Studies of Myocardial Function After Coronary Bypass Surgery and Prognostic Markers of Revascularization and Survival

Thesis by

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Oslo, January 2013

Camilla Lund Søraas

List of papers

I Larstorp AC, Lund Søraas C, Tønnessen T, Müller C, Kjeldsen SE, Mangschau A.
Scintigraphic demonstration of myocardial perfusion and ischaemia associated with coronary artery bypass grafting.
Scandinavian Cardiovascular Journal 2006;40:354-62.

II Søraas CL, Larstorp AC, Mangschau A, Tønnessen T, Kjeldsen SE, Bjørnerheim R.
Echocardiographic demonstration of improved myocardial function early after coronary artery bypass graft surgery.
Interactive CardioVascular and Thoracic Surgery 2011;12:946-51.

III Søraas CL, Wachtell K, Okin PM, Dahlöf B, Devereux RB, Tønnessen T, Kjeldsen SE, Olsen MH.
Lack of regression of left ventricular hypertrophy is associated with higher incidence of revascularization in hypertension: The LIFE Study.
Blood Pressure 2010;19:145-51.

IV Søraas CL, Friis C, Engebretsen KV, Sandvik L, Kjeldsen SE, Tønnessen T.
Troponin T is a better predictor than creatine kinase-MB of long-term mortality after coronary artery bypass graft surgery.
American Heart Journal 2012 – published online ahead of print.

The papers are referred to by their Roman numeral throughout the thesis.

Abbreviations

CABG	Coronary artery bypass grafting
CK-MB	Creatine kinase-myocardial band
cTnT	Cardiac troponin T
ECG	Electrocardiogram
EuroSCORE	European System for Cardiac Operative Risk Evaluation
HDL	High-density lipoprotein
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
PCI	Percutaneous coronary intervention
WMSI	Wall motion score index

Introduction

Coronary artery disease and coronary artery bypass grafting

Coronary artery disease is the predominant cause of cardiovascular disease, which is the leading cause of death worldwide[1]. The number of affected individuals is expected to rise further in the coming years due to changing lifestyles in the developing world[2]. Coronary artery disease refers to a spectrum of clinical conditions in which the pathophysiology is impaired supply of oxygenated blood to the myocardium, usually caused by atherosclerotic or thrombotic narrowing of the coronary arteries. Treatment aims to prolong survival, relieve symptoms of ischemia, improve functional status and thereby improve quality of life[3]. This may be achieved by optimal medication and, for selected groups of patients, by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

The Russian surgeon Vasilii Kolessov in 1964 performed the first sutured bypass grafting using the internal mammary artery without use of cardiopulmonary bypass[4]. The CABG procedure as we know today developed rapidly in the USA during the next years and surgical revascularization went from being experimental to become a standard treatment option for coronary artery disease. This was largely aided by the development of cardiopulmonary bypass and the angiography technique[5]. Further advances in coronary surgery, among them better myocardial preservation, use of arterial conduits and improved postoperative care, have reduced mortality and morbidity despite increasing age and greater co-morbidities in patients undergoing surgical revascularization[6-9]. Today, CABG is the most common type of cardiac surgery for adults, with more than 400,000 operations per year in the United States alone[10]. In Norway this number averages more than 2,300 procedures annually, which constitutes approximately 55% of all open-heart surgery procedures[11].

In 1977 PCI was developed as a non-surgical alternative to CABG and has since been increasing in popularity[12,13]. A recent study reported that PCI rates in the United States were stable in the period 2001-2008, but the rates of CABG substantially declined during this time period. The indications for CABG versus PCI have long been an issue of debate due to few randomized trials and the evolution of drug-eluting stents showing promising results. To address this issue, the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) study was conducted. This prospective randomized trial concluded that CABG remains the standard of care for patients with previously untreated three-vessel or left main coronary

artery disease[14]. These findings were important to re-emphasize the role of CABG as the evidence-based treatment of choice for these patient groups[15].

Myocardial stunning and hibernation

Myocardial ischemia occurs when there is an imbalance between myocardial oxygen supply and demand, and this is usually a result of atherosclerosis. As the coronary artery lumen gradually narrows, blood flow is reduced and a myocardial adaption to ischemia evolves. Perfusion and contractile function seem to be matched, and consequently, if the ischemia continues, this may result in reduced contractile function[16,17]. If contributions from collaterals, plaque morphology, and abnormal microvasculature are ignored, coronary stenosis below approximately 40 percent will not influence blood flow[18,19]. Between approximately 40 and 80 percent stenosis, resting myocardial blood flow will remain normal whilst maximum blood flow will be reduced. Thus, episodes of increased oxygen demand may result in a limited period of reversible left ventricular dysfunction, also characterized as myocardial stunning. A stenosis exceeding 80 percent of the vessel lumen may be associated with reduced resting blood flow and consequently reduced left ventricular contraction through perfusion-contraction matching. As defined by Rahimtoola, hibernating myocardium is a condition of persistently impaired myocardial function at rest due to chronically reduced blood flow[20]. If the myocardial oxygen/demand relationship is favorably altered, left ventricular function may be partially or completely restored. Both myocardial stunning and hibernation share several common features, and there may be considerable overlap between the two states[21]. Possibly, they reflect a continuum, for example, repetitive stunning may contribute to the development of myocardial hibernation [22,23].

The aim of revascularization is to restore myocardial oxygen supply to the myocardium and thereby reduce symptoms of myocardial ischemia. Patients with dysfunctional, but viable, myocardium may additionally regain regional and global contractile function after revascularization[24]. However, the time course of improvement in myocardial function after CABG is not fully described. In patients with viable myocardium, the time needed to recover left ventricular function is quite variable and may take weeks, months or even more than a year[25-28]. Especially the early changes after revascularization, during the first days and weeks postoperatively, have been insufficiently documented.

Several methods are available for detecting changes in myocardial perfusion and function. Myocardial perfusion scintigraphy, using radionuclide tracers, is a well-established

noninvasive method of evaluating coronary blood flow[29,30]. Echocardiography is a widely used diagnostic tool for evaluating myocardial function. It has the advantage of being noninvasive, widely available and inexpensive, but is limited by being dependent on the examiner`s experience[31].

Diagnosis of perioperative myocardial infarction

Perioperative myocardial infarction is a complication of CABG and an important cause of postoperative mortality[32,33]. The incidence of perioperative myocardial infarction varies in the literature and has been reported ranging from 1.3 % to 25% in different populations[34-36]. The diagnosis can be difficult to make after CABG since release of myocardial biochemical markers caused by direct surgical manipulation, global ischemia or inadequate myocardial protection is common[37] and may be difficult to distinguish from myocardial damage owing to an acute infarction. New Q-waves in the ECG have been considered the most reliable diagnostic measure, yet, their clinical relevance for prognosis has also been questioned[38,39]. The Joint Task Force of the European Society of Cardiology/American College of Cardiology in 2007 defined a CABG related myocardial infarction as a biomarker elevation > 5 times the upper limit of normal within the first 72 hours postoperatively when associated with the appearance of new pathological Q-waves or new left bundle branch block, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium[40]. However, the cut-off chosen for biomarker elevation lacks supportive evidence, and these recommendations have been an issue of debate[40,41].

