FACULTY OF HEALTH SCIENCE, AARHUS UNIVERSITY

Impact of dialysis-requiring acute kidney injury on 5-year mortality after acute myocardial infarction-related cardiogenic shock – A population-based nationwide cohort study

Research year report

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Preface

This research year report is based on a study carried out during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark, from September 1 2013 to August 31 2014. I have been introduced to the science of epidemiology and statistics during this year.

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Abbreviations

ACE	Angiotensin converting enzyme
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ARB	Angiotensin receptor blocker
ATE	Population average treatment effect
ATT	Average treatment effect among treated
CABG	Coronary artery bypass grafting
CAG	Coronary angiography
CI	Confidence interval
D-AKI	Dialysis-requiring acute kidney injury
DCRS	Danish Civil Registration System
DHSPR	Danish Health Service Prescription Registry
DNRP	Danish National Registry of Patients
GFR	Glomerular filtration rate
GLM	Generalized linear model
HR	Hazard ratio
ICD	International Classification of Diseases
ICD-8	International Classification of Diseases, 8th revision
ICD-10	International Classification of Diseases, 10th revision
IQR	Inter quartile range
MI	Myocardial infarction
MRR	Mortality rate ratio
NSAID	Non steroid anti-inflammatory drugs
NSTEMI	Non ST-elevation myocardial infarction

OR	Odds ratio
PCI	Percutaneous coronary intervention
PS	Propensity score
RAAS	Renin-Angiotensin Aldosterone System
RIFLE	Risk, Injury, Failure, Loss, and End stage kidney disease (criteria for acute kidney injury)
RR	Relative risk
SCr	Serum creatinine
SMRW	Standardized mortality ratio weighting
STEMI	ST-elevation myocardial infarction

Contents

Abstract

Background: Myocardial infarction with cardiogenic shock is serious and often complicated by acute kidney injury. We examined the impact of dialysis-requiring acute kidney injury (D-AKI) on mortality and assessed the role of comorbidity.

Methods: In this population-based cohort study conducted in Denmark during 2005–2012, we used population-based medical registries to identify patients diagnosed with first-time myocardial infarction with cardiogenic shock and assessed their D-AKI status. We computed in-hospital mortality risk and adjusted relative risk (RR) of in-hospital mortality. For hospital survivors, we computed 5-year mortality after discharge using Kaplan-Meier methods. We estimated 5-year hazard ratios (HRs) for death after discharge, comparing D-AKI with non-D-AKI patients using a propensity-score adjusted Cox regression model.

Results: We identified 5,131 patients with cardiogenic shock, among whom 13% had D-AKI. The in-hospital mortality rate for D-AKI patients was 60% (95% confidence interval (CI): 56%–64%), and that for non-D-AKI patients was 36% (95% CI: 35%–38%). D-AKI remained associated with increased in-hospital mortality after adjustment (adjusted RR=1.67, 95% CI: 1.56–1.79). Among the 3,059 hospital survivors, 5-year cumulative mortality for D-AKI patients compared with non-DAKI patients was 43% (95% CI: 37%-53%) vs. 29% (95% CI: 29%-31%). The adjusted HR for death within 5 years was 1.55 (95% CI 1.22–1.96) for D-AKI patients compared with non-D-AKI patients. The relative impact of D-AKI lessened with increasing comorbidity level.

Conclusion: Patients with D-AKI following myocardial infarction-related cardiogenic shock have both higher short-term and long-term mortality than non-D-AKI patients with this cardiac condition.

Dansk resumé

Baggrund: Kardiogent shock som komplikation til akut myokardieinfarkt (AMI) er en alvorlig tilstand, som ofte kompliceres med akut nyresvigt. Vi undersøgte effekten af dialyse-krævende akut nyresvigt (D-AKI) på mortalitet efter AMI med kardiogent shock, samt den mulige betydning af komorbiditet på effekten af D-AKI.

Metode: Vi udførte et populationsbaseret kohortestudie i Danmark fra 2005-2012 ved brug af danske nationale medicinske registre. Vi identificerede alle patienter med et førstegangstilfælde af AMI og kardiogent shock samt eventuel behandling med akut dialyse. Vi beregnede den absolutte mortalitetsrisiko under indlæggelse samt den justerede relative risiko (RR) for død under indlæggelse. For kohorten af patienter, der overlevede til udskrivelse, beregnede vi 5-års mortaliteten efter udskrivelsen ved brug af Kaplan-Meier metoden. Vi anvendte Cox regressionsmodel til at beregne den propensity score justerede hazard ratio (HR) for 5-års mortalitet efter udskrivelse ved at sammenligne patienter med D-AKI med patienter uden D-AKI.

Resultater: Vi identificerede 5.131 patienter med AMI-relatered kardiogent shock, hvoraf 13 % havde D-AKI. Mortalitetsrisikoen under indlæggelse var 60 % (95% CI: 56 %-64 %) for patienter med D-AKI, mens den for patienter uden D-AKI var 36 % (95% CI: 35 %-38 %). D-AKI var associeret med øget mortalitet under indlæggelse (justeret RR=1,67 (95% CI: 1,56-1,79)). Blandt de 3.059 i kohorten af patienter i live indtil udskrivelse var 5-års risikoen for død for patienter med D-AKI til sammenligning med patienter uden D-AKI 43% (95% CI: 37-53) vs. 29% (95% CI: 29-31). Den propensity score justerede HR for 5-års mortalitet var 1,42 (95% CI: 1,11-1,81) for D-AKI patienter sammenlignet med ikke-D-AKI patienter. Resultaterne var mindsket hos patienter med kroniske tilstande.

Konklusion: Patienter med D-AKI efter MI med kardiogent shock har både en forhøjet mortalitet under indlægglse og op til 5 år efter udskrivelse sammenlignet med patienter uden D-AKI.

Exctract

Introduction

Despite considerable improvement in treatment, acute myocardial infarction (MI) remains a leading cause of death worldwide.[1,2] The predominant cause of death in patients hospitalized for MI is cardiogenic shock.[3,4] The risk of this complication is approximately 5%–9%.[3, 5-7] Subsequent in-hospital mortality is as high as 45%–65%,[4,6] almost ten times higher than in MI patients without cardiogenic shock.[4,8,9]

Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function, ranging from mild kidney dysfunction to severe AKI with need for dialysis. AKI is a complication in half of patients with MI-related cardiogenic shock and causes a marked elevation of in-hospital mortality risk.[10,11] In one study, 25% of cardiogenic shock patients with AKI required dialysis,[11] which was associated with an excess in-hospital mortality risk of 16% compared with patients without need for dialysis (62% vs. 46%).[11] However, the impact of D-AKI on long-term mortality and the influence of comorbidity are unknown.

Our objective was to examine the prognostic impact of dialysis-requiring AKI (D-AKI) in-hospital and up to 5 years after first-time MI-related cardiogenic shock, and to assess its influence in various subgroups of patients with MI-related cardiogenic shock.

Methods

Design and setting

We conducted this nationwide population-based cohort study using data from medical registries in Denmark. The Danish National Health Service provides universal tax-supported health care, guaranteeing free access to general practitioners and hospitals, and partial reimbursement of prescribed medications.[12] The unique 10-digit Danish Civil Personal Register number, assigned to all Danish citizens at birth and to residents upon immigration, allows unambiguous linkage of

registries.[13] The study was approved by the Danish Data Protection Agency (record number 2009-41-3987).

First-time myocardial infarction patients with cardiogenic shock

We used the Danish National Registry of Patients (DNRP) to identify all persons with a first-time admission for MI-related cardiogenic shock from 2005 through 2012. The DNRP contains data on all non-psychiatric hospital admissions since 1977 and on all hospital outpatient and emergency contacts since 1995.[14] Each admission is assigned one primary diagnosis code and up to 19 secondary codes classified according to the *International Classification of Diseases,* 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter.[14] Important components of critical care, including dialysis and treatment with inotropes/vasopressors, have been coded routinely with high validity since 2005.[15] The study cohort included only patients with first-time MI events, *i.e*., patients without a previous diagnosis of MI since 1977. The cohort was further restricted to MI patients with cardiogenic shock, defined either by a concurrent diagnosis code of cardiogenic shock and/or by medical treatment with inotropes or vasopressors during the MI admission. Patients treated with inotropes or vasopressors, but without a diagnosis code for cardiogenic shock, were excluded if they had a diagnosis code for septic shock, hypovolemic shock, or shock without further specification during the MI admission. A flowchart of the inclusion and exclusion criteria is provided in the supplemental material (Figure e1). The MI admission period was defined as the initial admission for MI including transfers to other departments and hospitals.

Dialysis-requiring acute kidney injury

The DNRP provided data on treatment with acute dialysis during hospitalization.[14] To restrict the cohort to patients with first-time D-AKI related to the MI under study, patients with prior dialysis treatment for acute or chronic kidney disease were not included in the analysis.

Study outcomes

Information on migration and all-cause mortality was obtained through linkage to the Danish Civil Registration System (DCRS).[13] This registry was established in 1968 and contains information on date of birth, residence, immigration, and vital status, updated daily.[13]

Covariates

The DCRS was used to identify the gender and age of patients.[13] Data on comorbidities were obtained from the DNRP using primary and secondary inpatient diagnoses and outpatient hospital diagnoses during a fixed period of 10 years preceding the current admission for MI. We included comorbidities that could act as potential risk factors for D-AKI and have a potential impact on mortality: congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, hypertension, atrial fibrillation/flutter, venous thromboembolism, chronic kidney disease, liver disease, diabetes, obesity, and cancer. All diagnosis codes used in the study are provided in Table e1.

