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INFLUENCE OF RENAL DYSFUNCTION ON THERAPY AND PROGNOSIS IN PATIENTS WITH MYOCARDIAL INFARCTION

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ABSTRACT

The aim of this thesis is to evaluate the influence of renal dysfunction on the presentation for myocardial infarction (MI), its treatment and outcome. Patients between 2003 and 2006 were selected from the nationwide Swedish coronary care unit (SWEDEHEART) registry. The renal function was estimated with the Modification of Diet in Renal Disease (MDRD) study formula.

In **article I** the characteristics of an unselected MI population (n=57 477) is presented. The mean (SD) renal function was 72 (28) ml/min/1.73 m^2 and 33% had at least moderate renal dysfunction. Patients with lower renal function differed by being older and having more co-morbidities. They presented less often with chest pain and ST-elevation MI. After adjustments, lower renal function was independently associated with a less frequent use of in-hospital therapies. In-hospital mortality increased exponentially from 2.5% in those with normal renal function to 24.2% in those with renal failure.

In **article II** the Cockcroft-Gault (CG) and the MDRD formula were compared in 36 137 patients. The largest difference between the formulas was seen in females, the elderly and in those with low body weight, where renal function was estimated lower with the CG formula. The CG formula classified more patients as having at least moderate renal dysfunction, who after multivariable adjustment had higher one year mortality.

In **article III** medical and invasive therapy in 23 262 patients with non-ST-elevation MI were compared at different renal function stages. Invasive therapy was used less frequently in those with lower renal function (36% in those with moderate renal dysfunction compared to 62% in normal renal function). After multivariable adjustment, invasive therapy in patients with mild-to-moderate renal dysfunction was associated with lower one year mortality. The advantage with invasive therapy decreased in those with severe renal dysfunction with no benefit in those with renal failure.

In **article IV** in-hospital survivors of MI (n=42 814) were analyzed to assess the association of statin therapy at discharge with one year survival. After multivariable adjustment, statin at discharge was associated with a 37% reduction in one year mortality (HR 0.63, 95% CI 0.58-0.68, $p<0.001$). With lower renal function statin therapy was associated with an improved survival, although the effect declined and was less certain in those with renal failure.

In **conclusion**, renal dysfunction is present in about a third of patients admitted with a MI. It identifies patients with a worse prognosis who are treated less often both medically and invasively. A less frequent use of available treatments may partially explain their worse prognosis.

Key words: myocardial infarction, renal dysfunction, revascularization, statin, prognosis.

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1 LIST OF PUBLICATIONS

This thesis is based on the following studies, which are referred to in the text by their Roman numerals:

I. Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome - data from the SWEDEHEART register.
Szummer K, Lundman P, Jacobson SH, Schön S, Lindbäck J, Stenestrand U, Wallentin L, Jernberg T; SWEDEHEART.
Journal of Internal Medicine, 2009, Dec 3 (epub ahead of print).

II. Cockcroft-Gault is better than the Modification of Diet in Renal Disease study formula to predict outcome following a myocardial infarction - data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)
Szummer K, Lundman P, Jacobson SH, Lindbäck J, Stenestrand U, Wallentin L, Jernberg T; SWEDEHEART.
Accepted American Heart Journal

III. Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction – data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART).
Szummer K, Lundman P, Jacobson SH, Schön S, Lindbäck J, Stenestrand U, Wallentin L, Jernberg T; SWEDEHEART.
Circulation. 2009; 120(10):851-8.

IV. Association between statin treatment and outcome in relation to renal function in myocardial infarction survivors - data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART).
Szummer K, Lundman P, Jacobson SH, Schön S, Lindbäck J, Stenestrand U, Wallentin L, Jernberg T; SWEDEHEART.
Manuscript.

2 ABBREVIATIONS

AUC	Area under curve
CABG	Coronary artery bypass surgery
CHF	Congestive heart failure
CI	Confidence interval
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
HDL	High-density-lipoprotein
HR	Hazard ratio
IQR	Interquartile range
LDL	Low-density-lipoprotein
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
NKF K/DOQI	National Kidney Foundation Kidney/Disease Outcome Quality Initiative
NSTEMI	Non-ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive care Admissions
ROC	Receiver operating curve
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

3 INTRODUCTION

Renal dysfunction is recognized as an independent risk factor for the development of cardiovascular disease[1]. There is a gradual increase in risk with renal impairment, with a sharp increase at and below a moderately reduced renal function[2, 3]. Most patients with renal dysfunction are more likely to die because of cardiovascular disease, than to progress to renal failure[4].

In patients with a MI, the assessment of kidney function and the recognition of renal impairment are relevant. Presence of renal dysfunction identifies patients both in need of dose adjustment to avoid associated toxicities[5, 6], and those at high-risk of subsequent adverse events [7, 8]. The prognosis remains remarkably poor, with in-hospital death increasing from 1.4% among those with normal renal function to 12-32% among those with severe renal dysfunction[9, 10].

Part of the worse outcome following a MI may be explained by atypical presentation, co-existing diseases, more advanced cardiac disease, less frequent use of evidence-based therapies, side-effects of treatments and more frequent complications[5, 8, 9, 11-16]. Few clinical trials evaluating treatment have focused on patients with renal dysfunction, and therefore the evidence to guide treatment is limited[17]. Current use of therapies in clinical practice and their effect on outcome in patients with MI and renal dysfunction need further evaluation.

3.1 RENAL FUNCTION

3.1.1 Assessment of renal function

The most accurate method to assess kidney function is to measure the glomerular filtration rate. One standard method is to inject an exogenous marker, such as inulin or iohexol, which is neither metabolized nor absorbed, and measure the plasma or urine concentration. An alternative is to assess creatinine clearance by collecting a timed urine sample and relating it to the serum level. As all these methods are cumbersome, the most commonly used method in clinical practice is to measure endogenous creatinine level in serum alone or to use creatinine-based equations to estimate glomerular filtration rate.

Creatinine is not ideal to assess renal function. It is secreted in the distal tubuli and has an inverse and non-linear relationship to glomerular filtration rate. About 10% of creatinine is eliminated through tubular secretion. This becomes an important way of elimination in those with lower renal function, and therefore the eGFR may be

over-estimated. In the normal-to-moderate renal function range, an increase in creatinine level can appear modest but still represent a substantial reduction in eGFR.

Creatinine level is affected by many factors. Creatinine is a break-down product of creatine phosphate in the skeletal muscle, and differences in muscle-mass cause a large variability between individuals. This may lead to an overestimation of renal function in the elderly, female and in those with low body weight. The level of creatinine will vary with body habitus, such as malnutrition, obesity, de-conditioning and neuromuscular disorders. With increasing age there is a steady decline in renal function and glomerular filtration rate[18, 19]. To a smaller degree, creatinine level is affected by the meat-content in different diets.

Cockcroft-Gault formula (ml/min):

$$\frac{(140\text{-age}) * \text{weight(kg)} * 1.23}{\text{creatinine}(\mu\text{mol/L})} \quad (* 0.85 \text{ if female})$$

Abbreviated MDRD formula (ml/min/1.73m^2):

$$186 * [\text{creatinine}(\mu\text{mol/L})/88.4]^{-1.154} * \text{age}^{-0.203} \quad (* 0.742 \text{ if female}) \quad (* 1.212 \text{ if black})$$

Figure 1. Renal function estimation equations.

Several equations based on creatinine have been developed to improve the estimation of renal function to account for the variation with age, weight and gender. The two most commonly used equations are the Cockcroft-Gault[20] and the MDRD formulas[21, 22] (figure 1, table 1). The Cockcroft-Gault formula includes weight and gender, and was developed to estimate creatinine clearance. In contrast, the MDRD equation includes race but not weight, and gives an eGFR which has been normed to a body surface area of 1.73m^2. The two equations differ in renal function estimations in populations with varying age, gender and body mass[23-25].

The accuracy of the eGFR obtained with the two equations differs at varying levels of renal function. All patients included to obtain the MDRD estimation had chronic kidney disease. The MDRD estimates are therefore more accurate in those

with moderate-to-advanced renal dysfunction than the Cockcroft-Gault formula[26, 27]. By comparison, the MDRD equation often underestimates renal function in the normal range, whereas the Cockcroft-Gault may over-estimate it[28].

Recently a new equation has been developed to increase the accuracy of renal function estimation in those with renal function in the normal range[29]. Alternatives to creatinine-based estimations of renal function, such as cystatin C[30-32], are being evaluated.

Table 1. Original study population used to obtain the Cockcroft-Gault and the MDRD renal function estimation equations.

	Cockcroft-Gault	**MDRD**
N	249	1628
Predicted estimation	Creatinine clearance	Glomerular filtration rate by ^{125}I-iothalamate
Mean creatinine (µmol/L)	87[a] -123[b]	203±106[e]
Estimated renal function	115[c]-37[d]	39.8±21.2[f]

Mean creatinine and estimated creatinine clearance in the age group with the lowest creatinine (age group 18-29 years[a,c]) and in the age group with the highest creatinine (age 80-92 years[b,d]); [e]Mean±SD. [f]Mean measured glomerular filtration rate±SD (ml/min/1.73m^2).

3.1.2 Staging of kidney disease

The National Kidney Foundation has presented a classification of patients with chronic kidney disease to guide their clinical management (table 2)[33, 34]. Chronic kidney disease is defined as an eGFR <60 ml/min/1.73m^2 present for 3 months, or an eGFR ≥60 ml/min/1.73m^2 together with signs of kidney damage, such as albuminuria or abnormalities on imaging results.

In a MI population about a third of patients have at least moderate renal dysfunction[8-10]. The prevalence of chronic kidney disease in a general population is 13%[18]. Presence of albuminuria is an independent predictor of cardiovascular events both in patients with and without known coronary disease, regardless of eGFR[35-38].