Left ventricular hypertrophy and albuminuria

Left ventricular hypertrophy (LVH), determined by the Cornell voltage product or Sokolow-Lyon voltage in the ECG or by echocardiography, is an independent predictor of cardiovascular morbidity and mortality[42-44]. A study by Liao et al[45] found that LVH was associated with a greater risk of all-cause mortality than coronary artery single-vessel or multivessel-disease verified by coronary angiography or left ventricular systolic dysfunction. The exact pathophysiological mechanisms are unknown, but may involve systemic inflammation, atherosclerosis, endothelial dysfunction and direct myocardial alterations. LVH has been associated with coronary artery calcium and carotid plaque[46-48], supporting that LVH is associated with subclinical atherosclerosis.

The urine albumin-to-creatinine ratio is a measure of endothelial damage at the glomerulus, reflecting early dysfunction in the vascular tree in general[49]. It has been related to subclinical atherosclerosis in the general population[50,51] as well as in hypertensive patients[52]. Regression of left ventricular hypertrophy and albuminuria during antihypertensive treatment is shown to reduce the risk of cardiovascular events[53,54]. However, the effect of regression of LVH and albuminuria regarding the end point revascularization has not been studied, despite the fact that several studies link these two risk factors with atherosclerosis[48,51].

Biochemical markers of survival after CABG

Elevations of creatine kinase myocardial-band (CK-MB) and cardiac troponins are common after CABG. CK-MB is an isoenzyme of creatine kinase which is located in the cytosol and mainly expressed in the myocardium[55]. Troponin is a protein complex of three subunits (T, I and C) that modulates the calcium-mediated interaction between actin and myosin in skeletal and cardiac muscle tissue[56]. As cardiac troponins are the most sensitive and specific among the cardiac biomarkers, they are regarded as "the gold standard" for diagnosing acute coronary syndromes[40]. When it comes to biomarkers post-CABG, both CK-MB and troponins have been associated with short- and mid-term mortality[57-60], but their long-term prognostic value remains unclear. Furthermore, few studies have compared the prognostic effects of CK-MB and troponins with the aim to determine the better predictor.

Aims of the thesis

Paper I To test the hypothesis that myocardial perfusion scintigraphy may elucidate myocardial perfusion and ischaemia associated with CABG. To test the hypothesis that myocardial perfusion scintigraphy can detect more cases of perioperative myocardial infarction after CABG than cardiac biochemical markers and ECG.

Paper II To test the hypothesis that left ventricular function improves during the first seven weeks postoperatively after CABG.

Paper III To test the hypothesis that regression of left ventricular hypertrophy (LVH) and urine albumin-to-creatinine ratio is associated with the incidences of coronary and peripheral revascularization in hypertensive patients and to test whether regression of LVH after completed coronary or peripheral revascularization reduces cardiovascular mortality.

Paper IV To test the hypothesis that CK-MB and cTnT are predictors of long-term mortality after CABG and to determine which of these two biochemical markers is the better predictor.

Materials and methods

Papers I and II

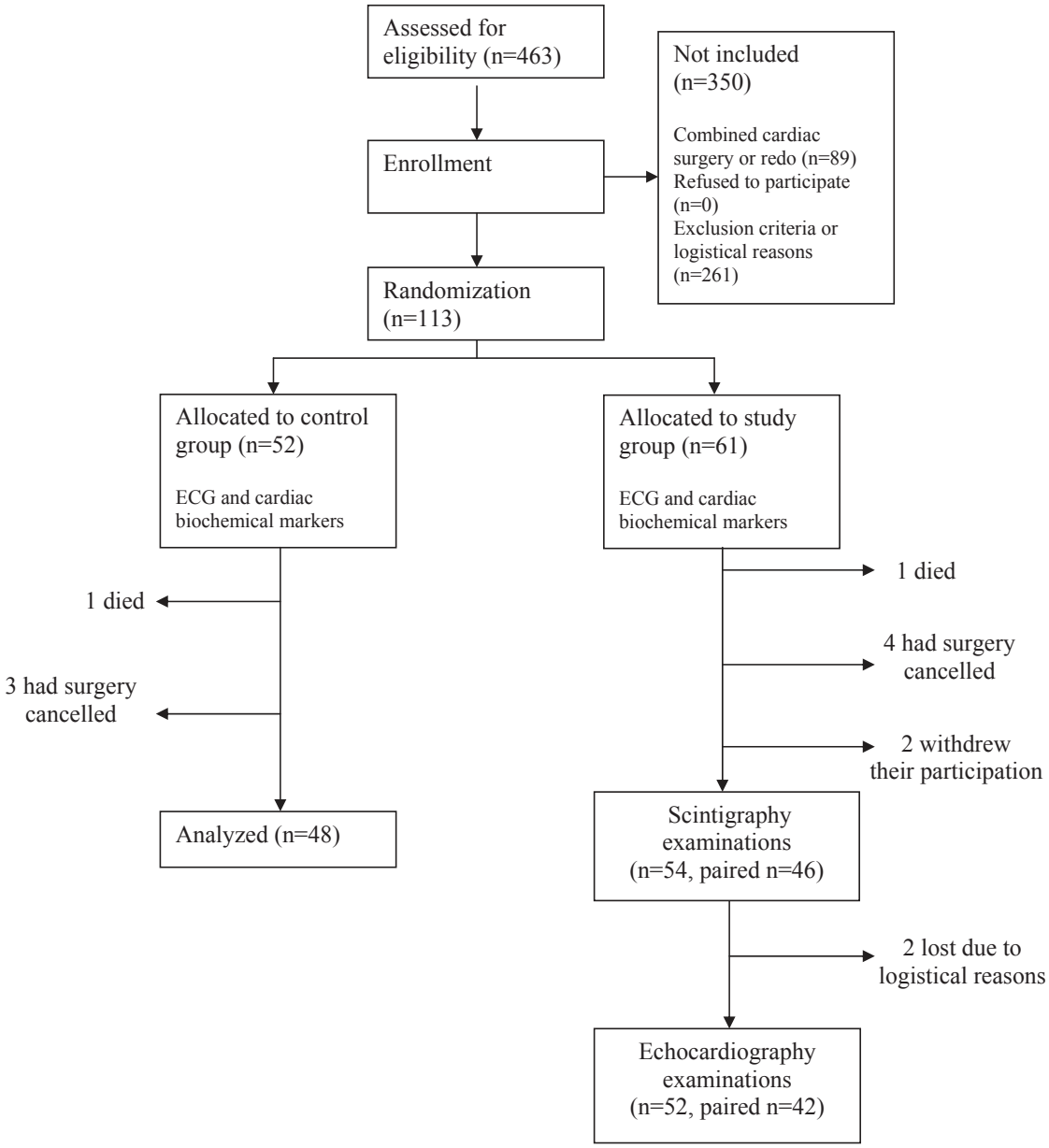
Patient population

113 patients scheduled for first-time elective CABG at Oslo University Hospital, Ullevål were included in the prospective SCENARIO (SCintigraphic EvaluatioN of Aortacoronary Revascularization Inhospital Organization) study from January 2002 to August 2003. The indication for operation was symptomatic coronary artery disease with at least one significant coronary artery stenosis (>50% lumen diameter reduction) determined by angiography, not suitable for PCI. The pre-specified exclusion criteria were combined procedures, renal failure, chronic obstructive pulmonary disease, body mass index > 30 kg/m^2 and age above 80 years. The research protocol was approved by the Regional Ethics Committee of Eastern Norway. All patients gave verbal and written informed consent.

