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Coronary Artery Bypass Grafting – Postoperative Employment and 20-year Mortality

Impact of obesity, metabolic syndrome and diabetes mellitus

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Impact of obesity, metabolic syndrome and diabetes mellitus

ACADEMIC DISSERTATION
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ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Kanta-Häme Central Hospital, Department of Emergency Medicine
Finland

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To my Family

It is good to have an end to journey toward;
but it is the journey that matters,
in the end.

~Ernest Hemingway

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Hämeenlinna, June 2019

Ville Hällberg

ABSTRACT

Background

Cardiovascular disorders play a crucial role in the global burden of diseases, being in most countries the leading cause of death. Coronary artery bypass, introduced in the mid-1960s, became the standard treatment in severe coronary artery disease (CAD) in the 1980s also in Finland. The role of preventive measures in long-term survival of CAD became evident in the 1980s and 1990s. Most studies addressing long-term survival after coronary artery bypass grafting (CABG) have covered study periods ranging from five to ten years and thus their ability to find slow alterations has been limited.

Aims

The aim of this study was to evaluate the postoperative prognosis of CABG patients for up to 20 years. It was approached through postoperative employment together with total and cardiovascular mortality. The aim was also to examine how long-term survival was related to obesity, metabolic syndrome (MetS) and diabetes mellitus (DM). The effect of statin treatment upon survival was also studied.

Subjects and methods

Two different populations were included. The follow-up studies comprised 922 CABG patients operated on during the period 1 January 1993 – 30 June 1994 at Tampere University Hospital. The study population for the annual cohorts consisted of 946 CABG patients treated in Kanta-Häme Central Hospital during the time period 1 January 1990 – 31 December 2009. Study data was collected from patient records, questionnaires and national registries. The relative survival rates compared to matched background populations were analysed using the Life Table method. To study the independent significance of obesity, MetS and DM for clinical outcome, multivariate analysis based on the Bayesian approach was used.

Results

Almost 60 percent of patients, preoperatively not retired, remained employed after surgery. Age and length of preoperative sick leave or temporary retirement were the most important factors affecting postoperative employment. Having once returned

to work, patients' retention at work was comparable to that in the general population. Diabetes mellitus already during the first postoperative decade and obesity and MetS during the second postoperative decade were related to impaired survival. Patients without DM or MetS had an equally good prognosis as their operation year, age and gender matched background populations. Scant statin use was also related to poor survival. Statin use in the annual cohorts population increased up to 20-fold during the study period.

Conclusions

The retention of working capacity is high after CABG. Effective and prompt treatment of coronary heart disease and its risk factors significantly improves long-term prognosis and continuation in employment. Obesity, MetS and especially diabetes mellitus have deleterious impact on mortality rates. In addition, non-adherence to statin use is associated with increased mortality. The results encourage the effective treatment of metabolic risk factors among patients with coronary artery disease.

TIIVISTELMÄ

Tausta

Sydän- ja verenkiertoelimistön sairauksilla on tärkeä merkitys ihmiskunnan tautikirjossa, koska ne ovat useimmissa maissa johtava kuolinsyy. Sepelvaltimoiden ohitusleikkaus, joka ensimmäisen kerran tehtiin 1960-luvulla, kehittyi Suomessakin vaikean sepelvaltimotaudin rutiininomaiseksi hoitotavaksi 1980-luvulla. Sekundaariprevention keskeinen merkitys sepelvaltimotaudin pitkäaikaishoidossa tuli ilmeiseksi 1980- ja 1990-luvuilla. Pääosa sepelvaltimoiden ohitusleikkauksen jälkeisistä pitkäaikaisennustetta selvittävistä tutkimuksista on ollut pisimmillään 5 – 10 vuoden kestoisia ja siten ne ovat tarjonneet rajallista tietoa hitaiden muutosten merkityksestä.

Tavoitteet

Tutkimuksen tavoitteena oli selvittää sepelvaltimoiden ohitusleikkauksen jälkeistä ennustetta 20 vuoden seurannassa leikkauksen jälkeen työssä olon, kokonaiskuolleisuuden ja sydänkuolleisuuden avulla. Tarkoituksena oli myös selvittää, miten pitkäaikaisennuste korreloi lihavuuteen, metaboliseen syndroomaan (MetS) ja diabetekseen (DM). Statiinilääkkeiden käyttöä selvitettiin osana ennustetta.

Aineisto ja menetelmät

Tutkimusprojekti käsitti kaksi eri aineistoa. Seurantatutkimukseen osallistui 922 sepelvaltimoiden ohitusleikkauspotilasta, jotka leikattiin 1.1.1993 – 30.6.1994 Tampereen yliopistollisessa sairaalassa. Vuosikohorttien tutkimukseen osallistui 946 Tampereen yliopistollisessa sairaalassa leikattua ja Kanta-Hämeen keskussairaalassa 1.1.1990 – 31.12.2009 jatkohoidettua sepelvaltimoiden ohitusleikkauspotilasta. Tutkimustiedot kerättiin sairauskertomuksista, potilaskyselyistä ja kansallisista arkistoista. Suhteellista ennustetta verrattiin vastaavaan taustaväestöön ja analysoitiin Life Table-menetelmällä. Lihavuuden, MetS:n ja DM:n itsenäistä merkitystä ennusteeseen selvitettiin Bayesin filosofiaan pohjautuvalla monimuuttuja-analyysillä.

Tulokset

Lähes 60 % leikkausta edeltäen eläköitymättömistä ohitusleikkauspotilaista palasi leikkauksen jälkeen työelämään. Ikä ja leikkausta edeltävän sairasloman tai määräaikaisen työkyvyttömyyseläkkeen kesto olivat tärkeimmät työkykyyn vaikuttavat tekijät. Leikkauksen jälkeen työhön palanneiden potilaiden työkyvyn säilyminen oli verrattavissa saman ikäiseen muuhun väestöön. Diabetes jo ensimmäisellä postoperatiivisella vuosikymmenellä ja lihavuus tai MetS toisella vuosikymmenellä huononsivat merkittävästi potilaiden ennustetta. Toisaalta potilaat, jotka eivät sairastaneet diabetesta tai MetS:a pärjäsivät yhtä hyvin kuin leikkausvuosi, ikä ja sukupuolivakioitu taustaväestö. Vähäinen statiinien käyttö liittyi huonoon ennusteeseen. Vuosikohorttien tutkimuksessa statiinien käyttö lisääntyi 20-kertaiseksi seuranta-aikana.

Johtopäätökset

Sepelvaltimoiden ohitusleikkauspotilaiden työkykyyn ja ennusteeseen vaikuttavat olennaisesti sepelvaltimotaudin ja sen riskitekijöiden tehokas ja viiveetön hoito. Lihavuus, metabolinen oireyhtymä ja erityisesti diabetes lisäävät kuolleisuutta. Niin ikään statiinien vähäinen käyttö assosioituu huonoon ennusteeseen. Tutkimustulokset kannustavat sepelvaltimotautipotilaiden metabolisten riskitekijöiden tehokkaaseen hoitoon.

CONTENTS

ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
AHA/NHLBI	American Heart Association/National Heart, Lung and Blood Institute
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid
BMI	Body mass index (kg/m^2)
BMS	Bare metal stents
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CKD–EPI	Chronic Kidney Disease Epidemiology Collaboration
CPB	Cardiopulmonary bypass
CV	Cardiovascular
CVD	Cardiovascular disease
DES	Drug eluting stents
DM	Diabetes mellitus
DSDI	Daily statin dose index
EF	Ejection fraction
FFA	Free fatty acid
GFR	Glomerular filtration rate
HDL	High-density lipoprotein (particle)
HDL–C	High-density lipoprotein cholesterol
HRQoL	Health related quality of life
IDF	International Diabetes Federation
IDL	Intermediate-density lipoprotein (particle)
IDL–C	Intermediate-density lipoprotein cholesterol
Kela	Finnish National Social Insurance Institution

LAD	Left anterior descending artery
LDL	Low-density lipoprotein (particle)
LDL–C	LDL cholesterol
LITA	Left internal thoracic artery
LR	Likelihood ratio
LV	Left ventricle
MetS	Metabolic syndrome
MI	Myocardial infarction
NCP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NS	Not significant
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
RCT	Reverse cholesterol transport
RTW	Return to work
SD	Standard deviation
SR	Scavenger receptor
STEMI	ST-elevation myocardial infarction
SVG	Saphenous vein graft
T–C	Total cholesterol
TIA	Transient ischaemic attack
TG	Triglyceride
T2DM	Type 2 diabetes mellitus
VLDL	Very-low-density lipoprotein (particle)
VLDL–TG	Very-low-density lipoprotein triglyceride
W-CABG	Working After Coronary Artery Bypass Grafting
WHO	World Health Organization
4S study	The Scandinavian Simvastatin survival study

ORIGINAL PUBLICATIONS

I	Hällberg V, Palomäki A, Kataja M, Tarkka M; Working after CABG study group. Return to work after coronary artery bypass surgery. A 10-year follow-up study. Scand Cardiovasc J. 2009; 43:277-284.
II	Hällberg V, Kataja M, Tarkka M, Palomäki A; Working after CABG study group. Retention of work capacity after coronary artery bypass grafting. A 10-year follow-up study. J Cardiothorac Surg. 2009; 4:6.
III	Palomäki A, Hällberg V, Ala-Korpela M, Kovanen P, Malminiemi K. Prompt impact of prospective statin mega-trials on postoperative lipid management of CABG patients: a 20-year follow-up in a single hospital. Lipids Health Dis. 2016; 15:124.
IV	Hällberg V, Palomäki A, Lahtela J, Voutilainen S, Tarkka M, Kataja M; Study Group (W-CABG). Associations of metabolic syndrome and diabetes mellitus with 16-year survival after CABG. Cardiovasc Diabetol. 2014; 13:25.
V	Hällberg V, Palomäki A, Lahtela J, Tarkka M, Innamaa T, Kataja M, W-CABG study group. Obesity paradox disappears in coronary artery bypass graft patients during 20-year follow-up. Eur Heart J Acute Cardiovasc Care. 2017; 6:771-777.

1 INTRODUCTION

Cardiovascular diseases (CVD) play a crucial role in the global burden of diseases being in most countries the leading cause of death and outweighing all cancers and pulmonary diseases. Clinically significant atherosclerotic lesions typically evolve over the course of decades. However, the symptoms may also manifest suddenly. In the worst case, the first symptom of coronary artery disease (CAD) is sudden death. Primary prevention, treatment and secondary prevention of cardiovascular diseases have changed completely in our lifetime. During the last half-century the nature of the disease has often become preventable. In the best case, the course of disease may be reversed from progression to regression [1,2].

The recent successes of CAD treatment are numerous. Coronary artery bypass grafting (CABG), introduced in the mid-1960s, became during the following two decades the standard treatment for patients with severe CAD. Percutaneous coronary intervention (PCI) with intensive postoperative antithrombotic care has developed over the past 30 years into an effective and less demanding alternative to CABG for most patients. The Scandinavian Simvastatin Survival Study (4S study) published in 1994 served to promote statin treatment and secondary prevention of CAD, and today we talk about comprehensive risk factor management including both lifestyle interventions and medication [3,4].

In the review of the literature the epidemiology, aetiology, progress and treatment of CAD are discussed, with particular interest in medical therapy and CABG. The main scope of the studies incorporated in this dissertation is on secondary prevention and long-term prognosis after CABG as well as postoperative employment and risk-factors affecting it.

2 REVIEW OF THE LITERATURE

2.1 Definition of coronary artery disease

Atherosclerosis is a lifelong process. Advanced lesions involve disorganization of the intima and deformity of the artery, but their precursors are latent minimal changes starting in the childhood with an increase in the number of intimal macrophages evolving into foam cells and fatty streaks [5]. If primary prevention of coronary artery disease (CAD) fails, lesions grow gradually expanding to extensive coronary atherosclerosis found in autopsy studies even in patients without known CAD. At some point of life, the patient may exhibit acute coronary syndrome (ACS) and afterwards remain stable for years or even decades with few or no symptoms [6,7].

In ACS, a gradually growing plaque or sudden thrombosis of ruptured or eroded plaque obstructs coronary blood flow. The patient may have severe underlying CAD, but on occasion there may be only non-obstructive coronary atherosclerosis or no angiographic findings at all. Coronary spasm, endothelial dysfunction, tachy- and bradyarrhythmias and various extracardial diseases may lead to imbalance between myocardial oxygen supply and demand, and thus to a clinical manifestation of ACS [8,9].

2.2 Epidemiology of coronary artery disease

Cardiovascular diseases (CVD) are the most common causes of death worldwide in all World Health Organization (WHO) regions, the only exception to this being Africa [10]. Out of 54.7 million deaths occurring worldwide in 2016, 17.6 million (32%) were due to cardiovascular diseases[11]. CAD mortality peaked in the 1960s in the United States and in the 1970s in Western Europe, including Finland [8,12–15]. Since then this mortality has decreased in Finland to less than one fifth [16,17].

The increase in death rates seen earlier in developed countries is nowadays seen in developing countries [10]. According to Statistics Finland, the National Statistical Service, CAD mortality in Finland was 18.9% (10,183 out of 53,964 deaths) of total yearly mortality in 2016 [18]. According to Kela, the Finnish National Social Insurance

Institution, 174,596 inhabitants had special medical reimbursement for CAD in the same year [19].

In Finland, the North Karelia Project was initiated in 1972 for a comprehensive community based cardiovascular (CV) prevention programme involving two provinces and subsequently extending nationwide [20]. In 1972, men in Finland had the highest CV age adjusted mortality in the world, 500/100,000 and even higher in North Karelia, as shown in the Seven Countries Study [20,21]. As a result of the programme in North Karelia risk factors fell, total cholesterol (TC) from 6.9 mmol/l to 5.4 mmol/l, blood pressure (BP) from 150/90 mmHg to 130/80 mmHg and smoking (men) from over 50% to less than 30% in the period 1972 to 2012. In North Karelia CAD mortality decreased during the study period from 690/100,000 to below 100/100,000, reaching the international average level. About 2/3 of the decline in CAD mortality can be explained by risk factor modification related to life style changes and 1/3 by the new treatments for CAD since 1980 [20]. Similar, although smaller changes in CAD risk factors were found around Europe as documented *e.g.* in Euroaspire studies since 1990 [22].

From the beginning of the 1970s the nature of coronary heart disease has evolved. Large, often fatal MIs in middle-aged men have been replaced by smaller non-fatal MIs in senior citizens. Beneficial life-style changes especially during the first decades, development of medical treatment, thrombolysis and coronary surgery since the 1990s and eventually percutaneous coronary interventions in the 2000s have decreased CV mortality [15,22,23].

2.3 The atherosclerotic process

Atherosclerosis is a chronic arterial process involving inflammation. It leads to the formation of an atheromatous plaque, a focal lesion located within the intima of large and medium-sized arteries [24,25]. Crucial for this process is the infiltration and retention of apolipoprotein B (apoB) containing lipoproteins, such as low-density lipoproteins (LDL) and remnants of very-low-density lipoproteins (VLDL) and chylomicrons, in the artery wall [26,27].

To reach their target organ cells apoB containing lipoproteins have first to exit circulation [28,29]. The endothelial cells of the arteries react to mechanical and molecular stimuli to regulate tone, haemostasis and inflammation throughout the circulation [30–32]. The impaired integrity of this endothelial barrier is the initial step in atherosclerosis and is more likely to occur at arterial curves and branches characterized by turbulent blood flow and low shear stress [33,34]. This leads to increased accumulation and retention of subendothelial atherogenic apoB containing lipoproteins, essentially LDL [26,35].

The flow of lipoproteins to the media layer is inhibited by a dense and elastic lamina between the intima and the media. Due to the properties of cell intima causing slow drain, the concentration of LDL particles increases to resemble that of plasma and tenfold to resemble that of the interstitial fluid of other cells [36].

LDL particles remaining in the subendothelial space may become oxidatively or enzymatically modified. Cell cultures as well as animal studies and research conducted on CAD patients have shown that oxidation of LDL plays a key role in atherogenesis [37–43]. Modified LDL induces intimal smooth muscle cells to excrete chemotactic proteins, which in turn contribute to the activation of endothelial cells and recruitment and transendothelial migration of circulating monocytes [44,45]. Oxidized LDL is eventually taken up by the scavenger receptors (SRs) of monocyte-derived macrophages in an uncontrolled manner [37,46]. Once within the arterial wall, the return of macrophages to plasma is prevented by oxidized LDL [37,43,47]. Thus, a continuous inflammatory process predominates in the atherosclerotic intima causing endothelial dysfunction.

When accumulation of LDL is not matched with reverse cholesterol transport (RCT) (see next paragraph), macrophages may become saturated by cholesterol during the continuous process and turn into foam cells [47–49]. When foam cells die, their cholesterol remains in the arterial wall forming the necrotic nucleus of an atherosclerotic plaque. Inflammatory macrophages stimulate infiltration and proliferation of vascular smooth muscle cells, which produce an extracellular matrix providing a stable fibrous barrier between the prothrombotic factors of the plaque and the circulating platelets [50]. Recent studies also suggest that smooth muscle cells may undergo phenotype switch and give rice to a significant number of foam cells [51]. However, progressive inflammation renders stable plaques vulnerable, manifesting in increased smooth muscle cell death, decreased extracellular matrix production and collagen degradation by macrophage proteinases. Rupture of the thinning fibrous cap or its superficial erosion promotes thrombus formation causing clinical ischaemic events [8,52–54] (Figure 1).

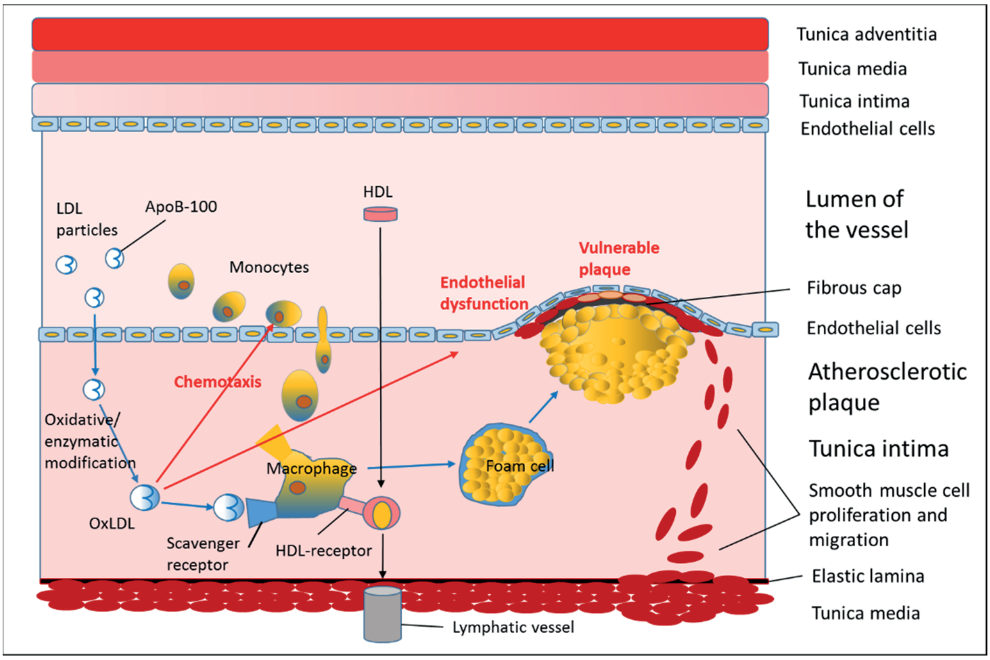

Figure 1. Schematic view of the evolution of the atherosclerotic plaque [18,54,56]. ApoB: Apolipoprotein B, HDL: High-density lipoprotein (particle), LDL: Low-density lipoprotein (particle), OxLDL: Oxidized LDL.

Apolipoprotein A1 (apoA1) is the major protein in high-density lipoprotein (HDL) and provides both its structure and function along with phospholipids. Small, discoidal pre-β HDL particles increase in size, creating larger, mature alpha-HDL particles as they collect cholesterol and are capable of delivering it to the liver for elimination [57]. Macrophage cholesterol efflux to HDL reduces inflammation and oxidative stress and thus atherosclerotic burden, and is the first step in RCT [58–60]. Epidemiological studies have shown an indisputable association between low high-density lipoprotein cholesterol (HDL-C) and increased CVD risk independent of other risk factors [61,62]. In recent studies, however, the rate at which cholesterol flows through the RCT pathway, named HDL efflux capacity or HDL function, has been more closely associated with CAD risk than HDL-C [63,64]. HDL particles carry a wide variety of proteins, lipids and nucleic acids, which contribute to their different beneficial functions. Besides RCT, anti-inflammatory, antithrombotic, anti-apoptotic and anti-oxidative as well as endothelial barrier maintaining and hormone like cell-signalling properties are associated with HDL [27].

2.4 Risk factors of coronary artery disease

Traditional risk factors of CAD, which were established in population based studies like the Framingham study, the Seven Countries Study and the FINRISK Study, comprise age, elevated TC, low HDL-C, current smoking, elevated blood pressure, male gender, diabetes mellitus (DM) and positive family history of CAD [21,65,66]. Oxidation of LDL is exacerbated by smoking and increased angiotensin activity is associated with hypertension.

Traditional risk factors are estimated to account for about 50% of CV events at individual level due to the complex interplay among CV risk factors, genetic predisposition and personal atheroprotective elements [65].

2.4.1 Hypercholesterolaemia

At any given level of hypercholesterolaemia there is considerable variation in the clinical manifestation of the disease. Even siblings with familial hypercholesterolaemia and very closely matched cholesterol levels may have clinical coronary heart disease at very different ages [67]. Although the physiologic plasma concentration of low-density lipoprotein cholesterol (LDL-C) in several mammals including primitive human tribes is around 1.0-1.5 mmol/l, its concentration in Finnish population often is around 3 to 3.5 mmol/l, which increases the risk of developing atherosclerosis [17,68–71].

In practice the atherosclerotic burden of lipoproteins is estimated by measuring TC, HDL-C and triglycerides (TG) and measuring or calculating LDL-C. It appears that apoB (reflecting the number of apoB-containing particles) is a risk marker equal to LDL-C, but seems to be less susceptible to laboratory error [72]. Non-HDL-C comprises cholesterol located essentially in all pro-atherogenic lipoproteins and predicts CVD risk even better than LDL-C [73]. In the most recent European guidelines issued by the European Society of Cardiology (ESC) on CVD prevention it has been proposed as a reasonable treatment goal, especially for patients with elevated TG [4]. Further, the apoB:apoA1 ratio is apparently the strongest single CAD risk marker, but due to its laboratory costs, limited availability and insufficient evidence as a treatment goal, it is not routinely used [4,74].

2.4.2 Obesity and insulin resistance

Obesity has become a widespread health issue in developed countries and an increasing problem even in developing countries [75]. Internationally, the age-standardized prevalence of obesity has increased from 3.2% in 1975 to 10.8% in 2014 in men, and from 6.4% to 14.9% in women [76]. Further, 2.3% of men and 5.0% of women are severely obese (BMI > 35.0 kg/m²) [76].

In 2010, overweight (body mass index (BMI) 25.0 – 29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) were estimated to cause 3.4 million deaths, i.e. 3.9 years of life lost per person affected. Both genetic and environmental factors facilitate the development of insulin resistance. Chronic insulin resistance stimulates insulin secretion and subsequently progressive beta cell dysfunction, decreased insulin levels and increased plasma glucose can be observed [77–79].

In obese patients the release of free fatty acids (FFA) and cytokines from adipose tissue impairs insulin sensitivity [79]. FFAs have an attenuating effect on the phosphorylation of nitric oxide synthase resulting in decreased production of nitric oxide, endothelial dysfunction and vascular remodelling [80]. They precipitate the oxidative process leading to increased expression of inflammatory adhesion molecules and cytokines.

Once increased amounts of FFAs have infiltrated the liver, hepatic VLDL and apoB production are intensified resulting from increased substrate availability, decreased apoB degradation and increased lipogenesis. In metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) patients these changes lead to a lipid profile characterized by decreased plasma concentration of HDL-C and increased concentrations of TG, remnant lipoproteins and small dense LDL particles, which are especially prone to oxidative modification [78,81,82].

2.4.3 Metabolic syndrome

Abdominal obesity and sedentary lifestyle are associated with insulin resistance and beta cell failure being followed by decreasing second-phase insulin response and continuing hyperglycaemia [83]. Abdominal obesity along with hypertension, hyperglycaemia, hypertriglyceridaemia and decreased HDL-C are the key components of metabolic syndrome (MetS), and microalbuminuria, later addressed as albuminuria, has also been proposed as a component [84–86]. MetS should however not be considered an absolute cardiovascular risk indicator, because it does not include many of the factors that determine absolute CV risk like age, sex, cigarette smoking and LDL-C levels[85]. The cluster of cardiovascular risk factors called MetS is associated nevertheless with a two-fold increase in CVD risk and a five-fold increase in the development of T2DM [78,87–89].

MetS was initially introduced in 1988 by GM Reaven, who originally proposed the concept of "syndrome X", later renaming it MetS [90]. Since then, multiple international organizations and expert groups have published their definitions of MetS [86]. The definition most commonly used in recent years is a consensus statement agreed on by CV disease treating organizations and includes the IDF and AHA/NHLBI definitions, intended to harmonize MetS (Table 1) [85].

Table 1. Diagnostic criteria of metabolic syndrome (MetS). Diagnosis is made if any three of the criteria are fulfilled. Modified from Alberti et al [85].

Criteria of MetS
Elevated waist circumference (according to population and country-specific definitions)
Triglycerides ≥ 150 mg/dL (1.7 mmol/l)
HDL-cholesterol < 40 mg/dL (1.03 mmol/l) in men and < 50 mg/dL (1.30 mmol/l) in women or drug therapy with fibrates or nicotinic acid
Blood pressure ≥ 130/85 mmHg or antihypertensive treatment and history of hypertension
Fasting blood glucose ≥ 100 mg/dL (5.6 mmol/l) or blood glucose lowering drug therapy

2.4.4 Type 2 diabetes mellitus

In the pathophysiology of T2DM the crucial defects are insulin resistance, which stimulates insulin secretion, and progressive beta cell dysfunction, which is thought to be strongly genetically predisposed. These result eventually in decreased insulin concentration and gradually elevated blood glucose [77–79].

Insulin resistance and its consequences have been associated with low-grade endothelial inflammation and dysfunction with further development of macrovascular disease even prior to the diagnosis of diabetes [83,91,92]. T2DM results in a roughly two-fold excess risk for a wide variety of vascular diseases, regardless of other traditional risk factors. The adjusted hazard ratios are according to the Emerging Risk Factors Collaboration 2.00 for CAD, 2,27 for ischemic stroke and 1,73 for the aggregate of other CV deaths [93]. T2DM typically develops after middle age, but due to increasing obesity in the young and in non-Caucasian populations, there is a trend towards a lower age of onset [78,94].

2.4.5 Hypertension

Treating hypertension was shown to improve exercise tolerance in patients with angina pectoris as early as in the 1960s [95]. In a 10-year follow-up study of CABG patients, hypertension was already observed in the 1990s to be an incremental and independent risk factor of recurrent angina [96]. The prevalence of hypertension in adults is 30-45% worldwide and has increased globally during the last two decades [4].

There is a constant association between elevated blood pressure and the likelihood of cardiovascular events. According to epidemiological studies cardiovascular risk increases from very low blood pressure levels (BP), systolic BP 115 mmHg, upwards [97,98]. Recent studies strongly support the lowering of systolic BP below 130 mmHg in a wide range of CVD patients. The current guidelines recommend, when drugs are used, that BP should be lowered to <140/90 in all patients and to $\leq$130/80 in most patients [98,99].

2.4.6 Sedentary lifestyle and physical activity

Physical activity and exercise are essential in the prevention and treatment of CVD. Accordingly, sedentary lifestyle is one of the major risk factors for CVD [100]. In a recent Finnish study both the number and accumulated length of exercise bouts were associated with CVD risk in primary prevention [101]. Regular exercise also enhances endothelial function and arterial compliance and reduces oxLDL and local vascular low-grade inflammation [102–104]. Both aerobic and exercise training should be encouraged. ESC guidelines recommend today at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity training weekly [4].

Several studies have addressed the effect of postoperative physical activity on recovery after CABG. Studies both immediately after the operation and later in secondary prevention have found that exercise training improves the recovery and exercise capacity of CABG patients [105–108]. These lifestyle interventions are also important in the prevention and management of hypertension, MetS and T2DM, prominent risk factors for CVD [109–112].

2.4.7 Other risk factors of coronary artery disease

Sleep disorders are connected with cardiovascular (CV) prognosis. A recent meta-analysis found a significant association between getting less than six hours' sleep and increased risk of stroke, myocardial infarction (MI) and congestive heart failure and between more than eight hours' sleep and angina symptoms [113]. Untreated obstructive sleep apnea has been related to CV outcomes in several studies [114].

Psychological stress has been analysed in multiple reports, but due to discrepancy in the stress models used, the best evidence of psychosocial stress as a CV risk factor is still to be found in epidemiological studies [74,115]. At individual level, it has been shown that acute mental stress increases vascular reactivity and decreases endothelial function resulting in apical ballooning syndrome or so-called Takotsubo cardiomyopathy [65,116].

Some epidemiological studies have associated moderate alcohol consumption with decreased CV risk [74,117]. A large meta-analysis of 59 epidemiological studies found on the contrary no evidence for the benefit of even moderate alcohol consumption, thereby suggesting that any amount is associated with elevated BP and BMI [118]. According to current ESC guidelines on CV disease prevention, alcohol consumption should be limited to 20 g/day alcohol beverages for men and 10 g/day for women. Drinking 30 g or more daily is associated with higher CVD risk [4].

Endothelial dysfunction is a systemic disorder widely affecting arterial circulation. Like elevated concentration of high-sensitive C-reactive protein, it can be regarded as a sum of overall CV risk factors, genetic risk and environmental elements and also of vasculoprotective factors [65,119,120]. Likewise arterial stiffness is associated with increased CAD risk in MetS patients [89,121]. Both endothelial dysfunction and arterial stiffness can be seen as an interphase between CAD risk factors and actual disease and may form an attractive target in optimizing individualized treatment [119].

The risk and protective factors of coronary artery disease (CAD) are summarized *e.g.* in the INTERHEART Study [74]. This was a standardized case control study of acute MI in 52 countries representing every inhabited continent with ~15,000 cases and controls. Current smoking, diabetes, hypertension, abdominal obesity, psychosocial factors and abnormal ratio of lipid particles were found to be risk factors, while consumption of fruit and vegetables, regular physical activity and alcohol consumption were reported to be protective factors. Together, they accounted for 90% of the population attributable risk in men and 94% in women (Figure 2) [74]. The strongest single predictors of CV outcome have been smoking, hypercholesterolaemia, hypertension and diabetes mellitus in the INTERHEART as well as in many other studies. The risk depends on the number of cigarettes smoked, cholesterol concentration and duration of DM [4]. The risk is cumulative so that every risk factor increases and every protective factor decreases the probability of the index outcome in individual subjects [66].

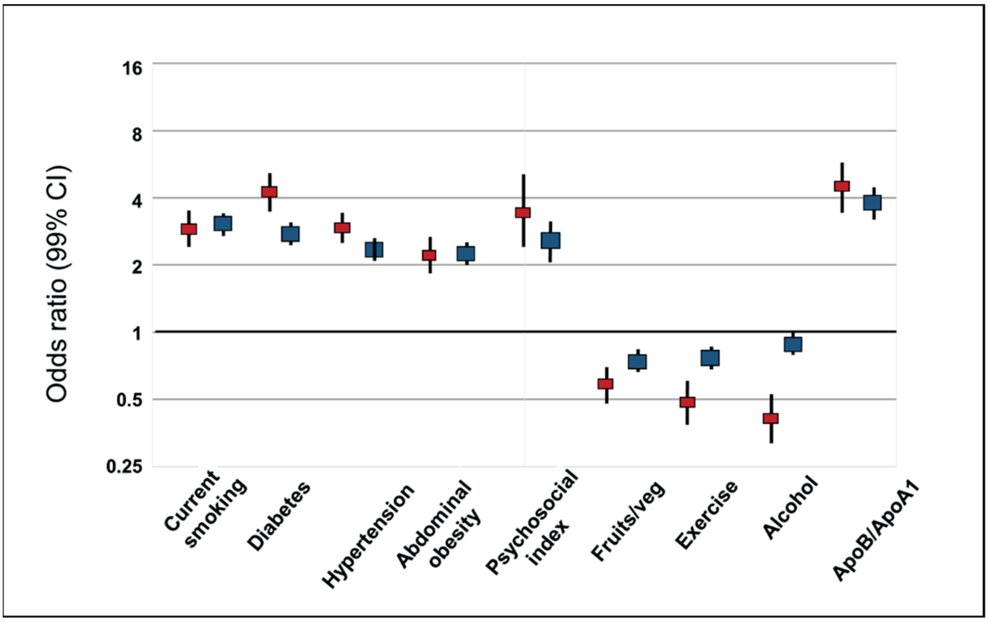

Figure 2. Association of risk and protective factors with acute myocardial infarction in men (blue square) and women (red square) after adjustment for age, sex and geographic region (presented on a logarithmic scale). Above 1 risk is increased. Modified from Yusuf et al 2004 [74].

2.5 Treatment of coronary artery disease

Treatment of coronary artery disease comprises risk-modifying *i.e.* preventive therapy and symptomatic treatment. The target of secondary prevention of CAD is to enhance long-term survival and quality of life [122]. Treatment includes lifestyle changes and medical treatment. Statins, other cholesterol lowering medications like proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitors and ezetimibe, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARB) and acetylsalicylic acid (ASA) and, with certain limitations, β-blockers are considered effective means in the secondary prevention of coronary artery disease [4,123,124]. Nitrates and calcium channel inhibitors have been found to be symptomatic treatment of CAD [125,126].