Table 2. National Kidney Foundation classification of chronic kidney disease[34].

Stage	Renal function	eGFR ml/min/1.73m^2	Distribution of eGFR[b] in a general population
1	Normal[a]	≥90	40.7%
2	Mild[a]	60-89	51.2%
3	Moderate	30-59	7.7%
4	Severe	15-29	0.4%
5	Kidney failure	<15 or dialysis	0.2-0.09% [c,d]

[a]Requires signs of kidney damage such as imaging abnormalities/albuminuria for staging. [b]Distribution of eGFR in stage 1-4 (n=13233) from the national survey NHANES between 1999-2004 in the United States[18]. [c,d]This is an underestimation, as only patients treated with dialysis are included. Data from the [c]USRDS[39] and [d]the Swedish Renal Registry[40].

3.1.3 Use of renal function assessment in cardiovascular disease

Among patients with cardiovascular disease, it is now recommended that all patients should have their renal function estimated and classified, to identify and treat risk-factors early[41]. The MDRD equation is suggested for the detection and classification of renal dysfunction[41], and the Cockcroft-Gault formula is advised for adjustment of drug doses[5, 42].

The value of the two equations for predicting cardiovascular events varies with the population that is evaluated. In heart failure, the MDRD equation provides better prognostic information than the Cockcroft-Gault formula[43], whereas the Cockcroft-Gault is a better predictor in chest pain populations[44]. In patients with MI, the association of the two renal function estimations to outcome has not been compared.

3.2 RENAL DYSFUNCTION AS A RISK FACTOR FOR MI

Presence of renal dysfunction substantially increases the risk for cardiovascular events and death[2]. Traditional risk factors for cardiovascular disease are frequent, but also non-traditional factors specific to renal dysfunction have been suggested (table 3)[45].

Several of the risk factors for cardiovascular disease are shared and either cause or develop during renal impairment[2]. The number of risk factors accumulates with lower renal function. In moderate renal dysfunction about 71% have hypertension, 23% have diabetes and 60% have dyslipidemia[46]. Diabetes nephropathy is the second most common cause of renal failure requiring renal replacement therapy in Sweden.

Glomerulonephritis is still the most frequent cause. Diabetes nephropathy is currently responsible for 19% of these cases, and the proportion is increasing[40].

Table 3. Risk factors for cardiovascular disease. Modified from Sarnak et al[45].

Traditional risk factors	Suggested risk factors present in renal dysfunction
Older age	Decreased eGFR
Hypertension	Proteinuria
Diabetes	Anemia
Elevated LDL, low HDL	Volume overload
Smoking	Abnormal calcium/phosphate metabolism
Family history	Inflammation
	Activated renin-angiotensin system
	Dyslipidemia
	Altered platelet/coagulation function

Renal dysfunction independently increases the risk of cardiovascular disease by mechanisms which are only partly understood (figure 2). With lower renal function, volume overload and anemia contributes to the development of left ventricular hypertrophy[47]. As kidney function deteriorates, phosphate is retained, which stimulates parathyroid hormone to increase calcium release from the bones. The increase of calcium and phosphate, together with alterations of lipid metabolism[48], promotes deposition in the vascular wall causing arterial wall stiffening and vascular calcification[49-51]. Vascular calcification is already often present in young individuals 20-30 years old who are treated with dialysis[52]. The risk of acute coronary syndrome is further increased both by changes in the function of platelets and increase in fibrinogen[53, 54].

3.2.1 Change in cardiac structure

Alterations in cardiac structure develop gradually with renal impairment. At the start of dialysis, clinical heart failure is present in 35% and prior myocardial infarction in 21% of patients[55]. The frequency of left ventricular hypertrophy increases with lower renal function. It is present in 27% in those with a creatinine clearance 50-75 ml/min, compared to 45% of those with a creatinine clearance <25 ml/min[47, 56]. The prevalence of left ventricular hypertrophy in a similarly aged general population is <20%[57].

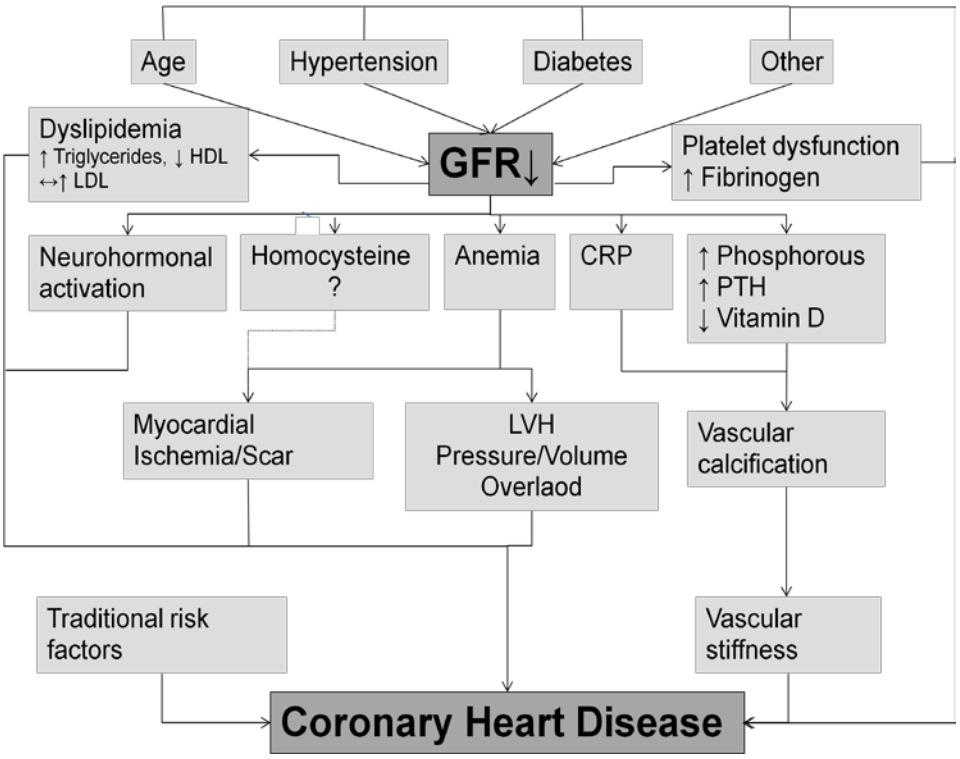
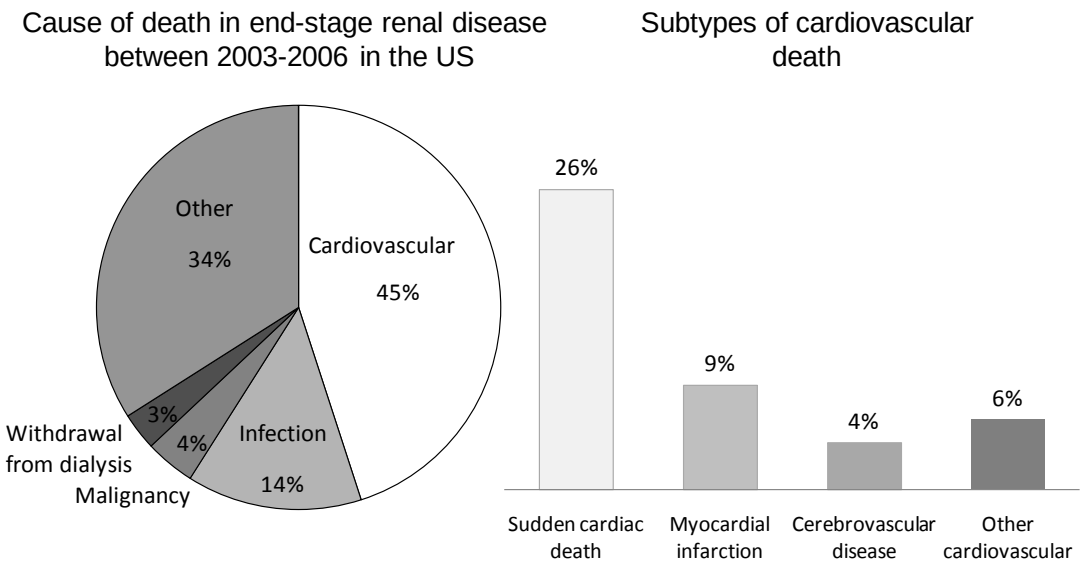


Figure 2. Association between renal dysfunction and coronary heart disease. Modified from Hage et al[58].

3.2.2 Cause of death

The risk of death, and in particular cardiovascular death, increases considerably with decreasing renal function[1, 59]. Among patients with hemodialysis in the Swedish Renal Registry, the annual mortality was 26%[40]. The absolute increase in risk is highest in the young. A 25 year old receiving dialysis has the same risk of death as an 80 year old without dialysis[60]. In older individuals, the absolute increase in risk with dialysis is smaller compared to an individual with the same age. The poor prognosis in patients treated with dialysis can be altered by kidney transplantation, which reduces but does not normalize the risk of cardiovascular events[60].

Cardiovascular mortality is the leading cause of death among dialysis patients (figure 3). The largest proportion of cardiovascular mortality is attributed to sudden cardiac death, which may be caused by arrhythmias[61, 62]. Whether sudden death can be prevented by implanting a cardiac defibrillator is currently being examined[63]. Only 9% of deaths are secondary to MI, but the prognosis in patients treated with hemodialysis who have a MI is particularly poor. After one year 59% will not be alive[64].



Figur 3. Cause of death and subtypes of cardiovascular death in the US renal registry[39]. Adopted from Hage et al[58]. By comparison, cardiovascular was the cause of death in 42% of patients in 2006 in the Swedish Renal Registry[40].

3.3 DIAGNOSING MI IN RENAL DYSFUNCTION

The diagnosis of MI relies on the triad of typical symptoms, ECG changes and biomarkers. In patients with renal dysfunction, the presentation of MI is often atypical.

