From The Institute of Environmental Medicine
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RENAL INSUFFICIENCY,
MORTALITY AND MYOCARDIAL INFARCTION

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Stockholm 2008
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Abstract

Background: Patients with dialysis-dependent renal insufficiency (RI) have a markedly increased risk of dying or developing cardiovascular disease. Among patients who have coronary heart disease (CHD), moderate or severe RI is associated with increased mortality. In the general population the association between mild or moderate RI and long-term risk of death or myocardial infarction (MI) is not well described.

Aims: To study the associations between mild, moderate or severe RI and death or MI among individuals with or without CHD. To investigate the importance of dyslipidemia, in particular the apolipoprotein (apo) B/apoA-1 ratio, in relation to MI among individuals with or without chronic kidney disease (CKD).

Methods and Results: In 6,711 patients undergoing coronary artery bypass grafting (CABG), already moderate RI was associated with mortality within 30 days of CABG (Odds ratio (OR) 1.4, (95% Confidence Interval (CI), 1.2 to 4.8) (Study I). Among those patients who survived 30 days post-operatively, the association between RI and incidence of MI and all-cause mortality within five years of CABG was investigated (Study II). All-cause mortality was associated with mild, moderate and severe RI; hazard ratio (HR) (and 95% CI) 1.2 (1.0 to 1.6), HR 1.8 (1.3 to 2.4) and HR 5.2 (3.1 to 8.6), respectively. Patients with moderate or severe RI had an increased incidence of MI. In 571,353 mainly healthy individuals from the AMORIS cohort, glomerular filtration rates were estimated using the Modification of Diet in Renal Disease study equation (GFR_{MDRD}) and the Mayo formula (GFR_{Mayo}) and related to all-cause mortality and incidence of MI (Study III). During 11.6 years of follow-up hazard ratios for MI, using GFR_{Mayo} were 1.11 (1.06 to 1.16) for mild, 1.32 (1.18 to 1.48) for moderate and 2.54 (1.90 to 3.40) for severe RI. Similar associations were found for all-cause mortality. Using GFR_{MDRD} the association between RI and adverse outcomes was weaker. In 142,394 individuals from the AMORIS cohort, the apoB/apoA-1 ratio and standard lipid measures, were evaluated as predictors of first MI in relation to presence or absence of CKD defined as GFR_{MDRD} 15-60 mL/min/1.73 m^2 (Study IV). For those without CKD the adjusted HR for the highest versus the lowest quartile of the apoB/apoA-1 ratio was 2.88 (2.54 to 3.26) compared to HR, 3.35 (2.25 to 4.91) for those with CKD. After adjustment for the total cholesterol/ high-density lipoprotein cholesterol ratio, an increase by one standard deviation of the apoB/apoA-1 ratio was associated with a HR of 1.44 (1.30 to 1.59) for MI, among individuals with CKD.

Conclusions: Renal insufficiency among patients undergoing CABG is related to an increased 30-day mortality, five-year mortality and incidence of MI. Renal insufficiency in the general population is related to an increased long-term incidence of MI and all-cause mortality. The apoB/apoA-1 ratio is a strong predictor for MI irrespective of renal function and may add information about risk of future CHD even after adjustment for standard lipid measures.

Key words: Renal insufficiency, mortality, myocardial infarction, chronic kidney disease, coronary artery bypass surgery, glomerular filtration rate, apolipoproteins, lipids, general population
This thesis is based on the following publications. They will be referred to by their Roman numerals henceforth:


# List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
</tr>
<tr>
<td>AMORIS</td>
<td>Apolipoprotein-related MOrtality RISk</td>
</tr>
<tr>
<td>Apo</td>
<td>Apolipoprotein</td>
</tr>
<tr>
<td>ARIC</td>
<td>Atherosclerosis RIsk in Communities</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>Ccr</td>
<td>Calculated creatinine clearance</td>
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<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
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<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection fraction</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>GFR-Mayo</td>
<td>Glomerular filtration rate estimated by the Mayo formula</td>
</tr>
<tr>
<td>GFR-MDRD</td>
<td>Glomerular filtration rate estimated by the MDRD study equation</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International classification of disease</td>
</tr>
<tr>
<td>IDL</td>
<td>Intermediate density lipoprotein</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LVF</td>
<td>Left ventricular function</td>
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<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
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<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NKF</td>
<td>National Kidney Foundation</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>Non high density lipoprotein</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PIN</td>
<td>Personal Identification Number</td>
</tr>
<tr>
<td>RI</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristics</td>
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<td>VLDL</td>
<td>Very low density lipoprotein</td>
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Introduction

The ancient Egyptians would remove all organs except for the heart and kidneys, before mummifying the dead body. They believed that these two organs were the site of thought and affection and that they contained evidence of how an individual had lived its life. In the Old Testament we learn that God would examine the heart and kidneys in order to reveal sins of the past life and thus be able to decide whether a man would go to heaven or hell.\(^1\)

Already in the Hippocratic Corpus a possible description of chronic renal failure is found.\(^2\) The ancient Greeks understood that if a patient develops signs and symptoms of kidney failure there is no hope of survival. No claims of understanding the underlying disease mechanisms were made at the time. During the Renaissance anatomical descriptions of the normal kidneys were provided and during the 18\(^{th}\) century the first description of sign and symptoms of renal failure were linked to specific changes of the kidneys anatomy. During the 19\(^{th}\) century descriptions of high levels of urea in the blood linked chemical abnormalities in the body to renal failure and by the end of the 19\(^{th}\) century it was clearly understood that mortality from renal failure depended on toxic accumulation of urea.

Not until 1974 it was pointed out clearly that patients with dialysis-dependent renal insufficiency have an excessive risk of cardiovascular disease and suffer from severe and accelerated atherosclerosis.\(^3\) Twenty-four years later this problem was re-emphasized by the American National Kidney Foundation.\(^4\) The authors pointed out that the risk of cardiovascular mortality was 10 to 30 times that of the general population among dialysis patients even after taking risk factors as age, gender and diabetes into account. The following years attention was turned to the increased risk of cardiovascular death seen already at lesser degrees of renal dysfunction, not only among those with previous illnesses, but also in the general population.\(^5-8\)

This thesis was written with the aim to add knowledge about, not only how mild and moderate renal insufficiency influences the risk of death, but also how it may influence the risk to develop cardiovascular disease.
Martin Holzmann
Renal insufficiency and chronic kidney disease

Definitions and classifications
There were no uniform definitions or classifications of renal dysfunction until 2002 when the (American) National Kidney Foundation (NKF) published guidelines on evaluation, classification and risk stratification in chronic kidney disease (CKD). Before that time commonly the term chronic renal failure was used in studies and it often referred to severe impairment of renal function. The definitions of different stages of renal dysfunction would vary from study to study, as well as the methods to assess renal function, making comparisons between studies difficult.

The NKF defines CKD as kidney damage for more than three months, with or without a decrease in glomerular filtration rate (GFR), or GFR less than 60 mL/min/1.73 m² for more than three months, with or without kidney damage (Table 1). Kidney damage is most commonly ascertained by measurement of proteins in the urine. The cut-off value for GFR of 60 mL/min/1.73 m² was selected because it represents a reduction by approximately half of the normal GFR value found in young adults. The guidelines recommend estimation of GFR with prediction equations which include serum creatinine, age and gender to reduce the misclassification of renal function using serum creatinine alone.

Prevalence
The prevalence of CKD stages 1 to 4 in the US population has been reported to increase from 10.0% in 1988-1994 to 13.1% in 1999-2004. Taking the increasing age of the population into account there was virtually no difference in prevalence between these two periods (10.0% vs. 10.3%). The proportion of individuals with GFR less than 60 mL/min/1.73 m² increased from 5.6% to 8.0%. This increase was also largely attributed to the increased age of the population (5.6% vs. 5.8 after age-adjustment). Similar prevalence numbers have been reported from a large

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
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<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly reduced GFR</td>
<td>60-90</td>
</tr>
<tr>
<td>3</td>
<td>Moderately reduced GFR</td>
<td>30-60</td>
</tr>
<tr>
<td>4</td>
<td>Severely reduced GFR</td>
<td>15-30</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 or dialysis</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate. For stages 1 and 2, kidney damage was defined as spot albumin-to-creatinine ratio > 17 mg/g (men) or > 25 mg/g (women) on 2 measurements.
European community-based cohort. Among individuals with GFR less than 60 mL/min/1.73 m² only 11.6% among men and 5.5% among women were aware of having weak or failing kidneys. With an ageing population and an increasing prevalence of diabetes, the proportion of individuals with kidney disease is expected to rise. Globally the number of patients with kidney failure requiring dialysis has been estimated to increase from approximately 1.4 million in 2004 to 2.0 million by 2010.

Later, in attempts to improve estimation of GFR the Modification of Diet in Renal Disease (MDRD) study equation and the Mayo formula were developed.

Serum markers of renal function

Creatinine
Creatinine is an amino acid derivative that is freely filtered by the glomerulus. Creatinine is also secreted by the tubular cells. This means that creatinine clearance normally exceeds GFR. Tubular secretion of creatinine varies dependent on renal function and other factors. Age, gender, body habitus, race and diet affects the generation of creatinine and largely accounts for the variation in levels seen between different populations. The single most important determinant of creatinine production is muscular mass. Thus, the relationship between levels of serum creatinine and GFR varies between persons and over time within persons, and the use of a single creatinine value to assess renal function may lead to misclassification of kidney function.

Creatinine measurement is also technically difficult. Several different methods have been developed to measure creatinine, with the Jaffé method being the most commonly used. Differences in specificity between different assays have made comparisons of creatinine measurements between different laboratories difficult. To overcome these problems a reference method using isotope dilution mass spectrometry has been developed.

Cystatin C
Cystatin C is a protein produced at a constant rate by all nucleated cells in the human body. It is freely filtered by the glomerulus and then metabolized by the proximal tubuli. There is no tubular secretion and only minimal extra-renal elimination. Therefore, the blood concentration of Cystatin C depends almost entirely on GFR. Since the production of Cystatin C is independent of muscular mass, it is also less variable between individuals and
over time. The level of Cystatin C is affected by the use of corticosteroids, and is related to age, sex, weight, height and smoking status. Several studies have suggested that Cystatin C may be superior to serum creatinine as a marker of renal function especially at GFR levels between 60 and 90 ml/min/1.73 m$^2$, in patients with abnormal muscle mass and in the early detection of acute kidney injury. No information on Cystatin C levels were available in the data sets used for the studies included in this thesis.

**Measured glomerular filtration rate and creatinine clearance**

There are several methods to measure GFR. They are all based on measurement of urinary or plasma clearance of ideal filtration markers (Iothalamate, Iohexol, Cr-EDTA or Inulin) which are freely filtered in the kidney. Creatinine clearance is measured by relating the creatinine excretion in a 24-hour collection of urine to a single serum sample of creatinine.

**Estimated glomerular filtration rate**

Several formulas to estimate GFR have been developed to overcome the limitations of serum creatinine alone as a marker of renal function. The two most frequently used formulas, and those proposed by the NKF, are the Cockcroft-Gaults formula and the MDRD study equation. The study populations used to develop these formulas have consisted mainly of patients with established kidney disease. By using regression techniques these formulas were developed on the basis of serum creatinine and demographic variables. The estimated GFR systematically deviates towards the mean measured GFR of the study populations where they were developed.

**Cockcroft-Gaults formula**

The Cockcroft-Gaults formula was developed in a predominantly male (96%) study population consisting of 249 patients with a measured creatinine clearance (Ccr) ranging from 30 to 130 ml per minute. This formula was created to estimate creatinine clearance and not GFR, and the values were not adjusted to body-surface area. Since creatinine is not only filtered by the glomeruli, but also secreted by the tubuli, the Cockcroft-Gaults formula, overestimates GFR generally regarded to be in the order of 10% to 20%. Several studies have validated this formula in different populations and it appears to work well among those with GFR between 20 mL/min/1.73 m$^2$ and 60 mL/minute/1.73 m$^2$ who are below 65 years. Among the elderly the Cockcroft-Gaults formula will underestimate GFR, and among the obese there will generally be an overestimation of GFR.

**Modification of Diet in Renal Disease study equation**

The Modification of Diet in Renal Disease study equation was developed in 1999 from a cohort of 1628 patients with established CKD. It was simplified in 2000 and modified later in order to be used with standardized creatinine values. The mean measured GFR was 40 mL/min/1.73 m$^2$ in the MDRD study population with mean age 51 years, including 12 percent black subjects. Patients with diabetes mellitus were excluded. The MDRD study equation works well in patients with GFR levels between 20 to 60 mL/min/1.73 m$^2$, but in those with normal or near-normal GFR it will consistently underestimate true GFR. The reported underestimation of GFR among healthy individuals has varied between 18 mL/min/1.73 m$^2$ and 29 mL/min/1.73 m$^2$. In a study where the NKF classification of kidney disease was used, 32% of subjects were classified in different categories of renal function by the MDRD study equation as compared with measured GFR.
may lead to a false positive diagnosis of CKD among individuals with no CKD in clinical practice and to underestimates of cardiovascular risk associated with RI in population studies.

**Mayo formula**
The Mayo formula was developed to estimate GFR among healthy individuals as well as in individuals with CKD. For this purpose 320 individuals referred for iohalamate clearance testing specifically for CKD evaluation, and 580 healthy individuals undergoing clearance testing for kidney donor evaluation were used. The mean age was 41 years and mean measured GFR 101 mL/min/1.73 m² among the healthy individuals. Among those with CKD the mean age was 53 years and mean measured GFR 48 mL/min/1.73 m². The Mayo formula has been shown to perform well among individuals with normal or near-normal GFR levels.