Approximately 25% of deaths in CAD are sudden cardiac deaths, the risk being higher in men and older persons due to the increasing prevalence of CAD in those patient groups [127,128]. In spite of improved primary and secondary prevention of CAD and better early revascularization strategies, some patients still end up with severely damaged left ventricles (LV). Primary treatment in ischaemic LV dysfunction is early revascularization and optimized medical treatment of CAD because ejection fraction may recover after revascularization. ICD/CRT is recommended to reduce all-cause mortality in patients with symptomatic heart failure and LBBB if ejection fraction remains $\leq$ 35% despite at least three months of optimal pharmacological therapy [128].

2.5.1 Lifestyle changes

Lifestyle management has a decisive role in the treatment of CVD. Smoking cessation, limited salt and alcohol intake, weight loss in obese patients and healthy nutrition are of central importance [4,129–133]. Healthy diet includes limited intake of saturated fatty acids and transisomers of fatty acids as well as monitored carbohydrate consumption and increased intake of dietary fibre [134–136].

In a series of epidemiological FINRISK studies, based on the North Karelia project, lifestyle changes have been monitored in Finland for 40 years between 1972 and 2012. During this period, smoking prevalence has halved in men and the unfavourable increasing trend in female smoking has turned into decrease. On the national level smoking has further decreased. In 2016, 16% of men and 15% of women were smokers. Between 1972 and 2012 T-C decreased 21%, in men to 5.4 mmol/l and in women to 5.3 mmol/l and systolic BP 10%, in men to 136 mmHg and in women to 129 mmHg and [20,22].

The Finnish Diabetes Prevention Study and the American Diabetes Prevention Program were conducted to determine the usefulness and impact of a lifestyle programme designed to prevent or delay the onset of T2DM in subjects with impaired glucose tolerance [137,138]. Lifestyle intervention incorporating physical activity and dietary chances, which reduced intake of total and saturated fat and increased intake of fiber, resulted in a weight loss and reduced the risk of new-onset diabetes by 58% [137,138]. The effect of the lifestyle intervention proved lasting in a follow-up survey of the Diabetes Prevention Study three years later [139]. A corresponding benefit of lifestyle intervention has later been confirmed in other diabetes prevention programmes [140,141].

2.5.2 Drug therapy

It is possible to delay the progression of coronary artery disease and even to convert the process to regression with effective drug therapy. Obvious positive effects on survival after CABG have been achieved with statins as such and in combination with certain other lipid lowering medications, several antiplatelet drugs, beta blockers and ACE inhibitors as well as ARBs [4,131].

2.5.2.1 Statin therapy

The crucial role of hypercholesterolaemia in the progress of CAD and the favourable prognostic value of lowering it with statins are extensively documented [4,142–144]. Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme-A reductase, the rate limiting enzyme of the mevalonate pathway of cholesterol synthesis. Inhibition of this enzyme decreases cholesterol production in the liver and thus activates the LDL receptors of the liver cells. This results in improved clearance of LDL-C from the bloodstream and decrease of LDL-C concentration in plasma [145,146]. In addition to their lipid-lowering effects, statins have been suggested to have pleiotropic effects; for example they increase apoA-1 concentration, improve endothelial function and inhibit inflammatory response thus stabilizing the plaque as well as downregulating blood coagulation and platelet function [147–151] (Figure 3).

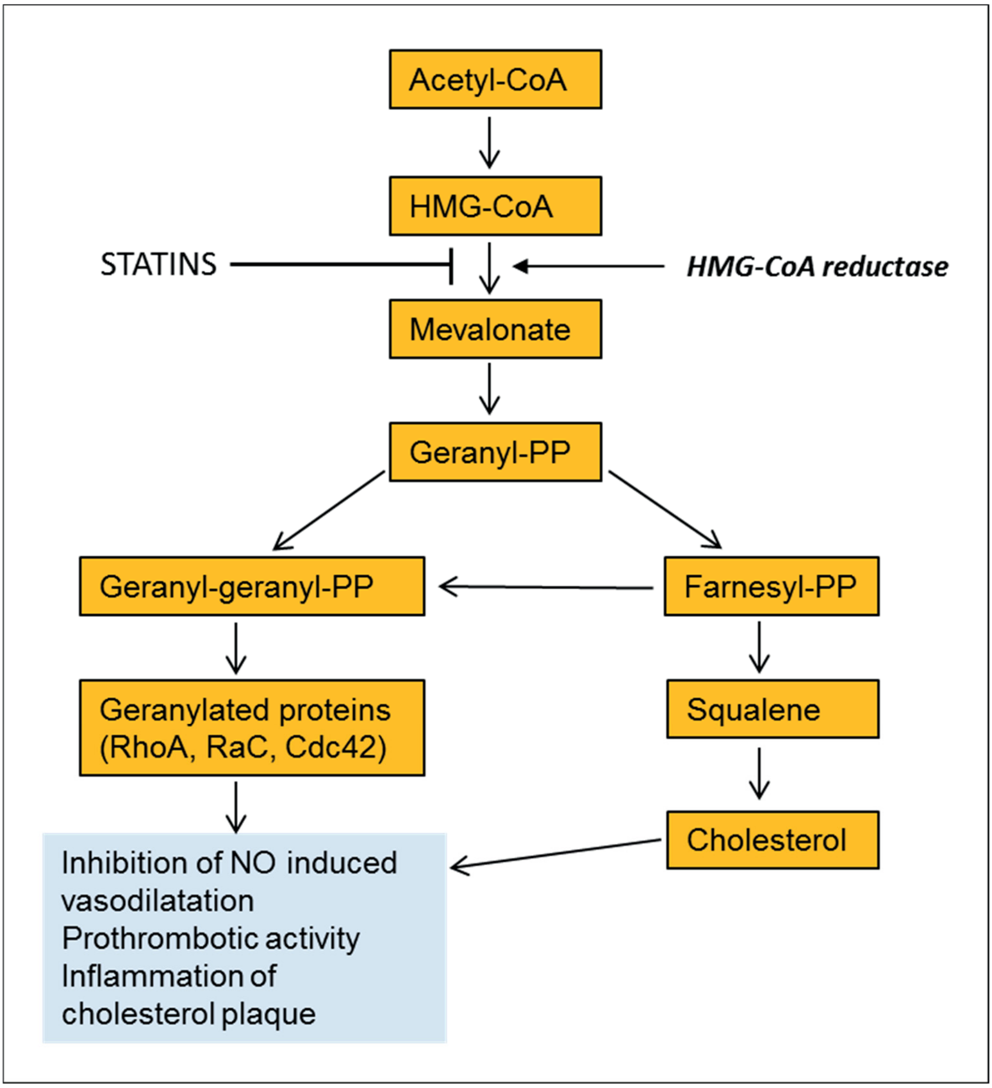

Figure 3. Cholesterol synthesis and statin mode of action (modified from Mason 2003) [146,151,152]. HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme-A, PP: Pyrophosphate, NO: Nitric oxide.

The first statin mega-trials in secondary prevention, namely the 4S [153], CARE [154] and LIPID [155], demonstrated that cholesterol lowering treatment with statins improved the prognosis of patients with CAD when compared with a placebo. Evidence on the efficacy of statins in preventing CVD events in diabetes was provided by the subgroup analysis of the Heart Protection Study (HPS) [156] and the Collaborative Atorvastatin Diabetes Study (CARDS) [157]. Studies like the Post Coronary Artery Bypass Graft Trial [158], REVERSAL [159] and Prove-It Timi 22 [160] and a meta-analysis of several studies [161] showed the advantage of aggressive statin versus moderate statin therapy in patients with CVD. Finally, the ASTEROID and SATURN trials demonstrated that aggressive lipid lowering to a mean plasma concentration of 1.6 mmol/l resulted in significant regression of atherosclerosis in CVD patients [1,162,163].

In the recent literature, statins as a group have been found to be diabetogenic. The effect seems to be dose-dependent and apparent in most effective statins. The mechanism is associated with impaired insulin sensitivity and insulin secretion. The excess risk of T2DM is considered to be 9 – 46% in most population based studies, depending on the population studied [164,165].

Taken together, controlled prospective trials involving over a hundred thousand patients have consistently demonstrated the effectiveness and safety of statin treatment in the prognoses of CVD patients [166,167]. In light of mounting evidence, the 2016 European (ESC) guidelines on cardiovascular disease prevention in clinical practice recommend for patients at very high cardiovascular risk an LDL-C goal < 1.8 mmol/l (< 70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/l [4]. The current state of lipid-goal attainment has been evaluated in large analyses both in the US and Europe [22,136,168]. According to them, only 20% to 26% of high CV risk patients achieve LDL-C < 1.8 mmol/l. Consequently, many patients without statin therapy or with insufficient cholesterol lowering drug therapy experience recurrent CV events [169,170].

2.5.2.2 Other cholesterol lowering drug therapies

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme involved in the regulation of LDL receptors and LDL-C. By targeting LDL receptors for destruction in the liver, PCSK9 increases concentrations of LDL-C. When its action is blocked, concentration of LDL-C in plasma is reduced [171,172]. Currently two monoclonal PCSK9 inhibitors are commercially available, alirocumab and evolocumab. The efficacy in reducing LDL-C and coronary atheroma volume was recently shown and the first large-scale prognostic study results in reducing CV events in secondary prevention of high-risk patients were just published with significantly better prognosis in the active arm when compared with the placebo [2,173,174]. With evolocumab CV benefit has even been shown at LDL-C concentrations below 0.5 mmol/l [173]. Large-scale, randomized phase III prognostic trials will eventually reveal their long-term benefits and harms and determine their significance for clinical practice.

Ezetimibe is a compound which blocks intestinal cholesterol absorption and thus decreases plasma LDL-C concentration. It has been on the market for a long time but with scanty prognostic evidence. The IMPROVE-IT trial (n=18,134), with a median follow-up of seven years, failed to show the benefit of ezetimibe over placebo in mortality when added to simvastatin [175]. However, ezetimibe significantly reduced primary endpoint, the risk of a composite of CV death, major coronary events, or stroke. The effect of ezetimibe on the primary endpoint was greater in patients with prior CABG than in those without [176].

2.5.2.3 Antiplatelet and antithrombotic therapy

Acetylsalicylic acid prevents platelet aggregation and has been widely used in the treatment of CAD patients since the 1970s [177]. In CABG patients ASA prevents adverse CV events and improves long-term survival by reducing the odds of graft occlusion when administered in low to medium daily doses (100 – 325 mg) [178–180]. In ASA-treated patients early graft occlusion rates have, however, been high, which is attributed to ASA resistance, a phenomenon where ASA is unable to effectively inhibit platelet function [181].

In patients with existing myocardial infarct (MI), stroke or peripheral arterial disease, clopidogrel, a thienopyridine antiplatelet agent that irreversibly inhibits the platelet P2Y12 receptor, has shown slight superiority with respect to ASA [182]. Combining ASA therapy with clopidogrel tends to have potent synergistic antithrombotic effects [183]. Several clinical trials to date have evaluated the use of clopidogrel after CABG with mixed results [184]. The benefit for dual antiplatelet therapy in reducing vein graft occlusion seems to be most applicable in patients undergoing off-pump surgery rather than on-pump surgery due to relative hypercoagulable state and increased postoperative platelet activity in the former procedure [131,184,185]. The secondary prevention statement of the AHA has recommended ASA alone for the majority of patients after CABG, whereas clopidogrel should be combined with ASA after off-pump surgery [131]. It should be noted, that a genetic Clopidogrel resistance exists due to $P2Y_{12}$ receptor gene polymorphism with potential effects to its antithrombotic efficacy [186].

Newer P2Y12 inhibitors, prasugrel and ticagrelor, have a more rapid onset of action than clopidogrel, and also more potent platelet inhibition and better prognosis in acute coronary syndromes [187,188]. Several trials are now ongoing to investigate their future role in the treatment of CABG patients.

Warfarin has been compared to ASA in several studies, notably in the 1980s and 1990s. When used alone or in combination with ASA it has reportedly not improved graft patency [179]. According to the current AHA guidelines, warfarin therapy should be reserved for CABG patients with other indications for its use, such as atrial fibrillation, a history of deep vein thromboembolism and for those undergoing valve replacement in conjunction with CABG [131].

2.5.2.4 Beta-blocker therapy

In the prevention of atrial fibrillation after CABG, treatment with beta-blockers is a key therapy [189]. Patients discharged with beta-blockers have a decidedly lower mortality rate during long-term follow-up after cardiac surgery [190]. Due to side-effects and lower BP reducing efficacy compared to other antihypertensive agents, beta-blocker therapy should not be used for hypertension after CABG, but should be reserved for patients with other cardiovascular conditions such as history of MI, heart failure and left ventricular dysfunction and thus, at risk of ventricular tachycardia [128,191,192].

2.5.2.5 Inhibition of the renin-angiotensin-aldosterone system

Drugs inhibiting the activity of the renin-angiotensin-aldosterone system have been widely studied. The effects of ramipril on high-risk patients with evidence of either vascular disease or diabetes were studied in the large HOPE trial [193,194]. Ramipril proved beneficial over placebo in reducing mortality, recurrent CV events and nephropathy [193,194]. Further, in the EUROPA trial, patients with stable CAD on perindopril had better CV prognosis than those on placebo [195]. In both ACE-inhibitor studies, the average patient had high normal BP, and systolic BP decreased by 3-5 mmHg more in the active treatment group than in the controls. In the ON-TARGET Study the ARB telmisartan was found to be equivalent to ramipril for high-risk patients in preventing major CV endpoints but the combination of the two drugs was associated with no additional benefit and more adverse events [196]. Moreover, in the ONTARGET/TRANSCEND study telmisartan and ramipril were equally good and better than placebo in reducing LVH [197]. Therefore, ACE inhibitors or ARBs should be considered for patients with CAD or at high risk of developing it.

The ACE inhibitor quinapril has been evaluated in two trials early after CABG. The results suggest that ACE inhibitors are beneficial after CABG, but their initiation should be individualized according to the patient's associated risk factors, the greatest benefit being experienced after the first three months [198,199]. Due to their cardioprotective and renoprotective effects, the use of ACE inhibitors or ARBs has been recommended for patients after CABG, especially for those with previous MI, heart failure or left ventricular dysfunction, hypertension, diabetes mellitus or chronic kidney disease [131,200].

2.5.2.6 Treatment of hypertension

In general, lifestyle changes, weight loss in obesity and modern drug therapy for elevated BP improve hypertensive patients' CV prognosis [98]. When studying various treatments, ACE inhibitor captopril was compared with beta-blocker and diuretic in the CAPP Study in hypertensive patients. Captopril was found to be superior to other medications in preventing CV events in patients with DM, although in other patients no such benefit was identified [201,202].

In the LIFE Study losartan, was compared with atenolol in the treatment of hypertension with LVH and found to be superior in preventing CVD mortality as well as all-cause mortality. New-onset diabetes was also less frequent in the losartan group. In patients with DM mortality results were comparable to those of all study patients and albuminuria was less frequent in losartan-based treatment [203,204]. In hypertensive patients amlodipin has reportedly provided protection against MI and stroke in several trials [205]. To prevent CAD complications in hypertensive patients who do not achieve their BP goal by taking ACE inhibitors or ARBs, calcium channel blockers, especially long-acting dihydropyridine calcium channel blockers and diuretics may be used as next therapy choices [192,206].

2.5.2.7 Glucose-lowering drug therapy in T2DM

In the landmark studies of CVD carried out during the last twenty years, 20 – 60% of patients have had diabetes [156,159,207,208], which underlines the significance of DM among CVD patients. On the other hand, diabetes is a known risk factor for CVD. T2DM, having lasted for a decade or co-occurring with proteinuria or with impaired kidney function, is considered a CAD risk-equivalent state [209–211].

In T2DM patients the results with glucose-lowering drug therapy on total or cardiovascular mortality have been variable and often disappointing [212–216]. Some studies even found that various glucose-lowering medications, in spite of improving glycaemic control and reducing the risk of microvascular complications, may increase the risk of CV events [217,218].

Among the controlled randomized trials carried out during the last 20 years the occurrence of CV death has been significantly reduced only through therapy with three types of drugs, namely metformin, glucagon-like peptide-1 receptor (GLP-1) agonists liraglutide and semaglutide, and some sodium glucose cotransporter 2 (SGLT2) inhibitor group drugs [219–226].

The UKPDS Study showed the benefits of intensive glucose lowering therapy against conventional therapy with diet in recently diagnosed diabetes patients. In overweight patients those assigned to drug therapy with metformin had a significantly lower risk of MI and overall mortality compared to those treated conventionally [219]. In a follow-up study of the UKPDS, 10 years after the cessation of randomized interventions, the risk reduction in MI mortality in patients initially treated with metformin persisted [221].

In the recently published large LEADER trial, patients with GLP1 analogue liraglutide had a 13% lower risk for composite CV endpoint of CV death, non-fatal MI or non-fatal stroke compared to those with placebo when liraglutide was added to usual medical therapy [222]. In a smaller Sustain-6 trial corresponding results with significant reduction in composite CV endpoint were seen in semaglutide treatment [227].

In the EMPA-REG Study, patients on empagliflozin treatment had a 14% relative risk reduction in composite CV endpoint. These favourable results were mainly due to a reduction in complications associated with heart failure and not with CAD [223]. Similar benefits in heart failure related cardiac outcomes were recently found with canagliflozin in CANVAS trial and with dapagliflozin in DECLARE study [223–225].

Trials using pioglitazone, have shown decreased CV mortality, but the tendency to increased adipose tissue mass and fluid retention followed by congestive heart failure have restricted the use of this glucose-lowering medication [228–231].

Apart from the UKPDS [212], the impact of insulin treatment on CV outcomes had not been extensively studied until the Origin Study [232]. The latter showed that basal insulin-glargine, when compared to standard non-insulin care, had a neutral effect on cardiovascular outcomes, but modestly increased weight.

2.5.3 Cardiac Interventions

Angina pectoris is associated with impaired quality of life in stable coronary artery disease, reduced physical endurance, mental depression and recurrent hospitalizations and outpatient visits [233]. Revascularization by either PCI or CABG is indicated in flow-limiting coronary stenosis to reduce myocardial ischaemia and related adverse clinical manifestations. In non-emergent patients, coronary artery bypass grafting (CABG) also improves survival of patients with left-main and/or multivessel disease [234,235].

In acute ST-elevation myocardial infarction (STEMI) primary PCI has replaced fibrinolysis, provided it can be performed in high-volume PCI centres without delay [236]. In selected cases in patients anatomically unsuitable for PCI and in cardiogenic shock, CABG may also be considered for acute STEMI patients [237].

Since 1993, the number of CABGs in Finland first increased from over 3,000 annually to 4,500 in 1997 and then decreased to 3,500 in 2006 and further to below 1,400 in 2017. During the same time period PCIs multiplied from a few hundred to 9,000 in 2006 and almost 14,000 in 2017 (personal communication professor emeritus Matti Tarkka, University of Tampere) [238,239]. It seems likely that during the next few years the number CABGs will remain constant but that of PCIs will continue to increase (personal communication, docent Vesa Virtanen, University of Tampere) (Figure 4).

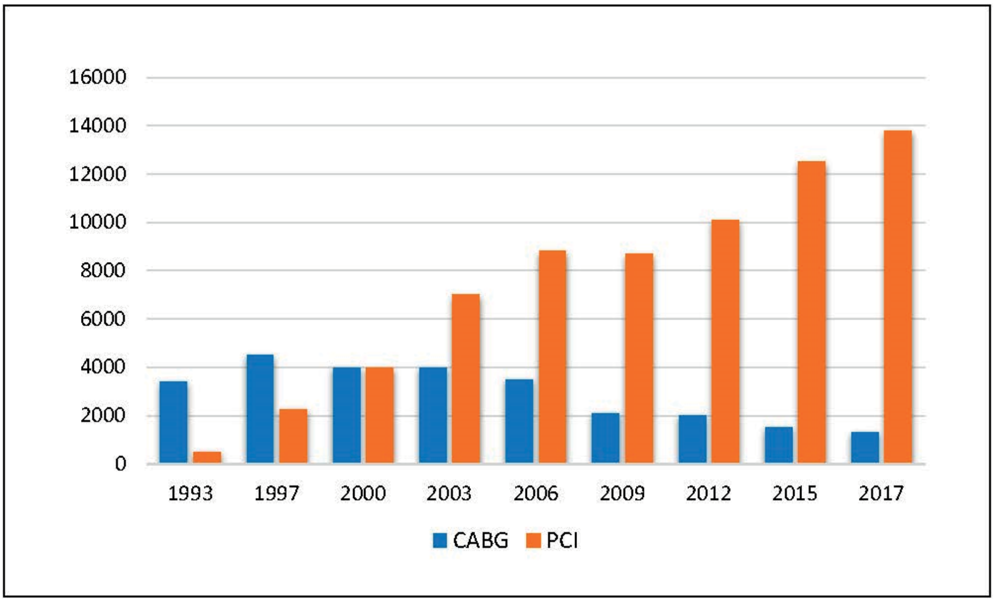

Figure 4. Number of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) done in Finland from the beginning of the study. Since 2006 the data is based on the statistics of the Finnish Cardiac Society, before that year it is estimated from several sources (personal communications professor emeritus Matti Tarkka and docent Vesa Virtanen) [238,239].

2.5.3.1 The early years of coronary artery bypass

A crucial point in modern CAD treatment was the development of coronary angiography and thus the ability to identify stenosis and occlusions requiring targeted therapy. The first CABGs were done in the mid-1960s with internal thoracic artery anastomosis by Kolesow and saphenous vein bypass from the ascending aorta to the anterior descending coronary artery by DeBakey and Favaloro [240,241]. When more than 10,000 CABG procedures performed before 1971 were evaluated, it was found that 60 – 70% of patients had become asymptomatic and as many as 95% had fewer symptoms [242]. On the other hand, the rates of operative mortality and MIs were high at the time, up to 10% and 15% in some large series, although decreasing gradually as experience accumulated [241].

While it was evident that CABG relieved angina, it was uncertain whether it also improved the long-term prognosis of CAD. The first modern prospective studies comparing medical therapy to elective CABG in selected patients with stable angina pectoris were published in the late 1970s. These were the Veterans Administration (VA) Cooperative Study in 1972 – 74 [243], the European Coronary Surgery Study in 1973 – 76 [244] and the Coronary Artery Surgery Study in 1975 – 79 [245] forming the basis for clinical decision-making in the early 1980s. A meta-analysis of these and several other trials showed the benefit of CABG over medical therapy during 10-year follow-up in medium and high-risk CAD patients [246].

2.5.3.2 Evolution of coronary artery bypass techniques

During the early decades, CABG surgery was performed using cardiopulmonary bypass (CPB) and the anastomoses were performed on the arrested heart. Myocardial protection was deemed crucial because perioperative myocardial injury led to left ventricular dysfunction and thereby poorer prognosis [247]. Advanced anaesthesia and CPB techniques, shorter operating times as well as more precise suturing and, possibly most crucially, developing myocardial protection, all reduced myocardial injury [248].

In the 1960s and 1970s saphenous vein graft (SVG) was mainly used in bypass procedures. In 1978 it was shown that venous bypass grafts occlude early and during the following years it was discovered that the failure rate was affected by graft thrombosis (early failure), intimal hyperplasia (late failure) and atherosclerosis (late failure) [249–252]. First internal thoracic artery grafting to the left anterior descending artery (LAD) yielded superior graft patency and survival compared to the use of SVG grafts alone and some years later bilateral internal thoracic artery grafting turned out to be even more favourable [253,254]. The radial artery proved its suitability for grafting, especially when its tendency to spasm and intimal hyperplasia had been solved by medical therapy [255,256]. Various techniques became available to achieve complete revascularization in multi-vessel coronary artery disease. In addition to internal mammary arteries and SVGs, the right gastroepiploic artery may also be used for anastomosis to the proximal descending artery or to the proximal right coronary artery and a hybrid procedure with PCI for non-LAD targets can be combined with minimally invasive left internal mammary artery (LITA) grafting to LAD [257].

CABG is most frequently done using cardiopulmonary bypass and cardioplegic arrest, which provide a stable and bloodless operating environment. Its complications have been systemic inflammatory response, increased red cell damage and risk of cerebrovascular embolization arising from manipulation and clamping of the ascending aorta [258]. Numerous technical improvements in perioperative care and myocardial protection, the implementation of sophisticated cardiopulmonary bypass and off-pump CABG methods, as well as optimizing postoperative medical treatment have improved operative results [241,259–261]. LITA-to-LAD minimally invasive procedures using a left mini thoracotomy and video-assisted LITA harvesting were introduced in the 1990s, gradually decreasing the operational risks [262]. Advanced video-assisted procedures and computer-assisted entirely endoscopic CABGs without the use of CPB have recently yielded excellent short-term results [235,263].

2.5.3.3 Prognosis after coronary artery bypass

All in all, 30-day survival after surgery has improved, even though patients have become older and operative risks greater. Operative mortality in elective CABG is currently in the range of 1-3% [264]. The incidence of stroke, predominantly ischaemic in nature, is also 1 – 3% of CABG patients [265]. Other significant complications of CABG are postoperative myocardial injury, renal failure, delirium, deep sternal wound infection, mediastinitis and atrial fibrillation [241,266].

The long-term advantage of CABG over medical therapy is more evident in patients with complex coronary disease, especially in those with left main disease [246]. Later trials have also shown benefit of CABG over medical therapy in previously challenging patients such as those with left ventricular dysfunction [267–269].

According to the World Health Organization’s definition, health is not only a biomedical, but also a biopsychosocial issue [270]. Health related quality of life (HRQoL) comprises physical, psychological and social well-being [271–273]. In the latest systematic review and meta-analysis both PCI and CABG showed significantly bigger positive effect on patients' HRQoL than did medical treatment. Between operative approaches there was no significant difference in HRQoL [273].

2.5.3.4 Percutaneous coronary interventions

The first PCI was performed by Andreas Grünzig in 1977 [274,275]. Over the decades PCI techniques have also undergone several major improvements. PCI was first done with only balloon angioplasty, but followed by bare metal stents (BMS) and drug eluting stents (DES) [276]. Stent restenosis has also decreased since recent studies demonstrated the advantage of DES and drug-coated balloons for this indication [277,278]. Together with these advances, improvements in antiplatelet and antithrombotic treatment have reduced adverse events, especially the need for repeat revascularizations [275]. PCI compared with optimal medical treatment has repeatedly shown benefit in relief from angina. However, in long-term prognosis both approaches have been equally good [279–281].

2.5.3.5 Coronary artery bypass grafting compared with percutaneous coronary interventions

After the landmark trial, the Bypass Angioplasty Revascularization Investigation (BARI) [282], the prognosis following CABG has been compared to that following PCI over the past three decades. Surgery was first compared with balloon angioplasty [282,283], then with BMS and finally with DES [284–286]. The total of almost 30 trials has shown the trend or superiority of CABG over PCI in the prognoses of patients with left main disease or complex multivessel disease *i.e.* patients with high Syntax score [275,287].

A recent trial comparing CABG with everolimus eluting stents in patients with multivessel CAD and severe left ventricular dysfunction highlights the differences in outcomes between the procedures. PCI was associated with higher risk of MI and repeat revascularizations, whereas CABG was associated with higher risk of stroke [288]. In patients with diabetes mellitus CABG was associated with a clearly better prognosis than PCI (Table 2) [289]. The current ESC revascularization guidelines recommend CABG instead of PCI for patients with diabetes and three-vessel disease and for patients without diabetes with left main or three vessel disease with medium or high anatomical complexity (syntax score) [235,289,290].

Table 2. Coronary artery bypass grafting (CABG) and percutaneous intervention studies (PCI) studies: Cumulative meta-analysis by year of publication of the difference in all-cause mortality between CABG and PCI in patients with and without diabetes. Modified from Herbison (article includes original references) [289]. Balloon: PCI without stenting, BMS: bare metal stent used, DES: drug eluting stent used, NS: Not significant.

		Patients included in the mortality analysis			
Study	Type of PCI	Diabetics		Non-Diabetics	
		CABG (n)	PCI (n)	CABG (n)	PCI (n)
RITA-I (1993)	Balloon	33	29	468	481
EAST (1994)	Balloon	41	49	153	149
CABRI (1995)	Balloon	60	64	453	477
BARI (1996)	Balloon	183	174	731	741
AWESOME (2001)	Balloon	79	65	153	157
ERACI-II (2001)	BMS	39	39	186	186
ARTS-I (2001)	BMS	96	112	508	489
SOS (2002)	BMS	74	68	426	420
MASS-II (2004)	BMS	59	56	144	149
CARDia (2010)	BMS + DES	254	256	-	-
SYNTAX (2010)	DES	221	231	676	672
FREEDOM (2012)	DES	947	953	-	-
VA-CARDS (2013)	DES	103	104	-	-
BEST (2015)	DES	186	177	261	261
		2375	2377	4159	4182
Cumulative all-cause mortality CABG v. PCI		RR 1.30 (95% CI 1.07 – 1.58), favours CABG		RR 1.04 (95 % CI 0.92 – 1.17), NS	

2.6 Life after CABG

2.6.1 Resuming work after CABG

The median age of CABG patients is rising, in the most recent large-scale studies being 63 to 65 years [284–286,288,291]. Roughly 50% of patients operated on are still in working age depending on the country of residence and retirement system. In recent years return to work after CABG has increased up to 59 to 87% varying due to the time and country of the study. In particular, the return to work of older people has improved [292–298]. During the first postoperative year 7% to 30% have had angina pectoris symptoms [299,300] and 7% experienced neuropsychological defects as determined six months after CABG [291,301]. Results were first improved using off-pump coronary artery bypass grafting but in later studies on-pump technique has shown comparable outcomes [261,302,303].

One in five of patients have reported their quality of life to be postoperatively no better than before the CABG [304]. Subjective well-being is not related to physical status. The reasons for difficulties in returning to work after CABG are multifactorial. Hence, psychological and socioeconomic factors may even play a more decisive role than medical factors themselves [298,305–308]. Staying at work also varies across countries. Most studies addressing postoperative working are focused on the first 12 months after CABG. Studies with a longer follow-up are rare [296,309].

The direct and indirect costs of CAD are enormous. Besides the financial burden, loss of leisure time activities and psychological stress are other significant losses for patients [310]. The restoration of normal functional capacity and quality of life, in which the resumption of professional activity is an important element, can be considered a major objective of coronary surgery [293,311].

2.6.2 CABG: Postoperative survival

2.6.2.1 Impact of statin treatment on survival

Impact of statin treatment on survival has been widely studied from different aspects. Its influence on prognosis after coronary syndromes and coronary procedures has been the focus of a multitude of studies, but lately short-term postoperatrive prognosis has also been reported. Preoperative statin therapy has been shown to be associated with decreased early cardiac mortality in general and more closely in hyperlipidaemic CABG patients [312–315].

Several studies have investigated the impact of statin treatment on postoperative cholesterol reduction after CABG. One of the landmark studies is the Post-CABG trial, where 1,351 patients who had had CABG earlier were randomized to aggressive or moderate cholesterol treatment. The aggressive treatment arm got lovastatin 40-80 mg daily achieving on average cholesterol levels of 2.5 mmol/l and the moderate treatment arm lovastatin 2.5 to 5 mg daily reaching on average 3.5 mmol/l during the study period. According to angiographic findings four years later, aggressive cholesterol treatment decreased the incidence of new vein graft occlusion (10% v. 21% aggressive v. moderate treatment) [316]. After extended follow-up of three more years, the aggressive treatment arm had a 30% lower need for repeat revascularization and a 24% reduction in adverse cardiovascular events [158]. Altogether, the Post-CABG Trial showed that aggressive lowering of LDL-C below 100 mg/dL (2,6 mmol/l) reduces both CV events and the progression of atherosclerosis in native coronary arteries and saphenous vein grafts [158,316]. On the whole in vitro and clinical studies have shown reduced progression of native coronary artery disease [317] and vein graft atherosclerosis [252,318–320].

Some studies have focused on high-intensity statin therapy to achieve an LDL-C reduction to < 1.8 mmol/l. In the Treating to New Targets (TNT) trial, 10,001 CAD patients were randomized to two study arms receiving either atorvastatin 80 mg or atorvastatin 10 mg daily. In those 4,654 patients who had previously undergone CABG, intensified statin therapy was associated with 27% lowered risk for CV events over a 4.9-year follow-up [321]. Other studies have come to similar conclusions [208,252].

The AHA guidelines in 2015 on secondary prevention after CABG emphasize the importance of long-term high-intensity statin treatment for all patients under 75 years of age in the absence of contraindications such as liver disease [131]. For patients older than 75 a lower statin dose is recommended [322]. The corresponding ESC guidelines are addressed in Chapter 2.5.2.1.

Several studies have reported prognoses of CABG patients in recent decades. In the Randomized Intervention Treatment of Angina (RITA-1) trial, the patients were randomized to CABG or PCI in 1988 – 1991. In the CABG group, after 6.5 years' follow-up, the cumulative rate of death was 8.6% and that of MI 7.4% [323]. In recent studies 5-year mortality has been between 5% and 15%, depending, for instance, on patients' age, other concomitant morbidities and severity of CAD [324,325]. Altogether, in multiple studies carried out during the last three decades, the mortality of CABG patients has decreased annually by 7% [289].

2.6.2.2 Impact of obesity and metabolic syndrome on survival

Obesity increases the likelihood of major CV disease risk factors such as dyslipidaemia, elevated blood pressure and glucose abnormalities associated with MetS and T2DM. It thus increases the risk of CAD. However, in spite of these CV disease risk factors, obese patients with established CAD typically have had a better prognosis than normal weight patients with the same disease. This phenomenon is called the obesity paradox [326].