Patients present less often with chest pain and more often with dyspnea and heart failure signs[14, 65]. A presentation without chest pain reduces the likelihood of adequate therapy for MI[66]. The ECG changes are more often non-specific and ST-elevation is less frequently present in patients with dialysis compared to a non-dialysis population[67]. The clinical presentation and ECG pattern in patients with MI infarction across the entire spectrum of renal dysfunction has not been evaluated recently.

A high proportion of asymptomatic patients with renal dysfunction have elevated baseline cardiac troponin, without the presence of an ongoing acute coronary syndrome. In patients with at least moderate renal insufficiency and in dialysis, 43% and 82% respectively will have an elevated troponin T[68, 69]. A time appropriate rise-and-fall pattern in troponins can still be used to make the diagnosis of MI.

3.4 MANAGEMENT OF MI IN RENAL DYSFUNCTION

The European Society of Cardiology[70, 71], American College of Cardiology/American Heart Association[42, 72] and the National Kidney Foundation[34, 73] recommend that the same therapies be given in patients with acute coronary syndrome and renal

dysfunction as in all other patients. Special attention has to be paid to medications that are eliminated by the kidney, and doses adjusted according to the estimated renal function, preferably by the Cockcroft-Gault formula.

Patients with renal dysfunction and MI are much less likely to be treated with recommended therapies[74-76]. The evidence obtained specifically in those with renal dysfunction supporting these recommendations is limited[17], as an elevated creatinine level has often been an exclusion criterion in clinical trials. This may partly explain the lower use of recommended therapies. In spite of an increase of adverse events and side-effects of therapies in patients with renal impairment, several treatments still appear efficient and reduce cardiovascular endpoints in post-hoc analyses and observational studies[74, 77-80]. An evaluation of whether renal dysfunction predicts a lower use of therapies, or whether other factors play a more important role, is needed to understand this clinical practice.

3.4.1 Revascularization in NSTEMI

Both European and American guidelines[42, 70, 81] recommend an early invasive approach in patients with a NSTEMI and with an elevated risk of cardiac events. An elevated creatinine level is one of the nine characteristics which identify patients at increased long-term risk[7]. A consensus statement recommends that "an invasive strategy may be reasonable in patients with chronic renal insufficiency"[42].

With an invasive approach, several randomized trials, a meta-analysis, and observational data have shown a reduction in recurrent MI, less severe angina, fewer re-hospitalizations and a trend towards fewer deaths[82, 83]. Two sub-studies of randomized trials[84, 85] and one meta-analysis[86] have shown maintained benefit and even larger absolute reductions in cardiovascular events in those with mild-to-moderate renal dysfunction, compared to those with normal renal function (table 4). Whether patients with severe renal dysfunction or with renal failure who are treated with revascularization have a similar reduction in events is unknown. Too few patients were included in randomized trials to evaluate the treatment effect in those with advanced renal impairment.

Patients with renal dysfunction, although at high-risk of adverse events, are referred less often for invasive therapies[15]. This has been termed the "treatment-risk paradox"[87, 88]. The most frequent explanation for non-referral for coronary angiography appears to be that patients are not considered to be at high risk[15]. Renal insufficiency was the reason for non-referral in only 2% of cases, although the risk of contrast-

induced nephropathy and dialysis following a coronary angiography increases with renal dysfunction[89]. The optimal revascularization strategy in patients with renal dysfunction has not been settled[75, 90].

Table 4. Invasive compared to medical therapy in post-hoc analyses of randomized trials and in one meta-analysis.

Study	CrCl ml/min	N (% invasive)	Noninvasive	Invasive	ARR
FRISC II[a]	<69	842 (51)	22.4 %	14.6%	7.8%*
	69-90	781 (52)	14.6%	9.9%	4.7%*
	>90	831 (47)	11.6%	11.2%	0.4%
TACTICS-TIMI 18[b]	<30	28 (--)	26.7%	30.8%	-4.1%
	31-60	393 (--)	13.0%	11.0%	2.0%
	61-75	374 (--)	11.3%	8.5%	2.8%
	>75	1395 (--)	7.5%	5.1%	2.4%
	eGFR ml/min/1.73m^2	N (% invasive)	Invasive versus Noninvasive RR (95% CI)		
Meta-analysis[c]	<30	267 (--)	0.94 (0.55-1.60)		
	30-44	see below	0.57 (0.32-1.00)		
	45-59	1186 (--)	0.84 (0.50-1.41)		

[a]FRISC II[85]: excluded creatinine >150µmol/L; endpoint: death/MI at 2 years.

[b]TACTICS-TIMI 18[84]: excluded >221µmol/L; endpoint: death/MI at 6 months.

[c]Meta-analysis (VINO, FRISC II, TIMI IIIB, TACTICS-TIMI 18, ICTUS)[86]; endpoint: death/MI at 1 year; N (total) =1453. *p<0.05.

3.4.2 Dyslipidemia and statin therapy following a MI

Renal dysfunction causes alterations in lipid metabolism, which results in a low HDL and elevated triglyceride level[48]. The total cholesterol level and LDL level in those with moderate renal dysfunction is usually similar to that in a general population[46]. These changes occur even without the presence of proteinuria.

In contrast to a general population, patients with hemodialysis have a J-shaped relationship between mortality and cholesterol level with higher annual mortality among those with low cholesterol level[91, 92]. The explanation for this may be the high frequency of malnutrition and inflammation which is associated with both a lower cholesterol level and higher mortality. When this is accounted for, the relationship between high cholesterol and cardiovascular events is similar to that found in a general population[93].

In secondary prevention following a MI, all current guidelines[42, 70, 81] recommend early treatment with statins. This is recommended to all patients regardless of baseline cholesterol level to lower the risk of subsequent re-infarction, stroke, revascularization and cardiovascular mortality. There are two sub-group analyses of randomized statin trials in patients with previous MI or cardiovascular disease and moderate renal insufficiency. In patients with a mean eGFR of 61 ml/min in the CARE[94] and 53 ml/min/1.73m^2 in the TNT-study[95] there was a 28%-32% relative risk reduction in cardiovascular events with statin therapy. Whether the reduction in cardiovascular events is maintained in those with more advanced renal dysfunction has not been examined.

3.4.3 Complications and prognosis

The prognosis of patients with renal dysfunction and MI is poor. Patients with renal dysfunction have a substantially higher risk of all types of in-hospital complications, both ischemic and non-ischemic. These complications include an increase in stroke from 0.7% to 1.3%, major bleeding from 2.3 to 8.1% and in-hospital mortality from 1.4 to 12.2% in those with normal compared to those with severe renal dysfunction[10]. The elevated risk of adverse events is not limited to the immediate in-hospital phase of MI, but persists during several years of follow-up[8]. In the long-term, the risk remains increased for stroke, heart failure, reinfarction, cardiac arrest and death.

Renal dysfunction independently predicts in-hospital bleeding events. The frequency of in-hospital bleeding is about 2.3-3.9% in international MI registries, with renal dysfunction increasing the risk by about 50%[10, 96]. Certain drugs may be preferred in those with renal dysfunction. Fondaparinux has lower bleeding risk compared with enoxaparin[97], and low molecular weight heparin appears favorable compared to unfractionated heparin[98]. Despite the fact that anticoagulants proportionately increase the bleeding risk, they may still reduce ischemia and cardiac death, giving a net clinical benefit[99, 100]. Part of the increase in bleeding events is related to excess dosing and use of contraindicated medication in those with lower renal function[6, 9]. Dose adjustment using the Cockcroft-Gault formula could reduce bleeding events[5].

The poor prognosis in renal dysfunction is only partly explained by co-existing disesase (figure 4). Under-utilization of known cardioprotective treatment, omission of therapy because of missing evidence, more frequent dosing errors, but also a differing pathobiology, where current therapies may be less effective, and frequent

adverse events are possible explanations. The mechanisms contributing to the poor prognosis remain to be fully explained.

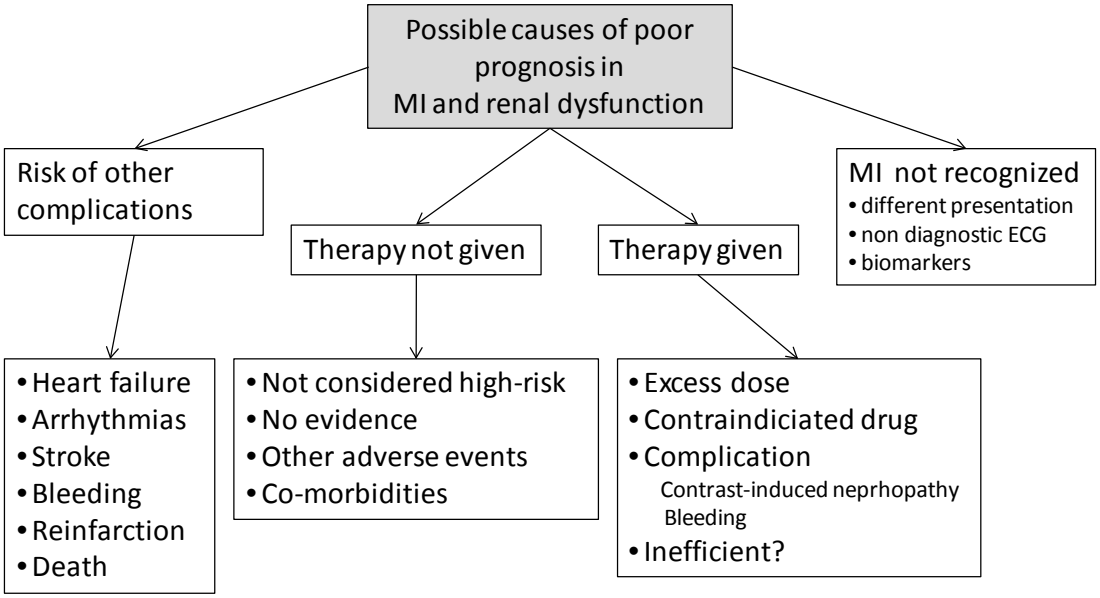


Figure 4. Possible explanations for a poor prognosis in renal dysfunction and MI.

