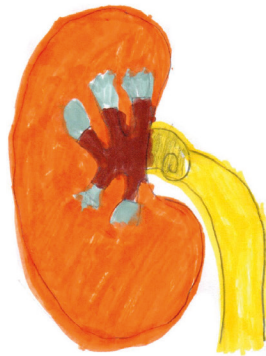


# Influence of Chronic Kidney Disease on Presentation, Treatment and Outcome in Patients with Coronary Artery Disease



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**To my family**

*“In your life expect some trouble,  
when you worry you make it double,  
don't worry, be happy.”*

Bobby McFerry, 1988

Department of Medicine, Division of Cardiology,  
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# INFLUENCE OF CHRONIC KIDNEY DISEASE ON PRESENTATION, TREATMENT AND OUTCOME IN PATIENTS WITH CORONARY ARTERY DISEASE

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# SAMMANFATTNING

## Bakgrund

Ungefär en tredjedel av alla patienter med akut hjärtinfarkt har njursvikt, vilket innebär en markant ökad risk för såväl komplikationer som nya hjärthändelser. Syftet med detta avhandlingsarbete var att undersöka vilken betydelse olika grader av njursvikt har för överlevnad och kliniska utfall, att utvärdera utfallen efter olika medicinska- och interventionella behandlingar och hur de skiljer sig åt hos patienter med njursvikt samt att utifrån blodprovsanalyser studera olika biomarkörers koppling till njursvikt och kardiovaskulära händelser.

## Metoder och resultat

Studie I: Data från det svenska hjärtsjukvårdsregistret SWEDEHEART användes för att undersöka hur olika grader av njursvikt påverkar risken för död och kliniska utfall efter en kranskärlsröntgen p.g.a. stabil kranskärlssjukdom. Resultaten påvisade att trots justering för flertalet kliniska bakgrundsfaktorer, samsjuklighet, grad av ischemi och olika revaskulariseringmetoder, hade patienter med njursvikt en signifikant ökad risk för död, återinsjuknande i akut hjärtinfarkt och hjärtsvikt.

Studie II: Registerstudie där alla patienter med hjärtinfarkt som registrerats i SWEDEHEART och som erhållit blodförtunnande behandling med antingen clopidogrel eller ticagrelor studerades. Samkörning av flera register utfördes. Jämfört med clopidogrel, var behandling med ticagrelor förknippat med lägre risk för död, återinläggning med hjärtinfarkt och stroke, dock på bekostnad av en ökad blödningsrisk, hos både njurfriska och patienter med måttlig njursvikt. Bland patienter med uttalad njursvikt observerades inte någon säker nytta, men däremot ökade risker för blödning.

Studie III: Alla patienter i SWEDEHEART som genomgått kranskärlsröntgen och erhållit en kranskärlsstent (läkemedelsbärande stent (n-DES) eller stent av metall (BMS)) inkluderades i denna studie, där risken för förnyad förträngning (restenos) och akut ocklusion (stenttrombos) i stenten studerades utifrån njurfunktion. I jämförelse med BMS, innebar stentinläggning med n-DES en lägre 1-årsrisk för både restenos och stenttrombos hos patienter med lätt eller måttlig njursvikt, medan ingen skillnad noterades hos patienter med uttalad njursvikt.

Studie IV: SWEDEHEART användes för både provinsamling och prospektiv långtidsuppföljning hos 1,098 patienter som vårdats med akut hjärtinfarkt. Blodprover sparades i SWEDEHEART-biobank och 175 olika biomarkörers uttryck analyserades hypotesfritt angående kopplingar till njursvikt och kliniska utfall, som registrerades i befolknings- och patientregistret. Resultaten påvisade att flertalet av de sex stycken biomarkörer som var starkast relaterade till njursvikt också var starkt relaterade till risken för att drabbas av död, hjärtinfarkt och hjärtsvikt.

## Slutsats

Njursvikt är en stark och oberoende riskmarkör för överdödlighet och kardiovaskulära utfall hos patienter med kranskärlssjukdom. Andra okända faktorer än de vi kunnat justera för (riskfaktorer, samsjuklighet, CAD, behandlingar) har betydelse för den försämrade prognos hos patienter med kranskärlssjukdom och njursvikt. Hos njurfriska och patienter med måttligt sänkt njurfunktion, medförde blodförtunnande behandling med ticagrelor jämfört med clopidogrel samt valet av stenttyp; ökad blödningsrisk, lägre risk för död, hjärtinfarkt och stroke, respektive lägre risk för stenthändelser, medan inga fördelar noterades hos patienter med uttalad njursvikt. Det påvisades att ett fåtal biomarkörer hade ett starkt gemensamt samband till både njursvikt, död, hjärtinfarkt och hjärtsvikt, vilket tyder på att biomarkörernas underliggande patologiska mekanismer kan förklara den försämrade långtidsprognos som ses hos patienter med kranskärlssjukdom och njursvikt.

# ABSTRACT

## Background

About one third of patients with myocardial infarction (MI) have renal dysfunction (RD). Concomitant coronary artery disease (CAD) and RD is accompanied by a markedly higher risk of death and subsequent cardiovascular (CV) events. The aims of this thesis were to examine the association between degree of RD, mortality and subsequent CV events in patients with stable CAD, to evaluate outcomes of different medical- and interventional treatment regimens in relation to renal function in patients with MI or undergoing percutaneous coronary intervention (PCI), as well as to study various biomarkers and their associations to RD and long-term outcomes in patients with MI.

## Methods and results

Study I: We used the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry to study the associations between renal function, death and CV outcomes in patients undergoing coronary angiography due to stable CAD. Despite adjusting for clinical background, risk factors, comorbidities, severity of CAD and mode of revascularization, patients with RD had a significantly higher risk of death, subsequent MI readmission and heart failure hospitalization compared to patients without RD.

Study II: Follow-up data in MI survivors enrolled in the SWEDEHEART was used to study the association between ticagrelor versus clopidogrel and death, MI or stroke and the risk of bleeds. Ticagrelor as compared with clopidogrel, was associated with lower risk for CVD outcomes and a higher bleeding risk in patients with normal- and moderately reduced renal function. In patients with severe RD, bleeds were more abundant in patients and the benefits less clear.

Study III: Observational SWEDEHEART study, that compared the 1-year risk of in-stent restenosis and stent thrombosis in patients treated with coronary artery stenting using either bare metal- (BMS) or newer generation drug eluting stents (n-DES), in relation to renal function. N-DES, as compared with BMS, was associated with a lower 1-year risk of in-stent restenosis and stent thrombosis in patients with normal- and moderately reduced renal function, whereas no differences were observed between stent type and stent events in patients with severe RD.

Study IV: SWEDEHEART was utilized for blood sample collection and prospective long-term follow up in 1,098 MI patients. Samples were saved in the SWEDEHEART-biobank and subsequently an untargeted analysis of 175 different biomarkers was conducted to study associations with RD, subsequent death, MI readmission and heart failure hospitalization. Six of the strongest biomarkers for RD also shared a strong variable importance for the studied long-term outcomes.

## Conclusion

RD is a strong and independent marker of worse outcomes in patients with CAD. Other unknown factors that were not possible to adjust for may play an important role for the risk of adverse outcomes observed in CAD patients with RD. In patients with no- or moderate RD, ticagrelor versus clopidogrel and the choice of coronary stent type were associated with higher risk of bleeds, lower risk of death, stroke or MI, as well as lower risk of stent events, respectively. However, in patients with severe RD no beneficial effects were observed following the same treatment regimens. The identification of six biomarkers with strong mutual associations with both RD and CV outcomes, may indicate the underlying mechanisms that may contribute to the poor prognosis seen in patients with concomitant MI and RD.



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## LIST OF ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin creatinine ratio
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
ARB	Angiotensin II receptor blocker
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
BMS	Bare metal stent
CABG	Coronary artery bypass surgery
CAD	Coronary artery disease
CCU	Coronary care unit
CG	Cockcroft and Gault formula
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula
CV	Cardiovascular
DES	Drug eluting stent
DM	Diabetes Mellitus
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESRD	End stage renal disease
FABP	Fatty acid binding protein 4 (adipocyte)
FGF-23	Fibroblast growth factor 23
GDF-15	Growth differentiation factor 15
HD	Hemodialysis
HDL	High-density lipoprotein
HR	Hazard ratio
HRPR	High residual platelet reactivity
HT	Hypertension
IHD	Ischemic heart disease
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes

LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease (MDRD) formula
MI	Myocardial infarction
MRM	Multiple Reaction Monitoring
N	Numbers
N-DES	New generation drug eluting stent
NSTEMI	Non-ST elevation myocardial infarction
NO	Nitric oxide
NYHA	New York Heart Association
O-DES	Old generation drug eluting stent
OR	Odds ratio
P2Y12	P2Y purinoceptor 12
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PEA	Proximity Extension Assay
PTCA	Balloon angioplasty
RCT	Randomized controlled trial
RD	Renal dysfunction
RRT	Renal replacement therapy
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCAD	Stable coronary artery disease
SIS	Stable isotope standards
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
ST	Stent thrombosis
STEMI	ST-elevation myocardial infarction
UA	Unstable angina pectoris
SIS	Stable isotope standards
SD	Standard deviation
TNF	Tumor necrosis factor
TNF-R1	Tumor necrosis factor receptor 1
TNF-R2	Tumor necrosis factor receptor 2
TRAIL-2	Tumor necrosis factor related apoptosis-inducing ligand receptor 2

# 1 INTRODUCTION

## 1.1 BACKGROUND

Renal dysfunction (RD) is a major public health problem with a prevalence of 10-15% in the general population of developed countries <sup>1</sup>. Ischemic heart disease (IHD) is the leading cause of death in patients with RD and cardiovascular (CV) mortality is greater than mortality due to the progression of end-stage renal insufficiency <sup>2</sup>. RD is also common in patients admitted to hospital for acute coronary syndrome <sup>3</sup>, where about one third have reduced renal function. The early stages of RD are usually asymptomatic and symptoms may often first appear together with complications in the later stages of the disease. Due to an ageing population with associated comorbidities and improved treatment regimens of ACS, the prevalence of patients with concomitant RD and coronary artery disease (CAD) is increasing <sup>4 5</sup>. Patients with RD and concomitant IHD not only have a poor prognosis, they also suffer from increased risk of bleeding, systemic drug toxicity, infection and adverse effects of interventions used to prevent or treat the condition <sup>6-10</sup>.

Very few randomized cardiovascular trials have included patients with RD and many recommendations concerning patients with RD and IHD are based on extrapolation of data from the general population <sup>11,12</sup>, leading to a gap in evidence-based treatment regimens for these patients. This has important treatment implications, as measures directed at preventing the progression of RD may also prevent cardiovascular morbidity and mortality. Due to a lack of knowledge of how to treat patients with concomitant RD and IHD, further evaluations of therapies in clinical practice and associated outcomes from real-world registries are important.

## 1.2 DEFINITION AND STAGING OF KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as pathology of the kidney structure or altered kidney function for a period of more than 3 months. According to the Kidney Disease: Improving Global Outcomes (KDIGO) <sup>13</sup> guidelines, the definition of CKD includes patients with evidence of kidney damage (albuminuria with an albumin:creatinine ratio (ACR) > 3 mg/mmol), hematuria, tubular dysfunction associated electrolyte abnormalities, histological abnormalities, structural damage detected by imaging modalities, prior kidney transplantation or patients with glomerular filtration rate (GFR) of less than 60 ml/min/1.73m<sup>2</sup> on at least two occasions 90 days apart. CKD is classified based on the GFR and the level of proteinuria and helps to risk-stratify patients. Patients are classified as G1-G5, based on the GFR, and A1-A3 based on the ACR (**Figure 1**).

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories, description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ), description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk;  
orange, high risk; red, very high risk.

**Figure 1.** Classification of Chronic Kidney Disease<sup>14</sup> based on GFR (glomerular filtration rate) categories G1-G5 and ACR (albumin:creatinine ratio) categories A1-A3. Moderate risk (yellow) – 73% of patients with CKD, High risk (orange) – 18% of patients with CKD, Very high risk (red) – 9% of patients with CKD.

*Reproduced with permission from Elsevier<sup>15</sup>.*

### 1.3 ASSESSMENT OF KIDNEY FUNCTION

Creatinine measurement is perhaps the easiest way to assess renal function but it is often not a reliable method to use since age, muscle mass, nutrition status, obesity and hydration may affect creatinine levels. An overestimation of renal function may occur in, for example, the elderly, females or individuals with low body weight. GFR is the key indicator of renal function and the most accurate method to obtain GFR is to inject a non-metabolizable and non-absorbent exogenous markers such as inulin or ioexhol and subsequent concentration measurement in the urine or plasma. In clinical practice this may, however, often prove to be impractical, time-ineffective and in many clinical situations the precise knowledge of GFR is not always necessary.

Various mathematical equations that use serum creatinine and combinations of age, sex, race and weight have been developed to obtain estimated GFR (eGFR). A number of recognized and well-validated formulae including the *Chronic Kidney Disease Epidemiology* (CKD-EPI) equation<sup>14</sup>, the *Modification of Diet in Renal Disease* (MDRD) study equations<sup>16, 17</sup> and

the *Cockcroft-Gault* equation (CG)<sup>18</sup> are often utilized. The CG equation was introduced prior to the use of standardized creatinine assays and is in contrast to MDRD and CKD-EPI, not adapted for use with creatinine values traceable to standardized reference materials. In contrast to CKD-EPI and MDRD, CG includes weight but not race and eGFR is expressed in ml/min which is not normalized to body surface area of 1.73m<sup>2</sup>.

In a study of 117 healthy individuals that underwent routine kidney donor evaluation, the ability of the MDRD and the CG equation was evaluated to predict GFR assessed by (125)I-iothalamate or (99m)Tc-diethylenetriamine-pentaacetic acid (DTPA)<sup>19</sup>. The study found that the MDRD equation underestimates GFR, whereas the CG equation overestimates GFR in people with normal renal function. In order to provide a more accurate estimate of GFR in patients with normal or only mildly reduced GFR, the CKD-EPI equation was developed and was associated with less bias, improved precision, and greater accuracy compared to the MDRD study<sup>14</sup>. In a meta-analysis that included 1 million adults from the general population as well as high risk cohorts, CKD-EPI versus MDRD equations resulted in a lower prevalence of CKD but a more accurate risk prediction for adverse outcomes was found<sup>20</sup>.

The main goal of using eGFR is to diagnose and classify CKD, to adjust dosage of medication, and to predict adverse prognosis. *The Kidney Disease: Improving Global Outcomes*<sup>13 13</sup> and National Institute for Health Excellence recommend using the creatinine derived CKD-EPI equation, since it gives the most accurate renal function estimate compared to GFR<sup>21</sup>. Even though in 2010 the Food and Drug Administration changed the guidance for the industry to allow MDRD estimated GFR for drug dosing<sup>22</sup>, CG estimated renal dose adjustment is widely used for the purpose of dose adjustments.

However, for prognosis, the choice of eGFR equation is less clear. In patients with heart failure, CG predicted mortality better than CKD-EPI and MDRD<sup>23</sup> and in another study CG versus MDRD was superior in identifying more patients with MI at higher risk<sup>24</sup>. In another study of patients with cardio-vascular disease (CVD), CKD-EPI as compared to MDRD more often diagnosed RD, and reclassified patients to a higher risk group and more accurate risk stratification<sup>25</sup>.

Some observational studies define RD according to *International Classification of Diseases* (ICD) codes for renal replacement therapy initiation or other related conditions such as hospitalization for RD<sup>26, 27</sup>. The use of ICD codes instead of eGFR will most often underestimate RD prevalence<sup>28</sup> and offers no possibility to assess risks associated with RD prior to renal replacement therapy.

In many ACS studies, the baseline creatinine value at the time of ACS presentation is often used to assess the GFR and the presence of RD. However, KDIGO<sup>13</sup> guidelines recommend creatinine to be measured when patients are in a stable condition in order to avoid the issue that kidney function instead reflects the ischemic severity of ACS. This is a limitation to observational studies in general as well as to this thesis, even though SWEDEHEART instructions for data collection recommend clinicians to use a creatinine value that best reflects the patients underlying condition. Documentation of duration is usually not available in epidemiologic studies. Since an eGFR below 60 ml/min/1.73m<sup>2</sup> is found to be closely



associated with increased risk of death even in the absence of albuminuria <sup>28, 29</sup>, an eGFR below 60 mL/min/1.73 m<sup>2</sup> is often defined as having CKD in routine clinical practice.

#### 1.4 PROGNOSIS OF RD PATIENTS IN THE GENERAL- AND CVD POPULATION

Renal origin of CV was first suggested by Richard Bright as early as in 1836. This has been confirmed by multiple epidemiological studies, where it is evident that patients with RD are at a high risk of developing CVD <sup>30</sup>. CVD, and more specifically IHD is a major cause of death and morbidity in patients with RD. In a population-based study of more than 1 million individuals, the adjusted Hazard Ratio (HR) for death increased with the rate of eGFR in an inverse fashion; HR 1.2, 95% confidence interval (CI) (1.1-1.2) for eGFR of 45–59 mL/min/1.73 m<sup>2</sup>, HR 1.8, 95% CI (1.7-1.9) for eGFR of 30–44 mL/min/1.73 m<sup>2</sup>, HR 3.2, 95% CI (3.1-3.4) for eGFR of 15–29 mL/min/1.73 m<sup>2</sup> and HR 5.9, 95% CI (5.4-6.5) for eGFR <15 mL/min/1.73 m<sup>2</sup>, respectively and the risk of cardiovascular events followed the same trend <sup>2</sup>. In a meta-analysis of 10 cohorts including more than 200,000 patients, eGFR as well as albuminuria were closely associated with the risk of all-cause mortality <sup>29</sup>. For every 10 mL/min/1.73 m<sup>2</sup> reduction in eGFR, the risk for cardiovascular mortality is increased by 5% <sup>31</sup>. Albuminuria has an independent and additive effect on reduced eGFR regarding the risk of cardiovascular mortality <sup>32</sup>.

Patients with end-stage renal disease (ESRD) and the early stages RD are associated with high rates of morbidity, despite similar rates of comorbidities, which may imply that complications of ESRD are evident before the onset of ESRD <sup>33</sup>. According to data from the Swedish Renal Registry the overall 5-year patient survival rate for patients on renal replacement therapy (RRT) is 23.1% whereas the 5-year survival rate of after kidney transplantation is about 85% <sup>34</sup>.

There is a strong relationship between RD, CV outcomes and mortality in patients with ACS <sup>10 3</sup>. The prognosis of RRT patients suffering from ACS is extremely poor, where 1-year survival rates of 41% have been described<sup>35</sup>.

#### 1.5 PROGNOSIS FOLLOWING CABG

Renal function is incorporated in the *European System for Cardiac Operative Risk Evaluation* (EuroSCORE) <sup>36</sup>, and several studies demonstrate that RD is associated with worse outcomes following Coronary artery bypass grafting (CABG) <sup>37, 38</sup>. Even mild renal dysfunction defined as Creatinine >130 µmol/L, is an independent risk factor for adverse outcome after CABG <sup>39</sup>. Patients with RD are at risk of developing acute kidney injury and may require RRT temporary or permanently following surgery. In particular, in patients with RD and history of diabetes, peripheral artery disease <sup>40</sup> and RRT there is a high risk of in-hospital complications and mortality <sup>41</sup>.

## **1.6 PROGNOSIS AFTER PCI**

The risk of complications, morbidity and mortality following percutaneous coronary intervention (PCI) is increased in CAD patients with RD as compared to patients with normal renal function<sup>10, 42</sup>. Even mild RD defined as Creatinine 97-130  $\mu\text{mol/L}$  predicts adverse outcome following PCI<sup>43</sup>. The use of contrast media during PCI is a common cause of acute kidney injury and patients with RD often have comorbidities that may increase the risk of periprocedural ischemic and bleeding events. Since RD defines a high risk population PCI is frequently underused in patients with renal dysfunction<sup>2</sup>, even though data support that patients with renal RD and multivessel disease that undergo PCI have better survival compared to medical therapy<sup>44</sup>.

## **1.7 PCI VERSUS CABG IN PATIENTS WITH RD**

Patients with RD are often excluded from randomized controlled trials (RCT) on myocardial revascularization and current data are mostly based on observational studies and post-hoc analyses from randomized trials. Few studies have specifically compared outcomes with PCI versus CABG in patients with moderate to severe RD.

