Turun yliopisto
University of Turku

ASPECTS OF CORONARY REVASCULARIZATION

- With Special Reference to Renal Impairment and Permanent Work Disability

Anna Lautamäki

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Anna Lautamäki

University of Turku

Faculty of Medicine
Department of Cardiology and Cardiovascular Medicine
University of Turku Doctoral Programme of Clinical Investigation
Heart Center, Turku University Hospital

Supervised by

Docent Tuomas Kiviniemi, MD, PhD
Heart Center
Turku University Hospital
University of Turku
Turku, Finland

Docent Jarmo Gunn, MD, PhD
Heart Center
Turku University Hospital
University of Turku
Turku, Finland

Professor Juhani Airaksinen, MD, PhD
Heart Center
Turku University Hospital
University of Turku
Turku, Finland

Reviewed by

Docent Jukka Juvonen, MD, PhD
Kainuu Central Hospital
University of Oulu
Kajaani, Finland

Docent Mikko Hippeläinen, MD, PhD
Cardiac Surgery
Heart Center
Kuopio University Hospital
University of Eastern Finland
Kuopio, Finland.

Opponent

Docent Leo Ihlberg, MD, PhD
Heart and Lung Center
Department of Cardiac Surgery
Helsinki University Hospital
University of Helsinki
Helsinki, Finland

To my Family

ABSTRACT

Anna Lautamäki

ASPECTS OF CORONARY REVASCULARIZATION – With Special Reference to Renal Impairment and Permanent Work Disability

Coronary artery disease (CAD) is a common cause of morbidity in the Western world and remains one of the leading causes of mortality worldwide. Treatment of CAD aims at improving quality of life and prognosis. The cornerstone of the treatment relies on controlling modifiable risk factors—and thus disease progression—by focusing on lifestyle improvements and medications. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are the treatment options in advanced stages of the disease. The differences between PCI and CABG have been widely investigated, but the choice of treatment modality is still uncertain in specific subgroups, such as young patients or those with renal impairment. In the current study, the differences between PCI and CABG were retrospectively investigated in special patient groups. Quality of life was assessed with questionnaires, and medical records were reviewed. Results showed that patients with severe chronic kidney disease may also benefit from surgical revascularization and should be viewed as candidates for CABG in indications similar to those with normal or only mildly impaired renal function. In young patients, the prevalence of repeated revascularization was fairly high despite the good overall survival and low rates of major cardiac events, suggesting a more aggressive disease in this patient group. Unexpectedly, young patients had a high prevalence of permanent work disability despite low incidences of heart failure, strokes, or myocardial infarction. This finding may be related to the underestimation of the remaining working capacity after major surgery. In all patient groups, deteriorating scores on health-related quality of life after CABG predict later adverse cardiovascular events after the procedure. The present study provides information on prognostic factors for the outcome and survival in special patient groups undergoing coronary revascularization. These findings may have an effect on the treatment strategy of these patients.

Keywords: coronary artery disease, coronary revascularization, young patients, chronic kidney disease, permanent working disability, quality of life

TIIVISTELMÄ

Anna Lautamäki

SEPELVALTIMOVERENKIERRON PALAUTTAMINEN - näkökulmia eri potilasryhmistä

Turun yliopisto, Lääketieteellinen tiedekunta, Kardiologia ja Kardiovaskulaarilääketiede, Turun Yliopiston kliininen tohtoriohjelma.

Sepelvaltimotauti on yleinen kansantauti länsimaissa ja se on edelleen yleisin kuolinsyy maailmassa. Tärkein hoitomuoto sepelvaltimotaudissa on muokattavissa olevien riskitekijöiden vaikutusten hallinta elintapamuutosten ja lääkityksen avulla. Edenneessä oireisessa taudissa pallolaajennus ja ohitusleikkaus ovat vakiintuneita hoitokäytäntöjä. Ohitusleikkauksen ja pallolaajennuksen hyötyjä on laajalti tutkittu, mutta selkeää käsitystä hoidon valinnasta ei ole syntynyt. Tämän retrospektiivisen tutkimuksen tarkoitus oli tutkia toimenpiteiden eroja erityisryhmissä. Elämänlaatua mitattiin kyselytutkimuksen avulla ja sairaskertomustiedot kerättiin. Tutkimuksessa havaittiin, että toisin kuin aiemmin on ajateltu, myös vaikeaa munuaisten vajaatoimintaa sairastavat potilaat hyötyvät kirurgisesta toimenpiteestä. Nämä potilaat olisi hyvä nähdä kandidaatteina ohitusleikkaukselle vastaavin kriteerein kuin potilaat ilman munuaisten vajaatoimintaa. Nuorilla potilailla todettiin suhteellisen paljon uusintatoimenpiteitä pallolaajennuksen jälkeen siitä huolimatta, että potilasryhmän ennuste on hyvä ja merkittävien sydäntapahtumien määrä on alhainen. Tämä löydös viittaa siihen, että nuorilla potilailla sepelvaltimotauti saattaa olla aggressiivisesti etenevä entiteetti. Tutkimuksessa havaittiin, että nuorilla potilailla esiintyy paljon työkyvyttömyyseläkettä. Tämä voi osittain olla selitettävissä oireilevalla taudinkuvalla, mutta osasyynä voi olla myös potilaan työkyvyn aliarviointi. Kyselytutkimuksen perusteella todettiin, että laskevat pistemäärät elämänlaadun mittarissa ohitusleikkauksen jälkeen ennustavat sydäntapahtumia myöhemmässä vaiheessa kaikilla potilasryhmillä. Tämä tutkimus antaa tietoa ennusteellisista tekijöistä tiettyjen myöhäisvaikutusten osalta potilailla, joille tehdään sepelvaltimotaudin vuoksi kajoava hoito. Nykytutkimus antaa tietoa pallolaajennuksen ja ohitusleikkauksen valinnasta erityispotilailla ja sillä saattaa olla vaikutuksia hoidon valintaan kyseisissä potilasryhmissä.

Avainsanat: Sepelvaltimotauti, nuoret potilaat, kajoava hoito, munuaisten vajaatoiminta, työkyvyttömyyseläke, elämänlaatu

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ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AMI	Acute myocardial infarction
AP	Angina pectoris
ARB	Angiotensin II receptor antagonist
ASA	Acetyl salicylic acid
ATR1	Angiotensin II type 1 receptor
ATR2	Angiotensin II type 2 receptor
BIMA	Bilateral internal mammary artery
BITA	Bilateral internal thoracic artery
BMI	Body mass index
BMS	Bare-metal stent
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
EES	Everolimus-eluting stent
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EQ-5D	European quality of life five dimension
HDL	High-density lipoprotein
HRQoL	Health-Related quality of life
ICA	Invasive coronary angiography
IMA	Internal mammary artery
LAD	Left anterior descending artery
LDL	Low-density lipoprotein
LIMA	Left internal mammary artery

LITA	Left internal thoracic artery
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiac and cerebrovascular events
MI	Myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PTCA	Percutaneous transluminal coronary angioplasty
PTP	Pre-test probability
PWD	Permanent work disability
QoL	Quality of life
RA	Radial artery
RAS	Renin-Angiotensin System
SPECT	Single photon emission computed tomography
STEMI	ST elevation myocardial infarction
SYNTAX	The Synergy between PCI with TAXUS and Cardiac Surgery
TIA	Transient ischemic attack
TLR	Target lesion revascularization
UAP	Unstable angina pectoris
ZES	Zotarolimus-eluting stent

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1   INTRODUCTION

On a global scale, cardiovascular disease remains the leading cause of mortality, with an estimated 7.4 million deaths due to coronary artery disease in 2012 alone (World Health Organization [WHO], The top 10 causes of death: 2014 update). The incidence of coronary artery disease (CAD) is increasing worldwide, while mortality due to the disease is decreasing. Diagnostics and treatments have significantly evolved over the years, which may explain the decreasing mortality rates (Lloyd-Jones et al. 2010; Ford et al. 2007).

The main aim in the treatment of CAD is to improve quality of life and prognosis, which can be achieved by controlling the risk factors by focusing on lifestyle improvements and medications. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are the treatment options in the advanced stages of symptomatic disease. In Finland, the number of PCIs has quadrupled and the number of CABGs has declined by two-thirds from 1994 to 2013 (Kiviniemi et al. 2016).

Current European guidelines recommend PCI over CABG in patients with single- or two-vessel disease, and CABG over PCI in patients with significant three-vessel disease with left main and/or proximal left anterior descending coronary artery stenosis. In general, PCI is associated with a higher need for repeat revascularization during follow-up. However, patients with CAD undergoing CABG have a higher risk for procedural stroke, but the CABG relieves angina more than PCI does (Bravata et al. 2007). Patients with complex CAD undergoing CABG have lower rates of major adverse cardiac and cerebrovascular events (MACCE), especially when patients with complex CAD had comorbidities such as diabetes (Parasca et al. 2016; Serruys et al. 2009; Mäkikallio et al. 2016; Mack et al. 2011; Kappetein et al. 2013).

There is a lack of studies assessing the effect of declining renal function on the revascularization outcomes of these two methods. Moreover, although CAD has

generally been described as a disease of elderly patients, cardiovascular diseases are the third most common indication for permanent work disability (PWD) in Finland, thus having remarkable socioeconomic effects. In Finland, there were 17,943 people in PWD for cardiac indication in 2008 (National Institute for Health and Welfare, Finland – THL).

The primary objective of the current study was to investigate prognostic factors for special late outcomes and survival in patients undergoing coronary revascularization and to provide information on different treatment options in special patient groups. These findings may have a direct influence on the current protocols. In addition, the novel finding of the current study may have a significant effect on the socioecomonic status of many young patients with CAD.

2   REVIEW OF THE LITERATURE

2.1   Development and symptoms of coronary artery disease

2.1.1   *Atherosclerosis*

Atherosclerosis is a progressive disease that begins in childhood but manifests clinically later in life. Coronary artery disease is caused by atherosclerosis, and it often leads to a symptomatic disease when progressing. Pre-existing lesions evolve and new lesions develop during follow-up when the disease progresses (Singh 1984). Early findings of the disease may already be observed at a young age (Tuzcu et al. 2001).

The development of atherosclerosis is multi-factorial: patients who have a genetic predisposition and varying environmental factors—nearly 300 have been identified altogether (Hopkins & Williams 1981)—may develop the disease. An atheroma develops and forms the typical plaque in the intima of the coronary artery. The growth of an atheroma leads to a decrease in the diameter of the lumen of the coronary artery, thus disturbing the normal blood flow. If the stenosis decreases the blood flow enough, the oxygen transport to the myocardium is decreased, followed by ischemia, and often (but not always) leads to clinical symptoms (Stary et al. 1994).

Early in the course of atherosclerosis, there are only mild changes in the inner layer (the intima) of the arteries (Graham et al. 2007). The development of a fatty streak starts when low-density lipoprotein (LDL) particles accumulate in the intima. These lipoproteins bind to proteoglycan, and will therefore become more susceptible to oxidative progress along with other chemical modifications of lipoprotein particles. Macrophages recognize modified lipoproteins and start uptake particles, which leads to the development of foam cells. When the foam cells die, the excess lipids are released into the extracellular space in the intima. Modified

LDL particles, extracellular lipids, and dead foam cells form a fatty streak in the artery wall (Libby et al. 2015; Kovanen et al. 2016).

The next phase of atherosclerosis presents solid and multiple extracellular lipids, and the fatty streaks progress to a fibrous plaque (Stary 2000). Fibroatheroma forms when the top of the fatty streak is covered with a fibrotic layer due to the collagen synthesis of smooth muscle cells (Kovanen et al. 2016). The development of a fibro-atheroma is generally slow (Worthley et al. 2001). Modified LDL particles, especially oxidated ones, cause an inflammatory response in the intima. Because of this response, the cytokines in the intima activate and lead to endothelial and smooth muscle cell activation. Cytokines can prevent the formation of collagen from the smooth muscle cells and can also lead to collagen death. This cascade can make the fibrotic layer on top of the atheroma thinner, which can lead to vulnerable plaque formation (Kovanen et al. 2016). These plaques have a high risk of disruption, which may cause an acute coronary syndrome. In 60–70% of patients with acute coronary syndrome, a plaque rupture can be detected (Falk et al. 1995; Hansson 2005). In an acute plaque rupture, rapid immunological responses are activated. In addition, increased inflammation may also be detected during a stable phase in patients with atherosclerotic lesions (Juvonen et al. 1999).

2.1.2   Symptoms

When the blood flow in coronary arteries is sufficiently diminished due to stenosis, symptoms occur. Typical angina pectoris symptoms are chest pain located substernally; chest pain characterized as squeezing, tightness, aching, or crushing; arm discomfort, dullness, fullness, heaviness, or pressure (Canto et al. 2002). Symptoms can be prolonged or fluctuating. It is not unusual to have uncommon symptoms such as dyspnea, diaphoresis, syncope, or pain in the arms, epigastrium, shoulder, or neck (Canto et al. 2002). Chronic stable angina pectoris symptoms occur when the atheroma is prominent enough to significantly prevent

blood flow in coronary arteries when the need for oxygen in the myocardium is increased, for example during exercise. When the blood flow is already impaired at rest, the disease manifests as an acute coronary syndrome that includes unstable angina pectoris (UAP), myocardial infarction (MI), and a sudden cardiac death. In most cases, acute coronary syndromes (ACS) are caused by plaque disruption and subsequent occlusion (transient or permanent) of the affected coronary artery (Worthley et al. 2001). Angina pectoris pain is provoked by stress, and the pain typically subsides with rest or nitroglycerin (Prinzmetal et al. 1959).

