Factors influencing prognosis in acute coronary syndrome

– a report from the SWEDEHEART registry

Oskar Angerås

Department of Clinical and Molecular Medicin
Institute of Medicin
Sahlgrenska Academy at University of Gothenburg

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UNIVERSITY OF GOTHENBURG

Cover illustration: Angiography visualizing a tight stenosis of the left anterior descending artery

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oskar.angeras@vgregion.se

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Abstract

Background: Acute coronary syndrome (ACS) is one of the major causes of mortality in the world. The prognosis for patients with ACS is affected by several factors, such as baseline characteristics and treatment before, during and after hospitalisation.

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Aims: To further elucidate the impact of body mass index (BMI), socioeconomic status (SES), cardiogenic shock (CS) and thrombus aspiration as adjunct to PCI using The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). A secondary aim was to explore statistical methods on how to improve analyses in observational registries.

Methods: All papers used SWEDEHEART merged with the National Cause of Death Register, the National Patient Registry (Paper I) and data obtained from the Swedish Central Bureau of Statistics, which holds information about SES by postcode (Paper II).
Multiple imputation was used to impute missing variables. Multivariate statistical models were fitted on both complete and imputed data. In Paper IV, instrumental variable analysis was used as the primary model to reduce bias due to unmeasured confounders.

Results: In Paper I, we found a U-shaped association between BMI and all-cause mortality. Patients with a BMI ~ 30 had the lowest risk of mortality.
In Paper II, we found that SES was an independent risk factor for mortality, especially in the lowest SES tercile compared to patients in the highest.
In Paper III, we observed a significant decrease in the incidence of AMI-induced CS and total mortality in patients with AMI, but CS-associated mortality increased during the study period.
In Paper IV, instrumental variable analysis showed no association between thrombus aspiration and 30-day or 1-year mortality. However, a significant association was found between thrombus aspiration and a reduced risk of stent thrombosis, both at 30 days..

Conclusion: In this thesis, we have confirmed that obesity and high SES is associated with a better prognosis after ACS, that the prognosis for AMI-induced CS has not improved, despite evolution in treatments and the fact that thrombus aspiration is not associated with a reduction in mortality in patients with STEMI. Observational registries can be used to study epidemiological associations and to give randomised trials external validity.

Keywords: Acute coronary syndrome, acute myocardial infarction, risk factors, obesity paradox, socioeconomic status, cardiogenic shock, thrombus aspiration, SWEDEHEART, SCAAR, RIKS-HIA

Sammanfattning på svenska

Akut koronart syndrom (ACS) är en av de vanligaste dödsorsakerna i världen. ACS är ett samlingsbegrepp av akut hjärtinfarkt och instabil kärlkramp. Orsaken till ACS är vanligtvis att en blodpropp bildas på ett åderförkalkningsplack i ett av hjärtats kranskärl vilket leder till att blodflödet som försörjer hjärtmuskeln med blod obstrueras helt eller delvis. När blodflödet hindras utvecklas syrebrist i hjärtmuskeln som tillslut dör och hjärtfunktionen minskar (hjärtsvikt).

I Sverige etablerades patientregister för hjärtsjukvården under 1990-talet. De flesta patienter som vårdas med diagnos ACS registreras i det nationella kvalitetsregistret SWEDEHEART. I SWEDEHEART ingår register för vården på hjärtintensiv vårdavdelningen (RIKS-HIA) och för kranskärlsröntgen och PCI (SCAAR).

Prognosen för patienter med ACS avgörs av många olika faktorer, bland annat patientens bakgrundsfaktorer och den behandling som ges under och efter sjukhusvistelsen. Syftet med detta avhandlingsarbete var att närmare studera hur bakgrundsfaktorerna fetma och socioekonomi påverkar prognosen, närmare studera utvecklingen över tid av akut hjärtsvikt utlöst av hjärtinfarkten samt effekten av att försöka suga ut blodproppen i samband med PCI hos patienter med akut hjärtinfarkt.

I delarbete I visar vi att hög kroppsvikt jämfört med normalvikt i förhållande till längden är associerad till bättre prognos efter ACS.

I delarbete II visar vi att lågt socioekonomiskt status är associerat med sämre prognos efter akut hjärtinfarkt.

I delarbete III visar vi att prognosen hos patienter som utvecklar akut hjärtsvikt i samband med akut hjärtinfarkt inte har påverkats mellan åren 1995 och 2013 trots att behandling med rutinmässig snabb kranskärlsröntgen fått stort genomslag. Dock är det färre patienter som utvecklar akut hjärtsvikt.

I delarbete IV bekräftar vi fynden från stora randomiserade studier där utsugning av blodproppen i samband med PCI hos patient med akut hjärtinfart inte påverkar prognosen.

Sammanfattningsvis visar denna avhandling att patientregister är ett viktigt verktyg att undersöka och bekräfta faktorer som har betydelse vid till exempel ACS. Patientregister är också ett viktigt komplement för att beräfta randomiserade studiers resultat och kontrollera effekten av etablerade behandlingar.

List of papers

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

I. Angerås O., Albertsson P., Karason K., Råmunddal T., Matejka G., James S., Lagerqvist B., Rosengren A., Omerovic E.

Evidence for obesity paradox in patients with acute coronary syndrome: a report from the Swedish Coronary Angiography and Angioplasty Registry

European Heart Journal 2013; 34: 345–353.

II. Bergström G., Redfors B., Angerås O., Dworeck C., Shao Y., Haraldsson I., Petursson P., Milicic D., Wedel H., Albertsson P., Råmunddal T., Rosengren A., Omerovic E.

Low socioeconomic status of a patient´s residential area is associated with worse prognosis after acute myocardial infarction in Sweden

International Journal of Cardiology 2015; 182: 141-147

III. Redfors B., Angerås O., Råmunddal T., Dworeck C., Haraldsson I., Ioanes D., Petursson P., Libungan B., Odenstedt J., Stewart J., Lodin E., Wahlin M., Albertsson P., Matejka G., Omerovic E.

17-year trends in incidence and prognosis of cardiogenic chock in patients with acute myocardial infarction in western Sweden

International Journal of Cardiology; 185: 256–262

IV. Angerås O., Haraldsson I., Redfors B., Fröbert O., Lagerqvist B., Petursson P., Albertsson P., Ioanes D., Odenstedt J., Olsson H., Witt N., Ruck A., Millgård J., Nilsson J., Persson J., Söderbom M., Erlinge D., James S., Råmunddal T., Omerovic E.

Impact of thrombus aspiration on mortality, stent thrombosis and stroke in patients with ST-elevation myocardial infarction: A report from the Swedish Coronary Angiography and Angioplasty Registry

Manuscript

Content

Abbreviations

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CS	Cardiogenic Shock
ECG	Electrocardiogram
IHD	Ischaemic Heart Disease
nSTE-ACS	non ST-elevation acute coronary syndrome
NSTEMI	Non ST-elevation myocardial infarction
PCI	Percutaneous Coronary Intervention
RCT	Randomised Clinical Trial
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive Care Admissions
RRCT	Registry Randomised Clinical Trial
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SES	Socioeconomic status
STEMI	ST-elevation myocardial infarction
SWEDEHEART	The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
TASTE	Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia
TOTAL	The Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI

Introduction

Acute coronary syndrome

Ischaemic heart disease (IHD) is caused by a flow limiting atherosclerotic plaque in the coronary artery causing ischaemia in the heart muscle distal to the plaque. IHD can be divided into two main categories: stable angina and acute coronary syndrome (ACS)[1].

