6% [2, 6-9]. Early postoperative cardiac tamponade is caused by surgical and/or microvascular bleeding. Late tamponade, per contra, evolves due to progressing PPE which in turn is connected to postpericardiotomy syndrome, an inflammatory reaction of the pericardium brought on by the surgical procedure [3, 10, 11]. Late symptomatic PPE, i.e. pretamponade, and cardiac tamponade necessitate invasive treatment, most commonly pericardiocentesis, percutaneous drainage, or surgical fenestration. PPE is more common after coronary artery bypass grafting (CABG) than valve replacement surgery, while the opposite is true for late cardiac tamponade [2, 6, 12]. Current evidence suggests that early chest tube removal and preoperative anticoagulant therapy as well as female gender are associated with late PPE and cardiac tamponade [12, 13].

Late PPE and cardiac tamponade requiring invasive treatment are significant complications of cardiac surgery increasing the length and number of hospitalisation periods and adding to welfare costs, yet compared to other established complications of cardiac surgery, such as atrial fibrillation and postoperative infections, not as thoroughly studied. The incidence of late cardiac tamponade may be underestimated and its risk factors remain ill defined [6]. Moreover, advances in percutaneous procedures on one hand and the development of surgical techniques and cardiac anaesthesia on the other have led to cardiac surgery patients becoming older and more clinically challenging than before emphasizing the need for up to date data. In this

72 study we hence sought to determine the incidence and presentation of and risk factors subjecting to late PPE
73 and cardiac tamponade requiring invasive treatment after contemporary cardiac surgery.

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MATERIALS AND METHODS

Study design

This study was a prospective single-centre cohort study of 1,356 consecutive cardiac surgery patients treated in Heart Hospital, Tampere University Hospital between January 2013 and December 2014 [14]. The series comprised all elective, urgent and emergency adult cardiac surgery performed at our clinic, including coronary artery bypass grafting, valve operations, surgery of the aortic root, ascending aorta or aortic arch, combined procedures, as well as redo-operations. The cohort was followed up for six months after surgery and the incidence, timing, and symptoms of late PPE requiring invasive treatment were recorded.

Postoperative echocardiography was performed routinely on all patients during the primary hospitalisation, usually on the fourth postoperative day, and three months after surgery. If cardiac tamponade or significant PPE was suspected, ultrasound examination was performed in all patients and the findings were confirmed by a cardiologist. Patients still on their primary hospital stay, those that were already discharged but become symptomatic and were readmitted, and those who were diagnosed with significant PPE during routine follow-up echocardiography were included in the study. Patients not surviving the first seven days were excluded from the analysis, as they could not develop late complications. The patients were treated according to clinic standards and were not included in any interventional studies. During the study period, pericardial drains were usually removed the morning of the first postoperative day unless they still produced significant (>50ml/h) volumes. Routine closure of the pericardium or posterior pericardiotomy were not performed at our clinic at the time. Epicardial pace wires were inserted at the end of each operation in all patients, and if no conduction disturbances were present, were usually removed on the fourth postoperative day. All patients received a prophylactic dose of low molecular weight heparin (LMWH) daily for the duration of the hospital period or until warfarin therapy was at a therapeutic level. In patients with chronic or new and recurring or

prolonged atrial fibrillation the LMWH dose was increased, and if not already prescribed, the initiation of warfarin was contemplated. Warfarin was prescribed for all patients undergoing valve surgery, initially for three months in patients undergoing valve repair with ring or implantation of a bioprosthetic valve, and indefinitely in patients in whom mechanical valves were implanted.

Definition and classification of late postoperative pericardial effusions

The indication for invasive treatment was a pericardial effusion of significant size (>10mm) associated with haemodynamic instability, signs of chamber compression in cardiac ultrasound, subjective symptoms, and/or an effusion significantly increasing in size during follow-up so that intervention was considered necessary. Postoperative pericardial effusions were considered late when the need for treatment occurred after the seventh postoperative day. The treated effusions were classified as causing either cardiac tamponade when associated with haemodynamic instability and/or chamber compression in cardiac ultrasound, or as pretamponade in absence of the aforementioned findings but when causing subjective symptoms or increasing in size. Whether medical treatment for PPE had been previously initiated was recorded. The width of the thickest portion of the pericardial effusion at the time of the procedure and the volume aspirated from the pericardium was recorded, as were the need of later re-interventions. The type of invasive treatment was subject to surgeon preference and most commonly consisted of surgical fenestration of the pericardium through left-sided parasternal minithoracotomy or subxiphoid approach, or by ultrasound-guided percutaneous drainage of the pericardium. The associations of preoperative patient factors, the type of procedure performed, and the clinical course of the primary hospital period - including relevant laboratory parameters - with the development of late PPE requiring interventions were analysed. Preoperative haemoglobin, leukocyte, and creatinine levels were obtained one to three days preoperatively. In addition, the highest haemoglobin, leukocyte, creatine kinase MB, C-reactive protein, creatinine, and the lowest haemoglobin and thrombocyte levels during the first seven postoperative days were analysed. In the

125 statistical analyses, late tamponade and pretamponade were analysed together when associations and risk
126 factors were measured.

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128 This study was performed according to the Helsinki Declaration and institutional review board approval was
129 obtained prior to the study. Statistical analyses were carried out using SPSS 16.0 statistical software for
130 Windows. Univariable analyses were performed using the chi square test and Fisher's exact test for
131 categorical data and the Mann-Whitney U-test for comparing the medians between groups in non-categorical
132 data. All statistically significant parameters in univariable analysis were subjected to multivariable analysis
133 using binary logistic regression. The cut-off value used for statistical significance was $p<0.05$.

134

RESULTS

Out of 1,356 operated patients 48 (3.5%) did not survive the first seven days and the final study cohort consisted of the remaining 1308 patients. Of these, nine (0.7%) were redo-cases. The combined in-hospital and 30-day mortality rate for included patients was 28 (2.1%). During the six month follow-up, invasive procedures for late pericardial effusions were performed on 81 (6.2%, 95% CI 4.9-7.5%) patients, of which none were after redo-operations. PPE was treated by surgical fenestration in 69 (85%) patients and by percutaneous drainage in 12 (15%) patients. Fifty-four (4.1%; 95% CI 3.1%-5.2%) patients were classified as having cardiac tamponade and 27 (2.1%; 95% CI 1.3-2.8%) patients as pretamponade. After treatment the condition recurred and required another pericardial intervention in six (7%) patients during follow-up. The rates of late tamponade and pretamponade according to the type of surgery performed is presented in Table 1.

The median delay between the primary operation and the treatment of late tamponade or pretamponade was 11 (range 8-87) days. At the time of intervention, the median maximal width of the effusion was 25mm (range 10-60mm), and the median amount of pericardial fluid initially aspirated was 500ml (range 200-2000ml). Medical treatment for PPE had been started prior to the intervention in eight (9.9%) patients. Haemodynamic instability was present in 28 (34.6%) patients, signs of cardiac chamber compression in 44 (54.3%) patients, and subjective symptoms, mostly dyspnoea (Figure 1), in 46 (56.8%) patients. Altogether 18 patients were asymptomatic, haemodynamically stable and without evidence of chamber compression in cardiac ultrasound, but underwent invasive treatment when the amount of pericardial fluid significantly increased during follow-up.

The preoperative characteristics of patients that developed late tamponade or pretamponade and other patients are compared in Table 2. Patients who required interventions for late PPE were statistically

significantly younger, typically underwent elective surgery, had lower median Euroscore-II rating, and had a lower prevalence of coronary disease, impaired left ventricular ejection fraction, and preoperative β-blocker medication, as well as higher median blood haemoglobin and lower median leukocyte levels when compared to other patients. The median aortic cross-clamp time and the median duration of perfusion were longer in patients who developed late tamponade or pretamponade than in other patients, 103 vs. 91 minutes, p=0.002, and 133 vs. 118 minutes, p=0.001, respectively. Postoperative use of non-autologous blood products, i.e. thrombocytes, erythrocytes, and/or fresh frozen plasma, was not associated with the development of late tamponade or pretamponade, but the median volume of returned autologous erythrocytes through the cell-saving suction system was higher, 1240 vs. 950ml, p=0.001, and the median drainage through chest tubes was lower, 600 vs. 720ml, p=0.021, in patients treated for late PPE.

Late tamponade or pretamponade was more frequent in patients who developed postoperative atrial fibrillation than in other patients, 7.5% vs. 4.5%, p=0.028, but was not associated with the development of infectious complications, stroke, or in-hospital and 30-day mortality. The highest median plasma creatine kinase MB -isoenzyme concentration and the highest median blood leukocyte level during the first seven postoperative days were higher, 42 vs. 34µg/L, p=0.005, and 12.4 vs. $11.9*10^9$/L, p=0.045, and the median minimum thrombocyte concentration lower, 95 vs. $109*10^9$/L, p=0.013, respectively, in patients treated for late tamponade or pretamponade than in other patients. There were no statistically significant differences in the postoperative C-reactive protein, creatinine or haemoglobin levels. The independent risk factors for late tamponade or pretamponade in multivariable analysis were single valve surgery and high preoperative haemoglobin level, while age 60-69 was associated with lower risk (Table 3).

DISCUSSION

Research concerning PPE is thus far mainly focused on postpericardiotomy syndrome but investigating the resource consuming late PPE and cardiac tamponade that necessitate invasive treatment would seem more clinically relevant. Furthermore, it has been suggested that the incidence of late cardiac tamponade is underestimated [6]. In the present study we determined the incidence and presentation of late PPE requiring invasive treatment, i.e. pretamponade and tamponade, in a cohort of modern cardiac surgery patients and identified significant predisposing risk factors. PPE was considered late when the need of intervention occurred after the seventh postoperative day. As early tamponades caused by postoperative bleeding were treated within the first days and the patients underwent routine echocardiography - usually four days after surgery - significant early pericardial effusions were either treated or excluded before the seventh postoperative day and the results should accurately reflect cases in which the effusion developed after the initial postoperative period, presumably by an inflammatory mechanism.