2.2 Classification of coronary artery disease

2.2.1 Stable angina pectoris

Stable angina pectoris is a clinical diagnosis of reversible chest pain under stress. In their research in the 1980s, Diamond and Forrester were using a generally well-accepted definition for stable angina. It contained typical angina defined as a substernal discomfort brought on by exertion that relieved within 10 minutes through rest or nitroglycerin. Therefore, the typical clinical symptoms are chest pain during physical activity and the relief from pain when resting. The level of physical activity that causes symptoms is a subjective experience for each patient. Traditionally, hemodynamically significant symptomatic disease has been considered angiographically as a $\geq 50\%$ narrowing in the left main coronary artery or a $\geq 70\%$ narrowing in other major coronary arteries that can lead to episodes of reversible myocardial supply mismatch or a fractional flow reserve of < 0.80 (Uren et al. 1994; Varnauskas et al. 1982). According to Steg et al. (2007), the risk for cardiovascular events (stroke, myocardial infarction, and cardiovascular death) increased significantly depending on the arterial disease location. Patients with only risk factors had a 2.2% risk for cardiovascular events over the one-year follow-up, and patients with established arterial disease in three locations had a 9.2% risk. Therefore, the prognosis of stable coronary artery disease depends on anatomical and clinical characteristics (Steg et al. 2007; Montalescot

et al. 2013). A recent meta-analysis reviewed the prognosis of the patients with stable CAD. It was found that patients with non-obstructive disease have significantly better prognoses than the patients with obstructive disease. However, even the non-obstructive disease presents poorer prognoses compared to the disease-free patients (Wang et al. 2017).

2.2.2   Acute coronary syndrome

ACS is a potentially life-threatening state including unstable angina pectoris, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) (Steg et al. 2002). According to Piironen et al. (2017), patients with ACS had a 37% occurence of recurrent cardiovascular events over the three-year follow-up. During the one-year follow-up, the prognosis after acute myocardial infarction improved, and therefore rates of mortality, recurrent acute myocardial infarction, and recurrent coronary vascular diasease events have declined (Brown et al. 2015). The prognosis of ACS has improved significantly during the past 18 years (Piironen et al. 2017). However, in spite of the improvement, the prognosis is still markedly worse when comparing to the general population (Piironen et al. 2017).

Patients with ECG abnormalities excluding ST segment elevation can be divided by the measurement of troponins, markers of a myocardial necrosis (Holmvang et al. 2003). UAP is defined as angina pectoris with at least one of the following three features: 1) the pain occurs at rest, 2) the pain is severe and is described as frank pain, or 3) the pain occurs with a crescendo pattern, including more severe pain (Braunwald et al. 2002). Contrary to NSTEMI patients, those diagnosed with UAP do not exhibit a troponin elevation. NSTEMI and UAP can result from the rupture of unstable atheromatous plaque, leading to the formation of the thrombus (typically subtotal occlusion in this patient group [Crea et al. 2013]), coronary arterial vasoconstriction, imbalance of supply and demand of oxygen in the myocardium, and the progression of atherosclerosis that leads to intraluminal

narrowing of a coronary artery (Libby et al. 2008, 1319–22). In this patient group, chest pain can occur with abnormalities in ECG, such as a T-wave inversion, an ST segment depression, or a T-wave flatness. An ECG in this patient group can be equally normal as well. Patients with abnormal or normal ECG with rising troponin as a sign of myocyte necrosis have an NSTEMI; patients with clinical symptoms and ECG findings without elevated troponin levels have a UAP (Holmvang et al. 2003).

The laboratory evidence of myocardial necrosis and persistence of ST segment elevation in an ECG shows that patients with chest pain have STEMI. An occlusive thrombus leads to necrosis that usually produces ST elevation on the ECG. If the vessel is not reperfused promptly, patients with STEMI will often develop Q-waves in the ECG as a sign of a transmural infarct, suggesting a myocardial necrosis at the full thickness of the ventricular wall (Libby et al. 2008, 1210–11).

2.3   Diagnosis of coronary artery disease

Resting ECG should be performed in all patients with suspected angina. However, in patients with stable disease, findings in ECG may be normal despite the presence of CAD (Cassar et al. 2009). According to Cassar et al. (2009), 50% of patients with normal resting ECG develop abnormalities in ECG during an episode of angina pectoris. In patients with stable CAD, the physical examination is often unrevealing (Cassar et al. 2009). The non-invasive stress tests are usually suitable for most patients with angina pectoris symptoms. Pre-test probability (PTP) estimates the probability of CAD in patients and is used as a tool to estimate the viability of stress testing in patients with suspected stable CAD. Major determinants of PTP are the nature of symptoms, age, and gender (Diamond et al. 1979). Patients with PTP between 15% and 85% most likely have beneficial impact from the stress test, unlike patients with low or high PTP. Because of this, ESC Guidelines (2013) on the management of stable coronary artery disease (Montalescot et al. 2013) do not recommend using stress tests in patients with a

PTP either below 15% or above 85%. The ECG exercise test is widely used because of its simplicity and widespread availability. According to the 2013 ESC guidelines (Montalescot et al. 2013), the main diagnostic abnormalities in ECG during exercise (treadmill or bicycle) are a horizontal or down-sloping ST segment depression of ≥ 0.1mV (persisting for at least 0.06–0.08s after the J-point) in one or more ECG leads. Stress echocardiography may be used instead of ECG to estimate the myocardial function (necrotic, ischemic, and normal) (Sicari et al. 2009). Myocardial perfusion scintigraphy (single photon emission computed tomography [SPECT]) is a tool that reflects relative regional myocardial blood flow in coronary arteries, and produced images from SPECT can reveal stress-induced ventricular dysfunction in patients with CAD (Ritchie et al. 1995). Perfusion scintingraphy can be use as an alternative choice for exercise stress tests (Montalescot et al. 2013). In addition, positron emission tomography (PET) perfusion imaging can be used to detect CAD. However, the SPECT technique is more widely available and less expensive when comparing to PET (Di Carli et al. 2007). Stress cardiac magnetic resonance (CMR) can detect wall motion abnormalities induced by ischemia in the myocardium, and this technique can be used to detect the myocardial ischemia itself (Nagel et al. 1999). Coronary computed tomography angiography assesses coronary anatomy and may be used to detect coronary stenosis. This coronary anatomy assessment technique can be an alternative choice to invasive coronary angiography in selected patient groups (Paech et al. 2011). Invasive coronary angiography (ICA) is a method of choice in patients with a high likelihood of significant coronary artery stenosis. In patients with high PTP and severe clinical symptoms, and in patients with high risk for cardiovascular events, early executed ICA without previous non-invasive stress tests may be a good choice to observe lesions in coronary arteries (Montalescot et al. 2013).

2.4   Risk factors of coronary artery disease

CAD has several risk factors. Well-known modifiable risk factors are high blood pressure, hypercholesterolemia, smoking, and diabetes (Wilson et al. 1998). In addition, obesity and family history are significant risk factors of CAD (Chow et al. 2011). Altogether, over 300 independent risk factors for CAD have been identified (Hopkins & Williams 1981). In patient care, however, the treatment focuses on modifiable risk factors.

2.4.1   Modifiable risk factors

2.4.1.1 Hypertension

The optimal level of systolic blood pressure depends on the other risk factors of a patient. According to ESH/ESC guidelines for the management of arterial hypertension, the goal for the systolic blood pressure is under 140 mmHg and the goal for the diastolic blood pressure is under 90 mmHg in patients at low-risk; for high-risk patients, including patients with comorbidities such as diabetes and renal failure, the goal is < 130/80 mmHg (Mancia et al. 2013). According to Stamler et al. (1993), in people over 35 years old, the level of blood pressure is mostly above the optimal.

High blood pressure causes excess pressure against the artery walls, eventually leading to artery damage, making them more vulnerable to complications. The high pressure inside the arteries leads to a response of muscles of the walls, making them thicker and thus narrowing arteries. In addition to the wall thickening, the extra pressure can damage the arterial endothelium. Furthermore, hypertension speeds up the reproduction of smooth muscle cells and may lead to the transformation of the endothelial cells into proinflammatory cells that increase the occurrence of monocytes in the walls of coronary arteries (Kovanen et al. 2016).

2.4.1.2 Diabetes

Diabetes is one of the major risk factors for CAD and cardiac morbidity (Haffner et al. 1998). Patients with diabetes have a two- to fourfold increased risk for CAD (Feskens et al. 1992). The fasting plasma triglyceride levels are increased and high-density lipoprotein cholesterol (HDL) levels are low in patients with hyperinsulinemia. Additionally, blood pressure in patients with hyperinsulinemia is significantly higher compared to patients with normoinsulinemia (Zavaroni et al. 1989). Prognosis after a coronary event is poor in patients with diabetes, and the long-term prognosis is worsened by increased rates of repeated myocardial infarctions, congestive heart failure, and death (Haffner et al. 1998; Malmberg et al. 2000).

2.4.1.3 Smoking

Smoking is a significant risk factor for CAD and is the leading preventable cause of the disease (Yusuf et al. 2004). Smoking precipitates the development of atherosclerosis and is a significant risk factor for coronary thrombosis (Burke et al. 1997, 1998). Long-term smoking may increase the oxidation of LDL and impair coronary artery vasodilatation that is endothelium dependent. In addition, smoking has inflammatory and hemostatic effects. It is also associated with spontaneous platelet aggregation (Bazzano et al. 2003). Compared to the healthy non-smoking population, smokers have a sixfold incidence of plaque development (Fausto 1998). According to Critchley et al. (2004), smoking cessation after myocardial infarction can reduce the risk of mortality by 36%.

2.4.1.4 Hypercholesterolemia

The Framingham Heart Study showed that high cholesterol levels are associated with an increased incidence of CAD. These findings have been corroborated repeatedly in other studies, showing that hypercholesterolemia is a major risk fac-

tor for CAD (Castelli 1988). Elevated serum cholesterol is significantly associated with the occurrence of coronary artery disease (LaRosa et al. 1990).

Low-density lipoprotein cholesterol (LDL) is the main player in the development of atherosclerosis (Badimon et al. 2012). Most of the total cholesterol in the plasma is low-density lipoprotein (Neaton et al. 1992; Kovanen et al. 2016). The serum LDL mainly causes the development of an atheromatous plaque as well as a vast majority of clinical events of coronary artery disease (Domanski et al. 2015). Small lipoprotein particles accumulate in the intima, which is the inner layer of the artery, and the proteoglycan of the intima forms aggregates along with lipoprotein particles. The binding of lipoproteins to proteoglycan seems to be an important component of the pathogenesis of early atherosclerosis, causing sensitivity to oxidative and other chemical modifications. Oxidized LDL particles are chemotactic to monocytes and are quickly taken up by macrophages, which then form foam cells (Kruth 2002; Williams et al. 2005). The development of atherosclerosis involves an inflammatory response, along with lipid and fibrotic tissue accumulation (Libby et al. 2002).

2.4.1.4.1   *Obesity*

Obesity (defined as a body mass index [BMI] scale $\geq$ 30 kg/m^2 [Lavie et al. 2009]) has been shown to be an independent risk factor for CAD (Jousilahti et al. 1996). According to McGill Jr. et al. (2002), there were already fatty streaks and lesions in coronary arteries in young obese male patients. In addition, the microscopic grade of atherosclerosis and stenosis in the left anterior descending artery (LAD) were associated with obesity in young men. Obesity is a well-documented factor associated with other coronary heart disease risk factors such as hypertension and diabetes. When BMI rises, there is a higher risk for atherogenic dyslipidemic changes, which can lead to higher levels of LDL cholesterol and triglycerides and lower levels of HDL cholesterol (Reeder et al. 1992; Denke et al. 1994). However, these findings of lipid changes are more consistently associ-

ated with central obesity (Després et al. 1989). Therefore, the waist-hip ratio as a marker of visceral fat is considered as a better predictor for CAD than the BMI scale (Yusuf et al. 2005). In addition to the other risk factors, obesity increases the risk of sleep apnea, which is associated with the risk of cardiac mortality and morbidity (Kohler et al. 2010).

2.4.2   *Impact of age on coronary artery disease*

Aging increases the risk of CAD (Anand et al. 2008). In general, CAD is considered a disease of middle-aged to elderly patients. However, the burden of risk factors for CAD can be surprisingly high in young people. Among them, abnormal lipid profiles are relatively common and can progress into a manifest CAD (Kuklina et al. 2010). The progression of atherosclerosis begins at a young age and early changes can already be found in 1 out of 6 teenagers (Yusuf et al. 2001). The conventional risk factors are the same in both young and old age.

In young patients, there are several prevalent risk factors for cardiovascular disease: smoking, elevation in body mass index, systolic blood pressure, and serum LDL cholesterol and triglyceride concentrations are related to atherosclerotic lesions in young people (Williams et al. 2002; Webber et al. 1979; Berenson et al. 1998). Hypertension leads to a fourfold increase in the incidence of plaque development when comparing with the healthy non-smoking population. In addition, obesity is a risk factor for the development of CAD in young patients (Fausto 1998). The incidence of CAD in patients under 40 years old is shown to be relatively low, accounting for only about 3% of all patients (Jalowiec et al. 1989). Young patients with symptomatic CAD have an excellent short-term prognosis, and mortality in this patient group is low compared to middle-aged and elderly patients (Hoit et al. 1986).

2.4.3 Effects of socioeconomic status

A low socioeconomic status is one of the independent risk factors for CAD. Low socioeconomic status was defined by several measures, including educational level, housing tenure, occupational status, and household income per consumption unit, economic difficulties, and economic satisfaction.

Smoking is associated with socioeconomic disadvantage (Laaksonen et al. 2005). In addition, smoking cessation among the low socioeconomic class seems less likely to be successful (Hiscock et al. 2012). Patients with low socioeconomic status are at higher risk of death from CAD events when compared to patients in the higher social group (Rose et al. 1981).

2.4.4 Chronic kidney disease and coronary artery disease

Chronic kidney disease (CKD) is a well-known risk factor for cardiovascular disease (CVD) (Schiffrin et al. 2007). Renal impairment often leads to other abnormalities, including changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, anemia, and homocysteine levels (McCullough 2002). However, before progressing into kidney failure, patients with early CKD are more likely to progress to fatal CVD. Therefore, patients with CKD are an important patient group when assessing risk factors and survival in CVD. Overall mortality in patients with CKD is significantly higher than in the general population, and the incidence of CVD in every stage of CKD is high (Foley et al. 1998; Parfrey et al. 1999; Keith et al. 2004; Liu et al. 2012).

Staging of CKD is typically performed according to estimated glomerular filtration rate (eGFR). According to the Kidney Disease Improving Global Outcomes (KDIGO) (Moe et al. 2009), patients can be divided into five different stages for risk stratification and clinical decision-making when weighing treatment options. Patients with stage 1 CKD have normal kidney function (eGFR 90+ ml/min/1.73m^2), but some features (e.g., abnormal urine) point to kidney disease.