**Lipid measures**

**Historical aspects**
The role of cholesterol as a cause of CHD remained controversial surprisingly enough until recently. Almost one hundred years ago atherosclerotic plaques were found in animals fed cholesterol-rich diets and the first clues to the pathogenesis of atherosclerosis were discovered. Coronary heart disease became the leading cause of death globally in the mid-twentieth century and we learned from several large epidemiological studies that cholesterol played a crucial role in the pathogenesis of cardiovascular disease. Many of the early intervention studies with cholesterol-lowering therapy showed reduction in coronary events, but no reduction in cardiovascular mortality and even a trend towards increased all-cause mortality. The first secondary prevention trial to show a reduction in mortality associated with lipid-lowering by statins was published 1994. In this study the patients had relatively high cholesterol levels, but the following years, studies were published where the benefits of statins were extended to subjects with average cholesterol levels. Also the effect of statins in primary prevention of CVD was demonstrated during these years in two studies. A few years later we learned that the relative risk reduction seen by cholesterol-lowering with statins was independent of the baseline level of cholesterol and that even individuals with very low levels of cholesterol had the same benefit of lipid-lowering therapy as those with high levels. Two recently published meta-analysis showed that the relative risk reduction of CHD is directly related to the lowering of the LDL cholesterol level, both among subjects with or without diabetes mellitus.

**Plasma lipoproteins**
Since lipids are insoluble in aqueous solutions, they are transported from sites of synthesis to sites of utilization in particles containing both lipids and proteins, lipoproteins. Apolipoprotein (apo) B and apoA-1, the main proteins which make this possible, are hydrophobic on one side and hydrophilic on the other. The coat of lipoproteins contains proteins and phospholipids, and the core consists of cholesterol and triglycerides. ApoB and apoA-1 assemble and secrete the lipoprotein, provide structural integrity, act as enzyme activators and bind to receptors on the cell surface facilitating uptake of cholesterol into the cells. The plasma lipoproteins are divided into different classes according to their density. The main triglyceride-carrying lipoproteins are chylomicrons and very low density lipoproteins (VLDL). Intermediate density lipoproteins (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are all formed by catabolism of VLDL and chylomicrons. The main cholesterol-carrying lipoproteins are LDL and HDL. In a normal individual, approximately 70% of cholesterol is contained in LDL and 20% in HDL. Low-density lipoprotein cholesterol is regarded as the
atherogenic lipoprotein, and a major cause of CHD. High-density lipoprotein cholesterol promotes the transport of cholesterol from foam cells and macrophages in the artery wall to the liver for elimination (reverse cholesterol transport) and is inversely related to CHD.68 High-density lipoprotein cholesterol and apoA-1 also has anti-inflammatory, antioxidant and antithrombotic properties.69, 70

**Total and low-density lipoprotein cholesterol**
Epidemiological studies have found the level of total cholesterol to be related to incidence of CHD in comparisons between populations in different geographical regions,48 in migration studies49 and within single populations.52, 56, 71 Total cholesterol levels are also related to recurrence of cardiovascular events.50, 72, 73 Serum total cholesterol has often been used in studies as a surrogate for the atherogenic LDL cholesterol since about 70% of total cholesterol resides in LDL cholesterol.

The relationship between serum total and LDL cholesterol levels and development of CHD is found for the whole range from low to high concentrations of LDL cholesterol. The higher the level the greater the risk.71 Early studies suggested that the risk of CHD leveled off at lower cholesterol levels, but later studies have found that there is no real plateau where risk disappears.52, 71, 74 In addition, studies across different populations reveal that those with higher levels of cholesterol have higher incidence of CHD than those with lower levels.48, 75

Strong evidence for LDL cholesterol as a cause of CHD is found among persons with familial hypercholesterolemia.76 In these individuals CHD occur at an early age even in the absence of other risk factors. Total cholesterol is normally analyzed with enzymatic techniques and does not require the patient to be fasting. Low-density lipoprotein cholesterol can be determined by calculation if levels of HDL cholesterol and serum triglycerides are known (triglycerides less than 4 mmol/L) by Friedewalds formula.77

**High density lipoprotein cholesterol**
There is strong epidemiological evidence linking low levels of HDL cholesterol to an increased incidence of CHD.57, 78-81 Conversely, high levels seem to protect the individual from CHD. There are several factors that contribute to low HDL cholesterol levels. These are: high serum triglycerides, obesity, physical inactivity, smoking and diabetes mellitus.82

**Serum triglycerides**
Some epidemiological studies have reported an association between elevated triglycerides and an increased incidence of CHD.83, 84 Early studies did not identify high levels of triglycerides as an independent risk factor for CHD.85 This may be explained by triglyceride levels being confounded and related to total, LDL and inversely related to HDL cholesterol. Also other risk factors as hypertension, diabetes and smoking are related to triglyceride levels.86 Thus, high triglycerides can be considered as a marker of other lipid and non-lipid risk factors rather than a risk factor of its own. Elevated triglyceride levels are also commonly related to an increased number of small dense LDL particles, the most atherogenic part of LDL. This is common in patients with the metabolic syndrome.87 Serum triglycerides are analyzed in the fasting state and by enzymatic methods. In fasting individuals practically all triglycerides are found in the VLDL fraction of the lipoproteins.

**Non-high density lipoprotein cholesterol**
Non-HDL cholesterol is calculated as total cholesterol minus HDL cholesterol and includes all lipoproteins that contain apoB and is highly correlated, but not identical with apoB.88, 89 It has been proposed that non-HDL should replace LDL cholesterol in risk assessment for CHD.90 One study showed a stronger correlation with coronary mortality for non-HDL than for LDL cholesterol.91
Some, but not all studies have supported this finding. These results have commonly been explained by the strong correlation between non-HDL and apoB.

**Apolipoprotein B**

Apolipoprotein B is the structural protein that carries VLDL and LDL from the liver and gut to their sites of utilization. Apo B is closely related to LDL since 80-90% of apoB is found in this density fraction. Also, apoB provides a direct measurement of the number of atherogenic particles present in serum. It has been suggested that apoB provides a better estimate of risk for CHD compared with LDL cholesterol and other lipids. Some, but not all studies have found apoB to be stronger than traditional lipid measures in predicting CVD.

Apolipoprotein B can be measured in the non-fasting state. The methods used for analysis of apoB are standardized to an international standard, which has been shown to improve agreement of apoB measurement among laboratories, even when different methodological approaches are used.

**Apolipoprotein A-1**

Apolipoprotein A-1 is the major protein of HDL. It acts as a structural protein, mediates transport of cholesterol from the cell surface to the lipoprotein particle and activates enzymes responsible for cholesterol esterification. ApoA-1-containing lipoproteins mediate reverse cholesterol transport, returning excess cholesterol from peripheral tissues to the liver for excretion.

Several studies, conducted in different populations have shown that apoA-1 is inversely related to CHD events. The protective properties of apoA-1 have been explained by the close relationship between concentrations of apoA-1 and the number of HDL particles present in plasma.

Like apoB, apoA-1 can be measured in a non-fasting state by methods which are standardized to an international standard and validated in different populations.

**Lipid ratios**

Many studies have shown that the total cholesterol/HDL-cholesterol ratio is a powerful predictor of future CHD. It has been argued that this ratio is an easy way to assess future risk of CHD. Similarly the apoB/apoA-1 ratio has been found to be a powerful predictor of CHD in several studies. In addition, the apoB/apoA-1 ratio has in some studies provided more information on future risk than other lipid ratios.

These two ratios reflect both the atherogenic (LDL cholesterol or apoB) as well as the anti-atherogenic component (HDL cholesterol or apoA-1) among lipids and combine them in a risk index. It has been suggested that the apoB/apoA-1 ratio provides an attractive way to illustrate risk of future CHD, and that it improves prediction compared to traditional lipids especially among individuals with normal or low LDL cholesterol levels.

**Renal insufficiency and cardiovascular disease**

Only approximately four percent of individuals with CKD will progress to kidney failure and require dialysis or kidney transplantation. Long before these individuals reach the level of kidney failure they will have an increased risk of death and CVD associated with CKD. Even in the elderly GFR has to fall to less than 15 mL/min/1.73 m² before the risk of progress to end-stage renal disease exceeds the risk of death. Among patients who already suffer from CVD, renal dysfunction has consistently been found to predict recurrent CVD events and all-cause mortality. Among patients with congestive heart failure RI has been associated with poor prognosis. Concerning individuals at high risk of developing, but without established CVD, most studies have suggested that reduced GFR is a risk factor for CVD and mortality.

In community-based studies the association between reduced GFR and adverse outcome
has not been consistent. Two of the earliest studies, addressing the question whether mild RI is associated with all-cause or cardiovascular mortality in the general population, did not find such associations.\textsuperscript{5, 6} Both these studies used a broad dichotomous definition of RI based solely on serum creatinine values. The first study, conducted in the Framingham Heart Study cohort, defined mild RI in men as serum creatinine 136 to 265 µmol/L and in women 120 to 265 µmol/L. Within that range of serum creatinine probably all levels of renal function and dysfunction will be found. Thus, if there was any association between RI and adverse outcome it was most likely diluted by misclassification of renal function.\textsuperscript{128} In the NHANES I cohort moderate RI was defined as serum creatinine 122 to 177 µmol/L among men and 104 to 146 µmol/L among women. No associations between moderate RI and all-cause (HR 1.0 (95% CI, 0.8 to 1.4)) or cardiovascular mortality (HR 1.2 (0.8 to 1.8)) was found. This finding probably also is explained by misclassification of renal function related to solely using serum creatinine values as an index of renal function. Later studies, have found that CKD is a risk factor for both cardiovascular mortality and all-cause mortality in the general population.\textsuperscript{7-8, 125-131} In all these studies GFR was estimated by the MDRD study equation and used to classify renal function. In the NHANES II cohort, with a mean age of 49 years, moderate RI defined as an estimated GFR (eGFR) less than 70 mL/min/1.73 m\(^2\) was related to all-cause mortality (HR 1.51 (1.19 to 1.91)) and cardiovascular mortality (HR 1.68 (1.33 to 2.13)). In the Atherosclerosis Risk in Communities (ARIC) study moderate RI defined as eGFR less than 60 mL/min/1.73 m\(^2\) was associated with an increased risk of MI, CHD death and stroke (HR 1.38 (1.02 to 1.87)). In the largest study to date on RI and mortality there was a graded increase in HRs for all-cause mortality associated with RI; eGFR 45 to 60 mL/min/1.73 m\(^2\), HR 1.2 (1.1 to 1.2); eGFR 30 to 45 mL/min/1.73 m\(^2\), HR 1.8 (1.7 to 1.9); and eGFR 15 to 30 mL/min/1.73 m\(^2\), HR 3.2 (3.1 to 3.4). The mean age in this study was 52 years and 18% of the study population had eGFR less than 60 mL/min/1.73 m\(^2\). This is several-fold higher than would be expected in the general population. Also a large proportion of the study cohort had their creatinine values taken while being hospitalized.

Several studies on RI as a risk factor for mortality and CVD have been conducted in elderly populations recruited from the general population.\textsuperscript{125, 130, 132, 133} In these studies renal function has been defined according to serum creatinine levels,\textsuperscript{132} Cystatin C levels,\textsuperscript{130} eGFR using the MDRD study equation\textsuperscript{125} or eGFR using the Cockcroft-Gaults formula.\textsuperscript{133} The outcomes have been all-cause or cardiovascular mortality, or a composite of cardiovascular mortality, stroke and CHD. The findings have been similar to those reported in younger community-based cohorts. Only one study has investigated the association between RI and incidence of MI,\textsuperscript{133} by relating quartiles of eGFR to incidence of MI. In this study it was found that RI was associated with an increased incidence of MI (HR 1.64 (1.03 to 2.59)) for the 2nd, HR 1.94 (1.21 to 3.10) for the 3rd and HR 3.06 (1.80 to 5.19) for the 4th quartile compared with the 1st quartile of eGFR). No previous study in a younger cohort from the general population has investigated the association between mild or moderate RI and incidence of MI.

### Risk factors for kidney and cardiovascular disease

Many of the risk factors for chronic kidney and cardiovascular disease are shared. In community-based studies of populations without previous CKD it has been shown that age,\textsuperscript{128, 134} diabetes,\textsuperscript{128, 134} treatment for hypertension,\textsuperscript{134-137} obesity,\textsuperscript{138, 139} smoking\textsuperscript{128, 134, 138-142} and dyslipidemia\textsuperscript{143} all are associated with subsequent kidney disease. In one study, conducted in subjects without
kidney disease, risk factors for developing kidney disease were studied. It was found that mildly reduced GFR, diabetes mellitus, age (per 10-year increment), hypertension, smoking, a low HDL cholesterol level and obesity were predictors of kidney disease. Both in low- and middle-income as well as in high-income countries, CVD is the leading cause of death and loss of disability-adjusted life years. The main modifiable risk factors for CVD are dyslipidemia, smoking, diabetes mellitus and hypertension. In the Interheart study, conducted in 52 countries around the world, it was shown that these risk factors were consistent, both among men and women, irrespective of geographic region or ethnicity. The two most important risk factors for MI were a high apoB/apoA-1 ratio and smoking. They accounted for as much as two thirds of the population attributable risk of a MI.

Randomised trials have shown that by lowering LDL cholesterol, blood pressure and inhibiting platelet function the incidence of MI and stroke can be reduced. It has been proposed that by offering a combination of blood pressure and cholesterol-lowering therapy and anti-platelet medication to everyone 55 years of age or older more than 80% of all CVD may be prevented.

In individuals diagnosed with CKD lowering blood pressure and introducing treatment with angiotensin-converting enzyme (ACE) inhibitors would not only prevent CVD but also most likely reduce further progress of renal dysfunction.

**Lipid metabolism in chronic kidney disease**

Patients with dialysis-dependent RI have a proatherogenic lipid profile with high levels of triglycerides and low levels of HDL and apoA-1. Clearance of VLDL, IDL and chylomicron remnants are impaired. Concentrations of total cholesterol and LDL cholesterol are in general not different from other people. Some studies have found similar lipid patterns among patients with lesser degrees of RI. High levels of apoB and low levels of apoA-1 have been associated with CKD, and also suggested as a possible mechanism for the increased risk for CHD seen among individuals with RI. Thus, in CKD traditional lipids may not fully detect dyslipidemia and may not provide the same prognostic information as in people with normal renal function. Previous studies have failed to show additional benefit with apoB and apoA-1, as well as other novel risk factors, as homocystein and C-reactive protein in the prediction of CHD among subjects with CKD.
The overall aim of this thesis was to investigate the importance of renal insufficiency as risk factor for premature death and myocardial infarction among individuals with or without previous cardiovascular disease.

The specific aims were:

To investigate if renal insufficiency predicts early mortality among patients undergoing coronary artery bypass grafting and to compare calculated creatinine clearance to serum creatinine in the prediction of death within 30 days of surgery (Study I).