The higher incidence of late cardiac tamponade and pretamponade found in this study compared to previous publications, 6.2% versus 1-2.6%, respectively, can be due to several factors [2, 6-9]. Firstly, the number of valve operations has increased while the number of CABG operations has decreased and late cardiac tamponade is known to be more common after valve surgery than CABG [2, 6, 12]. Secondly, pericardial drains were habitually removed in the morning of the first postoperative day with the objective of reducing postoperative infections but this practice can have increased the incidence of late pretamponade and cardiac tamponade as early removal of drains after cardiac surgery is associated with PPE requiring invasive treatment [13]. Thirdly, the incidence of postoperative atrial fibrillation (POAF) seems to be rising [14], which consequently increases the use of anticoagulants. Preoperative anticoagulant therapy has been found to increase late cardiac tamponade and it is possible that postoperative administration of these drugs would have the same effect [2, 12]. However, preoperative atrial fibrillation, usually associated with

anticoagulation, was not statistically significantly connected with the development late pretamponade or tamponade in this study. Finally, the follow-up of cardiac surgery patients has improved and echocardiography surveillance is likely to be more frequent enabling better detection of late PPE and timely patient referral for treatment. There may be some variance in the number of patients treated for postoperative complications in other hospitals between studies. While some of our patients may have been treated in other hospital districts, we believe this number to be very small in our setting.

Univariable analyses demonstrated late cardiac pretamponade or tamponade requiring invasive treatment to be a problem of younger, generally healthier patients with a lower prevalence of coronary disease and higher preoperative haemoglobin levels. The fact that these patients appear "better" in several aspects could be mainly attributed to age. It is possible that the effect of age is mediated through the inflammatory response brought on by the cardiac procedure which could vary between age groups although pro-inflammatory cytokine levels in the young and elderly have not been found to differ after CABG [15]. Contrary to prior knowledge, the present study found no gender difference in the incidence of late pretamponade or tamponade [12] The study population was, however, predominantly male, and therefore possibly underpowered in this regard. The longer median aortic cross-clamp time and duration of perfusion in patients treated for late PPE and tamponade may be associated with increased systemic inflammatory response. Interestingly, tamponade and pretamponade patients received more returned autologous erythrocytes via cell-saving suction system than other patients, possibly related to the length and type of procedure, as suggested by longer aortic cross-clamp time and duration of perfusion, and/or higher amount of perioperative bleeding and blood loss in these patients. According to previous studies the systemic levels of proinflammatory markers tend to be lower after cell saver use compared to direct retransfusion from the suction and cardiopulmonary bypass circuit [16, 17]. The present study found the amount of drain secretion to be lower in patients having to undergo treatment for late PPE and cardiac tamponade than patients free from this complication. Whether postponing chest tube removal in these patients would have enabled more complete pericardial drainage and inhibited later development of pretamponade or tamponade is worth considering.

Postoperatively pretamponade and tamponade patients demonstrated a greater creatin kinase MB -isoenzyme reaction compared to other patients. This can depict marginally greater myocardial damage or be associated with valve operations such as mitral valve repair, where cardiac chambers are opened. Additionally, the peak postoperative blood leukocyte levels were higher in patients treated for late PPE and cardiac tamponade, which potentially reflects a more severe inflammatory response after surgery in these patients.

Multivariable analysis found single valve surgery and high preoperative haemoglobin level to be independent risk factors for late pretamponade and tamponade. The effect of valvular surgery is in line with previous literature and is usually considered to be associated with anticoagulant therapy [2, 6, 12]. The intended or unintended opening of the left pleura when preparing the left mammary artery during CABG and consequent drainage of pericardial fluid through pleural drains via the pleural cavity might offer an additional explanation. This is supported by the finding that posterior pericardiotomy can prevent late PPE and cardiac tamponade requiring invasive treatment [18, 19]. The risk of postoperative tamponade or pretamponade was lower in patients aged 60-69 when compared to younger patients, which is a new discovery. The role of elevated preoperative haemoglobin as a risk factor for late pretamponade and tamponade is an interesting finding that to the best of our knowledge is unprecedented and merits further research. The occurrence of late PPE requiring interventional treatment was relatively high in our material. Based on the results of the present study, we chose to lengthen the time chest tubes were kept in place after surgery and will report its effect separately.

The main limitation of the current study is that only patients invasively treated for late PPE were included and the number patients with significant late effusions that resolved spontaneously or were medically managed is not known because many of these patients were treated in district hospitals. Most cases with significant PPEs in the series were treated relatively early, within two weeks, and the study did not have

enough statistical power to compare those with extremely late cases. Also, additional analyses of pericardial fluid or pericardial tissue samples could have offered further information concerning the aetiology of the postoperative effusions and should be included in future studies. Finally, this was a single-centre study and the results may reflect local patient selection and/or treatment protocols restricting the generalizability of the results.

In conclusion, we described the incidence, presentation, and risk factors of late pretamponade and tamponade after cardiac surgery in a large cohort of consecutive patients. The condition mostly affects young, low-risk patients undergoing valve surgery. The pathophysiology of and methods for preventing late tamponade warrant further research.

CONFLICTS OF INTEREST

We report no conflicts of interest.

FUNDING

This research did not receive any specific grant.

278 FIGURE LEGENDS

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280 Figure 1. The dominant signs in patients with subjective symptoms presenting with late tamponade or
281 pretamponade after cardiac surgery.

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296 TABLES

297 Table 1. The occurrence of late postoperative tamponade or pretamponade within six months after cardiac
298 surgery according to the type of procedure performed.

	Late tamponade	95% Confidence interval	Late pretamponade	95% Confidence interval
CABG*	1.3%	0.4%-2.3%	0%	
Single valve	6.6%	4.2-9.0%	3.9%	2.0-5.8%
Multiple valve	4.3%	0-9.2%	5.7%	0.1-11.3%
CABG* and valve	2.5%	0.1-4.9%	2.5%	0.1-4.9%
Aortic** surgery	9.3%	4.0-14.7%	1.7%	0-4.1%

299 *Coronary artery bypass grafting

300 **Includes surgery of the aortic root, ascending aorta and aortic arch as well as operations with concomitant
301 coronary and/or valve procedures.

302

303 Table 2. The associations of preoperative variables and the development of late postoperative tamponade or
304 pretamponade

	No tamponade	Late tamponade or pretamponade	p-value
Male (%)	882 (71.9%)	61 (75.3%)	0.506
Median age (range)	**68 (19-89)**	**65 (25-85)**	**0.007**
Urgent or emergency surgery (%)	**373 (30.4%)**	**15 (18.5%)**	**0.023**
Median Euroscore-II (range)	**1.85 (0.49-86.83)**	**1.74 (0.50-15.53)**	**0.033**
NYHA 3-4 (%)	297 (26.3%)	16 (21.9%)	0.492
Median BMI (range)	26.8 (10.5-61.3)	27.8 (16.8-43.0)	0.156
Coronary disease (%)	**783 (63.8%)**	**27 (33.3%)**	**<0.001**
LVEF <50% (%)	**232 (18.9%)**	**7 (8.6%)**	**0.017**
Hypertension (%)	801 (65.3%)	46 (56.8%)	0.121
Diabetes (%)	298 (24.3%)	12 (14.8%)	0.052
Dyslipidemy (%)	725 (59.1%)	41 (50.6%)	0.134
Preoperative atrial fibrillation[1] (%)	285 (23.2%)	24 (29.6%)	0.189
Chronic lung disease (%)	132 (10.8%)	9 (11.1%)	0.854
Active smoking (%)	172 (14.0%)	11 (13.6%)	0.912
Median preoperative creatinine level µmol/L (range)	83 (34-1036)	84 (48-206)	0.920

Median preoperative haemoglobin g/L	**139 (82-178)**	**143 (104-180)**	**0.025**
Median preoperative leukocyte *10^9	**6.9 (2.0-112.0)**	**6.4 (4.0-25.0)**	**0.043**
Preoperative statin (%)	697 (56.8%)	39 (48.1%)	0.128
Preoperative β-blocker (%)	**793 (64.6%)**	**37 (45.7%)**	**0.001**

[1]Includes chronic and paroxysmal atrial fibrillation

307 Table 3. Risk factors for late postoperative pericardial effusions requiring invasive treatment after cardiac
308 surgery in multivariable analysis. Significant associations are highlighted. Included variables represent those
309 with statistically significant associations in univariable analysis.

	Odds Ratio	95% Confidence interval
Single valve[1]	**4.34**	**1.08-17.45**
Multiple valve[1]	5.17	0.91-29.34
CABG and Valve[1]	2.76	0.65-11.74
Aortic[1]	3.97	0.74-21.20
Urgent or emergency surgery	0.57	0.22-1.48
Median Euroscore-II	1.01	0.93-1.10
Age 50-59[2]	0.69	0.25-1.87
Age 60-69[2]	**0.31**	**0.10-0.94**
Age 70-79[2]	1.10	0.39-3.13
Age ≥80[2]	0.73	0.17-3.06
Coronary disease	0.71	0.26-1.96
LVEF[3] <50%	0.50	0.16-1.52
Preoperative β-blocker	0.67	0.35-1.27
Median preoperative haemoglobin	**1.03**	**1.00-1.05**
Median preoperative leukocyte level	0.92	0.78-1.10

Median aortic cross-clamp time	1.00	0.99-1.02
Median perfusion time	1.00	0.98-1.01
Median highest postoperative leukocyte level[4]	1.07	0.98-1.16
Median highest postoperative creatine kinase MB[4]	1.00	1.00-1.01
Median lowest postoperative thrombocyte level[4]	1.00	0.99-1.01
Median volume of returned autologous erythrocytes	1.00	1.00-1.00
Median chest tube production	1.00	1.00-1.00