Patients were at inclusion randomized consecutively into two groups; a study group and a control group (Figure 1). Randomization was performed by drawing sealed envelopes. All included patients underwent standard CABG surgery and standard postoperative care at our hospital. Daily ECGs and cardiac biochemical markers at 7, 20, 44 and 72 hours postoperatively were registered for all patients. The study group additionally underwent myocardial perfusion scintigraphy and echocardiography at rest 1-7 days preoperatively, 2-4 days postoperatively and 6-7 weeks postoperatively. Surgery was cancelled for seven patients and two patients withdrew their informed consent. Due to this fairly small, but uneven withdrawal rate, we had to re-randomize and continue inclusions, leaving a total of 102 patients for analysis; 48 in the control group and 54 in the study group.

A few patients did not participate in all three examinations, either because of their clinical condition (pain, reduced mobility or postoperative confusion) or due to logistical reasons as the high turnover in the department resulted in rapid transferral of patients to their local hospitals. Therefore, data were presented both as data for all patients with at least one examination and as paired data for patients having a complete set of all three examinations (n=46 undergoing scintigraphy in paper I and n=42 undergoing echocardiography in paper II).

Figure 1. Flow chart of the patients in papers I and II.



Surgical procedure

CABG with cardiopulmonary bypass was performed during moderate hypothermia (32-34°C) via median sternotomy. Myocardial revascularization was performed by a left internal mammary artery graft to the left anterior descending (LAD) coronary artery and saphenous vein bypass grafting to other diseased vessels. The distal anastomoses were completed first and the proximal anastomoses were completed after removal of the cross-clamp.

Myocardial perfusion scintigraphy

Patients were injected with 400-500 mega-bequerel (MBq) ^{99m}Technetium-tetrofosmin (99mTc) (Myoview™, Amersham Health, Buckinghamshire, UK) at rest and given a light meal to accelerate hepatobiliary clearance. Thereafter, 32 projection images were acquired using a dual-head rotational gamma camera (Sophy DST, Sopha Medical Vision). Images were checked for patient motion and slice reconstruction was performed with standard filtered back projection technique by a technician blinded for clinical information, but not for time of examination. No attenuation- or scatter-correction was used. Data processing was performed by the use of a dedicated Sophy NXT computer system to produce short-axis, vertical and horizontal long-axis tomographic slices, and bull's eye plot of the left ventricle. Based on the size and severity of the perfusion defect in the bull's eye plot, the program calculated a hypoperfusion index. The hypoperfusion index was defined as the product of the defect extent (in percent of left ventricular surface) by its mean severity, expressed in percentage of the expected total heart uptake[61]. The best perfused area was defined as 100% radionuclide uptake and perfusion in all other areas was relative to this.

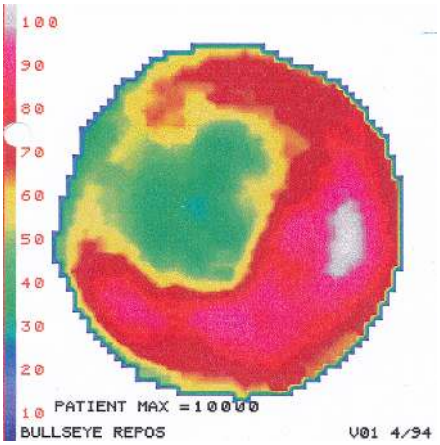


Figure 2. Bull`s eye plot.
A resting myocardial perfusion scintigram, bull`s eye plot, from one of the study patients preoperatively. The red colored area demonstrates normal radionuclide uptake (normal perfusion), whilst the green/yellow area anteroseptally demonstrates a region with reduced radionuclide uptake (reduced perfusion). The hypoperfusion index was 31.2%.

Definition of perioperative myocardial infarction

In the control group, perioperative myocardial infarction was defined as CK-MB ≥ 70 ng/ml and/or cTnT ≥ 3.5 ng/ml and peak value on the first postoperative day and ECG changes. In the study group, the same definitions as in the control group were used and in addition, perioperative myocardial infarction was defined as an increase in the hypoperfusion index ≥ 5 from the preoperative scintigraphic examination to the 2-4 days postoperative examination, with a fixed perfusion defect at the 6 weeks postoperative examination.

Echocardiography

Transthoracic two-dimensional echocardiography at rest was performed using a Vivid 5 scanner (GE Vingmed, Horten, Norway), equipped with a 1.7 MHz transducer in the second harmonic mode. M-mode echocardiographic analysis was based on the criteria of the American Society of Echocardiography[62]. Volumes and left ventricular ejection fraction (LVEF) were calculated using Simpson`s biplane method. Four standard views of the left ventricle were digitally stored in EchoPAC (GE Vingmed, Horten, Norway) for subsequent off-line analysis; parasternal long- and short-axis views and apical two- and four-chamber views. Echocardiography was performed by an experienced cardiologist blinded for clinical data, but not for the time of surgery. The intra-observer variation coefficients for end-diastolic volume and ejection fraction were 6.5% and 9.5%, respectively[63].

Regional wall motion was evaluated using a 16-segment model recommended by the American Society of Echocardiography[64]. The left ventricle was divided into six basal segments (anterior, anterolateral, inferolateral, inferior, inferoseptal and anteroseptal), six middle segments (same subgroups) and four apically located segments (anterior, septal, inferior and posterior). By visual analysis of systolic wall thickening, including in patients with abnormal septal motion after opening the pericardium during surgery, segments were assigned a wall motion score as follows: 1 = normal or hyperkinetic (normal endocardial excursion and systolic wall thickening), 2 = hypokinetic (reduced excursion and wall thickening), 3 = akinetic (absent excursion and wall thickening) and 4 = dyskinetic (paradoxic systolic outward wall motion). Wall motion score index (WMSI) was calculated by dividing the sum of all wall motion scores by the total number of segments analyzed. An improvement of segmental wall motion score ≥ 1 grade after revascularization was considered clinically significant.

Figure 3. The 16 segment model.

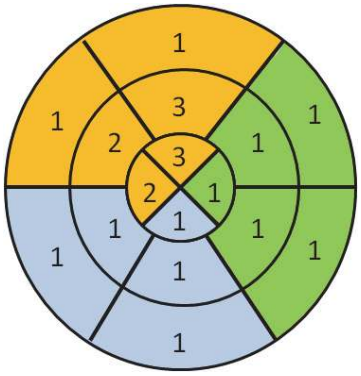


Illustration of the 16 segments left ventricular model with standardized segmentation and theoretical perfusion territories. In this patient, the sum of the wall motion scores of all segments was 22, giving a WMSI of 22/16 = 1.38. The orange segments are generally perfused by the left anterior descending (LAD) artery, the blue segments are perfused by the right coronary artery (RCA) and the green segments are perfused by the circumflex (CX) artery. Modified after Grenne et al[65].

Myocardial biochemical markers

Serum cTnT concentration and serum CK-MB concentration were determined by using electrochemiluminescence immunoassay (ECLIA) on the Roche Elecsys 2010 immunoassay analyzer (Roche Diagnostics, Mannheim, Germany) at the Department of Clinical Chemistry, Oslo University Hospital, Ullevål. The normal reference area for the cTnT test was 0-0.10 ng/ml and for CK-MB 0-5 ng/ml.

Electrocardiography

A serial 12-lead ECG was recorded preoperatively and on the first, second and third postoperative day. The ECGs were evaluated using World Health Organization criteria[66] by a cardiologist who was blinded for clinical data and had long experience in using these criteria. New Q-waves of ≥ 40ms duration or new QS-waves in multiple leads were considered more significant than ST-segment or T-wave changes, conduction disorders and new Q-waves in single leads.