To investigate renal insufficiency in relation to the incidence of myocardial infarction and death within five years after coronary artery bypass grafting (Study II).

To investigate renal insufficiency as a predictor of myocardial infarction and death in the general population and to compare two different formulas to estimate glomerular filtration rates as predictors of adverse outcomes (Study III).

To investigate different lipid measures, in particular the ratio of apolipoprotein B/apolipoprotein A-1, as predictors of first myocardial infarction among individuals with or without chronic kidney disease (Study IV).
Subjects and methods

Study populations

The Stockholm Coronary Artery Bypass Grafting cohort
This cohort consists of all patients who underwent coronary artery bypass grafting (CABG) at the Karolinska Hospital, Stockholm, during 1970 to 2005. In the present thesis (Study I & II) we used all patients without dialysis-dependent RI undergoing a first isolated CABG during 1980-1995 (n=6,711). All these patients were operated on during cardiopulmonary bypass. Information on height, weight, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, left ventricular function (LVF), year of surgery, left main coronary artery stenosis, number of significantly obstructed coronary arteries, prior stroke, prior MI, unstable angina during the current admission, serum creatinine concentration, dialysis-dependent renal failure and prior cardio-thoracic surgery was extracted from medical records. All variables had been carefully defined beforehand and were extracted using a standardized protocol. Registers on Causes of Death, emigration/immigration and hospital discharges were linked to the cohort and used in the follow-up of the present studies. Information on LVF was missing in 17% of patients and 97% of the patients had complete information on the other variables. In Study I all (n=6,711) patients without dialysis-dependent RI were included. In Study II those surviving thirty days post-operatively were included (n=6,575).

The Apolipoprotein-related MOrtality RISk (AMORIS) cohort
The Apolipoprotein-related MOrtality RISk (AMORIS) cohort includes 689,714 Swedish men and women who during 1985-1996 were referred for clinical laboratory testing as part of health check-ups or from outpatient clinics. The physicians referring the patients decided which laboratory test would be analysed from predefined combinations of tests. One, Multitest, included all serum analyses available (more than 20). The other six panels of tests were based on clinical diagnosis or suspicion of disease: CHD; thyroid function; anaemia; liver function; kidney function or connective tissue disease. In addition, the physician could add five different alternatives: apoB and apoA-1; measured HDL cholesterol and calculated LDL cholesterol; serum prostate specific antigen; serum T4; and serum ferritin to any of the other prespecified combinations. There is no information on blood pressure levels or medication for the AMORIS cohort. No individuals were hospitalized at the time of investigation. Information on smoking is available for 8,278 women from the Swedish Medical Birth Register. All blood samples were analyzed at one laboratory, CALAB medical laboratories, Stockholm, Sweden. Information on sociodemographic characteristics including socioeconomic status and country of birth was collected from Swedish national censuses carried out in 1985 and 1990. Seventy-two percent of the study population was living in Stockholm County at the census closest to inclusion date. In all, 15% of the cohort was born in other countries than Sweden, which corresponds to the proportion of foreign-born individuals found in Stockholm County in 1990. Dividing social class into three categories; manual workers, lower non-manual employees and intermediate or
high non-manual employees there were 41%, 46% and 22% in each group, respectively. The corresponding figures for Stockholm county 1990 were 37%, 42% and 21%. The standardized mortality ratio was 0.86 for all-cause mortality in the AMORIS cohort compared with the general population of Stockholm.

The database was originally utilized primarily to assess the importance of apoB and apoA-1 as predictors of CVD. Study III, included all (n=571,353) individuals in the AMORIS cohort, 20 years of age or older, with at least one registered creatinine value, and no previous MI. Study IV included all individuals between 20 and 85 years of age, with at least one registered creatinine value, an eGFR more than 15 mL/min per 1.73 m², no previous MI, and complete information on apoB, apoA-1, glucose, triglycerides and total cholesterol (n=142,394).

Renal function

In Study I renal function was assessed by serum creatinine and by calculating creatinine clearance using the Cockcroft-Gaults formula. In Study II the Cockcroft-Gaults formula was used to calculate creatinine clearance. In Study III the Mayo formula, and the MDRD study equation were used to estimate GFR and the Cockcroft-Gaults formula was used to calculate creatinine clearance. In Study IV, the MDRD study equation was used to estimate GFR. For the Mayo and MDRD formulas, GFR was expressed in ml per minute per 1.73 m² body surface area. For the Cockcroft-Gaults formula GFR (CrCl) was expressed in ml per minute. These formulas are shown below:

**Cockcroft-Gaults formula**

Calculated creatinine clearance = (140-age) x (weight in kg) / (72 x (serum creatinine in µmol per litre /88.4)) for men. In women the value was multiplied by 0.85.

**The Modification of Diet in Renal Disease study equation**

Estimated GFR = 186.3 x (serum creatinine in µmol per litre/88.4)−1.154 x age−0.203. In women the value was multiplied by 0.742.

**The Mayo formula**

Estimated GFR = exp (1.911 + (5.249 / (serum creatinine in µmol per litre/88.4)) – (2.114 / (serum creatinine in µmol per litre/88.4)²) – (0.00686 x age) – 0.205 (if female)). If serum creatinine is less than 71 µmol per litre the value 71 is used in the equation.

Classification of renal function

In this thesis the terms mild, moderate and severe RI are used synonymously with mildly, moderately and severely reduced GFR (Table 1). In Study IV the term CKD is used synonymously with an estimated GFR of less than 60, but more than 15 mL/min per 1.73 m². The different stages 1 to 5 of CKD proposed by the NKF (Table 1) were not used in this thesis since we had no information on markers of kidney injury.

Laboratory methods and other variables

**Study I & II**

*Serum creatinine*

Serum creatinine was measured at the time of hospital admission, usually the day before surgery. Coronary angiography was normally performed several weeks before measurement of serum creatinine. During the entire study period serum creatinine was analyzed by a nonkinetic alkaline picrate method (Jaffé), at the same laboratory.
Other variables
If patients were defined as having diabetes, hyperlipidemia or hypertension in the medical record that information would be used in the database. Otherwise, patients were defined as having diabetes if they were taking insulin or oral hypoglycemic agents and as having hypertension if they were taking antihypertensive medication. Patients taking lipid-lowering therapy were defined as having hyperlipidemia. Left ventricular function (LVF) was assessed either by echocardiography or ventriculography and defined as normal if the ejection fraction (EF) was greater than 55%, reduced if the EF was less than 55% but more than 30% and severely reduced if the EF was less than 30%.

Study III & IV
Serum creatinine
Serum creatinine was analyzed by a nonkinetic alkaline picrate method (Jaffé), using an AutoChemist-PRISMA (New Clinicon, Stockholm, Sweden) 1985-1992 and DAX-96 analyzer (Technicon/Bayer Corporations) 1993-1996. Coefficients of variation for creatinine determinations were less than 3.1% at 75.5 µmol/L, 1.7% at 212 µmol/L and 1.6% at 547 µmol/L. There was no significant change in age-adjusted creatinine levels during the inclusion period.
We could not standardize our creatinine values to the international standard suggested since no frozen plasma from the study subjects was available. Creatinine values in the AMORIS cohort were compared with values from the most recent NHANES surveys, which have been found to correspond to standardized values. Mean creatinine among white non-hispanics in these surveys was 2.6 µmol/L (0.03 mg/dL) lower as compared to those in the AMORIS cohort. No adjustment of creatinine values was made in the studies of the present thesis.
Only creatinine values recorded within one year of the inclusion date were used for estimating GFR in these studies. In 96.8% one, in 2.4% two and in 0.8% of the study population more than two creatinine values were recorded within one year of inclusion, respectively. Since creatinine values can change rapidly secondary to acute illness, dehydration and major surgery, among other things, all individuals (n=7,878 (1.4%)) with one creatinine value differing more than 20% from another within one year were scrutinized manually. In those with rising or decreasing values the last recording within one year was used. In those with one value differing considerably an average of the others was used. In 4,885 (0.8%) individuals with only two values within one year, but additional values thereafter, later values were used to judge which of the two values to regard as most representative.

Lipid measures
Blood samples were drawn after fasting overnight in most (64%) subjects, 16% were non-fasting and 20% had no information on food intake prior to examination. Total cholesterol and triglycerides were determined by enzymatic techniques and apoB and apoA-I by immunoturbidimetry. Levels of LDL cholesterol were calculated by a formula using concentrations of total cholesterol, triglycerides and apoA-I (see below). High density lipoprotein cholesterol was then derived using the LDL cholesterol estimate from this formula (see below). Development and validation of these formulas has been described in detail previously.
In four different populations, the correlation between concentrations of LDL cholesterol obtained by this formula and LDL cholesterol calculated by Friedewalds formula was between r=0.97 and r=0.99, with no systematic over- or underestimation of high or low LDL cholesterol levels. In a subset of 6,462 individuals of the AMORIS cohort HDL cholesterol was measured directly by enzymatic methods and calculated HDL was...
also available. Separate analyses were carried out in this group to compare results in those with measured as compared to those with only calculated HDL cholesterol.

**Formulas for estimating LDL and HDL cholesterol**

LDL cholesterol = $0.48 + 0.99 \times \text{total cholesterol} – 0.23 \times \text{triglycerides} – 1.58 \times \text{apoA-I}$

HDL cholesterol = total cholesterol – $0.45 \times \text{triglycerides} – \text{LDL cholesterol}$

**Outcome measures**

The outcome measure studied was in Study I, all-cause mortality, in Study II & III, all-cause mortality and incidence of MI and in Study IV, incidence of MI.

**Follow-up**

In Study I follow-up started at the time of surgery and ended at the time of death, or 30 days post-operatively, whichever came first.

In Study II follow-up started 30 days post-CABG and ended for MI at the time of death, emigration, MI or five years after surgery and for mortality at the time of death, emigration or five years after surgery, whichever came first.

In Study III & IV the index date was chosen according to concurrent measurement of serum creatinine, total cholesterol, triglycerides, apoB, apoA-1 and glucose. If not all these measurements were available from the same occasion the index date would be the occasion when serum creatinine, total cholesterol, triglycerides, apoB and apoA-1; or when serum creatinine, total cholesterol, triglycerides and glucose; or when serum creatinine, triglycerides and total cholesterol; or when only serum creatinine was available from the same date. At index date information on cholesterol levels were known for 95.1%, triglycerides 95.0%, apoB 27.5%, apoA-1 29.5%, iron 91.0%, serum albumin 86.7%, glucose 93.8%, calcium 91.8% and phosphate 67.0% and blood urea nitrogen for 67.3% of the cohort, respectively.

In Study III follow-up started at the index date, or in those cases when more than one creatinine value was used for estimation of GFR, when the last creatinine value was determined. Follow-up ended for MI at the time of death, emigration, MI or the 31st of December 2002, and for mortality at the time of death, emigration or the 31st of December 2002, whichever came first.

In Study IV the same index-date as in study III was used. Follow-up started when the last creatinine value used for estimation of GFR was analyzed and ended for MI at the time of death, emigration, MI or the 31st of December 2002.

**Mortality and myocardial infarction**

Every resident of Sweden has a unique Personal Identification Number (PIN). This number was available for all individuals included in the studies of this thesis and linked to the Swedish Causes of Death Register, the Swedish National Patient Register and a local Discharge Register in Stockholm County for identification of cases.

**The Swedish Causes of Death Register**

Already in 1749 a nationwide system for recording deaths was started in Sweden and statistics on Causes of Death has been published annually since 1911. The current Swedish Causes of Death Register was started in 1952 and is held and maintained by the Swedish National Board of Health and Welfare. From 1961 onwards all individuals residing in Sweden at the time of death are covered and registered in this computerized national register. The date of death and the underlying, as well as contributory causes of death are recorded. The causes of death are classified according to the 7th through the 10th version of International Classification of Disease (ICD). Previous studies have found the validity of this register to be satisfactory, and there is essentially no loss of deaths. Follow-up of mortality using this register was performed 1980-1995 (Study I), 1980-2000 (Study II) and 1985-2002 (Study III).
The Swedish National Patient Register

The Swedish National Patient Register (formally The Swedish Discharge Register or Inpatient Register) was started in the sixties by the Swedish National Board of Health and Welfare to register information on public in-patient care in Sweden. Initially it was covering all patients treated in psychiatric hospitals, but only a small part of those cared for as in-patients in somatic hospitals. In 1969 the register was covering 60% of the Swedish population in terms of in-patient care and 85% in 1983, including Stockholm County. From 1987 onwards all public in-patient care in Sweden was covered.

At discharge from hospitals, a form is completed locally for each patient and reported on a yearly basis to the Swedish National Board of Health and Welfare. Beside the PIN, the register contains information on age, gender, residency, dates of hospital admission and discharge, and the names of the hospitals and the departments giving care, surgical procedures performed and information on diagnosis at discharge, coded according to the 7th through the 10th version of ICD.

The underreporting of hospital stays for the period 1987-1991 is estimated to be two percent by the register holder. The number of stays 2003 with a missing PIN or discharge diagnosis was 0.7% and 0.5%, respectively. One study investigating how well cases of trauma, ischemic heart disease and cancer were reported to the register found that underreporting ranged from 3% to 5%. The proportion of falsely diagnosed cases was found to be low in the same study.164

Other registers

The Swedish Medical Birth Register was started in 1973 by the Swedish National Board of Health and Welfare and contains information on all pregnancies, deliveries and new-born children in Sweden. This register was linked to the AMORIS database and information on smoking for a subset of women in Study III & IV was obtained.

The Swedish Population and Migration register maintained by Statistics Sweden was used for information on emigration (Study I-IV). Information on socioeconomic status was collected from the Swedish censuses carried out in 1985 and 1990 by Statistics Sweden (Study III & IV).

Myocardial infarction

New cases of MI during follow-up were identified in Study II from registers of hospital discharges in Stockholm County (1980-1986) and in Study II-IV nationally (1985-2002) from the Swedish National Patient Register and the Swedish Causes of Death Register. Using these registries for case ascertainment has been found to have high sensitivity and positive predictive value in detecting incident cases of MI in a defined population in Sweden.165, 166

Statistical analyses

In all four studies statistical analyses were performed using statistical analysis software (SAS) version 8 or higher (SAS Institute, Inc, Cary, NC, USA).