The main difference between stable angina and ACS is the degree of obstruction of the blood flow caused by the coronary plaque. Stable angina is characterised by sufficient blood flow at rest. However during exercise, when the demand is increased the blood supply is insufficient and the heart muscle will become ischaemic[2]. In ACS, blood flow is also insufficient when the heart muscle is at rest. ACS can be caused by a very tight stenosis caused by coronary plaque but the main reason for ACS to develop is when the coronary plaque becomes unstable and ruptures, allowing platelets and the coagulation cascade to form a thrombus on the plaque rupture, hence limiting blood flow [3]. Severe ischemia of the heart muscle eventually results in cell necrosis and a loss of heart muscle mass, i.e., myocardial infarction. The larger the territory affected by vessel supplies, the larger the potential heart muscle injury, i.e., the area at risk; as a consequence, the risk of sudden death, malignant arrhythmias and heart failure is larger.

When the thrombus causes a total obstruction of the vessel, ST-elevation will typically appear on the electrocardiogram (ECG). On the other hand, if the thrombus is only partly obstructing the vessel, ST-depression will usually appear on the ECG. Hence, ACS can be divided into ST-elevation myocardial infarction (STEMI) and non-ST elevation ACS (nSTE-ACS). nSTE-ACS can further be divided, depending on whether or not biomarkers indicating heart muscle injury appear in the blood. In unstable angina (UA), there is no elevation of biomarkers compared to non-STEMI, where there is an elevation of biomarkers[4].

Risk factors

The traditional risk factors for developing ACS are age, male gender, smoking, hypertension, hyperlipidaemia and diabetes mellitus. Together with psychological factors and abdominal obesity, these risk factors account for >90% of the attributable risk factors in myocardial infarction[5].

However, most patients with risk factors do not experience ACS. The question of why coronary plaque rupture occurs in a certain individual but not in another with a comparable risk factor profile is still unresolved. Most likely, there are genetic factors and factors that the individual is exposed to, such as inflammation, imbalance in the neuro-hormonal homeostasis, turbulent blood-flow with altered shear-stress in the vicinity of the plaque. All these factors can negatively influence the individual risk for a person[6]..

Treatmeant

The treatment of ACS has at least two major aims. First, in the acute stage, the aim is to minimise the myocardial injury caused by the thrombus obstructing the coronary vessel and to prevent ischemia-induced arrhythmias, heart failure and sudden death. This is achieved by medical treatment with mainly antithrombotic agents, e.g., acetylsalicylic acid and fondaparinux, which limit the size of the thrombus and counteract further thrombus organisation and revascularisation by percutaneous coronary intervention (PCI) or coronary bypass surgery (CABG) that aims to achieve sufficient blood flow to the myocardial muscle. PCI is today the most common method to revascularise patients with IHD – especially in ACS[7-9].

To salvage heart muscle, the time from symptom onset to revascularisation, especially in STEMI where the vessel obstruction is complete, is crucial. Factors delaying revascularisation in ACS are geographical distances from the patient to the hospital and patient and doctor delay, i.e., symptoms being misunderstood or neglected by the patient, or the doctor's assessment of the patient resulting in a delay in revascularisation treatment[9].

The long-term aim in ACS treatment is to prevent future adverse events, e.g., sudden death, recurrent ACS, arrhythmias and heart failure. This is mainly achieved by medical therapy with beta-blockers[10], ACE-inhibitors[11], statins[12] and dual antiplatelet therapy[13], i.e., ASA and a P2Y12-receptor inhibitor. Coronary revascularisation also prevents further adverse events[14].

Prognosis

Although the morbidity rate caused by ACS has improved in recent years[15-17], IHD is still the most common cause of death in the Western world[1]. Approximately 10% of patients admitted to a hospital with ACS will die within one week of the event. Of the remainder, ~20% will experience a recurrent ACS, cerebrovascular stroke or cardiovascular death within the first year, and an additional 20% will suffer a new event within three years[18].

Prognosis depends on several factors like age, heart failure, peripheral artery disease, and treatment received during and after the hospitalisation[6]. In this thesis, we have chosen to focus on four factors and study their association with prognosis after ACS, with a special focus on patients' coronary angiography, obesity, socioeconomic status, acute heart failure and thrombus aspiration.

Classification	BMI (kg/m^2)	
	Principal cut-off points	Additional cut-off points
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 - 16.99	16.00 - 16.99
Mild thinness	17.00 - 18.49	17.00 - 18.49
Normal range	18.50 - 24.99	18.50 - 22.99
		23.00 - 24.99
Overweight	≥25.00	≥25.00
Pre-obese	25.00 - 29.99	25.00 - 27.49
		27.50 - 29.99
Obese	≥30.00	≥30.00
Obese class I	30.00 - 34.99	30.00 - 32.49
		32.50 - 34.99
Obese class II	35.00 - 39.99	35.00 - 37.49
		37.50 - 39.99
Obese class III	≥40.00	≥40.00

Table 1. The international classification of adult underweight, overweight and obesity according to BMI.
Adapted from WHO.

Obesity

Body mass index (BMI), defined as the weight in kilograms divided by length in meters squared, is a common way of classifying a person's height-weight index. According to the World Health Organization (WHO), a BMI < 25 - >18.5cm/m^2 is classified as a normal weight and a BMI >30cm/m^2 is classified as obesity (Table 1).

Obesity is associated with cardiovascular risk factors such as hypertension, diabetes mellitus and hyperlipidaemia and is, therefore, also linked to a higher risk of cardiovascular disease. In primary prevention, a BMI <25kg/m^2 is recommended[6]. This recommendation was previously also recommended for patients with established coronary disease, e.g., after ACS[19,20]. However, several studies indicate that obesity may actually be protective once disease has been established. This phenomenon is commonly called the 'obesity paradox', i.e., a counterintuitive inverse relationship between prognosis and weight. The obesity paradox was first shown in patients with end-stage renal failure[21] and, thereafter, similar patterns have been shown in numerous cardiac conditions such as heart failure[22], atrial fibrillation[23], sudden death[24] and IHD[25-27].

Socioeconomic status

Socioeconomic status (SES) is a measurement that reflects the level of education, income and occupation[28]. SES can be described either on individual or geographical area levels and is an independent predictor of outcome in numerous medical conditions[29]. The association between SES and the risk of developing coronary heart disease has been established both on individual and geographical area levels[30-32]. The area-level effect has been described both for larger areas, e.g., different economic regions and counties, and for smaller areas such as different neighbourhoods within the same city[32-35].

Cardiovascular mortality in Sweden has decreased by 60% over the past decade, and cardiac care in Sweden is considered to be excellent[36]. Sweden is one of the most egalitarian countries in the world, with a stated ambition of providing equal healthcare to its citizens regardless of SES[37]. Nonetheless, low SES is still independently associated with IHD incidence and mortality also in Sweden[34,38].