4 AIMS

The aim of this study was to

- Describe the presentation, in-hospital therapies and complications in relation to renal function in a broad and unselected MI population.

- Examine how the Cockcroft-Gault and the MDRD renal function estimations perform in a MI population and to assess how they predict outcome.

- Assess the current use of revascularization in patients admitted with a NSTEMI in relation to renal function and to determine the association with one year survival at different degrees of renal dysfunction.

- Evaluate the use of statin at discharge for MI and its association with one year mortality in relation to different degrees of renal dysfunction.

5 METHODS

5.1 PATIENT POPULATION AND REGISTRIES

This work is based on data collected in the SWEDEHEART register between 2003 and 2006, with additional data from other national Swedish registries.

5.1.1 SWEDEHEART

Each year about 25 000 patients have an acute MI in Sweden, and the majority of these patients are treated at a coronary care unit. If the patient permits, data on 100 variables including hospital presentation, electrocardiogram, baseline characteristics, in-hospital therapies, in-hospital complications, and discharge medication is collected and entered in the SWEDEHEART register[101]. Depending on the type and structure of the hospital, a proportion of patients with MI may not be treated at a coronary care unit and therefore may not be included.

The SWEDEHEART register started as a regional quality register to evaluate the care for MI patients treated at a coronary care unit in 1991. In 1995 this became a national quality register called RIKS-HIA. This register merged with the coronary angiography, the secondary prevention and the coronary by-pass surgery register to form the SWEDEHEART register in 2008. During the study period between 2003 and 2006 included in this work, nearly all hospitals in Sweden that admit acute MI patients participated in this register (73/78 in 2003, 72/77 in 2004, 72/75 in 2005 and 71/74 in 2006).

The time period considered in these studies is between 2003 and 2006. Creatinine became a mandatory variable in the SWEDEHEART register in 2003. The local physicians were instructed to include a single measurement of the in-hospital creatinine value that best represented the patient's underlying renal function. Data on dialysis status was not registered. The number of missing values for creatinine was 9.1%. The number of patients during this time period and the number of patients in the individual papers is shown in figure 5.

The agreement between the hospital charts and the data entered is high. In the year 2006, when a monitor examined data entered for 30 patients at 20 different hospitals, evaluating over 36 330 data entries, the agreement between the data entries and hospital charts was 96.5%[102]. In an evaluation during the same year, the agreement for the creatinine value was below this average, and was entered correctly in only

88.6% of cases. This corresponds to the large number of creatinine values that were not registered.

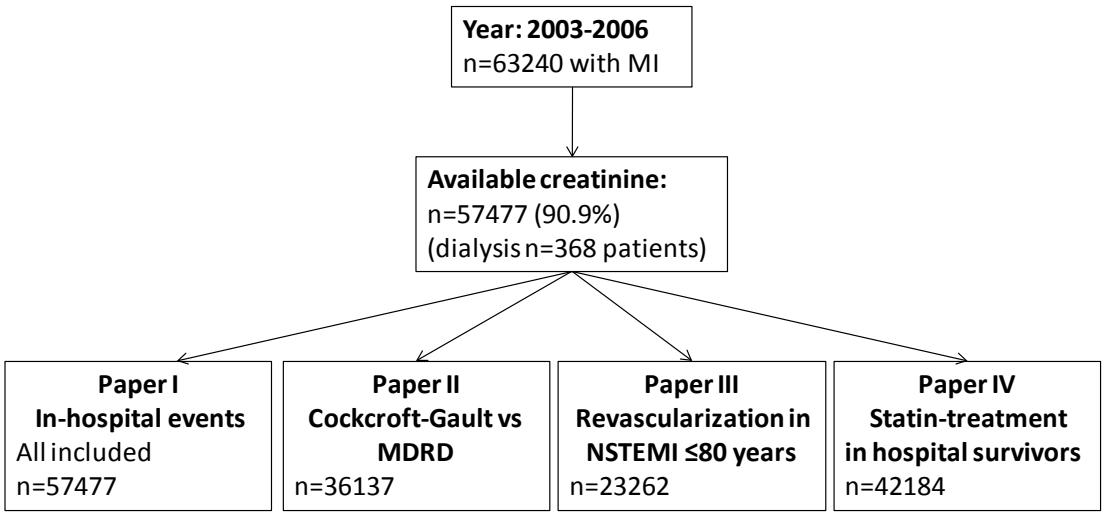


Figure 5. The SWEDEHEART register and number of patients in the different studies.

5.1.2 Additional registries

Data collected from the SWEDEHEART register has been complemented regarding prior diseases and vital status by merging with other registries.

The National Patient Registry[103] collects discharge diagnosis since 1987 for all patients who have been hospitalized. Information regarding previous chronic obstructive pulmonary disease, cancer diagnosis within the last 3 years and dementia was obtained from this registry. For a few other diagnoses, such as diabetes, congestive heart failure and prior stroke, information was obtained from both the SWEDEHEART and from the National Patient Registry. By combining data from the National Patient Registry, 2.9% more patients with a diagnosis of prior heart failure were identified than if data had been collected only from the SWEDEHEART register.

The Swedish Renal Registry[40], which is a nationwide registry since 1991, provided data on dialysis status of the patients included in the SWEDHEART register.

The National Death Registry[104] collects vital status on all Swedish citizens since 1961. The main outcome measure, all-cause mortality, was obtained from this registry.

5.2 DEFINITION OF MI AND RENAL FUNCTION

The diagnosis of MI was made by the local physician. Physicians were encouraged to use the most current guideline available for the MI diagnosis[105], which recommended

an elevated level of troponin T or I, or 2 successive creatine kinase-MB values above the 99th percentile for a reference population, or at least twice the decision limit within 24 hour of the index event.

Renal function in paper I-IV was estimated from creatinine by using the abbreviated 4-variable MDRD equation, which includes age, gender and race[21, 22]. All patients were assumed to be white. In paper II, creatinine clearance was calculated by using the Cockcroft-Gault formula, which is based on age, gender and weight[20]. The renal function was staged according to the 5 classes defined by the NKF K/DOQI[34].

5.3 ENDPOINT

In-hospital complications were evaluated in paper I. Data was collected directly from the SWEDEHEART case report form, and was available for reinfarction for 97.7% of patients, in-hospital heart failure for 99.6%, ventricular arrhythmias/cardiac arrest for 99.6%, new-onset atrial fibrillation for 97.2% and for major bleeding events for 74.3%. Data on in-hospital mortality was obtained both from the SWEDEHEART case report form and from the National Death Registry and was available for all patients. The main outcome measure for paper II-IV was all-cause mortality at one year. This was obtained from the National Death Registry, and was available for nearly all patients.

5.4 STATISTICS

5.4.1 Baseline characteristics

Continuous variables are presented either as mean (standard deviation) and assessed with analysis of variance, or median (25th-75th percentile) and compared with the nonparametric Kruskal-Wallis test. Categorical variables are presented as proportions and were assessed with the Chi-squared test. In paper II the two renal function estimates were obtained by both equations for the same patients, and were therefore compared using the paired Wilcoxon-rank sum test.

5.4.2 In-hospital complications and one year survival

In-hospital complications and survival in papers I and II were assessed with logistic regression models adjusting for several clinically important confounders. In paper I the likelihood of receiving evidence-based therapies in patients with renal dysfunction was also assessed with logistic regression analyses.

One year survival was evaluated in paper II-IV. The unadjusted one year survival for the Cockcroft-Gault, MDRD and 1/creatinine estimates was compared in

paper II with a receiver operating curve analysis. To account for time-to-event for one year survival (all-cause death in paper II-IV), a Cox-proportional hazard analysis model was used adjusted for confounders. An unadjusted presentation of survival at different function stages is displayed as a Kaplan-Meier curve in paper III.

In paper III revascularization was entered as a time-dependent variable in the Cox-proportional hazard model. Patients could be treated either medically or invasively. To belong to the invasively treated group, they had to be treated by either PCI or CABG within 14 days of admission. Since it was unknown which patients admitted with a NSTEMI would be revascularized, all patients initially belonged to the medically treated group. Patients who were revascularized provided event-free time to the medical treatment group until the day at which they were treated.

The model assumption for the Cox proportional hazards model was checked graphically.

5.4.3 Choice of variables in regression models

Several confounders were adjusted for in the logistic regression model for in-hospital complications and in the Cox proportional hazards analysis for one year survival. For the estimates in the multivariable models to be stable, based on empirical data, there should be at least 10 events for each covariate included in the model. In these studies, there was a large number of outcomes, and this recommendation was never a limitation in the number of variables included.

Adjustment was made for variables that are well-known risk factors, and for in-hospital complications or therapies that could alter the outcome. All in-hospital complications and therapies had to occur before the outcome in order to be included. Smoking habit, despite being a risk factor for MI and death, was a variable with a large percentage of missing values (about 9%), and was therefore excluded from the analysis.

5.4.4 Propensity score

In paper III and IV, the relationship between treatment and one year survival was assessed. Therapies in this observational cohort were not randomly assigned and the results could therefore be affected by selection bias. In clinical practice, certain patient characteristics are associated with the likelihood of receiving a therapy. In paper III, patients who were healthier, had fewer high-risk indicators and fewer in-hospital complications could have been selected for revascularization within 14 days. Alternatively, patients could have been referred to revascularization as a last resort

when they were unstable and had a worse prognosis. Similarly, statin therapy at discharge in paper IV may have been prescribed to patients with an overall better survival. This would result in much more benefit being attributed to the therapy given than really exists.