Logistic regression (Study I)

Logistic regression was used to estimate the odds ratios of early death associated with different degrees of RI in study I. These analyses were performed crude, adjusted for age and with multivariable adjustment for potential confounding from patient characteristics. The variables included in the final model were those with an influence of more than 10% on the estimated odds ratio for RI in relation to the outcome. To indicate the precision of the calculated odds ratios they were reported with 95% confidence intervals.

Cox proportional hazards regression (Study II, III & IV)

Cox proportional hazards regression was used to estimate hazard ratios crude and after multivariable adjustment for confounders to assess the association between RI and

Subjects and methods
the outcomes (Study II, III & IV). In order to preserve statistical precision, we used a “change-in-point-estimate” strategy, including only those variables in the final model which influenced the point estimate of the HR by at least 0.1 when adjusted for in multivariable analysis. The proportional hazards assumption was tested and satisfied in all studies by using log cumulative hazard plots (Study II-IV), Nelson-Aalen cumulative hazards function (Study II-IV) and Martingale residuals (Study II). To indicate the precision of the estimated HRs, we reported 95% confidence intervals.

**Receiver operator characteristics (ROC curves) (Study I & IV)**
The sensitivity and specificity of serum creatinine concentrations and calculated creatinine clearance, respectively, to predict early mortality after CABG were analyzed by ROC curves (Study I). In study IV the sensitivity and specificity of the apoB/apoA-1 ratio and total cholesterol/HDL cholesterol ratio, respectively, to predict MI were analyzed by ROC curves. The areas under the curves were calculated and compared by nonparametric methods using Mann-Whitney statistics together with a $\chi^2$ test for the differences in areas under the curves (Study I & IV).

**Population attributable fraction (Study III & IV)**
The attributable fraction was used to quantify the proportion of deaths and MIs that could be attributed to RI (Study III) or a high apoB/apoA-1 ratio (Study IV). The attributable fraction may be calculated by the following equation where $P_i$ represent the proportion of cases in each category of RI and $RR_i$ the relative risk for those exposed in that category in relation to those unexposed.

\[
\text{Attributable fraction} = \sum P_i (RR_i - 1 / RR_i) \]

In study III each level of RI (mild, moderate or severe) was taken into account when the attributable fraction was calculated using the formula above, where $i$ represent the different levels of RI. In Study IV hyperlipidemia was dichotomised using an apoB/apoA-1 level of 0.6, which corresponds approximately to the lowest quintile, as cut-off. The relative risks used for calculating attributable fraction were adjusted for confounders.
Results

Study I

Patient characteristics
There were 1262 (19%) women and 5449 (81%) men in the study (Table 2). Twenty-two percent of the study population had Ccr less than 60 mL/min. With increasing degree of RI the patients were older and had more comorbidity. Diabetes mellitus was not more common in patients with RI.

Table 2. Characteristics of 6711 patients undergoing coronary artery bypass grafting during 1980-1995 in relation to preoperative creatinine clearance

<table>
<thead>
<tr>
<th>CREATININE CLEARANCE (mL/min)</th>
<th>All patients*</th>
<th>≥ 90</th>
<th>60 – 90</th>
<th>30 – 60</th>
<th>&lt; 30</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (%)</td>
<td>6711</td>
<td>1888 (28)</td>
<td>3212 (48)</td>
<td>1391 (21)</td>
<td>64 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 9</td>
<td>54 ± 8</td>
<td>62 ± 8</td>
<td>69 ± 7</td>
<td>71 ± 9</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>26 ± 3</td>
<td>28 ± 3</td>
<td>26 ± 3</td>
<td>25 ± 3</td>
<td>24 ± 3</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>100 ± 31</td>
<td>85 ± 13</td>
<td>99 ± 16</td>
<td>118 ± 27</td>
<td>268 ± 158</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.1 ± 0.4</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.3</td>
<td>3.0 ± 1.8</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Year of surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980-1984 (%)</td>
<td>1372 (20)</td>
<td>448 (24)</td>
<td>667 (21)</td>
<td>163 (12)</td>
<td>4 (6)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>1985-1989 (%)</td>
<td>1842 (28)</td>
<td>486 (25)</td>
<td>952 (29)</td>
<td>358 (25)</td>
<td>14 (22)</td>
<td></td>
</tr>
<tr>
<td>1990-1995 (%)</td>
<td>3497 (52)</td>
<td>954 (51)</td>
<td>1593 (50)</td>
<td>870 (63)</td>
<td>46 (72)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>1126 (17)</td>
<td>276 (15)</td>
<td>486 (15)</td>
<td>317 (23)</td>
<td>25 (39)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>2011 (30)</td>
<td>549 (29)</td>
<td>945 (29)</td>
<td>450 (32)</td>
<td>34 (53)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>3862 (58)</td>
<td>1028 (54)</td>
<td>1845 (57)</td>
<td>856 (62)</td>
<td>49 (77)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>390 (6)</td>
<td>81 (4)</td>
<td>185 (6)</td>
<td>113 (8)</td>
<td>6 (9)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>451 (7)</td>
<td>70 (4)</td>
<td>219 (7)</td>
<td>139 (10)</td>
<td>9 (14)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>852 (13)</td>
<td>287 (15)</td>
<td>365 (11)</td>
<td>173 (12)</td>
<td>9 (14)</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin treatment (%)</td>
<td>298 (35)</td>
<td>82 (29)</td>
<td>143 (39)</td>
<td>67 (39)</td>
<td>2 (22)</td>
<td>0.02</td>
</tr>
<tr>
<td>Oral medication (%)</td>
<td>456 (54)</td>
<td>159 (55)</td>
<td>190 (52)</td>
<td>92 (53)</td>
<td>4 (44)</td>
<td>0.79</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One vessel (%)</td>
<td>537 (8)</td>
<td>186 (10)</td>
<td>264 (8)</td>
<td>62 (4)</td>
<td>3 (5)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Two vessel (%)</td>
<td>1547 (23)</td>
<td>497 (26)</td>
<td>741 (23)</td>
<td>257 (18)</td>
<td>7 (11)</td>
<td></td>
</tr>
<tr>
<td>Three vessel (%)</td>
<td>3410 (52)</td>
<td>919 (49)</td>
<td>1641 (51)</td>
<td>750 (55)</td>
<td>38 (60)</td>
<td></td>
</tr>
<tr>
<td>Left main stenosis (%)</td>
<td>1180 (18)</td>
<td>282 (15)</td>
<td>548 (17)</td>
<td>314 (23)</td>
<td>15 (24)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (%)</td>
<td>2757 (41)</td>
<td>793 (42)</td>
<td>1348 (42)</td>
<td>554 (40)</td>
<td>13 (20)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Reduced (%)</td>
<td>2460 (37)</td>
<td>676 (36)</td>
<td>1200 (37)</td>
<td>514 (37)</td>
<td>26 (41)</td>
<td></td>
</tr>
<tr>
<td>Missing (%)</td>
<td>1114 (17)</td>
<td>333 (18)</td>
<td>499 (16)</td>
<td>211 (15)</td>
<td>17 (27)</td>
<td></td>
</tr>
<tr>
<td>Postoperative morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early bleeding (%)</td>
<td>257 (4)</td>
<td>50 (3)</td>
<td>117 (4)</td>
<td>80 (6)</td>
<td>6 (9)</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Mediastinitis (%)</td>
<td>58 (1)</td>
<td>15 (1)</td>
<td>27 (1)</td>
<td>14 (1)</td>
<td>1 (2)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

BMI: body mass index; MI, myocardial infarction, * Includes 156 (2%) patients without data on serum creatinine

33
Early mortality and postoperative complications

There were 136 (2.0%) deaths within 30 days of surgery. The crude risk of early death increased both in men and women with decreasing Ccr. In patients with severe and moderate RI, early mortality was 10.9% and 4.2%, respectively, compared to 0.7% in patients with normal renal function (Table 3). Calculated creatinine clearance remained a strong predictor of early mortality after multivariable adjustment for confounders. In patients with severe or moderate RI, the risk of early death was higher OR 4.7, (95% CI 1.6-13.8) and OR 2.4, (95% CI 1.2-4.8), respectively, than in patients with normal renal function (Table 3).

Comparison of calculated creatinine clearance and serum creatinine

The area under the ROC curve for Ccr and serum creatinine was 0.71 and 0.62, respectively, yielding a difference of 0.08 (p=0.0004). This greater area for Ccr compared with serum creatinine is shown in Figure 1. Thus, the sensitivity and specificity of Ccr to predict early mortality after CABG was higher for Ccr as compared with serum creatinine alone.

Reoperation for bleeding or treatment for mediastinitis

We did not find an increased risk of early reoperation because of bleeding associated with RI. Also, there were few cases of mediastinitis, and we did not find an association between mediastinitis and RI.

Table 3. Early mortality after coronary artery bypass grafting during 1980-1995 in relation to gender and preoperative creatinine clearance. Odds ratio (OR) calculated in relation to patients with creatinine clearance ≥ 90 mL/min

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>≥ 90</th>
<th>60 – 90</th>
<th>30 – 60</th>
<th>&lt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>n=1715</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>12 deaths (0.7%)</td>
<td>39 deaths (1.5%)</td>
<td>42 deaths (4.6%)</td>
<td>4 deaths (9.8%)</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.0</td>
<td>1.3</td>
<td>0.6 – 2.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Multivariate adjustment*</td>
<td>1.0</td>
<td>1.3</td>
<td>0.6 – 2.6</td>
<td>2.8</td>
</tr>
</tbody>
</table>

| n=2661                       |      |         |        |      |
| Crude                        | 1.0  | 3.8     | 0.5 – 29.7 | 5.9 | 0.8 – 44.6 | 25.8 | 2.6 – 259.9 |
| Adjusted for age             | 1.0  | 3.0     | 0.4 – 24.3 | 3.9 | 0.5 – 32.0 | 15.5 | 1.4 – 176.2 |
| Multivariate adjustment†     | 1.0  | 3.1     | 0.4 – 24.1 | 4.5 | 0.6 – 34.6 | 15.4 | 1.5 – 164.1 |

| n=906                       |      |         |        |      |
| Crude                        | 1.0  | 2.3     | 1.3 – 4.3 | 6.3 | 3.4 – 11.5 | 17.7 | 6.8 – 46.1 |
| Adjusted for age             | 1.0  | 1.5     | 0.8 – 2.9 | 2.8 | 1.4 – 5.7 | 6.9  | 2.4 – 19.7 |
| Multivariate adjustment‡     | 1.0  | 1.4     | 0.7 – 2.6 | 2.4 | 1.2 – 4.8 | 4.7  | 1.6 – 13.8 |

*Adjusted for age, year of surgery, diabetes mellitus, and left ventricular function
† Adjusted for previous myocardial infarction, peripheral vascular disease and left ventricular function
‡ Adjusted for age, year of surgery, peripheral vascular disease, diabetes mellitus and left ventricular function
Study II

The study population in study II was the same as in study I (Table 2) except for 136 patients who died within 30 days of surgery. Thus, the patient characteristics did not differ considerably between the two studies. During the 15 year study period, the average age at surgery increased from 58 years for women and 56 years for men, 1980-1984, to 64 years for women and 61 years for men, 1990-1995. The proportion of patients with eGFR less than 60 mL/min increased from 13% to 26% between 1980-1984 and 1990-1995.

Mortality and myocardial infarction

There were 628 (10%) deaths and 496 (8%) fatal or non-fatal MIs within five years of CABG. We found a substantially lower five-year survival in patients with severe RI compared to those with better renal function. These differences persisted after adjustment for potential confounding factors and with application of a more differentiated classification of RI. Long-term mortality increased gradually with decreasing eGFR (Figure 2).

Figure 1  Receiver operating characteristics curves comparing calculated creatinine clearance and serum creatinine as predictors of early mortality in 6555 patients undergoing coronary artery bypass surgery.

Figure 2  Hazard ratio (HR) for death, after multivariable adjustment, according to different levels of renal function within five years of CABG calculated in relation to patients with estimated glomerular filtration rate ≥ 90 mL/min.
At all levels of RI an increased mortality within 5 years was present even after multivariable adjustment (Table 4). Compared to patients with normal renal function those with moderate or severe RI had almost two and five times increased mortality within five years of surgery, respectively. In addition, the incidence of MI was increased in patients with moderate and severe RI (Table 4). In terms of relative risk, RI was a strong risk factor of long-term mortality compared to other risk factors related to long-term prognosis after surgery (Table 5).

In analyses of eGFR as a continuous variable each 10 mL/min increase in eGFR decreased the mortality within five years of surgery by 12%; HR 0.88, (95% CI 0.84-0.93) per 10 mL/min increase in eGFR after multivariable adjustment for confounders.

Among patients with normal renal function who died during follow-up, 63% died of cardiovascular causes including stroke. The corresponding figures for mild, moderate or severe RI were, 67%, 71% and 64%, respectively. Cancer was the underlying cause of death among 20% of patients with normal renal function, 15% of patients with mild or moderate RI and among 3% of patients with severe RI.

Table 4. Five-year mortality and myocardial infarction (MI) after coronary artery bypass grafting in relation to preoperative estimated glomerular filtration rate (eGFR). Hazard ratio (HR) calculated in relation to patients with eGFR ≥ 90 mL/min

<table>
<thead>
<tr>
<th>eGFR not calculated</th>
<th>eGFR (mL/min)</th>
<th>≥ 90</th>
<th>60 – 90</th>
<th>30 – 60</th>
<th>&lt; 30</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=149)</td>
<td>(n=1875)</td>
<td>(n=3161)</td>
<td>(n=1333)</td>
<td>(n=57)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>15 deaths (10%)</td>
<td>107 deaths (6%)</td>
<td>281 deaths (9%)</td>
<td>199 deaths (15%)</td>
<td>118 deaths (46%)</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.0</td>
<td>1.6 (1.3 – 2.0)</td>
<td>2.9 (2.3 – 3.7)</td>
<td>11.4 (7.4 – 17.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable adjustmenta</td>
<td>1.0</td>
<td>1.2 (1.0 – 1.6)</td>
<td>1.8 (1.3 – 2.4)</td>
<td>5.2 (3.1 – 8.6)</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Multivariable p value</td>
<td>p=0.11</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>8 patients (5%)</td>
<td>118 patients (6%)</td>
<td>232 patients (7%)</td>
<td>127 patients (9%)</td>
<td>11 patients (19%)</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.0</td>
<td>1.2 (0.9 – 1.5)</td>
<td>1.6 (1.2 – 2.0)</td>
<td>4.0 (2.1 – 7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable adjustmenta</td>
<td>1.0</td>
<td>1.2 (0.9 – 1.5)</td>
<td>1.5 (1.1 – 2.1)</td>
<td>3.5 (1.8 – 6.8)</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Multivariable p value</td>
<td>p=0.22</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality or myocardial infarction</td>
<td>19 patients (13%)</td>
<td>191 patients (10%)</td>
<td>410 patients (13%)</td>
<td>261 patients (20%)</td>
<td>27 patients (47%)</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.0</td>
<td>1.3 (1.1 – 1.5)</td>
<td>2.1 (1.7 – 2.5)</td>
<td>6.4 (4.3 – 9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.0</td>
<td>1.1 (1.0 – 1.4)</td>
<td>1.7 (1.3 – 2.1)</td>
<td>4.9 (3.2 – 7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable adjustmenta</td>
<td>1.0</td>
<td>1.1 (0.9 – 1.4)</td>
<td>1.6 (1.3 – 2.0)</td>
<td>3.8 (2.4 – 6.1)</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Multivariable p value</td>
<td>p=0.24</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; MI, myocardial infarction.