The Danish Health Service Prescription Registry (DHSPR)[16] provided information on filled preadmission prescriptions for angiotensin-converting-enzyme (ACE)-inhibitors, angiotensin-II-antagonists, anti-diabetics, non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and cyclosporine. We identified prescriptions filled within 100 days before the MI admission because most drugs are sold in packages containing no more than 100 tablets. The DHSPR, established in 2004, includes virtually complete individual-level data on all filled prescriptions for reimbursed drugs in Denmark.[16]

We defined diabetes mellitus from its diagnosis code or filled prescriptions for anti-diabetic drugs, with a minimum 1-year prescription history preceding MI admission [16] (Table e1). Coronary arteriography (CAG), percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) during admission were identified from procedure codes in the DNRP.

Statistical analyses

We tabulated patient characteristics for the entire study population and for the cohort of patients surviving until hospital discharge (denoted as hospital survivors), including demographics, comorbidity, use of medication, and procedures during admission, according to D-AKI status.

We calculated the in-hospital mortality risk in D-AKI and non-D-AKI patients. Next, we computed the propensity-score-adjusted relative risk (RR) of death during hospitalization, comparing D-AKI patients with non-D-AKI patients, using a generalized linear model with a log-link function and a binomial error distribution.[17, 18] The propensity score was defined as the probability of developing D-AKI during admission conditioned on the observed baseline covariates (demographic, comorbidity, use of medication, and PCI or CABG)[19] and computed using a logistic regression model.[19]

We followed hospital survivors for up to five years following their hospital discharge date or until death, emigration, or the end of the study period on 31 December 2012, whichever came first. We used the Kaplan-Meier method to compute cumulative mortality following hospital discharge. Crude, multivariate and propensity-score adjusted hazard ratios (HRs) were computed using a Cox regression model. Proportional hazards assumptions in the Cox regression analyses were assessed graphically by plotting log(-log(survival function)) against time for patients with and without D-AKI and were found to be satisfactory.

To examine the potential differential impact of D-AKI within subgroups, we repeated the Cox regression analyses stratified by demographics, comorbidity, presence/absence of PCI and CABG, and subgroups of MI (STEMI, non-STEMI, and unspecified MI). We adjusted for propensity score; a propensity score calculated within each subgroup including the same baseline variables as in the overall propensity score except for the subgroup variable itself.[19]

Sensitivity analyses

We used propensity-score matching and standardized mortality ratio weighting (SMRW) to test the robustness of the long-term mortality results.[19,20] We repeated the Cox regression modeling to estimate the 5-year HR.

In addition, we examined the impact of changing the look-back period of comorbidity variables assumed not to result from MI-related cardiogenic shock (peripheral vascular disease, chronic pulmonary disease, hypertension, chronic kidney disease, liver disease, diabetes mellitus, cancer and obesity). In this sensitivity analysis, we defined the look-back period from 10 years preceding the MI admission and up until the discharge date, rather than the admission date.

We used STATA statistical software version 13.1 (StataCorp LP, Texas) for all statistical analyses.

Results

Patient characteristics

We identified 5,131 patients admitted with MI-related cardiogenic shock. The in-hospital study population consisted of 4,454 (87%) patients without D-AKI and 677 (13%) with D-AKI. Patient characteristics for the entire study population are provided in Table 1. Among the 3,059 hospital survivors, 2,805 (92%) did not have D-AKI and 254 (8%) had D-AKI during their admission. Patients without D-AKI were of similar age as patients with D-AKI, had a lower level of comorbidity, and had shorter in-hospital stays (Table 1). During hospitalization, 7% of PCI patients had D-AKI prior to PCI, 63% on the same day, and 30% after the procedure. Among patients with CABG, 5% of patients had D-AKI prior to CABG, 20% had D-AKI on the same day, and 75% had D-AKI after surgery.

Mortality

Among 677 patients with D-AKI, 408 died during admission, yielding an in-hospital mortality of 60% (95% CI: 56%–64%), while 1,612 out of 4,545 patients without D-AKI died during admission, yielding an in-hospital mortality of 36% (95% CI: 35-38). The corresponding propensity-score-adjusted relative risk of in-hospital death was 1.67 (95% CI: 1.56–1.79) for patients with D-AKI compared with patients without D-AKI (Table 2).

Total follow-up time for hospital survivors was 8,838 person-years. Six patients without D-AKI emigrated during follow-up. D-AKI patients had a median follow-up time of 2.2 years (interquartile range: 0.9–4.6 years) and non-D-AKI patients had a median follow-up time of 3.0 years (interquartile range: 1.2–5.2 years).

For patients with D-AKI, the mortality risks within 30 days, 1 year, and 5 years after discharge were 5% (95% CI: 3%-8%), 14% (95% CI: 10%-19%) and 45% (95% CI: 37%-53%). For patients without D-AKI the corresponding cumulative mortality risks were 3% (95% CI: 2%-3%), 10% (95% CI: 9%-11%), and 29% (95% CI: 29%-31%) (Figure 1). The propensity-score adjusted HR for death within 5 years after discharge was 1.55 (95% CI 1.22–1.96) for patients with D-AKI compared with patients without D-AKI (Table 3).

The association between D-AKI and mortality was surprisingly different between genders. Among males the complication of D-AKI increased the cumulative mortality risk after 5 years from 26% to 45% (Table e2), with a corresponding propensity-score adjusted HR of 1.85 (95% CI: 1.41-2.43) (Figure 2). Among females the impact of D-AKI increased the cumulative mortality risk after 5 years from 35% to 45% (Table e2), with a corresponding 5-year propensity-score adjusted HR of 1.04 (95% CI: 0.44-1.68) (Figure 2). Patients with comorbidity had a higher baseline absolute risk of mortality compared to patients without chronic illness (Table e2). The increased baseline mortality among patients with comorbidity was reflected in the HR comparing patients with and without D-AKI. It showed attenuation of the relative impact of D-AKI on 5-year mortality among patients with comorbidities (Figure 2). This was especially evident for patients with chronic

pulmonary disease, congestive heart failure, liver disease, and patients who did not undergo CAG, PCI, or CABG (Figure 2).

Sensitivity analyses

Our overall findings were confirmed in sensitivity analyses in which covariates were balanced after propensity-score matching and weighting (Table 4). Compared with the control group, the HR for patients with D-AKI was 1.66 (95% CI: 1.07–2.57) in the matched analysis; the HR was 1.63 (95% CI: 1.07–2.47) in the SMRW analysis (Table 5).

The proportion of patients with hypertension and chronic kidney disease increased substantially when variables were included up until discharge date (Table e3), rather than up until the admission date. The impact of this change in comorbidity definition slightly lowered the propensity-score adjusted 5-year HR to 1.42 (95% CI: 1.11–1.86)) (Table e4).

Discussion

The new finding of the present study is that the initial twofold increase in in-hospital mortality was followed by an approximately 50% increased mortality up to 5 years after discharge in cardiogenic shock patients with D-AKI, compared with non D-AKI patients. This association was confirmed in subgroups defined by gender, age, comorbidity status, in-hospital procedures, and MI subtypes. Surprisingly, there was no clear impact of D-AKI on 5-year mortality among females, although this finding was hampered by imprecise estimates. The impact of D-AKI was also less pronounced in patients with comorbidities.

Existing studies

Consistent with our findings, two previous studies reported markedly increased in-hospital mortality among cardiogenic shock patients with AKI compared with cardiogenic shock patients without AKI. In a cohort study of 97 patients hospitalized with STEMI and cardiogenic shock, 52

patients (55%) developed AKI (defined as a rise in creatinine > 25% from baseline).[11] Thirteen (13%) required dialysis. In-hospital mortality risk was markedly increased among patients with D-AKI compared with patients without AKI (62% vs. 2%)[11] Another study of 118 patients with cardiogenic shock following acute coronary syndrome between 1993 and 2000 revealed an AKI risk of 33% with an in-hospital mortality risk of 87% among patients with AKI and 53% among patients without AKI (OR=6.0, 95% CI: 2.1–17).[10] AKI thus remains a serious complication of cardiogenic shock, with poor in-hospital outcome despite aggressive interventional reperfusion treatments.

Cardiogenic shock has been reported as a complication in 5%–10% of STEMI cases and in 2%-4% of non-STEMI cases.[21,22] Nevertheless, non-STEMI complicated with cardiogenic shock has been reported to be associated with higher in-hospital mortality than STEMI complicated with cardiogenic shock.[22] We did not find any differences in long-term mortality between subgroups of patients with non-STEMI and STEMI in our examination of the impact of D-AKI among MI patients with cardiogenic shock.

Potential mechanisms

The mechanisms underlying our findings are not well understood. Cardiorenal crosstalk in acute MI involves multifactorial systems and has recently been classified as a cardiorenal syndrome type 1.[23] Classical mechanisms include low cardiac output and neurohormonal activation, release of vasoactive substances resulting in low renal perfusion, and possible renal ischemia with AKI.[23] In addition, a marked alteration of immune and somatic cell signaling has been implicated as an important contributor to kidney injury.[23] Coronary intervention was frequent in our population, so the potential for contrast-induced D-AKI must be considered in some patients.[24] Moreover, a potentially harmful effect of cardiac surgery on kidney function among CABG patients has been established.[25,26]

Strengths and limitations

The strengths of our study are its nationwide population-based cohort design with a well-defined study population in a country providing tax-financed universal healthcare. This design minimizes selection bias, with the study population including nearly all patients with the condition of interest. In addition, follow-up for mortality was virtually complete.

The positive predictive value (PPV) of MI as a primary diagnosis in the DNRP is 94%,[27] and the PPV of cardiogenic shock in the DNRP was found to be equally high in a validation study.[28] Nonetheless, we do not know if treatment with inotropes/vasopressors is a valid proxy for clinical cardiogenic shock. As the PPV of acute dialysis was 98%,[15] we assume that the potential for information bias was small. Any such information bias is expected to cause non-differential misclassification, because registration of D-AKI is unlikely to be dependent on mortality status and vice versa.

A study limitation is lack of creatinine measurements. Consequently, we could only discriminate between patients with and without the most severe form of AKI, namely D-AKI.