In stage 2 CKD (eGFR 60–68 ml/min/1.73m^2), patients have mildly reduced kidney function. Furthermore, in stages 3a and 3b CKD (eGFR 30–59 ml/min/1.73m^2), patients have moderately reduced kidney function; stage 4 CKD (eGFE 15–29 ml/min/1.73m^2) patients have severely reduced kidney function; and stage 5 CKD (eGFR und 15 ml/min/1.73m^2) have end-stage kidney failure. Significant renal dysfunction is defined by the National Kidney Foundation in the Kidney Disease Outcomes Quality Initiative classification of kidney function as an eGFR under 60 ml/min/1.73m^2 (i.e., stage 3 or worse) (Levey et al. 2003; Moe et al. 2009).

Prognosis is known to be poor in CKD patients with ACS. The outcome of patients with CKD undergoing coronary revascularization is also poor as compared to patients with normal renal function (Herzog 1999; Herzog et al. 1998; Schoebel et al. 1997; Ahmed et al. 1994; Rostand et al. 1988; Rinehart et al. 1995). According to a previous study, patients with severe kidney disease are also more likely to be treated with medical therapy alone, and the outcomes are poor in spite of the optimal medication therapy (Keeley et al. 2003).

2.5   Primary prevention of coronary artery disease

In general, modifying existing risk factors or preventing their development is considered primary prevention. Prevention of CAD development by using primary prevention is important and has a remarkable effect on public health. Patients at high risk for coronary events are recommended to receive primary prevention for the disease (Perk et al. 2012). According to Unal et al. (2005), primary prevention was four times as effective at decreasing mortality in comparison to secondary prevention in patients with coronary artery disease (Unal et al. 2005).

Lifestyle modification, including healthy nutrition and normal weight, decreases the risk of CAD. Physical activity is known to help prevent the development of coronary artery disease, and it seems to be as important as smoking cessation,

controlling blood pressure, and lowering levels of serum cholesterol (Powell et al. 1987; Kavey et al. 2003).

In the long term, decreasing the amount of risk factors and adequately controlling the modifiable ones slows the progression of atherosclerosis and improves prognosis.

Reducing the serum LDL cholesterol is beneficial in the primary prevention of coronary artery disease (Domanski 2007). The incidence of advanced CAD is reduced by drug therapy that lowers the lipid levels in the serum (Pedersen et al. 1994; Sacks et al. 1996). According to the ACC/AHA Guideline on the Treatment of Blood Cholesterol in 2013, a primary lipid-lowering drug is recommended to be the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, which are more commonly known as statins. Other serum lipid-lowering medications are fibrates (fenofibrate, gemfibrozil), nicotinic acid (niacin in immediate-, slow-, or extended-release form), bile acid sequestrants, ezetimibe, PCSK9 inhibitors, and omega-3 fatty acids (also called marine fatty acids, including eicosapentaenoic acid alone, docosahexanoic acid alone, eicosapentaenoic acid plus docosahexanoic acid, and alpha-linolenic acid). Statin therapy is recommended for primary prevention in patients aged 40–79 with low-density lipoprotein cholesterol levels between 4 mmol/l and 10 mmol/l, and when the risk for cardiovascular disease due to atherosclerosis is 7.5% or above (Stone et al. 2013). In Finland, the recommendation for primary prevention is an LDL below 3.0mmol/l in patients with a low risk profile and below 2.5mmol/l in patients at high risk (Käypä hoito). In patients with very high risk, the aim for the LDL level is below 1.8mmol/l (Käypä hoito).

Statins decrease hepatocyte cholesterol synthesis in the liver by a competition inhibition of HMG-CoA reductase enzyme. This enzyme catalyzes the conversion of the HMG-CoA into a mevalonate in cholesterol synthesis. Reduction of intracellular cholesterol concentration causes LDL receptor appearance on the hepatocyte cell surface in the liver and leads to decreasing levels of LDL choles-

terol in circulating system by extracting LDL cholesterol from the blood to intra-cellular space. In addition, statins have a beneficial impact on increasing the concentration of HDL cholesterol and decreasing the triglyceride levels (Hobbs et al. 1992; Schachter et al. 2005; Maron et al. 2000).

Smoking speeds the development of atherosclerosis and is also a major risk factor for sudden death and coronary thrombosis (Burke et al. 1997; Burke et al. 1998). According to Unal et al. (2005), between the years 1981 and 2000, the overall smoking prevalence declined by 35% in England and Wales. This prevalence reduction and smoking cessation led to fewer deaths in the study population (approximately 29,715). There were 5,035 fewer deaths in patients with established CAD (secondary prevention) and approximately 24,680 fewer deaths in the healthy population (primary prevention).

High blood pressure is a well-known risk factor for CAD (Wilson et al. 1998). According to Lewington et al. (2002), every 20 mmHg increase in systolic blood pressure or a 10 mmHg increase in diastolic blood pressure doubles the risk for cardiovascular events in patients aged 40–69 years old (Lewington et al. 2002). The cardiovascular death rates increase progressively and linearly from blood pressure levels of 115 mmHg systolic and 75 mmHg diastolic upward (Lewington et al. 2002). Antihypertensive treatment lowers blood pressure and significantly reduces the risk of cardiovascular morbidity and mortality (Perk et al. 2012). The commonly used regimen of antihypertensive treatment reduces the risk for cardiovascular events, and a larger reduction in blood pressure produces a larger reduction in risk (Turnbull 2003). ACE inhibitors as an antihypertensive treatment reduced the risk of cardiovascular death by 20%, and ACE inhibitors and calcium antagonists reduced the risk of cardiovascular events by 22% when compared to placebo (Turnbull 2003). It is recommended that the general population with blood pressure over 140/90 mmHg have antihypertensive treatment (Perk et al. 2012).

Diabetes mellitus is known to be a strong predictor of adverse cardiovascular events (Coutinho et al. 1999). In addition, diabetes mellitus is associated with more extensive atherosclerosis when comparing to non-diabetic patients. Diabetic patients had a greater atherosclerotic burden and impaired compensatory remodeling of the artery wall (Nicholls et al. 2008). In male patients with diabetes, the odd ratio for cardiovascular events was threefold and in female diabetic patients fourfold when comparing to patients without diabetes (Anand et al. 2008). Diabetic patients typically have multiple cardiovascular risk factors, which should be treated according to existing guidelines. Controlling these risk factors, including high blood pressure and dyslipidemia, will reduce the risk for developing CAD and cardiovascular events (Perk et al. 2012). According to Holman et al. (2008), patients treated with intensive medication of diabetes (either sulfonylurea or insulin or, in overweight patients, metformin) had a 15% reduction in risk of myocardial infarction (P=0.01) and a 13% reduction in risk for death from any cause (P=0.007) when comparing with patients treated only with dietary restriction. In the metformin group, there was a 27% reduction in risk of death from any cause (P=0.002) and a 33% reduction in risk of myocardial infarction (P=0.005) (Holman et al. 2008). In patients with type 2 diabetes and an existing cardiovascular disease, a recent study showed a significant reduction in cardiovascular-related deaths when treated with empaglifozin (Zinman et al. 2015), and a similar reduction in cardiovascular mortality was found when these patients were treated with liraglutide (Marso et al. 2016).

2.6 Treatment of coronary artery disease

The principles of CAD treatment are to relieve ischemic symptoms and to decrease myocardial oxygen demand or to increase the myocardial oxygen supply. In addition, the treatment aims to improve the prognosis, including decreasing the incidence of cardiovascular events, such as recurrent myocardial ischemia and cardiac death (Roffi et al. 2016).

2.6.1 *Medication therapy in patients with CAD*

Nitrates are angina symptom–relieving medications recommended for patients with ACS when their chest pain is persisting (Roffi et al. 2016). Nitrates may be useful during the acute phase, when patients have hypertension or heart failure. The nitrate medication is valuable when patients with STEMI have angina (Steg et al. 2012). In addition, nitrates are used in stable CAD to offer coronary arterial and venous vasodilatation that provides symptomatic relief of angina pectoris (Montalescot et al. 2013).

Previously, β-Adrenoceptor antagonists, known as beta-blockers, have played an important role after myocardial infarction. However, recently the efficiency of beta-blocker therapy in patients with stable CAD has been questioned. Beta-blockers are shown to be efficient in decreasing mortality and cardiac events in patients with recent myocardial infarction and in patients with systolic dysfunction or heart failure (Dargie et al. 2001; CIBIS-II Study 1999; Hjalmarson et al. 1981). According to the Reduction of Atherothrombosis for Continued Health (REACH) registry (Bangalore et al. 2012), in patients with a remote history of acute myocardial infarction or in patients with CAD without prior myocardial infarction, beta-blockers are not associated with a lower risk for cardiovascular events during the follow-up. Therefore it seems that asymptomatic patients with stable CAD may not benefit from beta-blocker therapy. Nevertheless, patients with recent myocardial infarction did benefit from beta-blocker therapy, and it was associated with a lower incidence of mortality, repeat myocardial infarction, stroke, hospitalization for later atherothrombotic events, and revascularization (Bangalore et al. 2012). Betablockers inhibit the function of cardiac β-adrenoceptors (mainly β1-adrenoceptors) in the heart. The endogenous effects of catecholamines, adrenaline, and noradrenaline are attenuated, which leads to a reduction in heart rate and the force of cardiac contraction. Therefore, the use of beta-blockers has a beneficial effect on blood pressure and angina (Baker 2005).

Calcium-antagonist medications are anti-anginal, and the anti-anginal mechanism is generally related to improving the balance between myocardial oxygen supply and demand (Cooper-DeHoff et al. 2013). Calcium-antagonists are recommended as an anti-anginal medication in patients with ACS when they also have vaso-spastic angina symptoms (Roffi et al. 2016).

Antiplatelet therapy is an important part of medication in patients with CAD. In these patients, it has been shown to reduce the risk of nonfatal myocardial infarction and stroke by 25–30%. In addition, antiplatelet therapy decreases rates of vascular death by 15% (Antiplatelet Trialists' Collaboration 1994). Daily use of acetyl salicylic acid (ASA) is recommended in every patient with coronary artery disease (Levine et al. 2011). The mechanism of ASA is based on the inhibition of platelet activation. Platelet function is an essential mediator of the process of hemostasis and thrombosis (Paez Espinosa et al. 2012).

P2Y12 receptor antagonists, including clopidogrel, prasugrel, and ticagrelor, are recommended in patients after acute coronary syndrome and/or coronary revascularization (Levine et al. 2011). Extracellular nucleotides and their receptors are involved in platelet activation (Burnier 2002). Adenosine diphosphate (ADP) has a major role in hemostatic involvement and in the development and extension of arterial thrombosis (Born et al. 1985). PY receptors are the receptors for extracellular nucleotides and P2Y receptors are receptors for ADP. Therefore, P2Y receptors contribute to platelet aggregation and the formation of a thrombus (Gachet 2008). P2Y12 receptors are also involved in increasing platelet secretion (Cattaneo et al. 2000). P2Y12 receptors are targets to antithrombotic drugs such as clopidogrel and prasugrel, and receptor antagonists have a major inhibitory effect on platelet function (Gachet 2008; Storey 2006).

2.6.2   Targets of secondary prevention

The European Action on Secondary and Primary Prevention by Intervention to Reduce Events III (EUROASPIRE III) survey has shown that a great number of patients with coronary heart disease do not achieve the targets for primary prevention (Kotseva et al. 2009). In fact, a majority of patients diagnosed with CAD do not succeed in achieving the guideline targets for secondary prevention either (Kotseva et al. 2016).

In secondary prevention, lifestyle modifications play a significant role in mirroring primary prevention. According to the European guidelines (Perk et al. 2012) and guidelines of the American Heart Association and the American College of Cardiology Foundation (Smith et al. 2011), patients with CAD should quit smoking completely, and other lifestyle changes should be evaluated. Patients who continue smoking after myocardial infarction have a 50% higher risk of recurrent coronary events compared to nonsmokers (Rea et al. 2002). Smoking cessation after myocardial infarction declines the risk for cardiovascular events over time. Three years after smoking cessation, the risk has been decreased to the level of the non-smoking population (Rea et al. 2002). Objective lifestyle parameters include weight control (BMI 18.5–24.9 kg/m2), physical activity (minimum of 30 minutes walking five days a week), moderate use of alcohol, and a healthy diet, including low-fat dairy products, vegetables, and fruits (Perk et al. 2012). In addition, according to Estruch et al. (2013), the Mediterranean diet, which includes extra-virgin olive oil and nuts, can reduce cardiac events in patients with high risk.

The goal for low-density lipoprotein cholesterol levels in secondary prevention using statin therapy is under 1.8 mmol/l (Perk et al. 2012), which associates with lowest risk of recurrent cardiovascular events (Baigent et al. 2010). If LDL cholesterol goals are not achieved by using statin therapy, other lipid-lowering medications can be used to optimize the serum levels of lipids. In addition to weight control, the waist circumference should also be taken into account. According to

the recommendations, the circumference should be under 89 cm in female patients and under 102 cm in male patients (Perk et al. 2012).

Patients with blood pressure over 140/90 mmHg are recommended (Perk et al. 2012) to use antihypertensive medication. An angiotensin-converting enzyme inhibitor (ACE inhibitor) is recommended for all coronary patients due to its renal protective effects unless the medication is contraindicated (Perk et al. 2012). The HOPE trial confirmed that use of ACE inhibitors (Ramipril 10 mg/d) reduced the incidence of myocardial infarction, stroke, and cardiovascular death in patients who had or were at high risk of having vascular disease in the absence of heart failure (Yusuf et al. 2000). Angiotensin II receptor antagonists (ARB) are a secondary option when ACE inhibitors are contraindicated (Perk et al. 2012). ACE inhibitors inhibit the conversion of Angiotensin I to Angiotensin II and interrupt the Renin-Angiotensin System (RAS), which is a specific effector on blood pressure progression. It also increases the plasma concentration of bradykinin, which has vasodilatory effects. In normal RAS, Angiotensin II activates Angiotensin II type 1 (ATR1) and type 2 (ATR2) receptors. ATR1 and ATR2 stimulation leads to vasoconstriction, sodium retention, water retention, and apoptosis. ARB inhibits Angiotensin II receptors (Burnier et al. 2000; Unger 2002).