To reduce the bias that patients were not randomly assigned, and that there could be remaining imbalance in the baseline covariates between the treatment groups, a propensity score was calculated. The propensity score describes every patient's individual likelihood of being treated based on the covariates included[106, 107]. The propensity score was obtained in a logistic regression model that included all covariates that could potentially have influenced the choice of therapy. The propensity score was then entered together with other covariates in the final Cox proportional hazards model to assess one year mortality.

The success of balancing the covariates in the two treatment groups by using propensity score can be examined in several ways. The variables used can be standardized according to the distribution of the propensity score in one of the treatment groups. The means or percentages can then be compared between the standardized and the other treatment group (Paper III, supplement 1). In addition, a standardized difference can be calculated, which describes the difference between the two groups (Paper IV, table 2).

One additional advantage of using a propensity score is that a large number of covariates are used and can be summarized into a single variable. In a multivariable model the number of covariates may have to be limited because including too many can lead to an unstable estimate. In a propensity score model, the number of variables included is less critical, as the aim is to obtain the best possible estimation of the probability of a certain treatment.

In general, the results of a model that includes a propensity score will be similar to the results obtained from a multivariable model adjusted for the same covariates. Compared to a multivariable model, the propensity score will give an estimate with less bias and a more precise estimate if the number of outcome variables is 7 or fewer for each covariate[108, 109].

A remaining limitation, as in all models, is that only covariates that have been measured can be included. Unmeasured confounders can still explain the results. Therefore, the results obtained with a multivariable model even with a propensity score can at best be suggestive of the treatment effect, and should preferably be confirmed in a randomized trial.

5.4.5 Interaction terms

The effect of treatment at different levels of renal function was evaluated by using interaction terms. This is a statistical method to test if there are treatment differences between different subgroups. Interaction terms are considered to have limited power[110-112]. An absence of a treatment difference between the renal function groups using an interaction term in a model does not necessarily mean that there is no difference.

5.4.6 Missing covariates and sensitivity analysis

The number of missing covariates in the analysis varied. To evaluate whether the individuals with missing covariates would have altered the main outcome, a new variable which included all missing values was used. In these analyses, the categorical covariates were coded as either yes, no or missing. This new covariate was then used in the multivariable model and the estimates compared to the estimates with missing covariates.

5.4.7 Ethics

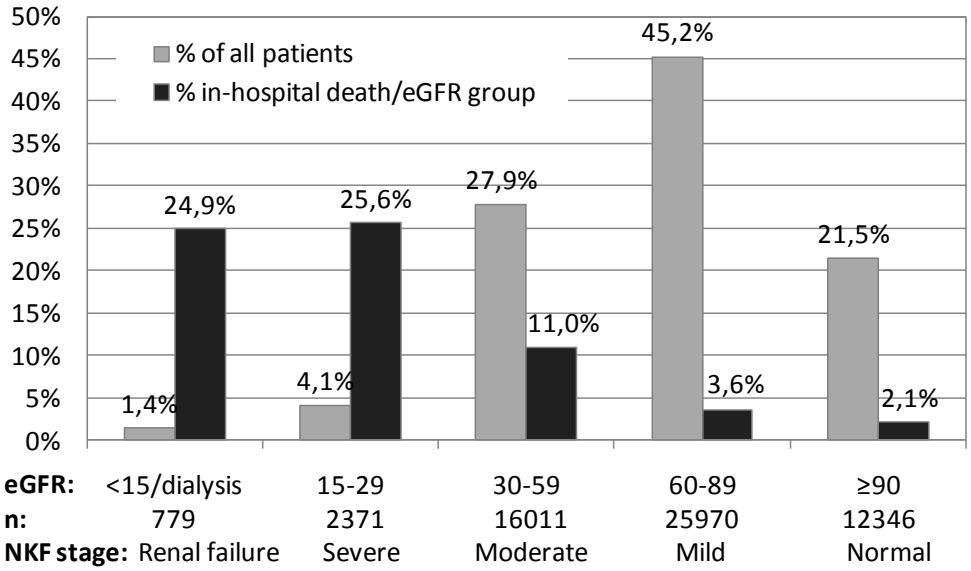
All patients were informed about participation in the SWEDEHEART registry, and had the right to refuse participation at any time. The merging of the different registries was done by the Epidemiologic Centre in Stockholm, which provided a file without any personal identity number after the merging. The local ethics committee at Uppsala University approved this study.

6 RESULTS

6.1 PAPER I: RENAL FUNCTION, THERAPIES AND COMPLICATIONS IN MI

6.1.1 Characteristics of MI patients with renal dysfunction

There were 57477 consecutive MI patients admitted between 2003 and 2006 who had available creatinine measurement or known dialysis status entered in the SWEDEHEART register. The mean (SD) eGFR was 72 (28) ml/min/1.73m^2 excluding the 368 patients receiving dialysis therapy. About a third (33.4%) of patients had at least moderate, whereas 5.5% had at least severe renal insufficiency according to the NKF K/DOQI definition (figure 6).

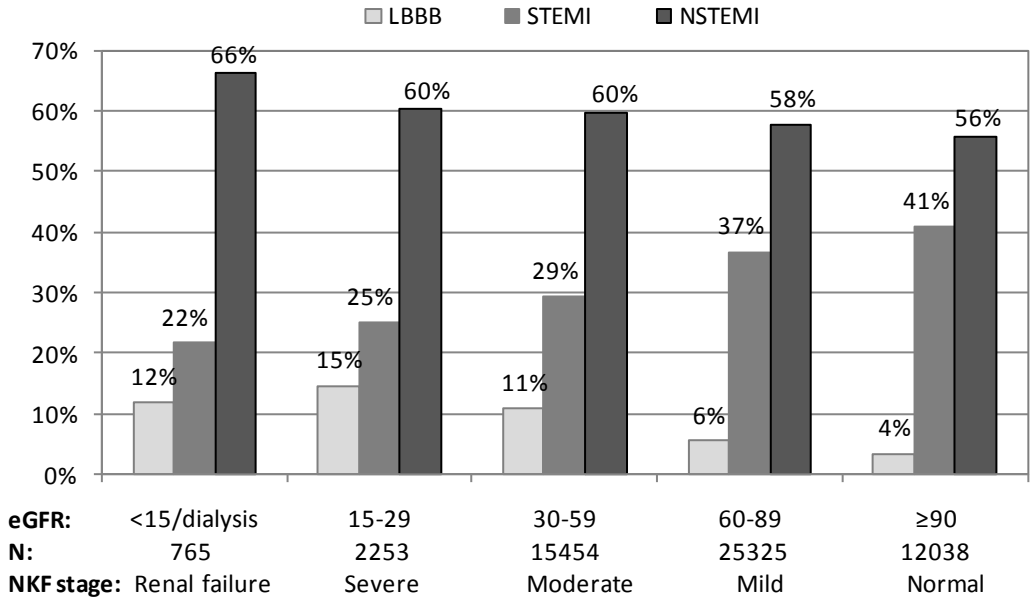


Figur 6. Distribution of renal function and in-hospital death in SWEDEHEART.

Patients with lower renal function had increasingly more co-morbidities and cardiovascular risk factors. Compared to patients with normal renal function, patients with renal failure were in median 12 years older. Prior diseases such as diabetes increased in those with normal renal function to those with renal failure from 18.2% to 46.8%; hypertension from 32.3% to 60.7%; prior MI from 12.1% to 35.2%. Only the number of current smokers decreased from those with normal renal function compared to those with renal failure, from 38.1% to 17.8%.

The majority of patients admitted presented with chest pain, although the number decreased with lower renal function; from 90% in normal renal function to

67% in renal failure. Symptomatic heart failure (Killip class ≥2) was much more common. The number of patients with STEMI decreased, whereas the number of patients with NSTEMI and LBBB increased (figure 7).



Figur 7. ECG pattern at different levels of renal dysfunction.

6.1.2 Use of therapies and in-hospital outcome

Use of therapies decreased with lower renal function. The use of intravenous/oral beta-blocker in-hospital was lower, but after adjustment their use was not predicted by renal function. The use of in-hospital anticoagulants and invasive therapy in NSTEMI, and the frequency of reperfusion for STEMI were lower and predicted by a lower renal function also after adjustment (figure 8). The type of reperfusion for STEMI shifted from primary PCI to thrombolysis in STEMI.

All in-hospital complications apart from reinfarction increased with lower renal function. The odds of cardiac arrhythmias, heart failure, bleeding, and mortality increased with worsening renal function (figure 9). The in-hospital mortality for the entire cohort was 6.5%, but varied with renal function (figure 6 and 9).