Adjusted for age, year of surgery, gender, diabetes mellitus, number of obstructed coronary arteries, hypertension, peripheral vascular disease, unstable angina and left ventricular function.

Cochran-Armitage test for trend.
Study III

Patient Characteristics

There were 571,353 study participants with a mean age of 46.3 years for women and 44.8 years for men. Normal renal function was present in 86.6% of the individuals when GFR was estimated by the Mayo formula (Table 6). In comparison only 37.4% had normal renal function using the MDRD study equation (Table 7). With increasing degree of renal dysfunction the subjects were more likely to have a history of diabetes mellitus or hospitalization for cardiovascular disease prior to inclusion (Table 6). Different distributions of GFR estimated by the two formulas are shown in Figure 3 and Table 6.

Myocardial infarction

There were 19,510 fatal or non-fatal MIs during follow-up. Adjusted hazard ratios for MI increased at all levels of renal dysfunction for GFR-Mayo, and for GFR-MDRD less than 60 mL/min/1.73 m² (Table 7). Gender-specific analysis gave similar results. When renal function was subdivided into six categories, already GFR-Mayo 75 to 90 mL/min/1.73 m² was associated with an increased incidence of MI whereas only GFR-MDRD less than 60 mL/min/1.73 m² had the same association. For each 10 mL/min/1.73 m² reduction of GFR-Mayo, the incidence of MI increased by 11% (95% confidence interval (CI), 9% to 14%) after adjustment for confounders. The corresponding figure for GFR-MDRD was 5% (95% CI, 4% to 8%). The population-attributable fraction for a decreased GFR, taking into account each level of RI, estimated by the Mayo formula, associated with MI was 4.0%.
Mortality
There were 56,367 deaths during follow-up (Table 7). The number of deaths per 10,000 person-years increased with worsening renal function for both formulas (Table 7). The hazard ratio of all-cause mortality was significantly increased at all levels of decreased GFR when the Mayo formula was used, but only at levels of moderately and severely decreased GFR-MDRD (Table 7).

Dividing renal function into finer categories, already GFR-Mayo 60 to 75 mL/min/1.73 m$^2$ was associated with an increased mortality, while this was only seen in subjects with GFR-MDRD less than 45 mL/min/1.73 m$^2$ (Figure 4). For each 10 mL/min/1.73 m$^2$ reduction of GFR-Mayo, the adjusted risk of death increased by 11% (95% CI, 10% to 12%). The corresponding figure for GFR-MDRD was 4% (95% CI, 3% to 5%). The population-attributable fraction for a decreased GFR, estimated by the Mayo formula, taking into account each level of RI, associated with mortality was 5.3%.

Cockcroft-Gault's formula
When, in a subset of individuals, renal function was assessed by the Cockcroft-Gault's formula, corrected for body surface area, similar hazard ratios for the association between renal impairment and both outcomes as for GFR-MDRD were found.

Table 6. Characteristics of Study Population According to GFR Estimated by the Mayo Formula

<table>
<thead>
<tr>
<th>Estimated GFR (mL/min/1.73 m$^2$)</th>
<th>All subjects</th>
<th>&gt; 90</th>
<th>60-90</th>
<th>30-60</th>
<th>&lt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. individuals (%)</td>
<td>N = 571,353</td>
<td>494,650 (86.6)</td>
<td>71,356 (12.5)</td>
<td>4,749 (0.8)</td>
<td>598 (0.1)</td>
</tr>
<tr>
<td>Age (years) [25th,75th percentile]</td>
<td>45.5 [34,55]</td>
<td>42.2 [32,51]</td>
<td>65.9 [58,75]</td>
<td>74.7 [69,83]</td>
<td>71.6 [62,83]</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>47.5</td>
<td>44.8</td>
<td>65.6</td>
<td>51.0</td>
<td>44.7</td>
</tr>
<tr>
<td>Diabetes mellitus* (%)</td>
<td>3.4</td>
<td>2.7</td>
<td>7.8</td>
<td>20.9</td>
<td>24.0</td>
</tr>
<tr>
<td>Socioeconomic status†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (%)</td>
<td>32.5</td>
<td>32.9</td>
<td>27.1</td>
<td>31.6</td>
<td>35.7</td>
</tr>
<tr>
<td>Middle (%)</td>
<td>24.9</td>
<td>24.6</td>
<td>28.8</td>
<td>23.1</td>
<td>30.7</td>
</tr>
<tr>
<td>High (%)</td>
<td>42.6</td>
<td>42.5</td>
<td>44.1</td>
<td>45.4</td>
<td>33.6</td>
</tr>
<tr>
<td>Prior hospitalization‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris (%)</td>
<td>0.1</td>
<td>0.03</td>
<td>0.2</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>1.8</td>
<td>0.9</td>
<td>1.8</td>
<td>8.6</td>
<td>24.8</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>1.0</td>
<td>0.6</td>
<td>3.6</td>
<td>10.2</td>
<td>11.9</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>1.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>1.0</td>
<td>0.7</td>
<td>0.9</td>
<td>3.9</td>
<td>13.1</td>
</tr>
</tbody>
</table>

| Laboratory values                 |             |     |     |     |      |
| Creatinine (µmol/L)               | 81.3 (15.5) | 79.3 (11.5) | 90.6 (15.6) | 129 (21.4) | 260 (137) |
| Total Cholesterol (mmol/L)        | 5.57 (1.17) | 5.48 (1.13) | 6.23 (1.19) | 6.21 (1.42) | 6.11 (1.56) |
| Triglycerides (mmol/L)            | 1.32 (0.99) | 1.29 (0.97) | 1.54 (1.07) | 1.97 (1.40) | 2.14 (1.39) |
| LDL cholesterol (mmol/L)          | 3.65 (1.08) | 3.60 (1.06) | 4.10 (1.10) | 3.82 (1.12) | 4.48 (2.48) |
| HDL cholesterol (mmol/L)          | 1.50 (0.43) | 1.50 (0.42) | 1.54 (0.47) | 1.28 (0.34) | 1.27 (0.28) |
| Glucose (mmol/L)                  | 4.99 (1.28) | 4.93 (1.16) | 5.37 (1.78) | 6.01 (2.84) | 5.95 (2.74) |
| SUN (mmol/L)                      | 5.18 (1.46) | 5.02 (1.25) | 5.94 (1.51) | 9.18 (3.02) | 17.20 (7.21) |

GFR, glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein; SUN, serum urea nitrogen; *includes individuals with fasting glucose > 126 mg/dL or prior hospitalization for diabetes. Laboratory values are given as means with standard deviations. †Low, is defined as manual workers; Middle, lower non-manual employees and High, intermediate or high non-manual employees. ‡Hospitalization prior to inclusion. To convert creatinine values to mg/dL, divide by 88.4. To convert total, LDL and HDL cholesterol to mg/dL, divide by 0.02586; to convert triglycerides to mg/dL divide by 0.01129; to convert SUN to mg/dL divide by 0.357 and to convert glucose to mg/dL divide by 0.05551.
Table 7. Hazard Ratios of Myocardial Infarction and All-cause mortality in Relation to Glomerular Filtration Rate Estimated by the Mayo and MDRD Formulas.

<table>
<thead>
<tr>
<th>Estimated GFR (mL/min/1.73 m^2)</th>
<th>&gt; 90</th>
<th>60-90</th>
<th>30-60</th>
<th>&lt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects (%)</td>
<td>571,353</td>
<td>213,675 (37.4)</td>
<td>494,650 (86.6)</td>
<td>333,002 (58.3)</td>
</tr>
<tr>
<td>No. of cases (%)</td>
<td>19,510 (3.4)</td>
<td>4,102 (1.9)</td>
<td>12,557 (2.5)</td>
<td>13,093 (3.9)</td>
</tr>
<tr>
<td>MI rate*</td>
<td>27.5</td>
<td>20.5</td>
<td>18.8</td>
<td>17.8</td>
</tr>
<tr>
<td>Crude</td>
<td>1.0</td>
<td>1.0</td>
<td>1.95 (1.88–2.02)</td>
<td>4.14 (4.01–4.26)</td>
</tr>
<tr>
<td>Adjustment for age</td>
<td>1.0</td>
<td>1.0</td>
<td>1.06 (1.02–1.10)</td>
<td>1.18 (1.13–1.22)</td>
</tr>
<tr>
<td>Multivariable adjustment†</td>
<td>1.0</td>
<td>1.0</td>
<td>1.01 (0.96–1.05)</td>
<td>1.11 (1.06–1.16)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of individuals</td>
<td>571,353</td>
<td>213,675</td>
<td>494,650</td>
<td>333,002</td>
</tr>
<tr>
<td>No. of cases (%)</td>
<td>56,365 (9.9)</td>
<td>11,326 (5.3)</td>
<td>30,432 (6.2)</td>
<td>35,113 (10.5)</td>
</tr>
<tr>
<td>Mortality rate‡</td>
<td>84.3</td>
<td>70.4</td>
<td>59.2</td>
<td>52.7</td>
</tr>
<tr>
<td>Crude</td>
<td>1.0</td>
<td>1.0</td>
<td>1.88 (1.84–1.92)</td>
<td>5.93 (5.83–6.03)</td>
</tr>
<tr>
<td>Adjustment for age</td>
<td>1.0</td>
<td>1.0</td>
<td>0.77 (0.75–0.78)</td>
<td>1.06 (1.04–1.11)</td>
</tr>
<tr>
<td>Multivariable adjustment§</td>
<td>1.0</td>
<td>1.0</td>
<td>0.77 (0.75–0.79)</td>
<td>1.06 (1.03–1.09)</td>
</tr>
</tbody>
</table>

Hazard ratios presented with 95% confidence intervals.
* Myocardial infarctions per 10,000 person-years adjusted for age.
† In multivariable analysis adjustment for age, gender, serum urea nitrogen, total cholesterol, glucose, albumin and triglycerides were made.
‡ Numbers of deaths per 10,000 person-years adjusted for age.
§ Hazard ratios for all-cause mortality were adjusted for age, gender, total cholesterol, albumin, calcium and triglycerides. All laboratory measurements were analyzed in serum. CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; MDRD, Modification of Diet in Renal Disease.
Study IV

Study participants
In 34.7% of study participants eGFR was more than 90 mL/min/1.73 m² and 4.1% had CKD defined as eGFR less than 60 mL/min/1.73 m² (Table 8). Average eGFR among women, with or without CKD, was 54 and 82 mL/min/1.73 m² and among men, 52 and 89 mL/min/1.73 m², respectively. Individuals with CKD were older, more likely to be female and had diabetes mellitus more frequently than those without CKD. Hospitalization prior to inclusion for angina pectoris, heart failure or stroke was unusual, 1.7%, 1.3% and 0.9%, respectively. In both men and women HDL cholesterol decreased with worsening renal function. Apolipoprotein A-1 was unchanged in men, but increased in women with decreasing eGFR. Low-density lipoprotein cholesterol, non-HDL cholesterol, triglycerides, the total cholesterol/HDL cholesterol ratio and the apoB/apoA-1 ratio was increased in both genders among those with CKD (Table 8).
In a subgroup of 8,278 women similar smoking patterns were found among those with GFR less than 60 mL/min/1.73 m$^2$ (16% smokers) as compared to those with GFR more than 60 mL/min/1.73 m$^2$ (17% smokers).

**Incidence of MI**

During 12.1 years of follow-up there were 5,466 fatal or non-fatal first MIs. The overall age-adjusted MI rate was 11 and 29 cases per 10,000 person-years, for women and men, respectively. The cumulative incidence of MI was higher among those with, 9.2% (n=535) as compared without CKD, 3.6% (n=4,931). After adjustment for age, glucose, triglycerides and total cholesterol the hazard ratio for MI among men associated with CKD was 1.32 (95% CI, 1.14-1.53) and for women with CKD 1.04 (95% CI, 0.91-1.18). Using eGFR less than 50 mL/min/1.73 m$^2$ as a cut-off among women, gave a HR for incidence of MI of 1.22 (95% CI, 0.99-1.50).

Among individuals with CKD strong associations with MI were found, in particular, for apoB, non-HDL cholesterol and ratios of apoB/apoA-1 and total cholesterol.