2.6.3   Indication for coronary revascularization

Despite optimal medical therapy, patients with symptomatic CAD are considered as candidates for coronary revascularization. Either > 70% diameter stenosis by visual estimations or a fractional flow reserve of < 0.80 in an epicardial coronary artery is generally considered a sign of hemodynamically significant CAD in invasive coronary angiography. In patients with stable CAD, only those with left main, symptomatic three-vessel disease or proximal left anterior descending artery (LAD) stenosis can derive prognostic benefit from revascularization. In general, however, revascularization improves symptoms, but is not associated with

improved prognosis compared to medical therapy alone (Boden et al. 2007). In patients with ACS, in contrast, revascularization of significant epicardial stenosis improves both symptoms and prognosis (Wallentin et al. 2000; Cannon et al. 2001; FRISC-II 1999).

Current European guidelines recommend PCI over CABG in patients with single- or two-vessel disease, and CABG over PCI in patients with significant three-vessel disease with left main and/or proximal left anterior descending coronary artery stenosis (Roffi et al. 2015; Steg et al. 2012). The decision of elective performance of coronary revascularization should be based on the risk stratification and individual characteristics of a patient. Different risk stratification score tools can be used for coronary revascularization candidate patients. SYNTAX (A The Synergy between PCI with TAXUS and Cardiac Surgery) score predicts adverse outcomes and a EuroScore predicts surgical mortality (Head et al. 2012; Nashef et al. 1999; Capodanno et al. 2009). In addition, the heart team, a multidisciplinary decision-making forum, has been shown to improve outcomes when making decisions between different treatment options (Holmes et al. 2013). The heart team approach is important when considering coronary revascularization in this patient group (Holmes et al. 2016). The indication to perform a coronary revascularization in patients with stable CAD is the persistence of symptoms in spite of optimal medical therapy (Davies et al. 1997).

According to the FRISC II prospective multicenter study (FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators, 1999), early invasive strategy in patients with unstable coronary syndrome (including UAP and NSTEMI) is the optimal treatment of choice. Invasive procedures decrease death rates and myocardial infarction. In addition, symptoms of ischemia were relieved significantly in patients undergoing invasive treatment (FRISC II, 1999). The study showed that the early invasive procedure implemented within seven days decreases the risk of myocardial infarction and death in patients with high or moderate risk. The use of invasive treatment should be preferred in patients with unstable coronary syndrome with signs of ischemia in ECG or raised

levels of biochemical markers of myocardial damage (Wallentin et al. 2000). Moreover, a meta-analysis showed a significant risk reduction for all-cause mortality, late myocardial infarction, and re-hospitalization for unstable angina after early invasive treatment versus conservative treatment options (Bavry et al. 2006).

The 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST segment elevation (Roffi et al. 2016) supports the invasive treatment strategy and highlights the role of risk stratification in the process of decision-making. Early invasive coronary angiography is recommended for moderate- or high-risk patients (Roffi et al. 2016). In patients at low risk for ischemic events, a non-invasive stress test should be performed before deciding on an invasive strategy (Roffi et al. 2016; Amsterdam et al. 2010).

The Global Registry of Acute Coronary Events (GRACE) score is used to assess ischemic risk and it provides accurate risk stratification in patients with ACS (Granger et al. 2003). The risk calculation includes age, systolic blood pressure, pulse rate, serum creatinine, Killip class at presentation (Killip et al. 1967), cardiac arrest at admission, elevated cardiac biomarkers, and ST deviation (Granger et al. 2003). ESC guidelines (Roffi et al. 2016) for invasive strategy timing recommend early invasive treatments in high-risk patients (within two hours for very-high-risk patients and within 24 hours in patients with a high risk profile). The patients with no recurrence of symptoms and without any of the typical risk criteria are considered to be at low risk for ischaemic events and due to this, a non-invasive stress test is recommended before deciding on an invasive strategy (Roffi et al. 2016). The invasive strategy is shown to be associated with lower risk for recurrent ischemia and major adverse cardiac events, and also with shorter duration of in-hospital stay in NSTE-ACS patients (Katritsis et al. 2011). In addition, high-risk patients defined as a GRACE score of > 140 benefit from early invasive strategy because it lowers the risk for death, myocardial infarction,

and stroke. Differences were not significant when comparing with strategies in patients with a GRACE score of < 140 (Mehta et al. 2009).

ESC Guidelines for the management of patients clinically presenting with STEMI (Steg et al. 2012) recommend restoring (mechanical or pharmacological strategy) coronary flow and myocardial tissue reperfusion as early as possible. Early reperfusion within 12 hours of the beginning of symptoms is associated with improved survival among improved results with myocardial outcomes (Fibrinolytic Therapy Trialists' [FTT] Collaborative Group, 1994). It is unclear whether mechanical reperfusion (PCI) is beneficial in the majority of patients still presenting over 12 hours from symptom onset with the absence of clinical evidences of lack of reperfusion in myocardial tissue (Schömig et al. 2005). However, PCI may be an alternative choice and should be considered in patients with current clinical evidence of ongoing ischemia even when the symptoms have persisted for over 12 hours (Hackett et al. 1987). If the primary PCI is not performed in 120 minutes, fibrinolysis should be considered as an option, especially when given pre-hospitally. The pre-hospital fibrinolysis improves the time-to-treatment significantly, but it is associated with an increased risk of major bleeding as well (Morrison et al. 2000).

2.6.4 *Coronary artery bypass grafting (CABG)*

Since the late 1940s, experiments on coronary artery bypass grafting were started in human subjects (Vineberg 1949). The first successful CABG in a human patient was performed in 1960 (Konstantinov 2000). At first, CABG was implemented via saphenous vein grafting (Favaloro 1969). Use of the left internal mammary artery (LIMA) as a graft was popularized in the West in the 1970s (Green et al. 1970).

Surgical techniques have evolved and current evidence suggests that the choice of graft affects the outcome. LIMA grafts and other arterial grafts (the radial ar-

tery and the right internal mammary artery) appear to have survival benefits over saphenous vein grafts and are therefore the primary choice, and saphenous vein grafts are a secondary choice (Locker et al. 2012; Pick et al. 1997; Taggart et al. 2001). The long-term patency of the LIMA grafts is superior to that of the saphenous vein graft (Goldman et al. 2004). According to Goldman et al. (2004), the patency at 10 years after the operation was 61% in the saphenous vein graft group and 85% in the IMA group; the results using a saphenous vein graft are better than the results from the 1970s. This may be explained in part by the development of secondary prevention, especially lipid-lowering therapy (Goldman et al. 2004). In the long term, the use of arterial grafts, especially bilateral IMA, maximizes the benefits of CABG (Boylan et al. 1994). In current practice, in addition to the IMA, the radial and rarely the gastroepiploic arteries are used as grafts in CABG. The bilateral IMA (BIMA) is associated with improved long-term survival (Benedetto et al. 2014; Aldea et al. 2016), and the use of a bilateral internal mammary artery decreased the incidence of major adverse cardiac events when comparing with use of a radial artery (RA) and a left internal mammary artery (LIMA) (Kurlansky et al. 2010; Ruttmann et al. 2011). According to Glineur et al. (2016), 10-year survival after bilateral IMA bybass was $83.8 \pm 3.2\%$, and freedom from cardiovascular events was $96.1 \pm 1.7\%$, freedom from myocardial infarction was $96.0 \pm 1.6\%$, freedom from ischemia was $80.2 \pm 3.8\%$, and freedom from repeat revascularization was $89.7 \pm 2.5\%$. However, according to Taggart et al. (2016), there were no significant differences at 5 years in mortality rates and in rates of cardiovascular events between patients treated with single or bilateral internal mammary artery grafting. Patients treated with bilateral IMA had more sternal wound complications than did patients treated with single IMA (Taggart et al. 2016). The radial artery is a relatively good alternative when using BIMA is a contraindicated option (Schwann et al. 2012).

The improvement of surgical techniques provides the possibility of performing CABG without cardiopulmonary bypass (off-pump technique). However, despite great hopes of decreased cerebrovascular and renal events when off-pump surgery was introduced, when comparing the off-pump and on-pump techniques,

there is no unequivocally proven significant difference at one year after the operation in the rates of repeated revascularization, in quality of life, or in neurocognitive function (Lamy et al. 2013). In the short-term (30 days after the operation), there were no differences in rates of myocardial infarction, death, stroke, and renal failure requiring dialysis. The use of the off-pump technique reduced rates of transfusion, reoperation for perioperative bleeding, respiratory complications, and acute kidney injury. On the other hand, it increased the risk for early repeated revascularization (Lamy et al. 2012; Takagi et al. 2013). According to Kowalewski et al. (2016), there are no significant differences in all-cause mortality and myocardial infarction between the two techniques. The off-pump technique was, however, associated with a reduction in the odds of cerebrovascular stroke. This may be due to the fact that the off-pump technique leaves the ascending aorta untouched (Misfeld et al. 2011). However, in the long run, the off-pump technique seems more likely to be associated with all-cause mortality (Takagi et al. 2014).

2.6.5   Percutaneous coronary intervention (PCI)

Outcomes after PCI have seen a significant global improvement in the past decades, and this development can also be seen in Finland (Williams et al. 2000; Kiviniemi et al. 2016). Development started in the 1970s from the percutaneous transluminal coronary angioplasty (PTCA), which used balloon catheters. The occurrence of restenosis in the treated segment of a coronary artery was a limitation using PTCA with balloon catheters, even when the procedure was successful (Nobuyoshi et al. 1988). The outcome after the procedure in patients with a single-vessel disease was significantly better when comparing to the patients with a multivessel disease (Gruentzig et al. 1987).

In the 1980s, atherectomy devices were introduced to improve the outcomes of coronary revascularization. Atherosclerotic plaque was excised and evacuated from the target lesion instead of expanding the coronary diameter with the bal-

loon catheter in the target segment. However, the new technique did not offer any improvement with clinical outcomes over the long term (Topol et al. 1993; Bittl 1996).

In the 1990s, bare metal stents were introduced in cath labs. Placement of a single stent reduced the occurrence of restenosis and the need for repeated revascularization when comparing to coronary angioplasty with a balloon catheter (Ellis et al. 1992; Fischman et al. 1994). However, the main limitation with bare metal stents was a sub-acute thrombotic occlusion, which could lead to myocardial infarction and death (Serruys et al. 1991). To avoid this, medication to decrease coagulation was used to prevent postprocedural occlusion (Serruys et al. 1995). However, oral anticoagulation therapy did not eliminate sub-acute thrombotic occlusions and it caused higher incidence of bleeding complications.

To improve the outcomes after stent implantation, the stents were coated with heparin. This reduced the incidence of sub-acute stent thrombosis and allowed for a reduction in anticoagulant therapy (Serruys et al. 1996). The dual antiplatelet therapy including aspirin and clopidogrel reduced the risk for stent thrombosis and due to this, bare metal stents are still suitable in specific patient groups. Bare metal stents are acceptable to use in non-diabetic patients with lesions less than 15 mm in vessels with over 3 mm diameter (Iqbal et al. 2013). In addition to the sub-acute stent thrombosis, the risk for in-stent restenosis was significant when using bare metal stents (Iqbal et al. 2013).

Bare metal stents were coated with many different substances including for example gold, carbon, heparin and phosphorylcholine to prevent sub-acute stent thrombosis and in-stent restenosis. However, these coated bare metal stents did not confer any benefits before stents were coated with anti-proliferative drugs (sirolimus or paclitaxel) (Iqbal et al. 2013).

First-generation drug-eluting stents including sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) significantly decreased the incidence of restenosis

when comparing to bare metal stents (Stone et al. 2005; Moses et al. 2003). The main concern with first-generation stents was the appearance of late-stent thrombosis (> 30 days after the index procedure). Late-stent thrombosis using first-generation stents is relatively rare. The clinical consequences are generally severe and cause significant morbidity and mortality (Kerner et al. 2003; McFadden et al. 2004; Camenzind et al. 2007; Bavry et al. 2006). In spite of the reduction of the repeated target lesion revascularization using first-generation drug-eluting stents, the late long-term safety and effectiveness have been the main concern (Mukherjee et al. 2009).

The second-generation drug-eluting stents (i.e., the everolimus-eluting stent [EES] and the Zotarolimus-eluting stent [ZES]) were developed to solve these safety issues. EES and ZES seem to be as efficient as first-generation SES and are more efficient than PES. The incidence of myocardial infarction and stent thrombosis were lower in patients treated with EES (Navarese et al. 2014). The cumulative major adverse cardiac events rates are lowest for EES after two years postprocedure when comparing with bare metal stents, which have the highest rates. PES and ZES were associated with intermediate risk for major adverse cardiac events. (Stone et al. 2008; Stone et al. 2009; Valgimigli et al. 2014). After 5 years, EES significantly reduced the risk for target lesion revascularization when comparing with ZES. However, the risk was not lower for target vessel revascularization. Long-term safety (stent thrombosis, mortality, myocardial infarction, and major adverse cardiac events) and efficacy seems to be similar in ZES and EES (Qi-Hua et al. 2015). A large meta-analysis of randomized controlled trials comparing bare metal stents and first- and second-generation DES found that cobalt-chromium EES was the only DES with a risk of stent thrombosis lower than in bare metal stents (Palmerini et al. 2012).

Restenosis is defined as a reduction in coronary artery lumen diameter after PCI. After stent implantation, restenosis is usually due to excessive tissue proliferation in the luminal vessel of the stent, called neointimal proliferation. If there is no stent implantation during PCI, restenosis is usually due to vessel remodeling

(Buccheri et al. 2016). Restenosis often leads to anginal symptoms, which may lead to repeated reintervention, usually called target lesion revascularization (TLR) (Alfonso et al. 2014). Drug-eluting stents decrease the development of restenosis by reducing neointimal proliferation (Stone et al. 2005). However, it can lead to incomplete stent apposition that can increase the risk for stent thrombosis (Souteyrand et al. 2016). The pathophysiology of stent thrombosis is not fully understood (Kimura et al. 2010). According to Souteyrand et al. (2016), optical coherence tomography identified underlying morphological abnormality in 97% cases of confirmed stent thrombosis. In this study, struts malapposition (34%), ruptured neoatherosclerosis (22%), and major stent underexpansion (11%) were the most frequently observed causes of stent thrombosis (Souteyrand et al. 2016).