Availability and validity of variables to measure potential confounding factors are crucial, and unmeasured and residual confounding must be considered. In observational studies the impact of uncontrolled confounding is a major concern. Since the propensity score method and multivariate adjustment only include known confounders, the potential for unmeasured confounding exists, particularly from smoking[29] and socioeconomic status.[30]

Heart failure has an impact on long-term-mortality risk after MI,[31,32] but we lacked data to examine whether the impact of AKI was mediated through reduced left ventricular ejection fraction (EF) at discharge. However, even if the data were available, it would be inappropriate to adjust for a factor in the causal pathway between D-AKI and mortality.

A high absolute mortality risk was seen for subgroups of patients with chronic pulmonary disease, congestive heart failure, and liver disease and those who did not undergo CAG, PCI, or CABG, independent of D-AKI status. Clinical guidelines recommend that all patients with MI-

related cardiogenic shock be treated with either PCI or CABG unless contraindicated by a patient's pre-operative condition.[33,34] A potential for confounding by indication is apparent in this setting when the most severely affected patients with comorbid diseases are not offered dialysis or PCI/CABG due to their expected high mortality.

Clinical perspectives

D-AKI may act as an in-hospital and long-term prognostic marker of increased mortality among patients with MI-related cardiogenic shock. Since no treatment exists for D-AKI, it is important to investigate methods for preventing its development.

Furthermore, future studies are needed to examine the cause of increased long-term mortality, *e.g*., increased risk of a second cardiovascular event. If a specific cause were identified, long-term follow-up of high-risk patients would be the next step to prevent new cardiovascular events.

Conclusion

D-AKI is associated with both increased in-hospital mortality and increased mortality up to 5 years after discharge. Comorbidity increased the absolute mortality risk for all MI patients with cardiogenic shock, while the relative impact of D-AKI on 5-year mortality decreased with increasing comorbidity level.

Supplementary information

Introduction

Dialysis-requiring acute kidney injury

The kidneys removes waste products from the organism and control the water fluid levels.[35] They keep the levels of electrolytes as sodium, potassium and phosphate stable, and they produce hormones that help regulate the blood pressure and induce the making of red blood cells.[35] This means, that several and important physiological systems gets affected whenever the function of the kidneys decrease.[35]

Up until 2004 no consensus existed about the diagnostic criteria for acute renal failure,[36] a term often used for those patients transferred to the intensive care unit with need of acute dialysis.[36] Based on the findings that an increased serum creatinine (SCr) of 0.3 mg/dl was independently associated with increased in-hospital mortality,[37] in 2004 the Risk, Injury, Failure, Loss, and End stage kidney disease (RIFLE) criteria was developed to standardize the diagnostic process,[38] and in 2007 these criteria was updated to the Acute Kidney Injury Network (AKIN) criteria.[39]

By this, acute kidney injury (AKI) is defined as one of the following: (1) an increase of serum creatinine (SCr) by 0.3 mg/dl, or more, within 48 hours; (2) increase in SCr to 1.5 baseline, or more, which is know or presumed to have occurred within the prior 7 days; or (3) urine volume less than 0.5 ml/kg/h for 6 hours.[40] To address the stage of severity three levels was defined from 1 to 3 ranging from the mildest degree of AKI to the most severe stage with dialysis-requiring AKI (D-AKI) (Appendix table e5). [39]

Acute dialysis is most often performed in an intensive care unit in collaboration between anaesthesiologists and nephrologists.[35] Dialysis is initiated on the basis of the clinical setting and conditions that can be improved by dialysis,[40] and life-threatening changes in fluid, electrolytes and acid-base balance are important indicators of when to begin the treatment.[40] However, some potential complications must be considered before initiation of dialysis. A risk of developing

hypotension and arrhythmias during dialysis exists,[40] which may delay the treatment or act as a contraindication for dialysis.[40] Both hypotension and arrhythmias are potential conditions after MI-related cardiogenic shock,[33] and the clinician must consider whether the beneficial effects of the treatment outweigh the risk of initiating dialysis.[40]

MI-related cardiogenic shock

Despite the improved treatment of myocardial infarction (MI),[2] the risk of MI-related cardiogenic shock has stagnated around 5%-9% during the MI hospitalization.[3,5-7] This stagnation may be due to the fact, that the prevalence of patients with high age, prior MI, heart failure, diabetes mellitus, hypertension, all risk factors for MI-related cardiogenic shock,[5] increase as a results of improved treatment of MI.[4]

The GUSTO-1 trial showed an improved 30-day and 1-year mortality for patients with acute MI complicated with cardiogenic shock if they were treated with revascularization compared to medical treatment.[41,42] In 1999, the randomized controlled SHOCK trial found that among patients with MI-related cardiogenic shock early mechanical revascularization improved 6-months mortality risk compared with patients treated with medical intervention.[43] This created the basis of the American College of Cardiology Foundation/American Heart Association guideline for the treatment of ST-elevation MI (STEMI) complicated with cardiogenic shock recommending, that all patients suitable for invasive treatment had emergency revascularization performed (either PCI or CABG).[33] Non-suitable patients for PCI or CABG are patients with advanced age, poor functional status and extensive level of comorbidity.[33] The in-hospital mortality risk for MI-related cardiogenic shock has declined in parallel with increased use of PCI in treatment of the condition from 60.3% in 1995 to 47.9% in 2004.[3,4]

PCI and CABG may induce the development of AKI[24-26] – especially among patients with disposing risk factors as diabetes mellitus, chronic kidney disease, congestive heart failure and use of nephrotoxic drugs.[44, 45] Contrast media used during angiography may cause vasoconstriction in

the kidney leading to ischemic injury of the renal cells and may have a cytotoxic effect on the renal cells causing inflammation and oxidativ stress.[44] If CABG is indicated after angiography, the added hemodynamic insult, nephrotoxicity and inflammation in the kidney during cardiopulmonary bypass increases the risk of AKI.[46] However, in the emergency setting, the benefits of acute intervention outweigh the risk of AKI.[44] Increased focus has been put on the prevention of AKI after angiography,[44] and the risk of D-AKI after angiography is around 1% of patients.[44]

Cardiorenal syndrome

A possible pathophysiological pathway leading to AKI among cardiogenic shock patients is the cardiorenal syndrome type 1.[47] Cardiorenal syndrome is defined as combined disorder heart and kidney, where the acute or chronic dysfunction of either the heart or kidney induces dysfunction of the other organ.[47] Type 1 is the acute failure of the heart leading to the acute dysfunction of the kidney as in the setting of this study. Besides haemodynamic alterations as the cause of kidney injury, venous congestion, anaemia, activation of the renin-angiotensin aldosterone system (RAAS), hypothalamic-pituitary stress reaction, inflammation and immune cell signalling has been suggested as part of the pathogenesis.[47] Also in this setting, hypertension, diabetes mellitus, chronic kidney disease and use of nephrotoxic medications predispose to this combined condition of heart and kidney failure.[47]

Methods

Design and setting

We wanted to examine the impact of D-AKI on 5-year mortality after MI-related cardiogenic shock. To do so, we designed an observational nationwide population-based cohort study[48] using data from Danish registries. A cohort study is able to demonstrate the temporal relation between exposure and outcome, and can be highly cost-effective.[48] One disadvantage with register data is,

however, that only existing data is available making more or less study limitation if the data is missing or unavailable.[48]

From the source population being the entire Danish population we identified from the DNRP[14] the study population of patients with MI-related cardiogenic shock in the study period from 2005-2012. The study period was chosen to begin in 2005 because registration on treatment with acute dialysis on the intensive care units was observed from that year and onward.[15]

We excluded all patients having previous MI to avoid any potential confounding from MI-caused morbidity. In addition we excluded all patients with any previous dialysis to include only those patients having first-time dialysis in relation to the MI-related cardiogenic shock.

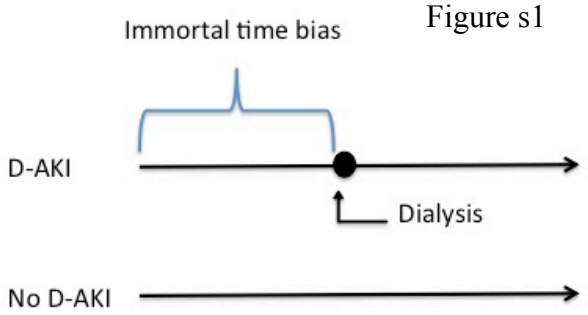
The exposure of interest was need of acute dialysis during MI-admission also identified using the DNRP. We chose D-AKI since this was a clinically useful parameter of severe kidney injury, and because twe only had acess to data on SCr in parts of Denmark.

We defined two study populations: (1) an in-hospital study population in a cross sectional study design (we did not know the exact course of the in-hospital events of MI-related cardiogenic shock and dialysis), and (2) a cohort of hospital survivors surviving until hospital discharge date (follow-up design).

Follow-up among hospital survivors

We followed the patients from date of discharge until death, emigration, up until 5-years of follow-up or end of study period. Date of discharge was chosen as the beginning of follow up to avoid immortal time bias.[49] Immortal time bias is defined as a period of time in which the study participant cannot experience the outcome.[49] If we had chosen to begin follow up from admission date, those patients being exposed defined as need of acute dialysis during admission would contribute with person time

Figure s1



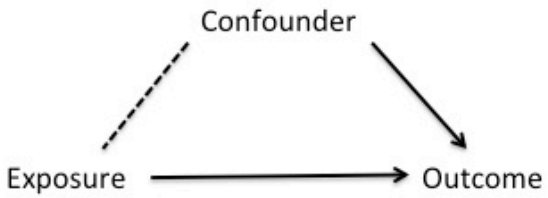
in the exposed group of patients without being exposed yet (figure s1). The mortality rates and the mortality rate ratio (MRR) would then have been biased towards a decreased effect of D-AKI on mortality.

In a cohort study the beginning of follow-up must be started at the same time in the course of the disease for all study participant (time zero), but the time of observation each study participant contribute with can vary.[50] We choose 5-years of follow up as an endpoint to measure long-term mortality. The median time of follow-up were for D-AKI and non-D-AKI patients 2.2 years (inter-quartile range (IQR): 0.9-4.6 years) and 3.0 years (IQR: 1.2-5.2 years), respectively, meaning that some patients either emigrated (n=6), died or end of study period was reached before 5-years of observation.