### Table 8. Characteristics of Study Population in Relation to Glomerular Filtration Rates Estimated by the Modification of Diet in Renal Disease Study Equation

<table>
<thead>
<tr>
<th>Estimated GFR (mL/min/1.73 m$^2$)</th>
<th>All</th>
<th>&gt; 90</th>
<th>60-90</th>
<th>15-60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All individuals</strong></td>
<td>142,394</td>
<td>49,411</td>
<td>87,145</td>
<td>5,838</td>
</tr>
<tr>
<td>Percent of study population</td>
<td>100</td>
<td>34.7</td>
<td>61.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Age, † (years)</td>
<td>47.7 (13.5)</td>
<td>41.3 (12.0)</td>
<td>50.2 (12.5)</td>
<td>64.5 (12.2)</td>
</tr>
<tr>
<td>Female sex, (%)</td>
<td>43.3</td>
<td>28.9</td>
<td>49.3</td>
<td>77.1</td>
</tr>
<tr>
<td>Diabetes mellitus* (%)</td>
<td>3.3</td>
<td>2.5</td>
<td>3.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Estimated GFR, † (mL/min/1.73 m$^2$)</td>
<td>85.1 (15.8)</td>
<td>102 (10.8)</td>
<td>77.7 (7.7)</td>
<td>53.3 (6.7)</td>
</tr>
<tr>
<td>Glucose, † (mmol/L)</td>
<td>5.07 (1.33)</td>
<td>4.97 (1.13)</td>
<td>5.09 (1.33)</td>
<td>5.56 (2.35)</td>
</tr>
</tbody>
</table>

**Lipid measures men†**

| Total cholesterol (mmol/L)        | 5.84 (1.15) | 5.64 (1.16) | 5.99 (1.12) | 6.12 (1.34) |
| Triglycerides (mmol/L)            | 1.54 (0.99) | 1.45 (0.97) | 1.59 (1.00) | 1.91 (1.12) |
| LDL cholesterol (mmol/L)          | 3.75 (1.05) | 3.58 (1.05) | 3.88 (1.02) | 3.98 (1.20) |
| HDL cholesterol (mmol/L)          | 1.40 (0.41) | 1.41 (0.40) | 1.40 (0.42) | 1.29 (0.45) |
| Non-HDL cholesterol (mmol/L)      | 4.44 (1.22) | 4.24 (1.22) | 4.59 (1.19) | 4.84 (1.37) |
| Total cholesterol/HDL cholesterol ratio | 4.69 (2.53) | 4.49 (2.39) | 4.83 (2.59) | 5.58 (3.42) |
| ApoB (g/L)                        | 1.29 (0.35) | 1.23 (0.35) | 1.34 (0.33) | 1.40 (0.38) |
| ApoA-1 (g/L)                      | 1.37 (0.21) | 1.36 (0.21) | 1.38 (0.21) | 1.35 (0.24) |
| ApoB/apoA-1 ratio                 | 0.97 (0.30) | 0.93 (0.30) | 1.00 (0.30) | 1.06 (0.32) |

**Lipid measures women†**

| Total cholesterol (mmol/L)        | 5.83 (1.22) | 5.40 (1.14) | 5.90 (1.20) | 6.46 (1.28) |
| Triglycerides (mmol/L)            | 1.17 (0.73) | 1.04 (0.65) | 1.17 (0.72) | 1.54 (0.91) |
| LDL cholesterol (mmol/L)          | 3.59 (1.12) | 3.25 (1.03) | 3.65 (1.11) | 4.11 (1.21) |
| HDL cholesterol (mmol/L)          | 1.71 (0.43) | 1.69 (0.40) | 1.73 (0.43) | 1.66 (0.48) |
| Non-HDL cholesterol (mmol/L)      | 4.11 (1.26) | 3.72 (1.15) | 4.17 (1.24) | 4.80 (1.36) |
| Total cholesterol/HDL cholesterol ratio | 3.66 (1.62) | 3.41 (1.43) | 3.67 (1.58) | 4.34 (2.21) |
| ApoB (g/L)                        | 1.19 (0.35) | 1.07 (0.32) | 1.21 (0.34) | 1.37 (0.37) |
| ApoA-1 (g/L)                      | 1.52 (0.24) | 1.48 (0.23) | 1.52 (0.24) | 1.53 (0.25) |
| ApoB/apoA-1 ratio                 | 0.80 (0.28) | 0.74 (0.25) | 0.81 (0.27) | 0.93 (0.31) |

Abbreviations: GFR, glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo, apolipoprotein.

*Includes individuals with fasting serum glucose > 7.0 mmol/L (> 126 mg/dL) or prior hospitalization for diabetes. † Age, GFR, lipid ratios and all laboratory values are given as means with standard deviations. To convert total, LDL and HDL cholesterol to mg/dL, divide by 0.02586; to convert triglycerides to mg/dL divide by 0.01129 and to convert glucose to mg/dL divide by 0.05551.
The incidence of MI increased also substantially for levels of the apoB/apoA-1 and total cholesterol/HDL cholesterol ratios, when comparing individuals with or without CKD, in the highest quartiles. Gender-specific analyses yielded similar results as those seen in table 9. When corresponding analyses were performed in 6,442 individuals with measured HDL cholesterol and another

| Table 9. Hazard Ratios* of Myocardial Infarction with 95 percent Confidence Intervals in Relation to Quartiles of Lipoproteins and Lipid Ratios by Level of Estimated Glomerular Filtration Rate. All individuals (n=142,394). |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Quartile                        | 1               | 2               | 3               | 4               |
| Apolipoprotein B† (g/L)         | 0.84 [<1.00]    | 1.10 [1.00-1.21]| 1.33 [1.22-1.45]| 1.72 [1.45-1.86]|
| No. of MIs                      | 312             | 951             | 1,541           | 2,663           |
| GFR ≥ 60                        | 1.00            | 1.50 [1.31-1.72]| 1.92 [1.68-2.20]| 2.58 [2.22-3.00]|
| < 60                            | 1.00            | 1.83 [1.12-3.00]| 2.44 [1.50-3.96]| 3.55 [2.13-5.90]|
| Apolipoprotein A-1 (g/L)        | 1.16 [1.28]     | 1.35 [1.28-1.41]| 1.48 [1.42-1.56]| 1.74 [1.56-1.88]|
| No. of MIs                      | 1,865           | 1,417           | 1,131           | 1,053           |
| GFR ≥ 60                        | 1.00            | 0.72 [0.67-0.77]| 0.57 [0.52-0.62]| 0.47 [0.43-0.51]|
| < 60                            | 1.00            | 0.78 [0.61-0.98]| 0.67 [0.52-0.85]| 0.42 [0.33-0.55]|
| ApoB/apoA-1 ratio               | 0.56 [0.69]     | 0.77 [0.69-0.85]| 0.95 [0.86-1.06]| 1.30 [1.06-1.60]|
| No. of MIs                      | 389             | 802             | 1,523           | 2,752           |
| GFR ≥ 60                        | 1.00            | 1.41 [1.24-1.61]| 1.99 [1.76-2.24]| 2.68 [2.54-2.96]|
| < 60                            | 1.00            | 1.42 [0.93-2.15]| 2.47 [1.69-3.60]| 3.35 [2.25-4.91]|
| Total cholesterol (mmol/L)      | 4.44 [4.50]     | 5.41 [5.10-5.73]| 6.13 [5.74-6.50]| 7.36 [6.50-8.60]|
| No. of MIs                      | 539             | 974             | 1,504           | 2,449           |
| GFR ≥ 60                        | 1.00            | 1.38 [1.24-1.54]| 1.68 [1.52-1.87]| 2.24 [2.03-2.48]|
| < 60                            | 1.00            | 1.25 [0.87-1.81]| 1.39 [0.98-1.97]| 1.81 [1.30-2.53]|
| Triglycerides (mmol/L)          | 0.58 [0.84]     | 0.94 [0.84-1.21]| 1.38 [1.22-1.69]| 2.55 [1.69-3.69]|
| No. of MIs                      | 505             | 1,130           | 1,477           | 2,354           |
| GFR ≥ 60                        | 1.00            | 1.25 [1.12-1.40]| 1.71 [1.54-1.90]| 1.96 [1.76-2.18]|
| < 60                            | 1.00            | 0.88 [0.60-1.30]| 1.18 [0.82-1.71]| 1.43 [1.00-2.04]|
| LDL cholesterol (mmol/L)        | 2.39 [2.92]     | 3.27 [2.92-3.60]| 3.96 [3.61-4.35]| 5.10 [4.35-5.90]|
| No. of MIs                      | 447             | 1,017           | 1,502           | 2,500           |
| GFR ≥ 60                        | 1.00            | 1.58 [1.44-2.34]| 2.02 [1.77-2.30]| 3.06 [2.61-3.59]|
| < 60                            | 1.00            | 1.81 [1.22-2.69]| 2.14 [1.43-3.20]| 3.11 [1.95-4.95]|
| HDL cholesterol (mmol/L)        | 0.99 [1.26]     | 1.40 [1.26-1.52]| 1.65 [1.53-1.80]| 2.11 [1.80-2.51]|
| No. of MIs                      | 2,204           | 1,336           | 1,080           | 846             |
| GFR ≥ 60                        | 1.00            | 0.70 [0.64-0.75]| 0.56 [0.52-0.61]| 0.40 [0.36-0.44]|
| < 60                            | 1.00            | 0.71 [0.56-0.90]| 0.58 [0.44-0.76]| 0.39 [0.29-0.52]|
| No. of MIs                      | 334             | 966             | 1,553           | 2,613           |
| GFR ≥ 60                        | 1.00            | 1.80 [1.58-2.06]| 2.41 [2.09-2.77]| 3.54 [2.98-4.19]|
| < 60                            | 1.00            | 1.60 [1.01-2.53]| 2.13 [1.36-3.34]| 3.40 [2.05-5.63]|
| No. of MIs                      | 421             | 864             | 1,547           | 2,634           |
| GFR ≥ 60                        | 1.00            | 1.44 [1.27-1.63]| 2.11 [1.88-2.38]| 3.13 [2.78-3.52]|
| < 60                            | 1.00            | 1.59 [1.05-2.40]| 2.28 [1.55-3.35]| 3.54 [2.43-5.17]|

Abbreviations: Apo, apolipoprotein; GFR, glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein; TC, total cholesterol.
*Adjusted for age, gender, glucose, triglycerides and total cholesterol. † Lipoprotein values and ratios are given as means with range in square brackets. GFR was estimated by the Modification of Diet in Renal Disease study equation.
89,528 subjects known to be fasting, respectively, similar results were obtained. There was an increase in incidence of MI, from the lowest to the highest deciles of the apoB/apoA-1 ratio among subjects with or without CKD, respectively. This was also found when analyses were done for each gender separately. The population-attributable fraction for hyperlipidemia defined as a ratio of apoB/apoA-1 more than 0.6, associated with MI was 38% and 61% among women with or without CKD, respectively. The corresponding figures for men were 55% and 56%, respectively.

The synergy index for an apoB/apoA-1 ratio in the highest quartile and eGFR between 15-60 mL/min/1.73 m² was calculated and yielded an estimate of 1.33 for women and 1.68 among men. A synergy index more than 1 indicates that the absolute excess risk for those exposed both to CKD and a high apoB/apoA-1 ratio is greater than the sum of the absolute excess risks for those exposed to each separate factor.

Comparisons of different lipid measures
The ratio of apoB/apoA-1 was compared with other lipid measures regarding association with incidence of MI, using standardized

Table 10. Pairwise comparisons between the ApoB/apoA-1 ratio and other lipid measures for prediction of MI in individuals with or without chronic kidney disease

<table>
<thead>
<tr>
<th></th>
<th>Estimated GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 60</td>
</tr>
<tr>
<td></td>
<td>HR (95 % CI)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td></td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.43 (1.38-1.49)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.09 (1.05-1.14)</td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.36 (1.31-1.42)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>1.17 (1.12-1.22)</td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.53 (1.48-1.58)</td>
</tr>
<tr>
<td>TC/HDL cholesterol</td>
<td>1.00 (0.97-1.02)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.42 (1.37-1.48)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.11 (1.06-1.16)</td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.37 (1.31-1.43)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>1.16 (1.11-1.22)</td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.55 (1.49-1.61)</td>
</tr>
<tr>
<td>TC/HDL cholesterol</td>
<td>0.98 (0.95-1.02)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.39 (1.30-1.49)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.04 (0.96-1.12)</td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.29 (1.20-1.39)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>1.15 (1.06-1.25)</td>
</tr>
<tr>
<td>ApoB/apoA-1 ratio</td>
<td>1.38 (1.29-1.47)</td>
</tr>
<tr>
<td>TC/HDL cholesterol</td>
<td>1.03 (0.99-1.08)</td>
</tr>
</tbody>
</table>

Abbreviations: GFR, glomerular filtration rate; LDL, low density lipoprotein; HDL cholesterol, high density lipoprotein cholesterol; Apo, apolipoprotein; TC, total cholesterol; HR, hazard ratio; CI, confidence interval. Hazard ratios were adjusted for age, glucose and the lipid measures compared. All lipid measures were analyzed as continuous variables and hazard ratios with 95 % confidence intervals were calculated for a 1 standard deviation increase of each lipid measure. Standardized variables.
variables. Hazard ratios were calculated for one standard deviation increase of each lipid measure (Table 10). An increase in the apoB/apoA-1 ratio was associated with an increased incidence of MI after adjustment for LDL cholesterol, non-HDL cholesterol or the total cholesterol/HDL cholesterol ratio. This was seen both among men and women, with or without CKD. Among men and women with CKD, none of LDL cholesterol, non-HDL cholesterol or the total cholesterol/HDL cholesterol ratio added information about risk of future MI after adjustment for age, glucose and the apoB/apoA-1 ratio. Separate analyses were carried out in 6,442 individuals with measured HDL cholesterol and yielded similar results. In ROC analysis regarding prediction of MI, the area under the curve (AUC) for the ratio of apoB/apoA-1 was 0.77 for men, and 0.83 for women without CKD, and 0.65 and 0.74 among men and women with CKD, respectively. The corresponding areas for the ratio of total cholesterol/HDL cholesterol were 0.75 and 0.81, for men and women without CKD, respectively, and 0.61 and 0.72, for men and women with CKD, respectively. The AUCs for the apoB/apoA-1 ratio, for men and women, with or without CKD were significantly (p<0.0001) larger than corresponding curves for the ratio of total cholesterol/HDL cholesterol. This was also true when AUCs were calculated for non-HDL cholesterol and LDL cholesterol and compared with the AUC for the apoB/apoA-1 ratio.
Discussion

Methodological considerations

Two types of error afflict epidemiological studies: systematic error (or bias) and random error. Systematic error introduced into a study will result in an incorrect estimate of the association between the exposure and the outcome in the study. There are three main categories of systematic error in epidemiologic studies: selection bias, information bias and confounding.\textsuperscript{167} Random error, the influence of chance, affects the precision of estimates. The precision is inversely related to the study size.