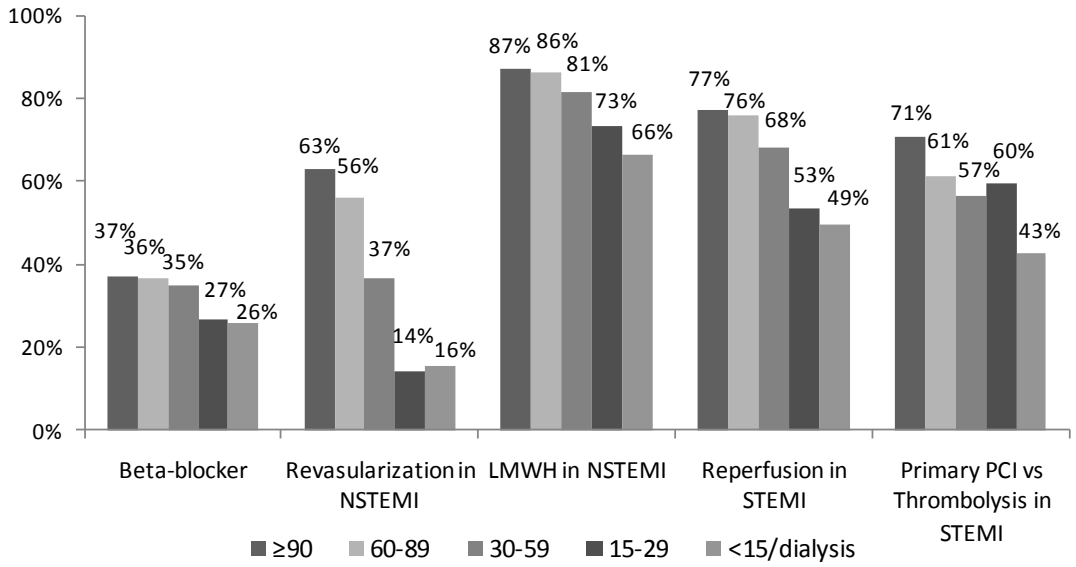
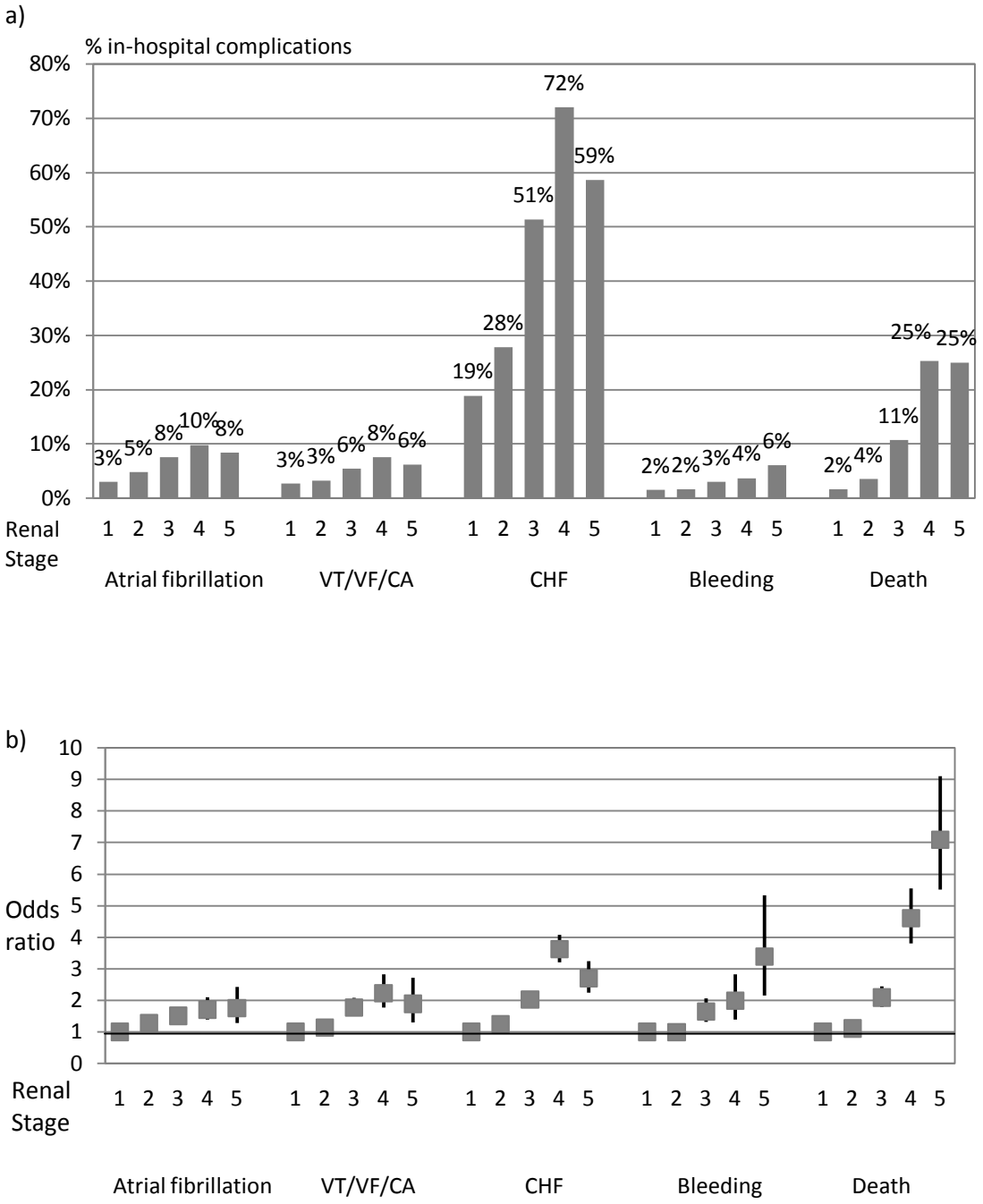


Figure 8. Use of in-hospital therapies at different levels of renal function.

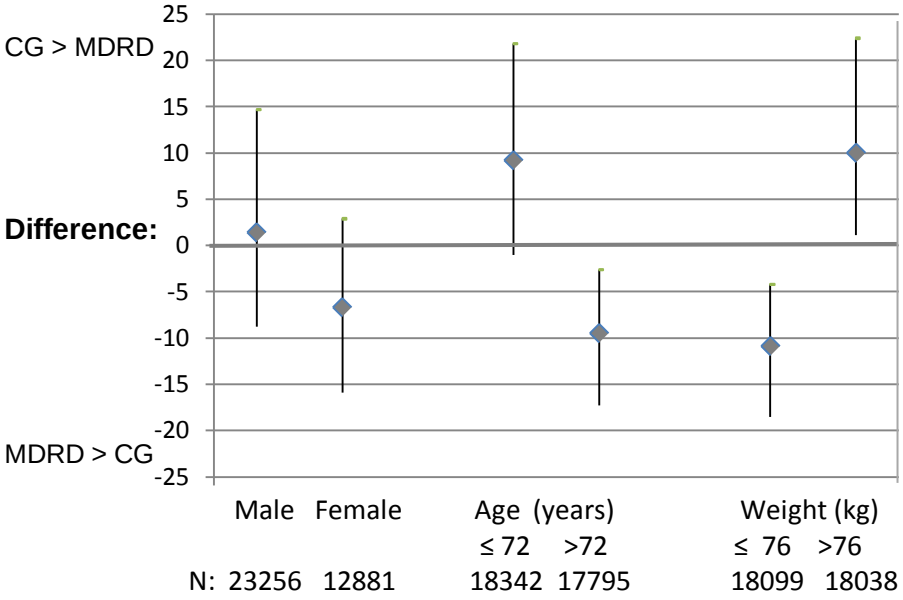
6.2 PAPER II: COMPARING THE COCKCROFT-GAULT AND MDRD FORMULA

Consecutive MI patients in SWEDEHEART for whom renal function could be estimated with both the Cockcroft-Gault and the MDRD formula were included in this study (n=36137). More patients with at least moderate renal dysfunction were identified with the Cockcroft-Gault formula than with the MDRD formula (39.8% versus 31.1%, $p<0.001$). The corresponding number was higher for patients with at least severe renal dysfunction (7.6% versus 4.4%, $p<0.001$).

The largest difference between the two renal function estimates was seen on the variables included in the equations (age, gender and weight) (figure 10). In patients with an estimated normal renal function, the largest difference was seen between the Cockcroft-Gault and the MDRD equations, where the Cockcroft-Gault estimated a higher median (IQR) by 15 ml/min (-0.6 to 30.6). In comparison, in moderate renal function the MDRD estimated a higher median eGFR (median 7.6; IQR -14.5 to -0.7) compared with the Cockcroft-Gault formula.



Figur 9. a) In-hospital complications and renal function
b) Adjusted odds ratio of in-hospital complications by different renal stages.
(NKF Stage (ml/min/1.73m^2): ≥90; stage 2: 60-89; stage 3: 30-59; stage 4: 15-29; stage 5: <15/dialysis. VT: ventricular tachycardia. VF: ventricular fibrillation. CA: cardiac arrest. CHF: Congestive heart failure).



Figur 10. Difference between Cockcroft-Gault and MDRD at gender, median age and median weight. (CG: Cockcroft-Gault.)

In a ROC-analysis, the association between renal function and one year mortality was stronger when the Cockcroft-Gault equation (AUC: 0.78; 95% CI 0.77-0.79) was used compared to when the MDRD (AUC 0.73, 95% CI 0.72-0.74) or 1/creatinine (AUC 0.70; 95% CI 0.69-0.71) were used.

At each renal function stage classified by the MDRD equation, the mortality increased with decreasing renal function according to the Cockcroft-Gault equation (figure 11). After multivariable adjustment, Cockcroft-Gault predicted one year mortality better than the MDRD (renal failure versus normal renal function: HR 3.00 (95% CI 2.42-3.71) with the Cockcroft-Gault; HR 2.56 (95% CI 2.10-3.11) with the MDRD).