[1]Baseline group isolated coronary artery bypass grafting

[2]Baseline age <50

[3]Left ventricular ejection fraction

[4]During the first seven postoperative days

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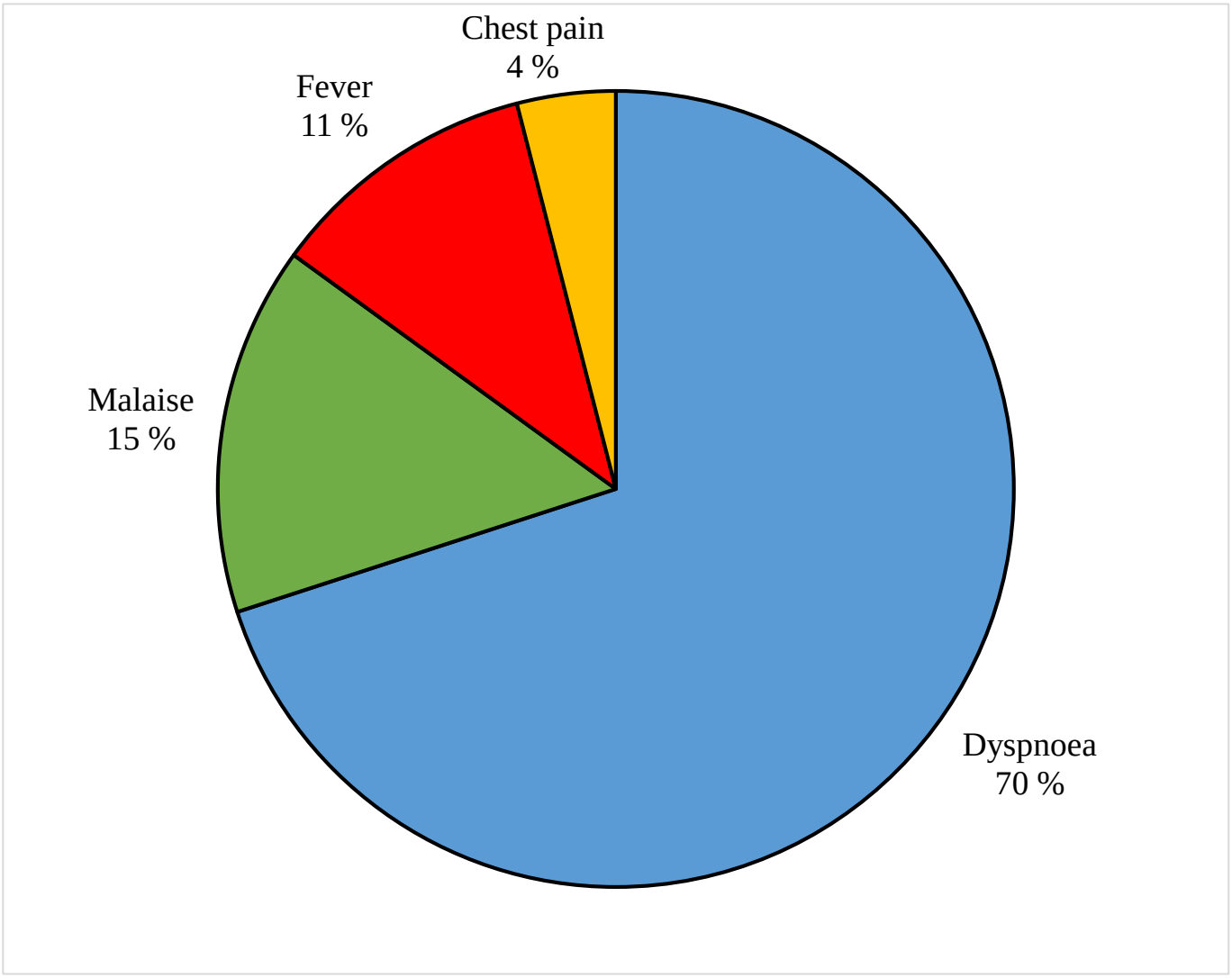
Chest pain
4 %
Fever
11 %
Malaise
15 %
Dyspnoea
70 %

PUBLICATION III

Hyperglycemic episodes are associated with postoperative infections after cardiac surgery

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Scandinavian Journal of Surgery, 107 (2): 138-144
doi: 10.1177/1457496917731190.

SJS SCANDINAVIAN JOURNAL OF SURGERY

Original Research Article

HYPERGLYCEMIC EPISODES ARE ASSOCIATED WITH POSTOPERATIVE INFECTIONS AFTER CARDIAC SURGERY

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ABSTRACT

Background and Aims: **To describe the incidence of and risk factors for postoperative infections and the correlation between postoperative hyperglycemia despite tight blood glucose control with infectious and other complications after contemporary cardiac surgery.**

Material and Methods: **The study comprised 1356 consecutive adult patients who underwent cardiac surgery between January 2013 and December 2014 and were followed up for 6 months. Patients surviving the first 2 days were included in the analysis. Preoperative demographic information, medical history, procedural details, and the postoperative course were recorded. The target range for blood glucose levels was 4–7 mmol/L and repeated arterial blood samples were obtained during the intensive care unit stay. The associations of blood glucose levels during the first postoperative day and the occurrence of postoperative infections and other significant complications were analyzed.**

Results: **Of the study cohort, 9.8% developed infectious complications which were classified as major surgical site infections in 2.2%, minor surgical site infections in 1.1%, lung infections in 2.0%, unclear fever or bacteremia in 0.3%, cannula or catheter related in 2.6%, multiple in 1.5%, and other in 0.2%. The incidence of deep sternal wound infection was 2.0%. Repeated hyperglycemia occurred in 39.7% of patients and was associated with increased rates of postoperative infections, 12.1% versus 8.2%, $p=0.019$; stroke, 4.9% versus 1.5%, $p<0.001$; and mortality, 6.1% versus 2.1%, $p<0.001$, when compared to patients with single or no hyperglycemia.**

Conclusion: **Every 10th patient develops infectious complications after cardiac surgery. Repeated hyperglycemia is associated with increased rates of infectious complications, stroke, and mortality.**

Key words: Cardiac surgery; coronary artery bypass; glycemic control; hyperglycemia; infection; postoperative complications

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Scandinavian Journal of Surgery
2018, Vol. 107(2) 138–144

DOI: 10.1177/1457496917731190
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INTRODUCTION

Infectious complications are a significant cause of morbidity, mortality, and increased healthcare costs after major procedures such as cardiac surgery. Besides operation-related factors, including extensive operations, long procedure times, and the use of cardiopulmonary bypass, cardiac surgery patients are subjected to prolonged intubation and mechanical ventilation, numerous vascular and urinary catheters, and chest tubes contributing to risk of postoperative infections. Furthermore, evolution of surgical techniques and cardiac anesthesia enables surgery in older patients presenting with substantial comorbidities, possibly influencing the susceptibility for postoperative complications. The incidence of postoperative infections in previous studies ranges from 5.0% to 14.1% (1, 2).

Acute physiologic stress induced by major surgery may elevate blood glucose levels even in patients without diabetes (3). Hyperglycemia, in turn, is associated with impaired wound healing, leukocyte function, and phagocytosis and has been found to increase rates of infectious complications after cardiac surgery (4, 5). Implementing tight glycemic control has been shown to reduce mortality and morbidity in a surgical intensive care unit (ICU) and the incidence of deep sternal wound infection (DSWI) after coronary artery bypass grafting (CABG) (6, 7). However, in the NICE-SUGAR study, comprising mostly non-surgical patients treated in the ICU, tight glucose control was associated with increased mortality (8).

The optimal target range for blood glucose levels after cardiac surgery remains unclear and merits further research. The aim of this study was to determine the incidence and risk factors of postoperative infections and the correlation between postoperative hyperglycemia with infectious and other complications after contemporary cardiac surgery, both in diabetic and nondiabetic patients.

MATERIALS AND METHODS

PATIENTS

This study was an analysis of a cohort of 1356 prospectively collected consecutive patients who underwent cardiac surgery in Heart Hospital, Tampere University Hospital, Tampere, Finland, between January 2013 and December 2014 and has been described in a previous study (9). The cohort included all adult open heart surgery performed at our clinic. Preoperative demographic information, previous medical history, and procedure-related details were recorded. The patients were treated according to clinical standards and were not subjected to any interventions for this study. Preoperative antimicrobial prophylaxis in all patients without contraindication for its use was Cefuroxime 3 g intravenously before surgical incision, and an additional 1.5 g was administered if the duration of the procedure exceeded 4 h. After surgery, all patients were followed up at the cardiac ICU at least until the morning of the first postoperative day, after which most patients were referred to either a regular or a high-dependency department. Mortalities and the occurrence of postoperative complications, including infections, need for reoperations, arrhythmias, and stroke, were recorded. The diagnosis of postoperative stroke was based on computed tomography performed in patients with clinical suspicion of intracranial pathology postoperatively and was confirmed by a neurologist in each case.

DIAGNOSIS AND CLASSIFICATION OF POSTOPERATIVE INFECTIONS

The occurrence and type of infectious complications, results of microbial culture, and the delay after which the first symptoms presented following surgery, both during the primary hospital stay and repeat hospitalizations within 6 months, were recorded. Patients surviving at least 48 h were included in the analysis, as those that did not survive the operation and the immediate postoperative period could not develop postoperative infections. Clinical signs of infection, such as local symptoms, fever, leukocytosis, and increase in the serum C-reactive protein concentration, along with positive findings in imaging studies and/or microbial culture were required for the diagnosis. Infectious complications were classified according to clinical presentation. DSWIs, empyema, and endocarditis after valve surgery were classified as major surgical site infections (SSI), while superficial sternal and other wound infections were classified as minor SSI. Other infections were considered as either pulmonary, cannula and catheter related, unclear fever or sepsis, or other infections. When more than one infectious complication occurred in the same patient, the patient was classified as having multiple infections and the delay in the onset of the first infection was recorded.

GLYCEMIC CONTROL AND MEASUREMENTS

During the ICU stay, repeated arterial blood samples were obtained every 4 h to follow up the hemoglobin, arterial gases, pH, glucose, and lactate levels (*ABL90 FLEX blood gas analyzer; Radiometer Medical ApS, Brønshøj, Denmark*). Additional blood samples were analyzed with a hand-held device (*FreeStyle Lite; Abbott Diabetes Care Inc, Alameda, CA, USA*) if frequent measurements were needed when values out of target range were treated. If insulin treatment was initiated in the ICU, we used a high initial bolus dose to provide enough insulin coverage to reduce blood glucose levels to the target range of 4–7 mmol/L followed by intravenous insulin infusion adjusted according to subsequent blood glucose measurements. This has been proved a safe and rapid manner to achieve compliance with the protocol (10). Any hypoglycemic values were treated promptly with glucose infusion. The amount of insulin given and blood glucose levels obtained by serial arterial blood samples during the first 24 h after surgery in the ICU were recorded. The associations between blood glucose levels and the amount of insulin given during the first 24 h and postoperative infections were analyzed using statistical methods. Type I and type II diabetics were grouped together in the analysis.