Statistics

Statistical analysis was performed using SPSS versions 12.0 and 16.0 (SPSS, Chicago, IL, USA). Data are presented as mean ± standard deviation with range in parentheses for continuous variables with distribution sufficiently close to the normal distribution, median and 25th and 75th percentiles for continuous variables with distributions deviating markedly from the normal distribution, and proportions for categorical variables with percentages in parentheses. An exception was done for WMSI, which was presented as mean value despite being non-parametric. Normally distributed data were compared by Student *t* test. Non-normally distributed data were compared by Mann-Whitney *U* test for independent samples and Wilcoxon signed ranks test for paired samples. In paper II Friedman`s test for repeated measures was used. Categorical variables were compared using Pearson`s chi-square test or Fisher's exact test when appropriate. A two-tailed significance level of 5% was used throughout.

Paper III

Patient population

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study prospectively included 9193 patients aged 55-80 years with previously untreated or treated essential hypertension (>160/90 mmHg) and electrocardiographic LVH. In double-blind fashion patients were randomized to a losartan- or atenolol-based regimen and treated to a target blood pressure of <140/90 mmHg. In all patients, urine albumin-to-creatinine ratio, LVH by electrocardiography, serum high-density lipoprotein (HDL) cholesterol, plasma glucose and blood pressure were measured after two weeks of placebo treatment and yearly during the

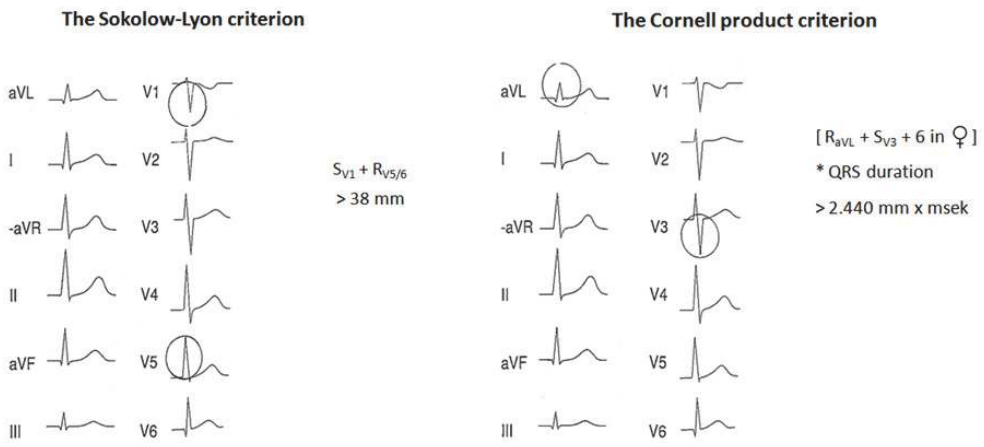
mean 4.8 years of anti-hypertensive treatment. All patients gave written informed consent, and the protocol was approved by regional ethical committees.

The revascularization analyses were a pre-specified part of the LIFE protocol with revascularization being a pre-specified secondary endpoint[67]. Each revascularization event was reported by the investigators and verified by an independent endpoint classification committee consisting of two cardiology experts and based on definitions in a pre-defined endpoint manual. Coronary revascularization was defined as all coronary artery revascularization procedures (angioplasty, atherectomy and stent) and heart transplants (which constituted very few, n<5). Peripheral revascularization included all non-coronary artery vascular surgeries and revascularization procedures (aortic aneurysm repair, carotid and peripheral revascularizations and amputations due to arterial vascular insufficiency and diabetes mellitus).

Electrocardiography

Standard 12-lead ECGs were taken at baseline, at six months and at yearly follow-up intervals until study termination or patient death. ECGs were interpreted by experienced readers blinded to clinical data at the Core Laboratory at Sahlgrenska University Hospital/Östra in Gothenburg, Sweden. LVH was defined as the product of QRS duration multiplied by the Cornell voltage combination ($R_{aVL} + S_{V3}$, with 6 mm added in women) higher than 2,440 mm x ms or Sokolow-Lyon voltage ($S_{V1} + R_{V5/6}$) higher than 38 mm.

Figure 4. Diagnosis of LVH by the Sokolow-Lyon and Cornell product criteria.



Urine albumin-to-creatinine ratio

Albuminuria was measured by standard methods using a turbidimetric method (Hitachi 717 Analyser; Boehringer Mannheim, Mannheim, Germany) in a single spot urine collection on the morning of the baseline ECG and after 12 months. Both serum and urine creatinine were analyzed using the Jaffé reaction without deproteinizing and then quantified by a photo-metric method (Hitachi 717 Analyzer). The urine albumin concentration was expressed as a ratio to urinary creatinine concentration, to provide a composite measure of renal glomerular capillary permeability adjusting for urine dilution.

Statistics

Statistical analysis was performed using SPSS version 12.0. Continuous variables were compared using one-way analysis of variance (ANOVA) and Student *t* test. Categorical variables were compared using Pearson`s chi-square test. Cox regression analysis with time-varying covariates was used in order to evaluate the importance of baseline as well as in-treatment values through year five of treatment. After testing for linearity and the proportional hazard assumption and assessing the distribution of residuals from the models, urine albumin-to-creatinine ratio was log-transformed in the analyses. Multiple Cox regression analyses were used to adjust for randomized treatment, continent (USA vs. European countries), Framingham risk score (including age, gender, total- and HDL cholesterol, systolic blood pressure, smoking, diabetes and LVH[68]) and known cardiovascular diseases as well as in-treatment pulse pressure and in-treatment HDL cholesterol. Backward selection was used until all variables had $P < 0.10$, and these significant variables were included in the final models together with treatment and continent. In-treatment Sokolow-Lyon voltage and Cornell product were used both as continuous as well as dichotomous variables. Data were also analyzed using baseline and 1-year ECGs to predict revascularization after one year of treatment (excluding revascularization during the first year to avoid bias). In the time-varying analyses, however, all revascularization events were included. For all tests, two-tailed $P < .05$ was required for statistical significance.

Paper IV

Patient population

The study population consisted of all patients operated on consecutively for isolated CABG at Oslo University Hospital, Ullevål in the time period January 1, 2003 to December 31, 2006, which constituted 1350 patients in total. Patients undergoing additional surgery to CABG were excluded. The study was approved by an institutional review board. All patients underwent standard CABG operations and had routinely measurements of CK-MB and cTnT at 7 hours, 20 hours and 44 hours postoperatively.

The endpoint was all-cause mortality, and death status was assessed by the Norwegian National Death Registry by June 30, 2011 which gave a follow-up time of median 6.1 years. Data collection regarding death status was undertaken more than 3 months after this date to allow time for all deaths to be registered. A few patients had emigrated, and these were censored from the emigration date or date of last contact. Five patients were excluded because they could not be identified in the National Registry, and three were excluded because of missing postoperative blood samples. Thus, a total of 1,342 patients were eligible for further analysis. Of these, 1,294 had undergone elective surgery and 48 had undergone emergency surgery (3.6 %), based on the definition by European System for Cardiac Operative Risk Evaluation (EuroSCORE)[69].

Surgical procedure

All patients underwent median sternotomy and were operated on using the standard technique of cardiopulmonary bypass with ascending aorta cannulation, single venous cannulation and moderate systemic hypothermia, as previously described in the methods section of papers I and II.