CABG versus PCI in patients with moderate RD are associated with an increased risk of perioperative and short-term mortality (1 year), but lower medium-to-long-term mortality after CABG compared with PCI<sup>45 46</sup>. However, observational 5-year data from the United States Renal Data System of 21,981 patients with ESRD and multivessel coronary disease showed that CABG versus PCI was associated with significantly lower risks for death (HR 0.87, 95% CI (0.84-0.90)) and the composite of death or MI (HR 0.88, 95% CI (0.86-0.91))<sup>47</sup>. In the randomized Arterial Revascularization Therapies Study<sup>48</sup> *post hoc* analysis of patients with RD (25% of 1,205 patients) defined as estimated creatinine clearance  $\leq 60$  mL/min, CABG and multivessel PCI with bare metal stents (BMS) in patients with stable angina were compared. At 3 years of follow-up, no difference for the primary endpoint of death, MI or stroke (19% vs. 17%; HR 0.93, 95% CI (0.54–1.61)) was observed, but CABG versus PCI showed a lower risk of repeat revascularization (25% vs. 8%; HR 0.28, 95% CI (0.14–0.54))<sup>48</sup>. Similar results were also observed at 5 years follow-up, where higher rates of repeat revascularization with PCI compared to CABG were noted<sup>49</sup>. In the non-randomized ARTS II study<sup>50</sup>, drug eluting stents (DES) with sirolimus were compared with BMS and CABG. The 5-year results showed that the event-free survival rate of the combined outcome (Death, MI or stroke) was 87.1% in DES group, versus 86.0% ( $p = 0.1$ ) and 81.9% ( $p = 0.007$ ) in the CABG and BMS cohorts, respectively. However, data on patients with RD were not available.

In the CKD substudy of *Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery* (SYNTAX)<sup>51</sup>, the 5-year results of patients randomized to either sirolimus DES or CABG were studied and compared to CABG, PCI showed significantly higher rates of the combined endpoint (42.1% vs. 31.5%,  $p=0.019$ ), mainly driven by repeat revascularization (21.9% vs. 8.9%,  $p=0.004$ ) and all-cause mortality (26.7% vs. 21.2%,  $p=0.14$ ). The results of the aforementioned studies may be less applicable

in current clinical practice due to the emerging use of the newer generation of DES. Results from the randomized *Bypass Surgery Versus Everolimus-Eluting Stent Implantation Multivessel Coronary Artery Disease* (BEST) study <sup>52</sup> showed that PCI with the newer generation of DES (everolimus) versus CABG, was associated with an increased risk of repeat revascularization and spontaneous myocardial infarction but without any difference in death, however RD was not considered in the study. In a retrospective propensity-score matched study of 5,920 patients with eGFR<60, CABG was associated with higher short-term risk of death, stroke, and repeat revascularization, whereas PCI with everolimus-eluting stents showed higher risk of long-term risk of repeat revascularization MI but not death <sup>53</sup>. Moreover, the CKD subgroup analysis of the multicenter randomized *Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization* trial <sup>54</sup> (EXCEL), showed that there were no significant differences in the rates of the composite outcome (death, MI or stroke) after PCI with the newer generation of DES versus CABG, 23.4% versus 18.1% respectively; HR 1.25; 95% CI (0.79 to 1.98).

Before the results from the ongoing RCT on optimal long-term revascularization strategies in patients with stress-induced ischemia in the *International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Disease* <sup>55 56</sup>, the general condition, life expectancy, the least invasive appropriate method and frailty must be considered when selecting the most appropriate revascularization strategy.

## 1.8 RISK FACTORS AND PATHOLOGICAL MECHANISMS IN PATIENTS WITH RD AND CVD

The mechanisms involved in the interplay between RD and CAD are numerous and not yet fully understood. One possible explanation is that patients with RD that experience MI, are more likely to have co-existence of other predictors of adverse outcomes like frailty factors, age, hypotension, and lower body weight. These factors may serve as residual confounding in various studies despite advanced statistical adjustments. Moreover, it is possible that an adverse outcome such as death or cardiovascular mortality in the presence of RD may instead serve as an indicator of a more severe ACS <sup>57</sup>. However, there are numerous risk factors associated with having RD.

## 1.9 CORONARY ANATOMY AND CALCIFICATION

It has been postulated that RD accelerates atherosclerosis and coronary artery calcification through processes associated with both traditional CVD risk factors (diabetes, hypertension, dyslipidemia, smoking status, sex and prior history of MI) and non-traditional risk factors for CVD, such as bone and mineral disorders as well as systemic inflammation<sup>12</sup>. RD is associated with increased inflammatory activity, which may increase the risk of plaque rupture and a more pro-thrombotic state, which may increase the risk of MI when a plaque rupture occurs <sup>58, 59</sup>.

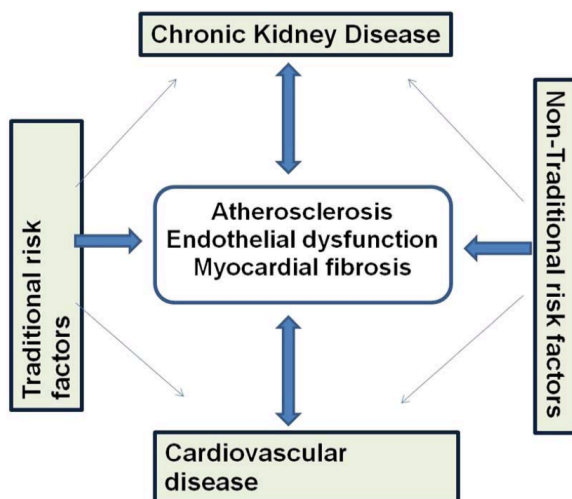
Patients with a moderate to severe RD have a higher prevalence of CAD and a higher risk of obstructive CAD <sup>60</sup>. However, less is known about the much larger proportion of patients with mild renal impairment. In a study of 261 subjects undergoing coronary angiography, a GFR value of <60 ml/min significantly increased the coronary obstructive burden of CAD compared to subjects with GFR > 60ml/min <sup>61</sup>. Preceding studies have shown that RD is significantly and independently associated with CAD severity based on angiogram findings <sup>62-61</sup>. Using noninvasive diagnostic imaging with coronary computed tomographic angiography, inverse significant associations between RD and increased coronary calcium scores and higher rates of coronary calcified plaques in proximal major coronary vessels have been described, when factors such as severity of disease and comorbidity are not considered <sup>63, 64</sup>

It is therefore possible that severity of CAD and subsequent revascularization <sup>65-66, 67</sup> would lie in the causal pathway between renal impairment and poor patient outcomes.

## **1.10 TRADITIONAL AND NON-TRADITIONAL RISK FACTORS**

The traditional risk factors for CVD as initially described by the FRAMINGHAM study <sup>68</sup> are increasing age, hypertension, dyslipidemia diabetes, smoking and obesity. These risk factors are highly prevalent in patients with RD <sup>69-70</sup> and are more frequent with decreasing renal function <sup>71</sup>. The increased incidence of CVD in patients with RD is not proportional and fully accounted for by the higher prevalence of traditional risk factors in these patients. When adjusting for the presence of traditional risk factors, the risk of CVD still remains high and the presence of RD is therefore often described as an independent risk factor <sup>72</sup>. Therefore, many studies have focused on other non-traditional or ‘novel’ risk factors unique to CKD.

Non-traditional risk factors are more prevalent in patients with RD than in the general population and increase with declining renal function. These uremia specific factors are associated with CVD and include, amongst others, albuminuria <sup>73, 74</sup>, abnormalities in bone and mineral metabolism<sup>75, 76</sup>, anemia <sup>77</sup>, hyperhomocysteinemia<sup>78</sup>, increased circulating levels of inflammatory markers <sup>70, 79</sup>, and endothelial dysfunction<sup>80</sup>. There is a complex interplay between traditional and non-traditional risk factors (see **Figure 2**) and it has been described that there is an additive effect that increases the progression of atherosclerosis and RD <sup>81</sup>.



**Figure 2.** The interplay between traditional and non-traditional risk factors and cardiovascular disease and chronic kidney disease.<sup>82</sup>

*\*With permission from BMJ Heart Asia.*

### 1.11 MANAGEMENT OF CAD IN PATIENTS WITH RD

Patients with RD may require drug dose adjustments and are at risk of drug-related adverse effects. The treatment regimens used for established CAD and ACS used in patients with normal renal function (e.g., revascularization and risk factor goal achievements) usually have similar benefits in patients with RD<sup>83</sup>, even though there is a gap in evidence since patients with RD are often excluded in major clinical trials in cardiology<sup>84</sup>. Several studies have shown that patients with RD and ACS are at high risk of underuse of evidence-based guideline therapies, less frequent utilization of coronary angiography, revascularization and standard medical therapy (angiotensin-converting enzyme inhibitors, beta blockers)<sup>42 3, 85</sup>.

### 1.12 ANTITHROMBOTIC THERAPY

According to the *European Society of Cardiology* (ESC) guidelines, invasive revascularization is considered the gold standard in the management of ACS patients due to associated reductions in death and MI<sup>86</sup>. In patients undergoing PCI in the management of ACS, the aim of antithrombotic treatment with P2Y<sub>12</sub>-receptor inhibition is not only to reduce ischemic outcomes but also to prevent stent-related complications. In patients with RD, not only is the risk of recurrent cardiovascular events after an ACS high, they also suffer from comorbidities, frailty and higher risk of bleeding. Patients with both ACS and RD are underrepresented or excluded from major clinical trials of antithrombotic treatment regimens which leads to an evidence gap regarding different antithrombotic therapies.

### 1.13 CLOPIDOGREL

Clopidogrel is a prodrug that requires a two-step activation by different Cytochromes P450 (CYP450) enzymes for conversion of the active metabolite that irreversibly binds and inhibits the P2Y purinoceptor 12 (P2Y<sub>12</sub>) subtype of the adenosine diphosphate (ADP) receptor in thrombocytes. Inhibition plays an important role in the platelet activation and cross-linking by the protein fibrin. Three large placebo-controlled clinical trials have evaluated clopidogrel for the secondary prevention in ACS; clopidogrel in Unstable Angina to Prevent Recurrent Events<sup>87 88</sup>, *Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction 28* (CLARITY-TIMI 28)<sup>89</sup> and the *Clopidogrel for the Reduction of Events During Observation* (CREDO) trial that evaluated timing and administration issues in PCI-treated patients<sup>90</sup>. Almost all of these primary studies lack data on patients with RD.

Secondary analyses of CURE<sup>88</sup> showed beneficial effects of adding clopidogrel to standard treatment in non-ST elevation ACS in all three tertiles of renal function (lower third tertile, HR 0.89 (95% CI, 0.76–1.05); medium third, HR 0.68 (95% CI, 0.56–0.84); upper third HR 0.74 (95% CI, 0.60–0.93) but at the cost of increased minor-, major- and life-threatening bleeds. In the CREDO secondary analysis paper<sup>91</sup>, the investigators concluded that clopidogrel versus placebo in mild or moderate renal dysfunction did not reduce ischemic outcomes (death, MI or stroke) and higher rates of minor- and major bleeds were observed. In CLARITY sub-study of patients with eGFR<60ml/min/m<sup>2</sup>, clopidogrel on top of aspirin (ASA) versus ASA single therapy, did not significantly reduce the risk of the primary combined ischemic outcome (OR 1.0, 95% CI (0.8–1.3)) whereas the risk of minor- and major bleeds was increased (OR 1.6, 95% CI (0.9–3.2))<sup>92</sup>. There are, however, limited data available on clopidogrel in patients with moderate- and severe renal dysfunction.

### 1.14 PRASUGREL

Prasugrel is a thienopyridine prodrug metabolized and converted by esterase enzymes in the intestine and serum via CYP450-mediated oxidation to the pharmacologically active metabolite. Prasugrel inhibits ADP-induced platelet aggregation more rapidly and to a greater extent than administration of clopidogrel<sup>93</sup>. In the *trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction 38* (TRITON-TIMI 38)<sup>93</sup> that compared prasugrel versus clopidogrel in invasively managed ACS patients, a significant reduction in primary combined endpoint (cardiovascular mortality, non-fatal MI, or non-fatal cardiovascular event) (HR 0.81; 95% CI (0.73-0.90) was found. On the other hand, there was also a significant increase in major bleeding (HR 1.32 (95% CI 1.03-1.68)) and no significant difference of death between treatment arms (HR 0.95; (95% CI 0.78-1.16)) was found. In the two renal function groups that were described (CrCl>=60 ml/min), the benefits of prasugrel were similar but with higher event rates in patients with CrCl<60ml/min.

In the TRILOGY ACS (*TaRgeted platelet Inhibition to cLarify the Optimal strateGY to medically manage Acute Coronary Syndromes*)<sup>57</sup> trial, no risk reduction of a similar primary endpoint with prasugrel in patients with medically managed ACS patients was found and described three renal function groups (CrCl>60 ml/min (HR 0.88, 95% CI ( 0.73-1.06);

CrCl=30-60 ml/min (HR 1.14, 95% CI ( 0.88-1.49) and CrCl<30 ml/min (HR 0.68, 95% CI ( 0.33-1.41).

In the *Program for a European Traffic with Highest Efficiency and Unprecedented Safety* (PROMETHEUS)<sup>94</sup> multicenter observational study that compared prasugrel versus clopidogrel in PCI-managed ACS patients, the 1-year composite outcome (death, MI, stroke, or unplanned revascularization) showed lower rates with prasugrel versus clopidogrel in CKD (18.3% vs. 26.5%;  $p < 0.001$ ) and non-CKD (10.9% vs. 17.9%;  $p < 0.001$ ) patients. These associations were, however, attenuated after propensity stratification and the rates of reinfarction in patients with CKD at 1 year were not significantly lower in prasugrel-treated versus clopidogrel-treated patients. In a recent registry study utilizing the *REgistry of New Antiplatelets in patients with Myocardial Infarction* (RENAMI) and *Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome* (BLEEMACS), 2,490 patients with ACS and eGFR<60, showed significantly lower rates of reinfarction (HR 0.07, 95% CI 0.01–0.54;  $P=0.01$ ) and death (HR 0.34, 95% CI 0.13–0.88;  $P=0.026$ ) at 1-year as compared to clopidogrel, but without higher rates of bleeds (HR 0.88, 95% CI 0.41–1.9;  $P=0.75$ )<sup>95</sup>. The number of patients was, however, small and there were no significant differences in clopidogrel versus treatment with potent P2Y<sub>12</sub> inhibitors regarding the efficacy outcomes in the subset of patients with eGFR<30<sup>95</sup>.

## 1.15 TICAGRELOR

Ticagrelor is, in contrast to prasugrel and clopidogrel, not a thienopyridine, but belongs to the cyclopentyl-triazolo-pyrimides class of P2Y<sub>12</sub> receptor inhibitors. Ticagrelor is a highly selective and reversible antagonist for the P2Y<sub>12</sub>-receptor. Additional properties of ticagrelor include the inhibition of P2Y<sub>12</sub> receptors in vascular smooth muscle cells leading to vasodilatation and the ability to augment the effects of endogenous adenosine in cardiac myocytes which may play a role in coronary blood flow<sup>96 97</sup>.

In the PLATO (*PLAtelet inhibition and patient Outcomes*)<sup>98</sup> trial, comparing ticagrelor and clopidogrel in patients with ACS, CKD defined as creatinine clearance below 60 mL/min was one of the enrichment criteria for inclusion. Overall, ticagrelor as compared to clopidogrel, significantly reduced the incidence of the primary endpoint (cardiovascular death, non-fatal MI or non-fatal stroke). In the subgroup of patients with available serum creatinine on admission (n=15,202), ticagrelor resulted in a greater risk reduction of the primary endpoint in patients with reduced creatinine clearance (CrCl) compared to patients with normal renal function (CrCl>60ml/min) (HR 0.77, 95% CI 0.65-0.90 versus HR 0.90, 95% CI 0.79-1.02), but with no significant interaction. Even though CKD was associated with an overall higher bleeding risk in PLATO, CKD patients treated with ticagrelor did not have a higher relative risk of PLATO-defined major bleeds as compared to non-CKD patients<sup>99</sup>.

## **1.16 INTERVENTIONAL TREATMENT WITH PCI**

PCI is a collective term used for both non-stent coronary artery procedures such as balloon angioplasty (PTCA) or atherectomy as well as stent interventions with stent implantations. The introduction of PTCA in the 1970s provided a less invasive revascularization treatment alternative to CABG. However, complications with recoil, coronary dissection, angiographic restenosis and recurrent angina and rates of repeat revascularization up to 30% within the first year of balloon angioplasty were described<sup>100 101</sup>.

## **1.17 BARE METAL STENTS**

BMS were developed to prevent abrupt artery closure due to recoil or dissection following PTCA. BMS versus PTCA significantly reduced the rates of acute closure early in the stent era and stenting became the standard of care for PCI<sup>102</sup>. Despite the advantages of stenting with BMS, the iatrogenic intimal injury from stenting often induced neointimal hyperplasia and subsequent in-stent restenosis requiring repeat revascularization<sup>103</sup>. This subsequently led to the development of drug-eluting stents (DES) coated with antiproliferative agents.

## **1.18 OLDER GENERATION DRUG-ELUTING STENTS**

The components of a DES are a metallic stent, a polymer coating, and an anti-restenotic drug that is released over a period of weeks to months after stent implantation to reduce the local proliferative healing response. The first generation DES are often referred to as the older generation of DES (o-DES) and the most commonly used drug components are:

- **Sirolimus**

Sirolimus-eluting stents were first introduced in the first-generation DES and it is an antibiotic with immunosuppressive and antiproliferative properties that inhibits cell cycle regulation. Sirolimus is also found in polymer-free and bio-absorbable polymer devices.

- **Paclitaxel**

Paclitaxel-eluting stents were also found in the first-generation of DES developed to prevent the proliferation of smooth muscle observed in in-stent restenosis. Paclitaxel is an antineoplastic drug that interferes with microtubules function in cell division.

The lower rates of in-stent restenosis of DES compared to BMS result from the inhibition of in-stent neointimal hyperplasia<sup>104</sup>. Randomized trials have demonstrated that DES versus BMS have lower rates of re-stenosis and need for revascularization<sup>103 105</sup>. However, concerns were raised since several studies indicated that DES was associated with incomplete neointimal coverage and increased risks of stent thrombosis (ST)<sup>106-109</sup>.



## 1.19 NEWER GENERATION DRUG-ELUTING STENTS

Despite the advantages of the first generation of DES (sirolimus and paclitaxel), increased rates of very late ST were observed <sup>110</sup>. The second or newer generation of DES (n-DES) with a thinner strut design, more biocompatible polymers associated with lower local inflammation, have resulted in lower risk of ST compared to first generation DES and BMS <sup>111-113</sup>.

Examples of common n-DES are:

- **Everolimus**

This is a derivate of sirolimus designed to prevent in-stent restenosis by rapid drug absorption into the coronary arteries due to lipophilic properties. Everolimus is used in durable polymer (cobalt chromium or platinum chromium) and bioabsorbable polymer DES (bioresorbable polymer on a platinum chromium platform) and considered a n-DES.

- **Zotarolimus**

This is also a lipophilic derivative of sirolimus with short-acting drug properties. There are several versions of zotarolimus-eluting stents, e.g. the *Endeavor* and the *Resolute* Zotarolimus stents. Endeavor, the first generation of zotarolimus is sometimes considered an o-DES<sup>114, 115</sup> and has a drug release within weeks, whereas resolute has an extended drug delivery over several months.

- **Biolimus** is a highly lipophilic sirolimus analogue found in bioresorbable polymer stents.

With regards to clinical outcomes, DES have similar rates of death and MI to BMS even though study results are divergent. Some studies report that first generation DES (sirolimus and paclitaxel) versus BMS are associated with lower rates of repeat revascularization <sup>116, 117</sup> but without any significantly different risk of long-term safety end points (death, MI or cardiac death) <sup>118, 119</sup> when on-label indications (de novo stenosis and not restenosis or grafts) are applied <sup>116 117, 120</sup>. However, observational studies with unrestricted use of stenting that compared first generation DES versus BMS have found lower rates of death or MI <sup>121, 122</sup>. It is possible that the observed adverse effects of BMS may be explained by selection bias and residual confounding due to frailty and underlying comorbidities.

A meta-analysis of everolimus versus BMS found a significant reduction of cardiac death (HR 0.67, 95% CI 0.49-0.91), and MI (HR 0.71, 95% CI 0.55-0.92) as well as definite or probable ST (HR 0.48, 95% CI 0.31-0.73) <sup>123</sup>. In another meta-analysis comparing contemporary DES with BMS, the risk of cardiac death and the risk of probable and definite ST were lower with the use of second-generation DES <sup>124</sup>.