A major contributor to random error is the process of selecting the specific study subjects, often referred to as sampling. Case-control studies involve a sampling process, whereas cohort studies often do not.\textsuperscript{167} In a broader view, the study subjects whether or not sampled, can be viewed as a sample of possible people who could have been included in the study. Another possible source of random error is the measurement of key study variables.

There was no sampling process involved in the selection of the individuals to the cohorts studied in this thesis. Nevertheless, it does not exclude the possibility that random error occurred in our studies.

Selection bias

Selection bias in a study comes from factors that influence study participation. It is present if the association between exposure and disease differs between those who participate in the study and those who do not.\textsuperscript{167} In retrospective cohort studies selection bias can be introduced if the study population is not well-defined or incomplete or if participants are excluded because of death or emigration before follow-up starts.

The study populations in Study III & IV were recruited mainly from health check-ups in company and primary health care. This means that the vast majority of these individuals was in active work and thus may have been healthier than the general population, introducing the \textit{healthy worker effect}. Also, the individuals who underwent these health controls and were included in the cohort may have done so because they were more health-conscious than the average individual in the general population. This is often the case when individuals from the general population randomly are invited to participate in studies screening for disease.\textsuperscript{168, 169}

We found that the standardized mortality ratio, for all-cause mortality was 0.86 in the AMORIS cohort as compared with the population of Stockholm County, indicating that it indeed was healthier. This means that the true prevalence of CKD most likely was underestimated in Study III & IV. However, it is unlikely that the associations found between RI and death or MI would have been very different if we could have included every adult person living in the greater Stockholm area. The participants in Study IV differed from those in Study III in the respect that all had information on apoB and apoA-1 in addition to other laboratory values. The reason why these apolipoproteins were analyzed may have been because of some characteristic of the subjects leading to selection bias. When we compared the mean values of different lipid measures between the two studies they were virtually identical.

In all four studies we used the PIN for linkage to the previously mentioned Swedish Causes of Death-, National Patient- and the Population and Migration Registers. Because
of the high quality of these registers, any loss to follow-up is most likely small.

**Information bias**
Information bias arises when the information collected from or about the study subject is incorrect. Misclassification can be differential or non-differential. Differential misclassification arises when the misclassification of either the exposure in a subject is affected by the disease status, or if the misclassification of the disease status is affected by the subjects’ exposure. Differential misclassification is a serious threat to any epidemiological study and can either exaggerate or underestimate the effect of an exposure.

Misclassification of renal function is of great concern in all studies included in this thesis. It is most likely non-differential by nature in the sense that it is probably not linked to subsequent death or MI. One source leading to misclassification of renal function may be measurement error of serum creatinine. In Study I & II and III & IV the same laboratories and the same methods were used throughout the inclusion periods. In Study III & IV we found only small changes in age-adjusted creatinine levels over time. In none of our studies the creatinine assays were standardized to the reference method suggested. In Study III & IV we found that our creatinine values were only 2.6 µmol/L higher. A difference of this magnitude will only have a marginal impact on classification of renal function at normal or mildly reduced GFR levels and virtually no impact at all on classification of renal function at moderately or severely reduced GFR levels.

In addition, all creatinine values in Study III & IV with more than a 20% change within one year were scrutinized manually to reduce measurement error. Since we did not measure GFR or information on measured GFR was available in any of our study subjects, we were confined to use serum creatinine and demographic variables to estimate GFR levels using three different prediction equations (the Cockcroft-Gaults formula (Study I-III), the MDRD study equation (Study III & IV) and the Mayo formula (Study III)) throughout all studies. We chose to use these formulas since they supposedly reduce misclassification of renal function as compared with using serum creatinine levels.

One of the aims with Study I was to compare serum creatinine with calculated creatinine clearance as a predictor of early mortality after CABG. The hypothesis was that by calculating creatinine clearance there would be a more correct classification of renal function as compared with only using serum creatinine and hence an improved ability to predict adverse outcome.

The Cockcroft-Gaults formula and the MDRD study equation classifies renal function relatively well in the range of GFR between 20 and 60 mL/min/1.73 m² but underestimates true GFR in the normal or near-normal range. The main reason for us to use the Mayo formula in Study III was that it may classify renal function among individuals with normal or near-normal GFR levels more correctly than the other two formulas. It is likely that the differences seen between the MDRD study equation and the Mayo formula in Study III in the ability to predict adverse outcome stems from the greater misclassification of renal function by the MDRD study equation among those with normal or near-normal GFR levels. In one study including 2,095 individuals with measured GFR, 36% of individuals with GFR between 60 and 90 mL/min/1.73 m² were misclassified when GFR was estimated by the MDRD study equation. In another study performed in individuals with normal
renal function the mean prediction error with the MDRD study equation was an underestimation of GFR by 18 mL/min/1.73 m² and only 65% of the estimated GFRs were within 30% of measured GFR. In the same study the Cockcroft-Gaults formula overestimated GFR by 17 mL/min/1.73 m² and only 58% of the estimated GFRs were within 30% of measured GFR. In another study which assessed the capability of different formulas to predict GFR, only 43% of the study subjects with GFR more than 90 mL/min/1.73 m² were classified correctly when the MDRD study equation was used. The corresponding figure using the Mayo formula was 81%. Among subjects with GFR 60 to 90 mL/min/1.73 m² the MDRD study equation classified 41% and the Mayo formula 65% correctly. The corresponding figures for subjects with GFR 30 to 60 mL/min/1.73 m² were 88% for the MDRD study equation and 57% for the Mayo formula. This study only included 200 subjects and the observations may have been affected by lack of statistical precision.

The misclassification of renal function that occurred in our studies, most likely, diluted the association between RI and the outcomes. If we would have been able to use measured GFR throughout, it would probably have strengthened our findings of RI as a risk factor not only for all-cause mortality (Study I-III) but also for MI (Study II-IV). Another possible source of misclassification in our studies may have been related to ascertainment of the outcomes. It is unlikely that all-cause mortality (Study I-III) was misclassified since death is an undisputable outcome and the registers used for recording the deaths that occurred are nationwide and of high quality and completeness.

Information on incident cases of MI (Study II-IV) may have been hampered for example by different diagnostic criteria being used in different hospitals. The diagnostic accuracy of MI among different hospitals in Sweden has been evaluated in repeated studies and found to be high. Also, the method used for identifying cases of MIs have been found to have a high sensitivity and positive predictive value in previous studies. In spite of this, some events would go unrecognized, among them so called silent MIs, and others would be incorrectly diagnosed as MI. It is unlikely that this would result in a misclassification of MI that was related to RI and thus, leading to non-differential misclassification and a dilution of the true association between RI and MI.

Confounding may arise when another factor than the one investigated, will distort the outcome studied. Confounding can lead to over- or underestimation of the associations studied and it can even change the direction of the association found. A confounder must be associated with both the exposure under study and the outcome.

Confounding is a major concern in the studies of the present thesis. Information on smoking status was not available to us in study I & II. In earlier studies on the prognostic importance of RI after CABG smoking has not been more prevalent among patients with RI compared to those with normal renal function. If smoking was not related to the exposure it could not have been a confounder. In Study III & IV we had information on smoking in a subset of 8,278 women but no information on hypertension, both determinants of MI, and mortality. In the women with information on smoking, it did not vary with presence or absence of CKD, a finding consistent with other studies. In addition, in previous studies investigating the association between CKD and CVD or mortality, adjustment for traditional risk factors among them smoking and hypertension has not changed hazard ratios significantly.

We could not control for all determinants known to be important for CVD when we calculated our estimates in any of the four studies included in this thesis. This means
that the estimates should be interpreted with caution, even though it seems unlikely that the strong associations found between RI and adverse outcome would be explained by residual confounding.

**External validity**

One possible limitation with Study I & II is that they were conducted at a single centre. If the thoracic surgeons at the Karolinska hospital for some reason had developed techniques or ways of operating their patients, which were not used anywhere else, and which affected outcome, this could have influenced the generalizability of our findings. This seems unlikely and we believe that our findings can be extended to other patients undergoing CABG, at other centres, in most parts of the world. One exception could be Sub-Saharan Africa or in North American centres with a large proportion of black patients. Using the Cockcroft-Gaults formula in blacks would increase the misclassification of renal function and the MDRD study equation may be more appropriate to use in these settings.

Study participants in Study I & II were included under a relatively long time period, 15 years. During this period average age at surgery increased from 56 years to 64 years. Also during these 15 years surgical techniques as well as medication may have changed considerably. In spite of this, the associations found between RI and all-cause mortality or MI were consistent throughout the entire period when we analysed data dividing this period into three. This indicates that our results are robust to changes or differences in patient characteristics, surgical techniques, postoperative care and medication.

Until recently most epidemiological studies on risk factors for CHD were conducted in mainly all-white North American or European populations. When the Interheart study, conducted in 52 countries around the world, was presented in 2004, we learned that traditional risk factors as hyperlipidemia, smoking, diabetes and hypertension had a similar impact on incidence of MI in all parts of the world including North America and Europe. Against this background, we believe that our findings in Study III & IV can be extended to not only the Swedish population living outside the Stockholm area, but also to populations beyond Sweden, Scandinavia and Europe.

**Findings and implications**

**Study I**

**Early mortality in relation to renal function post-CABG**

In Study I we assessed the importance of renal dysfunction on early mortality in patients undergoing CABG. In addition, the ability of Ccr as compared with serum creatinine alone to predict adverse outcome, was compared. Moderate RI more than doubled the risk, and severe RI increased the risk more than four times for death within 30 days of surgery. The finding that RI increased the risk of early death post-CABG was also found in earlier studies. However, all these studies used serum creatinine and not eGFR or Ccr as marker of renal function. We found that it is an advantage to use Ccr as an index of renal function compared with serum creatinine alone. Since GFR in patients with CHD is estimated with similar accuracy by the MDRD study equation as with the Cockcroft-Gaults formula it is likely that the use of the MDRD study equation would yield a valid estimate of risk preoperatively as well.

The finding that RI increased the risk of early death post-CABG may be interpreted as a reason for denying patients with RI to undergo CABG and instead use medical therapy or percutaneous coronary intervention (PCI). Several studies have suggested that patients with RI are less likely to receive medication or therapies known to lower the risk of a future cardiovascular event such as betablockers, ACE-inhibitors, thrombolytic therapy, CABG and PCI. Patients with RI do have similar benefit of these therapies as patients with normal
renal function and they should not be denied CABG or PCI on these premises.\textsuperscript{177-179} One study has shown that CABG among patients with non-dialysis-dependent RI offer a survival benefit over medical therapy at all levels of renal function.\textsuperscript{177} The same study showed that PCI improved survival compared with medical management among patients with mild or moderate, but not severe RI. Maybe more importantly, CABG offered a survival benefit over PCI at all levels of renal function. Another study found similarly that CABG improve survival at all levels of renal function, including dialysis-dependent RI, compared with no revascularization.\textsuperscript{179} The same study showed that PCI did not decrease mortality compared with medical management alone among patients with non-dialysis-dependent RI. This indicates that among patients with RI, CABG may be the treatment of choice for symptomatic CHD. Before accepting or sending patients for CABG the cardiologist and the thoracic surgeon need to do a risk assessment. Naturally, we want the benefit of surgery for the patient to be larger than the risk of postoperative complications or death. Our results should be interpreted in that context, as an aid for achieving an accurate preoperative risk assessment.

**Study II**

**Renal insufficiency, mortality and incidence of myocardial infarction after CABG**

In Study II we found that already mild RI predicts long-term mortality, and moderate or severe RI long-term risk of death or MI in patients undergoing CABG. Our results confirmed the findings from previous studies on mortality,\textsuperscript{172, 173} and showed that the long-term incidence of MI after CABG is associated with renal dysfunction. In survival analysis there was a markedly increased mortality among those with severe RI, where almost half were dead within five years of surgery. On the contrary those with normal renal function had an excellent survival with 94% being alive five years after CABG. The increased mortality is to a large extent related to age. A reduced GFR becomes more common with advanced age, and the incidence of CVD as well as the risk of dying increases in the elderly. Even after adjustment for age in multivariable analysis we found almost a doubled risk of death for those with moderate, and five times the risk of death for those with severe RI within five years of surgery. The associations with MI were also strong, with a 50% increased incidence among those with moderate RI and more than three times increased incidence among those with severe RI. Interestingly, after we had adjusted for age, further adjustment for other variables of prognostic importance changed the point estimates only marginally, or not at all. This is in line with previous studies, and indicates that renal function is an independent risk factor for CHD.

After adjustment for confounders, we investigated the association between each clinical variable available to us and five-year mortality and found that severe RI was the strongest predictor of death. Moderate RI had a stronger association with five-year mortality than diabetes, prior stroke, prior MI or hypertension.