Myocardial biochemical markers

Serum cTnT concentration and serum CK-MB concentration were determined by using the third- or fourth-generation TnT test (Troponin T STAT) on the Roche Elecsys 2010 immunoassay analyzer (Roche Diagnostics, Mannheim, Germany) according to the manufacturer recommendations. Serum CK-MB concentration was determined by using two monclonal antibiodies (CK-MB STAT) on an Elecsys 2010 analyzer (Roche Diagnostics) by

electrochemiluminescence immunoassay. The upper normal reference limit was 0.10 µg/Lfor cTnT and 5 µg/L for CK-MB.

Statistics

Data management and analysis were performed with IBM SPSS version 19.0 software. Mean values were compared using Student *t* test for normally distributed data and Mann-Whitney *U* test for non-parametric data. Categorical variables were compared using the chi-square test or Fisher`s exact test when appropriate. Event rates were calculated and plotted according to the Kaplan-Meier product limit method. The independence of the relationship of cTnT and CK-MB to mortality was evaluated in Cox proportional hazards models. The proportional hazards assumption was verified by plotting log minus log of survival against survival times. All clinical relevant baseline and procedural variables were tested in Cox univariate analyses. Variables with a univariate $P < .10$ were included in the multivariate Cox model. Collinearity was checked by assessing the variance inflation factor, and a factor <5 was accepted. The variable EuroSCORE provided a high variance inflation factor, and was thus excluded from the multivariate analysis with other clinical variables. The relationship of CK-MB to mortality was also evaluated in a multivariate Cox model with baseline variables, but not with cTnT as covariate. Furthermore, CK-MB and cTnT were analyzed separately and together in Cox models adjusting for EuroSCORE. There was no significant interaction between CK-MB and cTnT. For all tests, two-tailed $P < .05$ was required for statistical significance.

Summary of the results

Paper I

The hypoperfusion index, assessed by myocardial perfusion scintigraphy at rest, was significantly reduced from preoperatively to 2-4 days after CABG. This demonstrated an improvement in myocardial perfusion. There was no further change in the hypoperfusion index at 6 weeks postoperatively. Three patients (2.9%) were diagnosed with a perioperative myocardial infarction based on increases in cardiac biochemical markers and ECG changes. No additional cases of perioperative myocardial infarction were demonstrated by myocardial perfusion scintigraphy.

Paper II

Resting WMSI, assessed by echocardiography, was significantly reduced from preoperatively to 2-4 days after CABG. This demonstrated an improvement in contractile function. Furthermore, there was a borderline significant reduction in WMSI in the period between 2-4 days postoperatively and 6-7 weeks postoperatively ($p=0.06$). 101 of 670 segments (15%) had abnormal contraction preoperatively; of which 69 were hypokinetic and 32 were akinetic. At 6-7 weeks postoperatively a normalization in contractile function was found in 35 (51%) hypokinetic segments and a deterioration to akinesia was found in 5 segments. Nineteen (59%) of the akinetic segments had improved contractility at 6-7 weeks postoperatively.

Paper III

During the mean 4.8 years of follow-up in the LIFE study, 337 patients underwent coronary revascularization and 231 patients underwent peripheral revascularization. Higher Sokolow-Lyon voltage, but not higher Cornell product or urine albumin-to-creatinine ratio, was associated with coronary and peripheral revascularization. Of the 568 patients who underwent either coronary or peripheral revascularization, 46 died of cardiovascular disease within the study period. There was no association between LVH defined by Sokolow-Lyon criteria and cardiovascular mortality after revascularization. In contrast, LVH defined by Cornell product was associated with higher cardiovascular mortality after revascularization.

Paper IV

One thousand three hundred fifty patients were followed for a median 6.1 years after CABG and during this period 207 patients (15.3%) died. Nearly all patients had elevated levels of cTnT and CK-MB postoperatively. Both peak CK-MB and peak cTnT independently predicted long-term all-cause mortality when analyzed in separate multivariate Cox regression models adjusting for baseline characteristics and perioperative variables. However, when analyzed together in the same Cox model, cTnT was a highly independent predictor, whereas CK-MB was nonsignificant. Cardiac Troponin T and CK-MB were also analyzed together in a model adjusting for EuroSCORE, and in this model cTnT, but not CK-MB, was a significant predictor of mortality. Strict quartile analysis of the two biomarkers gave the same results, with only quartiles of cTnT being significantly associated with long-term mortality. The biomarker value at 44 hours postoperatively had a stronger association with mortality than the biomarker values at 7 or 20 hours postoperatively or the peak value.

Discussion of materials and methods

Papers I and II

There were several reasons for choosing a randomized study design for the SCENARIO study. First, by adding a control group neither examined with myocardial perfusion scintigraphy nor echocardiography, we obtained a control to whether scintigraphy and echocardiography adds useful information beyond ECG and specific cardiac enzymes in detecting perioperative myocardial infarction. Second, as we had permissions (by hospital) to do scintigraphy in 50 patients, doubling the number of participants made it more likely that patients randomized to undergo scintigraphy and echocardiography were representative for the patients that qualified according to inclusion and exclusion criteria and underwent CABG at our hospital in the time period of the study.

To study isolated CABG patients without combined valve surgery or other procedures was chosen to obtain a relatively homogenous study population undergoing the same type of cardiac surgery. Patients with renal failure, chronic obstructive pulmonary disease and age above 80 years were excluded as these patients may follow an extended and more complicated postoperative course with a higher tendency of respiratory problems and longer intensive care unit stay, which potentially could make it difficult to undergo the examinations at 2-4 days postoperatively. Also, chronic obstructive pulmonary disease may deliorate image quality obtained by echocardiography. Body mass index > 30 kg/m^2 was initially chosen as an exclusion criteria because of the narrow examination bench used for the scintigraphy examinations. However, this turned out to be less a problem, and a few patients with higher body mass index were included after a subjective assessment. Due to the exclusion criteria, our study population was biased. It was therefore not representative of a typical elective first-time CABG population and can be viewed as a best-case population of CABG-operated patients in our center. Hence, our results cannot be extrapolated to patients with co-morbidities of chronic obstructory pulmonary disease or renal failure, age above 80 years or obesity.

Including patients into such a study was quite cumbersome and as many as 261 patients were not included because of exclusion criteria or logistical reasons. The logistical reasons were mainly due to unavailability of the study investigators to include patients and limited availability of myocardial perfusion scintigraphy in a busy clinical department.

To elucidate myocardial perfusion, myocardial perfusion scintigraphy at rest, which is a well-established noninvasive and safe technique for evaluating coronary perfusion, was undertaken[70]. Administration of nitroglycerin before the examination may increase coronary blood flow in ischemic myocardium, and thus facilitate radionuclide uptake in ischemic regions with viable myocytes[71,72]. This was not used in our study, but in retrospect we acknowledge that this might have limited the number and size of uptake defects. In addition, the use of gating would have enabled us to simultaneously evaluate left ventricular function[73].

All patients had ECGs taken routinely and these were copied and read by an experienced cardiologist. Electrocardiographic changes were classified based on ischemic severity, and we focused on the presence of new Q-waves in multiple leads for the diagnosis of perioperative myocardial infarction. Due to sternotomy bandages postoperatively, the electrodes were not always optimally placed and there may therefore be some minor day-to-day variations. However, this was inevitable and reflects clinical practice.

As there was no consensus on the diagnosis of perioperative myocardial infarction after CABG when this study was designed, we had to make our own definitions based on available literature[38,74]. We chose to require both changes in biochemical markers and in the ECG for the diagnosis. We found no consensus regarding changes in the hypoperfusion index in the case of perioperative myocardial infarction. However, as an increase or reduction in the hypoperfusion index ≥ 5 in the same patient was considered a true change[75], we chose this cut-off for the diagnosis of perioperative myocardial infarction determined by myocardial perfusion scintigraphy.