This is a descriptive study and consequently no preceding power analysis was performed. The study

TABLE 1
Demographic data of study patients.

	All patients (n = 1329)	CABG only (n = 527)	Single valve (n = 410)	Multiple valve (n = 72)	CABG and valve (n = 164)	Aortic[a] (n = 126)
Elective (%)	931 (70%)	281 (53%)	361 (88%)	58 (81%)	124 (76%)	89 (71%)
NYHA 3 or 4 (%)	323 (24%)	168 (32%)	60 (15%)	17 (24%)	37 (23%)	33 (26%)
Median Euroscore 2 (range)	1.8 (0.5–86.8)	1.7 (0.5–52.6)	1.3 (0.5–21.6)	3.1 (0.6–28.6)	2.9 (0.6–56.4)	3.0 (0.5–86.8)
Male (%)	955 (72%)	418 (79%)	260 (63%)	46 (64%)	115 (70%)	99 (72%)
Median age (range)	68 (19–89)	68 (40–89)	68 (19–88)	71 (22–85)	74 (42–87)	63 (28–79)
Median BMI (range)	27 (10–60)	27 (17–60)	27 (10–60)	27 (14–45)	27 (17–41)	26 (19–61)
Median LVEF (range)	59 (19–84)	55 (19–80)	60 (25–84)	60 (28–81)	57 (25–82)	60 (20–80)
Coronary disease (%)	825 (62%)	527 (100%)	95 (23%)	16 (22%)	161 (98%)	26 (21%)
Hypertension (%)	859 (65%)	382 (72%)	234 (57%)	35 (49%)	119 (73%)	75 (60%)
Diabetes (%)	314 (24%)	177 (34%)	61 (15%)	13 (18%)	46 (28%)	15 (12%)
Dyslipidaemia (%)	773 (58%)	407 (77%)	173 (42%)	27 (47%)	115 (70%)	44 (35%)
Chronic lung disease (%)	144 (11%)	57 (11%)	44 (11%)	5 (7%)	21 (13%)	16 (13%)

CABG: coronary artery bypass grafting; NYHA: New York Heart Association Functional Classification; BMI: body mass index; LVEF: left ventricular ejection fraction.
[a]Includes aortic root, ascending aorta, and aortic arch procedures with or without bypass and/or valve surgery.

was carried out according to the Helsinki Declaration, and institutional review board approval was obtained. Statistical testing was done with SPSS 23.0 statistical software using the chi-square test and Fisher's exact test to compare proportions in categorical data and the Mann–Whitney U test and the Kruskal–Wallis H test to compare the differences in medians between groups. Multivariable analysis was performed using binary logistic regression analysis and by including variables with statistically significant associations in univariable analysis. A p value <0.05 was considered statistically significant.

RESULTS

Of the 1356 patients who underwent cardiac surgery during the study period, 1329 (98%) survived the first two postoperative days and were included in the analysis. The demographics of the study population are presented in Table 1. Altogether 7% of diabetics in the study population had type I diabetes. The main outcomes for the study patients include a combined 30-day and in-hospital mortality of 3.7%, a stroke rate of 2.9%, reoperations for bleeding and other complications in 13.2%, postoperative atrial fibrillation in 45.4%, and infectious complications in 9.8%. The median length of postoperative hospitalization was 6 (range 0–53) days including one patient referred for heart transplantation postoperatively.

POSTOPERATIVE INFECTIONS

The occurrence of postoperative infections and infection types is shown in Table 2, excluding unclear fever or bacteremia detected in 0.3% and other infections observed in 0.2% of patients. The most common pathogens detected per infection type are shown in Fig. 1. Increased infection rates were observed after urgent or emergency surgery, in patients with impaired left ventricular function, in those aged 70 years or more, and in patients with body mass index (BMI) ≥ 27 kg/m^2. Pulmonary infections were more common in non-elective cases and in patients with higher New York Heart Association Functional Classification (NYHA) score and worse left ventricular ejection fraction. Higher BMI was associated with increased rates of SSIs, while females and patients aged 70 years or more showed higher rates of cannula and catheter-related infections. The rate of DSWI in the study was 2.0% and was not statistically significantly associated with the type of procedure.

The median delay in the development of the first symptoms of postoperative infections was 6 (range: 0–174) days after surgery, 8 (range: 2–174) days for major SSI, including one prosthetic valve endocarditis presenting within 6 months after operation, 7 (range: 2–26) days for minor SSI, 3 (range: 1–10) days for lung infections, 8 (range: 4–15) days for unclear fever or bacteremia, 6 (range: 0–20) days for cannula- and catheter-related infections, 7 (range: 3–177) days for multiple infections, and 3 (range: 2–3) days for other infections ($p < 0.001$). Altogether 17 (1.3%) patients were readmitted due to infectious complications after primary referral or hospital discharge. In patients with postoperative infections, bacterial culture was positive in 97 (75%) and blood cultures in 18 (14%) patients. Patients who developed postoperative infections had longer postoperative length of intubation, median 5.8 versus 4.3 h, $p < 0.001$; longer primary ICU stay, median 1.7 versus 0.9 days, $p < 0.001$; longer hospitalization, median 11 versus 5 days, $p < 0.001$; and higher combined in-hospital and 30-day mortality, 10.8% versus 2.9%, $p < 0.001$. Mortality was 20.7% in patients with major SSI, 15.4% in patients with lung infections, 5.7% in patients with cannula- and catheter-related infections, 10% in patients with multiple infections, and 0% in patients with other infections ($p < 0.001$).

HYPOGLYCEMIA

Altogether 16 (1.2%) patients did not receive any insulin, and hypoglycemia did not develop in any of these

TABLE 2

The occurrence of postoperative infections and the most important infection types in study patients as well as the most important patient subgroups.

	Any postoperative infection	Major SSI	Minor SSI	Lung infection	Cannula or catheter related	Multiple infections
All patients	9.8%	2.2%	1.1%	2.0%	2.6%	1.5%
CABG	8.9%	2.5%	0.9%	2.1%	1.7%	**1.1%***
Single valve	8.8%	2.0%	1.0%	0.7%	3.4%	**1.2%***
Multiple valve	12.5%	0%	0%	4.2%	4.2%	**2.8%***
CABG and valve	15.9%	3.0%	2.4%	3.0%	3.0%	**4.3%***
Aortic	8.7%	2.4%	0.8%	3.2%	2.4%	**0%***
Elective	**8.6%***	2.0%	0.9%	**1.3%****	2.7%	1.3%
Urgent or emergency	**12.6%***	2.5%	1.5%	**3.5%****	2.5%	2.0%
NYHA 1–2	9.1%	2.1%	1.1%	**1.2%****	2.9%	1.2%
NYHA 3–4	12.1%	3.1%	0.9%	**3.7%****	1.9%	2.2%
LVEF ≥ 50%	**8.8%****	**1.8%***	1.1%	**1.4%****	2.8%	1.4%
LVEF < 50%	**14.3%****	**4.1%***	0.8%	**4.5%****	2.0%	2.0%
Age < 70	**8.1%***	1.5%	1.1%	2.0%	**1.7%***	1.3%
Age ≥ 70	**11.7%***	2.9%	1.0%	2.0%	**3.7%***	1.8%
BMI < 27	**8.0%***	**1.2%***	**0.4%***	1.3%	2.7%	2.1%
BMI ≥ 27	**11.5%***	**3.1%***	**1.5%***	2.6%	2.6%	0.9%
Male	8.9%	2.5%	0.9%	2.3%	**1.5%*****	**1.0%***
Female	12.0%	1.3%	1.3%	1.1%	**5.6%*****	**2.7%***
Diabetes	11.1%	2.9%	1.6%	2.2%	2.2%	1.3%
Coronary disease	10.8%	2.4%	1.2%	1.9%	2.9%	1.9%
Hypertension	10.0%	2.0%	1.3%	1.9%	2.8%	1.6%
Dyslipidaemia	9.7%	2.3%	1.4%	1.8%	3.0%	**0.9%***
Chronic lung disease	12.5%	2.1%	0.7%	**4.2%***	1.4%	**4.2%****

SSI: surgical site infection; CABG: coronary artery bypass grafting; NYHA: New York Heart Association Functional Classification; LVEF: left ventricular ejection fraction; BMI; body mass index.
Statistically significant differences between opposing groups and per grouping factor, for example, elective versus urgent/emergency and the type of procedure, are given in boldface.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

patients. A total of 101 (7.6%) patients were hypoglycemic (B-gluc < 4 mmol/L) during the study, and of these, 91 (6.8%) patients were hypoglycemic once, 9 (0.7%) patients twice, and 1 (0.1%) patient three times. Hypoglycemia was not associated with the type of procedure performed or with postoperative infections, in-hospital mortality, stroke rate, length of hospitalization, or postoperative atrial fibrillation.

HYPERGLYCEMIA

Hyperglycemia (B-gluc > 7 mmol/L) occurred in 915 (68.8%) patients and was detected once in 388 (29.2%) patients, twice in 237 (17.8%) patients, and three or more times in 290 (21.8%) patients. Repeated hyperglycemia was observed more frequently in patients with diabetes than in other patients, 53% versus 36%, $p < 0.001$, respectively. The median BMI was also higher in patients with repeated hyperglycemia compared to other patients, 27.7 versus 26.3 kg/m^2, $p < 0.001$, respectively. Repeated hyperglycemia was associated with increased occurrence of postoperative infections, 12.1% versus 8.2% in patients with single or no hyperglycemia ($p = 0.019$; Fig. 2). There were no statistically significant associations with the type of infection. The median average blood glucose concentration in all patients was 6.1 mmol/L (range: 4.0–11.6 mmol/L) and higher in patients with postoperative infections (6.3 versus 6.1 mmol/L, $p = 0.026$) and in patients with diabetes (6.3 versus 6.1 mmol/L, $p < 0.001$). The average amount of insulin given was higher in diabetics than in other patients (1.9 versus 1.5 IU/h, respectively, $p < 0.001$), but was not statistically significantly associated with later infections. In addition, repeated hyperglycemia was also associated with increased rates of stroke (4.9% versus 1.5%) in patients with single or no hyperglycemia ($p < 0.001$) and combined in-hospital and 30-day mortality (6.1% versus 2.1%, $p < 0.001$, respectively). In multivariable analysis (Table 3), repeated hyperglycemia was independently associated with increased risk of postoperative infections.