2.6.6 *CABG versus PCI*

The selection between coronary revascularizations (PCI and CABG) depends on many factors, such as comorbidities, clinical presentation, risk scores, frailty, cognitive status, estimated life expectancy, and anatomic severity of coronary artery disease (Roffi et al. 2016). CABG can provide complete revascularization in complex lesions, and in addition, CABG has a lower incidence of mortality in patients with multivessel disease (Mohr et al. 2013; Malenka et al. 2005). According to Fanari et al. (2014), in the long run, CABG should be considered the preferred choice of revascularization in stable patients with multivessel disease and no contraindication to surgery (e.g., minimal life-expectancy or prohibitive severe comorbidities). A SYNTAX score (SS) can be used to assess the risks in patients with NSTEMI undergoing PCI and is useful to predict death, myocardial infarction, and revascularization. It can also be useful when deciding on invasive treatment strategies (Palmerini et al. 2011). In patients with left main coronary disease, PCI and CABG have similar rates of major adverse events, including myocardial infarction, death, stroke, and repeat revascularization when the SYNTAX score is low (SYNTAX score $\leq$ 22) or intermediate (SYNTAX score

23–32). However, PCI is associated with a higher incidence of adverse events when the SYNTAX score is over 32. In patients with multivessel disease, rates of adverse events were similar when the SYNTAX score was low. CABG provided a lower incidence of MACCE in patients with intermediate or high SYNTAX score levels (Morice et al. 2010; Mohr et al. 2013). In addition to the current status of coronary artery disease, comorbidities can guide the decision about invasive strategies.

Patients with with three-vessel or left main disease undergoing CABG have lower rates of MACCE, and patients with complex disease undergoing PCI have repeated revascularization more often, predicting death and stroke in the long term after the procedure (Parasca et al. 2016; Serryus et al. 2009; Mäkikallio et al. 2016). However, in patients with low to intermediate anatomical complexity of coronary artery disease with left main coronary artery stenosis, PCI was not associated with higher rates of adverse events when comparing to CABG (Stone et al. 2016). Nevertheless, diabetic patients with left main or/and multivessel disease undergoing CABG have lower rates of MACCE than patients undergoing PCI (Mack et al. 2011; Kappetein et al. 2013). In addition, older patients (70 years old or older) with multivessel or left main disease undergoing CABG had lower rates of primary endpoints during follow-up (Chang et al. 2017). According to Hannan et al. (2014), in patients over 75 years old, there were no significant differences in outcome rates (myocardial, stroke, and death) between CABG and PCI groups when multivessel coronary artery disease was propensity matched using multiple patient risk factors. However, the rates of repeated revascularization were higher in the PCI group. Among patients with isolated proximal LAD CAD, the need for target vessel revascularization was higher in the PCI group, but there were no significant differences in mortality, myocardial infarction rates, and stroke rates between the study groups (Kinnaird et al. 2016). According to Bangalore et al. (2016), patients with severe ventricular dysfunction (EF $\leq$ 35%) along with multivessel disease had stroke during follow-up more often when undergoing CABG. However, PCI was associated with a higher risk of myocardial infarction and repeat revascularization. There were no significant

differences in myocardial infarction between study groups when the revascularization was complete after the PCI procedure. Long-term, CABG and PCI were associated with similar risks of death (Bangalore et al. 2016). In elderly patients (80 years old and older) with CAD, short-term mortality was higher in patients undergoing CABG. However, these patients had longer overall survival when compared to patients undergoing PCI. Patients undergoing PCI had significantly shorter hospital stays (Zhang et al. 2016). In young patients (50 years old or younger), the freedom from MACCE after the coronary revascularization procedure was lower in the PCI group. In addition, the freedom from repeat revascularization and myocardial infarction was higher in the CABG group. Short-term mortality, long-term survival, and stroke rates were similar between the study groups (Biancari et al. 2014).

The primary PCI is recommended as the first choice of reperfusion strategy in patients with STEMI. The primary PCI lowers the short-term risk of death, stroke, and repeated myocardial infarction. The mechanical reperfusion provides a short-term clinical advantage over in-hospital fibrinolysis (The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes [GUSTO Iib] Angioplasty Substudy Investigators 1997). The number of patients undergoing CABG in the acute phase of STEMI is relatively small. If PCI is not suitable due to anatomical issues of the patient or the coronaries, CABG may be an option (Steg et al. 2012). Early mortality in patients undergoing emergency CABG is significant. However, long-term survival is acceptable after emergency CABG (Axelsson et al. 2016). According to Boden et al. (2007), coronary revascularization does not decrease the risk of mortality and major cardiac events in the majority of patients with a current stable CAD when added to optimal medical therapy. However, patients with complex CAD might benefit from coronary revascularization when the disease is stable.

There are relatively few studies on percutaneous coronary revascularization and surgical coronary revascularization in patients with CKD (Rinehart et al. 1995; Ivens et al. 2001; Chang et al. 2012; Chertow et al. 2000). In patients with CAD

and CKD, survival after revascularization was markedly associated with current stages of CAD and CKD (Cooper et al. 2006; Szczech et al. 2001). Outcomes after surgical coronary revascularization in patients with CKD were mainly poor (Nakayama et al. 2003). Therefore, the optimal strategy and indications for coronary revascularization are still not determined, and the choice between different revascularization strategies should be based not only on location and severity of CAD but also on the severity of renal dysfunction (Hemmelgarn et al. 2004; Szczech et al. 2001).

2.6.7 *Antiplatelet therapy after coronary revascularization*

2.6.7.1 *Medication after PCI*

After PCI, efficacious dual antiplatelet therapy is needed to prevent stent thrombosis and the development of the potential *de novo* coronary plaque ruptures. Extended use of clopidogrel in patients treated with DES reduces the risk of death and myocardial infarction (Eisenstein et al. 2007). The duration of an ASA should be indefinite after PCI (Schömig A et al. 1996; Antithrombotic Trialists' Collaboration 2002; Smith et al. 2006; Baigent et al. 2009). Patients receiving a BMS or DES for ACS indication should use a P2Y12 inhibitor (ticagrelor, prasugrel, or clopidogrel) along with an ASA (dual antiplatelet therapy, DAPT) for 12 months postprocedure (Steg et al. 2012; Mehta et al. 2001; Wiviott et al. 2007; Wallentin et al. 2009). In addition, patients receiving DES for non-ACS indication should use a P2Y12 inhibitor for 12 months after PCI (Grines et al. 2007; Eisenstein et al. 2007; Brar et al. 2008).

DAPT is associated with reduced rates of cardiovascular events after DES. The extended duration of DAPT increases bleeding events (Basaraba et al. 2016). Long duration DAPT reduces myocardial infarction in comparison to short duration DAPT (D'Ascenzo et al. 2016). According to Palla M et al. (2015), the short

DAPT is safer after using second-generation DES and is as effective as standard duration DAPT.

2.6.7.2 Medication after CABG

Antiplatelet therapy decreases the risk for postoperative thromboembolic complications in patients undergoing CABG (Rafiq et al. 2012). In general, an ASA decreases the incidence of subsequent clinical events when using vein grafts (Chesebro et al. 1982). Clopidogrel medication before CABG is associated with increased risk for reoperations due to bleeding, blood loss, need for blood transfusion, and postoperative death (Biancari et al. 2012). In addition, clopidogrel is associated with increased risk of morbidity and mortality when used within 5 days prior to CABG (Ascione et al. 2005). Stopping the clopidogrel medication for 5 days prior to CABG leads to decreased risk of bleeding (Rapezzi et al. 2008; Firanescu et al. 2009). DAPT, including ASA and clopidogrel, seems to entail better early vein graft patency when compared to an ASA medication alone (Nocerino et al. 2013; Deo et al. 2013). On the other hand, DAPT has not been shown to affect arterial graft patency (Nocerino et al. 2013). However, DAPT may increase the risk of bleeding events (Deo et al. 2013). When comparing ticagrelor (reversible direct-acting P2Y12 inhibitor) to clopidogrel in ACS patients undergoing CABG, there were no significant differences in major CABG-related bleeding complications between study groups when the P2Y12 inhibitor was discontinued 5 days prior to operation. However, it seems that more bleeding complications occurred in patients treated with ticagrelol when the P2Y12 inhibitor was used up to the day before surgery (Hansson et al. 2014).

2.7 Cardiac rehabilitation

Cardiac rehabilitation goals are to increase the compliance of the medication therapy and to provide knowledge of lifestyle changes, including smoking cessation and regular physical exercise. In addition, it allows for dietary counseling

and weight control options (Chow et al. 2010; Clark et al. 2005). According to Taylor et al. (2004), cardiac rehabilitation was associated with significant reductions in all-cause mortality and total cardiac mortality. Cardiac rehabilitation was associated with the reduction of modifiable risk factors: total cholesterol levels and systolic blood pressure were reduced. In addition, the proportion of patients who reported smoking was reduced significantly (Taylor et al. 2004). In their study, however, van Halewijn et al. (2017) did not show a reduction in all-cause mortality. Thus, cardiovascular mortality was reduced by 58%, myocardial infarction by 30%, and cerebrovascular events by 60%. The differences between the results in all-cause mortality may be explained by the fact that coronary revascularization and cardioprotective medications have been advanced, and those managements of cardiovascular diseases have generally resulted in lower mortality rates in patients with cardiovascular disease (West et al. 2012; Kuulasmaa et al. 2000; van Halewijn et al. 2017).

2.8   Coronary revascularization and quality of life

Quality of life itself is a subjective assessment of health and is defined by the WHO as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Previously, the most important outcomes were objective. The prognosis after coronary revascularization has improved over the years, and it is currently more important to take the improvement of quality of life into account. A number of studies on health-related quality of life (HRQoL) after cardiac surgery describe improvement as compared to baseline scores and to those of matched general populations, even in the elderly (Ghanta et al. 2011; Vicchio et al. 2012; Cohen et al. 2011; Sen et al. 2012).

The EQ-5D questionnaire instrument is a standardized and validated instrument used to measure health outcome (EuroQol Group 1990). It contains two sections: the first measures the five core domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain consists of three levels,

including no problems (0), some problems (1), and severe problems (2). The second section of the EuroQol is a vertical visual analogue scale (VAS) ranging from 0 to 100, with 0 representing the worst and 100 the best imaginable health state.

According to Fatima et al. (2016), the quality of life was better in patients undergoing CABG than in patients undergoing PCI at 6 months after the procedure. These findings were similar in 5 out of 9 evaluated studies. In one year, 9 out of 10 studies showed that CABG was associated with better outcomes in quality of life after the operation when comparing with PCI. However, coronary revascularization after both CABG and PCI improves the HRQoL significantly (Pocock et al. 1996; van Domburg et al. 2008). Jokinen et al. (2008) investigated different factors, which were associated with the impaired quality of life in patients undergoing CABG at the age of ≥ 70 years old. Among the 40 studied variables, five were associated with impaired QoL. These associated factors were diabetes, low energy score and high pain score at 15 months, the treatment in an intensive care unit with the duration of over 3 days, and the preoperative duration of symptoms. The long-term QoL in this patient population was comparable to QoL of the age and gender matched reference population (Jokinen et al. 2008). Differences in the outcomes of health-related quality of life after surgical revascularization between female and male patients seem to be better in male patients at one year after operation (Lindquist et al. 2003). In addition to coronary revascularization, secondary preventive cardiac rehabilitation improves the quality of life (Shepherd et al. 2012).

2.9   Permanent work disability and coronary artery disease

Cardiovascular diseases are the third most common indication for PWD and the socioeconomic effects are significant. In Finland, there were 17,943 people in PWD for cardiac indication in 2008. According to Pasternak et al. (1980), a total of 22% of patients with angina symptoms and normal coronary anatomy or coro-

nary luminal narrowing of less than 30% had quit working or had changed jobs due to chest pain. Patients at high risk for premature work disability can be identified by medical and nonmedical risk factors, including lower initial functional status followed by older age, black race, congestive heart failure, lower education level, extracardiac vascular disease, poorer psychological status, and lower job classification (Mark et al. 1992). Patients undergoing CABG were at especially high risk for disability pension (Zetterström et al. 2015).

Myocardial revascularization is associated with a low procedural risk in young patients. After coronary revascularization, the rates of major adverse events are relatively low in this patient group (Zimmerman et al. 1995; Fleissner et al. 2015; Biancari et al. 2014). However, young patients under 50 years old undergoing PCI are at high risk for subsequent permanent disability for cardiac diagnoses (Gunn et al. 2015). In patients 40–59 years of age undergoing CABG, several medical variables (cardiac status and comorbidity) had minor effects on re-employment after the operation. In addition, the patients based their experience of the disability on their overall health status and former job satisfaction (Mittag et al. 2001).

3   AIMS OF THE STUDY

1.   To evaluate the changes in HRQoL in patients undergoing surgical revascularization and to investigate whether the changes in HRQoL predict later morbidity.

2.   To assess the predictors for late outcomes among young patients (50 years old or younger) undergoing PCI.

3.   To compare late morbidity after PCI and CABG in patients with stage 3b–5 CKD.

4.   To evaluate the incidence of PWD in young patients after coronary revascularization (either PCI or CABG).

4 MATERIALS AND METHODS

4.1 Patient population in different studies

In study I, the study population consisted of 699 patients who underwent an isolated CABG between 2008 and 2010. All operations were performed at the Turku University Hospital, Turku, Finland. There were 404 patients, who were included in the analysis. These patients filled out the EQ-5D (European Quality of Life Five Dimension) questionnaire both at baseline and at six months after operation.

The study population in study II includes 1617 patients who were under 50 years old and were undergoing PCI between 2002 and 2012. The study is a part of a multicenter retrospective registry study (CRAGS). The data for this sub-study was collected from seven European centers of cardiology and cardiac surgery, and the patients undergoing CABG were excluded from analysis.

Study III comprises consecutive patients with stage 3b–5 chronic kidney disease who underwent coronary revascularization between 2007 and 2010. The study population includes 110 patients undergoing PCI and stent replacement, and 148 patients who underwent an isolated CABG. PCI procedures were performed at the Turku University Hospital, Turku, Finland, and CABG operations at the Turku University Hospital, Turku, Finland, and at the Oulu University Hospital, Oulu, Finland.