Our study population was unselected regarding preoperative left ventricular function. The preoperative echocardiography examination revealed a mean WMSI of 1.19 and 85% of the segments had normal contractility, demonstrating a relatively well-preserved function for the population as a whole. A normal contracting segment with a wall motion score of 1.00 preoperatively cannot improve further in function. As a consequence, we might have experienced a greater improvement in contractile function if our study patients had been pre-selected regarding low ejection fraction. Moreover, our patients were not pre-selected regarding image quality. Care was taken to obtain good images, however, image quality was variable and especially the 2-4 days postoperative examination may have been influenced by patient immobility and bandages. Wall motion scoring may be limited by dependence of the experience and the subjective interpretation of the observer. Yet, our patients were analyzed by an experienced cardiologist with acceptable intra-observer variability.

Paper III

The LIFE study included a large population and was a multi-center trial, thereby strengthening the generalizability of our results. However,, it must be recognized that the LIFE population, as in many other randomized trials, had strict inclusion criteria and obviously represented a selected cohort of patients. Patients with angina pectoris requiring treatment with a beta-blocker or a calcium antagonist, severe vascular disease, heart failure, known LVEF < 40% or recent myocardial infarction within the past six months were excluded from this study. Hence, our results may not be representative of the typical hypertensive population undergoing revascularization, and this limits the external validity of the results. The LIFE study was designed for the primary composite endpoint, not for the secondary endpoints like revascularization. Our results from regression analysis should therefore be interpreted with caution as they demonstrate associations between variables and not necessarily imply a causal effect. Large randomized trials like the LIFE study are not designed to explain pathophysiological issues, but have an important role in generating hypotheses to be investigated in future prospective studies.

Revascularization procedures are based on several factors. In addition to being a consequence of arterial disease, revascularization is also a therapeutic intervention influenced by clinical decision-making. Therefore, it is not only a natural event, but a clinician-driven outcome influenced by physicians` decision-making based on individual preference and local availability as well as guideline recommendations[76]. The proportion of the patients undergoing coronary revascularization among the LIFE population was highest in the United States with 8.4% and ranged from 1.5 to 8.0% in European countries[77]. To account for these country-related differences in procedure rates, we adjusted the multivariate analyses for continent (US vs. Europe). The analyses were also adjusted for study drug treatment, as atenolol might worsen peripheral artery disease symptoms while it might weaken angina in comparison to losartan.

Paper IV

The study population consisted of all consecutive patients undergoing isolated CABG in our center during three years and was thus a heterogeneous cohort regarding co-morbidities, ejection fraction and operation risk. Including all patients was seen as an advantage because it increases the generalizability of our results to the clinical setting. We chose also to include the 48 patients undergoing emergent surgery to avoid potential selection bias. All-cause mortality

was chosen as end-point as this is a strict and objective definition[78]. Since data were registered prospectively in a database, the variables encoded were pre-determined. Further information on postoperative outcomes, e.g., inotropic support and short-term complications would have been an advantage; however, the study design did not allow this. Available blood samples before operation were recorded, but these had been taken at variable times in the weeks or days before the operation and could therefore not give reliable information regarding the biomarker level preoperatively. Some patients with recent myocardial infarction may therefore have had elevated biochemical markers preoperatively that could contribute to the rise in biomarker levels postoperatively. The timing of the measurements of CK-MB and cTnT at 7, 20 and 44 hours postoperatively was according to the already established routine at the Cardio-thoracic department.

Discussion of the results

Paper I

Improvement in hypoperfusion index after CABG

The finding that CABG early postoperatively re-establishes myocardial blood flow may from a clinical point of view seem quite obvious. However, as the scintigraphic examinations were performed at rest, this was an interesting finding. Radionuclide uptake is a process requiring adequate perfusion and vital myocytes with intact cell membranes[79,80]. In a rest situation in which a patient has no symptoms of angina pectoris one would assume that perfusion would be adequate. Yet, our patients showed an improvement in radionuclide uptake at rest after CABG. Because radionuclide uptake requires vital myocytes, we believe that myocytes that appeared to be necrotic preoperatively actually may have been viable hibernating myocytes.

We found no change in hypoperfusion index between the two postoperative examinations at 2-4 days postoperatively and 6 weeks postoperatively. The improved radionuclide uptake within the myocytes therefore occurred relatively fast after revascularization. Other studies have revealed more gradual changes in myocardial perfusion, but comparisons with other studies are complicated by various methods of analyzing radionuclide uptake and different patient materials. Anderson et al[81] reported that resting technetium-99m-sestamibi uptake defects were unchanged 1 hour after CABG, increased in severity after 1 week and were less than recorded preoperatively after one year. Raff et al[82] found that 16% of the hypoperfused segments at rest were improved during the first week after CABG. Several studies have documented improvements in resting perfusion with examinations at 3 months[83,84] and 6 months[85] after CABG.

Diagnosis of perioperative myocardial infarction

Using our definition requiring changes in cardiac biochemical markers and in the ECG, we found two patients with perioperative myocardial infarction in the control group and one patient in the study group. We had anticipated finding several patients fulfilling the criteria of perioperative myocardial infarction by myocardial perfusion scintigraphy; however, we detected none. Thus, a total of three patients (2.9%) were diagnosed with a perioperative myocardial infarction. This is a small number that does not allow further analysis and we could therefore not compare the incidences of perioperative mycoardial infarction in the two groups as originally planned. The finding that myocardial perfusion scintigraphy did not

detect more cases of infarction than ECG and biochemical markers, must be interpreted with caution. With our limited sample size it is likely that we did not find relationships that could have been detected studying a larger population (type II statistical error). Moreover, it is possible that we used too strict diagnostic criteria. Five patients had a significant increase in the hypoperfusion index between the two postoperative examinations, which may represent a new myocardial infarction or early graft failure. Unfortunately, our patients did not undergo coronary angiography postoperatively; which ultimately is the gold standard in diagnosing restenosis or early graft failure.

Paper II

Improvement in WMSI after CABG

As outlined in the introduction, the time course of recovery of left ventricular function in dysfunctioning myocardium after CABG has not been described in detail. Despite the relatively well-preserved contractile function in our study population preoperatively, we demonstrated improvement in resting WMSI postoperatively. This suggests present viability, due to the existence of (repetitively) stunned or hibernating myocardium. We found a gradual improvement of regional function during the seven weeks after CABG, indicating that the myocytes gradually resume their contractility several weeks after perfusion is restored. There was a significant improvement in function between preoperatively and 2-4 days postoperatively, in accordance with other studies[86-88]. A study by La Canna et al[89] showed that regional wall motion score improved significantly immediately after CABG with no further improvement at 2 weeks or 3 months. Vanoverschelde et al[25] found that patients with reversible dysfunction had improved wall motion score within 10 days postoperatively. Mintz et al[90] reported no improvement in wall motion one week after CABG, but significant recovery at two months and one year postoperatively. Other studies have found no change[91] or a deterioration of contractile function[92] during the first weeks postoperatively, which may owe to perioperative ischemia, reperfusion injury or other factors that may have a negative effect on contractile function.

Only 101 segments (15%) in the study had abnormal contractile function preoperatively, which thereby limited the number of available segments for improvement after CABG. Sixty-nine of these (68%) were hypokinetic and the remaining were akinetic. The majority of both the hypokinetic and akinetic segments gradually improved in function during 6-7 weeks postoperatively.