This is, however, in contrast to evidence from randomized *Norwegian Coronary Stent* <sup>125</sup> (NORSTENT) trial, where 9,012 patients with stable or unstable CAD were randomly

assigned to PCI with contemporary n-DES (everolimus and zotarolimus) or BMS. At 6 years follow-up, there was no difference in the rates of the primary outcome (composite of death or MI) between the stent groups (16.6% versus 17.1%, respectively; HR 0.98, 95% CI (0.88-1.09)). The rates of ST were lower with n-DES versus BMS (0.8% and 1.2%, respectively ( $p = 0.0498$ ))<sup>125</sup>.

## **1.20 CHALLENGES IN RD AND CAD**

Patients with RD and concomitant CAD differ from CAD patients without RD, in terms of higher risk profile for adverse outcomes and complications, but the reasons for this are not yet fully understood. Moreover, there is a lack of large multi-center studies that are able to capture the whole spectrum of RD in unselected patients with a known CAD.

Due to the lack of large-scale RCT studies in the specific patient population of patients with concomitant RD and CAD, clinical decision-making may often prove to be difficult in general. Specifically, studies that evaluate treatment regimens in terms of optimal choice of stent type and use of antithrombotic strategies, in patients with RD are needed.

It is also possible that the underlying mechanism for the less beneficial prognosis in patients with RD and CAD is different from patients with normal renal function. Novel biomarkers can be useful to determine and differentiate targeted treatment with risk profile management at an earlier stage well as assist in understanding the pathological mechanisms involved in MI patients with RD, which is important to identify new treatment targets.

## 2 AIMS

The overall aim of this thesis was to assess the influence of RD on long-term outcomes in patients with CAD and to evaluate different treatment regimens in relation to renal function in patients with CAD. Furthermore, we sought to determine the importance of different biomarkers in predicting RD and long-term outcomes in MI patients.

Specifically, the objectives were:

### **Study I**

To investigate the influence of RD on baseline presentation and long-term outcomes in stable CAD patients undergoing coronary angiography.

### **Study II.**

To evaluate two different antithrombotic treatments (clopidogrel and ticagrelor) and their associations with safety- and efficacy outcomes, in patients treated for acute MI and in relation to renal function.

### **Study III.**

To examine the risk of stent-related outcomes of different types of stents (newer generation drug-eluting- versus bare metal stents) in relation to renal function in patients undergoing percutaneous coronary intervention.

### **Study IV.**

To perform an untargeted study of different biomarkers and their associations with RD, death, reinfarction and hospitalization with heart failure, in patients treated for acute MI.

### 3 THESIS AT A GLANCE

Study	I	II	III	IV
<b>Design</b>	Cohort study	Cohort study	Cohort study	Cohort study
<b>Data source</b>	SWEDHEART, National Patient Registry, Swedish Population Registry	SWEDHEART, National Patient Registry, Swedish Population Registry	SWEDHEART, National Patient Registry, Swedish Population Registry	SWEDHEART, SWEDHEART-BIOBANK, National Patient Registry, Swedish Population Registry
<b>Time of data collection</b>	2005-2010	2010-2013	2007-2013	2008-2014
<b>Study population</b>	Patients undergoing coronary angiography due to stable CAD	MI patients discharged alive and treated with clopidogrel or ticagrelor in addition to ASA	Patients treated with PCI-stenting with BMS or n-DES	Discharged MI survivors
<b>Numbers included in analyses</b>	N=45,348	N=45,206	N=92,994	N=1,098
<b>Follow-up time</b>	Up to 6 years post-coronary angiography	During hospitalization and 1 year post-discharge	1 year post-coronary stenting	Up to 6 years post-discharge
<b>Outcomes</b>	Death, reinfarction or hospitalization with stroke or heart failure	Death, reinfarction or hospitalization stroke and in- and out of hospital bleeds	In-stent restenosis and definite stent thrombosis	Death, reinfarction or hospitalization with heart failure
<b>Main statistical analyses</b>	Cox regression	Cox regression, logistic regression and propensity score matching	Cox regression, Fine-Gray regression	Random forests, penalized regression using lasso analysis, cox regression
<b>Conclusion</b>	RD was strongly associated with worse outcome in patients with CAD, independent of traditional CVD risk factors, comorbidities, CAD severity, and subsequent revascularization.	Treatment with ticagrelor versus clopidogrel in patients with MI, was associated with lower risk for the composite of death, MI or stroke and a higher bleeding risk across all strata of eGFR.	Hyperkalemia at admission is associated with in-hospital mortality and hypokalemia is associated with cardiac arrest and new-onset atrial fibrillation in patients admitted with suspected ACS.	In patients with MI, six biomarkers (adrenomedullin, TNF R-1, FABP-4 TRAIL-2, GDF-15 and TNF R-2) with the strongest association with RD, were also among the most important predictors of long-term outcomes.

## 4 METHODS

### 4.1 DATA SOURCES

All studies (**Studies I-IV**) were conducted using data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. The Swedish National Patient Registry<sup>126</sup>, that holds data on discharge diagnoses of all hospital stays in Sweden since 1987 and the Swedish Population Registry<sup>127</sup>, that contains vital status data for all Swedish residents, were merged with the SWEDEHEART registry by using the unique personal identification number of the patients.

### 4.2 SWEDEHEART

SWEDEHEART was formed in 2009 after incorporation of *the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions* (RIKS-HIA), *the Swedish Coronary Angiography and Angioplasty Registry* (SCAAR), *the Swedish Heart Surgery Registry*, and *the Secondary Prevention after Heart Intensive Care Admission* (SEPHIA). In addition, SWEDEHEART also contains the *Cardiogenetic Registry* and the national percutaneous valve device registry *SWENTRY*.

RIKS-HIA started as a regional registry in the early 1990s but became a national registry in 1995 with the addition of SEPHIA in 2005. RIKS-HIA annually enrolls about 18,000 patients hospitalized because of MI and about 100 variables including data on demographics, prior medical history, clinical presentation, laboratory measurements, in-hospital course data, interventional treatment data, diagnosis and medication at discharge, are collected prospectively. Creatinine has been a mandatory variable since 2003. The local treating physicians are instructed to enter a single creatinine value of the hospital stay that can best reflect the patients' underlying kidney function. The coverage of MI hospitalizations in RIKS-HIA is about 96% for patients under the age of 80 years and about 80% for elderly patients<sup>128</sup>. The agreement between hospital records and SWEDEHEART-entered data is high (>95%) and to ensure correctness of recorded registry data and information in medical charts, randomly assigned monitor visits to approximately 25% of participating hospitals take place annually.

The RIKS-HIA registry forms of 2018 are shown in **Figures 3-5**. The present thesis is based on SWEDEHEART data collected from 2005 and onwards.

In the 1990s there were two national coronary interventional registries, a national angioplasty registry and a coronary angiography registry, that in 1998 were merged to develop SCAAR. All Swedish centers (n=29) performing coronary angiographies and PCI participate in the registry and the coverage is 100%. The registry is internet-based and the treating physician reports each procedure via a web-interface directly from the catheterization laboratory. The

registry contains information on more than 150 different variables, including clinical characteristics, angiographic findings, angioplasty procedure results, treatment regimens and complications. The existence of any type of restenosis is mandatory. A detailed interactive presentation of the patients previously treated coronary segments is displayed together with information about date, hospital, and name and dimension of stents used. Since 2005 information about acute occlusions in the specified stents is also collected as well as non-occlusive angiographical stent thrombosis since 2007. SCAAR data were used in **studies I-III** and data from 2005 and onwards were used. The SCAAR registry forms of 2016 and 2018 are shown in **Figures 6-7**.

For **study IV** patients enrolled in SWEDEHEART due to MI hospitalization, provided an additional blood sample that was collected in the SWEDEHEART-biobank that so far includes three Biobanks in Sweden (LUNDHEARTGENE, Uppsala SWEDEHEART-biobank and StockholmHeartBank). This is a unique combined registry and biobank, that enables analyses from blood samples from a cohort of ACS patients that are treated according to standard medical care. The SWEDEHEART cohort is then followed prospectively and by using the personal identification number, data on long-term outcomes such as death, CV death, hospital admission diagnoses can be obtained using other national registries. Data from biomarker analyses from 2008 and onwards were used in **study IV**.

### **4.3 PROTEOMICS AND BIOMARKERS**

The word proteome is a collective term for the combination of genome and protein. The technical development enables analysis of a large number of proteins simultaneously from very small sample volumes. This technique offers unique possibilities to identify new markers and areas of protein regulation pathways.

For this purpose, **study IV** analyzed blood samples from MI patients and utilized two different panels of biomarkers, which are described in detail below. After informed oral and written consent, patients provided blood samples that were taken during fasting during their hospital stay for acute coronary syndrome. Samples were centrifuged usually within 20 minutes, and stored in -80°C until analysis. Biomarkers are listed in **Table 1**.

### **4.4 PROXIMITY EXTENSION ASSAY**

The Proseek® Multiplex CVD I<sup>96x96</sup> chip (Olink Bioscience, Uppsala, Sweden) is a commercially available analysis kit with a panel of 92 selected proteins that are related to CVD. It utilizes the proximity extension assay (PEA) <sup>129, 130</sup> technology in order to simultaneously detect and quantify biomarkers that are coupled by their corresponding antibody pairs using multiplex immunoassay. In brief, 1 µl plasma is required for the analysis of all 92 biomarkers (**Table 1**) For each biomarker, matching antibody pairs that are linked to a unique DNA molecule (proximity probe) bind to the corresponding target protein. This results in probes being in close proximity to each other, which gives rise to hybridization. A DNA-polymerase is then added resulting in an extension of the hybridizing oligonucleotide

so that a new DNA sequence is formed. This specific DNA sequence is then amplified and subsequently quantified using quantitative real-time polymerase chain reaction (PCR) (Fluidigm BioMark™ HD real-time PCR platform). Results are provided as normalized protein expression data (on a log scale), where a high value corresponds to a high protein concentration.

## 4.5 MULTIPLE REACTION MONITORING ASSAY

The multiple reaction monitoring assay (MRM) is an analytical method that can determine and quantify a large number of proteins in a single sample by utilizing mass spectrometry. The technique was developed at Lund University by Marko-Varga and colleagues and has been previously described in detail <sup>131, 132</sup>. Briefly, several steps are involved in the workflow of the spectrometer. Firstly, samples are ionized and vaporized followed by acceleration. The ability for an ion to accelerate and to move forward is proportional to its mass. In addition, the tendency for electromagnets to subsequently deflect the ion is proportional to its charge and the path the ion takes is proportional to its mass-charge ratio. The next step involves detection of the ion sequence that is matched to a known peptide sequence, which in turn is matched to a known protein. A mass spectrometer (TSQ Vantage) was used for the MRM assay, involving 2 acceleration sequences analyzing the mass-to-charge ratio. The nano spray Flex Ion source and EASY n-LC II pump were used. In **study IV**, 87 different proteins (**Figure 8**) that are putative cardiovascular disease markers, including the three isoforms of apolipoprotein E and markers of fibrinolysis and inflammation <sup>131, 132</sup> were quantified. The protein targets from the MRM assay were quantified using concentration-balanced stable isotope standards (SIS).

## 4.6 DEFINITIONS

## 4.7 DEFINITIONS OF OUTCOMES

The diagnosis of the index MI that defined the population in **studies II and IV** was made by the local physicians at the treating hospitals and reported in SWEDEHEART. For **studies I-IV** readmission due to stroke (ICD codes I60 – I64), MI (ICD codes I21 – I22) and heart failure (ICD codes I50, K761, I11) was defined by discharge diagnoses from hospital stays obtained from the National Patient Registry. Only hospital stays with main ICD codes as the main diagnoses were considered. In **study II**, readmission with bleeding was defined as receiving treatment during the hospital stay with at least one of the following conditions: hemorrhagic stroke (I60 – I62), gastrointestinal bleeding (K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922, I850), anemia-related bleeding (D629, D500) or other bleeding (N421, N938, N939, N950, R041, R042, R048, R049, R210, R319, T810, N501A). PCI-related in-hospital bleedings were also studied in **study II** and were defined by information from the SCAAR complication form (**Figure 6**) and included puncture site hematoma, pseudoaneurysm or bleeding leading to prolonged compression, blood transfusion, surgery

or a drop in hemoglobin. In **study III** in-stent RS was considered as the clinically driven and angiographically visual assessment (>50% stenosis) or a fractional flow reserve (FFR)  $\leq 0.80$  in a previously stented segment. Definite ST was defined as either an acute occlusion in the specified stents or as non-occlusive thrombus (**Figure 7c**). Both stent outcomes were reported by the angiographer.

#### 4.8 DEFINITIONS OF CORONARY STENT TYPES

The following definitions of coronary stent types were used in **studies II and III**:

**“newer generation” drug-eluting stents (n-DES):** *Zotarolimus* - Endeavor Resolute, Resolute Integrity (Medtronic Inc., Minneapolis, Minnesota); *Everolimus* - Xience V, Xience Prime, XienceXpedition (Abbott Vascular, Santa Clara, California); *Everolimus* - Promus and Promus Element (Boston Scientific, Natick, Massachusetts), *Biolimus* – Biomatrix (Biosensors, Tokyo, Japan), Nobori (Terumo Corporation, Tokyo, Japan), *Sirolimus* - Osiro (Biotronik, Bulach, Switzerland).

**“first” or “older” drug-eluting stents (o-DES):** *Sirolimus* - Cypher and Cypher Select (Cordis Corporation, Miami, Florida), *Paclitaxel* - Taxus Express and Taxus Liberté (Boston Scientific), and *Zotarolimus* - Endeavor (Medtronic).

**Bare metal stents (BMS):** Multilink Vision, Multilink MiniVision, Multilink 8, and Multilink Flexmaster (Abbott Vascular); Driver, Micro Driver coronary, and Integrity (Medtronic); Liberté (Boston Scientific); Braun Coroflex Blue (B. Braun, Melsungen, Germany); and Chrono stent (CID, Saluggia, Italy).

#### 4.9 DEFINITIONS OF RENAL DYSFUNCTION

In this thesis kidney function was defined by eGFR (in ml/min/1.73m<sup>2</sup>) derived from the creatinine-based CKD-EPI equation;

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

$S_{cr}$  is serum creatinine in  $\mu\text{mol/L}$ ,  
 $\kappa$  is 61.9 for females and 79.6 for males,  
 $\alpha$  is -0.329 for females and -0.411 for males,  
 min indicates the minimum of  $S_{cr}/\kappa$  or 1, and  
 max indicates the maximum of  $S_{cr}/\kappa$  or 1



Creatinine values were extracted from SWEDEHEART as described in **section 4.2**. In this thesis we lacked information on duration of any previous RD and since we only had a single measurement of creatinine, RD was defined by the patients' stratified GFR-strata and not considered as CKD classes as suggested by KDIGO <sup>15</sup>. In **study I**, patients were stratified according to eGFR (mL/min/1.73 m<sup>2</sup>) higher or equal to 90 (eGFR $\geq$ 90, normal function), eGFR  $\geq$ 60 but below 90 (eGFR $\geq$ 60–90, mildly impaired), eGFR  $\geq$ 30 but below 60 (eGFR $\geq$ 30–60, moderate dysfunction), eGFR  $\geq$ 15 but below 30 (eGFR $\geq$ 15–30, severe dysfunction), and eGFR $<$ 15 (eGFR below 15, ESRD). In **study II**, patients were stratified according to following groups of eGFR (mL/min/1.73m<sup>2</sup>); higher or equal to 60 (eGFR $\geq$  60), eGFR  $\geq$ 30 but  $<$ 60 (eGFR30– 60) and eGFR 30 (eGFR $<$ 30). In **study III**, normal kidney function was defined as eGFR (mL/min/1.73 m<sup>2</sup>) higher or equal to 60 (eGFR $>$ 60, normal function); eGFR higher or equal to 30 but below 60 (eGFR 30-60, moderate CKD); eGFR below 30 (eGFR $<$ 30, severe CKD). In **study IV**, CKD was defined as the ordinal outcome of eGFR groups during the hospital stay for MI according to: eGFR higher or equal to (eGFR $>$ 90) defined normal renal function, mild CKD if higher or equal to 60 but below 90 (eGFR 60- $<$ 90), moderate CKD if eGFR  $\geq$ 30 but below 60 (eGFR 30- $<$ 60) and eGFR below 30 defined severe CKD (eGFR $<$ 30).

## 4.10 STUDY POPULATION

### 4.11 STUDY I

We included all consecutive patients registered in SCAAR between 1 January 2005 and 30 December 2010 that underwent an elective coronary angiography due to suspicion of or established stable angina pectoris, silent ischemia or chest pain of uncertain origin. Patients with missing creatinine values were excluded (N=8,027) and in patients that underwent multiple angiographies (N=6,862) only the first index procedure was considered.

### 4.12 STUDY II

All consecutive patients  $>$ 18 years of age discharged alive with a diagnosis of non-ST-elevation MI (NSTEMI) or ST-elevation MI (STEMI) and who received dual antiplatelet therapy (DAPT) with ASA and clopidogrel or ticagrelor, between 1 January 2010 and 31 December 2013 were included. For patients with multiple hospital stays for MI, only the first admission was included and we excluded patients treated with anticoagulant therapy at discharge (n=6,912), patients with missing creatinine (n=4,744) and patients that underwent CABG (n=3423). The study population consisted of 45,206 patients. PCI-related in-hospital bleeding was, only evaluated in a subset of this MI cohort (N=36,392) that had PCI during the admission.

#### **4.13 STUDY III**

All consecutive patients who underwent PCI with coronary stenting recorded in SCAAR between 1 January 2007 and 31 December 2013 were included. We excluded patients with cardiogenic shock (N = 1,461), multiple registry re-entries (n = 64,038), other PCI procedures without stenting (N= 819), patients with missing creatinine (N = 10,215) and patients that received o-DES (N = 10,216). In patients that received several different types of stent during the same procedure (n = 9,567), only one stent was randomly selected and followed over the study period. Analyses were made per patient and based on the type of stent implanted at the first registered procedure and the final study population included 92, 994 individuals.

#### **4.14 STUDY IV**

We included 1,263 patients hospitalized due to ACS and registered in the SWEDEHEART-biobank between 2008 and 2014. Patients with incomplete biomarkers test (N=59), patients without a diagnosis of MI (N=105) and patients with missing creatinine (N=1) were excluded, resulting in a final study population of 1,098 patients.

#### **4.15 STATISTICS**

Continuous variables are described as median and interquartile range (IQR) or mean with standard deviations <sup>83</sup>. Categorical data are expressed as numbers (N) and proportion of patients (%). In all studies, a p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS (IBM Corp., Armonk, NY) version 22.0 <sup>73</sup>, R V.3.3 with package coxme V.2.2–5 (R Foundation for Statistical Computing, Vienna, Austria) (**study II**), SPSS version 23.0 and STATA version 15.1 (StataCorp, College Station, Texas, USA) (**study III**) and SPSS for Mac and R 3.4.0, software package, R-package ranger (**study IV**).

#### **4.16 STUDY I**

The associations between different degrees renal dysfunction and long-term outcomes: all-cause mortality, readmission with MI, stroke and heart failure and the composite of death or MI were assessed. Multivariable Cox proportional hazard models were applied using three models adjusting for baseline characteristics (age, sex, smoking status, body mass index (BMI), hypertension, history of previous MI, CABG, PCI, heart failure, stroke, peripheral artery disease, cancer, dementia, chronic obstructive pulmonary disease, diabetes and hyperlipidemia (model 1). Adjustments for differences in angiogram findings (defined as one-, two-, or three vessel disease or left main stenosis) (model 2) and revascularization with CABG or PCI as a time-dependent variable (model 3) were added to previous models. Interaction analysis for the influence of diabetes and severity of CAD on the association of renal function and the combined outcome was also performed.