Study IV is part of the CRAGS study (Biancari et al. 2014) and includes 1003 patients who underwent PCI and 146 patients who underwent CABG at three university hospitals and one at central hospital in Finland between 2002 and 2012. Altogether, 21 (14.4%) patients undergoing CABG and 93 (9.3%) patients undergoing PCI were excluded from analysis due to permanent work disability prior to the coronary revascularization.

4.2   Study design

Studies I and III

Studies I and III were retrospective cohort studies. The data on baseline characteristics, discharge medication, and postoperative outcomes during follow-up were collected from local electronic hospital registries. The cause and date of death information were retrieved from the Finnish National Registry, Statistics Finland.

In study I, the health-related quality of life was measured with the EQ-5D questionnaire. HRQoL scores were measured for all patients as part of the routine quality control at the Turku University Hospital. Patients filled out the questionnaire prior to the operation except for the patients undergoing emergency CABG, who filled it out when they were capable. Patients were asked to evaluate the HRQoL of the previous two weeks preoperatively. The follow-up time was 38.6 months.

In study III, the study population had stage 3b–5 chronic kidney disease (i.e., eGFR under 45 ml/min/1.73^2), calculated by the MDRD (Modification of Diet in Renal Disease) formula. The formula takes the serum creatinine into account and includes variables for age, gender, and race (African and non-African). In the third study, the median follow-up time was 25 months.

CRAGS (Studies II and IV)

Studies II and IV were parts of a multicenter retrospective registry CRAGS (Coronary aRtery diseAse in younG adultS) study (registered in ClinicalTrials.gov, identifier NCT01838746). This multicenter study is designed to describe the outcomes after coronary revascularization in patients under 50 years old. Data for the CRAGS study were collected from 15 European centers of cardiology and cardiac surgery. Eligible criteria for the study population were patients aged 18–50 years with a diagnosis of stable angina, unstable angina, silent ischemia, NSTEMI, or STEMI. All patients underwent either CABG or PCI.

In study II, the data on late outcomes was acquired by contacting patients, their relatives, and their general practitioners, and by reviewing the electronic patient

records. The complete clinical follow-up was available to all patients and the median follow-up was 3.0 years.

In study IV, the baseline data on permanent work disability including the primary and the secondary diagnoses were acquired from the Finnish Centre for Pension, Finland. The periprocedural data, baseline characteristics, and data on post-procedural morbidity were collected from local hospital registries and the median follow-up was 41 months.

4.3   Outcomes in different studies

Study I

The major adverse cardiac and cerebrovascular events were defined as a composite of stroke/transient ischemic attack, myocardial acute coronary syndrome (including acute myocardial infarction and unstable angina pectoris), and cardiac death after completion of the second EQ-5D questionnaire. Late MACCE was the main outcome and was postoperatively recorded after six months. Transient ischemic attack (TIA) was defined as a transient neurologic deficit diagnosed as TIA by a neurologist. Stroke was defined by imaging studies or the diagnosis was otherwise verified by clinical assessment.

Study II

MACCE was the primary endpoint of the second study, and the secondary endpoints were individual components of MACCE. MACCE was defined as a myocardial infarction, a repeated coronary revascularization during follow-up, TIA or stroke, and death from any cause. TIA was defined as a focal transient (< 24h) neurological deficit adjudicated by a neurologist; stroke was defined as a permanent focal neurological deficit adjudicated by a neurologist and was confirmed by computed tomograghy or magnetic resonance imaging. Stent thrombosis was diagnosed through the presence of ACS with angiographic evidence of either

vessel occlusion or thrombus within the stent or during autopsy. Revasculariza-
tion due to non-target lesions was considered to represent disease progression.

Study III

MACCE was the main outcome along with all-cause mortality. It included a
composite of all-cause mortality, myocardial infarction, stroke, or repeated re-
vascularization. Secondary endpoints were the commencement of permanent di-
alysis, cardiac mortality, repeated revascularization, stroke, and acute myocardial
infarction. Stroke was diagnosed by a neurologist and confirmed by imaging. The
acute myocardial infarction was defined by ischemic chest pain with elevated
biochemical markers of myocardial necrosis to at least twofold when comparing
to reference limits.

Study IV

The main outcome was a postoperative permanent work disability defined as a
grant of disability pension during follow-up. The incidence of MACCE was ana-
lyzed, and it included myocardial infarction, stroke, and repeated revasculariza-
tion, but excluded death.

4.4   Statistical analysis

All the statistical analyses were performed using SPSS software. Version 17.1
(IBM Corporation New York, USA) was used in the first study. In the second
study, version 16.0 or higher (SPSS Inc., Chicago, IL, USA) was used. Statistical
analysis was performed using version 22.0 (IBM Corporation, Released 2013,
Armonk, New York, USA) and R version 2.15.3 in the third and fourth studies.

Continuous variables were reported as the mean ± standard deviation. Categori-
cal variables were reposted as counts and percentages. OR indicates odds ratio,
HR indicates hazard ratio, and CI indicates confidence interval. A p-value of <
0.050 was considered statistically significant.

Study I

An independent samples t-test was used to analyze baseline differences between patients with and without late MACCE. Determinants of survival were identified using a Cox proportional hazards model. A backward (WALD) stepwise selection procedure was used to build the model, including age, gender, history of stroke, preoperative atrial fibrillation, left ventricular ejection fraction, length of in-hospital stay, postoperative resternotomy, EQ-5D scores, and postoperative stroke.

Study II

Chi-square tests and ANOVAs were used to compare categorical and continuous variables. Univariate modeling was used to assess the independent determinants of any postprocedural events, and those associating with any late outcome at p-level < 0.10 were included in a stepwise backward Wald Cox regression analysis. The Kaplan-Meier method was used to estimate the rate of late outcomes.

Study III

The Chi-square test, Fisher's exact test, and the Mann-Whitney U test were used as appropriate. Kaplan-Meier test analysis with the log-ranks method was used to compare groups. The Cox regression method with backward selection including clinically relevant variables with p-value < 0.10 in univariate analysis was used to perform multivariable analysis. One-to-one propensity score matching between the study groups was performed with a caliber width of 0.2 on the standard deviation of the logit of propensity score.

Study IV

A Fisher's exact test, Chi-square, an independent samples t-test, and a Kaplan-Meier were used as appropriate. Due to the significant baseline differences between study groups, the propensity score for assignment to PCI was calculated with logistic regression with a non-parsimonious model by including all preprocedural variables (Hosmer-Lemeshow test, p-value=0.617). The obtained propensity score was used for adjustment on multivariable analysis.

5 RESULTS

5.1 Occurrence of late MACCE and changes in HRQoL in patients undergoing CABG (I)

Altogether, 59.2% of all patients filled out a questionnaire six months after CABG, and they each completed the follow-up. Thirty-five patients had 36 occurences of major adverse cardiac or cerebrovascular events (MACCE) after 6 months postoperation, of which 8 cases were due to cardiac death, 11 due to non-fatal acute coronary syndromes, and 17 due to either TIA or stroke. Baseline characteristics are shown in Table 1 for patients with late MACCE (MACCE group) and without late MACCE (No MACCE group).

Table1. Baseline characteristics

Variable	No MACCE group	MACCE group	P-value
Number of patients	369	35	
Age (years)	66.1 ± 8.1	67.6 ± 9.5	0.35
Gender (female)	86 (23.3%)	8 (22.9%)	0.95
Hypertension	357 (96.7%)	35 (100%)	0.90
Diabetes	102 (27.6%)	11 (31.4%)	0.63
Extracardiac arteriopathy	24 (6.5%)	3 (8.6%)	0.64
Preoperative AF	25 (6.8%)	4 (11.4%)	0.53
History of stroke	11 (3.0%)	2 (5.7%)	0.60
EF 30–50%	49 (13.3%)	7 (20.0%)	0.27
EF <30%	15 (4.1%)	5 (14.3%)	0.008
Left main stenosis	155 (42.0%)	15 (42.9%)	0.95
No of diseased vessels			0.98
1	21 (5.7%)	2 (5.7%)	
2	93 (25.2%)	8 (22.9%)	
3	254 (68.8%)	25 (71.4%)	
Recent AMI (within 90 days)	59 (16.0%)	6 (17.1%)	0.86
History of PCI	65 (17.6%)	7 (9.7%)	0.73
History of cardiac surgery	6 (1.6%)	1 (2.9%)	0.59
Urgent or emergent surgery	144 (39.0%)	14 (40.0%)	0.91
Off pump-surgery	49 (13.4%)	7 (20.0%)	0.28
No of distal anastomoses	2.7 ± 0.8	2.5 ± 0.8	0.47
LIMA graft	358 (91.3%)	34 (97.1%)	0.97
In-hospital stay (days)	7.6 ± 3.5	8.8 ± 7.0	0.08
Postoperative infection	4 (1.1%)	0 (0%)	0.54
Postoperative resternotomy	31 (8.4%)	2 (5.7%)	0.58
Postoperative AMI	2 (0.5%)	0 (0%)	0.66
Postoperative stroke	2 (0.5%)	8 (22.9%)	0.001

AMI = acute myocardial infarction within 90 days; EF= left ventricular ejection fraction; LIMA= left internal mammary artery. Continuous variables are reported as means and standard deviation.

The patients with late MACCE had more often a left ventricular ejection fraction under 30% and suffered from in-hospital postoperative stroke.

Differences and changes in EQ-5D scores between study groups are shown in Table 2.

Table 2. Changes and differences in EQ-5D-scores

EQ-5D-scores	No MACCE group	Any MACCE group	P-value
VAS, baseline	65.9 ± 21.2	67.1 ± 14.9	0.77
VAS, 6 months	77.2 ± 16.5	68.2 ± 20.2	0.004
Mobility, baseline	1.51 ± 0.62	1.49 ± 0.66	0.86
Mobility, 6 months	1.37 ± 0.50	1.43 ± 0.56	0.52
Caring for self, baseline	1.13 ± 0.40	1.12 ± 0.33	0.90
Caring for self, 6 months	1.10 ± 0.33	1.20 ± 0.47	0.10
Usual activities, baseline	1.19 ± 0.46	1.08 ± 0.28	0.22
Usual activities, 6 months	1.31 ± 0.52	1.49 ± 0.66	0.06
Pain, baseline	1.71 ± 0.59	1.57 ± 0.61	0.18
Pain, 6 months	1.44 ± 0.53	1.51 ± 0.51	0.45
Anxiety/depression: Baseline	1.29 ± 0.51	1.11 ± 0.32	0.005
Anxiety/depression: 6 months	1.18 ± 0.40	1.17 ± 0.38	0.94
EQ-5D, changes between 0 and 6 months			
VAS	11.8 ± 24.1	3 ± 22.6	0.07
Mobility	−0.14 ± 0.69	−0.06 ± 0.68	0.52
Caring for self	−0.05 ± 0.43	0.16 ± 0.55	0.03
Usual activities	0.07 ± 0.60	0.48 ± 0.71	0.01
Pain	−0.27 ± 0.69	−0.06 ± 0.73	0.09
Anxiety/ Depression	−0.11 ± 0.58	0.06 ± 0.48	0.10

VAS, EQ-5D visual analogue scale (range 0–100). Higher VAS scores and lower scores on the five subscales indicate better outcome. Positive values for changes in VAS and negative values for changes in subscales indicate improvement.

The patients with late MACCE outcome had lower VAS scores than the No MACCE group. There was a trend (p-value of 0.07) toward better improvement in VAS scores between 0 and 6 months in patients without late MACCE. Predictors of adverse events on the Cox proportional hazard model were history of stroke (HR 7.23, P=0.009, and 95% CI 1.66–32.02), worsening of the usual activities score (HR 2.56, P=0.008, and 95% CI 1.28–5.25), in-hospital stay (day) (HR 1.08, P=0.02, and 95% CI 1.02–1.14), reduction per unit on VAS (0–6 months) (HR 1.05, P=0.02, and 95% CI 1.01–1.09), and a VAS score at 6 months (HR 0.92, P=0.02, and 95% CI 0.94–0.99).

5.2 Major adverse events and disease progression after PCI in patients under 50 years old (II)

In the Kaplan-Meier analysis at five years, survival was at 97.8%, freedom from MACCE at 74.1%, freedom from repeated revascularization at 77.8%, and freedom from myocardial infarction at 89.9%.

The independent predictors of MACCE after PCI were peripheral vascular disease (HR 2.09, P=0.025, and 95% CI 1.10–4.00), a previous myocardial infarction (HR 1.67, P=0.003, and 95% CI 1.19–2.34), diabetes mellitus (HR 1.63, P=0.001, and 95% CI 1.22–2.16), and a family history of CAD (HR 1.34, P=0.012, and 95% CI 1.07–1.69), while statin as a discharge medication decreased the risk of MACCE (HR 0.54, P=0.011, and 95% CI 0.33–0.87) in a Cox regression model that also included dyslipidemia, hypertension, renal impairment, STEMI, a calcium channel blocker as a discharge medication, and cerebrovascular disease. The baseline clinical characteristics are shown in Table 3 and discharge medications are shown in Table 4.

Table 3. Baseline characteristics

Variable	STEMI (n=737)	NSTEMI/UAP (n=598)	Stable AP (n=278)	P-value
Age (years)	44.4 ± 5.0	45.3 ± 4.3	45.7 ± 3.7	<0.001
Male gender	638 (87%)	508 (85%)	229 (82%)	0.24
One diseased vessel	509 (69%)	389 (65%)	180 (65%)	0.24
Two diseased vessels	162 (22%)	143 (24%)	78 (28%)	0.13
Three diseased vessels	66 (9%)	64 (11%)	20 (7%)	0.22
Hypertension	207 (28%)	221 (37%)	152 (55%)	< 0.001
Diabetes mellitus	73 (10%)	83 (14%)	51 (18%)	0.001
Dyslipidemia	194 (27%)	210 (35%)	166 (60%)	<0.001
Family history of CAD	317 (44%)	306 (52%)	179 (66%)	<0.001
Smoking	547 (74%)	417 (70%)	174 (63%)	0.001
Previous myocardial infarction	29 (4%)	53 (9%)	34 (12%)	<0.001
Previous PCI	24 (3%)	29 (5%)	33 (12%)	<0.001
Previous CABG	0 (0%)	5 (1%)	6 (2%)	0.001
Heart failure	2 (0%)	1 (0%)	5 (2%)	0.003
Peripheral vascular disease	8 (1%)	7 (1%)	7 (3%)	0.19
Cerebrovascular disease	7 (1%)	11 (2%)	6 (2%)	0.25

Continuous variables are reported as mean and standard deviation and nominal variables are reported as absolute number and percentage; ANOVA and Chi-square tests were used as appropriate.