Co-morbidity

To ascertain the presence of potential confounding comorbidity we used the DNRP to obtain information on the complete in-patient and out-patient (specialist clinics) medical history including visits to emergency rooms in a 10-year period preceding the MI admission. A confounder leads to systematic error since the effect of the confounder on the outcome of interest is not separated from the effect of the exposure of interest.[48] To be a confounder the variable must 1) be associated with the exposure (D-AKI), thus making an unequal distribution of the confounder between the exposed and the unexposed study participants, 2) increase the risk of the outcome (5-year mortality), hereby being a predictor of the outcome, and 3) it must not act as an intermediate variable in the causal relation between the exposure and the outcome (Figure s2).[48]

Figure s2



Dealing with confounding can be done in both the in the design phase (randomisation, restriction, matching) or in the analysis phase of the study (stratification, standardisation, and by multivariate regression).[48] In this observational study we sought to account for confounding by restriction and in the analysis phase.

The fixed time window of 10-years preceding MI admission was chosen to have an equal time period for all patients and to avoid influence of conditions from which the patient did not longer suffer from, e.g. cancer.

In-hospital mortality

We used a generalized linear model (GLM) with log link function and a binomial error distribution to calculate the relative risk (RR)[17,18] for in-hospital mortality in the in-hospital study population. We adjusted for the propensity score to be able to include the same variables as in the HR estimates. The propensity score was log transformed to be on the correct functional form.

Time-to-event analysis

In the cohort of hospital survivors we investigated the mortality rate in both groups based on outcomes (death) during follow-up period. Since study participants had different length of follow-up we used the 1-Kaplan Meier method to calculate 30-day, 1-year and 5-year cumulative mortality – estimates analogues to the absolute mortality risk.[50] When calculating the 1-Kaplan Meier estimate as the probability of dying, s_t, when an event occurs, d_t, at an exact time t and n_t being the total number of patients at risk of the outcome;[51]

$$s_t = \frac{n_t - d_t}{n_t}$$

some assumptions must be fulfilled: 1) independence between subjects, 2) all subjects at time zero (start of follow-up) have the same risk of dying, 3) time of death is either censored or observed

exactly, and 4) censored subjects have same probability of dying as uncensored subjects.[51] We did not discover any disproval of the assumptions in this study.

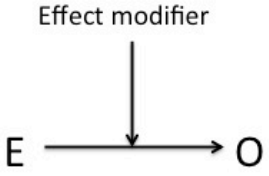
We then compared the mortality rates for the exposed and unexposed group of patients by estimating the hazard ratio (HR), the same as MRR, with use of Cox proportional hazards regression model. The hazard (mortality rate) is defined as the instantaneous rate of an event at a time t. The HR is therefore the ratio between the hazard rate for the exposed compared with the hazard rate for the unexposed group of patients.[51]

The proportional hazards assumption must be fulfilled when using Cox proportional hazards regression model.[51] It assumes, that the ratio of the rates between the exposed and unexposed groups, the HR, remains constant over time.[51] In addition, linearity of the included continuous prognostic predictors in the Cox regression model must be checked (see Results, *Checking linearity*).[51,52]

Effect-measure modification

We repeated the analyses for subgroups of gender, age, comorbidity, MI-subtype, and in-hospital procedures (PCI or CABG). This was done to examine the potential impact of effect measure modification on the relation between D-AKI and 5-year mortality. Effect measure modification modifies the association between the exposure, E, and the outcome, O (figure s3), and is a phenomenon that needs to be described as it may have clinical implications e.g. modification of an exposure on an outcome because of a biological effect of gender, genetics, height etc.[48] It is visualized if an exposure-outcome association is different within subgroups of a variable. If effect measure modification is present, the relation between exposure and outcome should be presented for the individual subgroups of the variable.[48]

Figure s3



Propensity score

The propensity score is defined as the probability of being exposed conditional on observed baseline characteristics.[19] With use of a propensity score matching an observational (non-randomized) study mimics some of the advantages in a randomized controlled trial because the observed baseline characteristics are equally distributed between the exposed and unexposed study participants.[19] However, only known baseline characteristics are included in the model, thus the potential of residual, unmeasured and unknown confounding remains.[19]

A logistic regression model is often used to estimate the propensity score.[20] It is important that the variables selected to estimate the propensity score is chosen with care since bias and less precision can be introduced otherwise.[20] All variables must be measured before exposure (not an intermediate step). True confounders associated with both exposure and outcome can be included.[20] However, variables only associated with outcome (predictors) are especially beneficial since these variables increase the precision of the estimate.[20] In contrary, including only variables associated with the exposure will decrease the precision and increase bias based on the presence of unmeasured confounding.[20]

Four PS methods have been defined:[19,20] matching, stratification, weighting, and covariate adjustment using the PS, and impact of the exposure on the outcome is often measured with one of the PS method in combination with a regression model.[20] Stratification, inverse probability weighting and propensity score adjustment is methods calculating the impact of the exposure that are generalizable to the source population from where the study population were sampled referred to as the population average treatment effect (ATE).[20] With use of propensity score matching or standardized mortality ratio weighting (SMRW) it is the impact of the exposure among people exposed that is estimated – the treatment effect in the treated (ATT).[20]

We adjusted on the propensity score in the Cox regression model in the primary analysis to be able to make the best comparison with the multivariate adjusted estimate, which was also the case in the subgroup analysis. In addition, one of the advantages of the propensity score is that the

flexibility regarding number of covariates in the model is increased.[19] At least 10 outcomes must be observed for each covariate included in the regression model, this defining the number of freedom degrees.[51] However, when using propensity score methods the number of freedom degrees is based on the number of exposed instead,[19] because the logistic regression model estimating the propensity score is modelled with respect to the exposure. This allows for a more adequate adjustment in analysis with a small number of outcomes - the case in the subgroup analysis.

In the sensitivity analyses we used matching and SMRW with Cox regression analysis to estimate the ATT, and to test the robustness of the findings in the primary analysis. The sample size is reduced when using matching, which may decrease the precision of the estimates.[20] The sample size is not reduced in SMRW analysis.[20]

Results

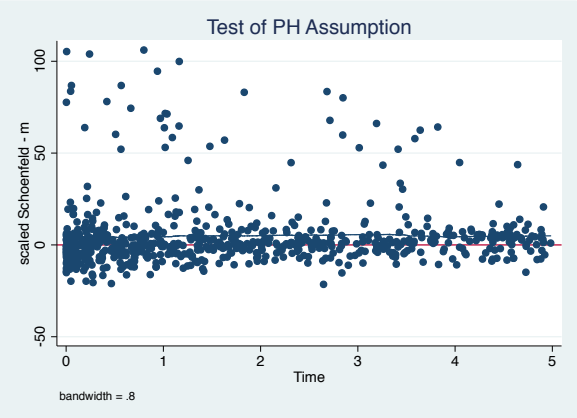
In-hospital mortality

In addition to the RR estimated with use of a generalized linear model with log link function and a binomial error distribution we calculated the odds ratio (OR) for in-hospital mortality with use of logistic regression. PS adjusted OR of death during hospitalization for D-AKI patients compared with non-D-AKI patients was 3.20 (95%CI: 2.69-3.8) (multivariate adjusted OR: 3.63 (95%CI: 3.08-4.35)). In comparison, the PS-adjusted RR calculated in the GLM was 1.67 (95% CI: 1.56–1.79). This emphasises the fact, that an OR cannot be interpreted as a RR when the outcome is not rare (<10%). [51]

Checking linearity

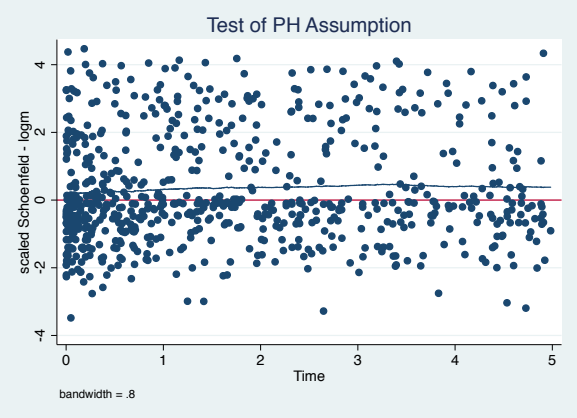
With use of the STATA syntax *estat phtest,*[53] a graphical presentation of the Schoenfeld residuals is provided.[52-54] It is visualized that the residuals is not horizontal and symmetric distributed around y=0, thus meaning that the PS does not fulfil the linearity assumption on its current functional form (figure s4).[52, 54]

Figure s4



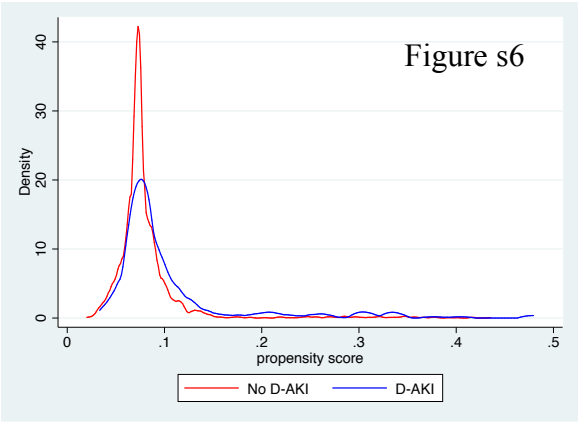
The PS is a continuous variable modelled with use of logistic regression with all known confounders as independent variables and exposure status as the dependent variable. Based on violation of the linearity assumption of the continuous variable we examined the best functional form of the variable to ensure a linear association between the PS variable and the exposure variable. This was done with use of fractional polynomials.[55] Fractional polynomials are used in regression models to fit non-linear associations,[55] and provides the best fitted functional form of the variable based on a predefined set of powers ($PS^{-2, -1, -0.5, 0, 0.5, 1, 2, or\ 3}$) used to test it.[56] For this model the power 0 was given as the best fitted model, for this specific power meaning ln(PS) transformation, and not $PS^0=1$.[56] After the transformation of the PS variable, the Schoenfeld residuals were symmetric distributed around y=0 (figure s5), and could be fitted in the Cox regression model as a continuous variable.