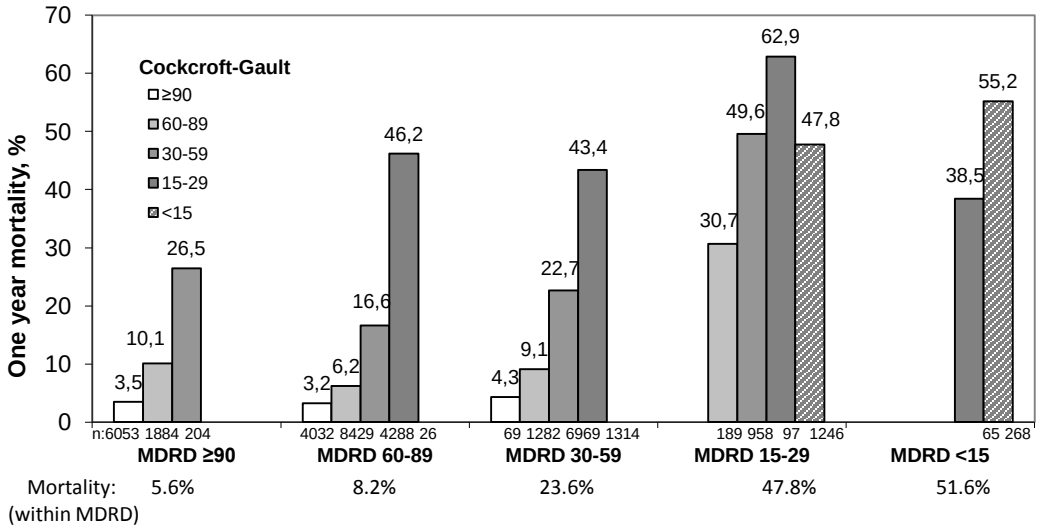


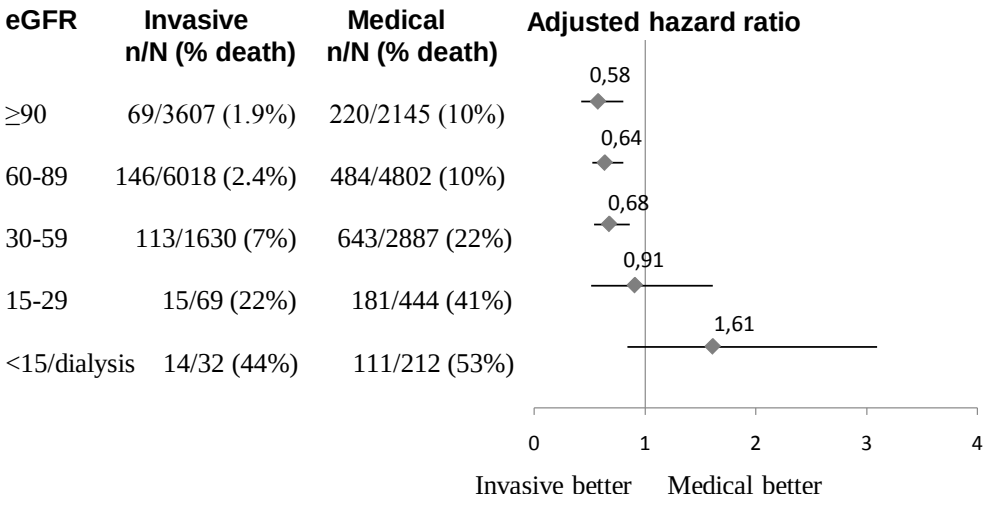
Figure 11. Unadjusted mortality classified according to the MDRD formula.

6.3 PAPER III: REVASCULARIZATION IN RENAL DYSFUNCTION AND MI

In SWEDEHEART there were 23262 patients registered with NSTEMI who were ≤80 years old between 2003 and 2006. There were 11232 (48.3%) patients who were treated medically and 12030 patients (51.7%) who were revascularized within 14 days of admission. The majority of patients treated with revascularization underwent PCI (83.8%). Patients who underwent coronary angiography without an intervention (n=4647) were considered medically treated.

There were significant baseline differences between the treatment groups. Medically treated patients were significantly older, had more cardiovascular risk-factors and co-morbidities. After propensity-score adjustment, the two treatment groups were comparable on the covariates included.

The frequency of revascularization decreased with lower renal function: eGFR ≥90 ml/min/1.73m^2 62%, eGFR 60-89 ml/min/1.73m^2 55%, eGFR 30-59 ml/min/1.73m^2 36%, eGFR 15-29 ml/min/1.73m^2 14%, eGFR <15 ml/min/1.73m^2 /dialysis 15% ($p<0.001$). After adjustment, the overall one year mortality was reduced by 36% (HR 0.64; 95% CI: 0.56-0.73, $p<0.001$) with revascularization. A comparable reduction in mortality was seen in patients with mild-to-moderate renal dysfunction treated with revascularization, but the effect decreased in those with severe renal dysfunction. In renal failure there was no certain effect or even a suggestion about harm with revascularization (figure 12). There was a significant interaction between revascularization and renal function group ($p<0.001$).



Figur 12. One year mortality with invasive compared to medical therapy in NSTEMI.

6.4 PAPER IV: STATIN USE AFTER MI AND RENAL DYSFUNCTION

There were 42814 in-hospital MI survivors without statin on admission in SWEDEHEART between 2003 and 2006. With decreasing renal function, the prescription at discharge decreased from 81.2% among those with normal renal function to 30.7% in renal failure ($p<0.001$).

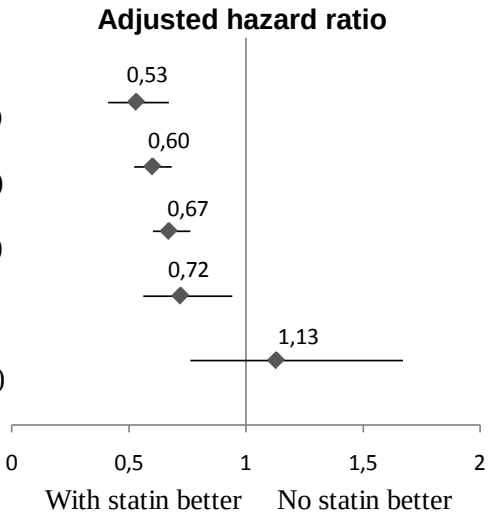
Baseline characteristics differed significantly among patients discharged with a statin from those without, but after propensity score adjustment the groups were balanced on the covariates included.

About a third of patients (33.2%) did not have cholesterol level reported. Among patients who received a statin at discharge, the LDL level was less frequently reported in those with lower renal function. There was a higher proportion of patients with an LDL-level ≥2.5 mmol/L in those with normal renal function (81.2%) compared to those with renal failure (70.0%).

The unadjusted one-year survival was significantly lower among patients without a statin compared to those with a statin at discharge at all renal function levels. After adjustment for propensity score and discharge medication, one year survival improved with statin use at discharge among those with normal-to-severe renal function. The effect was attenuated and less certain among those with renal failure

(figure 13). The interaction term for statin therapy and renal function was significant ($p<0.001$).

eGFR	No statin n/N (% death)	With statin n/N (% death)
≥90	240/1681 (14%)	191/7517 (2.5%)
60-89	813/4846 (17%)	465/13636 (3.4%)
30-59	1481/5101 (29%)	510/4958 (10%)
15-29	387/819 (47%)	81/330 (25%)
<15/dialysis	102/215 (47%)	37/94 (39%)



Figur 13. One year mortality with and without statin at discharge.

7 DISCUSSION

7.1 MAIN FINDINGS

About a third of patients have at least a moderate renal insufficiency on admission for a MI in this current real-world register. Among the two most frequently used estimations of renal function, the Cockcroft-Gault formula appears to be superior in identifying more patients with MI at higher subsequent risk compared to the MDRD formula.

Renal dysfunction is associated with a higher rate of in-hospital complications including both ischemic and non-ischemic events such as arrhythmias, heart failure and bleeding. This is not explained by co-existing diseases alone. Similarly, the one year mortality increases substantially for every degree of renal dysfunction.

The use of several in-hospital therapies is lower in patients with renal dysfunction. Invasive therapy in patients with NSTEMI is used less often, despite comparable benefit in those with mild-to-moderate renal dysfunction. Similarly, patients with lower renal function also receive a statin at discharge less often, although the benefit appears to be maintained in those with mild-to-severe renal dysfunction. The treatment effect differs and appears to decline in patients with more advanced renal dysfunction. Both for patients with severe renal dysfunction or renal failure undergoing revascularization and in those with renal failure receiving a statin, the treatment effect is less certain.

7.2 CURRENT PREVALENCE, THERAPIES AND SHORT-TERM OUTCOME

About a third of patients admitted with a MI have at least a moderate renal dysfunction. These results are similar to the results reported from other registries[3, 9, 10, 65]. Part of this high prevalence is explained by the older age, but in all age categories patients with MI have more renal dysfunction. Compared to a general population, the prevalence of a moderate or severe renal dysfunction in patients admitted with a MI is 33 times more common in patients 20-39 years old, 4 times as common in those 40-59 years old, and about twice as common in those $\geq$60 years old[113, 114].

The in-hospital outcome is remarkably poor in patients with renal dysfunction. Despite this being a report from a contemporary population, the short-term in-hospital mortality has changed very little over time, particularly among those with renal failure. The in-hospital mortality for patients with renal failure between 1977-1995 was 26%[64], compared to 25% in this more recent study. Other in-hospital complications increase

progressively in patients with lower renal function. This study confirms similar findings for arrhythmias, heart failure, and bleeding events[10, 65].

The explanation for the poor prognosis of patients with MI and renal dysfunction is unknown, but may be related to an overall increase in both ischemic and non-ischemic complications, a differing clinical presentation and therefore a lower suspicion of MI and less use of evidence-based therapies. A differing pathobiology specific for patients with renal dysfunction has also been suggested[115].

The presence of renal dysfunction alters the presentation for MI. Patients present less often with chest pain and fewer have ST-elevation on ECG. This is consistent with other studies, where heart failure symptoms and signs are more common[14, 65, 67].

Renal dysfunction is associated with and independently predicts a lower use of several evidence-based in-hospital therapies for ACS[9, 15, 75]. Despite a higher rate of side-effects and adverse events, there is no evidence for a lack of effect for several of these therapies[77]. There is a higher risk of bleeding complications in patients with renal dysfunction, which in part is related to a higher risk of excess dosing and use of contraindicated medication[5, 6, 9, 96]. It still remains unknown how prognosis would have changed for patients with renal dysfunction if therapies had been used more frequently.