Table 4. Discharge medications

Variable	STEMI (n=737)	NSTEMI/ UAP (n=598)	Stable AP (n=278)	P-value
Discharge medication				
Aspirin	720 (99%)	592 (99%)	272 (99%)	0.54
Clopidogrel	669 (92%)	560 (94%)	271 (99%)	<0.001
Warfarin	49 (7%)	8 (1%)	7 (3%)	<0.001
Prasugrel	30 (4%)	14 (2%)	2 (1%)	0.013
Statin	699 (96%)	583 (98%)	258 (97%)	0.13
ACE- inhibitor	527 (72%)	360 (61%)	109 (41%)	<0.001
Betablocker	669 (92%)	530 (89%)	225 (83%)	<0.001
Diuretics	73 (10%)	49 (8%)	31 (12%)	0.28
Calcium channel blocker	31 (4%)	37 (6%)	47 (18%)	<0.001

Clinical outcome events after procedure are shown in Table 5.

Table 5. Freedom from adverse postprocedural clinical outcomes

Outcome	1 year	3 years	5 years
Repeat revascularization (%)	89.4	83.2	77.8
Restenosis	96.0	94.2	92.9
Stent thrombosis	98.6	98.0	97.9
Disease progression %	95.4	91.0	86.5
Stroke (%)	99.6	98.5	98.0
Myocardial infarction (%)	97.0	92.9	89.9
MACCE (%)	87.8	79.4	74.1
Death (%)	98.9	98.1	97.8

MACCE: major adverse cardiac and cerebrovascular events.

Most of patients undergoing repeated revascularization during follow-up suffered from progression of coronary artery disease presented as the need to treat lesions other than the culprit lesion, which was treated during the index procedure. Freedom from repeated revascularization at five years was 86.5% due to disease progression, 92.9% due to restenosis and 97.9% due to stent thrombosis.

Independent predictors of repeated revascularization are shown in Table 6 and independent predictors of disease progression after PCI are shown in Table 7.

Table 6. Independent predictors of repeated revascularization

	Hazard Ratio	95% confidence interval	P-value
Multivessel disease	2.49	1.95- 3.18	<0.001
Peripheral vascular disease	2.19	1.17- 4.10	0.014
Previous myocardial infarction	1.65	1.16- 2.35	0.005
Diabetes mellitus	1.65	1.22- 2.23	0.001
Family history of CAD	1.37	1.07-1.75	0.013

CAD: Coronary artery disease

Table 7. Independent predictors of disease progression

	Hazard Ratio	95% confidence interval	P-value
Multivessel disease	3.22	2.30-4.50	<0.001
Diabetes mellitus	1.88	1.27-2.77	0.001
Hypertension	1.45	1.03-2.04	0.032

5.3 Outcomes after coronary revascularization in patients with stage 3b-5 chronic kidney disease (III)

Mean overall survival in CABG patients was 51.2 (± 2.5) months and 41.5 (± 2.7) months in PCI patients (P=0.07). In the eGFR group, under 30 ml/min/m² survival was better in patients undergoing CABG (Log rank p=0.043). Baseline characteristics of the study groups are shown in Table 8.

Table 8. Baseline characteristics

Variables	Overall series			Propensity score matched pairs		
	CABG (n=148)	PCI (n=110)	p-value	CABG (n=54)	PCI (n=54)	p-value
Gender	61 (41.2%)	48 (43.6%)	0.697	24 (44.4%)	25 (46.3%)	0.847
Age	70.7±9.9	73.1±9.9	0.051	72.0±8.5	72.5±10.4	0.790
eGFR (ml/min/m²)	32.2±12.0	33.2±11.2	0.499	32.2±10.9	30.8±11.2	0.427
eGFR<30 ml/min/m²	46 (31.1%)	32 (29.1%)	0.731	17 (31.5%)	22 (40.7%)	0.317
Dialysis	24 (16.2%)	13 (11.8%)	0.319	6 (11.1%)	9 (16.7%)	0.404
Kidney transplant	5 (3.4%)	4 (3.6%)	0.911	1 (1.9%)	2 (3.7%)	0.558
Atrial fibrillation	30 (20.3%)	21 (19.1%)	0.814	11 (20.4%)	10 (8.5%)	0.808
Diabetes	66 (44.6%)	58 (52.7%)	0.196	24 (44.4%)	30 (55.6%)	0.248
Hypertension	112 (75.7%)	93 (84.5%)	0.081	37 (68.5%)	46 (85.2%)	0.040
Prior stroke	16 (10.8%)	15 (13.6%)	0.449	5 (9.3%)	7 (13.0%)	0.490
Extracardiac arteriopathy	27 (18.2%)	19 (17.3%)	0.840	8 (14.8%)	10 (18.5%)	0.606
Congestive heart failure	15 (16.3%)	28 (25.5%)	0.114	4 (11.1%)	20 (37.0%)	
Pulmonary disease	22 (14.9%)	13 (11.8%)	0.480	11 (20.4%)	6 (11.1%)	0.186
Prior PCI	24 (16.2%)	21 (19.1%)	0.547	14 (25.9%)	12 (22.2%)	0.653
Prior cardiac surgery	3 (2.0%)	21 (19.1%)	<0.001	3 (5.6%)	7 (13.0%)	0.184
AMI <90 days	70 (47.3%)	22 (20.0%)	<0.001	20 (37.0%)	21 (38.9%)	0.843
LVEF						0.591
>50%	95 (64.2%)	83 (75.5%)	0.196	40 (74.1%)	38 (70.4%)	
30-50%	45 (30.4%)	23 (20.9%)	0.087	13 (24.1%)	13 (24.1%)	
<30%	8 (5.4%)	4 (3.6%)	0.505	1 (1.9%)	3 (5.6%)	
Urgent/emergent procedure	84 (56.7%)	77 (70.0%)	0.030	30 (55.6%)	29 (53.7%)	0.847
Left main stenosis	63 (42.6%)	14 (12.7%)	<0.001	9 (16.7%)	9 (16.7%)	1.000
Off pump CABG	69 (46.6%)	-	-	34 (63.0%)	-	-
LIMA-graft	132 (89.2%)	-	-	47 (87.0%)	-	-
Drug eluting stent	-	53 (48.2%)	-	-	26 (48.1%)	-

Continuous variables are reported as the mean and standard deviation; categorical variables are reported as counts and percentages; AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; eGFR: estimated glomerular filtration rate; LIMA: left internal mammary artery; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.

The outcomes after PCI and CABG are shown in Table 9.

Table 9. Postprocedural outcomes.

Outcome end-points	Overall series			Propensity score-matched pairs		
	CABG (n=148)	PCI (n=110)	P-value (Log-rank)	CABG (n=54)	PCI (n=54)	P-value (Log-rank)
All-cause mortality			0.068			0.041
30-day	12.2%	10.0%		11.1%	9.3%	
1-year	17.1%	24.6%		15.0%	33.3%	
5-year	33.9%	55.6%		34.2%	58.4%	
Myocardial infarction			0.668			<0.001
1-year	8.6%	14.6%		0%	20.3%	
5-year	35.6%	46.7%		0%	25.9%	
Repeat revascularization			<0.001			0.036
1-year	0.8%	9.0%		0%	6.3%	
5-year	0.8%	26.3%		0%	10.2%	
Stroke rate			0.750			0.204
30-day	5.4%	2.8%		4.7%	1.9%	
1-year	5.4%	4.8%		4.7%	6.3%	
5-year	5.4%	10.5%		4.7%	15.0%	
New onset dialysis			0.067			0.145
30-day	3.4%	0%		4.7%	0%	
5-year	29.3%	10.2%		13.2%	7.1%	
MACCE			0.004			0.006
1-year	19.3%	31.8%		15.0%	38.9%	
5-year	35.3%	72.4%		34.2%	63.1%	

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; MACCE: major adverse cardiac and cerebrovascular event.

Differences in overall survival between study groups were not statistically significant in patients with stage 3b–5 chronic kidney disease. However, unadjusted all-cause mortality tended to be higher in patients undergoing PCI. The difference for propensity matched pairs of patients with stage 3b–5 chronic kidney disease undergoing PCI and CABG is presented in Figure 1.
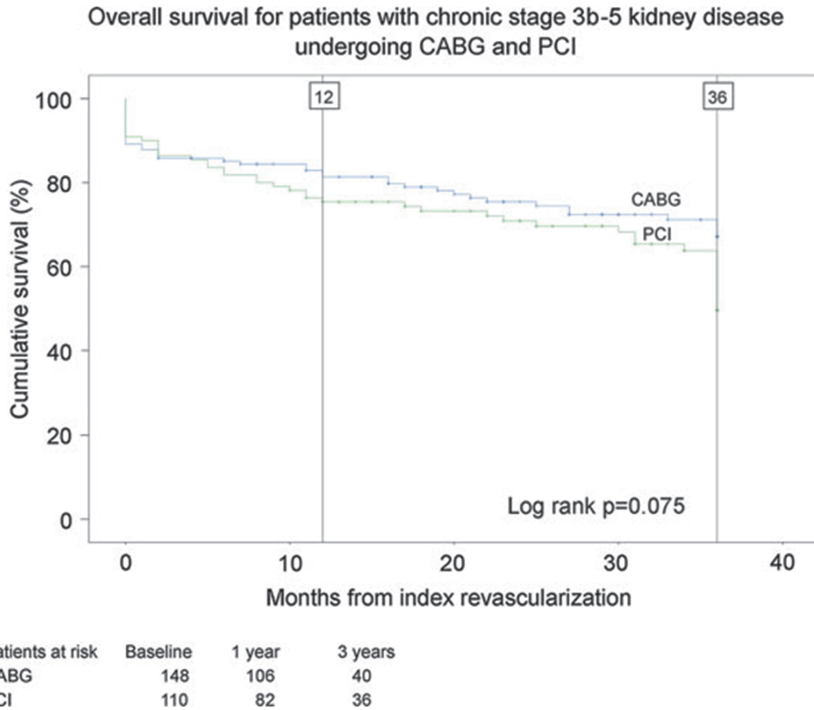

Figure 1. Overall survival. From original publication III. Reproduced with the permission of the copyright holder.

Estimates of cumulative freedom from MACCE for propensity matched pairs of patients with stage 3b–5 chronic kidney disease undergoing PCI and CABG are shown in Figure 2. In the eGFR under 30 ml/min/m2 group, survival was better for patients undergoing CABG (Log rank P=0.043).
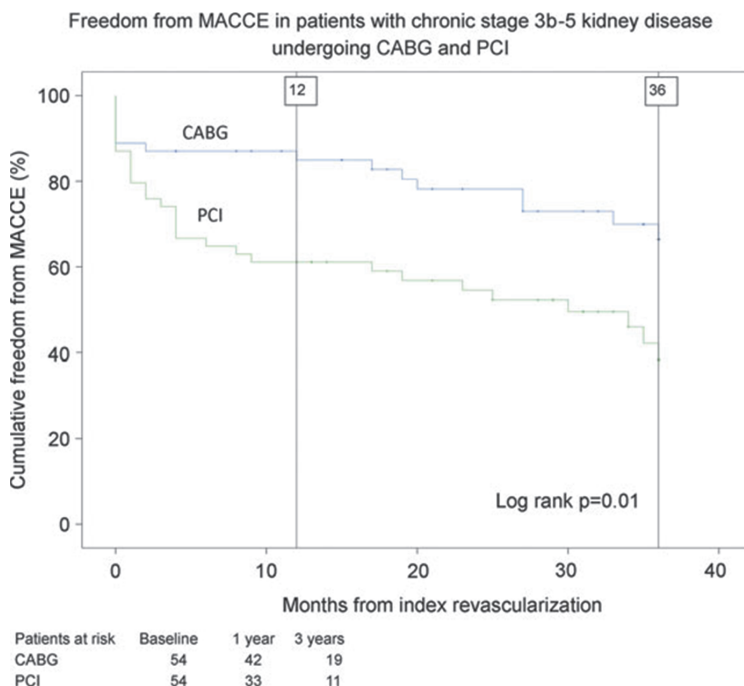
Figure 2. Freedom from MACCE. From original Publication III. Reproduced with the permission of the copyright holder.

5.4 Permanent work disability after coronary revascularization in patients under 50 years old (IV)

The independent predictors of permanent work disability were eGFR < 60 ml/min/m^2 (HR 3.46, P=0.004, and 95% CI 1.50–7.98), prior PCI (HR 2.86, P=0.001, and 95% CI 1.52–5.39), diabetes mellitus (HR 1.86, P=0.01, and 95% CI 1.15–3.00), preprocedural left ventricular ejection fraction ≤ 50% (HR 1.73, P=0.03, and 95% CI 1.06–2.81), and age (per each year) (HR 1.09, P=0.001, and 95% CI 1.03–1.15).

Baseline characteristics are shown in Table 10 and discharge medication in Table 11.