DISCUSSION

The overall incidence of postoperative infections in our patient population was 9.8%, the majority of which were cannula and catheter related, SSIs, pulmonary infections, and concordant with previous literature. The rate of DSWI in the series, 2.0%, was also standard. Significant variance in pre- and postoperative antibiotic prophylaxis protocols exists between different cardiac surgery programs and the issue is still controversial, perhaps subject to local circumstances, patient material, and clinical practices (11–13). Our protocol consisting of only a single dose of

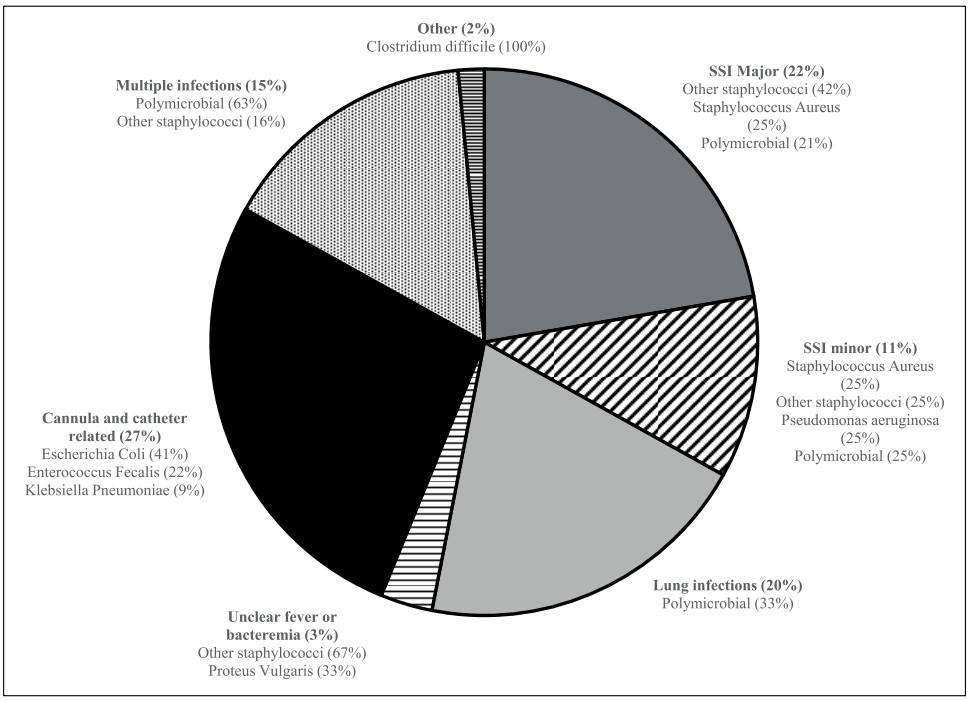

Fig. 1. Classification and distribution of postoperative infectious complications and the most common pathogens detected by bacterial culture.

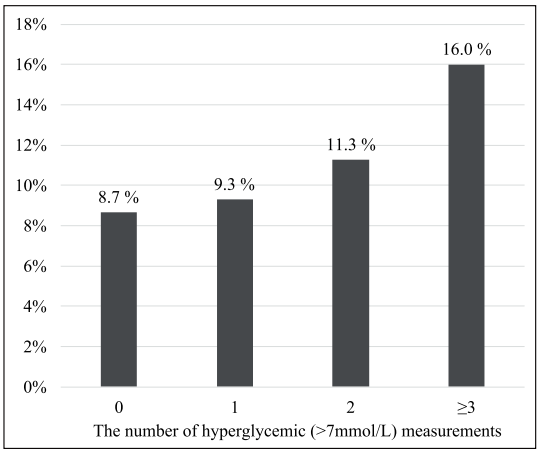

Fig. 2. Proportions of patients with infectious complications according to the number of hyperglycemic samples during the first day after surgery.

TABLE 3

Risk factors for postoperative infections in multivariable analysis.

	p	Odds ratio	95% confidence interval
Age ≥70 years	**0.017**	**1.57**	**1.09–2.28**
BMI ≥ 27	0.103	1.37	0.94–1.99
LVEF < 50%	0.051	1.54	1.00–2.38
Urgent/emergency procedure	0.144	1.34	0.91–1.98
Repeated hyperglycemia	**0.031**	**1.51**	**1.04–2.19**

BMI: body mass index; LVEF: left ventricular ejection fraction. Factors associated with postoperative infections in univariable analysis were included in the model. Statistically significant associations in the multivariable analysis are given in boldface.

Cefuroxime in most patients is conservative compared to that of others, but was not associated with increased infection rates. Postoperative infections, particularly major SSIs, were significantly associated with increased mortality, as in other studies (14, 15). Previously, immunosuppression, high and low BMI, bilateral internal mammary artery grafts, poor cardiac reserve, red blood cell transfusions, and postoperative respiratory failure have been associated with infectious complications (1, 16–19). In this study, preoperative factors that were significantly associated with the development of postoperative infections were older age, lower left ventricular ejection fraction, higher BMI, and urgent or emergency surgery. Patients with longer ventilator support times had more postoperative infections, suggesting either a causative role or an association with other risk factors in these patients. In

contrast to previous studies (20–22), we did not find diabetes to be significantly associated with postoperative infections. It is our impression that most diabetics in our study cohort were in good glucose control preoperatively and we suspect that variance in patients referred for surgery between studies might explain some of the observed differences. A significant portion (13%) of patients with infectious complications developed symptoms after primary hospital discharge or referral, emphasizing the importance of follow-up.

During the study period, we aimed at a strict 4–7 mmol/L glucose range during intensive care at our institution. The median average glucose level over the first postoperative day was 6.1 mmol/L in all patients and slightly higher, 6.3 mmol/L, in patients who developed infectious complications, well within target range. Despite that the average glucose level was acceptable in most patients, many had one or more hyperglycemic measurement. We found that repeated hyperglycemia and higher average blood glucose concentration despite significant effort toward normoglycemia was associated with increased rates of postoperative infections, while single hyperglycemia was not associated with adverse events. Previously, Furnary et al. (23) found 3 mmol/L increase in blood glucose to be an independent predictor of DSWI and mortality rate, while Omar et al. (24) reported higher percentage of out-of-range glucose values in diabetics and increased rates of wound infections in these patients. Some authors have reported that intensive glucose control may offer more benefit in nondiabetics compared to diabetics, while others report better outcomes in diabetics with tight glycemic control (25–28). In our study, repeated hyperglycemia was independently associated with later infectious complications, but whether it directly predisposes to later infections or is a surrogate marker of other comorbidities and a more severe clinical condition, as suggested by higher stroke and mortality rate, and how these patients should best be treated remain unclear. In a mixed ICU population, the benefits of tight glucose control are controversial (7, 8). Hypoglycemia is a potentially severe complication of glycemic control associated with worse prognosis. In this study, hypoglycemia occurred in 7.6% of patients, a smaller percentage than usually reported in patients treated with tight glycemic control (29, 30), and was not associated with adverse outcomes. Our results, and those of others, show that postoperative glycemic control is an important facet of patient care. Implementation of novel methods for glycemic control, such as continuous or semi-continuous blood glucose monitoring systems that offer therapeutic guidance, could improve clinical outcomes and should be explored.

The main strengths of this study are that we present a relatively large cohort of consecutive patients undergoing cardiac surgery including bypass, valve, aortic, and combined procedures. Also, we report the actual incidence of all postoperative infections in these patients, when many authors describe only the occurrence of SSIs. Furthermore, we describe real-practice-based encouraging results obtained with a single-dose conservative antibiotic prophylaxis regime and tight glucose control which both are still a controversial matter in cardiac surgery and intensive care. The main limitations of our study are heterogeneity of the study population limiting statistical power, the descriptive nature of this study, and the absence of a control group with alternative treatment.

In conclusion, we report that every 10th patient undergoing cardiac surgery develops an infectious complication and that mortality in these patients is significantly increased. Repeated hyperglycemia despite tight glycemic control during the first postoperative day is associated with increased risk of postoperative infections, stroke, and mortality.

ACKNOWLEDGEMENTS

K. M. J. and N. K. K. equally contributed to this article.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Received: March 2, 2017
Accepted: June 8, 2017

PUBLICATION IV

Extended Serum Lipid Profile Predicting Long-Term Survival in Patients Treated for Abdominal Aortic Aneurysms

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World Journal of Surgery, 42 (4): 1200-1207
doi: 10.1007/s00268-017-4281-3.

Extended serum lipid profile predicting long-term survival in patients treated for abdominal aortic aneurysms

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Short title: Serum lipid profile and survival in AAA patients

Keywords: Abdominal Aortic Aneurysm, Serum lipid profile, Extended Friedewald Formula

Grants: Academy of Finland (grant 286284 for T.L.), the Tampere University Hospital Medical Research Fund (grant X51001), the Finnish Foundation of Cardiovascular Research, the Finnish Cultural Foundation, the Tampere Tuberculosis Foundation, the Emil Aaltonen Foundation, and the Yrjö Jahnsson Foundation

Conflicts of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Word count: 2,681

Abstract

Background: Individuals treated for abdominal aortic aneurysms (AAAs) are high-risk patients in whom better risk prediction could improve survival. Contemporary serum lipid parameters, such as apolipoproteins and lipoprotein subfractions, may improve or complement the prognostic value of traditional serum lipids. The aim of this study was to ascertain the extended serum lipid profiles, long-term prognosis and their association in AAA patients.

Methods: Altogether 498 patients treated for AAAs and with available serum lipid values were retrospectively analysed. Contemporary lipid parameters were estimated using a neural network model, the Extended Friedewald formula.