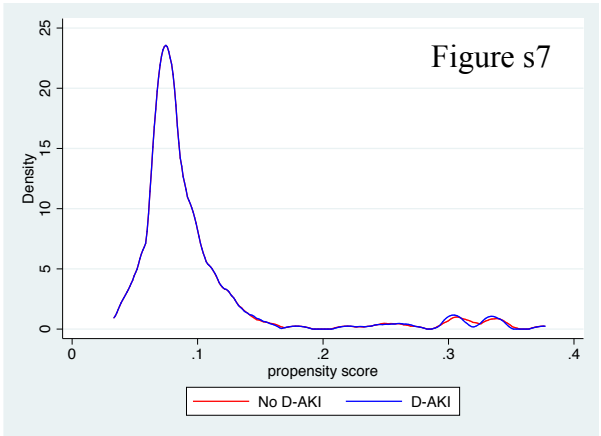
Figure s5



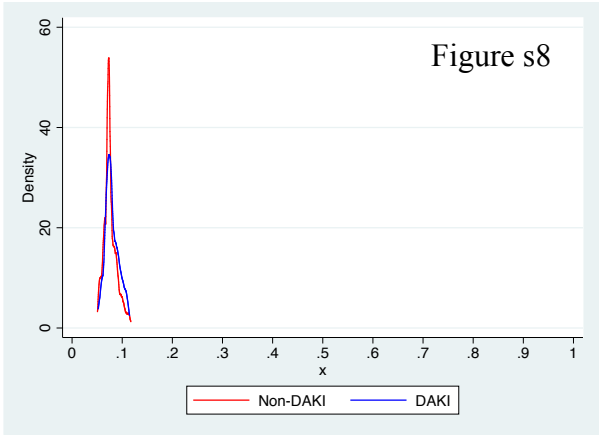
Kernel density plots

The kernel density plot shows the distribution of the estimated PSs for the study participants.[20] We see a great amount of overlap of PS between exposed and unexposed patients, thus making the populations comparable (figure s6).[20] This PS distribution among the entire study population is the one used in the PS-adjusted calculations, and by this, estimating the ATE. If only a low degree of overlap existed between the exposed and unexposed group of patients, the balance of potential confounders would be insufficient, and the PS model would need trimming to avoid bias of the association of interest.[20]





In the PS matched cohort, we matched 241 pairs of exposed and unexposed patients with the same PS. This is reflected in the following kernel density plot (figure s7), with a complete overlap of PS for the two patients groups, thus creating a matched cohort of patients with equal probability of receiving dialysis.



Finally, it is visualized how the unexposed patients were re-weighted to be representative of the exposed patients, thus making the distribution of PS among unexposed patients more similar to that of the exposed patients (figure s8). In addition, we trimmed the upper and lower 7% of the frail ends of the study population with either no-overlaps of

the PS between exposed and unexposed, or patients treated contrary to the PS prediction. This was done to avoid effect of confounding, e.g. confounding by contraindication based on treatment withholding among the sickest and/or oldest patients despite their high PS score.[57]

Discussion

Strengths and limitations

The nationwide population-based cohort design with a well-defined study population in a country providing tax-financed, universal healthcare minimizes selection bias.

One of the potential weaknesses in a study using historical data is the validity of the data.[48] In a prognosis study like this we are especially interested in a high PPV of data to avoid misclassification of patients, thus biasing the prognostic impact of D-AKI on mortality. The PPV for MI in the DNRP is 94%.[27] No study had previously examined the PPV for the ICD-10 code for cardiogenic shock in the DNRP, why we conducted a validity study and discovered a PPV of 94%.[28]

The potential of information bias was considered small since the PPV for acute dialysis is 98% in the DNRP.[15] Any such misclassification is expected to be non-differential because registration of D-AKI is not expected to be dependent of mortality status and vice versa. This means, that any potential information bias would have lead the association towards null. One of the strengths using historical data is, that the data is already prospectively collected, thus eliminating the effect of recall bias.

We sought to reduce residual confounding by including information from the prescription database for patients prescribed anti-diabetics, by this increasing the completeness on information on patients with diabetes.

Effect measure modification

A difference existed between the 5-year mortality PS-adjusted HRs for females versus males in the study visualized in the subgroup analysis. This may be effect measure modification by gender. However, the estimates were imprecise based on wide CIs, and overlaps existed between the CIs for HR for males and females, why we choose to present the combined results for both gender.

For almost all subgroups of comorbidity (except cerebrovascular disease and atrial fibrillation/flutter) the impact of D-AKI on 5-year mortality was reduced or missing in comparison with patients without comorbidity, why effect measure modification by comorbidity is an issue to consider. A high absolute mortality risk was seen for all subgroups of patients with comorbidity independent of D-AKI status, which attenuate the relative impact of D-AKI on mortality.

Most surprisingly, a clear difference in 5-year PS-adjusted HR was found between groups of patients treated with PCI or CABG and patients not offered this invasive treatment. Patients offered PCI or CABG had a substantial impact of D-AKI on 5-year mortality. In contrary, patients not treated with PCI or CABG had no effect of D-AKI on mortality, and a conspicuously high absolute mortality independent of D-AKI status is affecting the relation between D-AKI and mortality. The high baseline mortality among these patients may be the effect modifier seen in this setting. Because of the pre-existing poor prognosis for this group of patients, doctors may choose to withhold treatment with, CAG, PCI, CABG, and potentially dialysis, thus creating confounding by contraindication for treatment.

No difference in the relation between D-AKI and 5-year mortality existed for subgroup of age, and MI-subgroups.

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Tables

Table 1. Patient characteristics of both the entire study population and the hospital survivors by dialysis-requiring acute kidney injury (D-AKI) status.

	Entire study population			Hospital survivors		
Clinical features[a]	**Total n=5,131 (100)[b]**	**No D-AKI n=4,454 (86.8)[b]**	**D-AKI n=677 (13.2)[b]**	**Total n=3,059 (100)[b]**	**No D-AKI n=2,805 (91.7)[b]**	**D-AKI n=254 (8.3)[b]**
Sex						
Male	3,428 (66.8)	2,945 (66.1)	483 (71.3)	2,164 (70.7)	1,979 (70.6)	185 (72.8)
Female	1,703 (33.2)	1,509 (33.9)	194 (28.7)	895 (29.3)	826 (29.4)	69 (27.2)
Median age (years), IQR	71 (62-78)	70 (62-78)	72 (65-77)	68 (60-75)	68 (60-75)	69 (60-74)
Age groups (years)						
< 60	1,015 (19.8)	903 (20.3)	112 (16.5)	766 (25.0)	703 (25.1)	63 (24.8)
60-69	1,447 (28.2)	1,257 (28.2)	190 (28.1)	966 (31.6)	886 (31.6)	80 (31.5)
70-79	1,748 (34.1)	1,458 (32.7)	290 (42.8)	989 (32.3)	899 (32.1)	90 (35.4)
≥ 80	921 (18.0)	836 (18.8)	85 (12.6)	338 (11.1)	317 (11.3)	21 (8.3)
Comorbidities						
Congestive heart failure	335 (6.5)	285 (6.4)	50 (7.4)	166 (5.4)	145 (5.2)	21 (8.3)
Peripheral vascular disease	565 (11.0)	482 (10.8)	83 (12.3)	299 (9.8)	268 (9.6)	31 (12.2)
Cerebrovascular disease	591 (11.5)	508 (11.4)	83 (12.3)	307 (10.0)	284 (10.1)	23 (9.1)
Chronic pulmonary disease	534 (10.4)	471 (10.6)	63 (9.3)	257 (8.4)	232 (8.3)	25 (9.8)
Hypertension	1,149 (22.4)	972 (21.8)	177 (26.1)	633 (20.7)	559 (19.9)	74 (29.1)
Atrial fibrillation/flutter	400 (7.8)	347 (7.8)	53 (7.8)	185 (6.1)	166 (5.9)	19 (7.5)
Venous thromboembolism	81 (1.6)	71 (1.6)	10 (1.5)	36 (1.2)	31 (1.1)	5 (2.0)
Chronic kidney disease	177 (3.5)	129 (2.9)	48 (7.1)	95 (3.1)	67 (2.4)	28 (11.0)
Liver disease	55 (1.1)	49 (1.1)	6 (0.9)	21 (0.7)	19 (0.7)	2 (0.8)
Diabetes mellitus[c]	915 (17.8)	766 (17.2)	149 (22.0)	497 (16.3)	441 (15.7)	56 (22.1)
Cancer	442 (8.6)	394 (8.9)	48 (7.1)	214 (7.0)	202 (7.2)	12 (4.7)
Obesity	146 (2.9)	118 (2.7)	28 (4.1)	81 (2.7)	70 (2.5)	11 (4.3)
Medication use[d]						
Chemotherapeutics	11 (0.2)	9 (0.2)	2 (0.3)	7 (0.2)	7 (0.3)	0 (0)
ACE-inhibitors	1,032 (20.1)	885 (19.9)	147 (21.7)	589 (19.3)	526 (18.8)	63 (24.8)
Angiotensin-II-antagonists	673 (13.1)	584 (13.1)	89 (13.2)	413 (13.5)	379 (13.5)	34 (13.4)
NSAIDS	662 (12.9)	557 (12.5)	105 (15.5)	383 (12.5)	346 (12.3)	37 (14.6)
Aminoglycosides	0	0	0	0	0	0
Cyclosporine	0	0	0	0	0	0
In-hospital procedures						
Coronary arteriography	3,512 (68.5)	3,008 (67.5)	504 (74.5)	2,489 (81.4)	2,290 (81.6)	199 (78.4)
PCI	1,893 (36.9)	1,582 (35.5)	311 (45.9)	1,185 (38.7)	1,065 (38.0)	120 (47.2)
CABG	1,543 (30.1)	1,350 (30.3)	193 (28.5)	1,334 (43.6)	1,251 (44.6)	82 (32.7)

[a] Comorbidities registered as primary or secondary hospital in-patient and outpatient diagnoses within 10 years preceding current admission.
[b] Values are expressed in counts (percentages) unless otherwise indicated.
[c] Defined as either a diagnosis code for diabetes or a prescription redemption for anti-diabetics within 100 days before MI admission.
[d] Prescription redemption within 100 days before admission.
Abbreviations: ACE: Angiotensinogen converting enzyme, IQR: inter quartile range, NSAID: non-steroidal anti-inflammatory drug.