Cardiogenic shock

Acute cardiac failure in patients with ACS can be stratified into four groups based on severity, according to Killip class[39] (Table 2). Killip class is one of the most powerful predictors of in-hospital mortality in ACS[40,41]. The mechanisms for patients with ACS to develop Killip class IV, i.e. cardiogenic shock (CS), are heterogeneous such as mechanical complication, (e.g. mitral regurgitation secondary to papillary muscle rupture, ventricular septal defect), global subendocardial ischaemia and/or large transmural infarction. The main risk factors for development of CS are infarctions with large area at risk, long duration from symptom to revascularization and prior comorbidities, e.g. chronic heart failure, valvular disease or concomitant haemorrhage. In an all-comer registry, CS was associated with an in-house mortality rate of >60%[42]. Early revascularisation with PCI or CABG, compared to medical therapy, has been shown to improve

Killip class	Diagnostic criteria	
I	No heart failure	No signs of cardiac decompenasation
II	Heart failure	Lung rales or jugular venous distention
III	Severe heart failure	Overt pulmonary edema
IV	Cardiogenic shock	Persistent hypotension (systolic blood pressure <90 mmHg) and evidence of peripheral vasoconstriction such as oliguria, cyanosis and diaphoresis.

Table 2. Definition of Killip class

the prognosis[43]. However, in the recent IABP-SHOCK II trial, comparing intraaortic balloon counterpulsation (IABP) with no IABP, >97% of the patients were treated with early revascularisation and the mortality rate at 30 days was still ~40% in both treatment groups[44].
Although the mortality rate, despite modern therapies, in patients who have developed CS is discouraging, the frequency of patients with ACS developing CS has decreased during the past decades[45,46]. One reason for this trend could be the rapid implementation of early revascularisation with PCI or CABG[14,47,48].

Thrombus aspiration

A major factor in ACS is the thrombus formation on the ruptured plaque. The thrombus, apart from contributing to occlusion of the vessel, can embolise distally in the coronary artery tree, causing microvascular obstruction[49,50]. Microvascular obstruction is associated with impaired prognosis in patients with ACS[51,52]. Therefore, aspiration of the thrombus before implantation of stent to minimise thrombus burden is an intuitive and appealing approach in ACS patients, especially in patients with STEMI. Several smaller studies have reported that thrombus aspiration may be beneficial for patients with STEMI, due to improvement in coronary microcirculation, decreased infarct size and higher survival rate[53-56]. However, the two large-scale randomised clinical trials (RCT), the TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) and TOTAL (The Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI) trials, did not confirm the clinical benefits of routine thrombus aspiration in STEMI regarding short- and long-term mortality[57-60]. While, in the TASTE study, there was a trend for reduced risk of stent thrombosis and reinfarction, in the TOTAL study thrombus aspiration was associated with an increased risk of stroke[60]. Since the publication of TASTE, the frequency of thrombus aspiration in patients undergoing PCI due to STEMI has decreased in Sweden from 40% in 2011 to 12% in 2014[61].

SWEDEHEART and SCAAR

This thesis is based on studies of patients included in The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). SWEDEHEART was formed in 2009 by merging four existing national quality registries: The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA), The Swedish Angiography and Angioplasty Registry (SCAAR), the Swedish Heart Surgery Registry, and the National Registry of Secondary Prevention (SEPHIA)[62]. In 2010, the Registry for Percutaneous Valve Interventions was incorporated. SWEDEHEART is a national registry of all patients hospitalised for ACS or who are undergoing coronary or valvular intervention for any indication. The registry enrols approximately 80,000 cases each year: 30,000 with ACS, 40,000 undergoing coronary angiography or angioplasty, 7,000 undergoing heart surgery, and 6,000 who are followed for 12–14 months for secondary prevention after ACS.
SCAAR was established in 1999 after the unification of the Swedish Coronary Angiography registry (Acta Coronaria) and the Swedish Coronary Angioplasty registry (SCAP). SCAAR holds data on all patients from all hospitals that perform coronary angiography and PCI in Sweden.

SWEDEHEART, including SCAAR, is independent of commercial funding and is sponsored by Swedish health authorities only. The technology was developed and is administered by the Uppsala Clinical Research Center. Since 2001, the registry has had a web-based case-report platform, with automatic data surveillance. In total, there are 30 hospitals with coronary catheterisation facilities in Sweden, of which 9 are university hospitals. In SCAAR, a coronary angiography procedure is defined as ~50 variables, while PCI procedure is defined as ~200 variables. The information about clinical characteristics and procedural details is entered into the registry immediately after the procedure by the PCI physician, after a review of the clinical information. The information about in-hospital complications, e.g., bleeding and neurological complications, is entered into the registry at discharge, according to local routines at each hospital.

Every Swedish citizen has a unique personal identification number, which, together with name, address and hospital, is included in the registry. The use of personal identification numbers enables the merging of the SWEDEHEART database with the National Cause of Death Register (which includes information about the vital status of all Swedish citizens) and the National Patient Registry (which includes diagnoses at discharge for all hospital stays in Sweden). All patients are informed about their inclusion in the registry and the follow up, and have the right to decline inclusion. The National Board of Health and Welfare, the Swedish Data Inspection Board, and the ethical committee at Uppsala University approved the merging of the registries. Since this merging, researchers have had access to hospital identity but not patient identity.

The registry captures 100% of patients undergoing angiography, angioplasty, or heart surgery and 60% (with considerable variability between hospitals) of patients admitted to hospital due to ACS – the main reason for this is that some ACS patients are admitted to units other than coronary care units. The degree of patient-capture is higher in younger patients and in those with STEMI.

Observational contra randomised studies

In a randomised controlled trial (RCT), patients are randomly allocated a treatment. RCT is considered the gold standard for evidence-based medicine due to its ability to eliminate confounders between treatment groups[63]. However, an important limitation of the RCT design is its restricted external validity due to frequent selection bias of the patients included in the study[64-66]. Because patients included in the RCTs are often highly selected, the results from these studies may not be applicable to the considerable number of patients that were excluded based on specific inclusion and exclusion criteria. In general, patients included in RCTs are younger with fewer comorbidities and a lower risk of mortality[67]. High-quality observational studies, based on large-scale registries and adequate statistical modelling, provide valuable evidence for the external validity of RCTs. Thus, observational studies are an important complement to RCTs[66]. Furthermore, large-scale observational registries are well suited for descriptive stud-

ies to investigate associations between patient characteristics (such as obesity and socioeconomic status) and risk of disease and mortality.

On the other hand, there are many pitfalls that are inherent to observational studies. Because patients are not randomised, it is much more problematic to prove causation between exposure (e.g. risk factor, treatment) and clinical outcomes of interest[68]. When a specific treatment is not randomly assigned, other factors such as the preference of the physician, the hospital and/or patient may influence the choice, or a concomitant disease unknown both to the patient and physician that causes a phenotype (e.g., low BMI, affecting the life expectancy[69]) for which we are not able to adjust.

Statistical considerations in observational studies

The problem with confounders in observational studies is commonly dealt with by using multivariate adjusted regression analysis, e.g., logistic regression or Cox proportional-hazards regression. However, these methods also have their limitations and confounders, especially unmeasured confounders, can still result in biased risk estimates – even after adjustments. In this section, we discuss some methods that are considered useful for control and reduction of bias in observational studies.

Missing Data in Observational Studies

Missing data is a frequent problem in observational studies. A common approach in performing statistical modelling with missing data is to limit analyses to cases with complete data for all variables in the analysis. Such 'complete-case' analyses often introduce considerable bias and are always inefficient. Bias arises if individuals with missing data are not representative of the population of interest. Inefficiency is caused by reduced sample size, which decreases statistical power (e.g., by decreasing the number of events). In SWEDEHEART, there are differ-

ent reasons why some variables have missing data, e.g., some variables are compulsory to register and some are not. For variables that are not compulsory, e.g., smoking status, value of creatinine, weight and height, there is missing data because the value has not been registered. For variables that are compulsory, there is often a category 'unknown' – a form of ad hoc imputation that should be treated as missing data (see below). Variables in SWEDEHEART have been introduced at different times, therefore data for variables which were not a part of the registry at a certain time are missing. In SWEDEHEART, patients with missing data have a worse prognosis than patients without missing data, e.g., in Paper I[70], patients with missing data have a hazard ratio of 1.65 (95% CI 1.53-1.77) for mortality, compared to patients with complete data.