## 4.17 STUDY II

Cox proportional hazard models were used to evaluate the associations between ticagrelor as compared to clopidogrel and outcomes (readmission with bleeding, the combined or individual outcome of recurrent MI, stroke or death) at 1 year after hospitalization for MI. The multivariable analyses included the covariates ticagrelor treatment, sex, age, history of diabetes, hypertension, MI, heart failure, peripheral vascular disease, ischemic stroke, chronic obstructive pulmonary disease, cancer within the last 3 years, bleeding, calendar year, Killip class on admission >1, type of MI (STEMI vs NSTEMI), PCI during admission and drugs at discharge. Different sensitivity analyses were conducted and included censoring patients according to the intended treatment duration at discharge, specific calendar time-restricted analyses (2012–2013), adjusting for data on different stent types as well as propensity score matching. Multivariable logistic regression was used to study the secondary outcome of PCI-related in-hospital bleedings, where adjustments for calendar year, sex, age, history of diabetes, hypertension, MI, heart failure, peripheral vascular disease, ischemic stroke, chronic obstructive pulmonary disease, cancer within the last 3 years, bleeding, Killip class on admission >1, type of MI (STEMI vs NSTEMI), concomitant use of unfractionated heparin, IIb/IIIa inhibitor, radial versus femoral access and the use of vascular closure device, medication at discharge ( $\beta$ -blockers, ACE inhibitors or angiotensin receptor blockers and statins).

## 4.18 STUDY III

To study the associations between stent type (n-DES versus BMS) and stent outcomes, Cox proportional hazard analysis was utilized adjusting for demographic, clinical and procedural variables (age, sex, smoking status, BMI, hypertension, history of previous MI, CABG, PCI, heart failure, peripheral artery disease, stroke, peripheral artery disease, cancer, dementia, chronic obstructive lung disease, diabetes and hyperlipidemia, in-hospital course regimes such as acetylsalicylic acid, P2Y<sub>12</sub> receptor inhibitors, glycoprotein IIb/IIIa inhibitors, anticoagulant treatment, year of the index procedure, enrolling center, treated vessel, lesion type, bifurcation lesions, three-vessel or left main disease, indication of PCI, number of stents as well as stent length and stent diameter). Due to few stent events, the multivariate model was reduced to include adjustments of the presence of diabetes, smoking status, previous PCI, age, sex, stent length, stent diameter and P2Y<sub>12</sub> receptor inhibition regarding the outcome stent thrombosis. The effect of stent types at different levels of renal function and stent outcomes was tested using interaction terms. Several sensitivity analyses were also performed where patients that received several different stent types at the same PCI-procedure and patients with prior CABG were excluded. Additionally, a predictive Fine-Gray model was developed to test for death as a competing risk for stent outcomes and a secondary analysis of readmission with MI was conducted.

## **4.19 STUDY IV**

The main analysis of this study of 175 biomarkers and outcomes utilized the random forests method to construct flexible prediction models. Random forests with 5000 trees were formed using default values for all parameters. Variable importance plots are reported for each outcome to illustrate the valuable ability to predict outcomes. Here, 100% variable importance indicates the strongest predictor for the outcome. The random forests model considered all 175 biomarkers simultaneously (crude), but demography (age and gender), baseline characteristics (hypertension, diabetes, current smoking, eGFR<60 as well as previous history of MI, revascularization, heart failure, atrial fibrillation, stroke, peripheral artery disease, chronic obstructive pulmonary disease and cancer) were also adjusted for in a second model. In addition to this model, severity of disease (defined as the presence of STEMI, pulmonary rales or cardiogenic shock at admission) was considered in an additional model. Penalized regression with lasso analysis that considered all biomarkers simultaneously in order to determine which biomarkers provided discriminative information was used as a sensitivity analysis. Missing data were handled using simple imputation with age and gender as predictors. Cox proportional hazard analysis was used to describe the unadjusted associations of biomarker expression and outcomes (death, readmission because of MI and heart failure).

## **4.20 ETHICAL CONSIDERATIONS**

Patients received information about their participation in the SWEDEHEART registry during their hospital stay and had the possibility to opt out. Data were analyzed on a group level, thus limiting the possibility of results to be linked back to an individual patient. Written and oral informed consent was acquired before enrolment in **study IV** and patients that provided blood samples followed standard medical care. All studies were approved by the regional ethical review board in Stockholm and conducted in accordance with the declaration of Helsinki.

## SWEDEHEART – 2018

PatientID:

START – RIKSHIA (1/2)

(\* = obligatorisk)

<b>Överflyttad patient*</b>					
Överflyttad från	0 Nej	1 Omdirigerad ambulans	2 Annat sjukhus	3 Annan vårdenhet inom sjukhuset	4 Ej registrerande enhet
Ange sjukhus /enhet (om 1-4)					
<b>Beslutsgrundande EKG och ankomststatus*</b>					
EKG rytm	1 Sinus	2 Förmaksflimmer-/fladder			8 Övrigt
EKG QRS	1 Normalt	2 Pacemaker	3 Vänster-grenblock	4 Patol Q-våg	5 Höger-grenblock
Vänstergrenblock	0 Tidigare känt	1 Ej tidigare känt			
EKG STT	1 Normalt	2 ST-höjning	3 ST-sänkning	4 Patologisk T-våg	8 Övrigt
Hjärtfrekvens	/min				
Blodtryck Syst/diast	/				
Lungrassel	0 Nej	1 Basala rassel	2 Mer än halva lungorna		3 Lungödem
Cardiogen chock vid ankomst	0 Nej	1 Ja			
<b>Prehospitala uppgifter*</b>					
Intagningsorsak	1 Bröstmärta	2 Dyspné	3 Cirkulationsstillestånd		8 Övrigt
Symtomdebut	Datum		KI		
Ambulans	0 Nej	1 Ja, till Akuten		2 Ja, till HIA/PCI-lab	
Prehospitalt EKG Tidpunkt	Datum		KI		
HLR före sjukhus	0 Nej	1 Ja			
Prehospital trombolys	0 Nej	1 Ja			
Preh trombolys läkemedel				3 Rapilysin	4 Metalyse
Preh trombolys tidpunkt	Datum		KI		
<b>Ankomstuppgifter*</b>					
Ankomst till akuten	Datum		KI		
Avresa till PCI-sjukhus	0 Nej	1 Ja			
HIA/AVD/PCI-lab	Datum		KI		
<b>Klinisk bakgrund*</b>					
Längd	_____ cm				
Vikt	_____ kg				
Sysselsättning	1 Arbete	2 Sjukskrivning /sjuksättning	3 Arbetslöshet	4 Ålderspensionär	5 Studerar/Övrigt
<b>Risikfaktorer</b>					
Rökning*	0 Aldrig rökare		1 Ex rökare > 1 mån		2 Rökare
Snusning*	0 Aldrig varit snusare		1 Ex snusare > 1 mån		2 Snusare
Skörhet	1 Mycket vital	2 Vital	3 Klarar sig bra	4 Sårbar	5 Lindrigt skör
	6 Måttligt skör	7 Allvarligt skör	8 Mycket allvarligt skör	9 Terminalt sjuk	

Figure 3A. RIKS-HIA registry form. Data collected on admission.

## SWEDEHEART – 2018

PatientID:

START – RIKSHIA (2/2)

<b>Tidigare hjärtsjukdom*</b>					
Tidigare hjärtinfarkt	0 Nej	1 Ja			
Känd nedsatt vänsterkammarfunktion	0 Nej	2 Ja, lätt nedsatt (40-49%)	3 Ja, måttligt nedsatt (30-39%)	4 Ja, kraftigt nedsatt (<30%)	5 Ja, men okänd grad
Tidigare PCI	0 Nej	1 Ja			
Tidigare hjärtkirurgi (avser ej pacemaker)	0 Nej	1 CABG	2 Annan hjärtkirurgi		
<b>Tidigare sjukdomar*</b>					
Diabetes	0 Nej	1 Ja			
Hypertoni	0 Nej	1 Ja			
Tidigare stroke (ej TIA)	0 Nej	1 Ja			
<b>Medicin vid ankomsten*</b>					
ACE-hämmare	0 Nej	1 Ja			
A2-blockerare	0 Nej	1 Ja	2 ARB + Neprilysin		
Antikoagulantia	0 Nej	1 Waran	3 Dabigatran (Pradaxa)	4 Rivaroxaban (Xarelto)	5 Apixaban (Eliquis)
ASA	0 Nej	1 Ja			
Övriga trombocyt-hämmare	0 Nej	1 Clopidogrel (Plavix)	2 Tiklopidin (Ticlid)	3 Prasugrel (Efient)	4 Ticagrelor (Brilique) 8 Övrigt
Betablockerare	0 Nej	1 Ja			
Ca-hämmare	0 Nej	1 Ja			
Diabetesbehandling insulin	0 Nej	1 Insulin			
Diabetesbehandling per oral	0 Nej	1 Tablettbehandlad			
Digitalis	0 Nej	1 Ja			
Diuretika	0 Nej	1 Ja			
Aldosteronblockad	0 Nej	1 Spironolakton (Aldactone)	2 Eplerenon (Inspra)	8 Övrigt	
Statiner	0 Nej	1 Ja			
Ezetimibe (Ezetrol)	0 Nej	1 Ja			
Övriga lipid-sänkare	0 Nej	1 Ja	Om Ja: 2 Fibrater 3 PCSK9-antikroppar 4 Lipoproteinaferes 8 Övrigt		
Nitroglycerin långverkande	0 Nej	1 Ja			
<b>Kommentarer</b>					

Figure 3B. RIKS-HIA registry form. Data collected on admission (continued).

## SWEDEHEART – 2018

PatientID:

VÅRD – RIKSHIA

(\* = obligatorisk)

Ankomst HIA/Avd/PCI-lab*		Datum		KI	
Revaskularisering*					
Reperfusionsterapi	0 Nej	1 Trombolys	2 Primär PCI	3 Akut CABG	4 Akut kor. ai utan åtgärd
Trombolys	0 Nej	1 Streptokinas	2 Actilyse	3 Rapilysin	4 Metalyse
Trombolys kontraindikation	0 Nej	1 Ja			
Trombolys tidpunkt	Datum		KI		
Reperusionsgrundande EKG = Prehospitala EKG	0 Nej	1 Ja			
Reperusionsgrundande EKG Tid	Datum		KI		
Medicinering*					
iv/sc Antikoagulantia	0 Nej	1 iv Heparin	2 sc Fragmin/Klexane	3 Arixtra	
iv Betablockerare	0 Nej	1 Ja			
iv Diuretika	0 Nej	1 Ja			
iv Inotropa	0 Nej	1 Ja			
iv Nitroglycerin	0 Nej	1 Ja			
Utredningar och behandlingar*					
Typ av stresstest	0 Ej utfört	1 Myocardscint	2 Stress EKO	3 Arbetsprov	
Resultat av stresstest	1 Normalt		2 Patologiskt	3 Ej bedömbart	
Vänsterkammars-funktion mätt	1 Ekokardiografi		2 LV-angio	3 Annan metod	
Vänsterkammarsfunktion (LVEF)	1 Normalt (≥50%)		2 Lätt nedsatt (40-49%)	3 Måttligt nedsatt (30-39%)	4 Kraftigt nedsatt (<30%)
CABG	0 Nej	1 Ja, akut CABG	2 Ja, under vårdtillfället	3 Planerat efter utskrivning	
PM/ICD	0 Nej	1 PM permanent	2 ICD	4 CRT	5 ICD+CRT
CPAP	0 Nej	1 Ja			
Laboratorieuppgifter OBS! Ankomstprover: Hb, CRP, Krea och P-Glucos					
Infarktmarkör	0 Ej utfört	1 Trop T (µg)	2 Trop I	3 CKMB	5 HS Trop T (ng)
Maxvärde infarktmarkör		6 HS Trop I (ng)			
Kolesterol		Triglycerider		HDL	
LDL direktmätt:				ApoB	
P-Glucos		HbA1c		Prov 2	Prov 3
Kreatinin*		Dat	KI	Dat	KI
CRP		Dat	KI	Dat	KI
Hb		Dat	KI	Dat	KI
Komplikationer					
Reinfarkt under vårdtillfället*	0 Nej	1 Ja			
Blödning under vårdtillfället*	0 Nej	1 Dödlig	2 Cerebral	3 Krävande op/transfusion	
HLR/Defibrillering under vtf*	0 Nej	1 VT/VF	8 Övrigt		
Cardiogen chock*	0 Nej	1 Ja			
AV-block*	0 Nej/AV-I	1 AV-II-III			
Nytt förmaksflimmer*	0 Nej	1 Ja			
Mekanisk komplikation	0 Nej	1 Fri väggrupp	2 VSD	3 MI (Akut allvarlig MI)	
Överföring utskrivning*					
Överförs till vårdenhet/sjukhus					

Figure 4. RIKS-HIA registry form. Data collected from the hospital course.

## SWEDEHEART – 2018

PatientID:

SLUT – RIKSHIA

(\* = obligatorisk)

Ankomst HIA/Avd/PCI*	Datum						
Avliden*							
Avliden	0 Nej 1 Ja						
Medicinering*							
ACE-hämmare	0 Nej 1 Ja						
A2-blockerare	0 Nej 1 Ja 2 ARB + Nephylisin						
Antikoagulantia	0 Nej 1 Waran 3 Dabigatran (Pradaxa) 4 Rivaroxaban (Xarelto) 5 Apixaban (Eliquis) 8 Annat						
ASA	0 Nej 1 Ja						
Planerad behandlingstid	1 1 mån 2 3 mån 3 6 mån 6 >=12 mån						
Övriga trombocythämmare	0 Nej 1 Clopidogrel (Plavix) 2 Tiklopidin (Ticlid) 3 Prasugrel (Efient) 4 Ticagrelor (Brilique) 8 Övrigt						
Planerad behandlingstid	1 1 mån 2 3 mån 3 6 mån 6 >=12 mån 5 tillsvidare						
Betablockerare	0 Nej 1 Ja						
Ca-hämmare	0 Nej 1 Ja						
Diabetesbeh insulin	0 Nej 1 Insulin						
Diabetesbeh per oral	0 Nej 1 Tablettbeh						
Digitalis	0 Nej 1 Ja						
Diuretika	0 Nej 1 Ja						
Aldosteronblockad	0 Nej 1 Spironolakton (Aldacton) 2 Eplerenon (Inspra) 8 Övrigt						
Statiner	0 Nej 1 Ja						
Ezetimibre (Ezetrol)	0 Nej 1 Ja						
Övriga lipidsänkare	0 Nej 1 Ja Om Ja: 2 Fibrater 3 PCSK9-antikroppar 4 Lipoprotein-afäres 8 Övrigt						
Nitroglycerin långv	0 Nej 1 Ja						
EKG*							
EKG-rytm	1 Sinus 2 Förmaksflimmer/-fladder 8 Övrigt						
Diagnos*							
Infarkttyp	0 Ej infarkt 1 STEMI 2 NSTEMI						
Subklass. av hjärtinfarkt	1 Typ-1 2 Typ-2 3 Typ-3 4 Typ-4a 5 Typ-4b 6 Typ-5						
Diagnos 1	Diagnos 3			Diagnos 5			
Diagnos 2	Diagnos 4			Diagnos 6			
Utskrivning*							
Utskrivningsdatum							
Planerad koronarangio efter utskrivning	0 Nej 1 Ja						
Planerad PCI efter utskrivning	0 Nej 1 Ja						
Planerad CABG efter utskrivning	0 Nej 1 Ja						
Uppföljning	0 Nej 1 Kardiologi/Medicin 2 VC 3 Annan						
Uppföljande sjukhus/enhet							

Figure 5. RIKS-HIA registry form. Data collected at discharge.



Komplikationer på avdelningen - Återsänd ifyllt till angio-lab			
Personnr eller motsv.			
Namn*			
Datum för procedur*			
Komplikation*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Allergisk senkomplikation*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Någon form av blödning*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Blödning Major*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Blödning Minor*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Behandlingskrävande pseudoaneurysm*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Hematom > 5 cm diameter*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Hb fall> 20 g/L*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Förlängd kompressionstid > 6 tim*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Förlängd vårdtid > 1 dygn*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Gjordes ultraljudsundersökning / CT*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Blodtransfusion*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Kirurgisk åtgärd*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Annan behandling utöver kompression*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Förtida utsättning / uppehåll av antitrombotisk beh.*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Vaskulär (endast icke coronara kärl)*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Neurologisk komplikation*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Nyttillkommen njurinsufficiens*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Tamponad*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Komplikation - Re-PCI (behandlat segment)*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
CABG (p g a komplikation, ej från lab)*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Hjärtinfarkt*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Annan allvarlig komplikation*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Avliden*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
Procedurrelaterad död*	<input type="checkbox"/> Nej	<input type="checkbox"/> Ja	<input type="checkbox"/> Okänt
<b>Biokemiska infarktmärkörer</b>			
CKMB värde före			
CKMB värde efter			
Troponinmetod före	<input type="checkbox"/> Troponin T	<input type="checkbox"/> Troponin I	<input type="checkbox"/> Okänt
Troponinvärde före			
Troponinmetod efter	<input type="checkbox"/> Troponin T	<input type="checkbox"/> Troponin I	<input type="checkbox"/> Okänt
Troponinvärde efter			

Definitioner på komplikationer finns på <http://www.ucr.uu.se/scaar/Manualer/kompavd.pdf>

**Figure 6.** SCAAR registry form. In-hospital complications.

## SWEDEHEART – 2016

PatientID:

SCAAR – ANGIO+PCI

( \* = obligatorisk)

Överflyttad patient*			
Patienten kommer närmast från	0 Ambulans från sjukhuset primära upptagningsområde	1 Ambulans från annat upptagningsområde	
	2 Annat sjukhus	3 Annan vårdenhet inom sjukhuset	4 Ej registrerande sjukhus
Ange vårdenhet (om 1-4)			

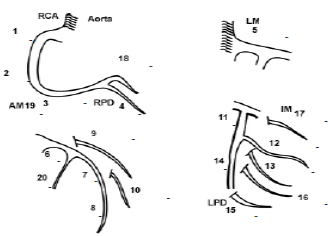
Grunduppgifter					
Datum för procedur					
Typ av registrering	1 Angio	2 PCI	3 Angio + PCI		
Jourtid	1 Planerad på kontorstid	2 Akutfall på kontorstid	3 Akutfall på jourtid	4 Subakut på kontorstid	5 Subakut på jourtid

Kliniska bakgrundsdata				
Längd (cm)				
Vikt (kg)				
S-Kreatinin (µmol/l)				
Tidigare PCI	0 Nej	1 Ja		9 Okänt
Tidigare CABG	0 Nej	1 Ja		9 Okänt
Diabetes	0 Nej	1 Ja		9 Okänt
Insulin	0 Nej	1 Ja		9 Okänt
Rökning (gäller även bruk av vattenpipa)	0 Aldrig rökare	1 Ex-rökare > 1 mån	2 Rökare	9 Okänt
Snusning	0 Aldrig varit snusare	1 Ex-snusare > 1 mån	2 Snusare	9 Okänt
Behandlad hypertoni	0 Nej	1 Ja		9 Okänt
Lipidsänkande medel	0 Nej	1 Ja		9 Okänt
Tidigare infarkt	0 Nej	1 Ja		9 Okänt

**Figure 7a.** SCAAR registry. Data collection (admission logistics and clinical background data) at the catheterization laboratory.

Angiografiska bakgrundsdata				
Angiograför				
Indikation	1 Stabil angina pectoris	Canadian class: 1 I 2 II 3 III 4 IV 9 Okänt		
	21 Instabil angina pectoris	Myocardskademarkör: 0 Nej	1 Ja	9 Okänt
	22 NSTEMI	ST-segment sänkning: 0 Nej	1 Ja	9 Okänt
	3 STEMI	Datum symtomdebut: _____		
	51 STEMI > 24 h	Klockslag symtomdebut: _____		
	4 STEMI/Rescue PCI	Datum reperfusionsgrundande EKG: _____		
	52 Riskvärdering efter lyckad trombolys	Klockslag reperfusionsgrundande EKG: _____		
	161 Hjärtstopp med STEMI			
	162 Hjärtstopp utan STEMI			
	6 Oklara bröstmärtor	9 Vitieutredning	8 Arytmiutredning	
	12 Hjärtsvikt/kardiomyopatiutredning	15 Kontroll inför eller efter transplantation	7 Tyst ischemi	
	10 Mekanisk komplikation efter hjärtinfarkt	14 Aortaaneurysm/dissektion	11 Forskning och utveckling	
13 Misstänkt komplikation Angio/PCI	17 Misstänkt komplikation vid CABG			
88 okänt				
19 Komplettering av tidigare PCI	Staged procedur: 0 Nej	1 Ja	9 Okänt	
Killip klass	1 Killip I	2 Killip II	3 Killip III	4 Killip IV
Punktionsställe	1 A Femoralis 3 A Brachialis 4 A Axillaris 5 A Radialis hö 6 A Radialis vä 7 A Radialis + A Femoralis 8 A Femoralis konverterad från radialis 9 A Radialis konverterad från A femoralis 88 Övriga			
Punktionsdatum och klockslag	Datum: _____		Klockslag: _____	

**Figure 7b.** SCAAR registry. Data collection (presentation and access sites) at the catheterization laboratory (continued).