Table 2. In-hospital mortality by D-AKI status.

Exposure	**Absolute mortality risk (95% CI)**	**Relative risk (RR) (95%CI)**	
		Crude (95% CI)	Adjusted * (95% CI)
No D-AKI	36 % (35–38)	1 (reference)	1 (reference)
D-AKI	60 % (56–64)	1.67 (1.55–1.79)	1.67 (1.56–1.79)

* Adjusted using a propensity score based on sex, age group, and presence/absence of congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, hypertension, venous thromboembolism, atrial fibrillation/flutter, liver disease, chronic renal disease, diabetes mellitus, obesity, cancer, use of ACE-inhibitors, angiotensin-II-antagonists, and/or NSAIDs, and PCI/CABG.

Table 3. Five-year mortality estimates for patients with and without dialysis-requiring acute kidney injury (D-AKI) following first-time hospital admission with myocardial infarction and cardiogenic shock.

Exposure	**No. of deaths**	**No. at start**	**Hazard ratio (95% CI)**		
			Crude	Adjusted*	Adjusted†
Non-D-AKI	589	2,805	1 (reference)	1 (reference)	1 (reference)
D-AKI	81	254	1.67 (1.32–2.11)	1.42 (1.11–1.81)	1.55 (1.22–1.96)

* Cox proportional hazards regression model adjusted by sex, age group, and presence/absence of congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, hypertension, venous thromboembolism, atrial fibrillation/flutter, liver disease, chronic renal disease, diabetes mellitus, obesity, cancer, use of ACE-inhibitors, angiotensin-II-antagonists, and/or NSAIDs, and PCI/CABG.

† Cox proportional hazards regression model adjusted using a transformed propensity score.

Abbreviations: CABG: coronary artery bypass graft, CI: confidence intervals, D-AKI: dialysis-requiring acute kidney injury, NSAIDS: non-steroid anti-inflammatory drugs, PCI: percutaneous coronary intervention.

Table 4. Characteristics of hospital survivors, including the propensity-matched cohort and the standardized mortality ratio-weighting (SMRW) pseudo-cohort, by dialysis-requiring acute kidney injury (D-AKI) status.

	All hospital survivors		Hospital survivors Matched cohort		SMRW pseudo-cohort	
Clinical features*	**No D-AKI n=2,805 (91.7) †**	**D-AKI n=254 (8.3) †**	**No D-AKI n=242 (50.0) †**	**D-AKI n=242 (50.0) †**	**No D-AKI n=200 (51.1) †**	**D-AKI n=192 (48.9) †**
Sex						
Male	1,979 (70.6)	185 (72.8)	177 (73.1)	177 (73.1)	147 (73.1)	143 (74.5)
Female	826 (29.4)	69 (27.2)	65 (26.9)	65 (26.9)	54 (26.9)	49 (25.5)
Median age (years), IQR	68 (60-75)	69 (60-74)	69 (59-75)	69 (60-74)	67 (59-74)	67 (58-73)
Age groups (years)						
< 60	703 (25.1)	63 (24.8)	66 (26.9)	61 (25.2)	55 (27.4)	58 (30.2)
60-69	886 (31.6)	80 (31.5)	69 (28.5)	76 (31.4)	66 (32.7)	57 (29.7)
70-79	899 (32.1)	90 (35.4)	88 (36.4)	85 (35.1)	64 (32.0)	65 (33.9)
≥ 80	317 (11.3)	21 (8.3)	20 (8.3)	20 (8.3)	16 (7.9)	12 (6.3)
Comorbidities						
Congestive heart failure	145 (5.2)	21 (8.3)	16 (6.6)	16 (6.6)	9 (4.6)	8 (4.2)
Peripheral vascular disease	268 (9.6)	31 (12.2)	25 (10.3)	28 (11.6)	17 (8.6)	16 (8.3)
Cerebrovascular disease	284 (10.1)	23 (9.1)	13 (5.4)	20 (8.3)	14 (7.1)	13 (6.8)
Chronic pulmonary disease	232 (8.3)	25 (9.8)	19 (7.9)	23 (9.5)	15 (7.5)	17 (8.9)
Hypertension	559 (19.9)	74 (29.1)	69 (28.5)	66 (27.3)	37 (18.4)	35 (18.2)
Atrial fibrillation/flutter	166 (5.9)	19 (7.5)	17 (7.0)	17 (7.0)	11 (5.2)	9 (4.7)
Venous thromboembolism	31 (1.1)	5 (2.0)	7 (2.9)	4 (1.7)	2 (0.9)	1 (0.5)
Chronic kidney disease	67 (2.4)	28 (11.0)	16 (6.6)	17 (7.0)	0 (0)	0 (0)
Liver disease	19 (0.7)	2 (0.8)	0 (0)	2 (0.8)	1 (0.7)	1 (0.5)
Diabetes mellitus ‡	441 (15.7)	56 (22.1)	39 (16.1)	50 (20.7)	30 (15.1)	26 (13.5)
Cancer	202 (7.2)	12 (4.7)	14 (5.8)	9 (3.7)	5 (2.4)	2 (1.0)
Obesity	70 (2.5)	11 (4.3)	9 (3.7)	10 (4.1)	4 (2.2)	5 (2.6)
Medication use §						
Chemotherapeutics ‖	7 (0.3)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
ACE-inhibitors	526 (18.8)	63 (24.8)	51 (21.1)	59 (24.4)	39 (19.3)	42 (21.9)
Angiotensin-II-antagonists	379 (13.5)	34 (13.4)	29 (12.0)	31 (12.8)	23 (11.5)	22 (11.5)
NSAID	346 (12.3)	37 (14.6)	37 (15.3)	35 (14.5)	28 (13.8)	28 (14.6)
Aminoglycosides	0	0	0	0	0	0
Cyclosporine	0	0	0	0	0	0
In-hospital procedures						
Coronary arteriography	2,290 (81.6)	199 (78.4)	199 (82.2)	191 (78.9)	167 (83.3)	152 (79.2)
PCI or CABG	2,097 (74.8)	183 (72.1)	173 (71.5)	176 (72.7)	154 (76.5)	143 (74.5)
PCI	1,065 (38.0)	120 (47.2)	87 (36.0)	117 (48.4)	77 (38.5)	98 (51.0)
CABG	1,251 (44.6)	82 (32.7)	99 (40.9)	79 (32.6)	93 (46.3)	61 (31.8)

* Comorbidities registered as primary or secondary hospital inpatient or outpatient diagnoses within 10 years preceding current admission.

† Values are expressed in counts (percentages) unless otherwise indicated.

‡ Defined as either a diagnosis code for diabetes mellitus or a prescription redemption of anti-diabetic medication within 100 days before MI admission.

§ Prescription redemption within 100 days before admission.

‖ Defined as either a procedure code for chemotherapeutics or a prescription redemption for a chemotherapeutic agent within 100 days before MI admission.

Abbreviations: ACE: Angiotensinogen converting enzyme, IQR: inter-quartile range, NSAID: non-steroidal anti-inflammatory drug.

Table 5. Sensitivity analysis: five-year HRs calculated in two different propensity score models including patients with and without dialysis-requiring acute kidney injury (D-AKI) following first-time hospital admission with myocardial infarction and cardiogenic shock.

Propensity score method	Exposure	Hazard ratio (95% CI)
Matching *	No D-AKI	1 (reference)
	D-AKI	1.66 (1.07–2.57)
SMRW †	No D-AKI	1 (reference)
	D-AKI	1.63 (1.07–2.47)

Propensity-score matched cohort

† Standardised mortality ratio weighting

Figures

Figure 1. 5-year cumulative mortality following hospital discharge by D-AKI status.