The epidemiology of MetS has been widely evaluated [327–329]. MetS can be used as a tool to characterize patients at elevated risk [102,330,331]. Several studies have suggested that the risks of premature death and cardiovascular disease or diabetes are higher among subjects with MetS than among those without. However, follow-up studies on long-term survival after CABG have yielded contradictory results with regard to the impact of MetS [332,333].

2.6.2.3 Impact of diabetes mellitus on survival

Diabetes mellitus is a major cardiovascular risk factor [74,209]. There is a considerable body of evidence of poor early outcome and higher in-hospital morbidity among patients with DM than among those without it after CABG [334–336]. On the other hand, the association of diabetes with over 10-year survival after CABG has not been extensively evaluated. The few trials studying the long-term prognosis of CABG patients with diabetes have come to varying conclusions [336–339].

3 AIMS OF THE STUDY

In the present study the postoperative prognosis of CABG patients for up to 20 years was studied. The specific aims of this study were as follows:

1. To ascertain whether CABG patients return to work after surgery and factors affecting postoperative employment.

2. To determine the retention of CABG patients at work after surgery.

3. To explore lipid treatment practices in recently operated CABG patents in a longitudinal analysis over a 20-year timespan.

4. To study total and CV mortality related to overweight and obesity in 20-year follow-up after CABG.

5. To document long-term survival according to metabolic status after CABG in relation to back-ground population.

4 SUBJECTS AND METHODS

4.1 Patients

This study includes two different populations. The population for *the follow–up studies* originally comprised 961 CABG patients operated on in the period 1 January 1993 – 30 June 1994 at Tampere University Hospital (TAUH) and treated postoperatively in secondary care hospitals of TAUH expert responsibility area. After exclusions, 922 patients were included in the analyses. The population for *the annual cohorts* consisted of 953 CABG patients operated on at Tampere University Hospital and treated postoperatively in Kanta-Häme Central Hospital during the time period 1 January 1990 – 31 December 2009. Of these 946 were included in the analyses. Patients operated on with CABG during the period 1 January 1993 – 30 June 1994 at Tampere University Hospital and treated postoperatively at Kanta-Häme Central Hospital (n=76) were included in both studies. Consequently, altogether 1,791 postoperative CABG patients were included in the analyses (Figure 5).

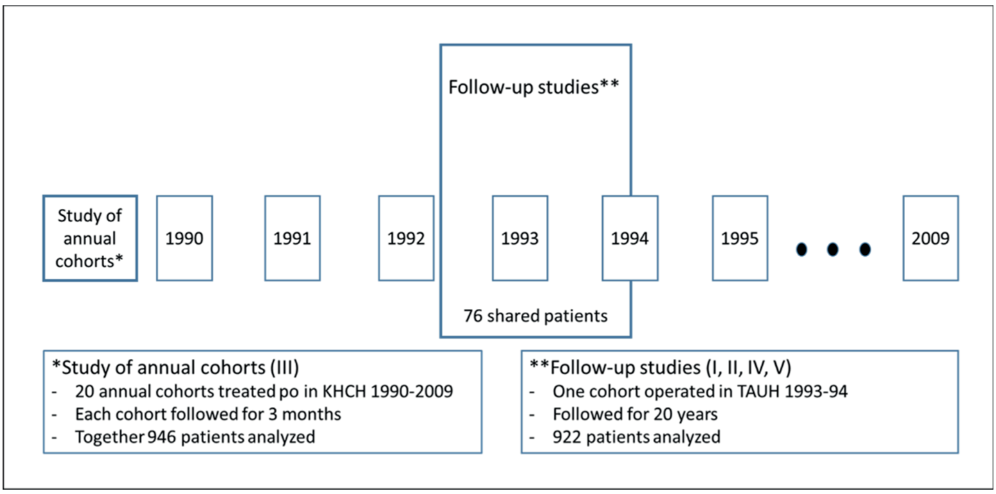

Figure 5. Patient populations of the studies. TAUH: Tampere University Hospital, KHCH: Kanta-Häme Central Hospital. Numbers I to V refer to the original publications of the studies.

4.1.1 Follow-up studies

The population of the follow–up studies consisted of all CAD patients who had undergone CABG at Tampere University Hospital between 1 January 1993 and 30 June 1994. Patients having simultaneous valve or carotid artery surgery were also included in the study. Those who survived beyond the immediate postoperative period of two months were included in the analyses and followed for up to 20 years. The catchment population of the hospital comprised 1.2 million inhabitants living in southern Finland, about 22% of the total population of the country.

After the first postoperative days the patients were transferred to their local hospitals to convalesce (the central and local hospitals in the hospital districts of Etelä-Pohjanmaa, Kanta-Häme, Päijät-Häme and Vaasa). They were discharged 10 to 14 days after the operation if no significant complications occurred. The patients attended a cardiology or internal medicine outpatient clinic 1 to 2 and 3 to 4 months after the operation. ECG and basic laboratory parameters were then analysed. After a few postoperative months, most patients were transferred to primary care for continued secondary prevention.

4.1.2 Study of annual cohorts

In Study III, 20 consecutive annual cohorts of CABG patients were evaluated. The aim was to analyse the development of postoperative lipid treatment practices over a twenty-year time period starting before the statin mega-trials were published and extending until the current treatment practices had been established.

All annual cohorts of CABG patients treated postoperatively in Kanta-Häme Central Hospital during the years 1990–2009 were studied. The primary catchment population of the hospital is 175,000 inhabitants living in Southern Finland. CABG was performed in Tampere University Hospital on 953 patients and after the operation they were transferred to Kanta-Häme Central Hospital to continue their recovery. After discharge the patients were followed up according to national policy.

4.2 Clinical definitions

The patient records were reviewed for cardiovascular and other relevant medical history and essential laboratory parameters. Renal function was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and renal insufficiency defined as a glomerular filtration rate less than 60 ml/min/1.73 m^2 [340]. Hypercholesterolemia was defined as total serum cholesterol $\geq$ 5 mmol/l (200 mg/dL) or a patient being on lipid-lowering drug therapy [341,342]. Estimation of perioperative myocardial damage was based on elevated creatinine kinase MB fraction. Smoking habits were elicited in a questionnaire completed 21 months postoperatively.

Obesity was defined according to BMI and calculated as mass/height^2 (kg/m^2). The study population was divided into normal weight (BMI 18.5 – 24.9 kg/m^2), overweight (BMI 25.0 – 29.9 kg/m^2) and obese (BMI $\geq$ 30.0 kg/m^2) groups. Only one patient had a BMI below 18.5 (17.9) kg/m^2 and was analysed along with the normal weight patients.

The classification of MetS was based on the NCEP/ATP III definition with the exception that body mass index (BMI) (kg/m^2) was used as a measure of obesity [333,343]. During the 1990s waist circumference was not commonly measured [344]. Modified MetS was defined as the presence of three or more of the following risk factors: BMI $\geq$ 30 kg/m^2 for men and $\geq$ 25 kg/m^2 for women, TG concentration $\geq$ 1.7 mmol/l, HDL-C < 1.03 mmol/l for men and < 1.30 mmol/l for women and systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85 mmHg or on antihypertensive medication. Elevated blood glucose was noted when the patient had fasting blood glucose $\geq$ 5.6 mmol/l (100 mg/dL) [341,345].

For the diagnosis of diabetes, the 1998 WHO criteria were retrospectively used, defining fasting blood glucose level ≥ 6.1 mmol/l (110 mg/dL) or random blood glucose ≥ 10.0 mmol/l (180 mg/dL). Beginning in 2001 corresponding plasma glucose cutoff values (fasting plasma glucose ≥ 7.0 mmol/l and random plasma glucose ≥ 11.1 mmol/l) were used [345].

In the follow-up studies the diagnosis of diabetes was based on either elevated glucose levels as stated above or antidiabetic medication according to hospital records at the time of the operation. A patient was also deemed having diabetes if on antidiabetic medication according to the Kela database during the ten years following CABG. The latter definition was used because in the 1990s and early 2000s patients with diabetes often had dietary therapy before starting antidiabetic medication. The patients with later medication probably already had diabetic metabolism during the first postoperative years and were consequently included in the patient group with DM [339].

In the study of annual cohorts, diagnosis of diabetes was based on hospital records.

Cardiovascular death was defined as any death caused by coronary heart disease or sudden death from two months to 20 years postoperatively. Deaths due to stroke and peripheral arterial disease were considered to be cardiovascular deaths.

Similar clinical definitions were used both in the follow-up studies and in the study of annual cohorts.

4.3 Methods

4.3.1 Follow-up study

4.3.1.1 Collection of pre- and perioperative data

Working After Coronary Artery Bypass Grafting (W-CABG) study personnel investigated hospital records after patients' transfer to primary care. Demographics and pre- and perioperative data including BMI were collected manually from medical records in both Tampere University Hospital and in the secondary care hospitals involved in the patients' postoperative recovery. A structured form was used for the data collection. Laboratory data including lipid and blood glucose values were collected from patient records. Standard analytical methods were used in Tampere university hospital and other hospitals included in the study.

4.3.1.2 Patient questionnaires

The first follow-up data collection was made with a detailed questionnaire in July 1995, i.e. on average 21 (range 12 – 30) months after the operation. A repeat questionnaire was sent two months later when necessary (total response rate 86%). Education, employment status, cardiac symptoms and clinical course of CAD were specifically elicited. Subjective well-being compared to patients' expectations as well as risk and protective factors were also evaluated.

The second follow-up was almost identical to the first; during 2003, i.e. 9 to 10 years after the operation (response rate 83%). Both times the follow-up included contact by phone if further clarification of the questionnaire responses was necessary.

4.3.1.3 National databases

Employment status or the date and the reason for retirement were checked from the Finnish Centre for Pensions ten years after the last operation. Use of antidiabetic and cholesterol lowering medication was ascertained from the reimbursement database maintained by Kela until the end of 2008. Possible death, date and cause of death were verified from Statistics Finland, with a final check in September 2016.

All relevant information concerning working status, medication and possible death and its cause were obtained from national databases for all patients included.

4.3.1.4 Analyses of working after CABG

In Finland the retirement rate increased rapidly at the age of 60 in the 1990s. Over 60% of unselected Finns were still working at ages 55 – 59, but only some 20% of those aged 60 – 64. Thus reasons other than medical seemed to exert a marked effect on retirement at that age. In analysing postoperative employment we therefore decided primarily to look at patients still younger than 60 years during follow-up. The results were compared with the pensioning rate among a matched Finnish population [346].

4.3.1.5 Survival according to BMI

Survival analyses were conducted after the end of the study period (30 June 2014) and were based on data obtained from Statistics Finland. Survival data and causes of death were available for a total of 20 years after CABG for all the patients included in the study.

Separate survival analyses (2 months to 10, 15 and 20 years) were carried out for all patients with sufficient BMI data and having survived beyond the immediate postoperative period. Survival analysis was conducted separately for each BMI group (normal weight, overweight and obese). The cumulative, relative mortality for each group was calculated against age-, sex- and time-specific national background populations as described in the statistical methods in section 4.4.1. Furthermore, the relationship of BMI to long-term survival (2 months to 10, 15 and 20 years respectively) was analysed by comparing the three patient groups.

4.3.1.6 Survival according to metabolic status

A second set of survival analyses (2 months to 10, 15 and 20 years) was conducted for all patients whose metabolic status could be ascertained. These patients were divided into those with neither DM nor MetS, those with MetS but not DM and those with DM with or without MetS. The cumulative relative mortality for each group was calculated in the same way as described in 4.3.1.5 above for BMI.

4.3.2 Study of annual cohorts

4.3.2.1 Data collection

The study personnel scrutinized the patient records of all patients treated after CABG in Kanta-Häme Central Hospital in the period 1990 to 2009 to obtain demographic data, relevant preoperative and perioperative information and postoperative cardiology outpatient clinic visits.

Data was collected primarily from the 3-month postoperative visit; postoperative visits until four months after CABG were included in the analyses. Patients for whom laboratory values were available at the first postoperative visit but not at the 3-month visit were also included; that is, a "last observation – carry forward" principle was adopted. Data collected on outpatient visits included postoperative medication, lipid values, blood pressure and absence/presence of various CAD risk factors including smoking habits, diagnosed diabetes and obesity (BMI).

4.3.2.2 Material analysis

The influence of the statin trials and recommendations regarding treatment goals were examined by comparing CABG patients' postoperative lipid values taken over a time span of 20 years. The study period was divided into four consecutive 5-year time periods, namely 1990–1994, 1995–1999, 2000–2004 and 2005–2009. During this 20-year timespan several new statins with different efficacies became available on the market. Thus the daily dose and LDL-C lowering effect of each individual statin had to be considered. This enabled us to compare the lipid-lowering efficacy of each statin therapy during the entire study period.

A daily dose of 20 mg simvastatin or equipotent dose of another statin is the smallest statin dose used in most prospective trials. Hence, this dose was defined as "daily statin dose index (DSDI) 1", which corresponds to a daily dose of 80 mg fluvastatin, 40 mg lovastatin or pravastatin, 20 mg simvastatin, 10 mg atorvastatin or 5 mg rosuvastatin. The lipid-lowering efficacy of each statin was assumed to be linearly correlated with the dose; i.e. the DSDI of 80 mg simvastatin was four [347–350].

4.3.2.3 Lipid analysis

Total and high-density lipoprotein cholesterol (HDL-C) concentrations were determined from plasma samples by using Hitachi 911 analyser with Boehringer-Mannheim reagents in 1990–1996. Roche Diagnostics enzymatic methods were used since 1996, which also applied to direct LDL-C analysis from 2000 onwards. All chemical analyses were carried out in the Laboratory of Kanta-Häme Central Hospital. Lipid analyses have been under the Nordic quality control during the entire study period.

In the calculation of classical Friedewald formula LDL-C is TC – HDL-C – (TG/2.2) in mmol/l concentrations. Since classical Friedewald formula is only valid provided serum TG < 4.5 mmol/l, we also applied a novel extended Friedewald approach, which is more tolerant of elevated triglycerides [351,352]. The extended Friedewald approach is based on artificial neural network regression algorithms which utilize data on classical Friedewald inputs[351]. This method allowed us to calculate LDL-C, intermediate-density lipoprotein cholesterol (IDL-C), and very-low-density lipoprotein triglyceride (VLDL-TG) concentrations. It also computationally yields estimates of apoB and apoA1 concentrations [351].

4.4 Statistics

4.4.1 Follow-up study

In the comparison of patient characteristics, categorical data are tabulated as frequencies and percentages, and continuous variables are expressed as means and standard deviations (SDs). Differences between the two groups were tested by Chi squared test and the Wilcoxon rank test, and in cases of more than two groups by Kruskal-Wallis test. Fisher's exact test was used when appropriate in two-by-two tables with directed hypothesis. Differences in mean values between two groups were tested by Student's t-test and in the case of more than two groups by analysis of variance.

The relative survival rates were analysed by age, gender, diabetes mellitus (DM), MetS, BMI and statin medication using the Life Table method [353]. In this approach, the observed survival rates of the groups are compared to the rates based on age-, gender- and time-specific (CABG year) life tables for the entire population of Finland. Calculation of survival rates was based on the individual life expectancies of the target population for the target years (reference population). For example, at the time of the operation (1994), the mean life expectancies of Finnish 65-year old men and women were another 14.6 and 18.6 years respectively. The survival of the reference population is effectively 1.00. If the survival curve of the group remains below that of the reference population there is excess mortality in the group.

The first two postoperative months were defined as perioperative due to increased mortality. In the follow-up studies patients' prognoses were calculated and relative mortality curves were presented for the 2-month to 20-year time period after CABG. Double arithmetic smoothing was applied when associations of BMI with adjusted all-cause mortality over 10, 15 and 20 years after CABG were presented.

To study the independent significance of MetS, DM and BMI for clinical outcome (2 months to 20 years), multivariate analysis was conducted using an optimizing stepwise procedure based on the Bayesian approach [354]. The model of the individual probability of remaining at work was created using the same method.

The multivariate analysis procedure was developed for nominal variables and does not require a perfect variable matrix. It selects by the heuristic approach the combination of variables which best explains the selected outcome factor. The Bayesian approach is applied by counting posterior likelihood ratios or odds ratios for each combination. The aim was to find an optimal subset of pre- and intraoperative variables to provide the best explanation. The parameters included in the multivariate analysis were age, gender, BMI, all significant cardiometabolic diseases and related operations likewise obstructive pulmonary diseases, lipid values and statin medication. Essential intraoperative characteristics of CABG and some supplementary parameters from the patient questionnaire were also included in the analyses. Altogether 40 parameters were applied in the Bayesian approaches (Appendix I - II).

4.4.2 Study of annual cohorts

The evolution of postoperative statin therapy and lipid values over 20 years was studied using ANOVA test in the 5-year groups. With dichotomous variables the 5-year groups were compared using extended λ^2 test [355]. D'Agostino's test was used to determine normality and scedasticity. Percentage or mean and standard deviation of demographic characteristics and lipid variables are presented. Multiple linear regression analysis was used when comparing lipid values with each other.

4.5 Ethical considerations

The study was conducted in accordance with the ethical principles outlined in the declaration of Helsinki [356]. Study material was collected with identification data including name and individual social security number allowing combination of different data sources. Study results were further analysed and papers published without patient identification.

The follow-up study (Studies I-II and IV-V) and its later amendments were approved by the Ethics Committee of Tampere University Hospital (reference numbers 95010, R02103). Study III concerning CABG patients evolving secondary prevention during a 20-year time-period, done in Kanta-Häme Central hospital, was approved by the Ethics Committee of Kanta-Häme Hospital District (reference number E511/08).

5 RESULTS

5.1 Study population

5.1.1 CABG patients for follow-up studies

Of the 961 CABG patients operated on in the period 1 January 1993 – 30 June 1994 at Tampere University Hospital, 33 died during the first postoperative month, and five more during the second month. In one single patient, a 70-year-old male, neither BMI nor metabolic status was ascertained. In total, 922 patients were included in the follow-up studies.

BMI was calculated for all of these 922 patients and the metabolic status was determined in 910 of those surviving for more than two months. The study on postoperative employment included 529 patients aged less than 64 years at the time of the operation (< 65 one year postoperatively). Twenty of these died during the first postoperative year. Data on postoperative employment was calculated from the remaining 509 patients. No one was lost during the 20-year follow-up (Figure 6).

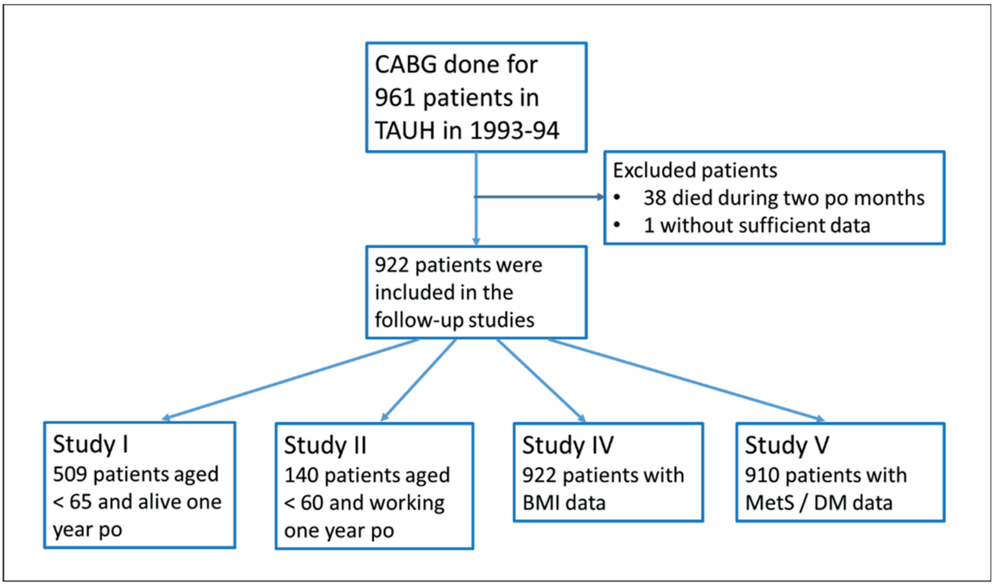

Figure 6. CABG patients for the follow-up studies. CABG: Coronary artery bypass grafting, TAUH: Tampere University Hospital, po: Postoperatively, BMI: Body mass index, MetS: Metabolic syndrome, DM: Diabetes mellitus.

5.1.1.1 Demography of patients according to BMI

Patients' demography and clinically relevant co-morbidities are presented according to BMI at the time of surgery for all 922 consecutive patients studied (Table 3). Overall, 25% were normal weight, 55% overweight and 20% obese. Their mean age was 62 (± 8) years and 21% were women.

According to data obtained by the questionnaire dispensed on average 21 months postoperatively, patients in three BMI groups (normal weight, overweight and obese) did not differ significantly from each other in the postoperative use of low-dose ASA, statins or ACE inhibitors. Patients who were obese at the time of CABG mostly remained obese according to a second questionnaire administered 9.5 years postoperatively. Correspondingly, the majority of patients with normal BMI continued to have normal BMI.

Table 3. Preoperative demographic data, clinical characteristics and severity of coronary heart disease in 922 patients according to BMI. Data on patients surviving two months after coronary artery bypass grafting.

	BMI < 25.0	BMI 25.0–29.9	BMI ≥ 30.0	Overall P-value
Demographic characteristics				
Number of patients	230	506	186	
Female (%)	21	20	25	NS
Mean age (years) (SD)	63 (9)	62 (8)	60 (8)	<0.05[1]
Concomitant Diseases				
Previous MI (%)	61	73	73	<0.05[1]
Previous TIA or stroke (%)	10	11	8	NS
Peripheral arterial disease (%)	13	8	0	<0.05[1]
DM (%)	17	27	43	<0.0001[2]
Hypertension (%)	54	62	70	<0.01[3]
Creatinine clearance				
GFR (ml/min) (SD)	76 (16)	75 (16)	75 (16)	NS
GFR < 60 ml/min/1,73m^2 (%)	16	16	16	NS
Lipid disorder				
Hypercholesterolaemia (%)	72	73	78	NS
Low HDL-C (%)	54	67	71	<0.001[4]
Elevated TGs (%)	37	58	73	<0.0001[2]
Preoperative Smoking (%)	63	64	67	NS
Severity of Heart Disease				
EF (%) (SD)	60 (14)	61 (14)	59 (14)	NS
Severely decreased EF	6	7	7	NS
NYHA II (%)	11	12	8	NS*
NYHA III (%)	58	57	59	
NYHA IV (%)	31	31	33	
Three–vessel or LM disease (%)	60	63	57	NS
Urgent / emergency operation (%)	30	29	31	NS

Abbreviations: BMI: Body mass index (kg/m^2), MI: Myocardial infarct, TIA: Transient ischaemic attack, GFR: Glomerular filtration rate, Hypercholesterolaemia: Total cholesterol ≥ 5.0 mmol/l or on lipid-lowering medication, Low high density lipoprotein (HDL) cholesterol: Men <1.03 mmol/l, women <1.3 mmol/l, Elevated triglyceride (TG): ≥1.7 mmol/l, EF: Ejection fraction, Severely decreased EF: EF ≤35%, NYHA: Angina pectoris symptoms according to New York Heart Association, LM: Left main, NS: Not significant. * Overall P-value for NYHA *vs*. BMI.

1 Unadjusted P<0.05 by the pooled t-test for the comparison BMI < 25.0 kg/m^2 against BMI ≥ 30.0 kg/m^2.

2 Unadjusted P<0.0001 by the pooled t-test for all comparisons.

3 Unadjusted P<0.01 by the pooled t-test for all comparisons.

4 Unadjusted P<0.001 by the pooled T-test for the comparison BMI < 25.0 kg/m^2 against both other groups.

5.1.1.2 Metabolic status of patients

Of the 910 patients, 41% had neither DM nor MetS, 31% had MetS but not DM and 28% had DM, when analysed 10 years postoperatively. At the time of CABG, only 14% had diagnosed DM. Patients with DM were on the average two years older than those without it. Patients with MetS had by definition metabolic abnormalities more often than those without MetS. Similar findings were obtained in patients with DM, of whom 83% had MetS. Renal dysfunction was more frequent in DM+ and DM-/MetS+ patients and severe heart disease represented by lower ejection fraction and New York Heart Association (NYHA) class IV was more common in those suffering from DM than in other groups. CVD history or operational characteristics did not differ significantly between patient groups.

5.1.1.3 Demography of the patients of working age

In those 509 patients operated on and being under 65 years of age and alive one year postoperatively, 13 out of 75 women (17%) and 138 out of 434 men (32%) returned to work. The average age of those who returned to work was 52 years and of those who retired was 58 years. Diabetes mellitus, previous transient ischaemic attack (TIA) or stroke and severe cardiac disease determined by decreased left ventricular ejection fraction and NYHA class IV were more common in patients who retired. They also had on average lower basic education.

5.1.1.4 Lipid treatment

In the follow-up study the statin use was evaluated on the average for the first 15 postoperative years. Patients were divided as follows: Group I, 368 patients (26% women) who had been on statins for at least 50% of their postoperative follow-up period, group II, 323 patients (16% women) who had been on statins for more than three months, but for less than 50% of their postoperative follow-up and group III, 231 patients (20% women) who had not taken statins postoperatively (or received at most one three-month prescription).

5.1.2 CABG patients for the study of annual cohorts

Of the 953 CABG patients treated in Kanta-Häme Central Hospital after CABG during the time period 1 January 1990 – 31 December 2009, 946 (99%) attended the cardiology outpatient clinic at least once during the first four postoperative months. They were divided into four consecutive 5-year periods according to treatment date, each group consisting on average of 237 patients, the proportion of male patients ranging from 72% to 80%. The patients' demographics evolved with an increasing proportion of patients with DM and older patients operated on as well as decreasing measured systolic and diastolic blood pressure in later years. (Table 4).

Table 4. Demographics of Kanta-Häme Central Hospital patients undergoing CABG during the period 1990-2009, divided into 4 consecutive 5-year periods

5-year period	**1990–1994**	**1995–1999**	**2000–2004**	**2005–2009**	**Overall P***
Number of patients	256	247	224	219	
Proportion of female (%)	22	20	28	21	NS
Proportion of DM patients (%)	10	14	19	27	< 0.01
Current and ex-smokers (%)	64	55	54	56	NS
Age (years) (SD)	62 (8)	64 (9)	65 (9)	67 (8)	< 0.0001
BMI (kg/m^2) (SD)	26.5 (3.5)	26.5 (3.3)	27.2 (3.7)	27.0 (4.1)	NS
Systolic BP (mmHg) (SD)	150 (25)	148 (23)	138 (22)	130 (20)	< 0.0001
Diastolic BP (mmHg) (SD)	85 (12)	82 (11)	80 (10)	78 (9)	< 0.0001

* Extended λ^2 test and ANOVA were used for overall analysis. Percentage or mean (SD) is presented. DM: Diabetes mellitus, BMI: Body mass index (kg/m^2), BP: Blood pressure, NS: Not significant.

5.2 Employment (I, II)

5.2.1 Resuming work after CABG

Of the 509 patients operated on while under 64 years of age (< 65 one year postoperatively) and who were alive one year after CABG, altogether 251 (49%) had retired preoperatively. The remaining 258 (51%) were working, unemployed or on short-term leave. Of these, 145 were working after the first postoperative year. The remaining 112 retired immediately after postoperative sick leave without returning to work or after only a couple of months working (one patient returned to work later). Of the preoperatively retired patients only six returned to work, while 245 continued in retirement after CABG. Hence, altogether 151 patients were working one year postoperatively. Working, retirement and one-year postoperative mortality data on all patients under 65 years (n = 529) and under 60 years (n = 329) one year postoperatively are shown in Figure 7.

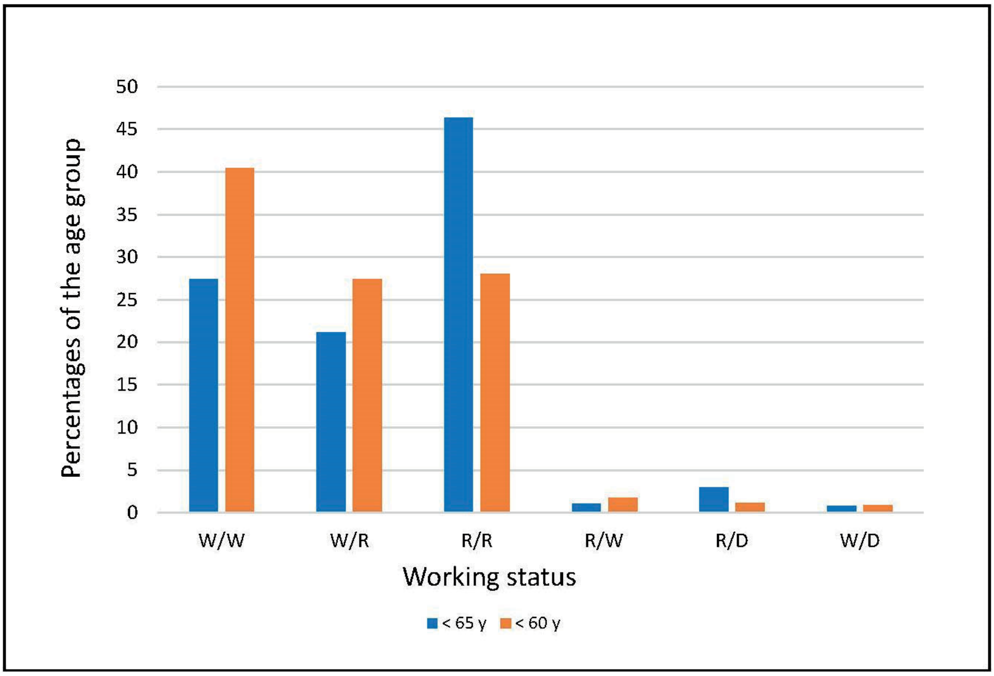

Figure 7. Working, retirement or postoperative death of coronary artery bypass grafting patients one year after the operation. Definitions: < 65 y: Under 65 years one year postoperatively. < 60 y: Under 60 years one year postoperatively. W/W: Working preoperatively, working one year postoperatively, W/R: Working preoperatively, retired one year postoperatively, R/R: Retired preoperatively, retired one year postoperatively, R/W: Retired preoperatively, working one year postoperatively, R/D: Retired preoperatively, died during the first postoperative year, W/D: Working preoperatively, died during the first postoperative year.

5.2.2 Factors affecting postoperative working

The most important factors having a positive effect on postoperative employment according to the univariate analysis were patient's younger age and shorter duration of absence from work ($P<0.001$). After the age of 55 years, preoperatively non-retired patients' return to work (RTW) diminished rapidly. Of those under 55 years at the time of CABG, 66% returned successfully to work during the first postoperative year, while the corresponding figures for older age groups, 55 to 59 and 60 to 64 years, were 51% and 35%. The mode and duration of preoperative sickness leave or pension were related to getting back to work in such a way that most patients (71%) being preoperatively only briefly on sick leave returned to work postoperatively, 9% of patients on interim benefit for three to six months returned to work as did only 2% of those who had been on interim benefit or disability pensioned for a longer time.

In univariate analysis higher level of education and absence of history of TIA or stroke also predicted better RTW ($P<0.001$). Patients' short height, family history of cardiac disease, high total cholesterol, DM, high preoperative NYHA class (IV), and low ejection fraction predicted lower return to work ($P<0.01$).

In stepwise Bayesian multivariate analysis, best sensitivity and specificity were found for a model which included patient's age, duration of preoperative sickness leave, a history of diabetes mellitus and signs of perioperative myocardial damage. In this model sensitivity was 94% and specificity 75%.

5.2.3 Continuing to work

The analysis of continuing to work included patients at work one year postoperatively. In the working status of those aged less than 55 years on the average five years after operation, 85% were working full-time and 5% part-time, of those aged 55 years to 59 years, 72% and 1% and of those aged 60 years to 64 years, 34% and 6% respectively. The corresponding employment figures in Finnish background population for 1999 in those aged 45 years to 54 years, 55 years to 59 years and 60 years to 64 years were 89%, 70% and 21% [346].

Out of 151 patients working postoperatively, 140 (9% women) were younger than 60 years at the beginning of the follow-up and 56 were still under 60 years of age ten years later. Of these 56 patients 67% were employed full-time and 8% part-time, while 25% had retired on disability pensions. Eight deceased patients, all of them due to non-CV causes, were excluded from the analysis. Likewise patients were removed from the analysis once they had turned 60 years. The ten-year postoperative employment status is presented in Figure 8.

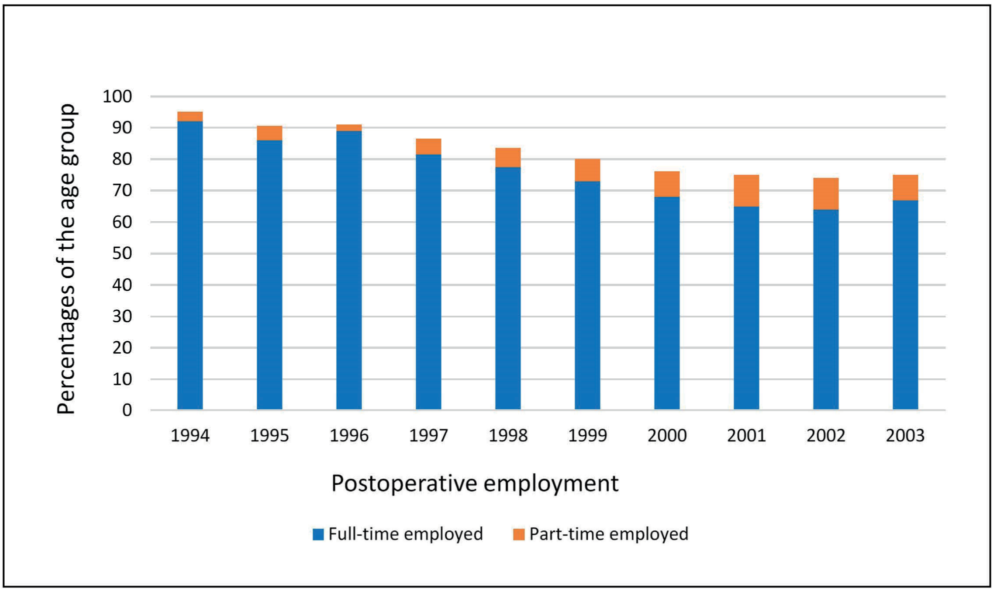

Figure 8. Postoperative employment of coronary artery bypass grafting patients at the end of each calendar year. A 10-year follow-up until 31 December 2003 of the originally 140 patients who were working one year postoperatively and under 60 years of age. A total of eight persons deceased during the follow-up are excluded. Patients were also removed from the analysis once they had turned 6o years.