Angiografi					
Angografiskt fynd					
					
Fynd		1 Normal/ateromatos 2 1-kärl ej HS 3 2-kärl ej HS 4 3-kärl ej HS 5 HS + 1-kärl 6 HS + 2-kärl 7 HS + 3-kärl 8 HS 0 Ej konklusiv undersökning			

Segment historik/Restenoser					
Datum	Segment	Graft	Procedur	Restenos 0 Nej 1 Ja	Ocklusion 0 Nej. 4 Nej, men misstänkt tromb 2 Ja, akut presentation (t.ex. SAT) 3 Ja, utan akut presentation 9 Okänt

**Figure 7c.** SCAAR registry. Data collection (angiographic findings) at the catheterization laboratory (continued).

Angiografi Avslut			
Angio fritext för utlåtande			
Angio fritext för patientutlåtande			
Stresskardiomyopati	0 Nej	1 Ja	2 Misstänkt
Primärt beslut	1 Ingen åtgärd 2 Fortsatt medicinsk behandling 3. Fortsatt utredning 4 Klaffoperation 5 CABG 6 Klaffoperation + CABG 7 PCI + CABG 8 PCI elektiv 9 PCI ad hoc 10 Remitterad till annat centrum 11 Annat operativt ingrepp		
Avböjd från operation	0 Nej	1 Ja	9 Okänt
Spontan kranskärlsdissektion	0 Nej	1 Ja	2 Misstänkt
PCI			
Operatör 1			
Operatör 2			

**Figure 7d.** SCAAR registry. Data collection (primary treatment decision) at the catheterization laboratory (continued).

Segment				
Segmentnummer				
Graft	0 Nej	1 Artär	2 Ven	
Nummer på stenosis i samma segment	1 Första	2 Andra	3 Tredje	4 Fjärde
Ocklusion	0 Nej	1 Ja, < 3 mån	2 Ja >= 3 mån	9 Okänt
Stenostyp	1 DeNovo	2 Övriga restenoser	3 In-stent restenos	
Stenosklass	1 A 2 B1 3 B2 4 C 5 B1 Bifurkation 6 B2 Bifurkation 7 C Bifurkation 88 Övrigt			
Procedurtyp	1 Ballongvidgning 2 Direkt stent 3 Ballong + stent 10 Ledarförsök 5 Atherectomi 6 Rotablator 7 Cutting Ballon 9 Diagnostik 11 Läkemedelsballong 12 Läkemedelsballong + stent 88 Annan terapi			
Ballongslut DEB	1 Proximala RCA 2. Mellersta RCA 3. Distala RCA 4. PDA/RPD 5. Vä huvudstam 6. Proximala LAD 7. Mellersta LAD 8. Distala LAD 9. Första diagonal 10. Andra diagonal 11. Proximala LCx 12. Första obtusa marginal 13. Andra obtusa marginal 14. Distala LCx 15. LPD 16. PLA från vänster 17. Intermediär 18. PLA 19. Högerkammargren 20. Septal 32. Vengraft 64. Artärgraft			
Lokal framgång	0 Nej	1 Ja		

**Figure 7e.** SCAAR registry. Data collection (angiographic findings and procedure characteristics) at the catheterization laboratory (continued).

Tillagda procedurer				
Segmentnummer	Graft	Ocklusion	Procedurtyp	Lokal framgång

Diagnostik (vid PCI)			
Någon diagnostik vid PCI	0 Nej	1 Ja	9 Okänt
Om Ja	Segmentnr	1 Proximala RCA 2. Mellersta RCA 3. Distala RCA 4. PDA/RPD 5. Vå huvudstam 6. Proximala LAD 7. Mellersta LAD 8. Distala LAD 9. Första diagonal 10. Andra diagonal 11. Proximala LCx 12. Första obtusa marginal 13. Andra obtusa marginal 14. Distala LCx 15. LPD 16. PLA från vänster 17. Intermediär 18. PLA 19. Högerkammargren 20. Septal	
	Graft	0. Nej 1. Artär 2. Ven	
	Metod	1. FFR 2. iFR 3. IVUS 4. OCT 5. NIRS 6. CFR 7. IMR 8. Pd/Pa 9. Pa-hyperemi 10. Pd-hyperemi	
		Före:	Efter:
		Före:	Efter:

**Figure 7f.** SCAAR registry. Data collection (angiographic findings and procedure characteristics) at the catheterization laboratory (continued).

Sekundärt beslut				
Sekundärt beslut	1 Ingen ytterligare åtgärd 2 Fortsatt PCI vid annat tillfälle 3 CABG akut 4 CABG ej akut 5 Klaffkirurgi + CABG 8 Annat			

Adjuvant terapi				
Någon adjuvant terapi		0 Nej	1 Ja	9 Okänt
Om Ja	Aortaballongpump	0 Nej	1 Ja	9 Okänt
	Annan vänsterkamarassistent	0 Nej	1 Ja	9 Okänt
	LUCAS	0 Nej	1 Ja	9 Okänt
	Distal protection device	0 Nej	1 Ja	9 Okänt
	Pacemaker	0 Nej	1 Ja	9 Okänt
	Trombectomi	0 Nej	1 Ja	9 Okänt
	Annat	0 Nej	1 Ja	9 Okänt
Labnamn				
Stråldos (mGy)				
Genomlysningstid (mmm:ss)				
Kontrastmedel				
Kontrastmedelsmängd (ml)				
Annan kontrastmedelsundersökning	0 Nej	2 Vänsterkamarangiografi		
	3 Thorakal aortografi	4 LV + Thorakal aortografi		
	8 Annan undersökning			

Artärförslutning	1 Femostop		
	2 Angioseal		
	3 Kvarlämnad artärskada		
	4 Perclose		
	5 Vasoseal		
	6 Starclose		
	7 Femoseal		
	8 TR-band		
	81 Radistop		
	9 Handkompression		
	10 Eget förband		
	11 Proglide		
	12 Radstat		
	88 Övrigt		
	General success	0 Nej	1 Ja

**Figure 7g.** Data collection (procedural characteristics) at the catherization laboratory (continued).



PCI fritext för utlåtande	
PCI fritext för patientutlåtande	

Antitrombotisk medicinerings före (inom 24h)			
Antitrombotisk medicinerings före PCI	0 Nej	1 Ja	9 Okänt
Om JA	Trombolys ASA Clopidogrel/ticlopidin (Plavix(Ticlid) Prasugrel (Efient) Ticagrelor (Brilique) Cangrelor (Kengrexal) Heparin Dalteparin (Fragmin) Enoxaparin (Klexane) Annat lågmolekylärt heparin Bivalirudin (Angiox) Fondaparinux (Arixtra) Abciximab (Reopro) Eptifibatid (Integrilin) Tirofiban (Aggrastat) Warfarin (Waran) Apixaban (Eliquis) Dabigatran (Pradaxa) Rivaroxaban (Xarelto) Övriga		

**Figure 7h.** Data collection (medication before angiography) at the catheterization laboratory (continued).

Antitrombotisk mediciner under/direkt i anslutning PCI			
Antitrombotisk mediciner under/direkt i anslutning till PCI	0 Nej	1 Ja	9 Okänt
Om JA	Trombolys ASA Clopidogrel/ticlopidin (Plavix/Ticlid) Prasugrel (Efient) Ticagrelor (Brilique) Cangrelor (Kengrexal) Heparin Dalteparin (Fragmin) Enoxaparin (Klexane) Annat lågmolekylärt heparin Bivalirudin (Angiox) Fondaparinux (Arixtra) Abciximab (Reopro) Eptifibatid (Integrilin) Tirofiban (Aggrastat) Warfarin (Waran) Apixaban (Eliquis) Dabigatran (Pradaxa) Rivaroxaban (Xarelto) Övriga		
Komplikation på lab			
Komplikation	0 Nej	1 Ja	9 Okänt
Om JA	Allergisk reaktion lätt/måttlig Allergisk reaktion allvarlig Behandlingskrävande arytmi Hemodynamisk komplikation Neurologisk komplikation Vaskulär (endast icke coronara kärl) Tappat stent Bestående sidogrensocklusion Perforation Tamponad Akut CABG från lab Annan allvarlig komplikation Avliden. Om JA: Prodecurrelaterad död – 0 Nej. 1 Ja. 9 Okänt		
Överflyttad till			
Överflyttad till	0 Nej 2 Annat sjukhus 3 Annan vårdenhets inom sjukhuset 4 Ej registrerande sjukhus		
Ange vårdenhets			
Anteckningsfält för inmatning			

**Figure 7i.** Data collection (medication during angiography and complications) at the catheterization laboratory (continued).

**Table 1.** List of biomarkers included in the Proximity Extension Assay (PEA) and Multiple Reaction Monitoring assay (MRM) analyses.

Full variable name	Type	Full variable name	Type	Full variable name	Type
Interleukin-8	PEA	Macrophage colony-stimulating factor 1	PEA	Chitinase-3-like protein 1	PEA
Vascular endothelial growth factor A	PEA	C-X-C motif chemokine 1	PEA	ST2 protein	PEA
Adrenomedullin	PEA	Lectin-like oxidized LDL receptor 1	PEA	TIM-1	PEA
CD40 ligand	PEA	TNF-related apoptosis-inducing ligand receptor 2	PEA	Beta-nerve growth factor	PEA
Growth/differentiation factor 15	PEA	Fibroblast growth factor 23	PEA	Membrane-bound aminopeptidase P	PEA
Placenta growth factor	PEA	Stem cell factor	PEA	TNF-related activation-induced cytokine	PEA
E-selectin	PEA	Interleukin-18	PEA	Hepatocyte growth factor	PEA
Epidermal growth factor	PEA	Interleukin-6 receptor subunit alpha	PEA	P-selectin glycoprotein ligand 1	PEA
Osteoprotegerin	PEA	Tumor necrosis factor receptor 2	PEA	Myoglobin	PEA
Proto-oncogene tyrosine-protein kinase Src	PEA	Matrix metalloproteinase-3	PEA	Thrombomodulin	PEA
Interleukin-1 receptor antagonist protein	PEA	Heat shock 27 kDa protein	PEA	Interleukin-16	PEA
Interleukin-6	PEA	Tumor necrosis factor ligand superfamily member 14	PEA	Matrix metalloproteinase-10	PEA
Cystatin-B	PEA	Prolactin	PEA	Urokinase plasminogen activator surface receptor	PEA
Monocyte chemotactic protein 1	PEA	Myeloperoxidase	PEA	C-C motif chemokine 4	PEA
Kallikrein-6	PEA	Growth hormone	PEA	Cathepsin D	PEA
Galectin-3	PEA	Matrix metalloproteinase-1	PEA	Receptor for advanced glycosylation end products	PEA
Proteinase-activated receptor 1	PEA	Resistin	PEA	C-C motif chemokine 3	PEA
TNF-related apoptosis-inducing ligand	PEA	Tumor necrosis factor receptor superfamily member 6	PEA	Matrix metalloproteinase-7	PEA
Kallikrein-11	PEA	Pappalysin-1	PEA	C-X-C motif chemokine 6	PEA
Angiopoietin-1 receptor	PEA	Pentraxin-related protein PTX3	PEA	Melusin	PEA
Tissue factor	PEA	Renin	PEA	C-X-C motif chemokine 16	PEA
Tumor necrosis factor receptor 1	PEA				
Platelet-derived growth factor subunit B	PEA				
Interleukin-27 subunit alpha	PEA				

Table 1. Continued.

Full variable name	Type	Full variable name	Type	Full variable name	Type
Dickkopf-related protein 1	PEA	Platelet endothelial cell adhesion molecule	PEA	Ig kappa chain C region	MRM
SIR2-like protein 2	PEA	N-terminal pro-B-type natriuretic peptide	PEA	Ig gamma-1 chain C region	MRM
Galanin peptides	PEA	Eosinophil cationic protein	PEA	Ig gamma-2 chain C region	MRM
Agouti-related protein	PEA	Mannan-binding lectin serine protease 2	MRM	Ig gamma-3 chain C region	MRM
Protein S100-A12	PEA	Apolipoprotein L1	MRM	Ig gamma-4 chain C region	MRM
Tumor necrosis factor receptor superfamily member 5	PEA	CD5 antigen-like	MRM	Ig mu chain C region	MRM
Tissue-type plasminogen activator	PEA	Apolipoprotein M	MRM	Ig alpha-1 chain C region	MRM
Heparin-binding EGF-like growth factor	PEA	Ceruloplasmin	MRM	Ig alpha-2 chain C region	MRM
Endothelial cell-specific molecule 1	PEA	Coagulation factor XIII A chain	MRM	Apolipoprotein AI	MRM
Vascular endothelial growth factor D	PEA	Prothrombin	MRM	Apolipoprotein E	MRM
Matrix metalloproteinase-12	PEA	Complement C1r subcomponent	MRM	Apolipoprotein C-I	MRM
Spondin-1	PEA	Haptoglobin	MRM	Apolipoprotein C-II	MRM
Caspase-8	PEA	Coagulation factor IX	MRM	Apolipoprotein C-III	MRM
Cathepsin L1	PEA	Plasminogen	MRM	Fibrinogen alpha chain	MRM
Fractalkine	PEA	Coagulation factor XII	MRM	Fibrinogen beta chain	MRM
Fatty acid-binding protein, adipocyte	PEA	Complement factor B	MRM	Fibrinogen gamma chain	MRM
Natriuretic peptides B	PEA	Carbonic anhydrase 1	MRM	C-reactive protein (peptide 1)	MRM
Leptin	PEA	Antithrombin III	MRM	Complement C1q subcomponent subunit A	MRM
C-C motif chemokine 20	PEA	Alpha-1-antitrypsin	MRM	Complement C1q subcomponent subunit B	MRM
Ovarian cancer-related tumor marker CA 125	PEA	Alpha-1-antichymotrypsin	MRM	Complement C1q subcomponent subunit C	MRM
NF-kappa-B essential modulator	PEA	Angiotensinogen	MRM	Complement component C9	MRM
Follistatin	PEA	Alpha-2-macroglobulin	MRM		
		Complement C3	MRM		
		Complement C5	MRM		
		Cystatin C (peptide 1)	MRM		

**Table 1.** Continued.

Full variable name	Type
Beta-2-glycoprotein 1	MRM
Leucine-rich alpha-2-glycoprotein	MRM
Tissue factor pathway inhibitor	MRM
Fibronectin	MRM
Apolipoprotein B-100	MRM
von Willebrand factor	MRM
Sex hormone binding globulin	MRM
Apolipoprotein D	MRM
Plasma serine protease inhibitor	MRM
Plasma protease C1 inhibitor	MRM
Complement factor I	MRM
Coagulation factor XIII B chain	MRM
Tetranectin	MRM
Complement C2	MRM
Apolipoprotein A-IV	MRM
Vitamin K-dependent protein S	MRM
Complement component C8 alpha chain	MRM
Complement component C8 beta chain	MRM
Complement component C8 gamma chain	MRM
Alpha-2-antiplasmin	MRM
Mannose-binding protein C	MRM

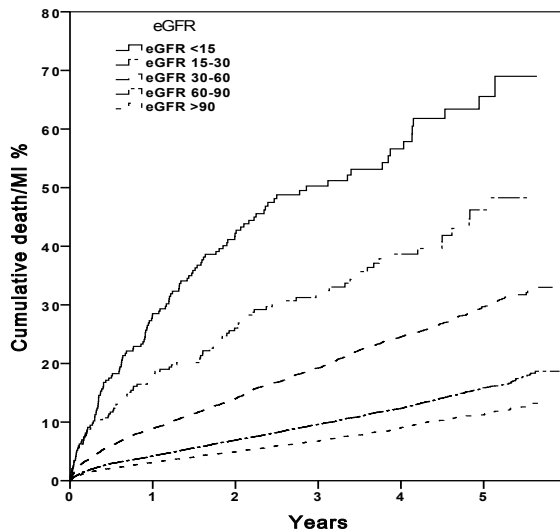
Full variable name	Type
Thrombospondin-1	MRM
Complement factor H	MRM
Coagulation factor XI	MRM
Vitamin K-dependent protein C	MRM
Complement component C7	MRM
Coagulation factor V	MRM
Complement component C6	MRM
L-selectin	MRM
Lipopolysaccharide-binding protein	MRM
Vitamin K-dependent protein Z	MRM
Mannan-binding lectin serine protease 1	MRM
Adiponectin (peptide 1)	MRM
N-acetylmuramoyl-L-alanine amidase	MRM
Clusterin	MRM
Complement C1s subcomponent	MRM
Complement C4-B	MRM

Full variable name	Type
Serum amyloid A-1 protein	MRM
Serum amyloid A-2 protein	MRM
Alpha-1-acid glycoprotein 1	MRM
Hemopexin	MRM

## 5 RESULTS

### 5.1 STUDY I

In **study I**, 45,348 patients with a known creatinine measurement underwent a coronary angiography between 2005 and 2010 with the indication of stable CAD. The median eGFR was 81.3 (interquartile range, IQR 67.5–92.3) and 6,813 (15%) patients had eGFR <60. The median follow-up time of 2.6 years (IQR 1.2–4.1 years) and 2,473 deaths, 2,869 recurrent MI, 3,950 hospitalizations with heart failure and 1,381 hospitalizations due to stroke were observed. The cumulative probability up to 3 years of death or MI increased with lower eGFR groups, ranging from 6.7% in patients with eGFR>90 to 50.5% in patients with eGFR<15 (**Figure 8**).



**Figure 8.** Cumulative risk of death or myocardial infarction in relation to estimated glomerular function.

Following the results of 3-year survival data, the risk of death increased in the crude and adjusted analyses with lower eGFR groups (**Table 2**). In comparison with patients with normal renal function (eGFR>90), patients with eGFR<60 showed markedly higher risks and HR ranged from 4.1 95% CI (3.6 – 4.7) to 17.7 (14.3 – 22.0) in the crude analysis. Even after using all adjusting models, the HR of death was substantially higher in patients with RD. Compared with patients with normal renal function (eGFR>90) or slightly impaired renal function (eGFR≥60 – <90), patients with impaired renal function had significantly higher HR for the endpoints MI, heart failure and the composite of death or MI, in the crude and

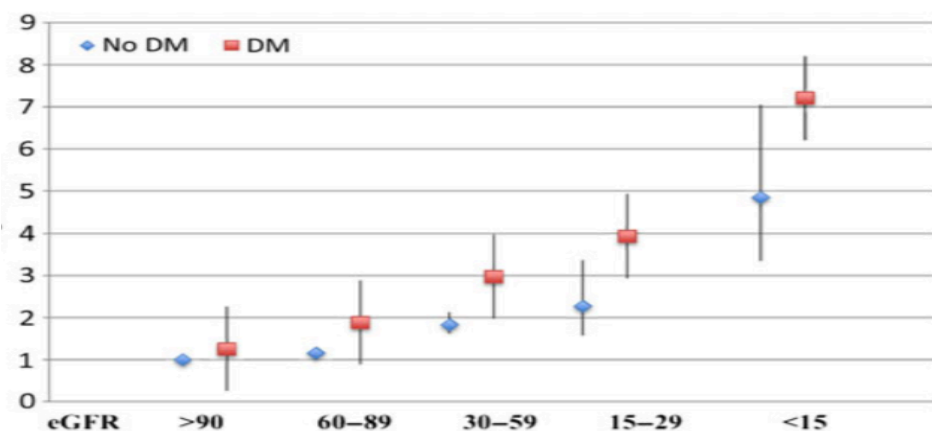
multivariable adjusted models, respectively (**Table 2**). Readmission for stroke did not differ significantly between renal function groups in the adjusted analyses at 3 years follow up.

The association between renal function and outcomes was similar regardless of presence of diabetes mellitus and despite severity of coronary angiogram findings, with no significant interactions (**Figures 9-10**).