Results: Younger age, smoking, and urgent or emergency surgery were associated with an unfavourable, and coronary disease and previous stroke with a favourable lipid profile. In multivariable analysis – in addition to advanced age, aneurysm rupture, smoking, pulmonary disease and diabetes – high triglycerides and traditional LDL cholesterol were significant independent risk factors for mortality, HR 1.84 (95% CI 1.20–2.81) and 1.79 (95% CI 1.18–2.73), respectively, while higher EFW-IDL cholesterol was associated with better survival, HR 0.31 (95% CI 0.19–0.65). Including serum lipid parameters improved the prediction of five-year survival (NRI=17.7%, p=0.016).

Conclusions: Extended serum lipid parameters complement risk prediction of patients treated for AAAs. An unfavourable lipid profile is associated with treatment of AAA earlier in life and with inferior long-term survival.

Introduction

The prevalence of abdominal aortic aneurysms (AAA) is 2.2-4.2% and up to 8.0% in men over 65. Individuals with AAAs represent high-risk patients who could benefit from improved methods of risk prediction.[1-4] Elective surgery carries a 30-day mortality rate of 4%, whereas emergency surgery is associated with rates exceeding 30% [5]. Female sex and advanced age seem to be connected to an unfavourable prognosis [6-8]. Elevated mortality is also found in patients with comorbidities such as renal insufficiency, congestive heart failure or chronic obstructive pulmonary disease (COPD) [9]. Endovascular aortic repair (EVAR) is associated with lower early and similar long-term mortality in elective surgery and equal 30-day mortality after ruptured AAA (rAAA) when compared to traditional open surgery [10-14].

Serum lipid parameters have been used to predict survival and morbidity in high-risk populations. Conventional lipid parameters comprise directly measured serum triglycerides (TG), serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) along with low-density lipoprotein cholesterol (LDL-C) usually estimated with the classic Friedewald formula.[15] Particularly LDL-C is considered significant and is included in several guidelines [16]. However, Friedewald-based LDL-C estimates represent a combination of LDL-C and intermediate-density lipoprotein cholesterol (IDL-C) and become unreliable when serum TG or lipoprotein (a) levels are high [15,17].

Apolipoproteins, key structural and functional components of lipoprotein particles, and lipoprotein subfractions, have been proposed as feasible prognostic markers that could improve or complement

traditional lipid parameters, and they have been included in modern clinical guidelines [16,18-21]. Apolipoprotein A1 (apoA1) is a constituent of HDL-C particles and a prerequisite for the removal of excess cholesterol from peripheral tissues in reverse cholesterol transport [22]. Apolipoprotein B (apoB) is a structural component in LDL-C, very-low-density lipoprotein cholesterol (VLDL-C) and IDL-C [23,24]. ApoA1 and apoB measurements have been used in cardiovascular risk assessment and the prediction of postoperative survival after carotid endarterectomy, where the inclusion of apoA to apoB ratio provided a net reclassification improvement (NRI) of 0.137 [25,26].

Apolipoprotein, true lipoprotein and lipoprotein subfraction concentrations are laborious to measure, but can be accurately estimated using a neural network model named the Extended Friedewald formula (EFW). The EFW-derived apoB, apoB to apoA1 ratio (apoB/apoA1), and IDL-C have been reported to be the best lipid parameter predictors of mortality in patients with type 1 diabetes.[27] In a working-age population, high-density lipoprotein cholesterol subfraction 2 (EFW-HDL_2-C), apoA1, apoB/apoA1, and very-low-density lipoprotein bound triglycerides (VLDL-TG) improved the prediction of non-fatal cardiovascular events and apoB that of cardiovascular mortality [28,29]. The aim of this study was to characterise the lipid profiles of AAA patients and ascertain the association of traditional lipid parameters and those obtained by means of EFW with long-term survival.

Materials and Methods

This study comprised patients treated for AAA both electively and in an emergency setting at the vascular clinic at Tampere University Hospital (TAUH), Finland, between March 2001 and September 2014. The indications for intervention in asymptomatic patients were an aortic diameter of 55mm or greater in men and 50mm or greater in women, or an aneurysm diameter growth of 10mm or more annually. Symptomatic and ruptured AAAs were operated on regardless of diameter. The treatment modality, open or endovascular, was chosen by a multi-disciplinary team, and in urgent or emergency cases, by the attending vascular surgeon. The elective study patients were habitually referred by primary care physicians or other specialists whereas urgent and acute cases were admitted through the emergency department.

The study subjects' demographic information, medical history, procedural details and follow-up data were prospectively recorded in an institutional structured database. The patients were classified as having dyslipidaemia when the diagnosis was previously established and statins or other lipid lowering medications had been prescribed. There was no institutional protocol for initiating statin therapy in adjunct to AAA treatment. Patients who had required open vascular or endovascular procedures prior to or after AAA treatment were classified as needing multiple procedures. The results of serum lipid analysis closest to the index procedure were retrieved from the Fimlab Laboratories Ltd database, and patients without available lipid measurements were excluded from the analysis. Baseline characteristics, including the age, sex and comorbidities of the included and excluded patients, were compared. The interval between lipid measurements and the operation for AAA was not restricted. The median time of cholesterol analysis was four days preoperatively, with an interquartile range of 390 days, and the majority, more than 90%, of lipid values were obtained

within three years prior to or after AAA treatment. There were no statistically significant differences in the time points of lipid analysis between elective and urgent or emergency cases. Serum TG, TC and HDL-C were obtained by direct measurements from fasting venous blood samples, and LDL-C was calculated using the classic Friedewald formula [15]. VLDL-TG, pure IDL-C, pure LDL-C, HDL_2 subfraction, ApoA1 and ApoB were estimated using EFW. Glomerular filtration rate (GFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [30]. The cohort was followed up until April 2015. The serum lipid profiles in all patients and the most important patient subgroups were ascertained, and the associations between serum lipid parameters and survival, as well as their value in risk prediction were analysed.

The study was performed according to the Declaration of Helsinki. Institutional review board approval was obtained. The statistical analyses were performed using SPSS 16.0 for Windows and R statistical software version 3.2.0. The statistical significance level was set at $p<0.05$. Univariable analysis was performed using the chi square test for categorical variables and the Mann-Whitney U test for nonparametric scale variables. Survival was analysed with multivariable stepwise Cox Regression analysis, prior to which inverse normal transformation was applied to the lipid parameters and GFR in order to reduce heteroscedasticity. Stepwise regression analysis was performed in forward and backward directions, and, otherwise, default criteria for stepAIC function were used. Risk factors for multiple vascular interventions were analysed with multivariable logistic regression. The predictive value of serum lipid parameters was analysed by calculating continuous NRI when including them with other factors associated with survival in the multivariable analysis. NRI was obtained using the R function IDI.INF in the survIDINRI package. A time point of five years and perturbation-resampling of 1000 iterations were used as parameters.

Results

Patient characteristics and vascular surgical burden

During the study period, 959 patients were treated for AAA at TAUH. Laboratory values were available for 498 patients, who formed the final study population. Sixty (12%) patients were female. The median age was 73 (range 44–92) years. Previous diagnoses included hypertension in 312 (63%), CAD in 206 (41%), dyslipidaemia in 167 (34%), pulmonary disease in 103 (21%), diabetes in 85 (17%), previous stroke or transient ischemic attack (TIA) in 62 (12%), and renal insufficiency in 45 (9%) patients. Smoking within 5 years prior to AAA treatment was present in 124 (25%) patients, and previous vascular surgical reconstruction(s) had been performed on 37 (7%) individuals. Seventy-two (14%) patients had aneurysm rupture. The excluded patients were slightly older (median age 75, p=0.003) and had a lower prevalence of diabetes (12%, p=0.032) and a higher prevalence of CAD (48%, p=0.048).

Endovascular treatment was chosen for 238 (48%) patients and open surgery for 260 (52%). The median follow-up time was 6.6 (range 0.5–14.0) years. A total of 89 (17.9%) patients had required multiple procedures. EVAR was associated with increased vascular surgical burden (OR 2.52, 95% CI 1.43–4.55), while older age and better GFR had the opposite effect (OR 0.96, 95% CI 0.92–0.99, and OR 0.66 for a 1-SD i.e. 21.05 ml/min increase, 95% CI 0.50–0.86, respectively).

Serum lipid profiles

Serum lipid values and EFW estimates are shown in Table 1. Significant differences in serum lipid profiles were found according to sex, age, the urgency and modality of operative treatment, as well as medical history. The key findings included a higher serum HDL-C, EFW-HDL_2 subfraction and EFW-ApoA1, but also elevated TC and TG, in women compared to men. Women were also older than men, with median ages of 76 and 73, respectively, $p<0.001$. Overall, age under 70 years was associated with a more unfavourable lipid profile in comparison to older patients. Smokers along with patients undergoing urgent or emergency operations had higher serum TC, LDL-C and EFW-LDL-C. The prevalence of dyslipidaemia was statistically significantly higher in patients with vs. without diabetes, 45% vs. 31%, $p=0.017$, respectively, and in patients with vs. without CAD, 44% vs. 26%, $p<0.001$, respectively. A similar non-significant trend was observed in patients with previous stroke. Patients with dyslipidaemia, diabetes, CAD, and stroke had significantly lower concentrations of TC, LDL-C and EFW-LDL-C. However, both dyslipidaemia and diabetes were associated with higher TG and EFW-VLDL-TG, with diabetics also displaying lower HDL-C and EFW-HDL_2 compared to non-diabetics.

Survival and the effect of serum lipid values

Survival for all patients as well as the patient subgroups is presented in Table 2. Age under 70 years was associated with improved survival at all time points. Furthermore, at 6 months' follow-up, EVAR, elective surgery, freedom from diabetes, dyslipidaemia, and freedom from renal insufficiency were also linked to better survival. The association of elective surgery with improved

survival persisted at 3 years of follow-up. At 5 years, dyslipidaemia was again connected to decreased mortality. Pulmonary disease, on the other hand, was associated with increased mortality at this time point and continued to do so at 10 years' follow-up. Hypertension was also associated with increased mortality at 10 years of follow-up. At 6 months, 3 years and 10 years, no statistically significant differences in traditional or EFW serum lipid values were found between survivors and non-survivors. Surprisingly, at the 5-year follow-up, survivors had lower HDL-C, HDL_2 subfraction and ApoA1 values compared to non-survivors, with median values of 1.14 (range 0.68–2.29) vs. 1.20 (range 0.68-2.41), p=0.019, 0.66 (range 0.31–1.80) vs. 0.72 (range 0.34–1.90), p=0.016, and 1.35 (range 1.02–2.08) vs. 1.40 (range 0.99–2.21), p=0.022, respectively.