5.2.4 Factors affecting continuing to work

In univariate analysis the three most significant factors ($P<0.001$) affecting continuing to work were patient's age at the time of the operation, duration of preoperative sickness benefit and patient's height. Several other factors describing patients' medical condition (e.g. preoperative kidney function, extent of cardiovascular disease, diabetes), postoperative activity and well-being as well as social situation also correlated with long-term continuation at work.

In Bayesian multivariate analysis several patterns of univariately significant factors were compared. The best balanced and most useful model included the following factors: patient's age, postoperative cardiac symptoms, patient's height, being married/non-married, diabetes mellitus and participation in household work (Table 5).

Table 5. Probabilities of remaining at work after coronary artery bypass grafting for at least three, six and nine years.

Variable	3 years (n = 119)	6 years (n = 92)	9 years (n = 59)
1. Age at the time of CABG			
$\leq$ 50	LR = 6.54	LR = 3.25	LR = 2.42
50 – 54	LR = 3.80	LR = 1.24	(LR = 0.20)
$\geq$ 55	LR = 0.68	(LR = 0.37)	(LR = 0.01)
2. Postoperative cardiac symptoms			
No	LR = 1.11	LR = 1.00	LR = 1.08
Yes	LR = 0.51	LR = 1.00	LR = 0.51
3. Height in centimetres			
< 175	LR = 0.59	LR = 0.58	LR = 1.00
175 – 179	LR = 1.43	LR = 1.80	LR = 1.00
180 -	LR = 6.29	LR = 2.13	LR = 1.00
4. Being married			
No	LR = 3.51	LR = 1.60	LR = 1.14
Yes	LR = 0.88	LR = 0.93	LR = 0.98
5. Diagnosed DM			
No	LR = 0.92	LR = 1.03	LR = 1.04
Yes	LR = 2.59	LR = 0.80	LR = 0.70
6. Participation in household work			
Daily	LR = 1.00	LR = 1.25	LR = 1.26
Less often	LR = 1.00	LR = 0.58	LR = 0.51
Precision of the model			
False-Positive	10	18	15
False-Negative	9	17	13
Sensitivity	55 %	63 %	82 %
Specificity	92 %	82 %	78 %
Correct predictions	86 %	75 %	80 %

In this model the individual probability of remaining at work (calculated one year postoperatively) is as follows: The patient's likelihood ratio (LR) for each characteristic is multiplied. Higher LR means greater likelihood of remaining at work. If the total LR is greater than 1.00, the probability of remaining at work is more than 50% for the given time (3 y, 6 y, or 9 y). Patients in age groups given in parentheses may remain at work over the age of 60 years. LR may be expressed as probability as follows: p = 100 * LR/ (1+LR).

As an example, we have a 52-year-old patient who is free of cardiac symptoms, is 176 cm tall, married, is not suffering from diabetes and does not participate in household work. His/her total likelihood ratio for continuing at work for at least six years is 1.24 x 1.80 x 0.93 x 1.03 x 0.58 = 1.24. According to the model 100 * LR/ (1+LR), we get a 55% probability of continuing to work for at least six years. If our patient were an active person, for example participating in household work, his/her total likelihood ratio of remaining at work for at least six years would increase to 1.24 x 1.80 x 0.93 x 1.03 x 1.25 = 2.67 and thus his/her probability would be 73%.

5.3 Lipid treatment (III)

5.3.1 Impact of statin treatment on survival after CABG

In a 20-year follow-up of study patients, the most favourable prognosis was seen in those patients who had been on statin therapy for at least 50% of their postoperative follow-up time, relative survival in comparison with the background population being 0.99 (95% CI, 0.89 to 1.08; (P=NS)). Patients having used statins for more than three months, but less than 50% of their postoperative follow-up had a poorer prognosis, 0.81 (95% CI, 0.67 to 0.94; P<0.001). The poorest prognosis was in those patients who had not taken statins at all or only purchased one three-month prescription, 0.32 (95% CI, 0.01 to 0.64; P<0.001). The prognosis of each statin user group is shown in Figure 9.

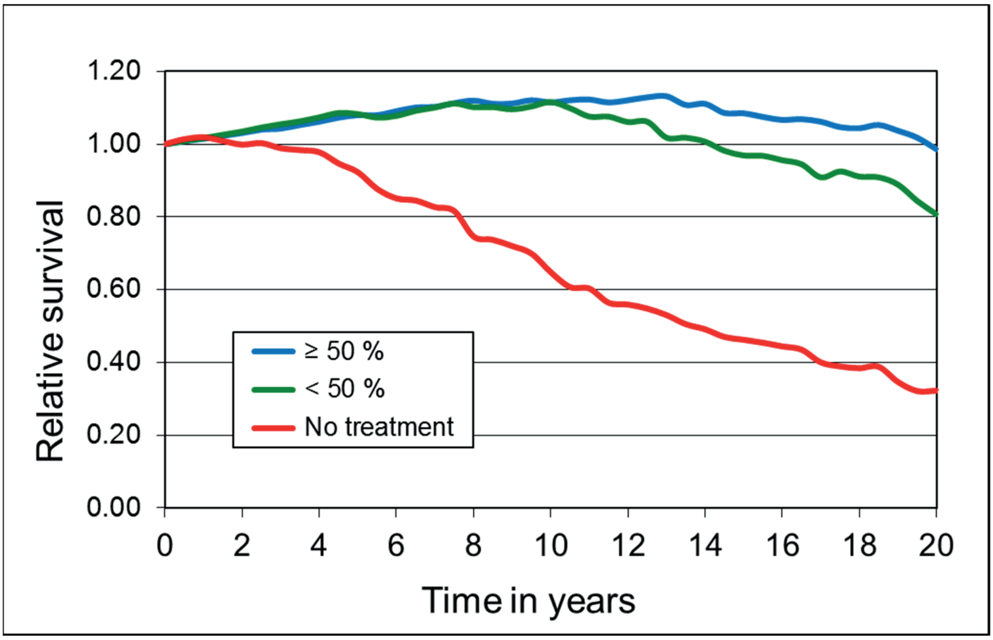

Figure 9. Relative 20-year prognosis of coronary artery bypass grafting patients alive 2 months postoperatively represented in relation to statin treatment (matched back-ground populations 1.00). Use of statins > 50% of time *vs.* < 50 % P<0.001, use of statins < 50% of time *vs.* no statin use P<0.001.

5.3.2 Lipid treatment practice in the study of the annual cohorts

Altogether 803 patients had their lipid values measured, their share increasing from 64% over the first five-year period (1990–1994) to 97% in the last period (2005–2009). During the same time the use of statins increased from 12.0% to 97%. In the last years of the follow-up, practically all CABG patients were on statin therapy (Figure 10A).

The daily statin dose indexes (DSDIs) were small in the early years, both due to scant use and low effective doses of statins increasing progressively during the study period. Thus, the average DSDIs of all patients, even when those without statin therapy were included, increased during four consecutive 5-year time periods from 0.07 to 2.52 (P for trend <0.001) (Figure 10B). The DSDI during the very last year of observation corresponds to a mean simvastatin dose of 57 mg/day.

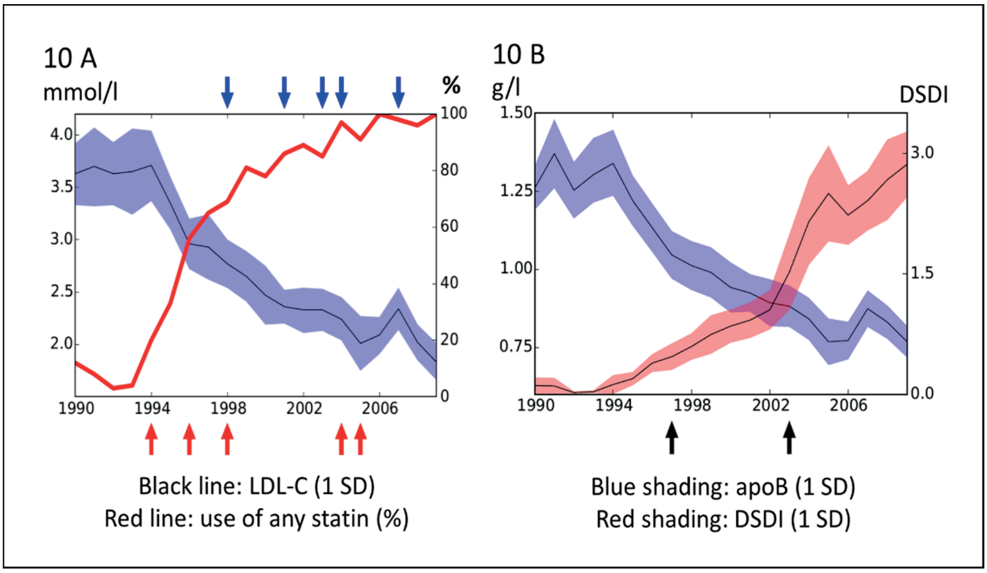

Figure 10. A. Statin treatment and low-density lipoprotein cholesterol (LDL-C) after coronary artery bypass grafting. Red arrows indicate the publication of landmark statin trials [1,3,154,155,357]. Blue arrows refer to the publication of lipid lowering recommendations [341,342,358–360].

B. Apolipoprotein B (ApoB) and daily statin dose index (DSDI) after coronary artery bypass grafting. Black arrows indicate the years, when atorvastatin (1997) and rosuvastatin (2003) entered the Finnish market.

5.3.3 Plasma lipid and apolipoprotein levels in the study of the annual cohorts

The respective mean concentrations of LDL-C were 3.7 and 2.1 mmol/l, and those of apoB 1.3 and 0.8 g/l during the initial (1990–1994) and final (2005–2009) 5-year time periods (Figure 10A, 10B). During the last year of follow-up (2009) the mean concentrations of LDL-C and apoB were 1.83 mmol/l and 0.78 g/l, respectively.

The decrease in apoB concentration was progressive throughout the 20-year time span. This is seen in the significant decrease of LDL-C concentration, as in the concentrations of other apoB-containing lipoproteins, such as VLDL-TG and IDL-C, which were reduced comparably. Further, HDL-C increased significantly from 1.02 to 1.22 mmol/l.

5.4 Survival (IV, V)

5.4.1 Overall survival

Perioperative mortality, defined as mortality during the first two postoperative months, was 4.0% (38 patients), 60% of them patients with diabetes. In patients younger than 65 years at the time of the operation 2.2% died perioperatively (13 patients).

At the end of follow-up, 20 years postoperatively, a further 574 patients had died of the 923 alive two months postoperatively. Thus at the end of follow-up 36% of the patients originally operated on were alive.

5.4.2 Impact of BMI on survival

During the first postoperative years the prognosis was favourable in all patient groups. Beyond the first ten years the survival curves diverged significantly.

Patients with normal BMI (< 25 kg/m^2) were associated in long-term follow-up with significantly inferior survival when compared to that of the background population already 10 years postoperatively. Twenty years postoperatively it was 0.68 (95% CI 0.49 – 0.87; $P<0.001$). The survival of overweight patients was comparable to that of the background population for the first 15 years, but subsequently deteriorated. At 20 years postoperatively the relative survival in this group was 0.82 (95% CI 0.71 – 0.92; $P<0.001$). The prognosis of obese patients was for the first

10 years similar to that of the background population and then decreased sharply during the second postoperative decade. Their survival was 20 years postoperatively 0.67 (95% CI 0.49 – 0.85; P<0.001). In normal weight patients most unfavourable 20-year prognosis was associated with the lowest BMIs and in the obese group in patients with BMI $\geq$ 35.0 kg/m².

Survival of the patients according to BMI group is compared in Figure 11, and the relative survival of the patients over time periods of 10, 15 and 20 years in Figure 12.

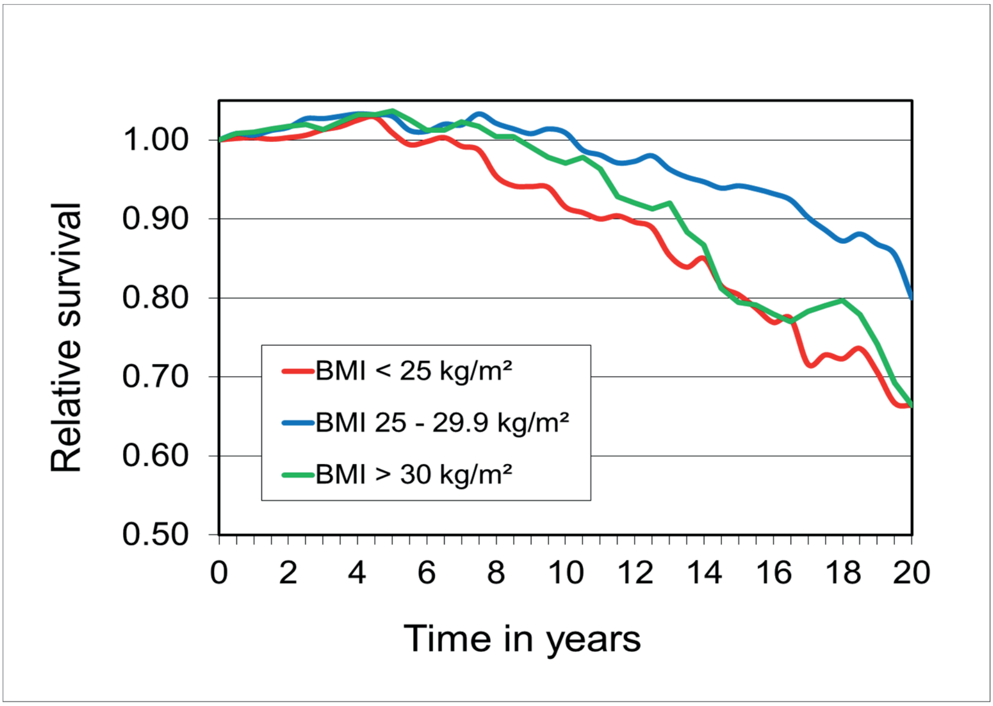

Figure 11. Relative survival of patients after coronary artery bypass grafting 2 months to 20 years postoperatively according to BMI group compared to matched background populations (relative survival 1.00). BMI: Body mass index.

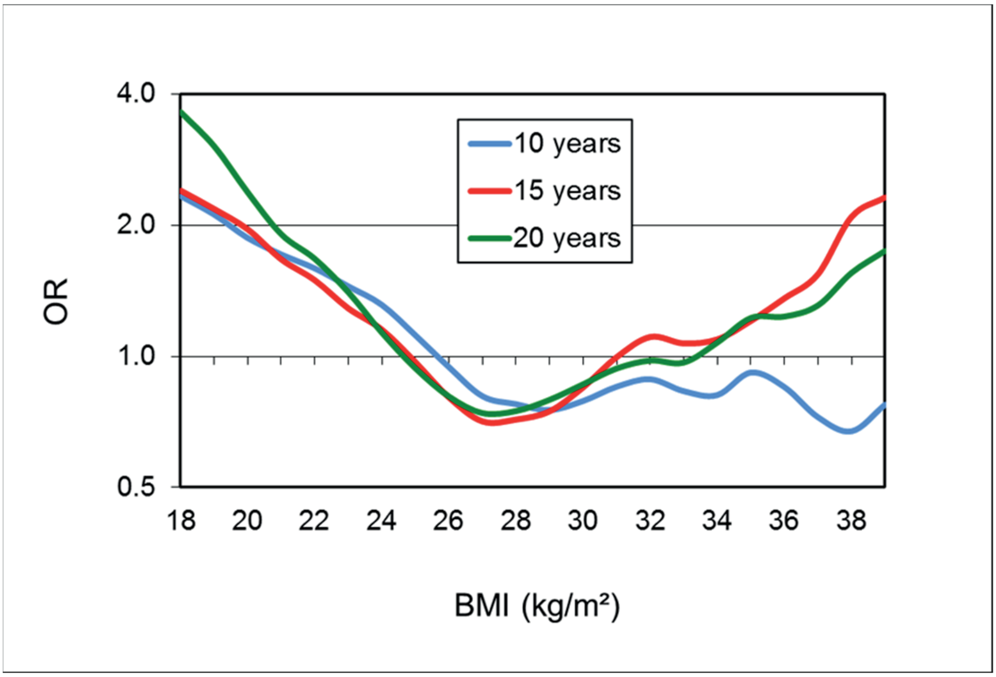

Figure 12. Association of body mass index (BMI) as a continuous variable with adjusted all-cause mortality using basic odds ratio (OR) formula 10, 15 and 20 years after coronary artery bypass grafting. An OR of 1.0 represents that of an average CABG patient. The curves are smoothed and represented on a logarithmic scale.

5.4.3 Long-term survival according to metabolic status

The prognosis of patients surviving for the first two postoperative months and without DM or MetS was comparable to that of background population. At the end of follow-up, 20 years postoperatively, their relative survival was 0.89, (95% CI, 0.78 – 1.00; P=NS), (Figure 13). In patients without DM but with MetS long-term survival was first comparable to that of background population, but over time it deteriorated and 20 years postoperatively was 0.80 (95% CI 0.66 – 0.93; P<0.01) (Figure 13).

The prognosis of patients with diabetes started to deteriorate during the first postoperative decade and was significantly less than that of patients without diabetes and that of their background population 10 years postoperatively. Their relative 20-year survival was 0.48 (95% CI 0.26 – 0.71 P<0.001) (Figure 13). Among patients with DM, MetS seemed not to affect postoperative survival after adjustment for age, gender and year of CABG (P=NS). In multivariate analysis, age, diabetes mellitus, BMI and left ventricular ejection fraction at the time of CABG had an independent impact on prognosis.

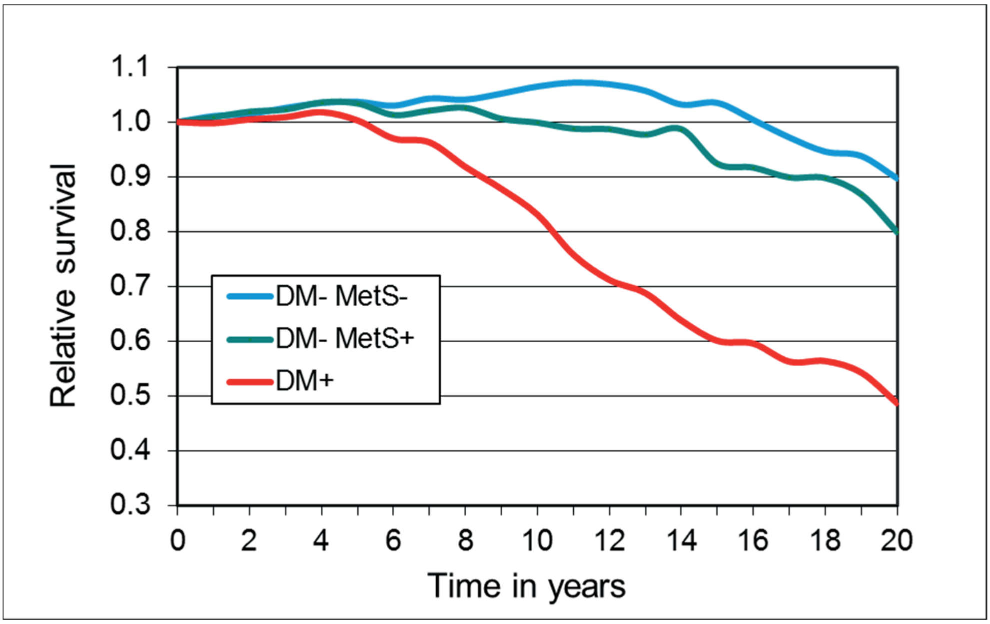

Figure 13. Postoperative relative survival of patients with coronary artery bypass grafting according to metabolic status (matched back-ground populations 1.00). DM: Diabetes mellitus, MetS: Metabolic syndrome.

5.4.4 Causes of death

Causes of death are known until the end of the follow-up. Both BMI and metabolic status, especially DM were related to cardiovascular mortality.

Cardiovascular disease was the primary cause of death during the first and second postoperative decade in normal weight patients in 56% and 60% and in overweight patients 60% and 57%, respectively (NS for both changes). In obese patients cardiovascular mortality increased significantly over time accounting for 44% of all mortality during the first postoperative decade and for 76% during the second decade ($P<0.05$).

When the patients were divided according to metabolic status, CV mortality was during the first and second postoperative decade in DM-/MetS- 60% and 55%, in DM-/MetS+ 54% and 55 % and in DM+ 62% and 69% of all mortality respectively. The excess mortality of patients with diabetes during second postoperative decade was largely due to cardiovascular causes. The increase was significant when compared to patients without diabetes ($p<0.05$).

In reported postoperative CV deaths stroke and ASO played a minor role accounting for respectively 10.0% and 0.8% of all CV mortality.

6 DISCUSSION

6.1 Introduction

The present study evaluates prognosis after CABG assessed in terms of resumption of work and survival. The influence of BMI, metabolic syndrome and diabetes mellitus as well as statin treatment were of special interest, but all relevant pre- and perioperative factors were also taken into account. Evolution of statin treatment has been addressed, as well. The major results are represented in table 6.

Table 6. Major results of the studies of patients with coronary artery bypass grafting included in the theses. The studies are numbered I to V according to the original publications.

Publications	Principal results
Employment (I, II)	1) Older age (> 55) and longer sick leave (> 6 months) impaired resuming work postoperatively. 2) Patients who returned to work continued working similarly to their age and gender matched background populations.
Statin treatment (III)	1) In long-term follow-up, duration of statin treatment correlated positively with good prognosis. 2) In annual cohorts between 1990 and 2009 both prevalence and dose of statin treatment increased substantially, especially after the publication of statin mega-trials and the availability of more potent statins.
BMI (IV)	1) The apparent obesity paradox disappears during the 20-year follow-up after CABG. 2) In the second postoperative decade obese patients died primarily of cardiovascular causes.
DM and MetS (V)	1) In the 20-year follow-up survival of MetS patients is inferior to that of their background populations. 2) The prognosis of patients with diabetes is remarkably worse than that of MetS patients without diabetes and their survival is less than 50% of that of their respective background populations.

6.2 Postoperative employment after CABG (I, II)

6.2.1 Postoperative working

The major objectives in CABG are restoration of normal functional capacity and quality of life. For patients of working age resumption of professional activity can be considered an essential goal of coronary surgery.

In our cohort 35% of patients aged 60 – 64 years, 51% of those aged 55 – 59 and 66% of those aged less than 55 and not retired preoperatively were working one year after CABG. The result for patients aged 60 – 64 years was good, since only 17% of the national background population of the same age were working in 1994. Employment in younger age groups of the background population was more frequent, being 63% and 89% in those aged 55 – 59 years and 45 – 54 years, respectively [346]. Our results are in accordance with other published results where patients' age has been an important predictor of postoperative employment [295,297,298,311,361].

The number of women returning to work postoperatively was low for reliable statistical comparisons. Therefore, the interpretation of their postoperative work activity must be made very carefully. Subsequently, we treated men and women as one group in our statistical employment calculations. Nevertheless, it appears that postoperative employment and continuing at work were more common among men than women.

The national unemployment rate may affect patients' return to work (RTW) [361]. The highest retirement rates in Finland since 1990 were found during a major economic depression in 1993 – 97 [346]. The postoperative recovery and rehabilitation phase of the W-CABG patients coincided with that period. Although retirement of younger subjects was fairly low in our study, the economic depression may have affected the RTW of older patients. A high unemployment rate may reduce social activities and motivation to take an active part in the rehabilitation process[361]. Patients' own wish for RTW and employers' attitudes towards the employment of previously disabled workers also have their effects on the probability of patients with CAD retiring [306].

It can be argued that working life is rigid during times of economic depression. In a Swedish study older age was associated with a lower rate of return to full-time work after CABG, PCI or MI [361]. However, CAD did not affect the return to work with reduced working hours. Economic depression is likely to manifest in fewer opportunities for working reduced hours. On the average, only 6% of patients in this study worked reduced hours postoperatively.

6.2.2 Factors affecting postoperative return to work

Longer preoperative sick leave and being granted a pension significantly deteriorate the likelihood of postoperative RTW [297,298,362]. Accordingly, in our study patients with short preoperative sick leave had the best options for postoperative employment, while there was a highly significant inverse correlation between preoperative granting of a pension and RTW. It is probable that economic depression, age and not working preoperatively have an even greater impact on postoperative employment than does health status.

In multivariate analysis, the best sensitivity was found in a model including only patient's age and retirement. The specificity increased when history of diabetes and perioperative myocardial damage were added to the model. The former has been confirmed as a predictor of poor prognosis [298,363], while the latter can be considered a sign of severe or diffuse coronary artery disease. Low ejection fraction has been confirmed to be a predictor of poor RTW [298].

6.2.3 Continuing to work and factors affecting it

In Finland the retirement rate increases rapidly after the age of 60, mainly for non-medical reasons. When considering only patients returning successfully to work and being aged less than 60 years, 85% continued to work for five years and 75% for ten years after CABG. According to earlier studies, 20 – 51% of CABG patients were employed for over five years after successful RTW in UK, Finland and the USA [296,297,364]. The encouraging results in this study may be due to effective secondary prevention. Another possible explanation is that only those patients returned to work who truly felt able to manage it. One might presume that in the early 1990s in Finland it was still relatively easy to get a disability pension after CABG.

In our study patients who returned to work also continued working comparably to age-matched Finnish general population. Only a few published studies have evaluated continuation at work over a longer time period. In a British cohort of originally 343 patients with a five-year follow-up, the most important predictors for continuation were age at the time of the operation, male sex, preoperative working and freedom from postoperative angina symptoms [297]. In a cohort of 409 PCI and

CABG patients in the USA, younger age at the time of the operation and preoperative working status, but also work-related medical insurance, were associated with more favourable long-term employment [364].

In this study the model of continuing at work included patient's age and height, postoperative cardiac symptoms, diabetes mellitus, being married/non-married and participation in household work. Patient's age and postoperative cardiac symptoms have elsewhere been associated with postoperative employment [297,298,364]. Patient's height is related to sex, which is a predictor of postoperative long-term employment [297]. Patient's non-married status may emphasize the importance of daily work both socially and financially and participation in household work may suggest activity also outside home. Diabetes mellitus seems to favour working three to five years postoperatively. The small number of diabetes patients in this group may affect the results.

6.3 Statin treatment (III)

6.3.1 Effect of statin treatment on survival

CABG efficiently relieves CAD symptoms. However, without effective secondary prevention it does not offer long-lasting help for cardiac symptoms or improvement in prognosis [192,316]. A central target of secondary prevention is effective lowering of LDL-C [3,365]. Statin treatment has been shown to be efficient in reducing CV risk, the benefit depending on the length of treatment. The balance of gains and harms of the treatment has been estimated to be so good that no further findings emerging on the effects of statin therapy are expected to alter it [366].

One branch of this study addresses the association of statin treatment adherence with mortality after CABG. The main finding was a significant overall risk reduction in all-cause mortality between high-adherent and medium-adherent and also between medium-adherent and non-adherent patients. This concurs with the results of a multitude of studies since the 1990s [4,170].

Pharmacy records have proven to be a useful method for assessing treatment adherence. This method is particularly suitable in statins and other drugs intended for long-term, constant use [367]. Data concerning other than statin medication in this study, in particular antiplatelet and antihypertensive medications, were not assessed. Also, the individual type and dosage of statins prescribed were not available; on the other hand virtually all statins on the market have proven their efficacy in CAD secondary prevention [350,368]. It is possible that the poor outcome of the patients not adhering to treatment with statins was explained not only by statin underuse but also, for instance, by underuse of prescribed medications in general [369,370].

In this study the data on statin use was limited to fifteen years. Nevertheless, according to the existing evidence it is likely that patients continued to take their medication in an approximately similar manner from that time on [371]. The good results of statin adherent patients must be due in part to the long use and exceptionally long, 20-year follow-up time in this study.

6.3.2 Evolution of statin treatment 1990 – 2009 in a non-university hospital (Kanta-Häme Central Hospital)

The praxis of statin's use in Finland, and particularly in one health care district of the main study, Kanta-Häme Health Care District, was addressed by means of a 20-year follow-up, since 1990. During this time period the following changes occurred in lipid treatment in sequence: 1) The percentage of patients with measured cholesterol levels, 2) the share of patients on statin therapy and 3) the efficacy of the therapy all increased consecutively. The DSDI of 2.86 ($\pm$0.41) during the very last year of observation corresponds to a mean daily simvastatin dose of 57 ($\pm$8) mg. The concentrations of LDL-C and of apoB, in which the latter reflects the number of atherogenic apoB-containing lipoprotein particles, decreased by 45% and 40% respectively.

The efficiency of secondary prevention of CAD in Europe has been evaluated in the Euroaspire studies. The Euroaspire II study was carried out in 15 European countries in the years 1999–2000 and also included CABG patients. Of these 42% had TC $<$ 5.0 mmol/l and 61% were on lipid-lowering medication [372]. At the same time the corresponding numbers in our patient population were 68% and 76% respectively. In an international cross-sectional study, the prevalence of lipid abnormalities was assessed in more than 22,000 European and Canadian patients on statin treatment in the period 2008–2009 [373]. In that study, 58% of cardiovascular high-risk patients had LDL-C $<$ 2.5 mmol/l. Their mean DSDI was 1.85, corresponding to a daily simvastatin dose of 37 mg [373]. These changes at the international level are parallel to the changes in our practice.

Although during the 20-year follow-up period the levels of total cholesterol in the Finnish population steadily decreased [374], the decrease in our patients was 3- to 4-fold greater when compared with that of the general population. These evidently beneficial changes are most likely partly due to lifestyle changes but also largely due to statin treatment.

The recent increase in the incidence of metabolic syndrome and diabetes has re-emphasized the necessity of obtaining additional data on atherogenic triglyceride rich lipoproteins like VLDL (remnants) and IDL and how to lower them.

The theoretical basis of statin treatment effect on Apo-B containing lipoproteins originates from the beginning of this century [375–377]. Our study confirms during a 20-year timespan the comparable reduction of VLDL-TG and IDL-C to LDL-C, corresponding to the increased statin dose. The HDL-C concentration grew simultaneously, and may also be regarded as an antiatherogenic change [376]. As far as we know, no observation of diminished IDL-C during gradually intensified statin treatment with lipid values taken and analysed over a 20-year timespan, has previously been reported.

It is also of interest that the changes in statin treatment mostly occurred before the publication of lipid lowering guidelines. This emphasizes the importance of active follow-up of high-impact professional literature and indicates the nature of the consensus statement of recommendations.

A limitation of this study is its retrospective nature, such that knowledge of possible statin intolerance is lacking, which is considered a notable problem in statin treatment. Although in observational studies as many as 10–30% of patients have reported muscle symptoms, most of them could be successfully treated with careful management [378–380]. During the last years of our study only about 2% of patients were not on statins. This may represent the maximal percentage of patients suffering from clinically relevant statin intolerance in this well-motivated patient population. A possible explanation for the success of statin therapy is the highly individualized care of the cardiovascular patients in our hospital. A corresponding figure has also been reported elsewhere [381,382].

In this study diabetogenicity of statin treatment was not analysed. During 10 postoperative years, patients got older and treatment practices evolved so that treatment of diabetes was initiated earlier. On the other hand, statin treatment may have had some influence on the increase of the use of antidiabetic medication for CABG patients over a 10-year postoperative period [165].

6.4 Survival after CABG (IV, V)

6.4.1 Impact of BMI

During the first postoperative decade the prognosis of overweight and obese CABG patients was as good as that of their background populations and better than that of normal weight patients. This phenomenon, called the obesity paradox, has been seen in a wide range of CAD manifestations including CABG patients [383–387].

Our finding was that the obesity paradox seems to be a consequence of too short follow-up. In obese CAD patients who had undergone CABG the initial prognosis was good but deteriorated when the follow-up period was extended to 20 years. There are several explanations. Obesity is often defined by BMI as it is an easily measurable parameter used in routine clinical practice. It has been criticized for its lack of accuracy in defining obesity hence it is an aggregate of varying amounts of fat-free mass and body fat [388,389]. Therefore people with low lean mass but increased body fat and conversely trained athletes with high body muscle mass may be misclassified by BMI.

Fat-free mass is widely considered a positive prognostic factor. CAD as a systemic disease can result in cachexia similar to that seen in heart failure [390]. Poor nutritional status has been shown to predict mortality after cardiac surgery [391,392]. Hence both fat-free mass and body fat may provide a protective metabolic buffer during the recovery period after CABG [393].

There are also other potential explanations for the obesity paradox. Obesity was earlier considered a perioperative risk factor in CABG [394]. It is therefore possible that high-risk obese patients, also in this study population, were excluded from revascularization, thereby creating a selection bias, as has been observed elsewhere [395]. Furthermore, it has been postulated that obese patients may receive better disease-modifying medication than do normal weight patients [384], although in our material they did not take significantly more ACE inhibitors, statins or ASA, according to the patient questionnaire.

The 20-year prognosis of overweight patients was better than the prognosis of normal weight and obese patients. Nevertheless, during the second follow-up decade their survival was also inferior to that of the background population. In our patient population diabetes was an important predictor of poor prognosis while 27% of overweight patients had diabetes (Table 4).