The literature about missing data in statistical modelling is extensive[71,72]. Ad hoc imputation methods, such as the 'last observation carried forward', the insertion of a 'missing category indicator', and the imputation protocols in which each missing value is replaced with an 'assumed or estimated value' are not recommended, as they often lead to reduction or exaggeration of the association of interest[73]. Instead, more accurate imputation methods have been developed based on classification of missing data mechanisms and on probability models[74-76].

Data are missing completely at random if the probability that a particular observation is missing does not depend on observable variables. Data are also missing at random if the probability that observations are missing is independent of the missing data. Data are missing not at random if the probability of missing still depends on the missing value, even after the available data are taken into account. When data are missing not at random, valid inferences require explicit assumptions about the mechanisms that led to the missing data. Missing data in health care registries are often missing at random. Methods to deal with data missing at random fall into three principal categories: likelihood-based approaches, weighted estimation, and multiple imputation. Multiple imputation is the most commonly used because of its flexibility, particularly when multiple variables have missing values. The general recommendations about how to report and handle missing data in observational studies is provided in the consensus document *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE).

Multilevel models

Most clinical registries are organised in levels, i.e., the data are hierarchical or clustered, where the studied object (e.g., patients) is organised into more than one level. One such example of this is that patients treated at the same hospital are likely to be treated in a similar fashion and differently to patients treated at another hospital. Therefore, the patients treated at the same hospital are not completely independent observations from each other. In multilevel models, the non-independent nature of observations belonging to the same cluster is taken into account[77]. In a regression model, data are fitted into the most suitable intercept and coefficient (slope) of the model, i.e., the estimated value for every observation. The difference between the true value and the estimated value is the residual. The estimated value in, for example, a linear regression, is the straight line with its origin from a certain intercept and with a certain slope. However, if data can be organised into different levels, each level is a potential source of unexplained variability. In a multilevel regression model, each level will have its own regression line. Multilevel models can have random intercepts, random slopes, or both (Figure 1).

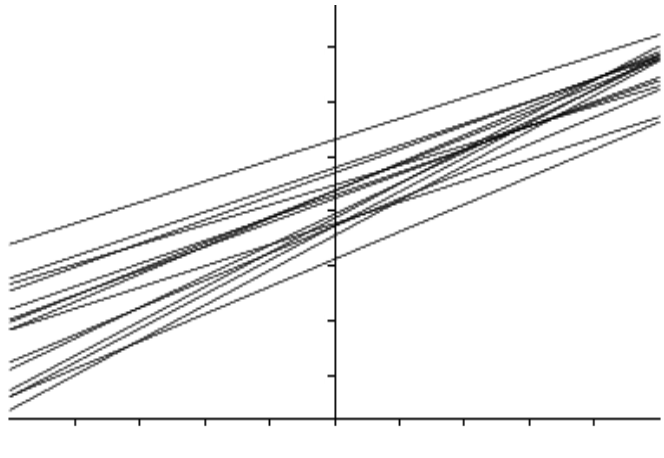

Figure 1. Multilevel linear regression model with random intercept and slope for each cluster.

Propensity score[78]

In observational studies, there are often major differences in the baseline characteristics of the different groups of patients. If a certain treatment is studied, the categorisation of whether a patient was treated or not is made in an intentional fashion, based on patient characteristics, treatment preferences of the hospital/physician and other factors. One way to handle this in a statistical analysis is to assign all patients a propensity score. The propensity score is the value of the probability that a certain patient will belong to a certain group of patients, e.g., treated or untreated. In an RCT, where treatments are randomly assigned (i.e., no consideration is given to patient characteristics) the propensity score is 0.50 for each patient, which is the equivalent of tossing a coin to decide which group each patient belongs to. The propensity score is usually calculated using logistic regression adjusted for the covariates, which are most influential when assigning the patients to the groups of interest. The studied groups of interest with the same propensity score will have equal patient characteristics.

Characteristics of an adequate propensity score are that it balances the difference between the baseline covariates between the groups, that the degree of overlap of the propensity score between the groups is large, and that the discriminatory property, i.e., that the score discriminates between which group a patient most likely belongs to, is high.

Propensity score analysis can be used in four major ways: stratification, matching, covariate adjustment and weighting. In matching, patients belonging to different groups but with similar propensity scores are matched and then the groups are compared. Matching requires a large sample with a large overlap of propensity scores of the groups, since observations not matched are dropped in the analysis. Using propensity score as a covariate adjustment means to simply enter it as a continuous variable in the equation. Stratification is achieved by stratifying the observations into equal-size groups, e.g., quintiles, depending on the propensity score and entering the strata as a covariate in the equation. Weighting is less commonly used and is a method where each patient is reweighted depending on their propensity score.

Instrumental variable analysis

Evaluation of treatment effect based on observational data is problematic due to the presence of unmeasured and/or unknown confounders which makes it difficult to prove causation[68]. Instrumental variable analysis can reduce bias due to unmeasured confounders. To use instrumental variable analysis, one must identify a naturally varying phenomenon in the observed data, which, like the act of randomisation in an RCT, predicts the treatment that will be assigned to the individual patient. To become a valid instrument, a variable has to fulfil some necessary criteria: first, it has to be strongly associated with the received treatment. Second, it must not be associated either directly or indirectly with the outcome, except through the effect of the treatment itself. The instrument, and indirectly the treatment, can thus be considered as allocated to a patient at random – thus mimicking the randomisation process in an RCT – and minimising the differences in unmeasured confounders between the groups. One commonly used instrument is geographical location, e.g., different countries or administrative health care regions[79-81]. The estimate of instrumental variable analysis is mainly determined by subgroups, whose treatment status depends on which category of the instrument the patient belongs to, e.g., patients with the same characteristics receiving different treatments in different geographical regions[82] (Figure 3). A common method of instrumental analysis is two-stage least squares (2SLS) regression analysis[83].

Aims

The major aims of this project were to elucidate factors that affect the prognosis in patients with ACS by using SWEDEHEART (especially SCAAR) and to explore statistical methods of how to improve analyses in observational registries.

Specific aims for each paper:

- To study the relationship between BMI and mortality in patients with ACS undergoing coronary angiography.
- To study the influence of area-level SES on mortality in patients hospitalised due to AMI.
- To investigate the trends in incidence and prognosis of AMI-induced CS between 1995 and 2013
- To study the impact of thrombus aspiration on mortality, stroke and stent thrombosis in patients with STEMI undergoing PCI

Patients and methods

All studies in this thesis are based on patient cohorts created from the national quality registries SCAAR or RIKS-HIA. In papers I and IV, a cohort of consecutive patients undergoing coronary angiography at all Swedish centres was created using SCAAR. In papers II and III, a cohort of consecutive patients admitted due to ACS to hospitals in Region Västra Götaland, western Sweden, was created using RIKS-HIA.