In multivariable analysis (Table 3), older age at admission, aneurysm rupture, active or previous smoking within five years, pulmonary disease and diabetes were associated with increased mortality. Conversely, patients with dyslipidaemia had lower mortality rates. Furthermore, LDL-C and TG were linked to greater mortality, whereas EFW-IDL-C was associated with a significantly lower mortality rate (Table 3). Applying TG, LDL-C and EFW-IDL-C, in addition to the other factors independently associated with survival, in the prediction of five-year mortality provided a continuous NRI of 17.7% (95% CI 2.2–27.7%, p=0.016). When comparing TG and LDL-C to EFW-IDL-C it was noted that neither the first two nor EFW-IDL-C alone had a significant effect on NRI. Including EFW-IDL-C in addition to TG, LDL-C and other independent risk factors yielded a better continuous NRI of 16.8% (95% CI 1.4–27.3%, p=0.028). However, a similar change was not found when including TG and LDL-C with EFW-IDL-C accompanied by other risk factors. This suggests that EFW-IDL-C is at least as valuable in risk prediction as TG and LDL-C combined. Survival at different time points according to the number of significant independent risk factors is presented in Figure 1. None of the investigated serum lipid parameters correlated with the need for multiple procedures.

Discussion

Contemporary serum lipid parameters, such as apolipoproteins and lipoprotein subfractions, may be superior or complementary to the traditionally used lipid parameters in cardiovascular risk prediction [18-21]. This study outlined the serum lipid profiles of patients operated on for AAAs and their association with survival and was the first to investigate novel computationally estimated EFW serum lipid parameters in a vascular surgical patient cohort.

The study patients had higher median LDL-C than recommended for patients with peripheral arterial disease, although the median serum TC, HDL-C and TG levels were acceptable [31]. However, no recommendations presently exist for optimal lipid levels for AAA patients [21]. In this study, women had higher serum HDL-C and ApoA1, while still presenting with higher TG levels. Younger patients treated for AAAs had a more unfavourable serum lipid profile than older patients, suggesting a possible role of serum lipids in the earlier development of AAA. A similar finding regarding TC and LDL-C was found in smokers and individuals undergoing urgent or emergency surgery. Dyslipidaemia, diabetes, CAD and stroke were associated with lower instead of higher TC, LDL-C and EFW-LDL-C, which is likely to be explained by concomitant statin therapy.

Dyslipidaemia was associated with improved survival, which may be attributed to statin use as well as more careful follow-up and treatment of comorbidities. Statin therapy has been found to improve postoperative survival and is currently recommended for all patients undergoing AAA treatment [32,33]. Aneurysm rupture, advanced age, smoking, pulmonary disease and diabetes were associated with increased mortality, which is in line with previous studies [5-9]. Acute and urgent

cases sometimes presented without prior healthcare contacts and suboptimal treatment of comorbidities. Although comorbidities and age influence survival appreciably, multivariable analysis was still able to demonstrate statistically significant independent associations of lipid parameters with mortality. EFW-IDL-C was associated with a significant reduction in mortality, whereas LDL-C and TG correlated with increased mortality. Data on the role of IDL-C in predicting cardiovascular risk is thus far limited and unclear. Findings from the RESOLVE trial [34] showed that patients with metabolic syndrome had a lower baseline IDL-C than healthy controls, although no association between atherosclerosis and IDL-C was found. In a recent study on patients with acute myocardial infarction, IDL-C was associated with reduced mortality in two-year follow-up (HR 0.80 for 1-SD increase in IDL-C, 95% CI 0.67–0-96) [35]. The present study found a HR for mortality of 0.36 for computationally estimated EFW-IDL-C, which suggests a protective role. EFW-IDL-C was also found to improve the prediction of mortality in patients treated for AAAs. Contrarily, Niemi et al. [27] stated EFW-IDL-C to be a significant risk factor for mortality in patients with type 1 diabetes. The present study did not differentiate between type I and II diabetics, and the total number of diabetes patients was only 85 (17.1%). There was no statistically significant difference in EFW-IDL-C values between diabetics and non-diabetics. As the findings concerning IDL-C are controversial they should be interpreted with caution. Traditional LDL-C was significantly associated with increased mortality, with a HR of 1.77, which agrees with current clinical knowledge [16,36]. Why a similar association was not found for EFW-LDL-C, although the values of these parameters correlate significantly, remains unclear. Moreover, as IDL-C is a part of the same endogenous cholesterol pathway as LDL-C, the opposing associations with mortality demonstrated in this study require further investigation. The association of serum TG with increased mortality is in line with previous evidence [37].

The main limitations of this study were its retrospective nature, the fact that the time interval between lipid measurements and AAA treatment varied, and that, in a significant portion of the treated patients, no lipid values were available, possibly causing patient selection. While the acquisition of lipid parameters over an extended period may have caused bias, it did, however, provide a good overall estimate of the lipid profiles and, as serum lipid values measured in an acute setting are likely to be inaccurate [36], also avoided a possible systematic error. The exact type and dosage of statins or other lipid-lowering medications as well as patient compliance was not controlled for in the study, but it is the impression of the authors that, for the majority of patients with dyslipidaemia, statins or other lipid lowering medications had been prescribed, as supported by the results of the lipid analysis.

Conclusions

This study ascertained the serum lipid profiles and long-term survival of a contemporary cohort of patients undergoing interventional treatment for AAAs and, for the first time, included computationally estimated EFW lipid parameters in vascular surgical patients. An unfavourable lipid profile was associated with the need for surgical treatment at a younger age and worse survival. Applying these lipid parameters can provide an adjunct to risk prediction in patients treated for AAAs, and investigating computationally estimated EFW parameters is worthwhile in future AAA studies and in other high-risk patients as well. The results of this study highlight the importance of serum lipid profiles and suggest a need for specific guidelines concerning lipid therapy for patients with AAAs.

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Table 1. Serum lipid values and lipid estimates obtained with the Extended Friedewald formula in patients treated for abdominal aortic aneurysms. Median values and ranges are shown for all patients and the most important patient subgroups. Statistically significant differences between opposing subgroups (i.e. male vs. female, diabetes vs. no diabetes, etc.) are highlighted.

	TC	LDL-C	HDL-C	TG	EFW-VLDL-TG	EFW-LDL-C	EFW-IDL-C	EFW-ApoA1	EFW-ApoB	EFW-HDL_2
All patients n=498	4.50 (2.50–9.10)	2.64 (0.4–56.26)	1.16 (0.68–2.41	1.23 (0.40–4.90)	0.70 (0.12–3.80)	2.78 (1.35–5.96)	0.22 (0.04–0.95)	1.36 (0.99–2.21)	0.94 (0.44–2.04)	0.68 (0.31–1.90)
Male n=438	**4.50 (2.50–8.20)***	2.66 (0.45–5.76)	**1.14 (0.68–2.37)*****	**1.20 (0.40–4.90)****	**0.67 (0.12–3.80)****	2.79 (1.38–5.40)	0.21 (0.08–0.78)	**1.34 (0.99–2.08)*****	0.94 (0.51–1.85)	**0.67 (0.31–1.90)*****
Female n=60	**4.65 (2.50–9.10)***	2.53 (0.49–6.26)	**1.37 (0.79–2.41)*****	**1.53 (0.70–4.90)****	**0.87 (0.22–3.62)****	2.75 (1.35–5.96)	0.23 (0.04–0.95)	**1.53 (1.04–2.21)*****	0.96 (0.44–2.04)	**0.82 (0.38–1.90)*****
Age <70 years n=176	**4.70 (2.50–8.20)****	**2.87 (0.45–6.26)****	**1.10 (0.68–2.37)****	**1.43 (0.40–4.90 *****	**0.83 (0.17–3.80)*****	**2.96 (1.42–5.96)***	**0.25 (0.09–0.77)*****	1.38 (0.99–2.08)	**1.05 (0.51–1.85)*****	**0.63 (0.31–1.90)*****
Age ≥70 years n=322	**4.40 (2.50–9.10)****	**2.53 (0.49–5.89)****	**1.17 (0.68–2.41)****	**1.18 (0.40–4.90)*****	**0.64 (0.12–3.62)*****	**2.71 (1.35–5.40)***	**0.20 (0.04–0.95)*****	1.35 (1.00–2.21)	**0.90 (0.44–2.04)*****	**0.70 (0.34–1.90)*****
Elective n=383	**4.40 (2.50–8.20)***	**2.58 (0.45–5.51)***	1.15 (0.68–2.41)	1.22 (0.40–4.90)	0.69 (0.12–3.80)	**2.74 (1.35–5.40)***	0.21 (0.04–0.78)	1.36 (0.99–2.15)	0.93 (0.44–1.83)	0.68 (0.31–1.90)
Urgent or emergency n=115	**4.70 (2.60–9.10)***	**2.79 (1.06–6.26)***	1.17 (0.68–2.33)	1.28 (0.50–4.90)	0.72 (0.16–3.62)	**2.96 (1.58–5.96)***	0.24 (0.10–0.95)	1.38 (1.00–2.21)	1.00 (0.53–2.04)	0.69 (0.32–1.80)
Open repair n=260	**4.60 (2.50–8.10)****	**2.78 (0.45–5.50)****	**1.14 (0.68–2.37)***	**1.32 (0.40–4.90)***	0.74 (0.12–3.80)	**2.91 (1.35–5.26)****	**0.23 (0.09–0.77)*****	1.37 (1.00–2.21)	**0.98 (0.53–1.85)*****	**0.66 (0.31–1.90)***
Endovascular repair n=238	**4.35 (2.50–9.10)****	**2.45 (0.66–6.26)****	**1.18 (0.68–2.41)***	**1.18 (0.40–4.90)***	0.65 (0.17–3.62)	**2.66 (1.38–5.96)****	**0.20 (0.04–0.95)*****	1.36 (0.99–2.14)	**0.90 (0.44–2.04)*****	**0.70 (0.34–1.90)***
Coronary artery disease n=206	**4.20 (2.50–8.20) *****	**2.35 (1.02–6.26) *****	1.15 (0.70–2.29)	1.22 (0.40–4.40)	0.69 (0.17–3.33)	**2.55 (1.47–5.96) *****	**0.20 (0.09–0.63) *****	**1.35 (1.01–2.09) *****	0.88 (0.51–1.73)	0.68 (0.34–1.80)
Diabetes n=85	**4.10 (2.50–7.00)*****	**2.20 (0.45–5.04)*****	**1.09 (0.69–2.15)****	**1.44 (0.50–4.10)*****	**0.84 (0.24–3.13)*****	**2.43 (1.38–5.06)*****	0.22 (0.10–0.54)	**1.29 (0.99–2.00)***	0.93 (0.53–1.64)	**0.62 (0.31–1.65)****
Hypertension n=312	4.50 (2.50–9.10)	2.58 (0.45–5.89)	1.14 (0.68–2.41)	**1.31 (0.50–4.90) ****	**0.74 (0.18–3.80) ****	2.73 (1.35–5.28)	0.22 (0.04–0.95)	1.35 (0.99–2.20)	0.93 (0.44–2.04)	0.68 (0.31–1.90)
Dyslipidaemia n=167	**4.30 (2.50–9.10) ***	**2.37 (0.45–5.89) *****	1.16 (0.69–2.41)	**1.32 (0.50–4.90) *****	**0.74 (0.20–3.80) *****	**2.58 (1.35–5.40) *****	0.22 (0.09–0.95)	1.38 (1.02–2.15)	0.92 (0.53–2.04)	0.69 (0.31–1.90)
Smoking[1] n=124	**4.70 (2.70–8.10) ****	**2.88 (1.28–5.76) ****	1.16 (0.69–2.41)	1.30 (0.40–4.40)	0.72 (0.17–3.33)	**2.97 (1.65–5.26) ***	**0.24 (0.09–0.77) ***	1.37 (1.03–2.15)	**1.02 (0.51–1.85) ***	0.67 (0.34–1.90)
Pulmonary disease n=103	**4.70 (2.60–9.10) ***	**2.91 (0.87–5.89) ***	1.18 (0.68–2.41)	1.13 (0.40–4.90)	0.62 (0.17–3.62)	**2.94 (1.38–5.26) ***	0.22 (0.08–0.95)	1.39–1.04–2.15)	0.96 (0.51–2.04)	0.70 (0.32–1.90)
Stroke[2] n=62	**4.00 (2.60–8.20) ****	**2.18 (0.49–5.51) *****	1.16 (0.69–2.22)	1.31 (0.60–4.10)	0.73 (0.22–3.13)	**2.39 (1.35–4.92) *****	**0.20 (0.04–0.78) ***	1.33 (0.99–2.09)	**0.88 (0.44–1.83) ***	0.70 (0.31–1.75)