6.4.2 Impact of metabolic status

Obesity is associated with MetS and T2DM via lipid abnormalities, insulin resistance and glucose intolerance combining to form complex relationships, where interacting pathophysiological roles are not yet fully understood [77,78,396,397]. Insulin resistance leads to glucose intolerance if the pancreatic compensation processes are incomplete [398]. Glucose abnormalities with or without diabetes predict cardiovascular events and mortality, the risk being a continuum with increasing glycemia [399–401]. In UKPDS study with newly diagnosed T2DM patients, each 1% reduction in updated mean HbA1C was associated with reduction in risk of 21 % for deaths related to diabetes and 14 % for myocardial infarction [402]. Further, MetS has been shown to impair the prognosis of CAD patients [403].

Our principal finding was that obesity, MetS and T2DM are deleterious to the long-term prognosis of CAD patients. Concerning MetS and DM our results confirm those of earlier studies [332,404–406]. The excessive death rate in the second postoperative decade of both obese patients and those with DM in our material was mostly related to cardiovascular causes. Our results corroborate the notion that long-lasting DM in particular is associated with a high risk of recurrent ischaemic coronary events [210,337,407,408].

6.5 Methodological considerations and study limitations

6.5.1 Strengths

Patients in the follow-up studies represent the expert responsibility area of Tampere University Hospital, one of the five university hospital districts in Finland, comprising totally more than one million inhabitants. The Tampere area has been one of the central migration destinations in the urbanization of Finland after World War II, thus representing a broad genetic view of the Finnish population.

The strengths of the follow-up study are the reliability and scope of the national registers used, allowing 100% coverage of the retirement, medication and mortality data [409]. Our follow-up includes all the subjects with CABG, including those who migrated within the country and even one patient who relocated to a neighbouring country. The length of the individual postoperative follow-up was exactly 20 years for all patients, enabling conclusions more reliable than those based on a shorter follow-up. In Finland unregistered and thus uninsured individuals did not present a health care problem during the study period, nor did they cause a possible bias in our results [410].

Concerning the cohorts study, between 1990 and 2010, Kanta-Häme Central Hospital has had a fairly stable catchment population without any significant national or international migration. Thus the genetic and ethnic backgrounds, two factors of potential importance considering the length of time analysed and the limited size of the study sample, have remained stable [411].

6.5.2 Limitations

Certain limitations should also be considered. Firstly, the perioperative data were collected retrospectively. Consequently, the researchers had to rely on medical records. Even though information was supplemented with patient questionnaires and direct contacts, one patient in Study IV (BMI) and 13 (1.4%) patients in Study V (DM/MetS) out of the 923 patients alive two months postoperatively were excluded due to insufficient data.

Secondly, in the follow-up study the observed survival rates of the study groups were compared to the rates based on age-, gender- and (operation) time-specific life tables for the whole population of Finland. This made comparisons between study groups easier, nevertheless ignoring some risk factors and concomitant diseases (Table 2). Partly due to this, statistically reliable results could not be obtained in smaller patient groups, such as women who returned to work.

Thirdly, in the definition of metabolic syndrome obesity (BMI $\geq$ 30 kg/m^2) was used instead of waist circumference. However, BMI is widely used in the definition of MetS and studies have demonstrated concordance between various definitions [75,344,331].

Lastly, the diagnosis of diabetes was based on either diabetes according to antidiabetic medication or elevated glucose values at the time of the operation or in follow-up study also according to the Kela special reimbursement database during the first decade after CABG. The latter definition was used because in the 1990s and early 2000s patients often had dietary therapy before antidiabetic medication. The patients with later glucose lowering medication probably had diabetic metabolism already during the first postoperative years and were therefore included in the group of patient with DM. However, due to the definition some patients may have been misclassified as regards diabetic status.

In addition, the cohorts study was a single-centre study and thus does not represent postoperative treatment of Finnish CABG patients in general. On the other hand, this may also constitute a strength in addressing results achieved with active secondary preventive treatment.

7 SUMMARY, CONCLUSIONS AND FUTURE PROSPECTS

At the beginning of the 1990s, most modern CABG techniques were already established, including myocardial protection during the operation and the use of arterial grafts. The benefits of secondary prevention in hindering progression of CAD in native coronary arteries as well as in venous grafts were known. The use of aspirin and β-blockers was well-established. The significance of statin therapy and ACE inhibitors would be revealed in the following years beginning with the 4S Study in 1994. Most CABG patients are still currently treated according to the same principles as in the late 1990s. Thus in many ways the findings of this study remain valid today.

In the present study the postoperative prognosis of CABG patients was studied for up to 20 years. The results can be summarized as follows:

1. Almost 60% of patients, who were not retired preoperatively, retained their working capacity after surgery. The best predictors of resuming work postoperatively were younger age, preoperative working as well as absence of diabetes and perioperative cardiac damage.

2. Having once returned to work, patients' retention at work was comparable to that in the general population with sharply increasing retirement at the age of sixty. This study also introduces a model which estimates the probability of remaining at work postoperatively including age, postoperative cardiac symptoms, diabetes and some nonmedical variables.

3. Among CABG patients both statin use and the doses prescribed have increased considerably since the beginning of the 1990s, the effective dose being 36-fold at the end of the 20-year follow-up period. This change in treatment practices has *de facto* halved the mean serum concentrations of LDL-cholesterol and apolipoprotein B. The changes in statin treatment practice mostly took place immediately after the publication of statin mega-trials justifying the use of new validated treatment methods.

4. The survival of overweight patients was as good as that of their age-, gender- and CABG-year-specific background populations for 15 years but deteriorated slowly thereafter, which may be associated with the significant number of patients with DM in that group. The obesity paradox, standing for unexpectedly good prognosis, disappeared soon after the first 10 postoperative years due to increasing cardiovascular mortality.

5. Metabolic syndrome is a cluster of cardiovascular risk factors, impairing the long-term prognosis of CABG patients. The deleterious effect of diabetes was worse than that of MetS without clinical diabetes. At the end of the 20-year follow-up, only half of the patients with DM were alive compared to their matched background populations. Those CABG patients who had neither diabetes nor MetS had prognoses as good as those of their matched background populations.

Additionally it was found that regular statin use for more than 50% of the postoperative follow-up time correlates positively with good prognosis. The poor prognosis was especially prominent among statin non-users, although part of it may be attributable, for instance, to low adherence to preventive measures in general.

Ability to work is a crucially important measure of quality of life. This study suggests the significance of prompt operative treatment of CAD patients, because besides patients' age, time spent on preoperative sick leave predicts resuming work. Several non-medical factors including psychosocial elements are also important in employment after MI and its operative treatment [298,306]. These nonmedical limitations of postoperative employment have not yet been fully ascertained and thus would benefit from further research.

When studying adherence, patients' non-adherent to statins had the worst prognosis. This finding may reflect the insufficient use of medications and other means in general [370]. We live in a time of "isms", internet and social media. Besides beneficial information, this exposes patients to non-evidence-based advice, even hearsay. Public campaigns and preventive educative presentations for CAD patients may be useful in explaining the difference between evidence-based medicine and hearsay and to improve the use of CV medications.

Implementation of new methods in clinical practice is often delayed. In the cohorts study, it was shown that with precise and individualized treatment almost all patients could obtain proper statin medication. This can probably be extended to all CV medication. It also includes effective preventive education of CAD patients.

Integrating evidence-based medical decision support tools directly into provider workflow in the electronic health records has already been studied in selected patient groups [412]. This kind of new technology is also worth of research on a wide scale in CAD patients.

At the time of the operation, 14% of the patients had the diagnosis of DM. Ten years later, 28% were being treated with antidiabetic medication. In addition, patients with diabetes had the worst prognosis in the follow-up study. One message of this study is that prevention of DM is of key importance for the secondary prevention of CAD. Further, likewise important is effective treatment of conditions predisposing diabetes in CAD patients, like obesity and MetS. New pharmacological treatments for T2DM offer promising results for the reduction of CVD burden among patients with T2DM. Further trials to evaluate the practices of prevention and treatment of T2DM in CAD patients are of interest in order to individualize and optimize their therapy.

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Appendix I

Parameters used in the analyses of working and 20-year mortality. P-values refer to univariate predictors of mortality according to BMI.

Preoperative Characteristics	***P-value***
Sex	NS
Age	p<0.0001
BMI group	p<0.05
CV disease heritage	p<0.05
DM	p<0.0001
Preoperative hemoglobin concentration	p<0.01
Preoperative kidney function	p<0.01
Central vascular disease (mainly stroke)	p<0.01
Peripheral vascular disease	p<0.0001
Hypertension	p<0.01
Congestive heart disease	p<0.0001
Atrial fibrillation	p<0.001
Obstructive pulmonary disease	NS
Number of myocardial infarcts	p<0.01
Earlier PCI	NS
Earlier CABG	NS
Ejection fraction	p<0.05
NYHA class	p<0.001
S-Cholesterol	p<0.05
S-HDL-cholesterol	NS
FS-Triglycerides	NS
Preoperative lipid lowering medication	p<0.01
Smoking	NS
Patients height	p<0.001
Characteristics of CABG	
Three-vessel disease	p<0.01
Left main disease	NS
Number of grafts	p<0.01
Use of arterial grafts	p<0.01
Concomitant operation	NS
Urgent or emergency operation	p<0.05
Creatinine kinase	p<0.05

Appendix II

Questions from the 51-item questionnaire used as supplementary parameters in the multivariate analyses of postoperative working.

1) Oletteko?
   1 Naimaton
   2 Naimisissa tai avoliitossa
   3 Eronnut tai asumuserossa
   4 Leski

2) Asutteko nykyisin?
   1 Kotona yksin
   2 Kotona muun perheen kanssa, keiden?____________________
   3 Vanhustentalossa tai palvelutalossa
   4 Laitoksessa (esim. vanhainkoti, terveyskeskuksen vuodeosasto)
   5 Muualla, missä? _____________________

3) Jos asutte muun perheen kanssa, kuinka usein teette **itse** kotiaskareita?

   1 Hoidatte itse kotiaskareet (siivous, ruuanlaitto, kaupassakäynti ym.)
   2 Autatte kotiaskareissa jokseenkin päivittäin
   3 Autatte kotiaskareissa viikoittain
   4 Autatte kotiaskareissa harvemmin kuin viikoittain
   5 Ette kykene sydänsairauden vuoksi tekemään kotiaskareita

5) Mikä on peruskoulutuksenne?
   1 Kansakoulu tai osa siitä
   2 Keskikoulu tai peruskoulu
   3 Ylioppilastutkinto

6) Mikä on ammattikoulutuksenne
   1 Ei ammatillista koulutusta
   2 Ammatillinen koulu tai koulutasoinen ammatillinen tutkinto
   3 Opisto tai opistotasoinen ammatillinen tutkinto
   4 Korkeakoulu
   5 Muu koulutus. Mikä? ________________________________

15) Leikkauksen jälkeiset rintakivut
   1 Minulla **ei** ole ollut rintakipuja leikkauksen jälkeen
   2 Minulla **on ollut** rintakipuja ja lääkärini on pitänyt niitä sydänperäisinä
      Mistä alkaen niitä on esiintynyt? __________________

3 Minulla on ollut rintakipuja, mutta lääkärini on pitänyt niitä muualta kuin sydämestä johtuvina
4 Minulla on ollut rintakipuja, mutta **en ole vielä** puhunut niistä lääkärilleni

18) Käytättekö **nykyisin** nitroa kielen alle tai suihkeena?
1 Ainakin kerran vuorokaudessa
2 Ainakin kerran viikossa
3 Ainakin kerran kuukaudessa
4 En tarvitse nitroa nykyisin

25) Mikä on painonne nykyisin? _________ kg
1 Painoni on pysynyt ennallaan viimeisen 6 kk aikana
2 Painoni on laskenut viimeisen 6 kk aikana, _______ kg
3 Painoni on noussut viimeisen 6 kk aikana, _______ kg

37) Tupakointi
1 En ole tupakoinut koskaan
2 Tupakoin edelleen
3 Olen tupakoinut aiemmin. Lopetuspäivämäärä? ___________
Olen tupakoinut yhteensä ______ vuotta

ORIGINAL PUBLICATIONS (I – V)

I

Return to work after coronary artery bypass surgery. A 10- year follow–up study

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Key words: *Coronary artery bypass, pensions, treatment outcome, rehabilitation*

Abstract

Objectives To establish which factors influence patients' return to work and how well they remain at work after coronary artery bypass grafting (CABG).

Design 569 consecutive CABG patients aged less than 65 years were followed for 10 years. Data were collected from patient records and by questionnaires supplemented with information from Finnish national archives.

Results Multivariate analysis showed the best predictors for return to work to be younger age, preoperative working, as well as absence of diabetes or perioperative cardiac damage. Almost half of the patients aged less than 60 and preoperatively not retired were working one year after CABG.

Five years postoperatively, 85% of patients younger than 60 years and once returned to work were still working. Correspondingly, of subjects remaining under 60 years during a 10-year follow-up, 75% continued working.

Conclusions Younger age and preoperative employment were the most important predictors of successful return to work. Once returned after CABG, patients' staying at work was comparable with that in the general population.

Introduction

Coronary artery bypass grafting (CABG) is an effective treatment for patients with symptomatic coronary heart disease (CHD). It alleviates angina pectoris and improves the life expectancy of patients with multivessel CHD. Most patients' physical capacity and quality of life are significantly enhanced. [1]

However, many CABG patients still of working age have retired before surgery, and only half are working postoperatively. [2,3] During the first postoperative year 20% to 30% have angina pectoris symptoms [4] and seven per cent experience neuropsychological defects as determined six months after surgery. [5] Results may be improved using off-pump coronary artery bypass grafting. [6]

One fifth of patients treated by CABG have reported their quality of life to be postoperatively no better than before the procedure. [7] Subjective well-being is not related to physical status. The reasons for difficulties in returning to work are multifactorial, and even freedom from symptoms does not necessarily mean that a patient will return to work postoperatively. [8]

The direct and indirect costs of coronary heart disease are enormous. Besides the financial burden, loss of leisure time activities and psychological stress are other significant losses for patients. [9] The restoration of normal functional capacity and quality of life, in which the resumption of professional activity is an important element, can be considered a major objective of coronary surgery. [10]

The aim of the Working after CABG (W-CABG) study was to ascertain what pre- or perioperative factors influence patients' return to work after CABG. We also studied how well patients once successfully returned to work continued at work.

Material and Methods
Subjects

CABG was undertaken for 960 patients in Tampere University Hospital from January 1, 1993 to June 30, 1994. The study population (age <65 years) consisted of 569 (59%) consecutive patients undergoing CABG. The catchment population of the hospital was 1.2 million inhabitants living in southern Finland, comprising about 22% of the total population of Finland.

After the first postoperative days patients were sent to their local hospitals for further recovery. They were discharged 10 to 14 days after the operation if no complications occurred. They attended a cardiology or internal outpatient clinic 1 to 2 and 3 to 4 months after the operation. ECG and basic laboratory parameters were then analysed. After a few postoperative months, most patients were transferred to primary care for secondary prevention. W-CABG study personnel checked hospital records after the transfer to primary care.

Data collection and follow-up

Pre- and perioperative anamnesis and morbidity were collected manually from the patient records in Tampere University Hospital. Data on the first postoperative months were collected from the patient records in the hospitals responsible for follow-up. Diagnoses of hypertension, claudication, previous myocardial infarction, and previous transient ischemic attack (TIA) or stroke were also noted. A patient was defined as having type 1 or type 2 diabetes mellitus (T1DM or T2DM) when on appropriate antidiabetic medication. Hypercholesterolemia was diagnosed when a patient was on lipid-lowering drug therapy or had total cholesterol ≥5 mmol/l. Smoking habits were established by questionnaire 21 months postoperatively.

The first follow-up data collection was made with a detailed questionnaire in July 1995, i.e. on average 21 (range 12 – 30) months after the operation. A repeat questionnaire was sent two months later when necessary (response 86% of patients). Especially employment status, heart symptoms and clinical course of CHD were asked. Subjective well-being against patients' expectations as well as risk and protective factors were also evaluated.

The second follow-up was made almost identically to the first during the year 2003, i.e. 9 to 10 years after the operation (response 83% of patients). Both times the follow-up included contact by phone if there was a need to clarify answers. Working status and other relevant information was obtained from all but two patients.

Possible death, its date and diagnosis were checked from the Statistical Office of Finland. Employment status or the date and the reason for possible retirement were checked from the Finnish Centre for Pensions 10 years after the last operation.

In Finland the retirement rate increases rapidly at the age of 60 years. Over 70% of unselected Finns work at 55 – 59, as against only 35% of those aged 60. Thus other than medical reasons seem to incline strongly towards retirement at that age. In analysing staying at work we therefore decided primarily to confine attention to patients still younger than 60 years during the follow-up (n= 372 at the time of CABG). The results were compared with the pensioning rate among a matched Finnish population. [11] The study was approved by the Ethics Committee of Tampere University Hospital.

Statistical methods

Categorical variables were tested using chi-square test and Wilcoxon test (return to work vs. pre-, peri- and immediate postoperative medical data, education, type of work, preoperative pensioning, patients' social situation and lifestyle elements such as exercise habits and smoking). A stepwise Bayesian approach with an analysis system created by one of the authors was used as multivariate analysis to determine posterior probabilities and likelihood ratios and to ascertain the sensitivity and specificity of the rule. [12] The model was calculated taking into account all patients alive twelve months after CABG. Patients were considered returnees to work if they were working at that time.

Results

Study material

Altogether 569 patients younger than 65 years underwent CABG during the study period. Patients' demographic data and job classification are shown in Table 1a. Clinical characteristics and severity of coronary heart disease are compiled in Table 1b.

A valvular operation was carried out for 3.7% (21 patients) and carotid endarterectomy for 0.4% (2) in the same operative session as CABG. Perioperative mortality was 2.2% (13). In addition, 2.1% (12) died during the first postoperative year. Of these 25 patients, 20 were already pensioned preoperatively and five died before return to work or retirement. Thus all together 544 patients (96%) remained alive one year postoperatively.

Return to work after CABG

Altogether 53 % (301) of patients younger than 65 years were pensioned preoperatively, forty-three of them having retired less than six months before the operation. The remaining 47 % (268 surviving patients) were working, unemployed or on short-term sick pay. Of those, 145 were working after the first postoperative year. The remaining 123 retired immediately after postoperative sick pay without returning to work or after only a couple of months working. Of preoperatively pensioned patients only six returned to work, while 295 remained pensioned after CABG. Hence, altogether 151 patients were working one year postoperatively (Figure 1).

Among patients younger than 60 years (n = 331), 43% (141) were working one year postoperatively, while 28% (93 patients) had been pensioned preoperatively without returning to work and 28% (94) retired during the first postoperative year. One per cent (3) of the non-pensioned patients died perioperatively or during the first postoperative months (Figure 1).

Factors affecting return to work

In univariate analysis, the most important factors affecting return to work were patient's age and duration of pensioning or cash rehabilitation benefit ($p<0.001$). There was an inverse correlation between age and return to work. At the age of 55 years preoperatively non-pensioned patients' return to work began to diminish rapidly. When the age was less than 50 years at the time of CABG, 70% returned and were successfully working one year postoperatively, while the figures for older age groups, 50 to 54, 55 to 59, and 60 to 64 years, were 64%, 48%, and 21%, respectively.

The mode and length of preoperative sick pay or pension was related to return to work as follows. Most patients (71%) being preoperatively only briefly on sick pay returned to work. Return took place in 9% of cases pensioned for less than six months as against only 1% of those pensioned for a longer time.

In univariate analysis higher basic education and absence of a history of TIA or stroke also predicted return to work ($p<0.001$). Patients' high total cholesterol, DM, high preoperative NYHA classes III-IV, and low ejection fraction seemed somewhat to diminish the return rate ($p<0.01$) (Table 1a and 1b). Short height (173.9 cm (SD 6.1) *vs.* 175.4 cm (SD 6.1) for men and 159.9 cm (SD 5.6) *vs.* 162.3 cm (SD 5.3) for women) and a family history of cardiac disease (78% *vs.* 84%, $p<0.01$) were also associated with reduced return rate. However, for example postoperative heart symptoms were not associated with return to work.

In stepwise Bayesian multivariate analysis, best sensitivity was found for a model which included only patient's age and pensioning. The specificity increased when history of diabetes mellitus as well as signs of perioperative myocardial damage were added. In this model sensitivity was 94% and specificity 75% (Table 2).

Staying at work

Analysis of continued employment involved patients at work one year postoperatively. All together 141 patients (13 women) out of 151 working postoperatively were younger than 60 years at the beginning of follow-up and 56 remained under 60 years of age 10 years after CABG. Of these 67% were still working full-time and 8% part-time, while 25% had retired on disability pension before the end of the 10-year follow-up. The postoperative follow-up of employment status (until Dec 31, 2003) is presented in Figure 2.

Looking at patients still alive 5 years postoperatively, 101 were under 60 years and 35 were 60 – 64 years. Of the former age group 80% were working full-time and 5% part-time. Altogether 15% were pensioned. After the age of 60 the retirement rate increased rapidly and in the age group 60 – 64 years only 34% were working full-time and 6% part-time (Figure 3).

We also compared patients five years after the operation with an unselected Finnish population, the material being obtained from the Finnish Centre for Pensions. It emerged that those CABG patients who had successfully returned to work stayed at work as well as did unselected Finns of the same age and gender (Figure 3).

Discussion

Principal findings

Follow-up of patients remaining under 60 years revealed that one fourth retired preoperatively and one fourth during the first postoperative year, while almost half successfully returned to work for a longer period. In multivariate analysis the best predictors for return to work were younger age, preoperative working, and absence of diabetes or perioperative myocardial damage.

After 5 years, pensioning of patients once successfully returned to work did not differ from that in the matched general population. Furthermore, 75% of patients aged <60 years were still working 10 years postoperatively.

Strengths and weaknesses of the study

The W-CABG study represents as far as we know the longest follow-up of CABG patients' staying at work. In general, the relatively high age of operated patients may be the major reason for the lack of longer follow-up data on patients' working status after CABG. A long follow-up is time-demanding, and patient drop-outs may constitute a serious problem for the accuracy of studies. The precision of national statistics and the willingness of patients to fill in questionnaires certainly helped us during the present study.

We analysed data on all consecutive patients operated over a period of 18 months. The catchment area of the study population contained more than 20% of the country's inhabitants. Patients came from both industrial and agricultural municipalities, well representing the Finnish population.

The study commenced with a retrospective analysis of patient records. Data were checked with written patient questionnaires and telephone contacts. Follow-up data on pensioning and mortality were also verified from national archives. In Finland as in other Nordic countries official statistics are particularly precise. Even after these measures some data might be missing, for instance if an individual patient record has contained errors and the subject has given insufficient information. We sought to ensure that this would cause no bias.

Differences in relation to other studies

Return to work

According to several studies carried out in the USA and Europe, return to work after CABG has been between 50% and 84% [3,13,14], and has not changed during the last 20 years. [10] In earlier Finnish CABG series, 40% to 60% of non-retired patients resumed work postoperatively. [2,15] However, very few pensioned patients seem to return to work. The possibility of a disability pension may influence postoperative return. [8] When considering only non-pensioned patients' return to work, our results were comparable with those in international studies.

Factors predicting return to work

Similarly to other investigators' findings, patients' age was here an important predictor of return to work. [3,8,10,16,17] Among patients at the age of 55 the return rate diminished fast, and when the age of 60 was reached the decrease became even steeper.

The national unemployment rate may affect patients' return to work. [16] Recently, the highest retirement rates in Finland (over 80% among those aged 60 to 64 years) were found during the years 1993 – 97, i.e. when a deep economic depression affected the country. [11] The postoperative recovery and rehabilitation phase of W-CABG patients fell during this same period. Though pensioning of younger subjects was fairly low in our study, the economic depression may have affected older patients' return to work. A high unemployment rate may reduce an individual's social activities and motivation to take an active part in the rehabilitation process. [16] Patients' own wish to return to work and employers' attitudes towards the re-employment of a disabled worker also have their effects on the probability of an individual's retirement. [17] It is conceivable that these factors together have an even greater impact on return to work than the medical reality.

In a Swedish study older age was found to be associated with a lower rate of return to full-time work but not with reduced working hours after CABG, PCI or myocardial infarction. [16] In Finland likewise some 20% of CABG patients have also earlier returned to an easier job. [15] In our study patients mainly returned to their previous employment and on average only 6% worked reduced hours during the 10-year follow-up. This rigidity in working life may also explain the retirement of patients with limited working capacity.

Preoperative working status was a very important baseline predictor for postoperative employment status. Our findings are in accord with those in earlier studies, where both pensioning [3, 18] and the length of preoperative sick leave [18] have been found to be highly significant predictors for return to work.

Preoperative DM and perioperative myocardial damage were related to return to work. Our definition for DM might contribute to a fairly small proportion of T2DM. According to this study, at least DM treated medically is related to pensioning. Also elsewhere DM has been found to predict poor resumption of work. [19] On the other hand, perioperative myocardial damage has not previously been confirmed as an independent predictor of postoperative retirement. Perhaps it should be understood above all as a sign of diffuse vascular disease. Contrary to some earlier findings, for example job characteristics or gender were not predictive for return to work in our study. [3,19]

Staying at work

In Finland, the retirement rate increases rapidly from the age of 60 solely for non-medical reasons. We therefore decided to follow patients in four age groups in order to reduce the effect of age as a confusing factor.

Five years after the operation 85% and ten years after the operation 75% of patients still under 60 years were engaged in working life (Figure 2). Staying at work among our CABG patients did not differ significantly from that in a matched general Finnish population. [11] In an earlier Finnish study, where a rehabilitation program was compared to usual care, only 39%, i.e. 23 out of 59 patients working one year postoperatively, were still working 4 years later. [2] According to patients' reports, cardiac condition was the most important reason for not working. In a British study more than 20% of patients working at 12 months postoperatively discontinued during the following four years on account of health and for other reasons not related to old age pension. [3] In an American study 51% of 177 CABG patients already returned to work retired on account of health problems and factors other than pension during a 4-year follow-up. [14]

One reason for our patients' relatively good persistence at work might be the steeply increased use of cardiac medication, notably statins and ACE inhibitors. Another explanation might be that in Finland only those patients returned to work who really felt able to work. In the early 90s it was still relatively easy to obtain a disability pension after CABG compared with many other chronic diseases.

When compared to a matched general population, CABG patients once successfully returned to work kept on working as well as the general population of the same age and gender. The only differences were seen in the youngest and oldest age groups, where the small number of patients might accidentally have influenced the outcome (Figure 3).

Meaning of the study

The W-CABG study, with a 10-year follow-up, is in a certain sense out of date, in that CABG took place in the last decade. Desirable shortening of waiting lists, improved operation techniques, novel pharmacological preconditioning of the heart during CABG, and aggressive preventive drug therapy with statins and ACE inhibitors have improved the prognosis of CHD patients. [21-24] However, without studies with a sufficiently long follow-up we cannot be assured of the effects of CABG in real life. Thus, only patiently conducted systematic research may resolve this uncertainty.

If the prognosis of coronary heart patients is to be substantially improved, there is still a continuous need to intensify preventive drug therapy. [25] Besides medical therapy, increased use of percutaneous coronary intervention with stenting as treatment for coronary stenosis and occlusion has changed the operational environment in the invasive treatment of CHD. [26] CABG has still an important place in this context. [13,26] Studies concerning the effect of shortening waiting lists on the comprehensive prognosis of CABG patients are thus urgently needed.

To conclude, age, preoperative retirement, diabetes mellitus, and perioperative myocardial damage negatively predicted return to work among CABG patients. However, patients once successfully returned had very good chances of remaining in working life until their usual pensioning age. For probable returnees to work shortening of preoperative waiting time as well as postoperative support and rehabilitation are thus clearly justified.

Acknowledgements

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Table 1a: Demographic data and job classification at the time of CABG

	Female patients <65 years working one year after CABG (n = 13) %	**Male patients <65 years working one year after CABG (n = 138)** %	**Patients <65 years working one year after CABG (n = 151)** %	**Patients <65 years not working one year after CABG (n = 418)** %
Age				
< 50	31	38	38	17 **
50 - 54	31	33	33	19 **
55 - 59	31	25	25	29 **
60 - 64	7	4	4	35 **
Education				
Less than high school	82	68	69	78 *
High school graduate	9	21	20	16 *
University graduate	9	11	11	6 *
Job classification				
Manual worker (Factory or construction work)	43	43	42	43
Employee lower level (salesperson, nurse)	17	17	17	16
Employee higher level (teacher, engineer)	16	16	16	14
Farmer	5	5	5	8
Employer or entrepreneur	19	19	20	19

There were no significant differences between male and female patients.
The asterisks represent significant differences between patients working and not working one year after CABG as follows: * $p < 0.01$, ** $p < 0.001$.

Table 1b: Clinical characteristics and severity of coronary heart disease before CABG

	Female patients <65 years working one year after CABG (n = 13) %	Male patients <65 years working one year after CABG (n = 138) %	Patients < 65 years working one year after CABG (n = 151) %	Patients <65 years not working one year after CABG (n = 418) %
Concomitant diseases				
Hypertension	77	34	38	43
Hypercholesterolemia	90	91	91	86 *
Diabetes mellitus	23	4	5	11 *
Previous MI	70	62	63	67
Previous TIA or stroke	0	3	3	9 **
Intermittent claudication	0	4	3	8
Preoperative smoking	27	60	57	65
Cardiac function				
EF 35 to < 50 %	8	9	9	12 *
EF < 35 %	0	3	3	7 *
NYHA II	8	19	18	14 *
NYHA III	59	65	65	61 *
NYHA IV	33	16	17	25 *
Severity of CHD				
Three–vessel disease	31	49	47	53
Left main disease	8	10	10	13
Elective operation	83	86	86	75
Urgent operation	17	12	12	19
Emergency operation	0	2	2	6

(MI = myocardial infarct, TIA = transient ischemic attack, EF = ejection fraction, NYHA = angina pectoris symptoms according to New York Heart Association, CHD = coronary heart disease)
There were no significant differences between male and female patients. The asterisks displayed as in Table 1a.

Table 2 Probability of being at work one year after CABG (n = 151 out of 544)

Pension before CABG	No pension	LR = 3.89
	< 6 months before CABG	LR = 0.34
	≥ 6 months before CABG	LR = 0.03
Age at the time of CABG	< 45 years	LR = 10.4
	45 – 49 years	LR = 2.86
	50 – 54 years	LR = 2.28
	55 – 59 years	LR = 0.80
	≥ 60 years	LR = 0.09
Diabetes mellitus	No DM	LR = 1.08
	T1DM	LR = 0.50
	T2DM	LR = 0.31
Signs of perioperative myocardial damage	No damage	LR = 1.07
	Damage*	LR = 0.63

LR = likelihood ratio. For an individual patient, the model is used by multiplying the patient's LR by all characteristics described. The greater LR is the better is the possibility of returning to work. LR may be expressed as percentage probability as follows:
p = 100 * LR/ (1+LR). Critical value of LR is 1.00 (Sensitivity of the rule 94%, specificity of the rule 75%). Total error rate of the model 20%.

* Damage = ECG or biomarker changes related to perioperative myocardial infarct or postoperative low output situation.

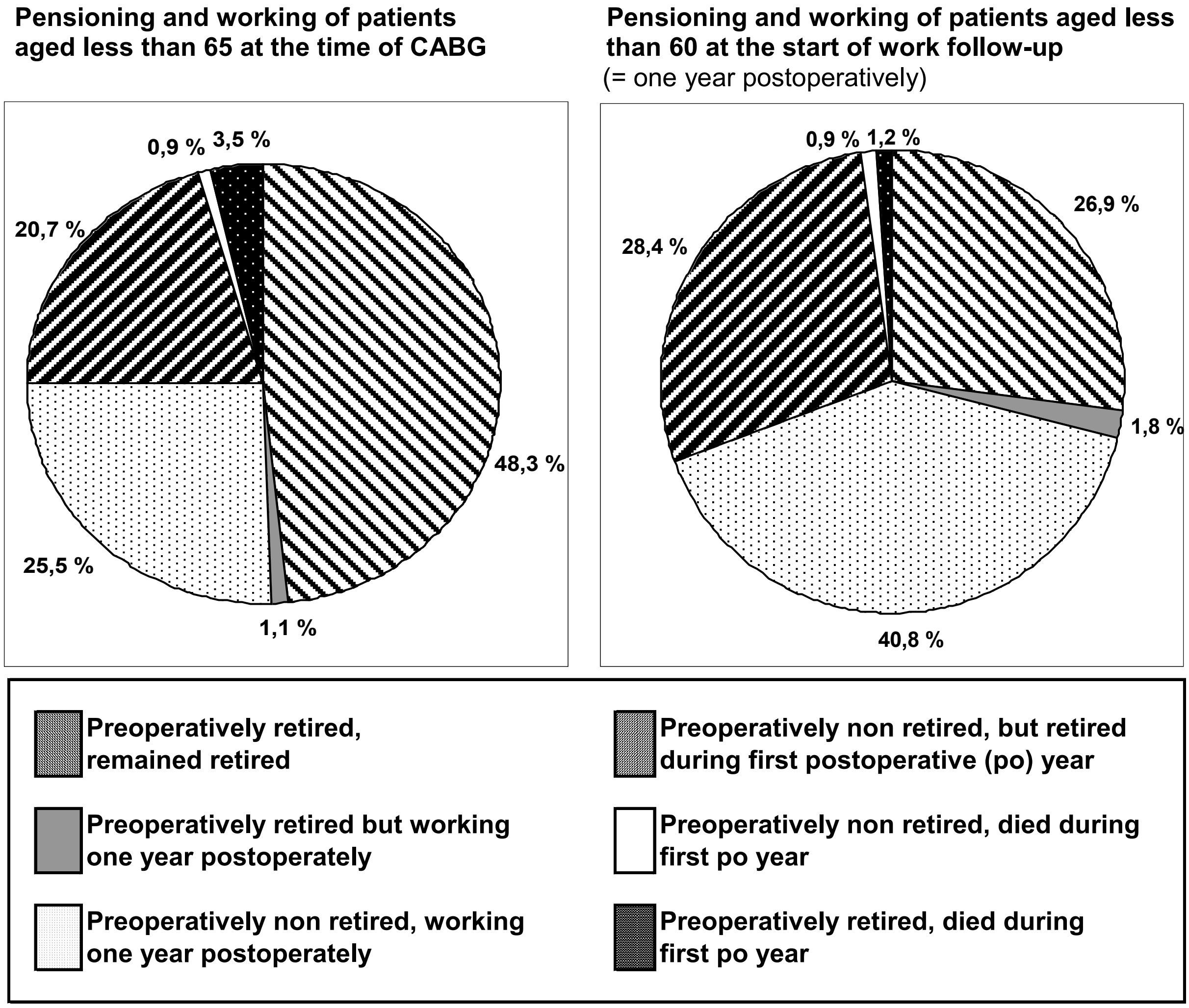
FIGURE LEGENDS

Figure 1 Patients' pensioning and working.