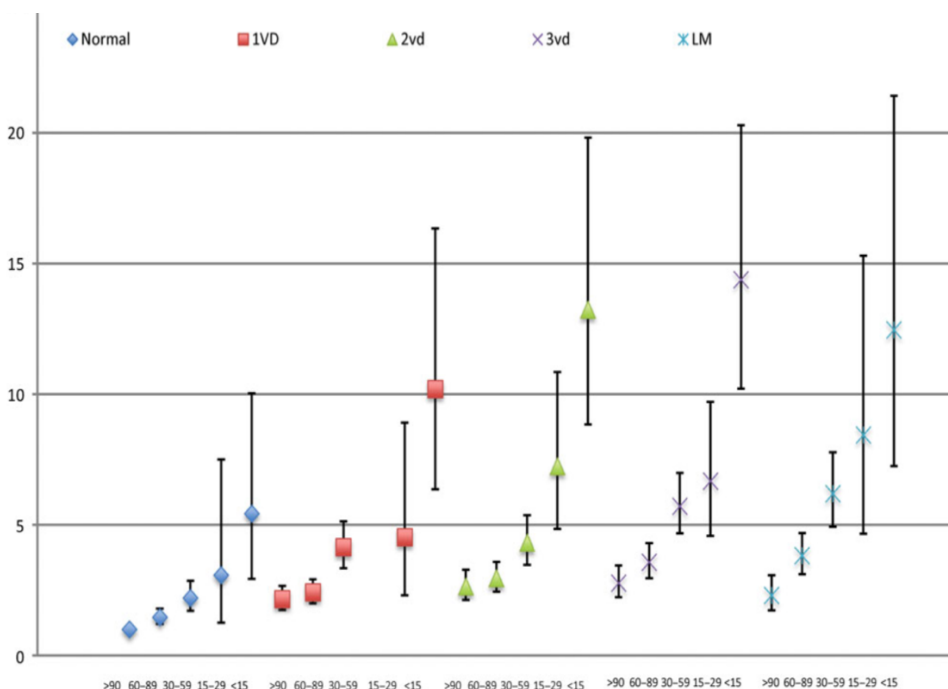
eGFR (mL/min/1.73 m <sup>2</sup> )	(>90)	(89–60)	(59–30)	(29–15)	(<15)	Deviance
All-cause mortality (n, %)	385 (2.8)	1206 (4.9)	705 (11.4)	72 (23.0)	105 (36.3)	
Cumulative probability at 3 years (%)	2.7	4.6	11.2	22.2	39.8	
Unadjusted (N = 45 348)	1	1.7 (1.5–1.9)	4.1 (3.6–4.7)	8.8 (6.8–11.2)	17.7 (14.3–22.0)	0
Model 1 adjustment (N = 43 211)	1	0.9 (0.8–1.1)	1.3 (1.1–1.5)	2.2 (1.7–2.9)	7.9 (6.2–9.9)	–5252
Model 2 adjustment (N = 42 821)	1	0.9 (0.8–1.1)	1.2 (1.1–1.5)	2.2 (1.6–2.9)	7.7 (6.1–9.7)	–6112
Model 3 adjustment (N = 42 821)	1	0.9 (0.8–1.1)	1.3 (1.1–1.5)	2.2 (1.6–2.9)	7.7 (6.1–9.8)	–5520
MI (n, %)	614 (4.5)	1436 (5.8)	685 (11.0)	58 (18.5)	76 (26.3)	
Cumulative probability at 3 years (%)	4.6	6.1	11.7	21.1	32.8	
Unadjusted (N = 45 340)	1	1.3 (1.2–1.4)	2.6 (2.3–2.9)	4.8 (3.7–6.2)	8.0 (6.3–10.1)	0
Model 1 adjustment (N = 43 203)	1	0.9 (0.8–1.0)	1.3 (1.2–1.5)	2.1 (1.6–2.8)	4.5 (3.5–5.8)	–5608
Model 2 adjustment (N = 42 814)	1	0.9 (0.8–1.1)	1.3 (1.1–1.5)	1.9 (1.4–2.6)	4.2 (3.2–5.4)	–6133
Model 3 adjustment (N = 42 814)	1	0.9 (0.8–1.0)	1.3 (1.1–1.5)	1.8 (1.4–2.5)	4.0 (3.1–5.1)	–7899
Combined endpoint (MI/death) (n, %)	937 (6.8)	2398 (9.7)	1182 (19.0)	100 (31.9)	133 (46.0)	
Cumulative probability at 3 years (%)	6.7	9.7	19.4	32.4	50.5	
Unadjusted (N = 45 348)	1	1.4 (1.3–1.52)	3.0 (2.7–3.2)	5.4 (4.4–6.6)	9.6 (8.0–11.6)	0
Model 1 adjustment (N = 42 821)	1	0.9 (0.9–1.0)	1.3 (1.1–1.4)	1.8 (1.5–2.3)	4.8 (3.9–5.8)	–10 413
Model 2 adjustment (N = 42 821)	1	0.9 (0.8–1.0)	1.2 (1.1–1.4)	1.7 (1.4–2.2)	4.7 (3.8–5.7)	–10 948
Model 3 adjustment (N = 42 821)	1	0.9 (0.8–1.0)	1.3 (1.1–1.4)	1.8 (1.5–2.3)	4.6 (3.7–5.5)	–11 092
Heart failure (n, %)	581 (4.2)	2021 (8.1)	1181 (19.0)	101 (32.2)	66 (22.8)	
Cumulative probability at 3 years (%)	4.4	8.6	20.7	33.9	30.2	
Unadjusted (N = 45 340)	1	1.9 (1.8–2.1)	4.9 (4.4–5.4)	9.3 (7.6–11.5)	7.4 (5.7–9.5)	0
Model 1 adjustment (N = 43 203)	1	1.2 (1.1–1.4)	1.7 (1.5–1.9)	2.6 (2.0–3.2)	2.5 (1.9–3.3)	–10 192
Model 2 adjustment (N = 42 814)	1	1.2 (1.1–1.4)	1.7 (1.5–1.9)	2.4 (1.9–3.1)	2.5 (1.9–3.3)	–10 500
Model 3 adjustment (N = 42 814)	1	1.2 (1.1–1.3)	1.7 (1.5–1.9)	2.5 (1.9–3.1)	2.4 (1.8–3.2)	–12 014
Stroke (n, %)	270 (2.0)	759 (3.2)	323 (5.2)	18 (5.8)	11 (3.8)	
Cumulative probability at 3 years (%)	2.0	3.2	5.7	6.1	6.2	
Unadjusted (N = 45 348)	1	1.7 (1.3–1.8)	2.7 (2.3–3.2)	3.1 (1.9–5.0)	2.5 (1.4–4.7)	0
Model 1 adjustment (N = 43 203)	1	1.0 (0.9–1.2)	1.1 (0.9–1.4)	1.1 (0.7–1.8)	1.4 (0.7–2.5)	–2090
Model 2 adjustment (N = 43 814)	1	1.0 (0.9–1.2)	1.1 (0.9–1.3)	1.0 (0.6–1.7)	1.4 (0.8–2.5)	–2502
Model 3 adjustment (N = 43 814)	1	1.0 (0.9–1.2)	1.1 (0.9–1.3)	1.1 (0.6–1.7)	1.4 (0.7–2.5)	–2615

Model 1 adjusted for baseline risk factors (age, gender, smoking status, BMI, hypertension, history of previous MI, CABG, PCI, heart failure, stroke, peripheral artery disease, cancer, dementia, chronic obstructive lung disease, diabetes, and hyperlipidaemia). Multivariate analysis Model 2 also adjusted for angiogram findings. In addition, Model 3 adjusted for waiting time for revascularization with CABG or PCI. Deviance is expressed as difference in  $-2 \log$  likelihood between the unadjusted and adjusted models. The cumulative proportion of the endpoint of interest at 3 years. N = cases available in the analysis.

**Table 2.** Different outcomes and hazard ratios expressed by univariate analysis and multivariate analysis (Models 1–3).



**Figure 9.** Adjusted hazard ratio distribution (y-axis) for the combined endpoint death or recurrent myocardial infarction within subgroups of estimated glomerular filtration rate (eGFR) in ml/min/1.73m<sup>2</sup> and in relation to presence of diabetes. P for interaction = 0.05.



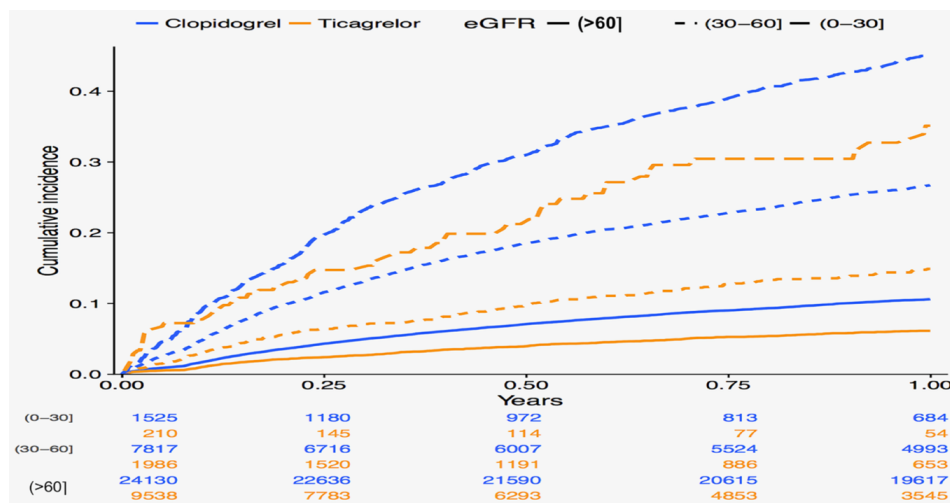
**Figure 10.** Adjusted hazard ratio distribution (y-axis) for the combined endpoint death or recurrent myocardial infarction within subgroups of estimated glomerular filtration rate (eGFR) in ml/min/1.73m<sup>2</sup> and



in relation to severity of CAD (1vd = one vessel disease, 2vd = two vessel disease, 3vd = three vessel disease and LM = left main stenosis). P for interaction = 0.7.

## 5.2 STUDY II

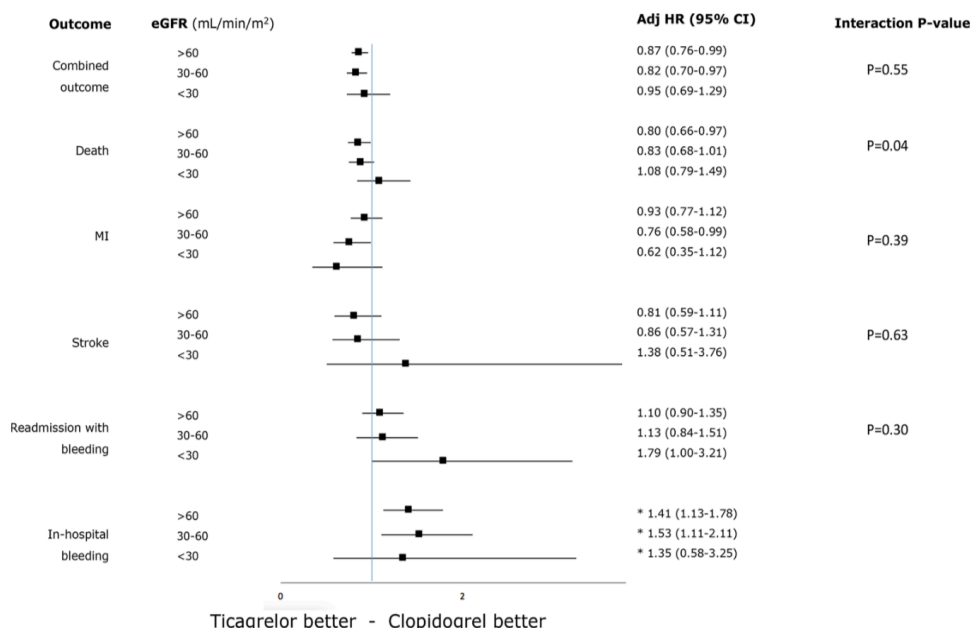
Between 1 January 2010 and 31 December 2013 45,206 MI patients were discharged alive and treated with ticagrelor (11,734 patients (26.0%)) or clopidogrel (33,472 patients (74.0%)) in addition to ASA in this study. The overall use of ticagrelor increased during the study period in all renal function groups. The incidence rate of the combined outcome (death, readmission for MI or stroke) at 1 year was higher in patients with RD (eGFR 30-60 and eGFR<30) than in those with normal renal function (eGFR>60) (**Figure 11**).



**Figure 11.** Cumulative incidence for the combined outcome (death, myocardial infarction or stroke) and numbers at risk stratified on estimated glomerular filtration rate (eGFR) groups in ml/min/1.73m<sup>2</sup>.

In the adjusted analysis, ticagrelor versus clopidogrel was associated with significantly lower risks for the combined outcome in patients with eGFR>60 and eGFR30-60, HR 0.87 (95% CI, 0.76 - 0.99) and HR 0.82 (95% CI, 0.70 - 0.97). The point estimate for patients with eGFR<30 was 0.95 in the adjusted analysis but the CI crossed the line of unity (0.69-1.29). In the analysis of the separate the outcomes of death, MI readmission and stroke, ticagrelor as compared with clopidogrel, showed associations of lower risks in patients with eGFR>60 and eGFR 30-60, but in patients with eGFR<30 wide CIs were noted (**Figure 12**). For the secondary safety outcomes, readmission with bleeding and PCI-related in-hospital bleedings, ticagrelor versus clopidogrel, was consistently associated with higher risks in all eGFR groups (**Figure 12**). There was no significant interaction between renal function and treatment with ticagrelor or clopidogrel with regards to the combined outcome, MI readmission, stroke, readmission with bleeding or in-hospital bleedings but a borderline significant p-value was noted for death (p=0.04) (**Figure 12**). The results of the sensitivity analyses with propensity score matching, censoring of patients according to the intended treatment duration, adjustments coronary stent types) as well as time-restricted

analyses 2012-2013, were similar to the main results of the combined outcome (death, MI or stroke hospitalization).

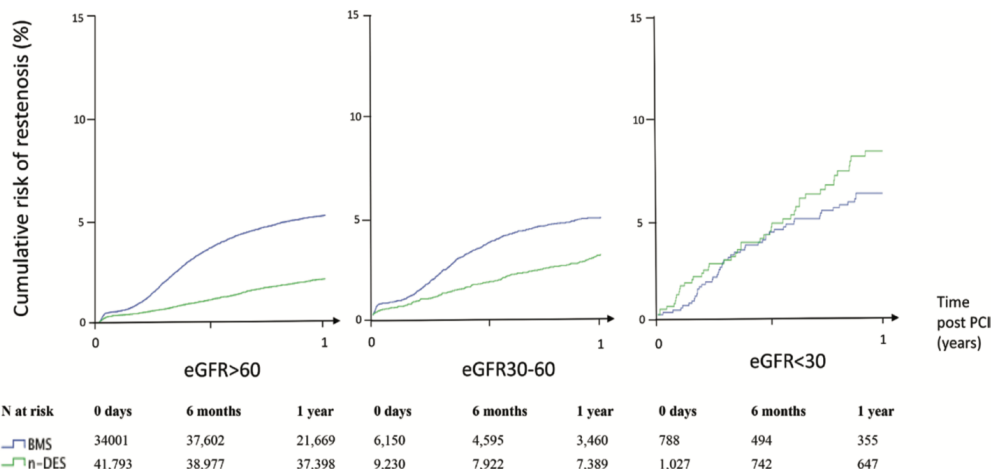


**Figure 12.** Forest plot illustrating the adjusted hazard ratio (adj HR) and the adjusted odds ratio (\*) for different outcomes stratified on estimated glomerular filtration rate (eGFR) groups (mL/min/1.73m<sup>2</sup>). MI, myocardial infarction.

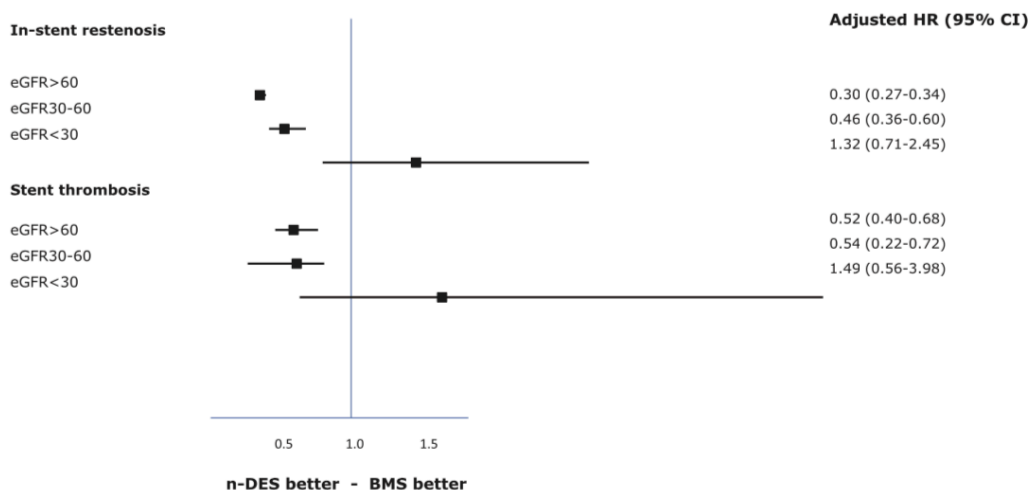
### 5.3 STUDY III

In this study, a total of 92,994 patients with a known creatinine underwent PCI with either BMS or n-DES stent implantation. Overall, 40,940 patients (44.0%) received n-DES and 52,054 (56.0%) received BMS. The use of n-DES increased from 0.5% to 90.6% and BMS decreased from 99.5% to 9.4% in the first and last calendar year of the study period (2007-2013), respectively. A total of 75,798 patients (81.5%) had normal kidney function (eGFR > 60); 15,381 patients (16.5%) had moderate RD (eGFR 30–60); and 1,815 patients (2.0%) had severe RD (eGFR < 30). N-DES-treated patients were younger than BMS patients, but had a higher prevalence of diabetes, previous MI, CABG, PCI and were more often treated with potent platelet inhibition. Stenting intervention with n-DES versus BMS, was associated with a lower 1-year risk of in-stent restenosis (**Figure 13**) in patients with eGFR >60 with a cumulative probability of 2.1% versus 5.3%, adjusted HR 0.30, 95% CI (0.27–0.34) and with eGFR 30–60: 3.0% versus 4.9%; HR 0.46 (0.36–0.60) (**Figure 14**). However, in patients with eGFR<30, n-DES as compared with BMS was associated with a cumulative probability of 8.1% versus 6.0%; HR 1.32 (0.71–2.45) (**Figure 14**). The association of n-DES versus BMS showed lower risk of ST (**Figure 15**) for patients with eGFR >60 and eGFR 30–60: 0.5% versus 0.9%; HR 0.52 (0.40–0.68) and 0.6% versus 1.3%; HR 0.54 (0.54–0.72), but not for patients with eGFR <30; 2.1% versus 1.1%; HR 1.49 (0.56–3.98) (**Figure 14**). There was a

significant interaction between choice of stent type and different subgroups of eGFR for both stent outcomes; in-stent restenosis ( $p=0.009$ ) and ST ( $p=0.027$ ). Sensitivity analyses that excluded patients that received more than one of the stent types at the same procedure, exclusion of patients with prior CABG as well as Fine-Grey competing risk for death analyses, resulted in similar results to the main analysis and in patients with  $eGFR < 60$  there was no significant difference in the occurrence of MI readmission between stent groups.

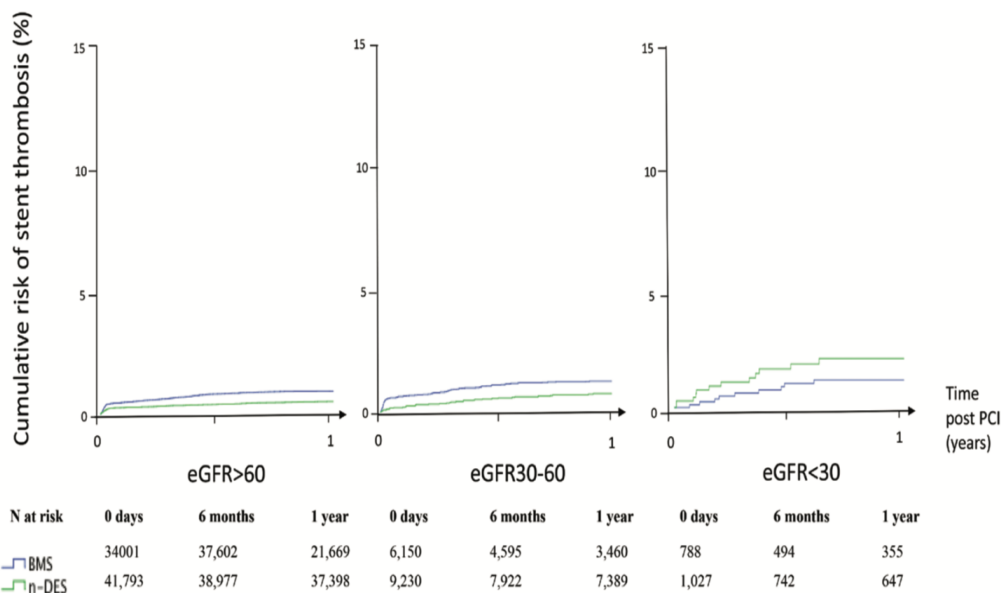


**Figure 13.** Stent choice and cumulative risk of in-stent restenosis in patients stratified by estimated glomerular filtration rate (eGFR) ml/min/1.73m<sup>2</sup> groups. BMS, bare metal stent; N, numbers; n-DES, newer generation drug-eluting stent; PCI, percutaneous coronary intervention.