Table 10. Baseline characteristics

Variable	Overall series		
	CABG (n=125)	PCI (n=910)	p-value
Age (years)	46.3 (4.2)	44.8 (4.7)	<0.001
Females	15 (12.0%)	143(15.7%)	0.28
eGFR<60 ml/min/m^2	8 (6.4%)	17 (1.9%)	0.002
Family history of CAD	80 (64.5%)	484 (53.4%)	0.02
Hypertension	62 (49.6%)	274 (30.1%)	<0.001
Smoker	86 (68.8%)	646 (71.0%)	0.61
Diabetes	27 (21.6%)	112 (12.3%)	0.004
History of MI	44 (35.5%)	56 (6.2%)	<0.001
History of PCI	14 (11.2%)	40 (4.4%)	0.001
History of CABG	1 (0.8%)	3 (0.3%)	0.428
Extracardiac arteriopathy	10 (8.0%)	10 (1.1%)	<0.001
Congestive heart failure	9 (7.2%)	4 (0.4%)	<0.001
Cerebrovascular disease	2 (1.6%)	10 (1.1%)	0.63
Indication for revascularization			<0.001
STEMI	15 (12.0%)	367 (40.5%)	
NSTEMI	32 (25.6%)	276 (32.5%)	
UAP	7 (5.6%)	80 (8.8%)	
Stable AP	71 (56.8%)	187 (20.6%)	
Urgency			<0.001
Elective	72 (57.6%)	193 (21.4%)	
Urgent	47 (37.6%)	494 (54.7%)	
Emergent	6 (4.8%)	216 (23.9%)	
LVEF			0.005
>50%	92 (74.2%)	494 (74.8%)	
30-50%	24 (19.4%)	155 (23.5%)	
<30%	8 (6.5%)	11 (1.7%)	
Left main stenosis	31 (25.2%)	10 (1.1%)	<0.001
No. of diseased vessels	2.6±0.7	1.4±0.7	<0.001
No. of treated vessels			<0.001
1	13 (10.4%)	630 (69.2%)	
2	30 (24.0%)	207 (22.7%)	
3	82 (65.6%)	69 (7.6%)	
Incomplete revascularization	3 (2.4%)	171 (18.8%)	<0.001
At least one IMA graft	119 (95.2%)	-	
Bilateral IMA graft	23 (18.4%)	-	
At least 2 arterial grafts	57 (45.6%)	-	
Drug eluting stent	-	531 (58.5%)	

Continuous variables are reported as mean and standard deviation and nominal variables are reported as absolute number and percentage. CAD: coronary artery disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting. STEMI: ST elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, UAP: unstable angina pectoris, AP: angina pectoris, IMA: internal mammary artery, MI: myocardial infarction; ASA: acetyl salicylic acid. LVef: left ventricular ejection fraction.

Table 11. Discharge medication.

Variable	Overall series		
	CABG (n=125)	**PCI (n=910)**	**p-value**
Discharge medication			
ASA	118 (95.9%)	900 (99.3%)	0.001
Clopidogrel	12 (9.9%)	859 (94.8%)	<0.001
Warfarin	3 (2.4%)	35 (3.8%)	0.58
Statin	118 (97.5%)	881 (97.1%)	0.81
ACE- inhibitotor/ AT2-antagonist	46 (37.7%)	535 (59.6%)	<0.001
Beta blocker	119 (98.3%)	834 (92.5%)	0.016
Diuretics	21 (17.2%)	64 (7.2%)	<0.001
Ca-blocker	6 (4.9%)	63 (7.1%)	0.36

Altogether, 11.3% of patients in the PCI group and 27.2% of patients in the CABG group were granted PWD postoperatively. The most common primary diagnosis for PWD after undergoing PCI and CABG in patients under 50 years old was any cardiac diagnosis (CABG 35.3% vs. PCI 36.9%).

Freedom from PWD was lower in the CABG group (Kaplan-Meier analysis at 5 years). The difference is shown in Figure 3.
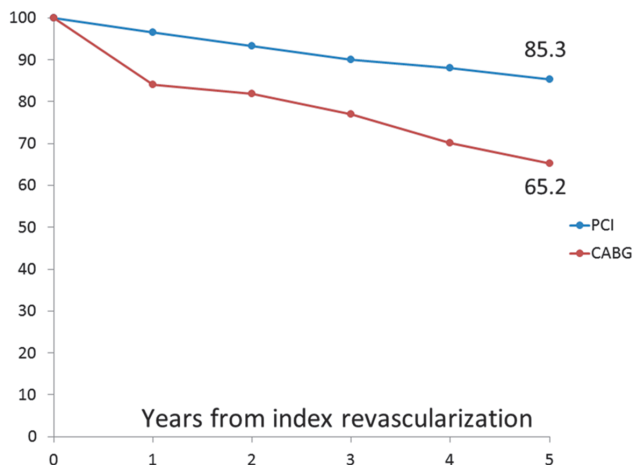
Figure 3. Freedom from PWD. From Original publication IV. Reproduced with the permission of the copyright holder.

Freedom from PWD at 5 years was 85.6% for patients without MACCE and 71.9% for patients with MACCE (p-value <0.001). The difference is shown in Figure 4.
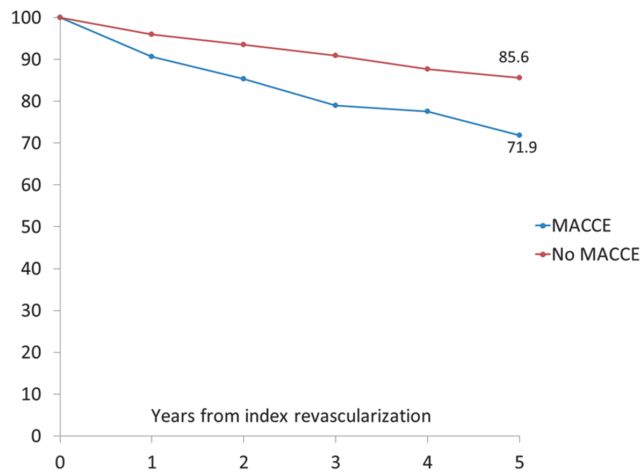
Figure 4. Freedom from PWD in patients with MACCE and without MACCE. From Original publication IV. Reproduced with the permission of the copyright holder.

6   DISCUSSION

6.1   Health-related quality of life

In study I, the main finding was that a lower score on the EuroQoL-5D Visual Analogue Scale at 6 months postoperation correlated with an occurrence of later MACCE in patients undergoing surgical revascularization when the follow-up time was 38.6 months. The EuroQoL-5D was used to assess the current quality of life. This study provides evidence that worsening postoperative scores on health-related quality of life predict later mortality and morbidity. Long-term risk factors are preoperative factors in most cases (Koch et al. 2003; Wu et al. 2012). Previous studies have described improvement in health-related quality of life after cardiac surgery as compared to baseline status (Ghanta et al. 2011; Vicchio et al. 2012; Cohen et al. 2011; Sen et al. 2012). The predictive value of health-related quality of life measures and its changes have previously been shown for patients with operative cancer and for those with heart failure (Pompili et al. 2013; Hoekstra et al. 2013; Djärv et al. 2011).

In this study, after 6 months postoperation, the patients who had MACCE had a lower quality of life more often when measured with the EQ-5D questionnaire. In contrast, the patients without MACCE had VAS values comparable to the general population (74.4 ± 7.6) (Kaarlola et al. 2004). Therefore, this study suggests that it might be beneficial in some cases to use an HRQoL questionnaire as a tool to identify patients at late risk for adverse events.

Altogether, 41.4% of all patients did not fill out a questionnaire, which may have an effect on the results. The conclusion from this study may be drawn only from the studied population, which includes the treated patients who filled out the questionare. Question-based studies often face the problem of missing information, and it is difficult to find a solution. Despite the missing answers, the current study reveals a significant relationship between poorer quality of life and

increased incident of MACCE. This reflects the importance of early cardiac re-habilitation after CABG in order to improve the immediate postoperative quality of life.

The patients undergoing urgent CABG were included in the study. These patients preoperatively evaluate the HRQoL of the previous two weeks. Assessing the HRQoL may be challenging in patients undergoing urgent cardiac events, and this might introduce bias and limit in this study. In addition, Study I consisted of a small patient population and was retrospective in nature. In the future, further studies with larger populations are required to confirm these findings.

6.2   Young patients undergoing coronary revascularization (CRAGS)

In general, coronary revascularization is associated with a low procedural risk, and postoperative risks for late events (stroke, myocardial infarction, and repeat revascularization) are minor in young patients (Zimmerman et al. 1995; Fleissner et al. 2015; Biancari et al. 2014). When comparing elderly patients with ACS (65 years old and older) to younger patients, long-term clinical outcomes after PCI are worse. In the long-term, the incidence of major adverse cardiac events, in-cluding cardiac death and nonfatal myocardial infarction, were higher in elderly patients (19.7% versus 12.0%, P=0.002) (Nammas et al. 2017). In young patients (50 years old and younger), the freedom from repeat revascularization was 77.6% at 5 years after PCI. The disease progression was the main reason for repeat re-vascularization after PCI in young patients (52.9%). Stent thrombosis was the reason for repeat revascularization in 10.9% of cases, and in-stent restenosis was the reason for repeat revascularization in 31.7% of cases (Biancari et al. 2014). In the patients with complex coronary artery disease, the rate of repeated revascular-ization after PCI was 25.9% at 5 years. Target-vessel revascularizations (89.6%) were the majority of all repeated PCI procedures, and approximately half of the procedures were target lesion revascularizations (55.7%) in this study population

aged 64.8 ± 9.2 years old. Repeat PCI on *de novo* lesion was performed in 33.3% of cases (Parasca et al. 2016).

Study II showed that despite the good overall survival, young patients undergoing PCI needed repeated revascularization due to the disease progression. Stent thrombosis and restenosis are known to cause a need for reinterventions after PCI (Palmerini et al. 2012; Mauri et al. 2007; Mohr et al. 2013; Bangalore et al. 2012). In this study, freedom from repeat revascularization was 86.5% due to disease progression, and freedom from repeat revascularization due to stent thrombosis was 97.9% and due to restenosis 92.9%. Therefore, disease progression was six times more common than restenosis and stent thrombosis in this young study population. The disease progression was a major reason for repeat revascularization in young patients. This can be partly explained by the fact that in young patients, CAD might be more aggressive by nature, which causes rapid disease progression and leads to non-target lesion-related revascularization. In spite of the optimal secondary preventive medication, 16.8% ended up needing repeat revascularization.

In spite of the good overall outcome after coronary revascularization in young patients, study IV showed that every third patient undergoing CABG and every seventh patient undergoing PCI were on permanent disability pension. Surgical revascularization was associated with disability pension, and the patients undergoing CABG had a higher risk for PWD when comparing with patients treated with PCI. This may be partly explained by the patient selection between procedures. In this present study, in most cases, the indication for CABG was stable angina pectoris, and more often, the patients undergoing CABG had a history of PCI that underlines the fact that CABG patients more often had an advanced disease. In addition, CABG patients also have comorbidities (severe renal dysfunction, diabetes) more often, and these findings can partly explain the unfavorable outcomes (Zhang et al. 2014; Carson et al. 2002; Holzmann et al. 2007). MACCE was associated with the incidence of permanent work disability. The risk of

disability pension was twofold at 5 years after PCI and CABG in patients with occurrence of MACCE.

In general, imminent causes for cardiac PWD are repeat revascularization, heart failure, and stroke. In this study population, the rates of these imminent reasons were low, so the high occurrence of permanent work pension due to cardiac causes introduced a discrepancy. In addition, the median time for PWD after CABG was equal to the maximum time of compensation due to illness in Finland (330 days). This finding suggests that patients undergoing CABG fail to return to work. Patients at high risk for disability pension after coronary revascularization need to be identified at an early stage, and an effective secondary prevention is especially needed in this patient group. Along with the effective secondary prevention, attitudes toward PWD must be taken into account. The high prevalence of disability pension might be partly explained by the pessimistic attitudes of the healthcare professionals and the patients towards the recovery of working ability after cardiac procedures. This study showed that the patients undergoing coronary revascularization actually have disability pension after procedures more often than might be needed. The attitude shift of the healthcare professionals and the patients toward permanent work disability may help to overcome this problem. Cardiac rehabilitation has been shown to be associated with a reduction of modifiable risk factors and cardiac mortality (Taylor et al. 2004; van Halewijn et al. 2017). Whether cardiac rehabilitation had any role in the reduction of PWD would be worth investigating.

There are some limitations in both studies, and the results should be viewed in the light of them. Both studies were retrospective, which causes the major limitation in study II. In addition, the compliance data on the secondary preventive medication was not available in this study. In study IV, the first limitation was that the employment status was not assessed—only permanent work disability. Altogether, in study IV, 11.2% of patients undergoing CABG had a history of PCI. Unfortunately, it is unknown whether the prior PCI was performed within 3

months before CABG, and therefore this limitation can introduce bias in this study. In addition, the data on sociodemographic factors were not available.

6.3   Coronary revascularization in patients with moderate to severe renal impairment

After coronary revascularization, patients with chronic kidney dysfunction have worse outcomes compared to patients with normal kidney function (Cooper et al. 2006; Nakayama et al. 2003). In addition, the CKD is a risk factor for cardiac mortality and morbidity, and decreasing eGFR is a prognostic factor for MACCE and postprocedural mortality and morbidity after CABG and PCI (Astor et al. 2008; Go et al. 2004). Study III showed that the patients with severe renal impairment undergoing CABG needed early postoperative dialysis more often. However, there was not a significant difference between study groups in the rates of dialysis at late follow-up. Therefore, the higher risk for the permanent dialysis might be overemphasized. Numerous studies have shown that chronic kidney dysfunction is a major risk factor for postprocedural major adverse events after coronary revascularization (Dohi et al. 2011; Keeley et al. 2003). In this study, the freedom from MACCE was higher in the CABG group (78.2%) at 2 years after operation than in the PCI group (54.4%). These findings suggest that the overall survival and long-term outcomes were better in the patients undergoing CABG, even when renal dysfunction was severe (eGFR less than 30). However, in spite of these results, the frail patients with a high operative risk might benefit more from PCI.

The patients in the 3b–5 stages of chronic kidney disease are at high risk for poor outcomes after coronary revascularization. Despite this fact, study III provides evidence that patients with moderate to severe renal impairment should not be denied the coronary artery bypass grafting based on kidney function alone.

The limitations of the study were its retrospective nature and a small patient population. In addition, the comparability of the patient groups is difficult due to the selection bias causing heterogeneity of the study subjects.

7   CONCLUSIONS

The following conclusions may be drawn from the present investigation.

Lower quality of life scores using the EQ-5D questionnaire at 6 months after surgery may predict later major adverse cardiovascular events. CABG offers a significant improvement in health-related quality of life after 6 months when comparing to the baseline.

Young patients undergoing coronary revascularization are at high risk for a permanent work disability. More attention should be paid on the young patients recovering from the procedures. Secondary prevention and changes in attitudes toward working capability are essential after coronary revascularization. In addition, more effective measures are needed to combat disease progression in young patients undergoing PCI.

Coronary patients with chronic kidney disease might benefit from surgical revascularization and the procedures must not be denied based on the kidney function alone.

ACKNOWLEDGEMENTS

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