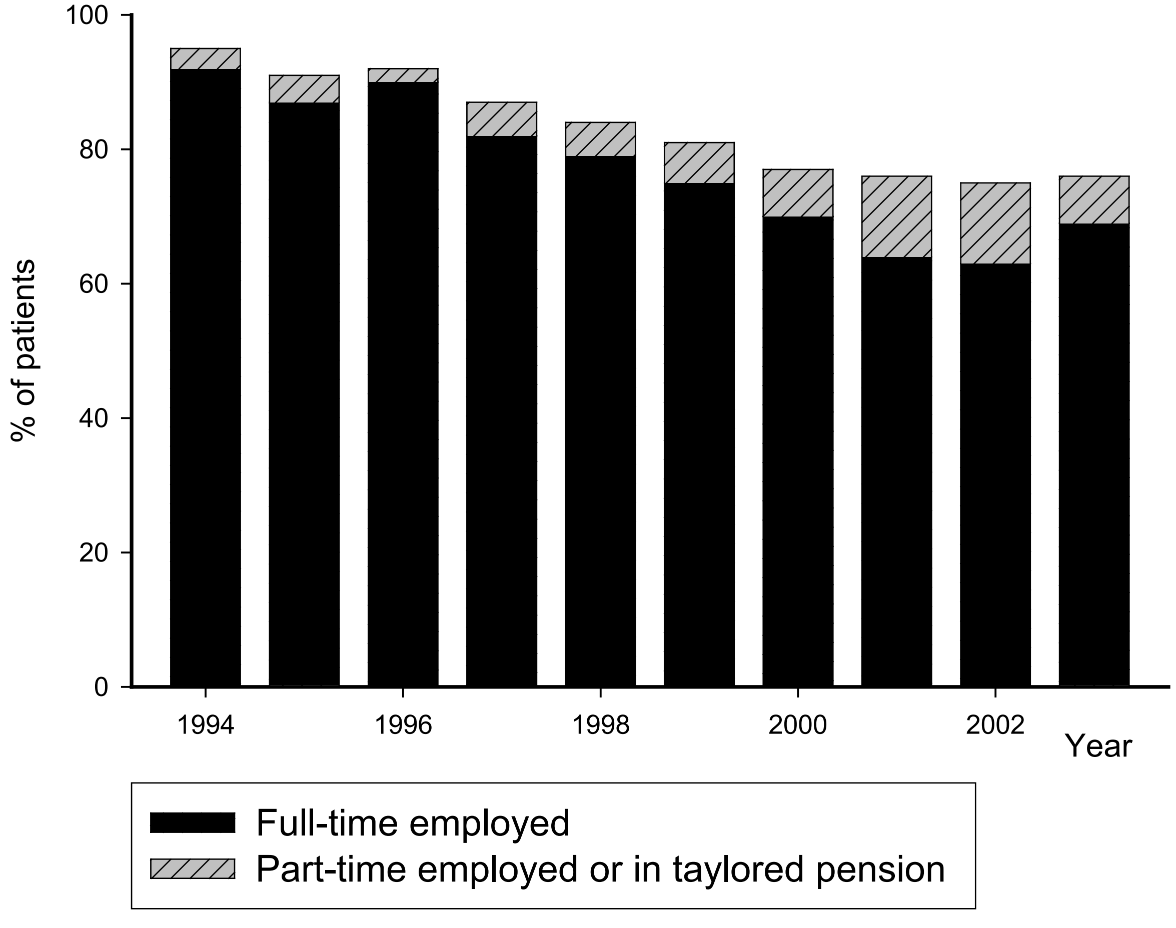
Figure 2 Postoperative employment status at the end of each calendar year. A 10-year follow-up of originally 141 patients (56 at the end of follow-up) who were working one year postoperatively and remained under 60 during the follow-up. Deceased persons, all together eight are excluded.

Figure 3 Pensioning status of those CABG patients who returned to work (n=136), on average five years after operation (Dec 31, 1998) together with unselected Finnish population, age and sex standardized.[10]
Age groups: 30 – 49 y (n = 22), 50 – 54 y (n = 31), 55 – 59 y (n = 48), 60 - 64 y (n = 35).

Hällberg et al, Figure 1



Hällberg et al. Figure 2



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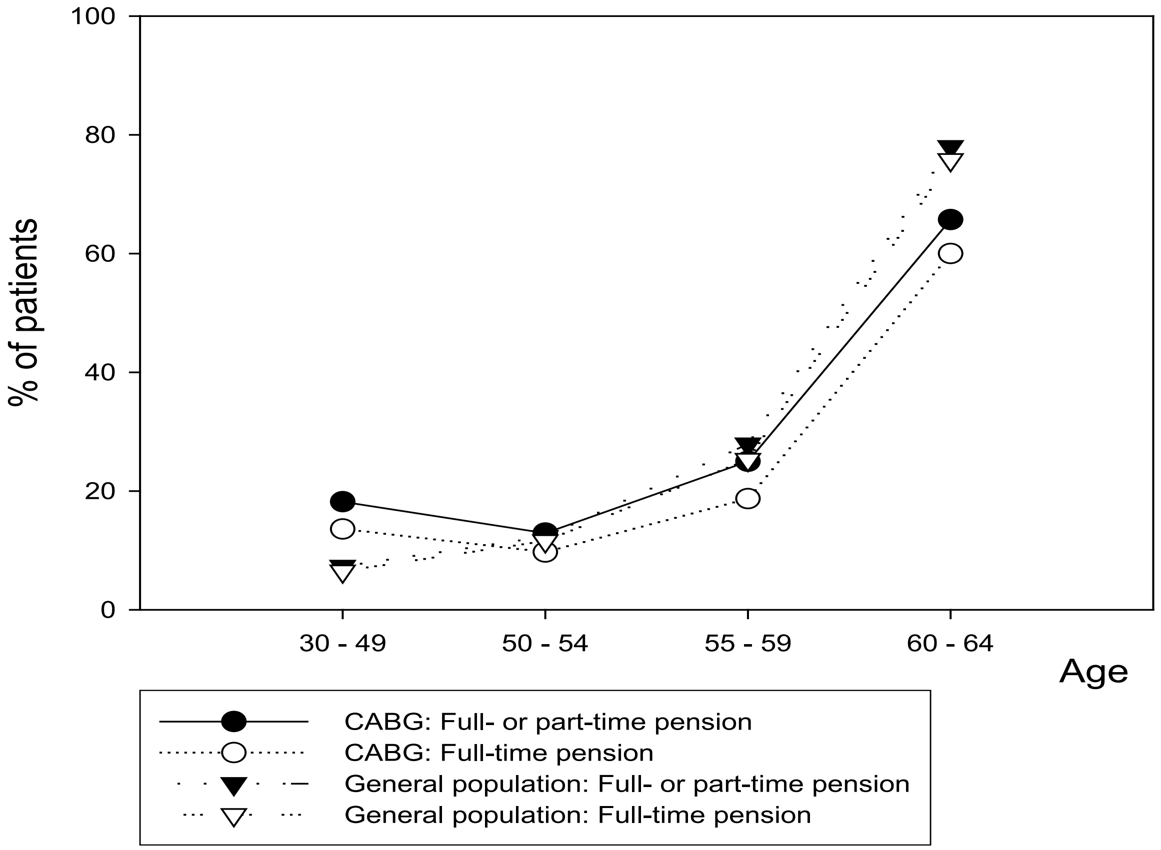

II

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Research article

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Retention of work capacity after coronary artery bypass grafting. A 10-year follow-up study

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Background

The major objectives in coronary artery bypass grafting (CABG) are restoration of normal functional capacity and quality of life as well as resumption of professional activity [1]. Factors predictive for return to work after CABG have been examined in various studies and are fairly well known. Return rates vary widely around the world, due to various factors such as different sick insurance systems, labour market conditions and sick listing traditions among physicians [2]. Only few studies have focused specifically on retention of work capacity after CABG.

In the earlier part of the Working after CABG (W-CABG) study we examined return to work and the length of continuation in a Finnish CABG patient population. According to the follow-up of patients remaining under 60 years, almost half returned to work successfully for a longer period. One fourth retired preoperatively and one fourth during the first postoperative year. After 5 years, pensioning of patients once successfully returned to work did not differ from that in the matched general population [3].

Aims of the present study

In this paper we report postoperative continuation in work life among men and women aged less than 60. It was of special interest to evaluate the following aspects:

1) Which factors influence patients staying on? Why do people who have resumed work after CABG retire prematurely?

2) What kind of model would help to estimate patients' possibilities of staying at work?

Methods

Material

The population of the W-CABG study has been described elsewhere [3]. Briefly, CABG was undertaken for 960 patients in Tampere University Hospital during a period of 18 months. The subjects of the present study comprised 141 consecutive patients aged less than 60 who had undergone CABG and were working one year postoperatively.

Data collection

Study personnel checked hospital records after transfer to primary care. The follow-up checks were made with a detailed questionnaire on an average 21 months after the operation and 9.5 years after the operation. The reply percents were 89 and 83 of patients alive, respectively. Working status and other relevant information was obtained from all but two patients.

Employment status or date and reason for possible retirement were checked from the Finnish Centre for Pensions 10 years after the last operation [3]. Possible death, its date and diagnosis were checked from the Statistical

Office of Finland. The study was approved by the Ethics Committee of Tampere University Hospital.

Statistical methods

Categorical variables were tested using chi-square test and Wilcoxon rank test (Return to work vs. pre-, peri- and immediate postoperative medical data, education, type of work, preoperative pensioning, patients' social situation and lifestyle elements such as exercise habits and smoking).

Bayesian analysis

A stepwise Bayesian approach was used in multivariate analysis to determine posterior probabilities and likelihood ratios and to ascertain the sensitivity and specificity of the rule [4-8]. The model was calculated taking into account all patients under 60 and working one year after CABG.

Theory

The Bayesian approach states how posterior probability of diagnosis D given symptom × is calculated using the prior probability of diagnosis D and its absence. These show how common the diagnosis D and its absence are in the population. The probabilities of symptoms given the diagnosis and its absence are commonly estimated by their frequencies in learning material [6,7].

In the case of a two-valued outcome, the Bayesian approach is commonly developed to give a **likelihood ratio** (probability of × given diagnosis D divided by probability of × given absence of diagnosis D). The likelihood ratio (L) of a set of observed symptoms or properties xi is written as the product of the probability ratios of each xi, also known in epidemiology as risk ratios.

The posterior probability of a given set of observations is calculated by dividing the likelihood ratio by "one plus likelihood ratio". Percentage is obtained by multiplying by 100.

Derivation of indices

One of the authors (MK) has developed an optimization procedure to facilitate the Bayesian analysis. The program goes through all variables given by the parameters and selects first only one variable which will best predict the selected outcome, staying at work over the median in our study. The program then goes through all the remaining variables and selects as second variable that which will best predict the outcome together with the first variable.

Adding one variable after another to the model, the program goes through all the variables. If there are variables which correlate with each other the program selects the best predictor and ignores others. The optimum is the number of variables which together give the smallest failure rate (maximum sum of sensitivity and specificity) in the study group. Usually the optimum does not include all given variables. Ultimately the program provides the best combination of variables which will most accurately predict the outcome.

The program gives the critical area for the total risk index, where the numbers of false-negative and false-positive results are minimal. It also calculates a Receiver Operating Characteristics (ROC) curve. It gives a graphic representation of the relationship between true-positive and false-positive rates and can be used to study the effect of changing the decision rule. The area under the ROC curve is commonly used to measure the predictive power of a statistical model [8].

Results

Study population

The study population comprised 141 CABG patients, 12 women and 129 men who were working one year postoperatively. Their demographic data and work classification are shown in Table 1. Clinical characteristics and severity of coronary heart disease are compiled in Table 2. Besides CABG an aortic valve replacement was carried out for one patient (male, age 52 years). Four patients had been pensioned before the operation and returned to work after CABG, 137 had been preoperatively at most on short-term sick pay.

Continuation at work after CABG

The yearly employment status (full-time or part-time work) gradually decreased in men from 100% to 85% (n = 95) in five years. Correspondingly, it was 73% (n = 49) ten years postoperatively. The results for women were affected by their small number (n = 7 five years and n = 3 ten years postoperatively) (Figure 1). Altogether 76% of patients aged < 60 years were still working 10 years after CABG.

All 141 patients were younger than 60 one year after CABG. Twenty-six of them (17%) retired on disability pension before the age of 60, the main reason being cardiac condition in 16 cases. Ten patients retired for other reasons (stroke, pulmonary embolism, psychiatric and musculoskeletal disorders). During the follow-up, a total of 15 CABG patients retired to adjusted old-age pension at the age of 57 – 60 mainly for non-medical reasons. Half of them retired 1 to 2 years after CABG.

Model of continuation at work

Results of univariate analysis

In univariate analysis, the three most significant factors ($p < 0.001$) affecting staying on were patients' age at the time

Table 1: Demographic data and job classification at the time of CABG

	Female (n = 12) %	Male (n = 129) %	All (n = 141) %
Age			
< 50	33	41	40
50 – 54	33	35	35
55 – 59	33	24	25
Education			
Less than high school	80	68	69
High school graduate	0	22	20
College graduate	20	10	11
Job classification			
Manual worker	25	46	44
Employee lower level	12	17	17
Employee higher level	25	16	17
Farmer	0	5	4
Employer or entrepreneur	38	16	18

of the operation, preoperative working status and patients' height.

Other factors describing different aspects of patients' medical condition and social situation evinced some lesser correlation with continuing to work. Some were related to preoperative conditions such as kidney function, some others to the extent of cardiovascular disease or postoperative well-being (NYHA class, nitrogen use and subjective well-being when compared to preoperative condition). Patients' size was shown not only by patients' height but also by sex and weight. Other factors described diabetic

Table 2: Clinical characteristics and severity of coronary heart disease before CABG

	Female (n = 12) %	Male (n = 129) %	All (n = 141) %
Concomitant diseases			
Hypertension	83	33	38
Hypercholesterolemia	90	91	91
Diabetes mellitus	25	4	6
Previous MI	70	61	62
Previous TIA or stroke	0	3	3
Intermittent claudication	0	4	3
Smoking			
Previous	30	60	58
Current	20	15	16
Cardiac function			
EF 35 to < 50%	9	7	7
EF < 35%	0	3	3
NYHA II	17	20	20
NYHA III	58	64	63
NYHA IV	25	16	17
Severity of CHD			
Three-vessel disease	33	48	47
Left main disease	8	10	10
Elective operation	91	86	87
Urgent operation	9	12	11
Emergency operation	0	2	2

(MI = myocardial infarct, TIA = transient ischemic attack, EF = ejection fraction, NYHA = angina pectoris symptoms according to New York Heart Association, CHD = coronary heart disease)

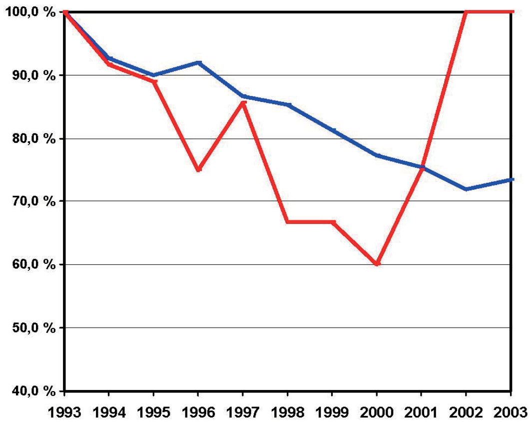


Figure 1
Postoperative employment status at the end of each calendar year. A 10-year follow-up of originally 141 patients, who were working one year postoperatively and remained under 60 during the follow-up. Deceased persons, altogether eight, are excluded. X-axis: Calendar years. Y-axis: Percentages of patients working at the end of each calendar year. Blue line: men, red line: women

burden (body mass index or diagnosed type 2 diabetes mellitus), overall physical activity (daily walking distance, walking restrictions and frequency of participation in household work) and social situation, e.g. patients' marital status.

Results of multivariate analysis
When forming the model for remaining at work by multivariate Bayesian analysis, we compared several patterns of the factors presented above. Finally, patient's younger age at the time of CABG was selected as the best predictor for continuation at work. The best balanced and most useful model also included the following factors: postoperative cardiac symptoms, patients height, marital status, diabetes mellitus and participation in household work (Table 3).

As an example, we have a 52 year old married patient, who does not participate in household work. He/she is 176 cm of height and is not suffering from diabetes or postoperative cardiac symptoms. Hence, the total likelihood ratio of remaining at work is $1.24 \times 1.80 \times 0.93 \times 1.03 \times 0.58 = 1.24$. According to the model [100 * LR/(1+LR)], we get 55% probability of remaining at work for at least six years. If our patient would be an active person for example participating into the household work, his/hers total likelihood ratio of remaining at work for at least six years would increase to $1.24 \times 1.80 \times 0.93 \times 1.03 \times 1.25 = 2.67$ and thus his/hers probability were 73%.

The ability of the model to predict continuation was analyzed in annual time intervals throughout the 10-year postoperative follow-up. In this population the total error rate was 14% to 26% (Fig 2). The corresponding ROC curves are shown in Fig. 3.

Discussion
Principal findings
In this paper we present a model for estimating patients' possibilities to remain in work after CABG. We also report that 73% of men who returned to work postoperatively and were aged less than 60 years were still working 10 years later. The number of women was not large enough for scrutinized statistical comparison, but their continuation at work resembled that of men.

Strengths and weaknesses of the study
To the best of our knowledge this study represents the longest follow-up of CABG patients' retention of work capacity. We analyzed data on all consecutive patients operated over a period of 18 months. Their urban and rural domiciles comprise more than 20% of the inhabitants of the country, thus well representing the Finnish population.

The study was commenced with a retrospective analysis of patient records. In addition, written patient questionnaires and telephone contacts were used. Follow-up data on pensioning and mortality were verified from national archives, which in Finland are particularly precise. Even after these measures some postoperative data, for instance in patient questionnaires, were missing.

Our study population was only 141 patients. In general, relevant long-term follow-up data on CABG patients' working status are somewhat difficult to obtain by reason of the relatively high age of the patients operated. Especially the female population was very small, and the interpretation of its postoperative work activity must be made very carefully. We therefore treated men and women as one group when forming the model. On the other hand, patients' uniformity in respect of age and burden of diseases made it easier to make significant calculations also from a fairly small material.

When building the model, possibly relevant parameters had first to be selected by univariate analysis. At this stage some, again, had to be left out owing to insufficiency of material. Some factors were not selected due to their low prevalence in the population studied. Of variables describing different aspects of the same feature, only the best was selected for the model.

Table 3: The probability of remaining at work for at least three, six and nine years

Variable	Over 3 years (n = 119)	Over 6 years (n = 92)	Over 9 years (n = 59)
1. Age at the time of CABG			
≤ 50	**LR = 6.54**	**LR = 3.25**	**LR = 2.42**
50 – 54	**LR = 3.80**	**LR = 1.24**	**(LR = 0.20)**
≥ 55	**LR = 0.68**	**LR = 0.37**	**(LR = 0.01)**
2. Postoperative cardiac symptoms			
No	**LR = 1.11**		**LR = 1.08**
Yes	**LR = 0.51**		**LR = 0.51**
3. Height			
< 175	**LR = 0.59**	**LR = 0.58**	
175 – 179	**LR = 1.43**	**LR = 1.80**	
180-	**LR = 6.29**	**LR = 2.13**	
4. Being married			
No	**LR = 3.51**	**LR = 1.60**	**LR = 1.14**
Yes	**LR = 0.88**	**LR = 0.93**	**LR = 0.98**
5. Diagnosed DM			
No	**LR = 0.92**	**LR = 1.03**	**LR = 1.04**
Yes	**LR = 2.59**	**LR = 0.80**	**LR = 0.70**
6. Participation in household work			
Daily		**LR = 1.25**	**LR = 1.26**
Less often		**LR = 0.58**	**LR = 0.51**
Precision of the model			
False-Positive	**10**	**18**	**15**
False-Negative	**9**	**17**	**13**
Sensitivity	**55%**	**63%**	**82%**
Specificity	**92%**	**82%**	**78%**
Correct predictions	**86%**	**75%**	**80%**

In this model, the individual probability of remaining at work (calculated one year postoperatively) is as follows:
The patient's likelihood ratio (**LR**) of each of six characteristics is multiplied. The greater LR, the better is the possibility of remaining at work. If the total LR is greater than 1.00, the probability of remaining at work is more than 50% for the given time (3 y, 6 y, or 9 y). Patients in age groups marked in parenthesis may remain at work for over the age of 60.
LR may be expressed as probability as follows: p = 100 * LR/(1+LR).

The Bayesian approach in multivariate analysis was used in view of its ability to analyze partly incomplete material from questionnaires. In this study it also seemed to be more illustrative than logistic calculations based on an iterative process.

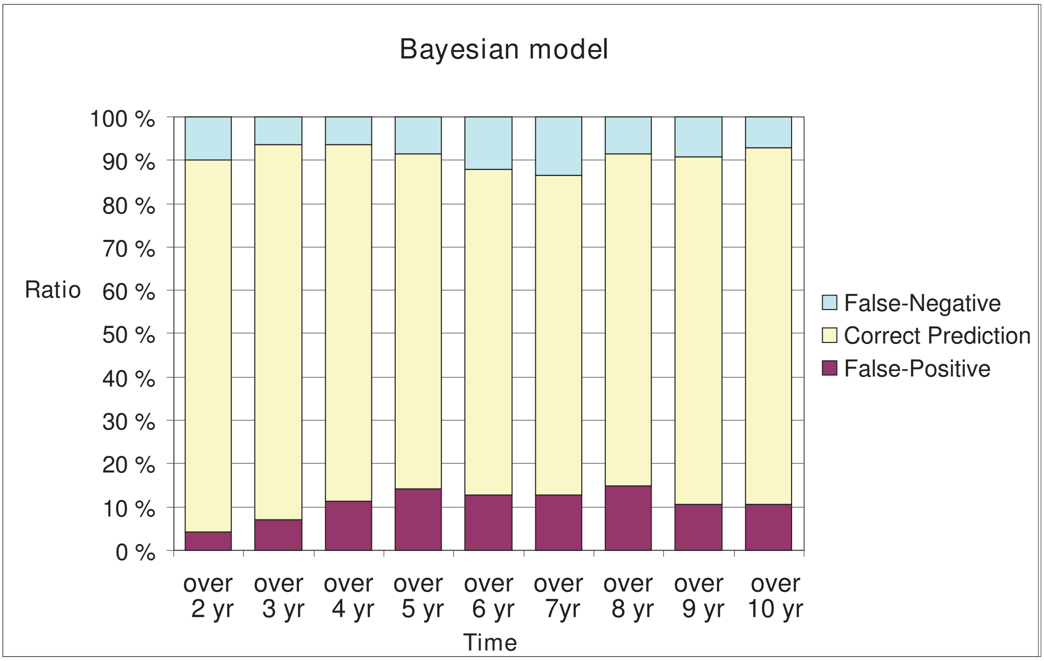
Retirement before the age of sixty

Three quarters of the patients less than 60 were in working life ten years after CABG (Fig. 1). The difference seen between genders was evidently induced by the small number of women returning to work postoperatively and working until the age of 60.

Some of the retired patients had evident worsening of cardiac disease after the initial CABG. However, the majority of patients in this group were pensioned off because of a wide range of postoperative problems not necessarily related to coronary insufficiency. Of retirees aged less than 60 who resumed work 27% were pensioned during the first follow-up year. This may reflect the early retirement and disability pensioning system in Finland, which favours working attempts after CABG before obtaining a pension.

Results in relation to other studies

Only a few published studies have evaluated continuation at work over a longer follow-up. None has introduced a model for remaining in work. However, it is possible to make some comparisons with shorter follow-up studies of two to five years which describe retention of working capacity after CABG. Skinner et al. have introduced a British material of originally 343 CABG patients [9]. At five-year follow-up the most important factors for continuation were younger age at the time of operation, male sex,



Target staying at work	> 2 yr	> 3 yr	> 4 yr	> 5 yr	> 6 yr	> 7 yr	> 8 yr	> 9 yr	> 10 yr
Positive	128	119	111	101	92	80	68	59	56
False-Positive	6	10	16	20	18	18	21	15	15
False-Negative	14	9	9	12	17	19	12	13	10
Specificity%	54	55	47	50	63	71	71	82	82
Sensitivity%	89	92	92	88	82	76	82	78	82
Total error rate%	14	14	18	23	25	26	23	20	18

The model correctly predicts 74 % to 86 % of patients' remaining at work depending on the time group (years after CABG)

Figure 2
The ability of the model to predict remaining at work.

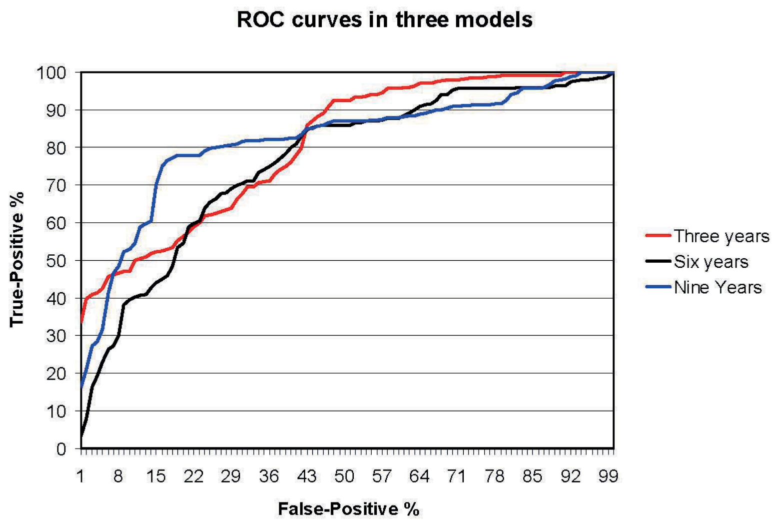


Figure 3
ROC curves of the ability of the model to predict remaining at work.

preoperative working and freedom from postoperative angina symptoms. Hlatky et al. have presented an American material of 409 patients with either CABG or PCI [10]. Long-term employment did not differ significantly between these groups. The authors also found that predictors of longer working postoperatively were younger age at the time of the operation and preoperative full-time work, but also a single private source of medical insurance, which would indicate the importance of social factors. Left ventricular function appeared as a single medical factor. In the RITA trial [11], over 1000 patients were randomized either to CABG or PCI. Factors predicting working two years postoperatively were positive preoperative working status, younger age and male gender.

In the present study the model of continuation in work included patients' age and height, postoperative cardiac symptoms, diabetes, patients' matrimonial status and participation in household work.

In previous CABG studies age has been the most important predictor of continuing at work. As in the present study absence of postoperative cardiac symptoms was important in remaining at work also in a study by Skinner et al. [9]. Cardiac condition was also found in an earlier Finnish material to be the most important reason for not working five years postoperatively [12]. Patient's height is closely related to sex, which has been found to be a predictor of return [13]. Also diabetes mellitus has emerged as a negative predictor for return but it is also associated with a poorer long-term outcome after CABG [14,15]. In this context it is quite logical that these were selected for the present model of resumption.

In our model it would appear that diabetes favours working for three to five years postoperatively. This is coincidentally caused by the small number of diabetics in this group (one patient).

Finland, like many other European countries, has a national medical insurance system and thus insurance issues did not affect remaining at work. Probably for the same reason type of work likewise did not influence remaining at work.

Being married often constitutes a form of social and financial security. Vice versa, being unmarried might accentuate the importance of daily work as both social and financial protection. Participation in household work was in our material associated with other physical activities such as daily walking distance and exercise habits (data not shown). This may thus be considered as one dimension of physically active life. Preoperative working status was not selected into our model, since almost all patients were working or only on short-term sick leave preoperatively.

Conclusion

In this part of the W-CABG study, we have analyzed patients' postoperative continuing to work. Age and height, postoperative cardiac symptoms, matrimonial status, diabetes mellitus, and participation in household work were selected into the final model. In the ten year follow-up, this model predicted 80% of continuation at work after coronary artery bypass grafting. Correspondingly, the most important single reason for premature retirement was found to be cardiovascular disease.

Our results encourage medical professionals to effectively treat the postoperative cardiac problems and diabetic burden of CABG patients as well as to activate them not only to undertake household work but also all kinds of social and physical activity.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

VH conceived of the study, and participated in its design and coordination and drafted the manuscript. MK performed the statistical analysis and helped to draft the manuscript. MT participated in the design and coordination of the study and revised it critically. AP participated in the design and coordination of the study and helped to draft the manuscript. VH and AP wrote the final manuscript, which was read and approved by all authors.

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Lipids in Health and Disease

RESEARCH Open Access

Prompt impact of first prospective statin mega-trials on postoperative lipid management of CABG patients: a 20-year follow-up in a single hospital

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Abstract

Background: The long-term success of coronary artery bypass grafting (CABG) depends on secondary prevention. Vast evidence provided by the results of cholesterol mega-trials over two decades has shown that effective reduction of LDL cholesterol improves the prognosis of patients with coronary heart disease. However, the implementation of these results into the clinical practice has turned out to be challenging. We analysed how the information derived from clinical statin trials and international recommendations affected the local treatment practices of dyslipidaemia of CABG patients during a 20-year time period.

Methods: The cohort includes all CABG patients ($n = 953$) treated in Kanta-Häme Central Hospital during the time period 1990–2009. At the postoperative visits in the cardiology outpatient clinic, each patient's statin prescription was recorded, and blood lipids were determined.

Results: During 1990–1994, 12.0 % of patients were on statins and during the following 5-year time periods the proportion was 57.2, 82.2 and 96.8 %, respectively. During the 20-year observation period (1990–2009), the effective statin dose increased progressively during these 5-year periods up to 36-fold, while the mean concentration of LDL cholesterol decreased from 3.7 to 2.1 mmol/l and that of apolipoprotein B from 1.3 to 0.8 g/l. In the very last year of follow-up, the mean concentrations of LDL-C and apoB were 1.83 mmol/l and 0.78 g/l, respectively. The most prominent increase in statin use and dosage took place during 1994–1996 and 2003–2005, respectively.

Conclusions: Among CABG patients the lipid-lowering efficacy of statin therapy improved dramatically since 1994. This progress was accompanied by significant and favourable changes of lipid and apolipoprotein-B values. This study shows that it is possible to effectively improve lipid treatment policy once the results of relevant trials are available, and that this may happen even before international or national guidelines have been updated.

Keywords: Coronary artery bypass, CABG, LDL cholesterol, Lipids, ApoB, Extended Friedewald, Statins, Statin intolerance

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Background

Coronary artery bypass grafting (CABG) efficiently alleviates coronary heart disease (CHD) symptoms. However, without an effective secondary prevention, it does not offer permanent improvement of cardiac symptoms or prognosis [1, 2].

The primary target of the secondary prevention of coronary heart disease is effective reduction of low-density lipoprotein cholesterol (LDL-C), which diminishes cardiovascular and total mortality [3–6]. The lipid-lowering therapy is based on two approaches, i.e. change in lifestyle and pharmacological therapy [7]. In acute coronary syndrome patients it is desirable to start an effective statin therapy immediately after the event, i.e. already during the hospital stay [8].

According to early mega-trials, the turning points in secondary prevention of coronary heart disease were the years 1994, 1996 and 1997 when the first statin mega-trials 4S and CARE as well as the Post-CABG trial were published, and showed that effective therapy with statins improves the prognosis of patients with CHD [2–4]. The next key observations with a major influence on statin therapy occurred in 2004–2005, when the beneficial effects of intensive statin therapy, as compared with moderate statin therapy, were published [6, 8].

Two lipid-lowering recommendations, one in the U.S. and the other in Europe, were published just before the first statin mega-trials, i.e. in 1994 [9, 10]. They pointed out the central importance of increased cholesterol concentrations in determining the CHD risk; yet, due to the lack of evidence, the recommendations were conservative in their drug therapy guidelines [9, 10].

In 1998, the European targets for total cholesterol (T-C) and LDL-C were set below 5.0 mmol/l and 3.0 mmol/l, respectively [11]. One year later in the USA, the target for LDL-C in CABG patients was set below 100 mg/dL (2.6 mmol/l) [12]. Further in 2001 and 2003 LDL-C targets were set below 2.6 mmol/l and 2.5 mmol/l in the USA and Europe, respectively [13, 14]. Even though the goals were more demanding, the major emphasis was still on therapeutic lifestyle changes. Eventually, in 2004 the American guidelines and in 2007 the European guidelines for cardiovascular disease prevention recommended that in patients with established coronary heart disease LDL-C should be lowered below 2.5 mmol/l, or below 1.8/2.0 mmol/l, "if achievable" [15, 16].