**Figure 14.** Association of stent type (n-DES and BMS) and the risk of in-stent restenosis and definite stent thrombosis according to estimated glomerular filtration rate (eGFR) in ml/min/1.73m<sup>2</sup> at 1 year.

BMS, bare metal stents; CI, confidence interval; HR, hazard ratio; n-DES, newer generation drug-eluting stents.



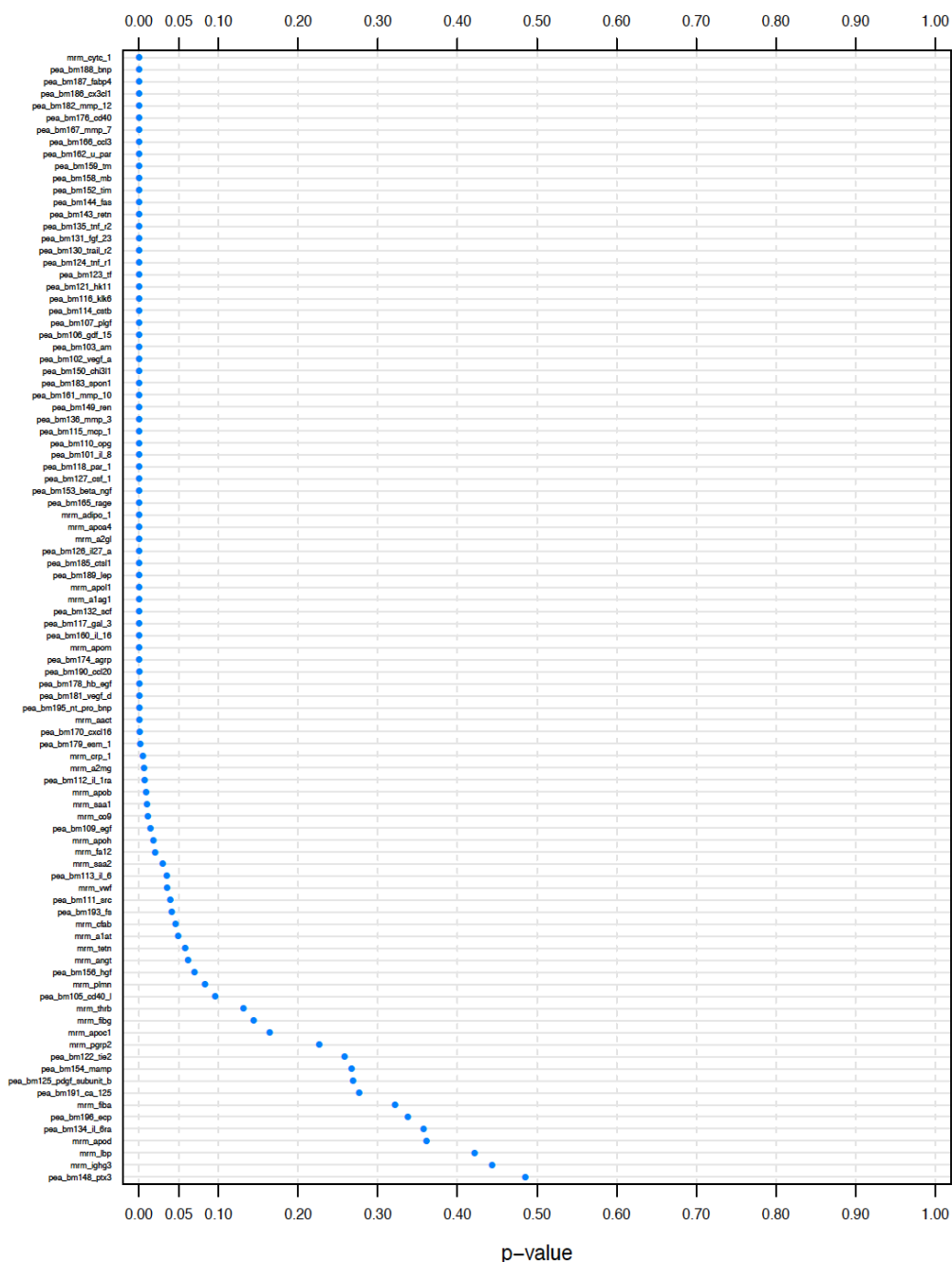
**Figure 15.** Stent choice and cumulative risk of definite stent thrombosis in patients stratified by estimated glomerular filtration rate (eGFR) ml/min/1.73m<sup>2</sup> groups. BMS, bare metal stent; N, numbers; n-DES, newer generation drug-eluting stent; PCI, percutaneous coronary intervention.

## 5.4 STUDY IV

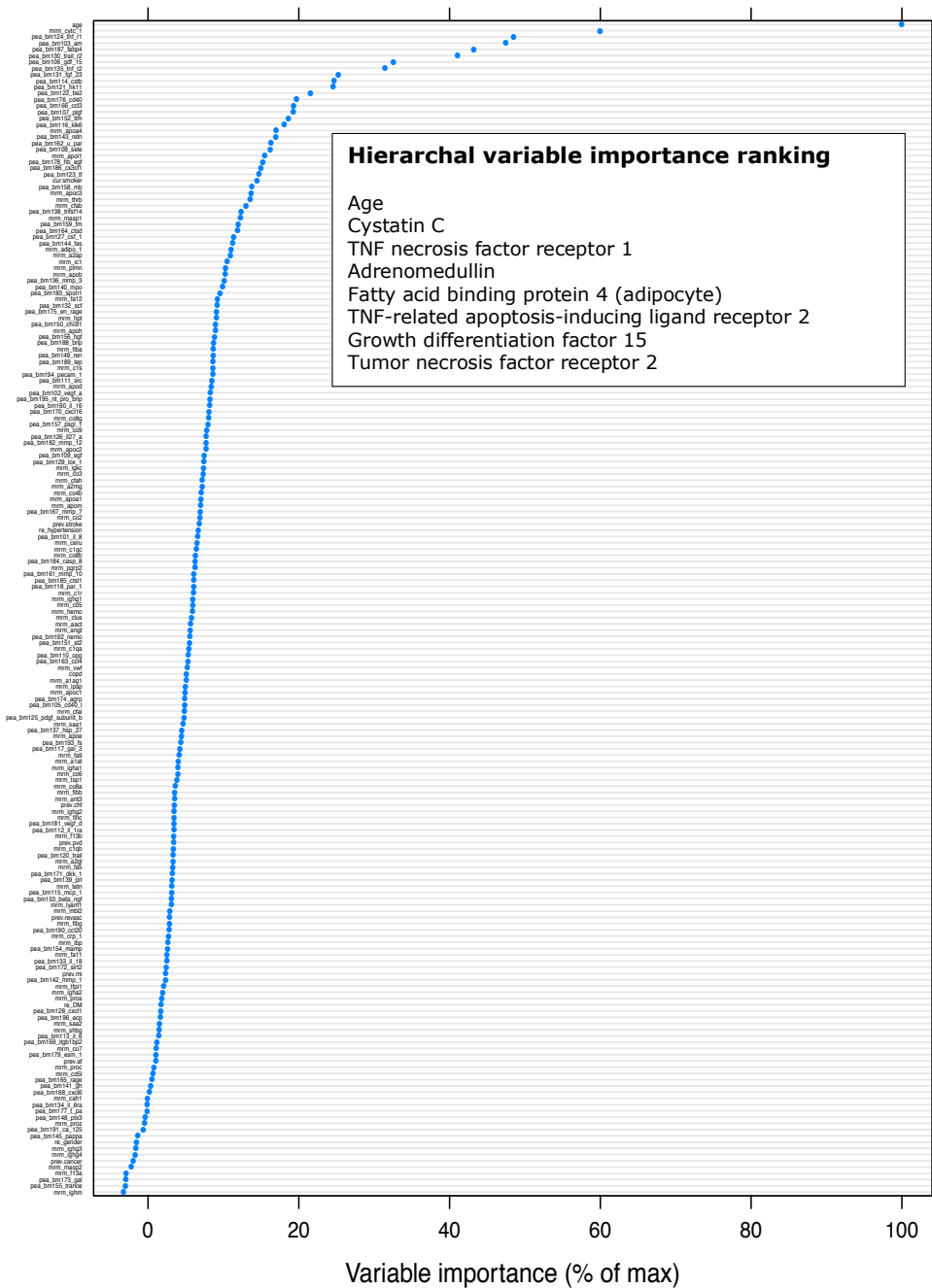
A total of 1,098 MI patients that were discharged alive were followed for a median time of 3.2 years. In the univariate analysis where biomarkers were analyzed individually, 72 biomarkers ( $p<0.05$ ) were associated with the outcome CKD (**Figure 16**). Following the results of the main analysis using random forests where all biomarkers were considered simultaneously, we found that, in addition to cystatin C, six biomarkers; adrenomedullin, tumor necrosis factor receptor 1 (TNF-R1), fatty acid binding protein 4 (adipocyte) (FABP-4), tumor necrosis factor related apoptosis-inducing ligand receptor 2 (TRAIL-2), growth differentiation factor 15 (GDF-15) and tumor necrosis factor receptor 2 (TNF-R2) were most strongly associated with CKD. When we adjusted for demography and baseline risk factors (model 1) and severity of disease (model 2), the aforementioned biomarkers and age retained the most significant variable importance (**Figures 17-18**).

All six aforementioned biomarkers (in addition to cystatin C) with the strongest association with CKD, were also among the 15 biomarkers with the strongest association with mortality. The most

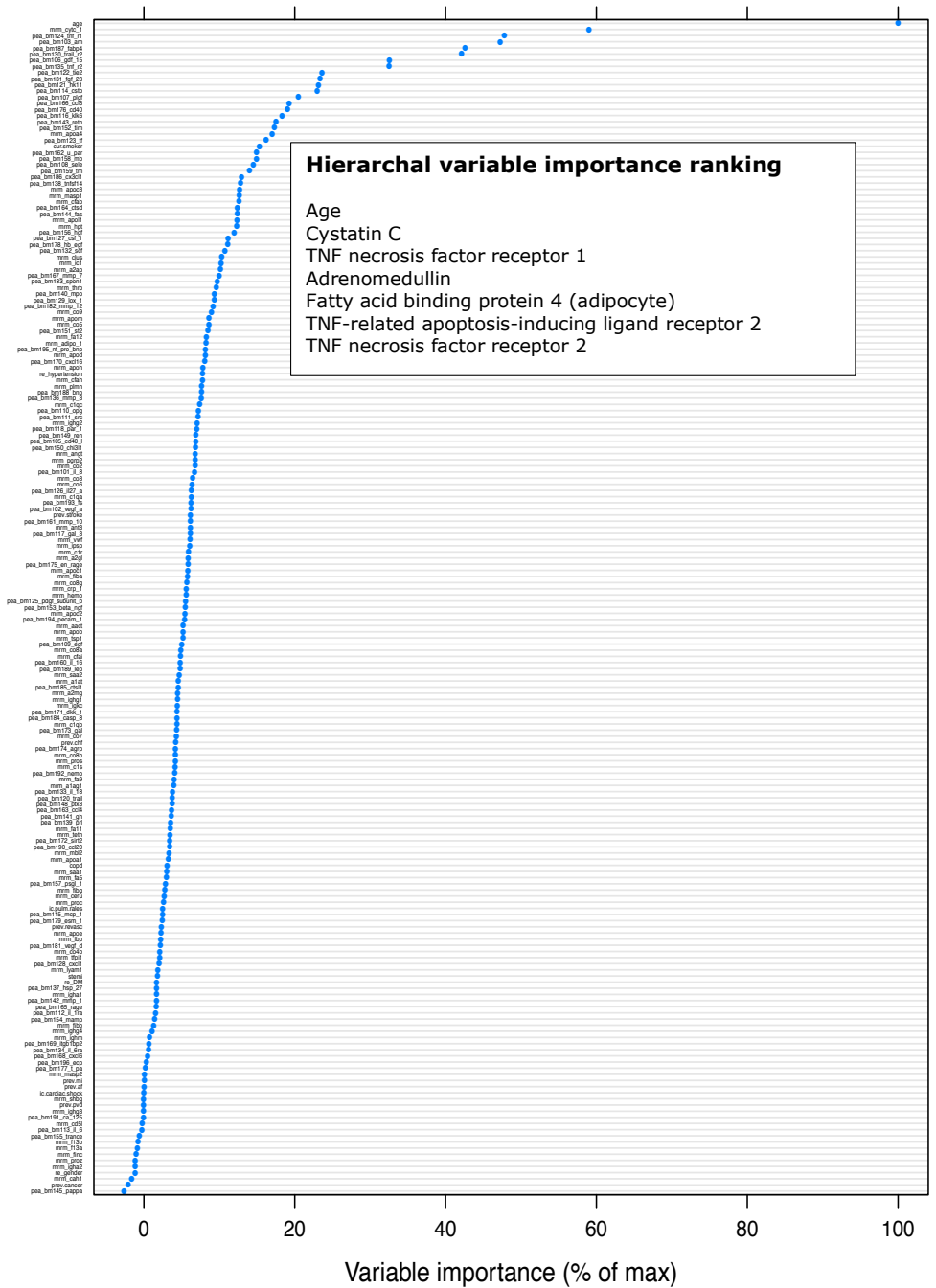
important biomarkers for predicting mortality were GDF-15, TRAIL-2, ovarian cancer-related tumor marker CA 125 (CA125), fibroblast growth factor 23 (FGF-23) and TNF-R1 (**Figure 19**). When we studied the association of biomarkers with subsequent MI, four (TRAIL-2, TNF-R2, GDF-15, TNF-R1) out of the six biomarkers also had the strongest association with CKD. TRAIL-2, vascular endothelial growth factor D, urokinase plasminogen activator surface receptor, TNF-R2, GDF-15, tissue factor and osteoprotegerin were the most important biomarkers for predicting MI readmission (**Figure 19**). In addition, four (adrenomedullin, GDF-15, TRAIL-2 and TNF-R1) out of the six biomarkers with the strongest association with CKD, were among the 15 biomarkers with the strongest association with subsequent hospitalization because of heart failure. FGF-23, adrenomedullin, natriuretic peptides B, GDF-15, TRAIL-2 and osteoprotegerin predicted heart failure hospitalization best (**Figure 19**). Sensitivity analyses using lasso methods confirmed many of our biomarker associations and outcomes described in the main analyses, but TRAIL-2 and TNF-R2 were not kept in the model for CKD and for subsequent MI readmission.



**Figure 16.** Univariate analysis with rank-transformed p-values of biomarkers and the prediction of chronic kidney disease.

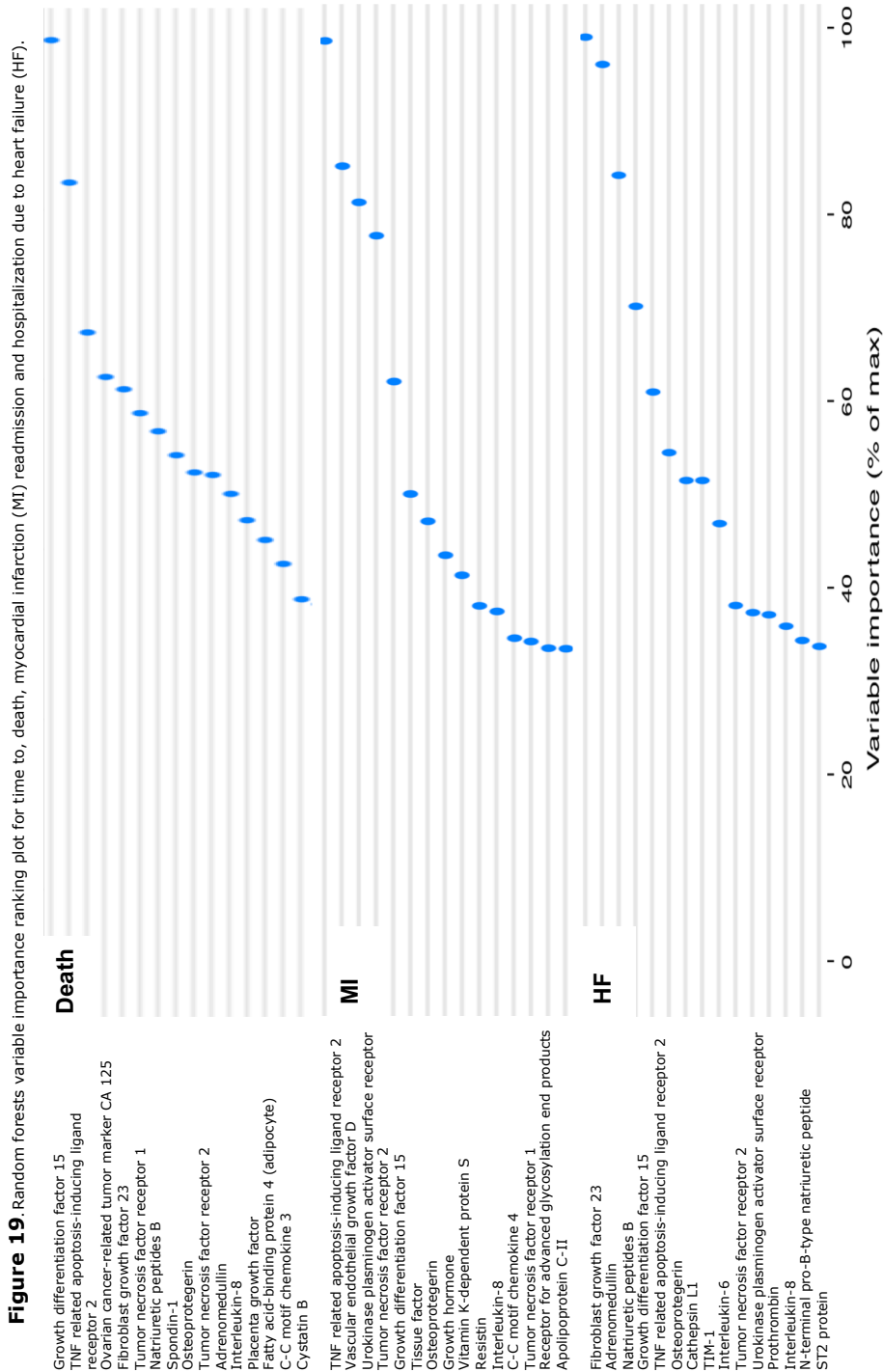


**Figure 17.** Random forests variable importance plot for chronic kidney disease adjusted for baseline and demography.



**Figure 18.** Random forests variable importance plot for chronic kidney disease adjusted for baseline and demography and severity of disease.





## 6 DISCUSSION

### 6.1 MAJOR FINDINGS

**Study I:** The associations between renal function, death, recurrent MI and hospitalization with heart failure, in patients undergoing coronary angiography due to stable CAD were strong and remained after adjustments for differences in clinical background, risk factors, co-morbidities, severity of CAD, mode and timing of revascularization. RD is a strong and independent marker of worse outcomes in these patients and other unknown factors than we could adjust for, play an important role for the risk of adverse outcomes observed in CAD patients with RD.

**Study II:** In MI survivors, ticagrelor, as compared with clopidogrel, was associated with lower risk for CV outcomes and a higher bleeding risk in patients with normal- and moderately reduced renal function. In patients with severe RD, bleeds were more abundant in patients and the benefit of ticagrelor less clear.

**Study III:** The 1-year risk of in-stent restenosis and stent thrombosis in patients treated with coronary artery stenting with n-DES versus BMS, was significantly lower in patients with normal- and moderately reduced renal function, whereas no differences were observed between stent type and stent events in patients with severe RD. Choice of stent in patients with severe RD does not seem to influence stent outcomes.