*p ≤ 0.05, **p ≤ 0.01, and ***p ≤ 0.001 (Mann-Whitney U test)

[1]Active smoking or smoking within five years

[2]Previous stroke or transient ischemic attack

Table 2. Survival in patients treated for abdominal aortic aneurysms. The number of surviving patients and patients included in follow-up at different time points are presented separately for all patients and the most important patient subgroups. Statistically significant differences between opposing subgroups (i.e. elective vs. urgent or emergency, diabetes vs. no diabetes etc.) are highlighted.

	6 months	3 years	5 years	10 years
All patients	455/498 (91.4%)	318/402 (79.1%)	207/312 (66.3%)	39/106 (36.8%)
Male	401/438 (91.6 %)	280/350 (80.0%)	185/273 (67.8 %)	33/89 (37.1 %)
Female	54/60 (90.0%)	38/52 (73.1%)	22/39 (56.4%)	6/17 (35.3%)
Age <70 years	**167/176 (94.9%)***	**124/141 (87.9%)*****	**93/112 (83.0%)*****	**24/39 (61.5%)*****
Age ≥70 years	**288/322 (89.4%)***	**194/261 (74.3%)*****	**114/200 (57.0%)*****	**15/67 (22.4%)*****
Elective	**367/383 (95.8%)*****	**255/306 (83.3%)*****	164/239 (68.6%)	29/83 (34.9%)
Urgent or emergency	**88/115 (76.5%)*****	**63/96 (65.6%)*****	43/73 (58.9%)	10/23 (43.5%)
Open surgery	**226/260 (86.9%)*****	179/225 (79.6%)	127/182 (69.8%)	29/67 (43.3%)
Endovascular repair	**229/238 (96.2%)*****	139/177 (78.5%)	80/130 (61.5%)	10/39 (25.6%)
Coronary artery disease	190/206 (92.2%)	130/169 (76.9%)	91/140 (65.0%)	20/61 (32.8%)
Diabetes	**72/85 (84.7%)***	43/61 (70.5%)	27/45 (60.0%)	5/12 (41.7%)
Hypertension	287/312 (92.0%)	189/243 (77.8%)	122/188 (64.9%)	**16/60 (26.7%)***
Dyslipidaemia	**159/167 (95.2%)***	105/125 (84.0%)	**75/98 (76.5 %)****	16/34 (47.1%)
Smoking[1]	118/124 (95.2%)	81/102 (79.4%)	50/75 (66.7%)	12/28 (42.9%)
Pulmonary disease	92/103 (89.3%)	55/77 (71.4%)	**33/61 (54.1 %)***	**2/15 (13.3%)***
Stroke[2]	53/62 (85.5%)	38/48 (79.2%)	23/39 (59.0%)	3/17 (17.6%)
Renal insufficiency	**72/85 (84.7%)***	43/61 (70.5%)	27/45 (60.0%)	5/12 (41.7%)

*p ≤ 0.05, **p ≤ 0.01, and ***p ≤ 0.001, when compared to controls (chi square test)

[1]Active smoking or smoking within five years

[2]Previous stroke or transient ischemic attack

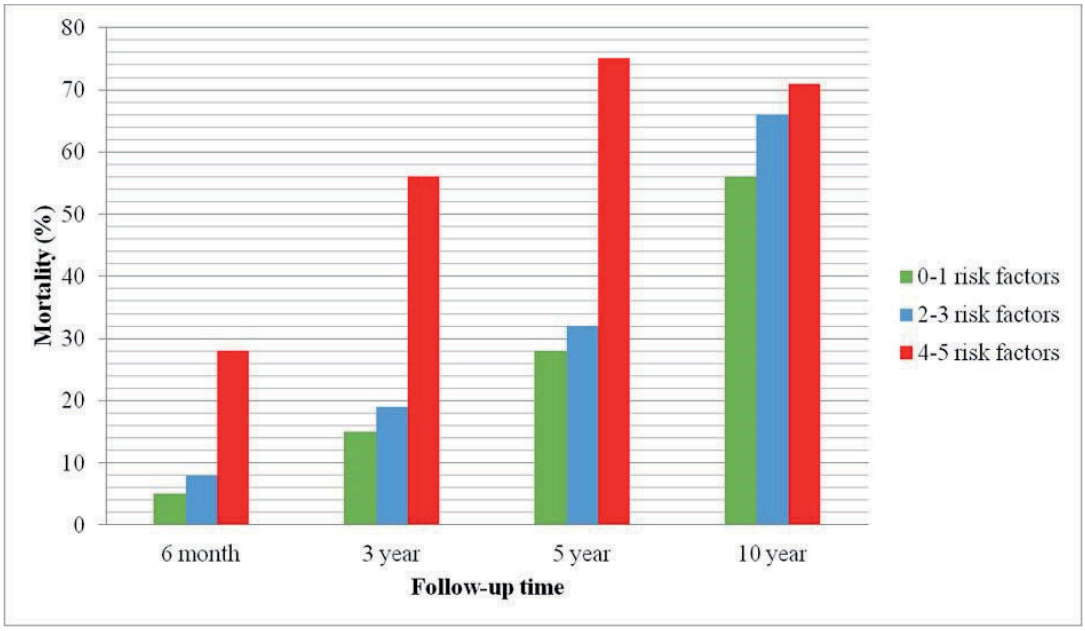
Table 3. Results of stepwise multivariable Cox Regression analysis on mortality. In serum lipids, the hazard ratios correspond to an increase of one standard deviation. Factors included in the Cox Regression analysis: age, sex, diabetes, dyslipidaemia, hypertension, coronary artery disease, stroke, pulmonary disease, renal insufficiency, previous reconstruction, active smoking or smoking within 5 years, aneurysm rupture, endovascular treatment, TC, LDL-C, HDL-C, TG, EFW-VLDL-TG, EFW-LDL-C, EFW-IDL-C, EFW-ApoA1, EFW-ApoB, EFW-HDL_2, GFR.

	HR	95 % CI	p-value
Age	1.08	1.05–1.10	<0.001
Aneurysm rupture	2.46	1.68–3.60	<0.001
Smoking[1]	1.70	1.16–2.49	0.006
Pulmonary disease	1.44	1.03–2.01	0.035
Dyslipidaemia	0.68	0.49–0.95	0.025
TG (SD=0.73mmol/L)	1.84	1.20–2.81	0.005
LDL-C (SD=0.97mmol/L)	1.79	1.18–2.73	0.006
EFW-IDL-C (SD=0.11mmol/L)	0.31	0.19–0.65	<0.001
Diabetes	1.50	1.01–2.25	0.046
Hypertension	1.30	0.96–1.76	0.090
Stroke[2]	1.39	0.94–2.06	0.094

[1]Active smoking or smoking within five years

[2]Previous stroke or transient ischemic attack

Figure 1. Survival at different time points according to the number of present risk factors (age ≥70 years, aneurysm rupture, active smoking or smoking within 5 years, pulmonary disease, diabetes, TG ≥2.3 mmol/L, LDL-C 2.6 ≥mmol/L)



PUBLICATION V

Serum apolipoprotein A-I concentration differs in coronary and peripheral artery disease

Khan, N., Khan, J., Lyytikäinen L.-P., Lehtimäki, T., Laurikka, J., Oksala, N.

Submitted.