**How big is the problem?** Only one percent of the study population had severe RI, however they were probably underrepresented in relation to all subjects with CHD, as CABG- and PCI-populations are in general, for reasons discussed previously (Study I). In all, 21% of the study population had moderate RI which posed a substantial threat to their health. With an increasing life span and increasing average age for those undergoing CABG the problem is growing. If we extend our results to other populations with CHD, where similar associations between RI and long-term outcomes have been found, the problem cannot be neglected.\textsuperscript{127, 175, 180}
Study III
Renal function, death and myocardial infarction in the general population

Study III was conducted in a cohort consisting of 571,353 individuals mainly from Stockholm County, with similar socioeconomic characteristics as the population of Stockholm. Because of the known misclassification of renal function seen at normal or near-normal GFR levels with the MDRD study equation and the Cockcroft-Gaults formula, renal function was also classified using the Mayo formula. This was a new formula published in 2004 and developed to assess renal function in healthy individuals, as well as in those with CKD, and had been shown to predict GFR more accurately at normal or near-normal levels.\textsuperscript{18, 38, 39, 44} Prior to our study it had only been used in two outcome studies both conducted in elderly populations with established cardiac disease.\textsuperscript{181, 182}

When we used the Mayo formula to classify renal function the incidence of MI was increased by 11\% at GFR levels between 60 and 90 mL/min/1.73 m\textsuperscript{2}. There was a slight increase in all-cause mortality of 6\% at the same level of renal function. When we used the MDRD study equation there was no increased incidence of MI seen, and the mortality was actually decreased with 23\% among those with GFR between 60 to 90 mL/min/1.73 m\textsuperscript{2}. Glomerular filtration rate estimated by the MDRD study equation had to fall to less than 30 mL/min/1.73 m\textsuperscript{2} to be associated with mortality. These findings may partly be explained by the misclassification seen around and above GFR 90 mL/min/1.73 m\textsuperscript{2} using the MDRD study equation.\textsuperscript{40, 43} The effect seen on the relative risks are most likely explained by the reference group being mixed up by patients who have low creatinine values secondary to severe illnesses causing wasting of muscle mass. The Mayo formula does not allow a creatinine value less than 71 µmol/L, providing protection against misclassification based on low creatinine values secondary to abnormal muscle mass. The U-shaped mortality curve for GFR levels estimated by the MDRD study equation has been found in other studies previously.\textsuperscript{7, 125, 181}

The increased incidence of MI and mortality seen at GFR between 60 to 90 mL/min/1.73 m\textsuperscript{2} has to be interpreted with caution. We only had information on smoking for a subset of women, and no information on hypertension or current medication. We cannot rule out that residual confounding would change our risk estimates among individuals with mild RI to non-significance even if previous studies indicate that adjustment for confounders other than age change corresponding estimates little or not at all.\textsuperscript{7, 8, 133}

The main reason for detecting CKD at an early stage is mainly to prevent cardiovascular disease and premature mortality. By using the Mayo formula in populations including mainly healthy individuals, which are those who seek medical attention in primary health care, we could improve our ability to find those at increased risk of MI and death associated with RI. The Mayo formula was not developed from a sample of the general population and is certainly not the final answer on prediction equations to be used in mainly healthy individuals. Other serum markers as Cystatin C may become more commonly used in prediction of GFR. Several studies have shown that elevated levels of Cystatin C are related to adverse outcome.\textsuperscript{121, 130}

We had no information on Cystatin C levels and could therefore not make any comparisons between prediction equations based on serum creatinine with those based on Cystatin C. The interpretation of our findings is twofold. Firstly, we conclude that already mild RI is associated both with increased all-cause mortality and incidence of MI. Secondly, the Mayo formula seems to be superior to both the MDRD study equation as well as the Cockcroft-Gaults formula in finding individuals in the general population
at increased risk of CHD and premature death related to RI.

What are the public health implications? Since we cannot with certainty know how many individuals that are affected by CKD, any estimate of the importance of CKD for the general population will be uncertain. Using the Mayo formula, GFR less than 75 mL/min/1.73 m$^2$ was related to both mortality and MI. Since we found that around 10% of a healthy population with an average age below 50 years were affected it needs to be considered as a major public health concern.

**Study IV**

**Different lipid measures in relation to CKD and incidence of myocardial infarction**

In Study IV we used a subset of 142,394 individuals with information on different lipid measures including apoB and apoA-1. The aim of the study was to investigate different lipids, with special emphasis on apoB and apoA-1 as a cause of MI in relation to renal function.

The principal finding was that the apoB/apoA-1 ratio is a strong predictor of MI irrespective of the presence or absence of CKD.

Since the mechanisms for the increased risk for CHD associated with CKD are not known, unfavorable levels of so called non-traditional risk factors, among them the apolipoproteins have been suggested as a possible explanation. Earlier studies investigating this matter have not been able to support this hypothesis. We did not find any evidence for the apolipoproteins or any other lipid measures having a greater impact on the risk of future MI among those with, as compared to those without CKD.

The role of the apolipoproteins as a tool for assessment of risk for future CHD has been discussed extensively the last few years. Because of the changes in lipid metabolism seen in CKD, hypothetically the apolipoproteins seem like an attractive alternative to standard lipid measures among individuals with renal dysfunction.

We found indeed that the apolipoproteins added information about risk of future CHD compared with standard lipid measures irrespective of renal function. None of the lipid measures, including the ratio of apoB/apoA-1, had a significantly stronger association with CHD among those with CKD versus those without.

Although Study III indicated that the Mayo formula classified renal function more accurately than the MDRD study equation in our cohort, we chose to use the latter in Study IV. By dichotomizing renal function and using the cut-off value 60 mL/min/1.73 m$^2$ for CKD we reduced the misclassification seen at higher GFR levels. Also, since our creatinine values were not standardized, we reduced the influence of measurement error of serum creatinine on classification of renal function.

We also wanted our study to be comparable to previous studies published on the same topic.
Conclusions

Renal insufficiency predicts early mortality in patients undergoing CABG
Renal dysfunction is common among patients undergoing CABG. Among patients with moderate RI the risk of dying within 30 days of surgery is more than doubled, and in patients with severe RI this risk is increased by almost five times. Calculated creatinine clearance is a better predictor of mortality within 30 days of CABG than serum creatinine alone.

Renal insufficiency predicts long-term outcome in patients undergoing CABG
Mild RI predicts all-cause mortality within five years of CABG. Among patients with moderate RI the risk of dying within five years post-CABG is almost twofold, and for those with severe RI almost fivefold. There is an increased incidence of MI for patients with moderate or severe RI within five years post-CABG.

Renal insufficiency is associated with all-cause mortality and first myocardial infarction in the general population
Mild RI is associated with both first MI and all-cause mortality in a community-based sample of adults if GFR is estimated by the Mayo formula. When GFR estimated by the MDRD study equation was used the associations between RI and adverse outcomes were weaker.

The apoB/apoA-1 ratio is a predictor of first myocardial infarction irrespective of presence or absence of chronic kidney disease
Both standard lipid measures and the apoB/apoA-1 ratio are associated with incidence of first MI irrespective of renal function. The apoB/apoA-1 ratio appears to add information about risk of future MI even after adjustment for conventional lipid measures.
Future studies

The major problem affecting every study of CKD and its relation to CHD performed in the general population, including Study III & IV in this thesis, is the lack of good prediction equations for estimation of GFR. There is a need for new formulas and they have to be developed in large community-based samples of adults containing an adequate number of individuals with CKD. Once we have one or several such formulas it may be necessary to recalculate and reevaluate our data, to once again try to understand what the associations between renal dysfunction, mortality and incidence of MI are. Most likely we will find that the association between CKD and CHD is stronger than earlier studies have shown.

More research is needed to investigate which mechanisms are involved in the pathogenesis of CHD among individuals with CKD. This would help us find possible interventions to reduce the risk of CHD associated with CKD.

Among patients undergoing CABG, studies investigating new therapies to reduce the increased risk of death and MI associated with CKD in the short, as well as in the long term are needed. Also studies which investigate which therapeutic option, CAGB, PCI or pharmacological therapy alone should be chosen for patients with CHD and concurrent CKD need to be done.
Svensk sammanfattning


Målsättningen med denna avhandling var att undersöka vilken betydelse en lindrigt, måttligt och uttalat nedsatt njurfunktion har för risken att dö och att insjukna i hjärtinfarkt bland individer med och utan tidigare känd hjärtkärlsjukdom. Dessutom ville vi undersöka betydelsen av blodfettssrubningar, med särskild tyngdpunkt på kvoten av apolipoprotein (apo) B och apoA-1, bland individer med och utan kronisk njursjukdom, som orsak till hjärtinfarkt.

I den första studien undersökte vi hur sambandet ser ut mellan lindrigt, måttligt och kraftigt nedsatt njurfunktion och dödlighet inom 30 dagar efter kranskärlskirurgi. Vi jämförde också förmågan hos serumkreatinin och beräknat kreatininclearance för att förutspå dödlighet efter kirurgi. Vi fann att redan en måttligt nedsatt njurfunktion ökar risken för död inom 30 dagar efter kranskärlskirurgi och att beräknat kreatininclearance är bättre än serumkreatinin på att förutspå tidig död efter kranskärlskirurgi.

I den andra studien undersökte vi sambandet mellan nedsatt njurfunktion och risken att insjukna i hjärtinfarkt eller att dö inom fem år efter kranskärlskirurgi. Vi fann att redan ett lindrigt nedsatt njurfunktion ökar risken för död och att mättligt eller kraftigt nedsatt njurfunktion ökar risken att insjukna i hjärtinfarkt inom fem år efter kranskärlskirurgi.


Sammanfattningsvis visar våra studier att redan en lindrigt och måttligt nedsatt njurfunktion ökar risken för tidig död och att drabbas av hjärtinfarkt både hos individer som redan har hjärtkärlsjukdom men även hos individer som tidigare är väsentligen friska.
There are many people I have met and things that have happened, some “by chance”, which led to this thesis being written and I would like to express my sincere gratitude especially to:

**Niklas Hammar**, my supervisor, for communicating the beauty of epidemiology in a way I could understand, and for always being honest not only to me and everybody else, but also to the scientific work we did. If I would not have met you, I would never have become PhD.

**Torbjörn Ivert**, my co-supervisor, for excellent guidance through the world of patients undergoing CABG, beside many other things helping me out with tables and figures in the early days when this was a struggle.

**Göran Walldius**, my co-supervisor, for introducing me into the world of apolipoproteins and the immense AMORIS cohort, and for encouraging e-mails from time to time.

**Jan Östergren**, my co-supervisor, and colleague at the Department of Emergency Medicine, for your intellectual input and critical mind in discussions and for being a skilled clinician, and for your dedication to teaching at medical school.

**Ingmar Jungner**, my co-author and the man behind the AMORIS database, for letting me use this unique dataset in this thesis and for answering all my questions regarding the individuals included.

**Staffan Ahnve**, my co-author, for letting me understand how important the abstract in a scientific paper is, and for always being very critical and helpful, and for your excellent skills in English.

**Kenneth Pehrson**, my co-author and former colleague at the Department of Cardiology, for your fantastic ability of being social, making a meeting a pleasure to join, for a vivid mind and for being a clinician to follow during my first stumbling steps in the field of cardiology.

**Kristina Klerdal** and **Lena Jörgensen**, my co-authors and statisticians, for providing me with numbers, sometimes understandable, sometimes not, and being patient when things had to be redone, slightly differently.

**Tobias Nordquist**, my co-author, statistician, and close collaborator, for always being helpful, quick and understanding when things did not go the way we wanted, and sharing the confusion I felt from time to time.

**Per Lindmarker**, head of the Department of Emergency Medicine, for being a good, helpful and generous person and chief, and executing a modern leadership making our clinic a stimulating and progressive Department to work in.

**Olle Lindstöm**, colleague and my closest chief, for being a true humanist, always wanting the best and together with **Per L** providing a leadership which is unique to our Company.

**Anders Danielsson**, my former colleague during my internship at Karlskoga Hospital for being an inspiring guide during my first cautious steps as a doctor years ago, **Hans Jonsson**, colleague at the Department of Emergency Medicine for taking care of me, communicating your immense experience in internal medicine, bringing me along to see all kind of interesting cases, and always giving me moral support letting me know that I was talented, **Gunilla Forsell**, my former colleague at the Department of Cardiology, for being the most skilled cardiologist I met, for always giving the right answers and taking the right clinical decisions, and always having time and patience with an inexperienced younger colleague.
Martin Holzmann

**Jonas Hörnsten** and **Per Svensson**, colleagues and friends who followed me from the internship in Karlskoga, to the Department of Emergency Medicine and later the Department of Cardiology at the Karolinska Hospital where **Frieder Braunschweig** and **Magnus Settergren**, colleagues and friends joined and with whom I have shared some of the happiest moments in my clinical career.

**All present and former colleagues at the Department of Emergency Medicine and Department of Cardiology at the Karolinska Hospital**, for making my day at the clinic easy and for being understanding when I during long periods was absent.

**Anders Ekbom** and **Michael Fored** for letting me attend the Research School for Clinicians which helped and enabled me to write this thesis. **All fellow students at the Research School for Clinicians** for sharing twenty wonderful weeks, escaping reality, having long lunches and great discussions about everything and nothing, dreaming about things that never would happen.

**Torgny Magnusson, Esbjörn Bergman, Thomas Gustafsson, Rickard Ljung** for sharing some of the best days of my life being my fellow students at medical school and thereafter being around whenever needed.

**Per-Ola Andersson**, former fellow medical student, colleague and friend, for sharing taste of life, for support and thoughts about the important things in life, for always being there.

**Hans Niklas Jonsson**, colleague and friend, for not only sharing joy and laughter, but also music over the years and for being admired by my sons Samuel and Elias.

**Abdeslam Nassef**, **Mohamed Ben Aiza** and **Abdu Zoubair** for being friends since more than twenty years, and in another twenty years, with lasting friendship, we will sit and drink mint tea together as retired men at Café Hafa in Tanger, watching the ferries on their voyage between Europe and Africa.

All friends I see more often, and those I see rarely, and their families for making everyday life outside work a joy: **Giles Khan**, **Piet** and **Pascale Veerbeck**, **Uzi** and **Lotta Geffenblad**, **Cecilia** and **Stefan Carlens**, **Martin Jonsson** and **Anna Carlqvist**, **Magnus Fux** and **Tina**, **Boris Kan**, **Roland** and **Emma Müller-Suur** and all previously mentioned friends families and wives.

My small Estonian family; **Naima Leonova** for being the brightest soon ninety-year old person I have known; **Helme Kivisalu** for always being generous making your home, once the home of my father, my home since many, many years; your husband the late **Olev Kivisalu** for being the finest man I have ever known; **Kristina**, **Leonid** and your children **Kevin**, **Claudia** and **Carmen** for reminding me and my children of their Estonian heritage and letting me practice Estonian from time to time. My Estonian friends, **Peep Talving**, **Karita Cullen** with Irish husband **Paul**, **Tönö** and **Annelie Velt** and **Kersti Talving** for sharing joy and being part of my journey through life.

**Abdullah** for being like a third son in the family and an older brother to my children, **Francisco De Corcuera** for introducing me to the mysteries of Tanger, being a generous, intellectual person always willing to discuss art or politics and being a character like taken from a novel or movie from a time which no longer exists, **Sylvie De la Riviere** for “bon voisinage”, **Abdeslam Ben Aiza** for always being there whenever we needed you, **Abdu** and your family for keeping an eye on our house, and all other neighbors and friends at Sidi Bouknadel, Tanger, Morocco for making this a wonderful place for a weary soul to rest.
My brother Robert with Karin, Alexander, Katarina and Karolina for always being there.

My wife Malin and our children Samuel, Elias and Hannah without you my life would be meaningless.

Finally my Mother, thanks for everything and my late Father for watching his son proudly from his heaven.

Financial support was provided by the Swedish Heart and Lung Foundation, Stockholm County Council and the Ansgarius Foundation.


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