The aim of this paper was to evaluate regional myocardial function using WMSI. However, for completeness, a full echocardiographic examination was done for each patient resulting in several more specific measurements. These were included in the article, but we were careful to draw conclusions on their basis. Due to a considerable number of measurements, the interpretation was prone to type I statistical error, i.e., a false positive result. Also, although all patients were considered hemodynamically stable at the time of examination, different loading conditions postoperatively could potentially contribute to transient changes in volumes or diameters[93].

The most widely used parameter of myocardial systolic function is the LVEF, which is calculated as stroke volume divided by the end-diastolic volume[94]. We found that LVEF was significantly reduced between the examinations preoperatively and 6-7 weeks postoperatively. The discrepancy between this decrease in global functioning and the simultaneous increase in WMSI is difficult to explain. However, a limitation of LVEF detection by echocardiography is that the biplane Simpson`s method is dependent on good endocardial border definition. Because LVEF measures volume changes secondary to myocardial contraction, it is not a direct measure of myocardial function as compared to WMSI. Furthermore, since all 16 segments contributing to the WMSI were analyzed independently and from multiple projections, this is likely to give a more robust assessment than LVEF. WMSI has been validated as a prognostic indicator after myocardial infarction showing results superior to LVEF[95-97]. Yet, both WMSI and LVEF are limited by the subjective assessment of the examiner.

Our study is limited by the sample size, and our results need confirmation from larger studies. The major limitation of this study is the lack of viability testing preoperatively. Improvement in systolic wall thickening postoperatively does strongly suggest the presence of viable segments preoperatively, but viability imaging with stress echocardiography could have validated this and estimated the number of viable segments preoperatively. Postoperative angiography to validate graft status and the success of the revascularization procedure would also have been an advantage.

Paper III

Left ventricular hypertrophy and revascularization

Our main finding was that higher LVH during anti-hypertensive treatment was independently associated with increased incidence of both coronary and peripheral revascularization. That

reduction of LVH is associated with less coronary revascularization seems biologically plausible because less myocardial tissue per vessel may decrease myocardial oxygen demand and thereby cause less angina pectoris symptoms. It has been reported that coronary flow reserve, i.e., the ratio of maximum to basal coronary flow, is impaired in the presence of LVH[98]. A study assessing coronary flow reserve in patients with aortic stenosis before and after aortic valve replacement found that coronary flow reserve increased after the operation, simultaneously with regression of LVH[99]. This suggests an association between regression of LVH and increase in coronary flow reserve. The exact mechanism of how LVH is related to peripheral revascularization is unknown, but as LVH is associated with atherosclerosis, endothelial dysfunction and systemic inflammation[46,100,101] it may be likely that patients with high LVH have more persistent peripheral structural vascular hypertrophy leading to more peripheral revascularization.

We found that the methods used for detecting LVH had different predictive abilities. High Sokolow-Lyon voltage was a significant predictor for revascularization, whereas Cornell voltage-duration product was not. We cannot explain this pathophysiologically. It may owe to different patient characteristics at baseline dependent on LVH classification by Sokolow-Lyon voltage or Cornell product. We know that patients with LVH defined by Sokolow-Lyon voltage were younger and leaner and had higher pulse pressure and HDL-cholesterol compared with patients without LVH with this method[102]. On the other hand, patients recruited by the Cornell criteria in the LIFE study had more metabolic risk factors and greater co-morbidity, possibly making them less suitable for invasive procedures. In a study of 2,461 patients with coronary heart disease only 37% of those with echocardiographically evidence of LVH underwent revascularization compared to 51% without LVH, although the patients with LVH had more three-vessel disease than the patients without LVH[103]. Similarly, Westerhout et al[104] found that cardiac catheterization and PCI procedures occurred less often in patients with LVH defined by electrocardiographic Cornell criteria, possibly because LVH patients were older with more co-morbidities. This supports the fact that revascularization procedures are influenced by other factors than the patients` disease burden, among them patients` co-morbidities.

Urine albumin-to-creatinine ratio and revascularization

We found no effect of regression of urine albumin-to-creatinine ratio on the incidence of revascularization. This was unexpected, because several other studies have found a relation between albuminuria and cardiovascular disease. The PREVEND study demonstrated that

microalbuminuria was independently associated with coronary heart disease, but not peripheral artery disease in the general population[105]. In the same cohort, albuminuria was found to significantly add information to the traditional risk factors for predicting the composite endpoint of cardiovascular disease which included revascularization procedures[106]. Ibsen et al[54] found that reductions in albuminuria translated to reductions in the composite end point in the LIFE study. The lack of association between reductions of urine albumin-to-creatinine ratio and revascularization in our study might reflect that patients without reduction in urine albumin-to-creatinine ratio had more generalized atherosclerotic disease and were therefore not candidates for revascularization. Another possibility is that this owes to a statistical type II error.

Cardiovascular mortality after revascularization

After revascularization (either coronary or peripheral) we found that continuing LVH by Cornell product was a significant predictor of cardiovascular death. Interestingly, continuing LVH by Sokolow-Lyon had no significant effect in this setting. This may owe to low statistical power because there was a lower prevalence of LVH by this criterion than by Cornell product criteria. Another hypothesis, which requires further studies, is that LVH assessed by Cornell product is associated with increased cardiovascular mortality by other mechanisms than coronary atherosclerosis. Several studies have shown that patients with LVH have increased in-hospital and long-term mortality after CABG surgery[107-109]. Taken together with our findings, this suggests that LVH regression should be an independent goal in the future therapy and follow-up after revascularization procedures.

Paper IV

Postoperative CK-MB and cTnT and mortality after CABG

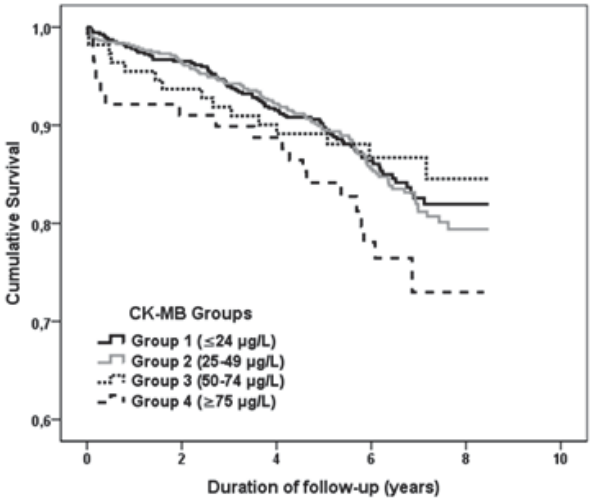
We found that cTnT is a better predictor than CK-MB of long-term all-cause mortality after CABG. Few previous studies have investigated and compared the predictive value of troponins and CK-MB in regard to mortality after CABG. Januzzi et al[110] found that cTnT was superior to CK-MB for predicting in hospital complications after CABG with or without combined valve surgery. Similarly, Kathiresan et al[111] documented that cTnT was the strongest predictor of 1-year mortality, whereas CK-MB added no independent information. Vikenes et al[112] reported on the effect of cTnI, cTnT and CK-MB in low-risk CABG patients with a long-term follow-up of median 7.7 years. CK-MB was superior to the cardiac troponins

in predicting long-term event-free survival after elective cardiac surgery. However, only 156 isolated CABG patients were included in this study. Muehlschlegel et al[113] compared the biomarkers CK-MB and cTnI and found that cTnI was more robust in predicting mortality with a mean follow-up of 3.3 years, in line with our findings. Interestingly, ECG analyses in the same study revealed that ECG diagnosis of perioperative myocardial infarction did not independently predict an increased risk of mortality or hospital length of stay. The authors therefore recommend the use of troponin screening after CABG and suggest that ECG should not be used in diagnosing perioperative myocardial infarction. Our findings of superiority of cTnT have been supported by two recent studies showing that cardiac troponin I was better than CK-MB for quantifying myocyte necrosis as assessed by magnetic resonance imaging after CABG[114,115] .