**Study IV:** Biomarker studies of 175 analytes in 1,098 MI patients, showed that six of the strongest biomarkers for the outcome RD also had a strong variable importance for death, and four of the RD predicting biomarkers were also among the most important predictors of heart failure readmission and subsequent MI. Thus, these biomarkers may reflect pathophysiological pathways that may partly explain the poor prognosis in patients with acute MI and RD.

### 6.2 INFLUENCE OF RD ON CVD OUTCOMES IN PATIENTS WITH STABLE CAD

In **study I**, a nationwide real-world registry of elective angiography patients with stable CAD, about 15% had moderate RD (eGFR<60). This is similar to the prevalence in the general population and about half of the prevalence seen in the acute setting of an MI<sup>1, 24, 57</sup>, where RD is found to be strongly associated with adverse cardiovascular outcomes. Less is known about the prognosis of patients with stable CAD undergoing coronary angiography and in contrast to several previous studies, that are often limited to single center experiences, we were able to capture the whole spectrum of RD in unselected patients with a known CAD.

We found that RD is also an independent and strong predictor of adverse CV outcomes in patients with stable CAD. All outcomes increased with lower eGFR, with the exception of stroke, for which there was no statistically significant multivariable association with RD. The associations remained strong even after adjustment for coronary artery disease severity and revascularization with CABG or PCI. The reasons for this are, however, not yet fully understood.

Patients with RD had more severe angiographically diagnosed CAD and underwent more interventions compared with patients with normal renal function. The interplay and

pathological mechanisms between RD and CAD are numerous and not yet fully understood. Coronary vascular calcification, that usually starts at an early stage in patients with RD (often before diagnosis of RD) may be associated to processes triggered by both traditional CVD risk factors and non-traditional risk factors for CVD, such as bone and mineral disorders as well as systemic inflammation<sup>12</sup>. RD and associations with inflammatory activity, endothelial dysfunction and a pro-thrombotic milieu may elevate the risk of plaque rupture<sup>58, 59</sup>. Since patients with RD and stable CAD have increased rates of coronary artery obstruction and cardiovascular comorbidities, we hypothesized that adjusting for such factors would attenuate the associations to outcomes. However, the relationship between RD and poor outcomes remained after adjusting for differences regarding CAD obstruction burden and subsequent revascularization with CABG or PCI and there was no significant interaction between CAD severity, RD and outcomes.

Patients with RD had higher rates of CV risk factors compared to patients with normal renal function. In particular, diabetes, a known risk factor for RD, was more prevalent in patients with RD (ranging between 18% and 52% in the different eGFR strata), but the presence of diabetes did not explain the association between RD and outcomes following interaction term analysis and adjustments.

The risk of hospitalization due to heart failure was higher in patients with worsening of renal function and remained so after adjustments. This confirms and points to the important and previously described interlink between RD and heart failure as well as the fact that RD can induce acute or chronic heart failure<sup>133-135</sup>.

Following the results of our study, in the adjusted analyses we could not confirm that RD was associated with increased HR for readmission due to stroke ( $p < 0.3$ ), but the point estimate suggested higher risks for patients with eGFR  $< 15$ . In contrast, in a study of previously revascularized patients with CAD, CKD defined as GFR  $< 60$  was associated with an adjusted HR for stroke of 2.3 (95% CI 1.2-4.7)<sup>48</sup> and our results could be explained by the limited power to detect differences between the groups. But it could also indicate that RD is not a strong risk factor for stroke in the present population, which is also a finding supported in a recent substudy of *PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia study* (PRODIGY) where no difference in the risk of stroke or transient ischemic attack was observed between those with and without RD at 2-years of follow-up (HR 1.97, 95% CI (0.79-4.92))<sup>136</sup>.

RD was also an independent and strong predictor of mortality across all layers of renal function and the association remained strong after adjustment for coronary artery disease severity and revascularization with CABG or PCI. It is plausible that the high mortality rates in patients with RD referred for an angiography are caused by the overall elevated mortality risk of the CKD population which we were not able to measure or adjust for. The study was not designed to evaluate any treatment effects and the clinical implications are to acknowledge RD as an important predictor of worse prognosis, so that patients with RD are managed individually and optimally in terms of risk factor treatments.

## **6.3 MANAGEMENT OF CAD PATIENTS WITH CONCOMITANT RENAL DYSFUNCTION**

### **6.4 DUAL ANTIPLATELET TREATMENT IN RELATION TO RENAL FUNCTION**

Post-hoc- and RCT data demonstrate that DAPT management in MI patients with ticagrelor as compared to clopidogrel in addition to ASA, is beneficial in reducing ischemic events (cardiovascular death, non-fatal MI or non-fatal stroke) in MI patients with normal- and moderately RD<sup>98, 99</sup>. **Study II**, expands upon previous findings by providing post-approval real-world registry data of unselected MI patients, as well as including patients with severely reduced renal function. We concluded that treatment with ticagrelor as compared to clopidogrel in addition to ASA, was significantly associated with a lower risk for the primary composite endpoint (death, MI or stroke) in patients with eGFR>60 and eGFR 30-60, at the cost of higher risk of bleeding. The impact of the study on clinical practice may influence the choice of DAPT in patients with severe RD, where no significant beneficial outcomes were observed.

In PLATO, the ischemic efficacy benefit of ticagrelor was even more pronounced with a larger absolute risk reduction in patients with RD, compared to patients with normal renal function but there was no significant interaction. Moreover, in the up to 3-year post MI-setting of stable ASA treated CAD patients, ticagrelor versus placebo in aspirin-treated patients with stable coronary artery disease resulted in a larger absolute risk reduction in RD patients than in non-RD patients<sup>137</sup>. It is possible that these findings can be explained by the higher risks and event rates observed in RD patients which may exaggerate subgroup analyses. However, pleotropic effects of ticagrelor with inhibition of adenosine transporters and endothelial function through elevated levels of activated protein C have also been a postulated explanation, which could account for some of the findings in patients with RD in previous studies<sup>96, 99, 138</sup>. The generalizability of the main studies<sup>98, 99</sup> may be limited as RD was defined as CrCl<60, patients in the lower range of creatinine clearance were few and patients on RRT were excluded.

Even though RD was associated with an overall higher bleeding risk in PLATO, RD patients treated with ticagrelor did not have a higher relative risk of PLATO-defined major bleeds as compared to non-RD patients<sup>99</sup>. There was, however, a 22% and 26% increase of PLATO- and TIMI-defined non-CABG major bleeding in the main study population and a similar trend was found in the substudy<sup>98, 99</sup>. The increased risk of bleeding regardless of kidney function found in the present study is closely in line with results from the aforementioned trials<sup>99, 137</sup>, although the absolute risks cannot be directly compared due to different definitions of bleeding.

In contrast, a recent registry study with 2,490 ACS patients with eGFR<60, showed significantly lower rates of death (HR 0.45, 95% CI (0.21-0.44)) and recurrent MI (HR 0.36, 95% CI (0.10–0.81) at 1-year as compared to clopidogrel<sup>95</sup>. Interestingly, the differences of major bleeds were not significant between DAPT treatment groups (HR 0.87, 95% CI (0.45–1.67)<sup>95</sup>. The number of patients was however small and there were no significant differences in clopidogrel versus treatment with potent P2Y<sub>12</sub> inhibitors regarding the efficacy outcomes

in the subset of patients with  $\text{eGFR} < 30$  <sup>95</sup>. In a recent meta-analysis of 31,234 patients with ACS, aggregated DAPT with ticagrelor or prasugrel versus clopidogrel in addition to ASA, was associated with lower rates of major cardiovascular events, HR 0.88, 95% CI (0.79–0.99) but without increased bleeds, HR 1.10, 95% CI (0.95–1.27)<sup>139, 140</sup>.

Until we have the answer from the randomized *TicagRelor Or Clopidogrel in Severe and Terminal Chronic Kidney Disease Patients Undergoing PERcutaneous Coronary Intervention for an Acute Coronary Syndrome* (TROUPER) <sup>141</sup> study that evaluates the clinical efficacy of ticagrelor and clopidogrel in patients with CKD stage 4 and 5 or on RRT undergoing PCI for ACS, very little is known about ticagrelor in patients with advanced RD.

RD is an independent predictor of both thrombotic and spontaneous and iatrogenic bleedings in response to medication and dosages. The observed higher risk of bleeding observed in **study II** is an expected finding due to a more potent ADP-inhibition with ticagrelor. The observed differences in ischemic- and bleeding outcomes in patients with severe RD may also be explained by disturbances in platelet adhesion and aggregation as well as higher platelet reactivity in clopidogrel-treated patients with RD <sup>142-144</sup>. However, some conflicting results exist regarding impaired efficacy of clopidogrel on platelet reactivity observed in RD, which may be due to confounding and heterogenous definitions of platelet reactivity <sup>145-148</sup>. Our study supports, however, that the overall effect of ticagrelor on the primary outcome is favorable in regardless of RD group, but our results regarding patients with severe RD do not allow definite conclusions.

## 6.5 STENT CHOICE IN CAD PATIENTS IN RELATION TO RENAL FUNCTION

The large registry results described in **study III** compared BMS with n-DES in unselected all-comers treated with PCI during the transition phase from BMS to n-DES. The key findings included that RD is a common comorbidity associated with a markedly increased risk of in-stent restenosis and definite ST. N-DES versus BMS was associated with lower 1-year risks of in-stent restenosis and definite stent thrombosis in patients with normal kidney function and in those with moderate RD, but not in patients with severe RD.

Data on safety and efficacy of different types of coronary stents in patients with RD are scarce, since these patients are often excluded from major interventional cardiology trials. Current evidence is based on registry data and post-hoc analyses from RCT. Many previous studies are limited to studying only one type of DES, which may lead to limited statistical power in detecting potential outcome differences between stent types <sup>149 150, 151</sup>. ESC guidelines on revascularization from 2014 recommend the use of DES over BMS in patients with RD <sup>152</sup>.

Registry data on patients with RD have shown heterogenous results regarding patients treated with DES versus BMS regarding all-cause mortality <sup>153-156</sup>, the risk of MI, and the risk of ST <sup>157</sup> and many studies do not distinguish between older- and newer-generation DES <sup>158, 159</sup>. Studies of the first-generation DES (sirolimus and paclitaxel) versus BMS in patients with

reduced renal function, have shown lower rates of angiographic restenosis but no significant difference in the occurrence of death, recurrent MI and ST at 1 year and up to 5 years follow up<sup>160, 161</sup>. In a study<sup>92</sup> comparing the o-DES with zotarolimus versus everolimus in STEMI-patients with RD, no significant difference in definite ST, major adverse cardiac events (MACE) or death at 1 year was found in the adjusted analysis. In the RENAL-DES randomized trial<sup>162</sup> comparing the everolimus stent (Xience V, Abbot, Santa Rosa) with BMS (Multilink, Abbot, Santa Rosa) in patients primarily with -moderate RD, the 1-year rate of clinically driven restenosis, defined as ischemia-driven target vessel revascularization, was significantly lower in the second-generation DES versus BMS treated group. Our study confirms these results in terms of reduced rates of in-stent restenosis and ST during the first year in DES versus BMS patients with normal or moderate RD. However, in patients with severe RD (eGFR<30), n-DES was not associated with a lower risk of restenosis.

In NORSTENT<sup>125</sup>, the rates of definite ST were significantly lower in DES- versus BMS-treated patients (0.8% versus 1.2% ) with an adjusted HR 0.64 (95% CI, 0.41-1.00, p=0.0498) at 5 years of follow-up. Since no information on creatinine was included in the study, the results cannot however be generalizable to patients with RD.

The lack of beneficial effects 1-year post stenting with n-DES versus BMS in patients with severe RD is far from fully explained. Probable mechanisms may include accelerated atherosclerosis, a higher prevalence complex coronary lesions, suboptimal stent implantation, underuse of guideline-recommended therapies, impaired P2Y2-inhibition, endothelial dysfunction and a pro-inflammatory and thrombogenic mechanisms that are not overcome by effects of n-DES<sup>77, 143, 145, 163</sup>. In **study III**, increased prevalence of type C coronary lesions and multivessel disease in patients with severe RD, may also contribute to the higher observed rates of adverse stent outcomes.

Future clinical perspectives should focus on ways to avoid stent complication issues in patients with RD. In selected cases, CABG may be preferred over PCI and development of newer stent types or novel stent techniques such as coronary shockwave lithotripsy<sup>164</sup> may play an important role in the future treatment for patients with severe RD.

## **6.6 PROTEOMICS TO PREDICT ADVERSE OUTCOMES IN MI**

Following the results of **studies I-III**, we acknowledged that patients with RD are at high risk of adverse outcomes but more importantly, RD patients respond less beneficially to given invasive and medical treatment regimens as compared to patients with normal renal function. Therefore, in **study IV** we wanted to identify biomarkers with the strongest association to RD and examine whether these biomarkers also were associated with outcome.

From an untargeted investigation of 175 different biomarkers measured in 1,098 MI patients, we found that adrenomedullin, FABP-4, GDF-15 and biomarkers of the TNF superfamily (TNF-R1, TNF-R2 and TRAIL-2) were most strongly associated with the presence of RD. Even after adjustments for differences in age, gender, comorbidities and severity of MI at

admission, these associations with RD remained. Interestingly, these biomarkers were also among the most important predictors of long-term outcomes (death, recurrent MI and heart failure hospitalization). Thus, adrenomedullin, FABP-4, GDF-15 and biomarkers of the TNF superfamily, may reflect important pathophysiological pathways that could at least partly explain the poor prognosis seen in patients with concomitant RD and MI.

The associations of the aforementioned six biomarkers and RD have also been described in a cohort study of elderly patients<sup>165</sup>. Moreover, other studies have found associations between adrenomedullin<sup>166</sup>, FABP-4<sup>167, 168</sup>, GDF-15<sup>169, 170</sup> and biomarkers reflecting the TNF superfamily<sup>171 172, 173</sup> and RD.

All six identified biomarkers associated with CKD were also among the 15 strongest predictors of mortality and four of them among the strongest predictors of readmission because of a new MI and heart failure. Compared with 1<sup>st</sup> quartile, the 4<sup>th</sup> quartile of biomarker expression of GDF-15, adrenomedullin, TNR-R1/R2, FABP-4 and TRAIL-2 were associated with a 4.7- to 17.7- fold increased risk of mortality, a 1.26- to 2.3- fold increased risk of readmission because of MI for GDF-15, TNR-R1/R2 and TRAIL-2 and a 4.7- to 8.8- fold increased risk of readmission because of heart failure. These findings are also strongly supported by a previous study<sup>174</sup>, where the same Proseek Multiplex CVD I panel was used in 847 consecutive patients within 72 hours of an acute MI. The six identified biomarkers in our study were among the eight biomarkers with the highest HR with regard to subsequent mortality when adjusting for age. The identified biomarkers may reflect several different underlying mechanisms.

Numerous factors and conditions that enhance the secretion of adrenomedullin have been described and include the presence of angiotensin II, noradrenaline, TNF, hypoxia and mechanical cardiac stress<sup>175</sup> as well as ischemia, hypertension, heart failure<sup>175</sup>, diabetic nephropathy<sup>176</sup> and hypertensive kidney failure<sup>177</sup>. Even though adrenomedullin exerts protective biological mechanisms, elevated plasma levels are associated with worse prognosis<sup>175, 178, 179</sup>. Biomarkers of the TNF protein superfamily (TNF-R1, TNF-R2 and TRAIL-2) are involved in extrinsic cellular apoptosis and inflammation, which plays an important role in the atherosclerotic disease development<sup>180-182</sup>. TRAIL-2 is also associated with cardiovascular outcomes in the general population and in patients with carotid plaques<sup>183 184</sup> in addition to associations of RD in elderly patients<sup>165</sup>. **Study IV**, reveals that cell apoptosis and inflammation via the TNF protein family may play an important role in the risk of reinfarction, developing heart failure, and mortality in patients with MI.

Associations of FABP-4 and obesity<sup>185</sup>, insulin resistance<sup>186</sup>, diabetes mellitus<sup>187</sup>, hypertension<sup>188</sup>, cardiac dysfunction<sup>189</sup>, atherosclerosis<sup>190</sup>, and cardiovascular events<sup>191</sup> have previously been described. In addition, high levels of FABP-4 have also been observed in patients with acute- and chronic kidney dysfunction as well as being a predictor of CKD in patients with stable coronary artery disease<sup>167, 168</sup>. The described long-term outcomes of RD in **study IV** may partly be explained by pathological pathways of FABP-4 involved in metabolic dysregulation and chronic inflammation.

GDF-15 is not usually expressed in normal tissues but increases in response to, for example, ischemia and inflammation and plays an important role in the cellular responses of tissue repair<sup>192</sup>. In **study IV**, GDF-15 was an important marker of both RD as subsequent MI, heart failure hospitalization and mortality. Elevated levels of GDF-15 are associated with worse outcomes in patients with MI<sup>193, 194</sup> as well as RD and kidney- related complications in diabetic patients and CABG patients, respectively<sup>169 170</sup> which further supports our findings.

## **6.7 LIMITATIONS**

In general, observational registry data studies have some advantages over RCT. They are less expensive and more patients are included due to lack of strict exclusion criteria, which leads to greater generalizability and understanding on how different treatments applied on a larger scale can be achieved. The disadvantages compared with RCT include lower quality data, selection bias and confounding. All the above concerns also apply to this thesis that used large-sized cohorts from SWEDEHEART.

In particular, the national representativeness of SWEDEHEART is good and provides good generalizability. It captures nearly, but not all, patients with MI, since some patients may be admitted at other departments that do not participate in SWEDEHEART data collection. Regular monitoring is performed to ensure data correctness of enrolled data. The subsequent cross linkage with national registries containing information on death minimizes loss to follow-up. For outcome measures other than death, the validity of the studied event relies on collected data. As with any observational study, even stratifications and the most rigorous multivariable adjustments cannot eliminate residual confounding and selection bias.

In all studies, creatinine was used from the SWEDEHEART. Missing creatinine data (especially in **study I**) and quality of data can be a limitation that introduces bias to the studies. Clinical trials with continuous monitoring of patients have the possibility to provide better quality of data and reduce missing data.

In **study I**, selection bias is certainly an important issue. Firstly, there is a selection by the fact that patients with RD that have CAD and did not undergo an angiography were not included. These patients may represent a different population (e.g. with more severe / less severe co-morbidity). The use and interpretation of registry data to study treatment effects (**studies II-III**) is a weakness since the treatment arms were not assigned at random. This also provides a source of selection bias that adjustments and propensity score matching may not fully adjust for. Treatment effects are often over-estimated in registry studies, since RCTs often have younger and healthier subjects with lower event rates and patients in registries that are selected for any treatment often already have a better prognosis at the outset.

In **studies I and III**, death as a competing risk is an issue. In **study I**, this was partly handled by an outcome that combined death and MI readmission and in **study II** a Fine-Gray competing risk regression model was conducted as a sensitivity analysis.



**Study IV** handled many data simultaneously which, in general, can lead to overfitting and multiplicity issues. To reduce these issues, advanced statistical methods using forests trees were utilized but we cannot exclude the possibility that some associations were found at random. Moreover, the analysis techniques used in PEA gave semi-quantified concentrations, with arbitrary units, that may be difficult to translate into standardized units and MRM utilized SIS. Additionally, we did not consider the fact that the expression biomarkers may vary over time (acute versus stable phase) <sup>195</sup>.

To summarize, even though this thesis has the potential for great generalizability due to the large-scale national representativeness, residual confounding may still exist and the data must be interpreted with caution.

## 7 CONCLUSION

RD is a strong and independent marker of worse outcomes in patients with CAD. Diabetes or the severity of coronary artery disease are not important mediators of the worse long-term outcomes in CAD patients with RD and other unknown factors that were not possible to adjust for seem to be important.

In patients with no- or moderate RD, ticagrelor as compared to clopidogrel was significantly associated with a lower risk of the combined endpoint (death, stroke or spontaneous MI), but bleeds were more abundant in all renal function groups, and in patients with severe RD the beneficial role of ticagrelor is unclear.

The choice of coronary stent type in terms of newer generation drug eluting- versus bare metal stents was associated with a lower risk of in-stent restenosis and definite stent thrombosis at 1-years follow-up in patients with normal or moderately reduced renal function. In contrast, no beneficial effects were observed in patients with severely reduced renal function.

A proteomic approach in patients hospitalized with MI identified adrenomedullin, FABP-4, GDF-15 and members of the TNF superfamily to be strongly associated with the presence of RD. These biomarkers were also among the most important predictors of long-term outcomes following MI. Thus, these biomarkers may reflect underlying mechanisms that may partly explain the poor prognosis seen in patients with concomitant MI and RD.

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