The evidence indicates that the combined use of different apolipoprotein (apo) measures might improve the risk assessment of cardiovascular disease [17, 18]. Regarding the atherogenicity of the lipoproteins, the apolipoprotein B (apoB)-containing lipoproteins are of primary importance. Since one apoB molecule is present in each very-low-density lipoprotein (VLDL), intermediate-low-density lipoprotein (IDL) and LDL particle [19, 20], the plasma concentration of apoB indicates the total number of circulating atherogenic apoB-containing lipoprotein particles. ApoB concentration as a complementary measure was included first in recommendations in 2008 [7], and in the highest risk patients, the treatment goal was set to 0.80 g/l. To achieve this goal, effective lipid-lowering drug therapy is needed [21].

The aim of our study was to assess whether statin mega-trials and the recommendations based on their results influenced the local treatment practice regarding statin-dependent control of lipid levels in CABG patients over the critical 20-year period (1990–2009) which encompassed milestone publications regarding LDL-C lowering-based pharmacotherapy in preventive cardiology. We also attempted to learn whether the evolving changes in the LDL-C targets were reflected in the concentrations of different lipid classes and apolipoproteins in the patient cohort.

Methods

Patients

We studied all annual cohorts of CABG patients treated in Kanta-Häme Central Hospital (K-HCH) during the years 1990–2009. The primary catchment population of the hospital is 175 000 inhabitants living in Southern Finland. CABG was performed in Tampere University Hospital for 953 patients and, after the operation, they were transferred to K-HCH for further recovery.

After discharge the patients were followed according to hospital policy. Of the patients, 946 (99.3 %) had at least one visit in the outpatient clinic of cardiology during the first three postoperative months.

Material analysis

Results of all patients who visited the outpatient clinic were analysed. Patients who had laboratory values on the first postoperative visit, but not on the 3-month visit, were also included; that is, a "last observation—carry forward" principle was adopted. Accordingly, data derived from the final postoperative outpatient visit are presented, 19 and 81 % of them being derived from the 1 to 3-month visits, respectively.

The year of CABG, postoperative lipid values, medication, and absence/presence of various CHD risk factors including smoking, hypertension, diabetes, and obesity (body mass index, BMI) were collected from the patient records. Patients' data were coded, and data analysis was carried out with the coded material only. The study was approved by the Ethics Committee of Kanta-Häme Hospital District (Dnro E511/08).

The influence of the statin trials and recommendations on treatment goals were examined by comparing CABG patients' postoperative lipid values taken at various time points over a time span of 20 years. The study period was divided into four consecutive 5-year time periods, namely 1990–1994, 1995–1999, 2000–2004, and 2005–2009. During this 20-year time period several new statins with different efficacies received their marketing authorisation. Accordingly, the daily dose and the dose-dependent LDL-C lowering effect of each individual statin had to be taken into account. This enabled us to compare the lipid-lowering efficacy of the statin therapy during the entire period.

A daily dose of 20 mg simvastatin or equipotent dose of another statin is the smallest statin dose used in most prospective trials, and this dose was defined as "daily statin dose index (DSDI) 1". In the Tables and Graphs, in which the effective doses of various statins are presented, the DSDI 1 corresponds to a daily dose of 80 mg fluvastatin, 40 mg lovastatin or pravastatin, 20 mg simvastatin, 10 mg atorvastatin or 5 mg rosuvastatin. The lipid-lowering efficacy of each statin was assumed to be linearly correlated with the dose; i.e. the DSDI of 80 mg simvastatin, 40 mg atorvastatin or 20 mg rosuvastatin was 4 [22–25].

Lipid analysis

Total and high-density lipoprotein cholesterol (HDL-C) concentrations were determined from plasma samples by using Hitachi 911 analyser with Boehringer-Mannheim reagents in 1990–1996. Roche Diagnostics enzymatic methods were used since 1996, which also applied to direct LDL-C analysis from 2000 onwards. All chemical analyses were carried out in the Laboratory of Kanta-Häme Central Hospital. Lipid analyses have been under the Nordic quality control during the entire study period.

For the calculation of LDL-C with the classical Friedewald formula (FW) data on T-C, HDL-C and triglycerides (TG) are required. Since FW is valid provided serum TG ≤ 4.5 mmol/l, we also applied a novel extended Friedewald (eFW) approach, which is more tolerant on elevated triglycerides [26, 27]. The eFW is based on artificial neural network regression algorithms which utilize data on classical FW inputs [26]. This method allowed us to calculate LDL-C, IDL cholesterol (IDL-C), HDL2 cholesterol (HDL2-C) and VLDL triglyceride (VLDL-TG) concentrations. It also computationally yields estimates of the apoB and apolipoprotein A-1 (apoA1) concentrations. To estimate HDL3 cholesterol (HDL3-C), the HDL2-C value obtained with eFW was subtracted from the measured HDL-C [26].

Statistical analysis

Evolution of postoperative statin therapy and lipid values over 20 years was studied using ANOVA test in the 5-year groups. With dichotomal variables, the 5-year groups were compared using extended χ^2 test [28]. D'Agostino's test was used to determine normality and scedasticity. Percentage or mean and standard deviation of demographic characteristics and lipid variables are presented. Multiple linear regression analysis was used when comparing lipid values with each other, and also when LDL-C values obtained by enzymatic methods were compared with those obtained by the classical Friedewald equation or by the extended Friedewald approach.

Results

Together 400 to 650 CABG patients were operated yearly in Tampere University Hospital during 1990–2009. On average, 50 patients of them were postoperatively treated annually in K-HCH. Patient records of altogether 946 subjects who attended postoperative cardiac outpatient clinic were analysed over a period of 20 years divided into four consecutive 5-year time periods, each consisting on average of 237 patients (ranging from 219 to 256 patients). The proportion of male patients ranged from 72 to 80 %. The changes in patients' demographics followed both national and international trends, and the demographic characteristics are presented in Table 1.

Lipid treatment practice

Altogether 803 patients had their lipid values measured, 81.3 % of them at the 3-month visit. During the first

Table 1 Demographics of patients undergone CABG during 1990–2009, divided into 4 consecutive 5-year periods

5-year period	1990–1994	1995–1999	2000–2004	2005–2009	Overall p[a]
Number of patients	256	247	224	219	–
Proportion of males (%)	78	80	72	79	0.5193
Proportion of diabetics (%)	10	14	19	27	0.0122
Current and ex-smokers (%	64	55	54	56	0.4544
Age (years)	61.9 ± 7.7	64.0 ± 9.2	65.4 ± 9.4	66.5 ± 8.3	<0.0001
BMI (kg/m^2)	26.5 ± 3.5	26.5 ± 3.5	27.2 ± 3.7	27.0 ± 4.1	0.0978
Systolic BP (mmHg)	149.6 ± 24.8	147.9 ± 23.2	137.8 ± 22.0	130.0 ± 20.4	0.0001
Diastolic BP (mmHg)	84.7 ± 11.6	82.1 ± 11.1	80.2 ± 9.8	77.5 ± 9.3	<0.0001

Abbreviations: *BMI* body mass index (kg/m^2), *BP* blood pressure
[a]Extended χ^2 test and ANOVA were used for overall analysis. Percentage or mean ± standard deviation is presented

5-year period, 63.6 % of the patients and during the subsequent 5-year periods 85.6, 94.2 and 96.8 %, respectively, had their lipids analysed. Thus, there was an initial strong and statistically significant ($p < 0.01$) increase in the proportion of patients having their lipids determined.

During the 20-year observation period, the use of statins increased markedly, the most prominent increase having taken place during 1995–1999 (Additional file 1: Table S1B). Within the last years of the follow-up, practically all CABG patients were on statin therapy (Fig. 1a).

The DSDIs were small during the initial years, and effective statin doses increased progressively during the last years of follow-up. Thus, the average DSDIs of all patients, even when those without statin therapy were included, increased during four consecutive 5-year time periods from 0.07 (±0.23) to 0.46 (±0.53), 1.25 (±1.19) and 2.52 (±1.52) (p for trend < 0.001) (Fig. 1b, Table 2). The DSDI 2.86 (±0.41) during the very last year of observation corresponds to a mean simvastatin dose of 57 (±8) mg/day.

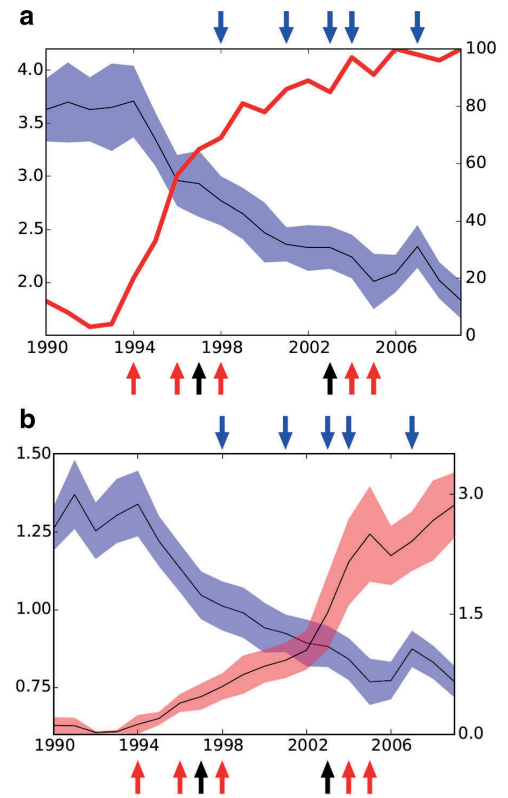

Fig. 1 **a** LDL-C ± 1 SD calculated by Friedewald formula (mmol/l, black line ± 1 SD blue shadowing) and the amount of statin users (%, red line) at postoperative visits. **b** Plasma correlation of apoB ± 1 SD (g/l, black line ± 1 SD blue shadowing) and daily statin dose index (DSDI, black line ± 1 SD red shadowing) (see Methods) at postoperative visits. Red arrows indicate the publication of landmark studies from left to right: 4S[3], CARE[4], LIPID[5], REVERSAL[6] and PROVE IT[8]. Blue arrows refer to the publication of lipid lowering recommendations from left to right: Second European Task Force[11], NCEP ATP III[12], Third European Task force[13], NCEP ATP III (Implication of recent clinical trials)[14], and Fourth European Task Force[15]. Black arrows indicate the years, when the two most effective statins entered the Finnish market, i.e. atorvastatin in 1997 and rosuvastatin in 2003. LDL-C was calculated by Friedewald formula and apoB was obtained using extended Friedewald approach (see Methods)

Plasma lipid and apolipoprotein levels

The mean concentrations of LDL-C were 3.7 and 2.1 mmol/l, and those of apoB 1.3 and 0.8 g/l, during the initial (1990–1994) and final (2005–2009) 5-year time periods, respectively (Fig. 1, Table 2). During the last single year of follow-up (2009), the mean concentrations of LDL-C and apoB were 1.83 mmol/l and 0.78 g/l, respectively.

The decrease in apoB concentration was progressive during the 20-year time span. It reflects not only the decrease in LDL-C concentration, but also in the concentrations of other apoB-containing lipoproteins, as seen in decreases of VLDL-TG and IDL-C, which were reduced proportionately (Fig. 2a). HDL-C increased from 1.02 (±0.29) to 1.22 (±0.34) particularly due to an increase in the concentration of HDL2-C, while the concentration of HDL3-C remained at a constant level of 0.45 mmol/l (Fig. 2b). The multiple linear correlations of different lipoproteins are presented in Additional file 2: Table S2B.

Discussion

Our main findings indicate that during a 20-year follow-up (1990–2009) of CABG patients the following beneficial changes in lipid and lipoprotein measurements and in lipid treatment efficacies occurred in sequence. First, the percentage of patients with measured cholesterol levels increased, and thereafter, the share of patients on statin therapy and the efficacy of the therapy increased consecutively. Moreover, the concentrations of LDL-C and of apoB, the latter reflecting the number of atherogenic apoB-containing lipoprotein particles, decreased by 45 and 40 %, respectively.

Importantly, the primary changes took place immediately after the first statin mega-trial had been published, i.e. before their results had been integrated into the updated formulations of the relevant international guidelines [3, 4]. The mean dosage of statin increased rapidly after 2002, when the most effective statin, rosuvastatin, had become available in the market. In 2002 and 2005 DSDI-values were 1.08 and 2.56, respectively, see Fig. 1b). Although during the 20-year follow-up period, the levels of total cholesterol in the Finnish population steadily

Table 2 Postoperative plasma lipid and lipoprotein levels in consecutive 5-year periods in statin-treated patients undergone CABG

5-year period	1990–1994	1995–1999	2000–2004	2005–2009	Overall p^a
DSDI	0.07 ± 0.23	0.46 ± 0.53	1.25 ± 1.19	2.52 ± 1.52	<0.0001
T-C (mmol/l)	5.70 ± 1.27	4.86 ± 1.00	4.20 ± 0.91	3.76 ± 0.82	<0.0001
LDL-C (mmol/l)[b]	3.70 ± 1.09	2.94 ± 0.85	2.35 ± 0.72	2.07 ± 0.64	<0.0001
HDL-C (mmol/l)	1.02 ± 0.29	1.12 ± 0.33	1.24 ± 0.32	1.22 ± 0.34	<0.0001
T-G (mmol/l)	2.20 ± 1.22	1.79 ± 0.96	1.56 ± 0.81	1.40 ± 0.65	<0.0001
Extended Friedewald approach (eFW)[c]					
VLDL-TG (mmol/l)	1.36 ± 0.85	1.12 ± 0.79	0.95 ± 0.6	0.85 ± 0.	<0.0001
IDL-C (mmol/l)	0.38 ± 0.14	0.28 ± 0.11	0.23 ± 0.11	0.23 ± 0.16	<0.0001
LDL-C (mmol/l)	3.55 ± 0.78	3.01 ± 0.71	2.49 ± 0.63	2.21 ± 0.51	<0.0001
HDL-2-C (mmol/l)	0.57 ± 0.23	0.67 ± 0.27	0.76 ± 0.27	0.77 ± 0.28	<0.0001
HDL-3-C (mmol/l)	0.46 ± 0.07	0.47 ± 0.07	0.48 ± 0.07	0.48 ± 0.07	0.0121
ApoA1 (g/l)	1.38 ± 0.22	1.38 ± 0.24	1.42 ± 0.24	1.37 ± 0.26	0.1864
ApoB (g/l)	1.30 ± 0.26	1.09 ± 0.26	0.90 ± 0.23	0.81 ± 0.18	<0.0001

Mean ± standard deviation are presented
Abbreviations: *DSDI* daily statin dose index, where the 1.0 corresponds the dose of simvastatin 20 mg per day (see Methods). In the intention to threat analysis all patients are included
[a]ANOVA was used for overall analysis
[b]LDL-C is determined using Friedewald calculation
[c]The eFW is based on artificial neural network regression algorithms which utilize data on classical FW inputs (see Methods)

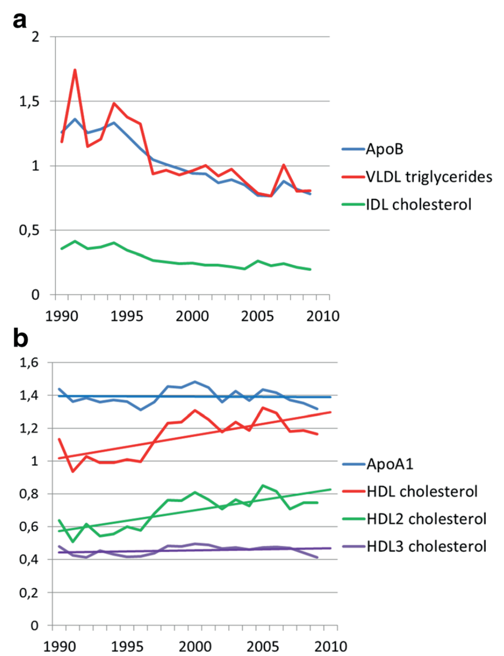

Fig. 2 **a** Apolipoprotein B (ApoB, g/l), VLDL-triglycerides (mmol/l) and IDL-cholesterol (mmol/l) at postoperative visits. **b** Apolipoprotein A-1 (ApoA1, g/l), HDL-cholesterol (mmol/l), HDL2-cholesterol (mmol/l) and HDL3-cholesterol (mmol/l) at postoperative visits are shown both as curves and as linear representations. All parameters except HDL-C were obtained using extended Friedewald approach

decreased [29], the decrease in our patients was 3- to 4-fold when compared with that of the general population. This finding accords with the notion that, at least the majority of the excess decrease in LDL-C among the CABG patients must have been due to statin treatment. Thus our results comply with the observed significant decreases in LDL-C found in mega-trials in which decreased cardiovascular morbidity and mortality with intensified statin therapy could also be achieved [3–6, 8].

The efficiency of secondary prevention of CHD in Europe has been evaluated in the Euroaspire studies I and II. In the Euroaspire II study (1999–2000) consisting of coronary patients (including also CABG patients) from 15 European countries, 42 % had their T-C < 5.0 mmol/l and 61 % were on lipid-lowering medication [30]. At the same time the corresponding numbers in our patient population were 68 and 76 %, respectively. In an international cross-sectional study by Gitt et al. [31], the prevalence of lipid abnormalities were assessed in 2008–2009 in more than 22 000 European and Canadian patients on statin treatment. In this study, 58 % of patients having a cardiovascular high-risk had their LDL-C < 2.5 mmol/l. Their mean DSDI was 1.85, corresponding to a simvastatin dose of 37 mg [31]. In another study carried out 2009–2010, out of 151 patients undergone CABG, 83.4 % had lipid profile measured during the first postoperative year [32]. In this group, the mean LDL-C level was 1.86 mmol/l, i.e. at the same level as it was during the last years of our study. It has recently been indicated, that physicians' lipid-lowering treatment choices are usually more conservative than guideline recommendations [33]. However, our results reveal that, in a proactive clinic, it is feasible to react without delay to the inflowing relevant information describing results of new well-conducted lipid-lowering trials published in peer-reviewed high-impact journals.

The concentrations of HDL-C and phospholipids, as well as the HDL2/HDL3-ratio, increased in the CABG patients during the 20-year observational period. Regarding the potential clinical significance of these observations, following points need to be considered. The apparently beneficial changes must have been partly due to statin treatment and partly to life style changes. Inasmuch as beneficial life style changes are accompanied by beneficial changes in various cardiometabolic measures, quantitation of the role of changes in Apolipoprotein A-I containing lipoproteins or their components is not feasible. Similarly, the clinical relevance of the minor statin induced increases in various parameters of HDL particles and their constituents remains uncertain. Interestingly, the moderate increase in HDL-C levels with statins correlates with regression of coronary atherosclerosis [34]. With respect to the size of the HDL particles, the larger HDL2 particles have been associated with greater CHD protection than the smaller HDL3 particles [35, 36]. However in recent meta-analysis of 80 published investigations, no differences in cardioprotective properties between these two HDL subclasses were discerned [37, 38]. Importantly, regarding the cardioprotective functions of HDL, the scientific interest is shifting largely to unravelling the biologic activity of HDL [38]. Thus, assigning any presumed clinical significance to the modest increases in the various metrics of Apo A-I containing lipoprotein fractions is not possible at present.

Although LDL is considered the main atherogenic cholesterol-rich particle, also other apoB-containing lipoproteins contribute to intimal cholesterol deposition, i.e. they also are atherogenic [20]. Importantly, the recent increase in the incidence of metabolic syndrome and diabetes has re-emphasized the requirement for obtaining additional data on triglyceride rich lipoproteins like VLDL and IDL. For example, IDL particles and their cholesterol are contributing to the progression of coronary and carotid artery atherosclerosis [39]. Besides the number of apoB-containing lipoproteins, also the size of these particles is considered a key determinant in atherosclerosis [40]. The small dense LDL particles, when being present in high numbers, particularly increase the risk of ischemic heart disease [41]. While the large chylomicrons fail to penetrate the arterial wall, triglyceride rich chylomicron remnants and VLDL remnants (IDL) with smaller particle sizes, enter the arterial wall and so drive atherogenesis [20, 42, 43]. To the best of our knowledge, an observation of diminished IDL-C during intensified statin treatment with lipid values taken and analysed 1–3 months postoperatively over a time span of 20 years, has not been reported earlier.

A limitation associated with this study is its retrospective nature. Therefore we lack knowledge of possible statin intolerance, which is nowadays considered a notable problem in statin treatment. Although in observational studies even 10–15 % of patients have reported muscle symptoms, most of them might be successfully treated with careful management [44, 45]. During the last years of our study only about 2 % of patients were not on statins. That might represent the maximal percentage of patients suffering from clinically relevant statin intolerance in this well-motivated patient population. A possible explanation for the success in statin therapy might be the highly individualized care of the cardiovascular patients in our hospital.

Due to the retrospective nature of this study, the investigators had to rely on medical records with all their imperfections. For example, information concerning laboratory values and medications was occasionally incomplete. Nevertheless, for 85 % of the patients all relevant data were available. Moreover, during the last four decades our hospital has had a fairly stable catchment population without any significant national or international migration. Thus the genetic and racial backgrounds, two factors of potential importance considering the limited size of our study sample, have remained stable.

Conclusions

To conclude, prominent increase of statin use in patients undergone CABG took place immediately after the first statin mega-trial was published. Further, over a 20-year period (1990–2009) the efficacy of statin treatment gradually increased and the concentration of LDL-C, measured 1–3 months postoperatively, gradually decreased. Also the decreases of apoB, IDL-C and VLDL-TG were favourable. Our results show that, based on the outcomes of relevant mega-trials, it is possible in a single centre to optimise clinical practice without delay even before they have led to reformulations of international guidelines.

Additional files

Additional file 1: Table S1B. Percentages in consecutive 5-year periods of patients having statin therapy after the CABG during 1990–2009. (DOCX 14 kb)

Additional file 2: Table S2B. Multiple linear regression analysis between lipid values obtained with different methods. (DOCX 16 kb)

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Availability of data and materials
The datasets analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
AP and VH designed the study and acquired the data. AP, VH and PTK drafted the manuscript. MA-K and KM carried out data maintenance and statistics and gave valuable contribution to the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Kanta-Häme Hospital District (Dnro E511/08).

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Associations of metabolic syndrome and diabetes mellitus with 16-year survival after CABG

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Abstract

Background: The associations of metabolic syndrome (MetS) or diabetes mellitus (DM) on long-term survival after coronary artery bypass grafting (CABG) have not been extensively evaluated. The aim of the present study was to assess the impact of MetS and DM on the 16-year survival after CABG.

Methods: Diabetic and metabolic status together with relevant cardiovascular data was established in 910 CABG patients operated in 1993-94. They were divided in three groups as follows: neither DM nor MetS (375 patients), MetS alone (279 patients) and DM with or without MetS (256 patients). The 16-year follow-up of patient survival was carried out using national health databases. The relative survival rates were analyzed using the Life Table method comparing the observed survival rates of three patient groups to the rates based on age-, sex- and time-specific life tables for the whole population in Finland. To study the independent significance of MetS and DM for clinical outcome, multivariate analysis was made using an optimizing stepwise procedure based on the Bayesian approach.

Results: Bayesian multivariate analysis revealed together six variables to predict clinical outcome (2 months to 16 years) in relation to the national background population, i.e. age, diabetes, left ventricular ejection fraction, BMI, perfusion time during the CABG and peripheral arterial disease. Our principal finding was that after postoperative period the 16-year prognosis of patients with neither DM nor MetS was better than that of the age-, sex-and time-matched background population (relative survival against background population 1.037, $p < 0.0001$). The overall survival of MetS patients resembled that of the matched background population (relative survival 0.998, NS). DM was associated with significantly increased mortality (relative survival 0.86, $p < 0.0001$). Additionally, mortality was even higher in patients receiving insulin treatment than in those without. Excess death rate of DM patients was predominantly caused by cardiovascular causes.

Conclusion: In this long-term follow-up study patient groups without diabetes had at least equal 16 years' survival after CABG than their matched background populations. Survival of DM patients started to deteriorate already few years after the operation.

Keywords: Coronary artery bypass grafting, Diabetes mellitus, Metabolic syndrome, Follow-up, Mortality

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Introduction

Metabolic syndrome (MetS), was first officially defined by the World Health Organization (WHO) and the National Cholesterol Education Program (NCEP) more than ten years ago [1,2]. Since that time its epidemiology has been widely evaluated [3,4]. MetS can be used as a tool to characterize patients at added risk [5-7]. Several studies have suggested that the risks of premature death and cardiovascular disease or diabetes are higher among subjects with MetS compared to those without. However, follow-up studies on long-term survival after coronary artery bypass grafting (CABG) have yielded controversial results with regard to the impact of MetS [8,9].

Diabetes (DM) is a prominent cardiovascular risk factor [10,11]. There is a considerable body of evidence on poor early outcome and higher in-hospital morbidity in diabetics compared with non-diabetic patients after CABG [12,13]. The association of diabetes on long-term survival after CABG has not been extensively evaluated. The few reports published comparing the type of treatment of diabetes to the long-term prognosis after CABG have come to conflicting conclusions [14,15].

Our aim was to evaluate the assumed detrimental impact of metabolic syndrome and diabetes mellitus on long-term prognosis after CABG, focusing on survival after the first two postoperative months.

Methods

Study population

The population of the Working after CABG (W-CABG) study has been described elsewhere [16]. Briefly, CABG was done on 961 patients in Tampere University Hospital during a period of 18 months in 1993-94. Data on MetS and DM were available on 945 operated patients and 910 patients survived two months after CABG (Figure 1). These patients formed the study cohort and were followed for 16 years.

We analyzed the survival of CABG patients in three groups as follows: neither DM nor MetS (DM-/MetS-), MetS alone (DM-/MetS+) and DM with or without MetS (DM+). We combined all DM patients in the same group regardless of their status concerning MetS, in primary analyses of diabetic patients the presence of MetS did not affect survival.

Data collection and clinical definitions

The background of the patients and perioperative data were collected from the medical records in Tampere University Hospital and the secondary hospitals involved in the postoperative care. A survival analysis was made after the closing day, June 30, 2010, based on data obtained from the Statistical Office of Finland. The results of the full completed 16-year follow-up are given.

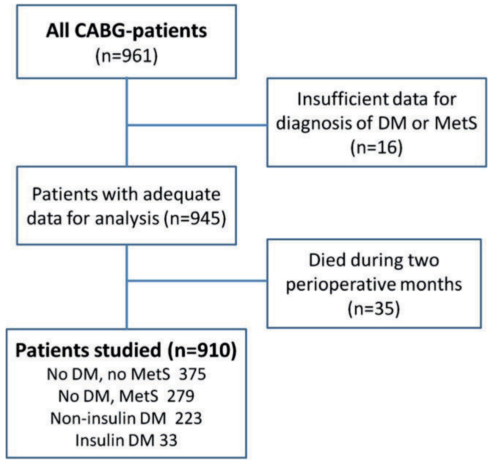

Figure 1 Schematic description of study patients. CABG = coronary artery bypass grafting, DM = diabetes mellitus, MetS = metabolic syndrome, Non-insulin DM = diabetic patients without insulin treatment. Insulin DM = diabetic patients treated with insulin.

Diagnoses of hypertension, peripheral vascular disease, previous myocardial infarction, and previous transient ischemic attack (TIA) or stroke were established from patient records. Renal dysfunction was defined as a glomerular filtration rate less than 60 ml/min/1,73 m^2 calculated with the CKD-EPI equation [17]. Patients were defined as hypercholesterolemic if they had total cholesterol ≥5 mmol/l (200 mg/dl) (NCEP ATP III) or were on lipid-lowering drug therapy. Smoking habits were based on a questionnaire completed 21 months postoperatively [16].

Classification of MetS was made according to the NCEP/ATP III definition with the exception that body mass index (BMI) (kg/m^2) was used as a measure of obesity. During the 1990s waist circumference was not commonly measured [9,18]. Modified MetS was defined as the presence of three or more of the following risk factors: BMI > 30 kg/m^2 for men and > 25 kg/m^2 for women, TGL concentration ≥ 150 mg/dL (1.7 mmol/l), HDL-C < 40 mg/dL (1.03 mmol/l) for men and < 50 mg/dL (1.3 mmol/l) for women and systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or on antihypertensive medication. Elevated blood glucose was defined as fasting blood glucose ≥ 100 mg/dl (5.6 mmol/l) [1,2]. For the diagnosis of diabetes the 1998 WHO criteria were used, defining fasting blood glucose level (fB-gluk) ≥ 110 mg/dL (6.1 mmol/l) or random blood glucose ≥ 180 mg/dL (10.0 mmol/l) [1]. A patient was also defined as diabetic if on antidiabetic medication according either to hospital records or the reimbursement database maintained by the Social Insurance Institution of Finland. Further they were divided in insulin-treated diabetics regardless of oral antidiabetic medication and in non-insulin-treated diabetics based on hospital records at the time of admission for CABG. BMI was calculated as mass/height^2 (kg/m^2).

Cardiovascular death was defined as any death caused by coronary heart disease or sudden death during 2 months to 16 years postoperatively. Stroke was considered as cardiovascular death.

Survival analysis

Overall survival (0-16 years postoperatively) was analyzed, including hospital and immediate postoperative survival for 945 patients. Separate survival analyses (2 months to 10 and 16 years) were then carried out for 910 patients, focusing on survival after the immediate postoperative phase. Survival analyses were made according to the metabolic status of the patients (DM-/MetS-, DM-/MetS+ and DM+). The cumulative relative mortality for each group was calculated in 2-month steps against age-, sex- and time-specific national background populations as described in Statistical methods. The first subanalysis was then made in similar manner to reveal survival of DM patients with and without insulin therapy. In the second subanalysis the association of MetS (yes or no) with survival was identically studied in DM patients. The study protocol was approved by the Ethics Committee of Tampere University Hospital.

Statistical methods

In the comparison of patient characteristics, categorical data are tabulated as frequencies and percentages, and continuous variables are expressed as mean and SD. Differences between two groups were tested by Chi squared test and the Wilcoxon rank test, and in cases of more than two groups by Kruskal-Wallis test. Fisher's exact test was used when appropriate in two-by-two tables with directed hypothesis. Differences in mean values between two groups were tested by Student's t-test and in the case of more than two groups by analysis of variance.

The relative survival rate was analyzed by sex, age, DM and MetS using the Life Table method [19]. In this approach, the observed survival rates of the groups are compared to the rates based on age-, sex- and time-specific life tables for the whole population in Finland. Calculation of survival rates was based on the individual life expectancies of the target population for the target years (reference population). The survival of the reference population is effectively 1.00. If the survival curve of the group remains below that of the reference population there is excess mortality in the group.

To study the independent significance of MetS and DM for clinical outcome (2 months to 16 years), multivariate analysis was made using an optimizing stepwise procedure based on the Bayesian approach [20]. This procedure was developed for nominal variables, and does not require a perfect variable matrix. It selects, by the heuristic approach, the combination of variables which best explains the selected outcome factor. The Bayesian approach is applied by counting posterior likelihood ratios or odds ratios for each combination. The aim was to find an optimal subset of pre-and intraoperative variables to provide the best explanation. The parameters included in the multivariate analysis were age, gender, BMI, all significant cardiometabolic diseases and related operations as well as cardiac, lipid lowering and psychiatric medications. Also essential intraoperative characteristics of CABG were included in the analysis. Altogether 31 parameters were included in the Bayesian approach (Additional file 1: Table S1).

Results

Study population

The essential clinical characteristics of the 910 patients are shown in Table 1. Their mean age was 61.6 (SD 8.4) years; 191 of them were women (mean age 64.8 [SD 7.5] years) and 719 men (mean age 60.8 [SD 8.4] years). Of the 910 subjects, 41% were free of MetS or DM and 31% had MetS without DM (Figure 1).

Non-diabetic patients with MetS had by definition more often metabolic abnormalities than those without MetS (Table 1). Similar findings were obtained in patients with diabetes, of whom 82% had MetS. Non-diabetic patients without MetS had more often normal renal function than others ($P < 0.01$). Diabetic patients were older having more angina pectoris and peripheral arterial disease than other patients (Table 1). Smoking habits and the prevalence of hypercholesterolemia did not differ between the three groups.

Overall survival

No patients were lost during the 16-year follow-up. The overall postoperative survival is presented in Figure 2. DM was associated with significantly unfavourable prognosis compared to the non-diabetic patients in the two other groups (both $p < 0.001$). The difference in survival was already seen during the course of the first two postoperative months, where a total of 35 out of 945 patients (3.7%) died. Among non-diabetic patients there was no difference between subjects with or without MetS.