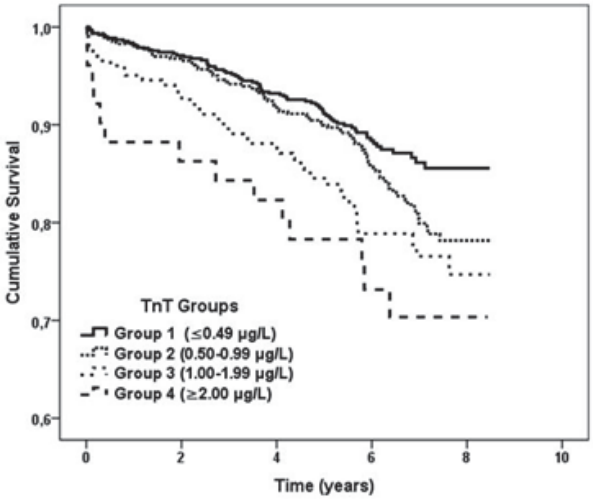
The finding that cTnT was a better predictor of mortality than CK-MB was consistent when analyzing the biomarkers as continuous variables, quartiles and also as groups based on clinical cut-off values[116]. The latter analysis was omitted from the published article as the American Heart Journal found these less objective than the strict quartile analysis (Figure 5). This is an interesting point of discussion because the clinical cut-off values without doubt have more relevance for clinicians in the hospital setting. Also, biomarker cut-off values defined as five times upper limit of normal are used in the current guidelines defining myocardial infarction post-CABG[40].

The pathophysiology behind the association between small leakages of troponins and increased mortality after CABG is unknown and most likely multifactorial. However, the same relationships are found after PCI[117], noncardiac surgery[118] and in the general population[119]. This indicates common underlying mechanisms and is interesting as the effect is found at time points long after the initiating stimulus. A recent study of nearly 10,000 individuals from a general population without known coronary heart disease or stroke found that even minimally elevated cTnT (≥0.003 μg/L) was independently associated with increased risk for mortality and heart failure[120]. Of note, cTnT was stronger associated with death and heart failure than coronary heart disease, suggesting that other factors than ischemia may contribute to the risk associated with cTnT. Other potential causes for troponin release from cardiac myocytes may be apoptosis, subclinical structural or functional abnormalities or coronary microvascular dysfunction, which occurs in hypertension, diabetes mellitus and left ventricular hypertrophy[121]. Cardiac troponin release has traditionally been associated with cardiomyocyte necrosis. However, there is some debate about whether troponins also may be released in the case of transient ischemia without cell death[122,123].

Figure 5. CK-MB and cTnT stratified in groups based on clinical cut-off values, in regard to all-cause mortality after CABG.



At risk	Year 0	Year 2	Year 4	Year 6	Year 8
Group 1	547	526	497	267	45
Group 2	595	568	543	325	64
Group 3	111	103	99	63	12
Group 4	89	81	77	48	5



At risk	Year 0	Year 2	Year 4	Year 6	Year 8
Group 1	622	601	576	312	38
Group 2	466	446	423	269	58
Group 3	203	187	176	95	24
Group 4	51	44	41	27	6

We focused on the peak values of cTnT and CK-MB in our analyses, as these are easier to use in a clinical setting. Interestingly, the biomarker values at 44 hours postoperatively had a greater prognostic power than the peak value, suggesting that routine biomarker sampling should continue for at least 44 hours. Some studies recommend that biomarkers should be measured even longer, until 48 hours or 72 hours postoperatively[124,125].

After CABG, risk stratification of patients to optimize further treatment is important both in the acute and in the long-term setting[126]. Cardiac biomarkers have been proposed as a tool for predicting outcomes after cardiac surgery and assisting in decision-making about therapeutic interventions. An interesting debate is whether postoperative biomarkers could be incorporated into the EuroSCORE or whether they have sufficient power to function as independent risk stratification markers. According to a study by Fellahi et al[127], the combination of EuroSCORE and postoperative cTnI provides the best discriminative power

for predicting adverse outcome after cardiac surgery, and this combination was suggested as being an effective model that improves early identification of high-risk patients.

The large size of our study population allowed us to adjust for a number of potential confounders. However, we cannot exclude the effect of potential other, yet unknown, confounders that may cause biomarker elevation and contribute to long-term mortality. Importantly, this is a single-center study and multi-center studies with a greater number of patients are needed.

Future perspectives

The global burden of coronary artery disease is expected to continue increasing and consequently also the use of CABG worldwide in the foreseeable future. This justifies further research within this area of cardiac surgery, to ensure optimal postoperative care. Our study dealt with the changes of myocardial function up to 6-7 weeks after CABG using myocardial perfusion scintigraphy and echocardiography. In the ten years since this study was initiated, several newer imaging modalities have become available and it would be of value to perform larger studies using magnetic resonance imaging and strain imaging to obtain an even better understanding of changes in myocardial function and the changes induced in hibernating myocytes early after CABG.

Regarding the diagnosis of perioperative myocardial infarction, larger studies with coronary angiography performed postoperatively are needed to verify which thresholds of cardiac biomarkers are diagnostic. Nevertheless, we doubt that strict criteria will be of value in the clinical setting. It seems impossible to set a certain threshold for the level of markers that may not be explained by the CABG procedure itself. Perhaps implementing the use of echocardiography or other imaging modalities as a routine postoperatively for patients with biomarkers above a certain level could be an effective diagnostic tool for perioperative myocardial infarction.

Our findings in this thesis point out the independent effects of continuing LVH in the ECG and high postoperative biomarker levels on survival after revascularization. Currently, the prognostic influence is not addressed in the guidelines. The results of our multivariate analyses are hypothesis generating and should be validated in prospective studies. It would be interesting to study whether a more intensive follow-up schedule after CABG with emphasis on implementing evidence-based medical therapy for patients with elevated postoperative biomarker levels may influence survival rates.

Conclusions

Paper I

Myocardial perfusion at rest improved 2-4 days after CABG and no further changes in perfusion were observed during the following six weeks. We could not detect more cases of perioperative myocardial infarction using myocardial perfusion scintigraphy compared with the use of ECG and cardiac biochemical markers.

Paper II

There was a gradual improvement of left ventricular contractile function at rest determined by the wall motion score index during the first 6-7 weeks after CABG, suggesting the presence of hibernating myocardium.

Paper III

Lack of regression of Sokolow-Lyon voltage was associated with higher incidence of coronary as well as peripheral revascularization. Regression of urine albumin-to-creatinine ratio was not associated with revascularization. After revascularization, continuing LVH by Cornell voltage-duration product was associated with cardiovascular death. Our data emphasize the importance of measuring LVH in hypertensive patients.

Paper IV

Both CK-MB and cTnT were predictors of long-term mortality after CABG. However, CK-MB did not provide independent prognostic information when analyzed together with cTnT. This suggests that cTnT is a better predictor than CK-MB of long-term mortality after CABG.

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