The Kaplan-Meier survival curve with log-rank test was used to examine unadjusted survival. Missing data were imputed using multiple imputation chained equations[84] with 5-20 data set. Adjusted models were fitted on both complete case data and on imputed data. Logistic regression (Paper IV) and multinominal regression (Paper II) were used to calculate the likelihood of a patient belonging to a certain group. The calculated propensity score was then entered into the models as quintiles (stratified).

Paper I

In this study, we used SCAAR merged with the National Cause of Death Register and the National Patient Registry, to establish a cohort of all consecutive patients who underwent coronary angiography for ACS in Sweden between May 2005 and December 2008. The patients were divided into nine BMI categories according to the National Institute of Health – AARP cohort[85]. The primary outcome was all-cause mortality in the patients who had significant stenosis (0.50% diameter narrowing) in one or more coronary arteries. The patients with significant CAD were divided into subgroups, according to the physician's initial treatment decision, such as coronary artery bypass grafting (CABG), PCI, or

medical therapy. The treatment strategy was defined based on the intention-to-treat decision following the index catheterisation.
To evaluate the association between BMI and mortality, the multivariable-adjusted hazard ratios (HR) were calculated using Cox proportional-hazards regression, adjusted for patient characteristics. The continuous risk relationship between BMI and all-cause mortality was analysed by entering BMI as a continuous variable into a fractional polynomial Cox proportional-hazards regression.

Paper II

In Paper II, we used RIKS-HIA to establish a cohort of consecutive patients admitted to one of three hospitals in the city of Gothenburg, Västra Götaland, due to NSTEMI or STEMI between 1995 and 2013. The data was merged with the National Cause of Death Register and with data obtained from the Swedish Central Bureau of Statistics, which holds postcode information about SES. Each postcode area within the city was ranked according to the average SES of its residents. SES was calculated as combined income and educational level.

The primary endpoint of the study was all-cause mortality. The three SES groups were compared using Cox proportional hazards regression and logistic or multiple linear regression. Differences in patient characteristics were accounted for by adjusting for covariates or by propensity scores. Multilevel models accounting for calendar year and/or clustering of patients within different hospitals were fitted and compared to single-level models. Subgroup analyses were performed, by inclusion of interaction terms in Cox proportional hazards models, to detect associations between area-level SES and calendar year, as well as gender, age, or presence of ST-elevation, respectively.

Paper III

In Paper III, we used RIKS-HIA, merged with the National Cause of Death Registry, to establish a cohort of patients admitted to hospital in Västra Götaland with ACS between 1995 and May 2013. We compared patients with CS to patients without CS. Patients with CS who had been hospitalised more than once for ACS were included in the analysis at the time they developed CS. All other patients were included at first occurrence in the registry.

We studied the contribution of the risk factor profile in developing CS after acute myocardial infarction by fitting a logistic regression model with patient covariates. We tested whether CS-associated mortality decreased over time by including an interaction term between calendar year, as a centred variable, and CS. We also tested whether the trends in incidence of CS and/or prognosis post-AMI differed between patients with STEMI and NSTEMI by including an interaction term if the patient presented after 2005 and whether they presented with STEMI or NSTEMI. We assessed the predictive power of risk factors and treatment choices on the prognosis of patients who developed CS with a logistic regression model on imputed data with survival up to 30 days as the dependent variable. We also compared the risk of dying among patients who developed CS before and after 2005, which was when primary PCI replaced thrombolysis as the preferred reperfusion strategy.

Paper IV

Paper IV includes all consecutive patients undergoing PCI due to STEMI between 2005 and September 2014 in SCAAR. Data was merged with the National Patient Registry. Patients were then categorised according to whether thrombus aspiration was used in conjunction with PCI or not.

The primary endpoint was mortality at 30 days. The secondary endpoints were mortality at one year, stent thrombosis at 30 days and at one year, and reported

in-hospital neurological complication. Stent thrombosis was defined as an acute stent occlusion verified by coronary angiography. Neurological complication was defined as a new neurological deficit during PCI or during in-hospital stay after index PCI.

Our primary model was based on an instrumental variable 2SLS regression, with administrative health care regions in Sweden based on geographical location as the treatment-preference instruments. Our secondary models were based on an unadjusted and propensity score-adjusted multilevel logistic regression with administrative healthcare regions and individual hospitals worked into the regression model as random-effects variables.

Results and conclusions

Paper I

Between May 2005 and December 2008, there were a total of 64,436 patients, of whom 54,419 had significant coronary artery disease (primary analysis). In 29% (18,743) of the cases, there were missing variables. The mean follow-up time was 21 months (SD±13 months). In the adjusted analysis of patients with significant coronary artery disease, with BMI entered as a continuous variable, we found a U-shaped association between BMI and all-cause mortality (Figure 2). Patients with a BMI ~ 30 had the lowest risk of mortality. When comparing complete case models to models with imputed data, we found that complete case models tended to magnify the differences in outcome between the BMI groups compared to the imputed models (Table 3).

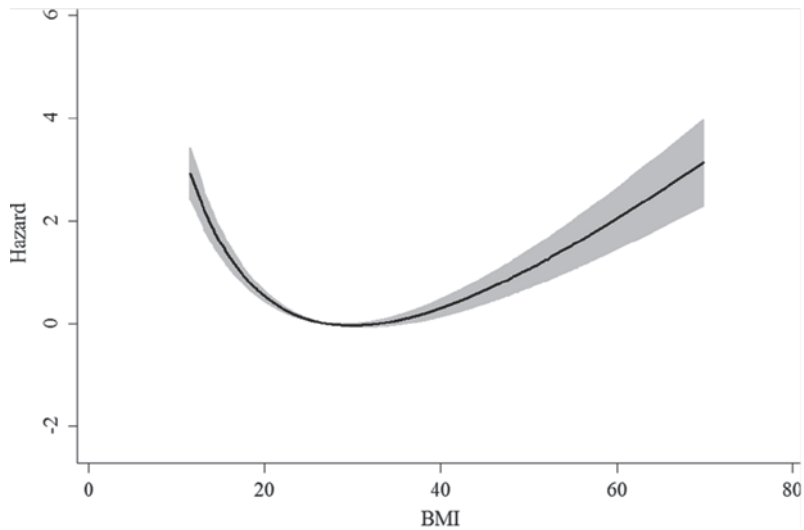

Figure 2. Adjusted fractional polynomial Cox-proportional-hazards regression (95% CI, shaded area)with continuous risk relationship between BMI and all-cause mortality in patients with ACS and significant coronary disease.

We further studied patients divided by choice of treatment (i.e., PCI, CABG or medical therapy) after angiography, and patients with no visible coronary artery disease on angiography and found similar patterns, although not all were statistically significant compared to the primary analysis.
In patients with significant coronary artery disease, there was no difference between the BMI categories of in-hospital, 30-day mortality, or in a recurrent hospitalisation due to ACS, heart failure or stroke.

Conclusion:
In this large and unselected group of ACS patients, the relation between BMI and mortality was U-shaped, with the nadir being among the overweight or obese patients, with the underweight and normal-weight patients having the highest risk. These data strengthen the concept of the obesity paradox. Multiple imputation methods seem to reduce confounders caused by missing data.