Long-term survival against background population

The analysis between 2 months and 16 years revealed that of the 910 patients alive two months postoperatively 432 (47.5%) had died. Figure 3A presents the relative survival of the three study groups matched by age, gender and calendar year against their respective Finnish background populations (relative survival = 1.00). After the

Table 1 Preoperative demographic data, clinical characteristics and severity of coronary heart disease in 910 patients surviving two months after CABG

	DM–/MetS– n = 375	DM–/MetS+ n = 279	DM+ n = 256	Overall p-value
Female (%)	15.2	26.2	23.8	<0.01[1,2]
Mean Age (years) (SD)	61.3 (8.2)	60.7 (8.6)	63.3 (8.4)	<0.001[2,3]
Variables of Modified MetS				
BMI (kg/ m^2)	25.8	28.7	28.1	NA
Elevated Blood Pressure (%)	40.9	83.1	67.5	
HDL Cholesterol (low, %)	44.9	90.2	65.3	
Triglyceride (high, %)	27.4	83.7	67.7	
Elevated Glucose or DM (%)	4.5	25.8	100.0	
Concomitant Diseases				
Hypercholesterolemia (%)	69.5	80.3	77.7	NS
Previous MI (%)	70.5	67.8	67.7	NS
Previous TIA or stroke (%)	8.9	8.6	13.9	NS
Intermittent Claudication (%)	6.2	4.7	18.6	<0.001[3,4]
Renal Function				
CreaCl (ml/min) (SD)	76.4 (13.8)	74.2 (18.2)	73.7 (16.9)	NS
CreaCl < 60 ml/min/1,73 m^2 (%)	11.0	19.0	19.7	<0.01[1,2]
Preoperative Smoking (%)	66.6	60.2	66.4	NS
Severity of Heart Disease				
EF (%) (SD)	60 (14)	61 (13)	58 (14)	<0.05[5]
EF ≤ 35% (%)	7	4	11	<0.05[5]
NYHA II (%)	11.9	13.0	6.5	
NYHA III (%)	59.9	54.3	56.3	<0.05[5]
NYHA IV (%)	28.2	32.6	37.2	
Operation Characteristics				
Three–vessel Disease (%)	61.1	59.7	58.6	NS
Left Main Disease (%)	13.1	16.6	14.1	NS
Number of Grafts	3.39	3.38	3.35	NS
Use of Arterial Grafts (%)	86.3	83.4	81.0	NS
Concomitant Operation (%)	6.1	3.3	7.6	NS
Perfusion Time (SD)	107.0 (36.6)	108.0 (58.8)	112.3 (34.2)	NS
Urgent or Emergency Operation (%)	26.7	29.9	33.5	NS

Abbreviations: *MI* myocardial infarct, *TIA* transient ischemic attack, *EF* ejection fraction, *NYHA* angina pectoris symptoms according to New York Heart Association, *CHD* coronary heart disease, *LM* left main, low HDL cholesterol: men < 1.03 mmol/l, women < 1.3 mmol/l, elevated triglycerides: ≥ 1.7 mmol/l,
NS = not significant, NA = not applicable.
[1]Unadjusted p < 0.01 by the pooled t-test for the comparison DM-/MetS+ against DM-/MetS-.
[2]Unadjusted p < 0.01 by the pooled t-test for the comparison DM+ against DM-/MetS-.
[3]Unadjusted p < 0.001 by the pooled t-test for the comparison DM+ against DM-/MetS+ .
[4]Unadjusted p < 0.001 by the pooled t-test for the comparison DM+ against DM-/MetS-.
[5]Unadjusted p < 0.05 by the pooled t-test for the comparison DM+ against other groups.

perioperative phase, the 16-year relative survival of DM-/MetS- patients was 1.037, (95% CI, 1.026 to 1.048; < 0.0001) compared to that of the background population. For the first 10 postoperative years the relative survival was 1.033 (95% CI, 1.021 to 1.045; p < 0.0001).

Metabolic syndrome and long-term survival

In non-diabetic patients with MetS the long-term survival between 2 months and 16 years was poorer than among patients without MetS (P < 0.0001). However, during the same period the relative survival of DM-/MetS+ patients

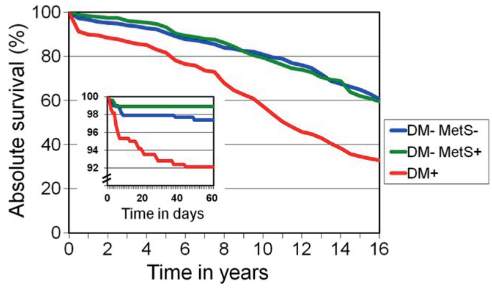

Figure 2 Postoperative absolute survival of patients with neither diabetes nor metabolic syndrome (DM-/MetS-), patients with only metabolic syndrome (DM-/MetS+) and patients with diabetes regardless of metabolic syndrome (DM+) during the 16-year follow-up. Comparison between DM-/MetS- and DM-/MetS+: NS Comparison of DM+ against both groups: P < 0.001. Follow-up of the first two months is shown in the small inset (n = 945).

resembled that of the matched background population (relative survival, 0.998; 95% CI, 0.978 to 1.018; NS).

During the first 10 postoperative years, the relative survival of DM-/MetS+ patients was 1.8% better than that of the matched background population (relative survival, 1.018; 95% CI, 1.010 to 1.026; p < 0.0001) but subsequently deteriorated thereafter (Figure 3A).

Diabetes mellitus and long-term survival

In the postoperative period of 2 months to 16 years, the survival of patients with DM was significantly inferior compared to the background population (relative survival, 0.86; 95% CI, 0.82 to 0.90) and to both non-diabetic patient groups (all p < 0.0001; Figure 3A). DM patients on insulin therapy had poorer survival than those with not on insulin (p < 0.01, Figure 3B).

Among patients with DM, MetS seemed not to affect postoperative survival (2 months-16 years) after adjustment for age, gender and time (absolute survivals, 0.39;

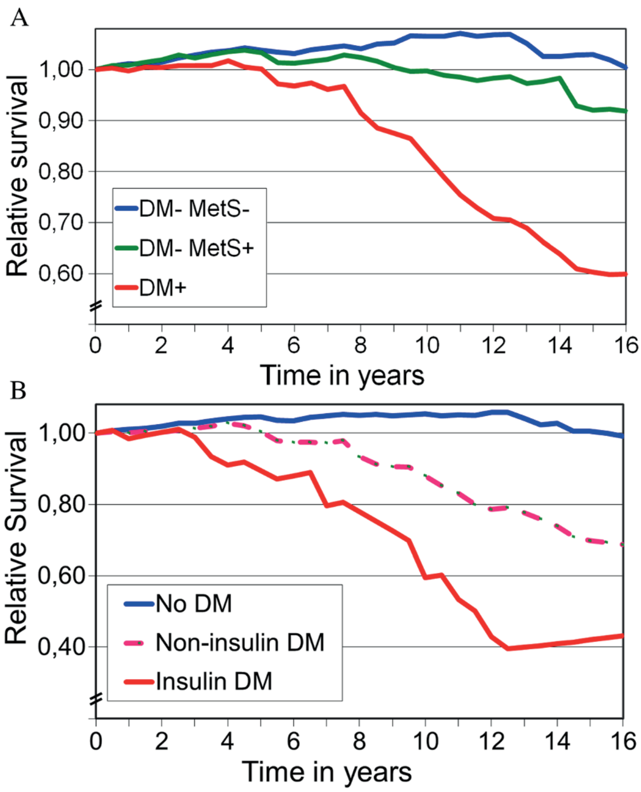

Figure 3 The actual survival 2 months–16 years postoperatively compared to that of the age-and sex-matched Finnish population (relative survival 1.00, n = 910). A. DM-/MetS- = patients with neither diabetes nor metabolic syndrome. DM-/MetS+ = patients with only metabolic syndrome. DM+ = diabetic patients. **B**. No DM = patients without diabetes. Non-insulin DM = diabetic patients without insulin treatment. Insulin DM = diabetic patients treated with insulin.

95% CI, 0.28 to 0.50 for DM+/MetS+ and 0.36; 95% CI, 0.10 to 0.62 for DM+/MetS-, NS).

Causes of death

Cardiovascular and non-cardiovascular death rates were 17.1% and 20.5% for DM-/MetS-, 18.3% and 21.5% for DM-/MetS+ and 38.7% and 28.1% for DM+ patients, respectively. Further, out of all deaths the corresponding proportions of cardiovascular deaths were 45.4%, 45.9% and 56.1%, respectively ($p < 0.0001$ between DM-and DM+ patients). Stroke was reported as a cause of death in only five patients.

Best predictors of long-term prognosis

Bayesian multivariate analysis revealed together six variables to predict clinical outcome (2 months to 16 years) in relation to the national background population, *i.e.* age, diabetes, left ventricular ejection fraction, BMI, perfusion time during the CABG and peripheral arterial disease. Using this model, the measure of agreement (kappa = 0.45) was moderate.

Discussion

To the best of our knowledge this study is the first in which the survival of non-diabetic and diabetic CABG patients was compared to that of matched background populations.

Our principal finding was that the long-term prognosis of patients with neither diabetes nor metabolic syndrome was better than that of the age-, sex-and time-matched background population. Further, in non-diabetic patients the presence of metabolic syndrome reduced long-term survival after CABG when compared to those without MetS. However, the mortality of MetS patients was not significantly inferior to that of the matched background population, which might reflect the careful postoperative follow-up and treatment of known risk factors of operated MetS patients.

Not surprisingly, DM was associated with significantly increased intermediate-and long-term mortality. Survival was even shorter if the diabetes treatment strategy included insulin compared to patients without insulin therapy. MetS *per se* did not impair survival among diabetic patients.

MetS, glucose intolerance and insulin resistance form together complex relationships, whose interacting pathophysiological roles are not yet fully understood. Insulin resistance leads to glucose intolerance, if pancreatic compensation processes are incomplete [21]. Glucose abnormalities with or without diabetes predict cardiovascular events and mortality [22,23]. Insulin resistance is also associated with MetS and its components [24]. Further, MetS has been shown to worsen the prognosis of coronary heart disease patients [25]. However, until recently no studies have specifically examined the prognostic significance of MetS for longer than 10 years after CABG.

Two studies have yielded different results regarding the impact of metabolic syndrome [8,9]. In the BARI trial no significant difference was seen in the death-rate or MI during the 10-year follow-up between patients with and without MetS [9]. In another study of CABG patients MetS predicted inferior outcome in the group of non-diabetic patients [8]. An increase in both all-cause and cardiac mortality became apparent approximately 10 years after surgery. The detrimental effect of MetS on survival was more marked in non-DM patients than in DM patients [8]. Our data are in concordance with and expand these findings.

Diabetes is associated with impaired outcome after CABG [26-28]. However, relation of insulin treatment on the long-term prognosis after CABG has been controversial [14,15,29]. Thourani and Alserius with their co-workers found independently that diabetic patients had a poorer 10-year prognosis than non-diabetic patients [14,29]. In both studies insulin-treated patients with diabetes had the poorest 10-year survival rate. Also, in a 10-year follow-up of CABG patients Mohammadi and colleagues found insulin-treated DM to be an independent risk factor for long-term cardiac mortality [15]. However, in DM patients not on insulin therapy, the cardiac-specific survival was similar to that observed in non-diabetic patients [15].

Our results are in accord with the findings of Thourani and Alserius, suggesting inferior survival of DM patients on insulin compared to those without insulin or to non-diabetics. Insulin treatment might suggest more severe and advanced diabetes in this cohort.

We found, that the excessive death rate of diabetics was mostly but not completely related to cardiovascular causes. Our results conform to the idea that long-lasting DM is associated with a generalized vascular disease which is characterized by impaired vascular endothelial function and hypercogulation [14,29].

The strength of the present study is the reliability and scope of the national registers used, allowing 100% coverage of the mortality data of our patients [30]. Our follow-up includes all subjects operated, like those migrated in the country and one patient moved in the neighbouring country. The length of the postoperative follow-up was exactly 16 years allowing conclusions more valid than those based on a shorter follow-up. According to Finnish health care policy every citizen has access to health care mainly financed by taxes. So in the background population such social factors, like a proportion of non-secured citizens, did not affect our results [31].

Certain limitations should also be considered. Firstly, the perioperative data were collected retrospectively [16].

Even though information was completed with patient questionnaires and direct contacts, 16 (1.7%) out of the original sample of 961 patients were excluded by reason of insufficient data. Secondly, we identified BMI-based obesity, not waist circumference, as a factor of the metabolic syndrome. Nevertheless, BMI is widely used in the modified definition of MetS and studies have demonstrated concordance between the definitions of MetS [7,18].

Conclusions

In this long-term follow-up study patients with neither DM nor MetS had extremely good prognosis for at least 16 years when compared to the matched background population. Also the survival of patients with MetS but without DM had a good prognosis. Survival of DM patients started to deteriorate already short after the operation.

Additional file

Additional file 1: Table S1. Univariate predictors of mortality. All variables presented here were taken into the Bayesian multivariate analysis.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

VH and AP designed the study. They acquired the final data and drafted the manuscript. MK carried out data maintenance and statistics. JL, MT and SV participated in the design and drafting of the manuscript. Other members of the W-CABG study group participated in their own hospitals in data acquisition. All authors read and approved the final manuscript.

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Obesity paradox disappears in coronary artery bypass graft patients during 20-year follow-up

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Abstract

Aims: Although obesity is a risk factor for coronary heart disease (CHD), it might be associated with a favourable prognosis in patients with CHD. The aim of the study was to evaluate this so called 'obesity paradox' during a follow-up period of 20 years in patients who had undergone coronary artery bypass grafting (CABG).

Methods and results: The study population consisted of 922 CHD patients who had undergone CABG between 1993 and 1994. Pre and perioperative data was collected from patient records and supplemented with patient questionnaires, telephone contacts and data from national archives. The 10-year postoperative prognosis of normal-weight patients (body mass index (BMI) 18.5–24.9 kg/m^2) was inferior to that of overweight (BMI 25.0–29.9 kg/m^2) and obese patients (BMI$\geqslant$30.0 kg/m^2) and to the background population. Beyond 10 years the prognosis of obese patients deteriorated when compared with the overweight group. At the end of the 20-year follow-up, survival of the normal weight group was 0.68 (95% confidence interval (CI), 0.49–0.87; p<0.001), the overweight group 0.82 (95% CI, 0.71–0.92; p<0.001), and the obese group 0.67 (95% CI, 0.49–0.85; p<0.001), when compared with their background populations (=1.00). Obese patients developed diabetes more frequently and died more frequently of cardiovascular disease than patients in the two other study groups during the second postoperative decade (p<0.01).

Conclusion: During long-term follow-up the obesity paradox seems to disappear due to progression of cardiometabolic disease in patients who have undergone CABG.

Keywords

Coronary artery bypass grafting, obesity paradox, diabetes mellitus, mortality

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Introduction

Obesity is an increasing health problem worldwide. Being overweight is defined as a body mass index (BMI)$\geqslant$25 kg/m^2 and obesity is defined as BMI$\geqslant$30 kg/m^2.[1] The global prevalence of obesity has almost doubled between 1980 and 2008.[2] According to the World Health Organisation (WHO), more than one third of adults worldwide over the age of 20 were overweight and 12% were obese in 2008.[2]

While obesity in itself seems to be a risk factor for coronary heart disease (CHD), it is associated with a cluster of important conditions including insulin resistance, dyslipidaemia and type 2 diabetes mellitus (DM2), which contribute directly and indirectly to the development and progression of CHD.[3,4] In addition CHD is linked to dietary problems and abnormal endocrine activity of adipose tissue, which further contribute to the risk of CHD in these patients.[5,6]

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Despite the evidence of causality between obesity and development of CHD as well as increased mortality in primary prevention,[7] several studies suggest that obesity might be associated with a better prognosis in CHD patients.[8] In a number of cardio-metabolic conditions the BMI-mortality curve has typically been U-shaped, with best survival in overweight patients and mild to moderate obesity and increasing mortality in slim patients and in patients with morbid obesity.[9,10]

Our aim was to evaluate the presumed finding of an obesity paradox in patients with coronary artery bypass grafting (CABG) over a follow-up period of 20 years, focusing on survival after the first two postoperative months.

Methods

Study population

The study population originally consisted of all CHD patients who had undergone CABG at Tampere University hospital from 1 January 1993–30 June 1994.[11] Patients undergoing simultaneous carotid artery or valve surgery were also included in the analysis. Patients, who survived beyond the immediate postoperative period (defined as two months postoperatively) were included in the analysis and followed for up to 20 years. The study protocol was approved by the Ethics Committee of Tampere University Hospital.

Data collection and clinical definitions

Patient demographics and perioperative data including BMI were collected from medical records at Tampere University Hospital and the secondary care hospitals involved in postoperative care. A survival analysis was conducted after the closing date (14 July 2014) and was based on data obtained from Statistics Finland (previously the Statistical Office of Finland). Survival data was available for a total of 20 years for all patients included in the study, and causes of death were available until 31 December 2012.

A history of hypertension, peripheral vascular disease, previous myocardial infarction, previous transient ischaemic attack (TIA) and stroke was collected from patient records. Renal function was evaluated preoperatively by glomerular filtration rate (GFR), calculated with the CKD-EPI equation originally presented by Chronic Kidney Disease Epidemiology Collaboration and a GFR of less than 60 ml/min/1.73 m^2 was regarded as evidence of impaired renal function.[12] Patients were defined as hypercholesterolaemic if total cholesterol was ⩾5 mmol/l (⩾200 mg/dl) (National Cholesterol Education Program Adult Treatment Panel III) or patients were on lipid-lowering drug therapy.[13] Smoking history was based on questionnaire data.[11] Persistence of obesity was recorded by a patient questionnaire 9.5 years after CABG.

Diabetes was defined by the 1998 WHO criteria with a fasting blood glucose level (fB-Gluc)⩾6.1 mmol/l or random blood glucose⩾10.0 mmol/l as diagnostic.[14] A patient was also classified as diabetic if hospital records or the Social Insurance Institution of Finland database demonstrated a history of antidiabetic medication. Obesity was defined according to BMI and calculated as mass/height^2 (kg/m^2). The study population was divided into normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) and obese (BMI⩾30.0 kg/m^2) groups. Only one patient was underweight with a BMI 17.9 kg/m^2 and was analysed with the normal weight patients.

Survival analysis

Separate survival analyses (2 months to 5, 10, 15 and 20 years) were carried out for 922 patients. The postoperative period was defined as two months to separate immediate postoperative period with higher mortality from the long-term follow-up.[11] Survival analysis was conducted on each BMI group (normal weight, overweight and obese) separately. The cumulative and relative mortality for each group was calculated against age-, sex- and time-specific national background populations as described in the Statistical methods section. Furthermore, the relationship of BMI to long-term survival (two months to 5, 10, 15 and 20 years, respectively) was analysed by comparing the three patient groups. Cardiovascular mortality was defined as death caused by ischaemic heart disease, stroke, peripheral arterial disease or sudden cardiac death.

Statistical methods

In the comparison of patient characteristics, categorical data was tabulated as frequencies and percentages, and continuous variables were expressed as a mean and standard deviation (SD).

Differences between two groups were tested by the chi square test and the Wilcoxon rank test. In the analysis of more than two groups the Kruskal-Wallis test was used. Fisher's exact test was used when appropriate in two-by-two tables with directed hypothesis. Differences in mean values between two groups were tested by the Student's *t*-test and in the case of more than two groups by analysis of variance.

The relative survival rate was analysed by sex, age, and BMI using the life table method as presented earlier.[11,15] With this approach, the observed survival rates of the groups are compared with the rates based on age-, sex- and time-specific life tables for the whole population in Finland. For example, at the time of the operation (1994), the mean life expectancies of Finnish 65-year old men and women were 14.6 and 18.6 years, respectively.[16] Double arithmetic smoothing was applied when associations of BMI with adjusted all-cause mortality over 10, 15 and 20 years after CABG were presented. Overall survival curves according to each BMI class were also generated with Kaplan–Meier method. Cardiovascular mortality was

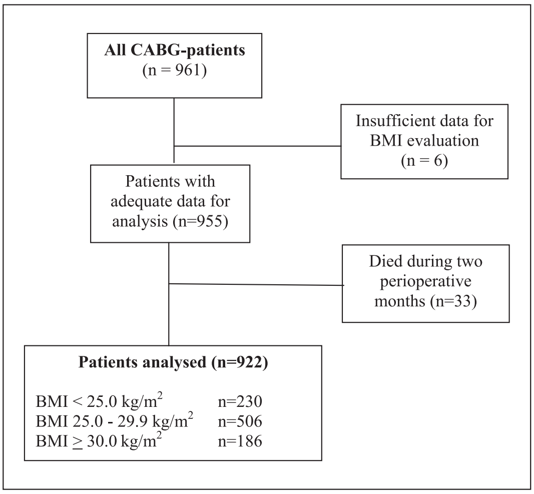

Figure 1. Study flow chart. BMI: body mass index (kg/m^2); CABG: coronary artery bypass grafting.

analysed as described above. If the overall *p*-value was <0.05, the head-to-head comparisons of the groups were analysed by Student's *t*-test.

To study the independent significance of BMI for clinical outcome, multivariate analysis was made using an optimising stepwise procedure based on the Bayesian approach.[11,17] This procedure was developed for nominal variables, and does not require a perfect variable matrix. It is also appropriate, when analysing curve linear variables. Starting from the best predictor in univariate analysis, it selects, by the heuristic approach, the combination of variables which best explains the selected outcome factor.

Results

Study population

A CABG was performed in total for 961 patients during the study period. Complete data was available for 922 CABG patients alive two months postoperatively (Figure 1). These patients formed the study cohort that was followed up for 20 years.

Patient demographics and clinically relevant co-morbidities at the time of surgery for all 922 consecutive study patients are presented in Table 1. Mean age was 61.7 (SD 8.4) years; 193 patients were women (mean age 64.9 (SD 7.6) years) and 729 patients were men (mean age 60.9 (SD 8.4) years). Overall 24.9% were normal weight, 54.9% overweight and 20.2% obese. No patients were lost during the 20-year follow-up. The absolute 20-year mortality was 67% in normal weight, 56% in overweight and 60% in obese patients. Cause of death data was available for 97% of deceased patients by the end of 2012.

When the three patient groups were compared, the proportion of women was slightly higher (not significant (NS)) and overall patients were younger in the obese group ($p<0.05$, BMI$\leqslant$24.9 kg/m^2 vs $\geqslant$30.0 kg/m^2). DM, hypertension and dyslipidaemia associated with metabolic syndrome (MetS) were more frequently found in the obese group and least frequent in the normal weight group (Table 1). Peripheral arterial disease defined as symptomatic claudication was significantly more common in the normal weight group than in the overweight and obese groups. Other concomitant diseases, rate of renal dysfunction, cardiac function, severity of CHD and preoperative smoking did not differ significantly between the groups (Table 1). Neither were the differences in postoperative smoking (in normal weight, overweight and obese patients 11%, 6% and 8%, respectively), nor in the use of low-dose acetylsalicylic acid (ASA), statins and Angiotensin Converting Enzyme inhibitors (ACE) inhibitors significant, when evaluated 21 months postoperatively.

According to data obtained by the questionnaire, patients who were obese at the time of CABG mainly remained obese at 9.5 years postoperatively and correspondingly patients with normal BMI remained with normal BMI ($p<0.001$), (Supplementary Material, Data File S1). In addition, during the first 10 postoperative years, 6.1%, 13.0% and 23.7% of patients ($p<0.01$) developed new onset diabetes in the normal weight, overweight and obese patient groups, respectively.

Survival

During the first postoperative years prognosis was favourable in all patient groups. At five years the relative survival was similar in normal weight patients 1.01 (95% confidence interval (CI), 0.97–1.05; *p*=NS), overweight patients 1.03 (95% CI, 1.01–1.06; $p<0.05$) and obese patients 1.04 (95% CI, 1.00–1.07; *p*=NS). Beyond the first five years the survival curves separated.

Normal BMI in long-term follow-up was associated with significantly inferior survival when compared with the background population. This prognosis was already seen 10 years after CABG 0.92 (95% CI, 0.88–0.96; $p<0.01$). Thereafter survival in these patients continued to deteriorate being 0.68 (95% CI, 0.49–0.87; $p<0.001$) at 20 years (Figure 2).

The survival of overweight patients at 10 years was as good as that of the background population 1.01 (95% CI, 0.99–1.03; *p*=NS), but it subsequently deteriorated. At 20 years postoperatively relative survival in this group was 0.82 (95% CI, 0.71–0.92; $p<0.001$) (Figure 2).

The relative survival of obese patients at 10 years was 0.98 (95% CI, 0.94–1.02; *p*=NS) and sharply decreased thereafter to 0.67 (95% CI, 0.49–0.85; $p<0.001$) (Figure 2) at the end of the follow-up period of 20 years.

In Figure 3, the relative survival of the three patient groups is compared in relation to each other, over the time

Table 1. Preoperative demographic data, clinical characteristics and severity of coronary heart disease in 922 patients surviving two months after coronary artery bypass grafting (CABG).

	BMI<25.0	BMI 25.0–29.9	BMI⩾30.0	Overall *p*-value
Number of patients				
At the time of CABG	230	506	186	–
10 Years postoperatively	167	407	150	–
20 Years postoperatively	75	224	75	–
BMI, kg/m^2	23.3	27.3	32.5	–
Female, %	20.6	19.7	24.9	NS
Mean age, years (SD)	62.6 (8.8)	61.7 (8.2)	60.3 (8.3)	<0.05[1]
Concomitant diseases				
Previous MI, %	60.5	72.6	72.9	<0.05[1]
Previous TIA or stroke, %	10.1	11.1	7.7	NS
Peripheral arterial disease	13.0	8.0	7.0	<0.05[1]
DM, %	29.8	36.2	52.4	<0.0001[2]
Hypertension, %	54.0	61.6	69.6	<0.01[3]
Glomerular filtration rate				
GFR, ml/min (SD)	75.6 (15.9)	74.7 (16.4)	75.0 (15.9)	NS
GFR<60 ml/min/1.73 m^2, %	15.7	15.7	16.3	NS
Lipid disorder				
Hypercholesterolaemia, %	71.8	72.9	78.3	NS
Low HDL cholesterol, %	53.5	67.4	71.4	<0.001[4]
Elevated triglyceride, %	37.1	58.4	73.0	<0.0001[2]
Preoperative smoking, %	62.5	63.7	67.4	NS
Severity of heart disease				
EF, % (SD)	59.5 (13.6)	60.7 (13.5)	59.2 (13.9)	NS
EF⩽35%, %	6.3	7.2	7.4	NS
NYHA II, %	10.8	11.9	7.7	
NYHA III, %	57.8	57.1	56.6	NS[5]
NYHA IV, %	31.4	31.0	32.1	
Three–vessel or LM disease, %	59.6	63.2	56.6	NS
Urgent or emergency operation, %	30.3	28.9	30.6	NS

BMI: body mass index (kg/m^2); MI: myocardial infarct; TIA: transient ischemic attack; GFR: glomerular filtration rate; Hypercholesterolemia: ⩾5,0 mmol/l or on lipid-lowering medication, Low high density lipoprotein (HDL) cholesterol: men <1.03 mmol/l, women <1.3 mmol/l, Elevated triglyceride: ⩾1.7 mmol/l; EF: ejection fraction; NYHA: angina pectoris symptoms according to New York Heart Association; LM: left main; NS: not significant.

[1]Unadjusted p<0.05 by the pooled t-test for the comparison BMI<25.0 against BMI⩾30.0 kg/m^2.

[2]Unadjusted p<0.0001 by the pooled t-test for all comparisons.

[3]Unadjusted p<0.01 by the pooled t-test for the comparisons for BMI⩾30.0 kg/m^2 against both other groups.

[4]Unadjusted p<0.001 by the pooled t-test for the comparison BMI<25.0 kg/m^2 against BMI 25.0–29.9 kg/m^2.

[5]NYHA II–IV as a group NS.

periods of 10, 15 and 20 years. During the first 10 postoperative years, obese patients had equally good survival as overweight patients. Thereafter survival decreased and at 20 years was similar to that seen in the normal weight group. In normal weight patients the most unfavourable 20-year prognosis was associated with the lowest BMIs and in the obese group in patients with a BMI⩾35.0 kg/m^2 (Figure 3).

Kaplan-Meier curves of absolute survival are shown as Supplementary Material, Data file S2. In multivariate analysis, age, diabetes, left ventricular ejection fraction at the time of CABG, and BMI had independent impact on prognosis. This is presented in a model calculating also probabilities of postoperative survival (Supplementary Material, Data File S3).

Cardiovascular mortality

During the first decade after CABG, cardiovascular disease was the primary cause of death in 56% of normal weight patients and in 66% of overweight patients and during the second postoperative decade this figure was 59% and 58%, respectively (NS for both changes). In obese patients cardiovascular mortality increased significantly with time and was 45% during the first postoperative decade and 77% during the second decade (p<0.01).

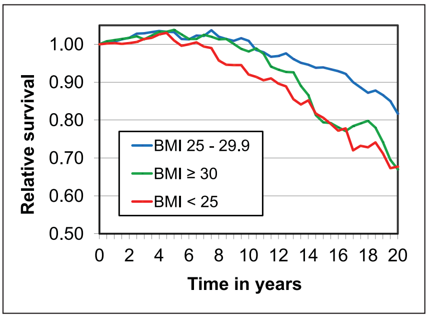

Figure 2. Relative survival two months to 20 years postoperatively according to each body mass index (BMI) class compared with national age-, sex- and time-matched background population (relative survival 1.00, *n*=922).

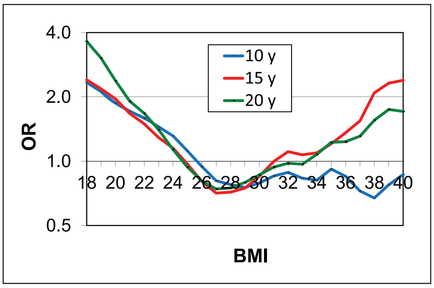

Figure 3. Association of body mass index (BMI) as a continuous variable with adjusted all-cause mortality using basic odds ratio (OR) formula 10, 15 and 20 years after coronary artery bypass grafting (CABG). An OR of 1.0 represents that of an average CABG patient (*n*=922). The curves are smoothed and represented in logarithmic scale.

Discussion

Our key finding was that obesity paradox seems to be a consequence of too short a follow-up period. In obese CHD patients who had undergone CABG, the initial prognosis was good but deteriorated when the follow-up period was extended to 20 years. In this study overweight patients (BMI 25–29.9 kg/m^2) had the most favourable prognosis. Their survival even outweighed that of normal weight patients. To the best of our knowledge, this is the first study, in which the survival of CABG patients graded by weight has been followed for two decades postoperatively and compared with matched national background populations.

During the first postoperative decade the prognosis of overweight and obese CABG patients was as good as that of their background populations. Prognosis in these patients was even better than the 10-year prognosis of normal weight patients. This phenomenon, called the obesity paradox, has been seen in a wide range of CHD manifestations including CABG patients.[4,8]

The prognostic impact of BMI in CABG patients over 3–7 years has been reported in several studies. In most analyses CABG patients with BMI <25 kg/m^2 had a less favourable prognosis, when compared with overweight and obese patients, with the best prognosis being in mildly obese and overweight patients.[18–20] In one study, being either obese or normal weight was associated with a reduced seven-year survival after CABG, when compared with being overweight.[21]

Several explanations may account for the obesity paradox, when the follow-up is restricted for a few years only. Obesity is most commonly defined by BMI as it is a readily measurable parameter used in routine clinical practice. BMI has been criticised for its lack of accuracy in defining obesity in a CHD population.[10,22] It is an aggregate of varying amounts of fat-free mass and body fat and correlates poorly with body fat especially in overweight subjects. In addition, it cannot differentiate central fat from peripheral fat. When body fat was measured by bioimpedance, BMI⩾30 kg/m^2 had a very high specificity (97%), but poor sensitivity (42%) in detecting obesity.[22,24] The main limitation of BMI is its inability to differentiate body fat from lean mass and central from peripheral obesity. Therefore, trained athletes with high body muscle mass and vice versa people with low lean mass but increase body fat may be misclassified by BMI.

Fat-free mass is widely considered as a positive prognostic factor, whereas CHD as a systemic disease can result in cachexia similar to that seen in heart failure.[25] Both fat-free mass and body fat might provide a protective metabolic buffer.[26] On the other hand, poor nutritional status predicts mortality after cardiac surgery.[27,28]

There are also other potential explanations through which the obesity paradox could arise. Obesity was previously considered a perioperative risk factor in CABG.[29] It is therefore possible that high-risk obese patients in this study population were excluded from revascularisation creating a selection bias. In addition, normal weight patients had an increased tendency for postoperative smoking and they had more peripheral arterial disease, which are both markers of poor prognosis.[7,30] This disparity of BMI groups has also been observed previously.[21] Furthermore, it has been postulated that obese patients might be receiving better disease-modifying medication than normal weight patients,[19] though in our material they did not use significantly more ACE inhibitors, statins or ASA.

After the first postoperative decade, prognosis of obese patients deteriorated and at 20 years postoperatively it was at the same level as that of the normal weight patients. Obesity persisted in our patient population during the follow-up period. In addition, patients who were obese at the time of CABG developed diabetes more frequently than the normal weight patients. DM is a known risk factor of cardiovascular disease[31] and seems to have impaired long-term prognosis in this group. Obese patients in this study had a substantial increase in cardiovascular mortality during the second decade following CABG, which accounts for their lower survival during long-term follow-up.

The 20-year prognosis of overweight patients was better than the prognosis of lean and obese patients. Nevertheless, during the second follow-up decade their survival was also inferior to that of the background population. We have previously shown that diabetes in our patient population was an important predictor of poor prognosis.[11] Out of the overweight patients, 36% were diabetic (Table 1), which would have affected long-term prognosis in this group.

Strengths and limitations

The strength of the present study is provided by the national registers, which allow 100% coverage of mortality data in our patients.[32] The length of the postoperative follow-up of each patient was exactly 20 years or until death (35.4% and 64.6%, respectively). Our study therefore allows more valid conclusions than those based on shorter follow-up data. In Finland, health care is mainly publicly managed, ruling out the existence of citizens without comprehensive health insurance coverage. Therefore, no significant economic factors in the background population affected our results.

Certain limitations should be considered. Firstly, the perioperative data was collected retrospectively.[11] Even though information was completed with patient questionnaires and direct patient contacts, six patients (0.6%) from the original sample of 961 were excluded on the grounds of insufficient data. Secondly, we identified obesity based on BMI, not on waist circumference or waist-hip ratio. Nevertheless, BMI is widely used as a measure of obesity in the modified definition of MetS and studies have demonstrated concordance between all these definitions.[33,34]

Conclusions

Based on our findings, the so-called obesity paradox disappears in CABG patients, when the follow-up period is extended to 20 years. The late survival of obese patients was obviously negatively affected by the presence of unfavourable cardiometabolic conditions, such as diabetes, which were observed during the postoperative years. Slightly overweight CABG patients had the best survival over a 20-year postoperative follow-up period. Our findings support the need for the prevention of obesity and effective weight loss in CHD patients, as permanent obesity is associated with increased late mortality following CABG.

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