7.3 RENAL FUNCTION ESTIMATION AND PROGNOSIS IN MI

The Cockcroft-Gault formula identifies a larger proportion of patients with MI who subsequently have higher one year mortality than the MDRD formula. Our results are consistent with a study in a chest pain population[44], but differ from the results in a heart failure population[43].

The superiority of the Cockcroft-Gault formula in the MI population is in part explained by the characteristics of the population examined. The MI population in this study consisted of elderly people with a median age of 72 years, compared to the heart failure population who had a mean age of 58 years[43]. Many patients in this study had a low body weight. Both lower body weight and older age are well-described characteristics, in which the Cockcroft-Gault formula will give a lower estimate of renal function compared to the MDRD formula[24, 113]. Although these two characteristics are related to worse prognosis in MI, even after adjustments in a multivariable model, the estimates obtained with the Cockcroft-Gault formula continued to indicate a higher risk than the estimate with the MDRD formula.

The true renal function was unknown in this study. In patients with renal function in the lower ranges, the MDRD will in general give a more accurate estimate

than the Cockcroft-Gault formula[26]. The superiority of the Cockcroft-Gault formula in predicting prognosis in a MI population may therefore not be explained by a more accurate estimation of the renal function. It is more likely that the relationship to prognosis in MI is related to the variables included and to the equation itself.

Current guidelines support the use of the MDRD equation for detection of renal dysfunction in MI[41] and the Cockcroft-Gault formula for dose adjustments[5, 42, 70]. Although the Cockcroft-Gault equation is more cumbersome to use as it also requires the weight of the patient, our study indicates that it is better for predicting prognosis in patients with MI.

7.4 THERAPIES FOLLOWING MI

7.4.1 Revascularization for NSTEMI

Revascularization was beneficial for NSTEMI in patients with mild-to-moderate renal dysfunction, but with lower renal function the effect declined. Patients with renal dysfunction have often been excluded from clinical trials that evaluate the efficacy of revascularization for NSTEMI. There are only two sub-studies and one meta-analysis that have shown a maintained benefit with revascularization in patients with moderate renal dysfunction range[84-86]. The results of this study support this data.

The decreasing efficacy of revascularization in patients with severe renal dysfunction and the suggestion of harm in those on dialysis are difficult to explain. The results may be limited by a lack of power in this study, since these patients groups were much smaller, or may reflect a true lack of effect in those with more advanced renal dysfunction. The absolute risk of adverse events, such as arrhythmia, heart failure or bleeding, is much higher in patients with advanced renal dysfunction and lead to a worse prognosis. Despite therapy, these events may not have been prevented by revascularization.

In patients with moderate renal dysfunction it is possible that the less frequent use of invasive therapy contributed to their worse prognosis. Withholding invasive therapies from patients with high risk is a well-known phenomenon termed the "treatment-risk paradox" [15, 87, 88, 116]. Patients with renal dysfunction are not perceived to be at high-risk, which explains why they are not referred for coronary angiography in about 42% of cases, and in only 7% of cases because of lack of supporting evidence[15].

7.4.1 Statin therapy at discharge for MI

Statin therapy at discharge for MI was associated with a one-year survival benefit in all patients except in those with renal failure. Our data confirm the results of several post-hoc analyses of clinical trials, in which there was a significant reduction in cardiovascular endpoints in those with mild-to-moderate renal dysfunction[94, 95, 117]. In this register, we also found a maintained treatment effect in those with severe renal dysfunction.

The lack of effect in those with renal failure is puzzling. It may be related to the smaller number of patients than there are with renal dysfunction, and therefore a difference in survival between those treated and untreated may not have been detected. Alternatively, there may have been no difference to detect.

Lack of effect with statin therapy for primary prevention has been reported from two randomized trials in patients on dialysis[118, 119]. Despite efficient lowering of the cholesterol level, there was no difference in cardiovascular events. In these trials the results may be related to a high discontinuation rate, a high rate of adverse events, and a different pathobiology with competing outcomes not preventable by cholesterol lowering. Compared to these trials, that only included dialysis patients where only 10-18% had a prior MI, all patients in this study had a recent MI and only a minority received dialysis. The groups in this study were too small to further evaluate differences of treatment effect of statin therapy among patients with eGFR <15 treated with or without dialysis therapy.

It is unknown whether hemodialysis patients differ also for secondary prevention, and whether there is a specific threshold of renal insufficiency at which statins are effective. Other methods of lowering cholesterol by combining a statin with ezetimibe for primary prevention in predialysis and dialysis patients is currently being tested in the "Study of Heart and Renal Protection" (SHARP) trial[120], which will be presented in late 2010.

7.5 USE OF DATABASES AND THEIR LIMITATIONS

Reports from registers have several advantages (table 5). In SWEDEHEART, all consecutive MI patients recently treated at a coronary care unit in Sweden were included. Since nearly all hospitals participated, the coverage is almost complete and therefore the generalizability is good. The data truly represents the current practice in Sweden.

There have been concerns raised about the completeness of this register. In particular, an uncertain number of patients are not treated at a coronary care unit for their MI. In one centre, such patients made up 40% of all MI patients treated at the hospital[121]. These patients differed significantly from the patients included in the register, by being nearly a decade older, having more co-morbidities and having a substantially worse prognosis. SWEDEHEART represents MI patients treated at a coronary care unit, but does not represent all MI patients treated in Sweden.

There are no selection criteria in a register. Compared to a clinical trial, a register provides valuable data on patient groups, such as those with renal dysfunction, which are understudied in clinical trials[17]. Specifically, current medications, therapies and in-hospital complications can be described accurately. A limitation may be the quality of the data entered and missing values, which introduces a bias. In this study, 9.1% of patients did not have creatinine measurement reported and nearly a quarter of patients had missing values for bleeding. Had this been a clinical trial, which has continuous monitoring of the data entered, there would have been less missing data.

The use and interpretation of register data for the evaluation of treatment effects is problematic. The treatments are not randomly assigned and the results are affected by selection bias. Despite adjustment for a large number of confounders and use of propensity score, only variables which are measured can be adjusted for. In a clinical trial randomization will balance both measured and unmeasured confounders between the treatment assignment groups.

The effect of treatments is often over-estimated in registries as healthier patients are selected for therapies in clinical practice[87, 88, 116]. Reports from registries that evaluate different treatment strategies are subject to selection bias. The already better prognosis of patients selected for therapies will be attributed to the treatment. In contrast, patients in a clinical trial are randomly assigned to treatments.

In a trial, some patients will cross-over between treatment assignments. The treatment effect can be analyzed both as an “intention-to-treat” and “as treated”. In a register only patients who actually receive a therapy will be evaluated, which gives more similar results to the “as treated” analysis from a randomized trial. In a recent analysis from the ICTUS trial, survival was improved in patients revascularized when the data was analyzed as “as treated”, which could not be verified in an “intention-to-treat” analysis[120]. This is attributed in part to the higher-risk patients among those randomized to an invasive selective therapy not being revascularized.

In summary, the studies from SWEDEHEART reporting the prevalence, therapies and complications in patients with renal dysfunction admitted with a MI to a coronary care unit provide good quality data on the current practice in Sweden. The studies reporting treatment effects are suggestive, but the results need to be interpreted cautiously. Further studies to confirm the treatment effects are needed, preferably from randomized trials.

Tabele 5. Comparison between clinical trials and registries.

	Clinical Trials	**Registries**
Strengths	Evaluate treatment effect	Includes all patients (good generalizability)
	Randomization balances measured/unmeasured confounders	Represents how treatments are currently applied
		Describes population outcomes
Weaknesses	Inclusion and exclusion criteria (lacks generalizability)	Cannot be adjusted for unmeasured confounders
	Expensive	Conclusions about treatment effects are unreliable (selection bias)
	Short duration	Lower data quality

7.6 CLINICAL IMPLICATIONS

The presence of renal dysfunction easily identifies patients with high-risk MI, where a more frequent use of in-hospital therapies might alter their poor outcome. Although both the risk associated with a MI in patients with renal dysfunction and the risk associated with therapies is high, there may still be a net clinical benefit. The absolute benefit in patients with renal dysfunction receiving evidence based treatments may still be considerable[122].

Several explanations for the worse prognosis following a MI in patients with renal dysfunction have been proposed. This may be explained by more frequent and more advanced co-morbidities. Renal dysfunction may have an abnormal vascular biology, which may make them less treatable with commonly used therapies for MI.

An under-use of guideline recommended therapies may contribute. A higher rate of complications is present, which may not be altered by the therapies given.

In the studies presented, therapies were used less often in patients with renal dysfunction. It is likely, but unknown, whether therapies would have changed the outcome if they had been used more frequently. Further studies directed both at understanding the underlying pathophysiology and to define the optimal therapy are needed to improve the prognosis in patients with renal dysfunction and MI.

8 CONCLUSION

Based on the present work from the SWEDEHEART registry, the following conclusions about patients with a MI and renal dysfunction can be made:

- About a third of patients admitted with a myocardial infarction have at least moderately reduced renal function. Renal dysfunction is associated with a lower use of in-hospital therapies and a higher rate of in-hospital complications. Estimation of renal function can be used to identify high-risk individuals.

- The Cockcroft-Gault formula classifies a higher proportion of patients to lower renal function stage compared to the MDRD formula in a MI population. These patients have a worse prognosis. The Cockcroft-Gault formula should be the preferred equation to estimate renal function in MI.

- Early revascularization in NSTEMI is used less frequently with lower renal function, although better one year survival with invasive treatment is seen in those with mild-to-moderate renal dysfunction. The advantage with therapy declines in those with severe renal dysfunction, and the effect is less certain in those with renal failure.

- Fewer patients with lower renal function receive a statin at discharge, despite an improved one year survival in all renal function groups, except in those with renal failure. It is possible that a more frequent use of statins at discharge would have improved outcome.

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