Paper II

Between1995-2013, 10,895 patients were hospitalised due to myocardial infarction in the Gothenburg metropolitan area. The three SES tertiles contained 4,280 (low), 3,570 (middle), and 3,048 (high) patients, respectively. SES predicted baseline risk factors like obesity, smoking, diabetes and hyperlipidaemia, but not hypertension. Although adjustments for known traditional risk factors and calendar year were made, SES remained an independent risk factor for mortality, with highest risk of mortality associated with areas with the lowest SES tertile (Figure 4). Adjustment with propensity score quintiles tended to give smaller differences in risk than complete covariate adjustment. SES did not affect the treatment, i.e., revascularisation or prescribed medical therapy that was given during the hospital stay or at discharge.
There was a significant interaction between SES and age and between SES and STEMI, i.e., the difference in prognosis between high and low SES is particularly seen in patients with age <75 years and in patients with STEMI. Patients with low SES were at higher risk of pre-hospital cardiogenic shock and in-hospital heart failure, but not for pre-hospital cardiac arrest.

		BMI group (kg/m^2)								
	n	<18.5	18.5 to 21	21 to < 23.5	23.5 to < 25	25 to <26.5	26.5 to <28	28 to <30	30 to <35	>35
Unadjusted analysis	41731	2.94 (2.27-3.83)	1.31 (1.08-1.59)	1.0	0.76 (0.65-0.88)	0.62 (0.53-0.73)	0.52 (0.44-0.62)	0.55 (0.46-0.65)	0.52 (0.44-0.61)	0.75 (0.60-0.94)
Adjusted* complete case analysis	38667	1.90 (1.41-2.55)	1.13 (0.92-1.40)	1.0	0.79 (0.67-0.93)	0.75 (0.63-0.89)	0.63 (0.52-0.76)	0.71 (0.60-0.86)	0.66 (0.55-0.79)	1.04 (0.81-1.34)
Unadjusted multiple imputation	54419	2.77 (2.13-3.61)	1.26 (1.05-1.52)	1.0	0.81 (0.69-0.94)	0.72 (0.63-0.84)	0.66 (0.57-0.77)	0.67 (0.57-0.78)	0.62 (0.53-0.73)	0.73 (0.58-0.92)
Adjusted* multiple imputation	54419	2.04 (1.57-2.04)	1.13 (0.93-1.34)	1.0	0.85 (0.73-0.99)	0.82 (0.71-0.95)	0.76 (0.65-0.88)	0.78 (0.66-0.92)	0.75 (0.64-0.89)	0.98 (0.78-1.24)

*Adjustments are made for age, gender, prior PCI, prior CABG, diabetes mellitus, smoking status, treated hypertension, treated hyperlipidaemia, previous MI, prior stroke, prior kidney failure, prior heart failure, prior cancer, prior peripheral vascular disease, prior dementia, prior chronic obstructive pulmonary disease, indication for coronary angiography, angiographical finding, and primary treatment decision

Table 3. Adjusted and unadjusted hazard ratios (95% CI) of cumulative mortality according to the BMI group from different Cox proportional hazards regression models in patients with acute coronary syndrome and significant stenosis on angiography.

Conclusion:
Even in a country with strong egalitarian traditions like Sweden, lower SES associates with worse prognosis after AMI, and this has not improved over the past decade. The association persists after adjustments for differences in traditional cardiovascular risk factors and for differences in received treatment.

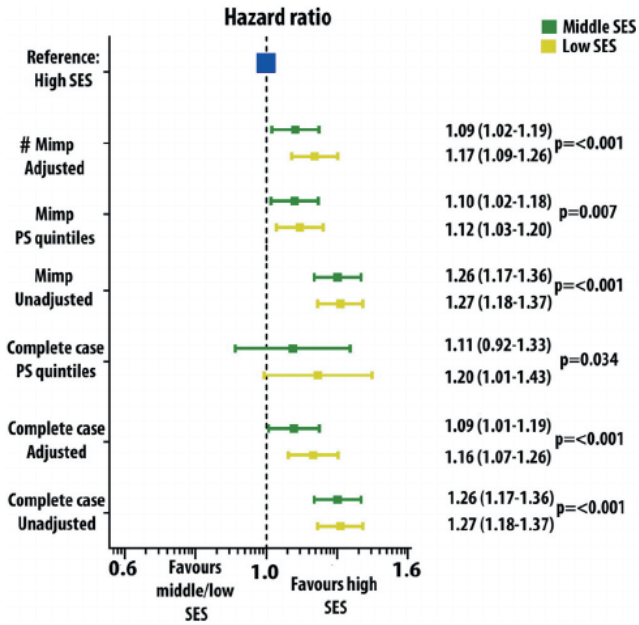

Figure 3. Hazard ratio, risk of death. Eight different statistical models were fitted to estimate hazard ratio after acute myocardial infarction for patients residing in areas of high, middle or low SES. P-values refer to test for trend across SES categories. Mimp, multiple imputation data; PS, propensity score; SES, socioeconomic status; # primary model.

Paper III

Between 1995 and May 2013 44, 414 patients were treated for AMI in Region Västra Götaland of whom 3,654 had CS. Patients with cardiogenic shock were older, more likely to be women, and have diabetes mellitus. They were also more likely to have previously had AMI and present with STEMI. On the other

hand, patients with cardiogenic shock were less likely to have hypertension or present with atrial flutter or fibrillation.

Between 1995 and 2012,we observed significant decreases in the incidence of AMI-induced CS (Figure 4A) and total mortality in patients with AMI (Figure 4B), but CS-associated mortality increased (Figure 4C). The incidence of CS decreased to a greater extent among patients with NSTEMI than patients with STEMI. Previous myocardial infarction, smoking, female gender, hyperlipidaemia, diabetes mellitus, age, atrial fibrillation and presenting with STEMI were all associated with an increased risk of developing cardiogenic shock, whereas hypertension and being admitted after 2005 were associated with a lower risk of cardiogenic shock (Table 4).

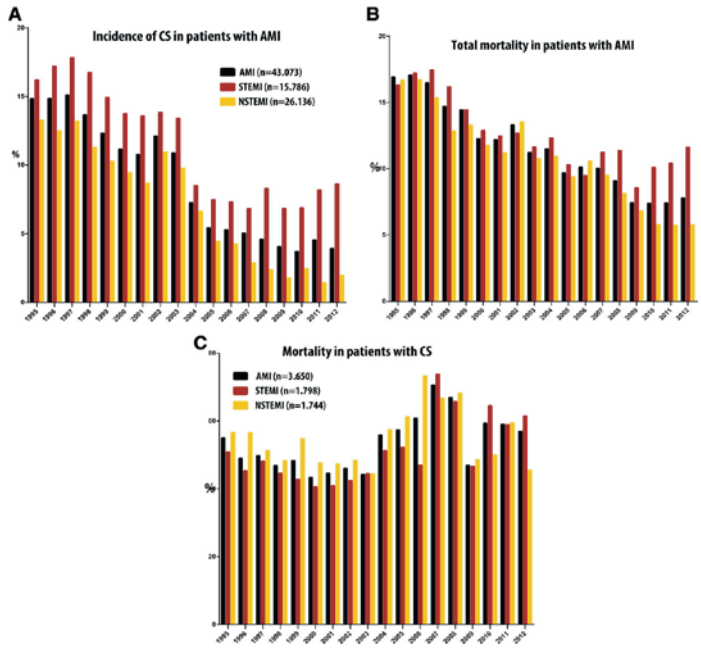

Figure 4. Trends in incidence and mortality in cardiogenic shock. A. Incidence of cardiogenic shock (CS) and admission to the ward in Region Västra Götaland per calendar year for all patients with AMI. B. Total 30-daymortality in patients with acute myocardial infarction (AMI) in Västra Götaland per calendar year. C. 30-daymortality in patients with AMI-induced CS at admission in Region Västra Götaland per calendar year. Non-ST-elevation myocardial infarction (NSTEMI); ST-elevation myocardial infarction (STEMI).