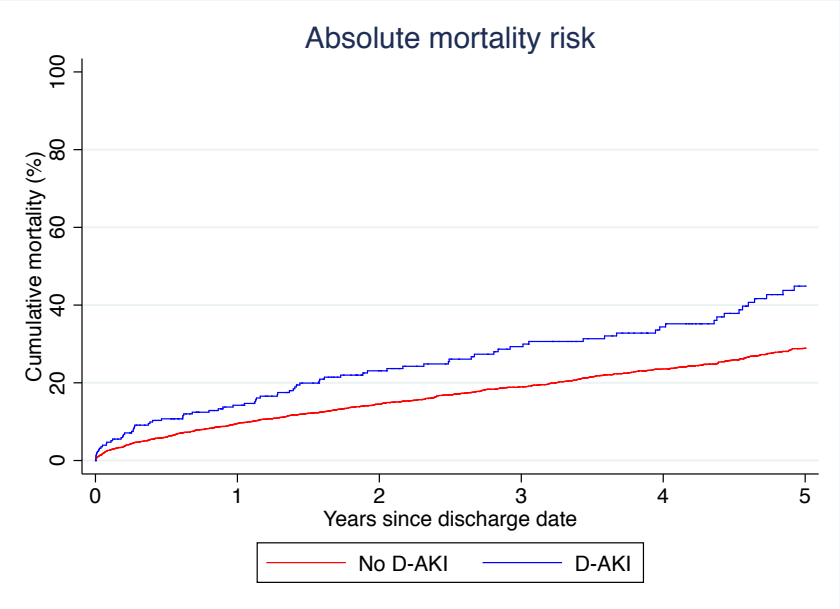
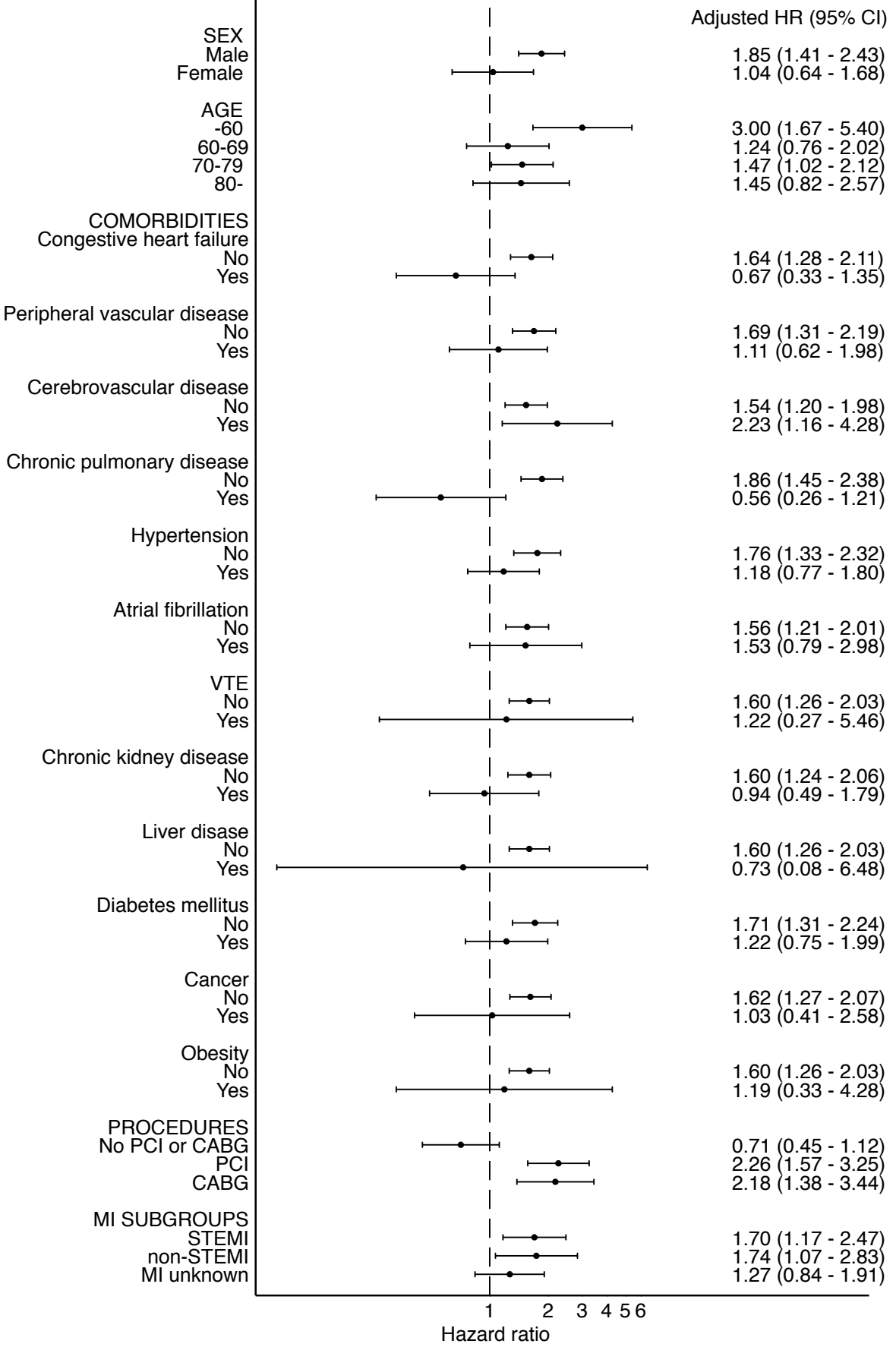


Figure 2. Forest plot of the subgroup analysis stratified by demographics, age group, comorbidity procedures, and MI subgroups showing propensity score-adjusted HRs with 95% confidence intervals.



Abbreviations: ACE-inhibitors: Angiotensin Converting Enzyme Inhibitors, ARBs: Angiotensin-II-Receptor Antagonists, CABG: Coronary Artery Bypass Graft, NSAIDs: Non Steroid Anti-Inflammatory Drugs, PCI: Percutaneous Coronary Intervention, STEMI: ST-elevation myocardial infarction, VTE: Venous Thromboembolism,

Appendix

Figure e1. Flowchart of study population including inclusion and exclusion criteria

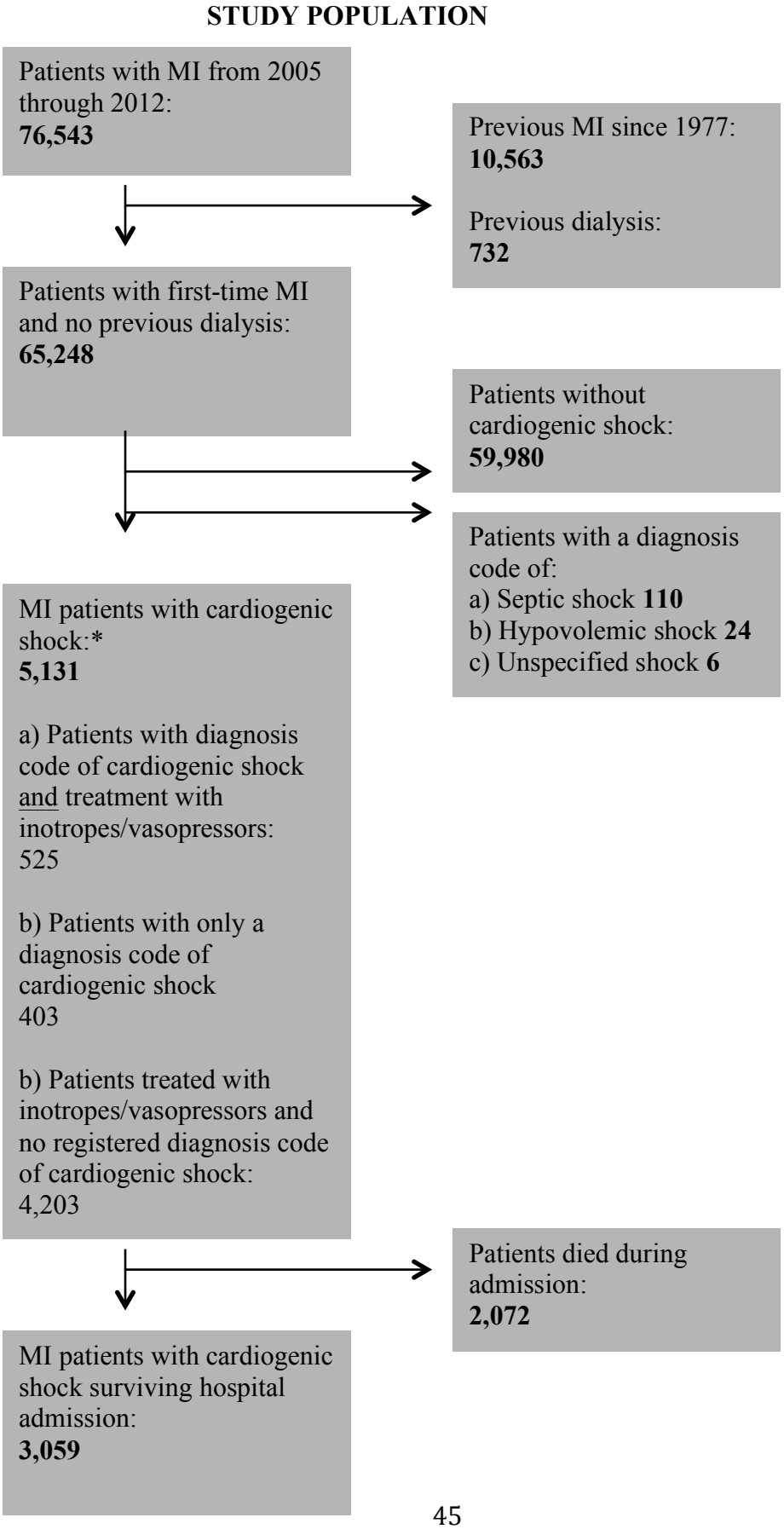


Table e1. Codes used to identify the study population, comorbidity, use of medicine, and in-hospital procedures**.**	
Definition of the study population	**ICD-8 and ICD-10 codes:**
Inclusion criteria: 1. Myocardial infarction from 2005-2012 2. Cardiogenic shock a) Diagnosis code with cardiogenic shock **b)** Procedure code of treatment with inotropes/vasopressors	 ICD-10: I21 ICD-10: R570 Procedure codes: BFHC93A-C, BFHC92B-E
Exclusion criteria: 1. Any previous myocardial infarction since 1977 **2.** Any previous dialysis procedure	 ICD-8: 410, ICD-10: I21-I23 Procedure code: BJFD
Comorbidity (registered in a 10-year period preceding MI admission)	**ICD-10 codes:**
Congestive heart failure	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	I70 - I74; I77
Cerebrovascular disease	I60-I69; G45; G46
Chronic obstructive pulmonary diseases	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Hypertension	I10-I13; I15
Atrial fibrillation/flutter	I48
Chronic renal disease	N04, N00, N01, N03, N05 I12, I13, I15.0, I15.1 N11, N14, N15, N16 Q61.1-Q61.4 E10.2; E11.2; E14.2, N08.3 N18-N19, N26, N27, N07, N08
Venous thromboembolism	I80.1-3, I26
Liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0 B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Diabetes	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9 E10.2-E10.8 E11.2-E11.8