Covariate adjusted logistic regression models fitted on imputed data, as well as complete case data, consistently revealed an approximately ten times higher risk of death among patients who developed CS. Unadjusted and adjusted cardiogenic shock-associated risk of death increased over the study period, with an odds ratio of 1.08 per year (1.06–1.10, p = b0.001), and 1.02 (1.01–1.03, p b 0.001), respectively. The odds ratio for dying once the patient had developed cardiogenic shock if he or she presented after 2005, compared to before 2005, was 2.44 (2.06–2.89, p b 0.001) or 2.89 (2.41–3.47, p b 0.001) in unadjusted and age- and gender-adjusted logistic regression models, respectively.

Variable	OR	95% confidence interval	p value
Female gender	1.11	1.03–1.19	0.007
Age	1.03	1.02–1.03	<0.001
Hypertension	0.85	0.79–0.92	<0.001
Hyperlipidemia	1.15	1.04–1.28	<0.001
Diabetes mellitus	1.20	1.10–1.30	<0.001
Smoking	1.36	1.24–1.50	<0.001
STEMI	2.34	2.17–2.52	<0.001
Previous myocardial infarction	2.07	1.91–2.25	<0.001
Previous PCI	0.98	0.83–1.15	0.788
Previous cardiac surgery	0.84	0.72–0.98	0.025
Atrial flutter/fibrillation	1.48	1.33–1.64	<0.001
Beta blocker treatment	0.73	0.68–0.78	<0.001
Admittance after 2005	0.39	0.36–0.42	<0.001

Table 3. Multivariate logistic regression (risk of developing cardiogenic shock). Covariate adjusted Logistic regression model on imputed data with development of cardiogenic shock as the dependent variable.

Conclusion:

In conclusion, our study demonstrates that the incidence of AMI induced CS has declined in western Sweden over the past decade. However, once CS develops the mortality is higher today than it was in 1995.

Paper IV

During the study period, we identified 45,151 patients who underwent primary PCI. We excluded patients without a Swedish personal identification number (n=2,142), patients with a missing follow-up time (n=17), and patients with missing information about treatment with thrombus aspiration (n=163). After the exclusion of these patients, 42,829 patients (29% female) were included in the study, of whom 10,660 (25%) were treated with thrombus aspiration. The frequency of thrombus aspiration varied between the administrative health care regions from 18% to 35%. The 30-day mortality rate was 6.1% in the thrombus aspiration group and 6.4% in patients who did not receive this treatment. . The primary analysis – 2SLS regression with health care region as the treatment preference instrumental variable – showed no difference in 30-day or 1 year mortality (Table 4). The primary model with instrumental variable analysis showed a significant association between thrombus aspiration and reduced risk of stent thrombosis both at 30 days and at one-year. However, landmark analysis after 30 days has shown no difference between the groups (Table 4). There was no difference in in-hospital stroke between the groups.
The secondary analyses, with multilevel logistic regression unadjusted and adjusted for propensity score quintiles, showed that thrombus aspiration is associated with an increased risk of mortality, but it is not as strongly associated with a decrease in the risk of stent thrombosis.

Conclusion:
This study provides important evidence for the external validity of the TASTE and TOTAL trials regarding mortality. Thrombus aspiration during primary PCI may decrease the risk of stent thrombosis and future studies should determine whether this treatment might be cost-effective for the prevention of stent thrombosis, even in the absence of survival benefit.

Compared to traditional multivariate analysis, instrumental variable analysis, accounting for unmeasured confounders, gives a result that is comparable to that reported by the large RCTs.

Table 4.

	IV-2SLS regression*	Unadjusted multilevel logistic regression#	Complete case PS-adjusted multilevel logistic regression#	PS-adjusted multilevel logistic regression after multiple imputation#
Death within 30 days	-1.2 (-5.4–3.0) p=0.57	0.95 (0.87-1.05) p=0.32	1.21 (1.07-1.37) p<0.01	1.16 (1.06-1.28) p<0.01
Death within one-year	-2.4 (-7.6–3.0) p=0.37	0.93 (0.86-1.01) p=0.07	1.16 (1.05-1.28) p<0.01	1.12 (1.04-1.22) p<0.01
Stroke or neurologic complications in-hospital	0.1 (-0.8-1.1) p=0.76	1.05 (0.70-1.58) p=0.80	1.31 (0.81-2.12) p=0.27	1.30 (0.86-1.95) p=0.22
Stent thrombosis within 30 days	-2.7 (-4.1 - -1.4) p<0.001	0.69 (0.50-0.95) p=0.02	0.74 (0.50-1.08) p=0.13	0.75 (0.54-1.03) p=0.08
Stent thrombosis within one-year	-3.5 (-5.3 - -1.7) p<0.001	0.74 (0.58-0.95) p=0.02	0.75 (0.55-1.02) p=0.06	0.79 (0.61-1.01) p=0.06
Stent thrombosis within one-year landmark¤	-0.47 (-1.5-0. 66) p=0.42	1.05 (0.73-1.51) p=0.79	1.15 (0.76-1.74) p=0.49	1.15 (0.79-1.67) p=0.46

IV-2SLS regression; instrumental variable two-stage least-squares regression, PS; propensity score

* Risk reduction/100 patients (95% CI)

Odds ratio (95% CI)

¤ landmark analysis after exclusion of patients with stent thrombosis within 30 days

Table 4.
IV-2SLS regression; instrumental variable two-stage least-squares regression, PS; propensity score
* Risk reduction/100 patients (95% CI)
# Odds ratio (95% CI)
¤ landmark analysis after exclusion of patients with stent thrombosis within 30 days

Discussion

Main findings

In this thesis, we have confirmed the presence of an obesity paradox after ACS in patients undergoing angiography and also that SES is a prognostic factor after ACS, even in an egalitarian country like Sweden. We also found that the prognostic impact of CS in patients with ACS has not improved, despite the evolution in treatments such as early revascularisation. However, the incidence of cardiogenic shock has decreased. We have confirmed and given external validity to the large randomised trials, which show that thrombus aspiration does not impact the prognosis after STEMI in patients undergoing primary PCI.

Obesity paradox

The mechanism for the obesity paradox is still unknown. All studies illustrating the obesity paradox are of epidemiological nature, making the relationship between BMI and mortality associative not causative. However, there are tentative explanatory theories. For instance, obesity may protect against malnutrition and energy wastage post-revascularisation and an altered neuroendocrine status in obese patients may play a role in the remodelling of the injured heart muscle after ACS. Further, the size of the coronary vessels increases with increasing BMI, and small vessels is a risk factor for worse outcome after PCI and CABG[86], hence the improved outcome in obese individuals. In Paper I, we tentatively propose that obesity may protect against malignant ventricular arrhythmias during and after ACS, and therefore decrease the risk of sudden death. This hypothesis is indirectly supported by clinical evidence from patients with heart failure (HF) secondary to AMI[24], with cautious support from the data in Paper I. During the follow-up period, the overweight and obese patients did not differ in

their frequency of hospitalisation for HF, ACS, and stroke – common causes of death in this population – suggesting that obesity is not associated with lower risk of these clinical events. By process of elimination, these observations strengthen the hypothesis that obesity may protect against malignant ventricular arrhythmias, as it is another frequent cause of mortality in patients with CAD. Experimental evidence is emerging that suggests adipose tissue, as the largest endocrine organ[87], produces hormones (e.g., leptin, adiponectin, resistin) that may have cardioprotective effects in ACS[88-91]. There is considerable evidence demonstrating that leptin and adiponectin have direct cardioprotective effects. These hormones possess anti-inflammatory, antiapoptotic, and anti-hypertrophic effects, as well as reducing infarct size[92-94]. All these effects may lower arrhythmogenicity in the infarcted myocardium and, therefore, potentially prevent sudden death.

The growing evidence for the existence of an obesity paradox in patients with ACS has been acknowledged by the ESC guidelines for cardiovascular disease prevention[6]. The evidence that weight reduction in itself has a positive prognostic value after ACS is very scarce. Actually, some evidence suggests that weight loss after ACSs might in fact have a negative effect[95]. However, a cautious interpretation of the current body of evidence is recommended and should not be taken as support of the status quo in obese patients. The attention should be on reaching the recommended targets for exercise, smoke cessation, blood pressure and lipid levels, rather than a BMI target.

BMI is the most commonly used measure of obesity, however it does not distinguish between adipose and lean tissue, or between central and peripheral adiposity. Combining BMI and waist circumference may predict risk better than BMI alone[96].

Socioeconomic status

One suggested explanation for the negative impact of SES on prognosis after ACS is that lower SES is associated with a lifestyle leading to a higher burden of

traditional cardiovascular risk factors[97-100]. An explanation for our findings could plausibly be that SES, in previous reports[101,102] reflects the adherence to prescribed medication and life style changes. Another possible explanation of SES's influence on prognosis may be 'status syndrome', which links perceived unfairness in society, less control over one's life and limited social participation (i.e., a psychological manifestation of social inequality) to negative biological effects caused by prolonged psychosocial stress[103]. The existence of status syndrome is supported by experimental studies that show how low social position is linked to increased activity of the sympatho-adrenomedullary axis and the hypothalamic-pituitary-adrenal axis[104]. Overactivity of these two systems after AMI could be expected to increase the risk of new myocardial infarction, sudden death and/or heart failure[104,105].

Despite well-developed social support for all citizens and a low poverty rate, prognosis after myocardial infarction is directly influenced by the SES of the area in which a patient resides. Thus, for patients with myocardial infarction, equity in health is not achieved by the Swedish health care system[106]. Furthermore, the situation does not appear to have improved over the past decade. Data obtained during the last part of the twentieth century indicated that Sweden and other Nordic countries, despite having long histories of egalitarian politics and low poverty rates, suffered from larger inequalities in cardiovascular mortality compared with central European countries[107]. Almost twenty years later, these health inequalities persist. It is possible that status syndrome is more detrimental in more egalitarian societies than in less egalitarian societies.

Cardiogenic shock

During the study period of Paper III, routine coronary angiography and revascularisation was adopted in NSTEMI patients and a treatment switch from thrombolysis to PCI took place for STEMI patients. It is reasonable to argue that this switch in treatment algorithm was responsible for the decrease in the mortality rate at 30 days after hospital admission, as well as in the incidence of CS. However, despite the progress in revascularisation treatment, the mortality rate in CS

patients increased during the study period. Patients who were hospitalised for CS after 2005 had a higher burden of cardiovascular risk factors and were therefore most likely at higher risk. Even if the risk of mortality was higher after adjustment for these risk factors, the residual confounder is a possible explanation as to why mortality increased during the study period. The lack of a temporal trend in the proportion of patients who developed CS after admission makes this assumption even more likely. Regardless of the mechanisms behind the increase in mortality, it is evident that care for patients with cardiogenic shock has not improved prognosis and development of new treatment regimens are needed. Neither inotropic drugs nor IABP has proven to improve mortality in CS patients[108,109]. However, as the availability of mechanical ventricular assist devices (VAD) is increasing, their use could be a realistic approach to assisting recovery in CS patients[110]. A large-scale RCT, randomising CS patients to VAD or medical therapy is highly warranted.

Thrombus aspiration

The large number of prospectively followed STEMI patients in SCAAR provided a unique opportunity to evaluate the association between thrombus aspiration and important clinical outcomes in unselected patients from everyday clinical practice. Prior to the TASTE and TOTAL trials, meta-analyses of smaller studies had shown diverging results. While some studies have reported improved survival with thrombus aspiration, others did not[56,111-113]. The results in Paper IV are in agreement with the results from the TASTE and TOTAL studies, which have shown that routine thrombus aspiration does not decrease mortality. The present study, therefore, constitutes important evidence for the external validity of these two trials regarding mortality. We used a statistical method based on treatment preference instrumental variable analysis with the 2SLS regression[82,83,114]. This method allows adjustment for measured as well as unmeasured confounders. If the central methodological assumptions are fulfilled (i.e., a valid instrument that reflects a naturally occurring randomisation process), observational studies based on the instrumental variable method mimic the act of randomisation in RCTs. Actually, the results from the instrumental variable-based statistical modelling

have shown risk estimates closer to those from the TASTE and TOTAL trials. Whereas the results based on the propensity score-adjusted logistic regressions are similar to a previous study on thrombus aspiration from SCAAR[115]. The differences in outcome between the analyses most likely reflect the presence of unknown selection bias in the study population, and they are in line with conclusions drawn in other fields[116].

Limitations

First, as described earlier, in observational studies one cannot rule out the possibility of selection bias, residual confounding and survival bias. By adopting the statistical methods mentioned earlier, especially instrumental variable analysis, we believe that this limitation is reduced but not omitted.

Secondly, the SWEDEHEART registry does not hold data on pharmacological treatment and compliance with pharmacological treatment after discharge.

Third, we do not have data on cause-specific mortality.

Fourth, a proportion of the patients in the studies have missing data. Patients with missing data had higher mortality and, therefore, their exclusion from analyses might have produced biased results. However, results from data in which missing variables had been imputed using the multiple imputation method were congruent with the data from complete case analyses.

Lastly, in all papers, several statistical models were used, which increases the risk of associations occurring by chance.

Future perspective

Considering the limitations of both RCTs and observational studies a new concept has been developed called the registry-based randomised clinical trial (RRCT). RRCT treatments are assigned to patients after randomisation within a clinical registry. The TASTE trial was the first RRCT and it randomised 7,244 patients to adjunct thrombus aspiration or PCI alone within SCAAR. All PCI centres in Sweden took part in the TASTE trial. During the study period, 11,709 patients underwent PCI due to STEMI, of whom ~60% were included in the study. As the randomisation and follow-up was mainly conducted within the registry, complete information is also known about patients who are entered into the registry but who are not taking part of the study[57,59]. A further advantage of the RRCT (particularly with a large number of participating hospitals) over traditional RCT is the capacity to include numerous patients over a short time in a cost-efficient way. In SWEDEHEART, several RRCTs have now been conducted or are ongoing. Both the DETOX trial[117] (comparing oxygen therapy to room air in 6,600 patients with suspected acute myocardial infarction) and the iFR-SWEDEHEART[118] study (comparing instantaneous wave-free ratio to fractional flow reserve in 2,000 patients with stable angina or non-STEMI ACS and intermediate stenosis of 30-80%) have been completely recruited during 2015. The VALIDATE trial, comparing unfractionated heparin to bivalirudin as an anticoagulation therapy during PCI in 6,000 patients with NSTEMI and STEMI is anticipated to be fully recruited during 2016 (http://www.ucr.uu.se/swedeheart/index.php/forskning-swedeheart/pagaende-rrct).

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