	ATC-codes: A10A; A10B For A10BA02; Metformin (patients with the diagnosis polycystic ovarian syndrome ICD-10: E282 excluded)
Cancer (Any tumor, leukaemia, lymphoma)	C00-C75; C91-C95; C81-C85; C88;
Obesity	E65-66
Drugs (registered 100 days preceding MI admission):	**ATC-codes/procedure codes:**
Chemotherapeutics	Procedure code: BWHA ATC-code: L01
ACE-inhibitors	ATC: C09A; C09B
Angiotensin-II-antagonists	ATC: C09C; C09D
NSAIDs	ATC: M01AE01, M01AE51; M01AE02; M01AE03, M01AE53; M01AE14; M01AC01; M01AG02 M01AB05, M01AB55; M01AB08; M01AX01; M01AC06. M01AH01; M01AH02; M01AH03; M01AH04; M01AH05.
Aminoglycoside	ATC: J01G
Cyclosporine	ATC: L04AD01
In-hospital* procedures †	**Procedure codes:**
PCI	KFNG; KFNF
CABG	KFNA-E; KFNH20
Coronary arteriography	UXAC85
Fibrinolysis	BOHA1
Subtypes of MI	**ICD-10 codes:**
STEMI	I210, I211, I212, I213
Non-STEMI	I214
MI unknown (unspecified)	I21, I219

For patients without a diagnosis code of cardiogenic shock and a procedure code for inotropi/vasopressor:	**ICD-10 codes:**
Septic shock	R572, A41.9A
Hypovolemic shock	R571
Unspecified shock	R57, R578, R579

*In-hospital is defined as the initial admission for MI, as well as any transfers to other departments on the same day or the day after discharge from first admission.

†Because some overlap between PCI and CABG procedures was observed, they were combined as one variable to reduce the potential for co-linearity to affect the results. CAG was not included as a variable in the adjusted models because even more co-linearity exists between this procedure and PCI/CABG.

Abbrevations: ACE: angiotensin convertin enzyme, CABG: coronary artery bypass graft, ICD: international classification of diseases, MI: myocardial infarction, NSAID: non-steroid anti-inflammatory drug, NSTEMI: non-ST elevation myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST-elevation myocardial infarction.

Table e2. Subgroup analysis of 5-year cumulative mortality following first time admission with myocardial infarction and cardiogenic shock comparing patients with vs. without dialysis-requiring acute kidney injury (D-AKI).

			Non-D-AKI	D-AKI
Exposure	**No of deaths**	**No at start**	**5-year risk (%) (95% CI)**	**5-year risk (%) (95% CI)**
Sex				
Male	479	2,164	26.3 (24.0-28.9)	44.7 (36.1-54.3)
Female	264	895	34.9 (31.0-39.1)	45.3 (30.2-63.7)
Age group (years)				
< 60	80	766	12.1 (9.3-15.5)	32.4 (20.0-49.8)
60-69	185	966	23.0 (19.8-26.6)	30.1 (20.5-44.7)
70-79	309	989	37.1 (33.2-41.3)	60.6 (45.5-76.1)
≥ 80	169	338	58.7 (51.7-65.7)	77.6 (51.9-95.3)
Comorbidties				
Congestive heart failure				
No	658	2,893	27.0 (24.9-29.2)	43.2 (35.2-52.1)
Yes	85	166	62.9 (52.9-73.0)	62.3 (36.6-87.6)
Peripheral vascular disease				
No	613	2,760	26.4 (24.3-28.7)	43.5 (25.2-52.7)
Yes	130	299	52.5 (44.9-60.4)	55.8 (36.2-77.3)
Cerebrovascular disease				
No	631	2,752	26.8 (24.7-29.1)	42.8 (34.8-51.7)
Yes	112	307	50.0 (42.0-58.7)	60.9 (39.6-82.6)
Chronic pulmonary disease				
No	632	2802	26.6 (24.5-28.8)	46.1 (37.9-55.1)
Yes	111	257	52.7 (45.1-60.7)	33.4 (17.3-58.1)
Hypertension				
No	668	2,874	27.8 (25.7-30.0)	42.5 (34.6-51.4)
Yes	75	185	47.8 (38.2-58.3)	68.4 (43.5-90.3)
Atrial fibrillation				
No	629	2938	28.1 (26.1-30.4)	44.4 (36.7-52.9)
Yes	74	195	50.1 (40.7-60.3)	70.0 (45.5-90.7)
VTE				
No	726	3,023	28.7 (26.6-30.8)	45.2 (37.3-53.8)
Yes	17	36	46.8 (30.1-67.2)	40.0 (11.8-87.4)
Chronic kidney disease				
No	694	2,964	28.0 (25.9-30.2)	41.9 (34.0-50.8)
Yes	49	95	67.9 (53.7-81.3)	75.5 (48.5-95.0)
Liver disease				
No	729	3,038	28.6 (26.5-30.8)	44.6 (36.9-53.2)
Yes	14	21	70.2 (45.3-91.2)	-
Diabetes mellitus				
No	590	2,562	26.8 (24.6-29.1)	42.2 (33.9-51.5)
Yes	153	497	41.6 (35.6-48.3)	58.0 (38.7-78.5)
Cancer				
No	661	2,845	27.5 (25.4-29.7)	44.7 (36.8-53.5)
Yes	82	214	47.2 (38.8-56.5)	49.2 (23.4-82.2)
Obesity				

No	724	2,978	28.8 (26.7-31.0)	44.7 (36.9-53.3)
Yes	19	81	31.7 (19.9-48.0)	60.2 (17.9-98.7)
In-hospital procedures				
No PCI/CABG	264	481	63.1 (57.5-68.6)	51.3 (36.7-67.8)
PCI	220	1,185	22.7 (19.7-26.2)	46.8 (35.7-60.8)
CABG	217	1,334	17.5 (15.0-20.2)	37.7 (25.8-52.7)
MI subgroups				
STEMI	252	1,199	25.8 (22.6-29.3)	39.8 (29.3-52.4)
non-STEMI	282	1,138	29.2 (26.0-37.8)	47.9 (30.9-68.3)
MI unknown	209	722	33.5 (29.2-38.3)	48.7 (36.0-63.1)

* Adjusted for propensity score.

Abbreviations: AKI: acute kidney injury, CABG: coronary arterial bypass graft, CI: confidence interval, D-AKI: dialysis-requiring acute kidney injury, PCI: percutaneous coronary intervention, STEMI: ST-elevation myocardial infarction, VTE: venous thromboembolism.

Table e3. Comorbidity characteristics registered in a 10-year period preceding admission either up until admission date or up until discharge date for comorbidities that are not a potential MI complication.

Clinical features	Registration until admission date[a]			Registration until discharge date[b]	
	Total n=3,059 (100)[d]	No D-AKI n=2,805 (91.7)[d]	D-AKI n=254 (8.3)[d]	No D-AKI n=2,805 (91.7)[d]	D-AKI n=254 (8.3)[d]
Comorbidities					
Congestive heart failure	166 (5.4)	145 (5.2)	21 (8.3)	145 (5.2)	21 (8.3)
Peripheral vascular disease	299 (9.8)	268 (9.6)	31 (12.2)	325 (11.6)	42 (16.5)
Cerebrovascular disease	307 (10.0)	284 (10.1)	23 (9.1)	284 (10.1)	23 (9.1)
Chronic pulmonary disease	257 (8.4)	232 (8.3)	25 (9.8)	329 (11.7)	31 (12.2)
Hypertension	633 (20.7)	559 (19.9)	74 (29.1)	1,099 (39.2)	127 (50.0)
Atrial fibrillation/flutter	185 (6.1)	166 (5.9)	19 (7.5)	166 (5.9)	19 (7.5)
Venous thromboembolism	36 (1.2)	31 (1.1)	5 (2.0)	31 (1.1)	5 (2.0)
Chronic kidney disease	95 (3.1)	67 (2.4)	28 (11.0)	134 (4.8)	88 (34.7)
Liver disease	21 (0.7)	19 (0.7)	2 (0.8)	23 (0.8)	7 (2.8)
Diabetes mellitus[c]	497 (16.3)	441 (15.7)	56 (22.1)	551 (19.6)	72 (28.4)
Cancer	214 (7.0)	202 (7.2)	12 (4.7)	231 (8.2)	16 (6.3)
Obesity	81 (2.7)	70 (2.5)	11 (4.3)	103 (3.7)	16 (6.3)

[a] Comorbidity defined as any primary or secondary ICD-10 codes registered 10 years preceding date for MI admission.
[b] Congestive heart failure, cerebrovascular disease, atrial fibrillation/flutter, venous thromboembolism defined as any primary or secondary ICD-10 codes registered within 10 years preceding date of MI admission. Peripheral vascular disease, chronic pulmonary disease, hypertension, chronic kidney disease, liver disease, diabetes mellitus, cancer and obesity defined as any primary or secondary ICD-10 codes registered within 10 years preceding date of MI admission and until date of discharge, since these comorbidities could be complications of MI.
[c] Defined as either a diagnosis code for diabetes or prescription redemption for an anti-diabetic drug within 100 days before MI admission.
[d] Values expressed in counts (percentages) unless otherwise indicated.

Table e4. Five-year mortality estimates when co-morbidities were defined up until discharge date.

Exposure	Sensitivity analysis[a] Hazard ratio (95% CI)	
	Mulitvariate-adjusted	**Propensity-score-adjusted**
No D-AKI	1 (reference)	1 (reference)
D-AKI	1.22 (0.95-1.58)	1.42 (1.11-1.86)

[a] Congestive heart failure, cerebrovascular disease, atrial fibrillation/flutter, venous thromboembolism defined as any primary or secondary ICD-10 codes registered within 10 years preceding date of MI admission. Peripheral vascular disease, chronic pulmonary disease, hypertension, chronic kidney disease, liver disease, diabetes mellitus, cancer and obesity defined as any primary or secondary ICD-10 codes registered within 10 years preceding date of MI admission and until date of discharge.

Tabel e5. Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 mmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m2	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

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