From the Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

DEPRESSION AND CARDIAC SURGERY

Malin Stenman

Karolinska Institutet

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Depression and cardiac surgery

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Malin Stenman

Principal Supervisor:
Associate professor Ulrik Sartipy
Karolinska Institutet
Department of Molecular Medicine and Surgery

Co-supervisor:
Associate professor Martin Holzmann
Karolinska Institutet
Department of Medicine, Solna

Opponent:
Anders Ahlsson, PhD
Örebro University
Faculty of Medicine and Health

Examination Board:
Professor Stefan Thelin
Uppsala University
Department of Surgical Sciences

Associate professor Rebecka Hultgren
Karolinska Institutet
Department of Molecular Medicine and Surgery

Associate professor Jonas Schwieler
Karolinska Institutet
Department of Medicine, Solna

To Lovisa & Gustav

“A sad soul can kill you quicker, far quicker than a germ.”

- John Steinbeck

ABSTRACT

Cardiovascular disease and depression are likely to be two of the three leading causes of global burden of disease. Depression is common in patients with coronary artery disease and is independently associated with increased cardiovascular morbidity and mortality. The incidence of major depressive disorder is two to three times higher in patients with cardiovascular disease than in the general population. In patients with coronary artery disease, clinically significant depression is prevalent in 31% to 45% of patients. Moderate to severe depression before coronary artery bypass grafting (CABG) is an indicator of worse long-term survival. The overall aim of this thesis was to study the association between depression and cardiovascular morbidity and mortality in patients undergoing cardiac surgery by epidemiological methods and cross-linking of national Swedish registers.

Study I investigated the association between preoperative antidepressant use and long-term survival following primary isolated CABG. Of 10884 patients 11% were using antidepressants before surgery. After multivariable adjustment, antidepressant use was associated with increased mortality hazard ratio (HR) 1.45; 95% confidence interval (CI) 1.18–1.77, compared with non-use of antidepressants. Antidepressant use was also associated with an increased risk of rehospitalization (HR1.40; 95% CI 1.19–1.65) and the composite endpoint rehospitalization or death (HR 1.44; 95% CI 1.26–1.65).

Study II We hypothesized that depressed patients would have lower use of guideline-directed medical therapy for secondary prevention of cardiovascular events following CABG. We included all 10586 patients who underwent primary isolated CABG in Sweden between 2006 and 2008. During the first year after CABG, 93% of all patients had at least two dispensed prescriptions for an antiplatelet agent, 68% for an ACEI/ARB, 91% for a beta-blocker, and 92% for a statin. 57% had prescriptions for all four medication classes. After four years (n=4034), 44% had filled prescriptions for all four medication classes. Preoperative depression was not significantly associated with a lower use of all four medication classes.

Study III investigated major depression in 56064 patients who underwent primary, isolated, non-emergent CABG. During a mean follow-up of 7.5 years, 114 patients (35%) with depression died, compared with 13767 patients (25%) in the control group. Depression was significantly associated with increased mortality and the combined end

point of death or rehospitalization for MI, heart failure, or stroke (multivariable-adjusted HR 1.65 95% CI 1.37 to 1.99 and 1.61, 1.38 to 1.89, respectively).

Study IV investigated if socioeconomic factors modified the association between preoperative depression and survival following CABG. Antidepressant use was a proxy for depression. During a mean follow-up of 4.1 years, 11% patients died in the antidepressant group and 9.7% patients died in the control group. The adjusted risk for death was higher in patients with preoperative antidepressant use (HR 1.27; 95% CI 1.13–1.43), and was practically unchanged after the addition of educational level, family disposable income, and civil status (HR 1.25; 95% CI 1.11–1.41).

Study V was a systematic review and meta-analysis performed to provide a summary estimate of the association between preoperative depression and long-term survival after CABG. Seven studies were included with a combined study population of 89490 patients (4002 depressed/85488 non-depressed). All studies observed a positive association between preoperative depression and all-cause mortality, and in 4 studies the association was statistically significant. Patients with depression had a pooled HR of 1.46 (95% CI: 1.23-1.73, $p<0.001$) for all-cause mortality with moderate heterogeneity ($I^2 = 50.1\%$ $p=0.061$).

In conclusion depression is a significant, independent risk factor, in patients with cardiovascular disease and should be considered as important as other well-known risk factors like for example heart failure and chronic kidney disease in patients undergoing CABG.

LIST OF SCIENTIFIC PAPERS

I. **Stenman M**, Holzmann MJ, Sartipy U.
Antidepressant use before coronary artery bypass surgery is associated with long-term mortality.
Int J Cardiol. 2013;167:2958–2962

II. **Stenman M**, Holzmann MJ, Sartipy U.
Use of secondary prevention medications after coronary artery bypass grafting in patients with depression.
Int J Cardiol: Heart & Vessels. 2014:37-42

III. **Stenman M**, Holzmann MJ, Sartipy U.
Relation of major depression to survival after coronary artery bypass grafting.
Am J Cardiol. 2014;114:698-703

IV. **Stenman M**, Holzmann MJ, Sartipy U.
Do socioeconomic factors modify the association between preoperative antidepressant use and survival following coronary artery bypass surgery?
Int J Cardiol. 2015;198:206-12

V. **Stenman M**, Holzmann MJ, Sartipy U.
Association between preoperative depression and long-term survival following coronary artery bypass surgery: A systematic review and meta-analysis.
Submitted

CONTENTS

LIST OF ABBREVIATIONS

ACEI	Angiotensin-Converting Enzyme Inhibitors
AHA	American Heart Association
ARB	Angiotensin II Receptor Blocker
ATC	Anatomical Therapeutic Chemical
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CI	Confidence Interval
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
HPA	Hypothalamicpituitary-Adrenocortical
HR	Hazard Ratio
MDD	Major depressive disorder
MI	Myocardial infarction
ICD	International Classification of Diseases
IL-6	Interleukin-6
LISA	Longitudinal integration database for health insurance and labor market studies
NPR	National Patient Register
PHQ	Patient Health Questionnaire
RR	Risk Ratio
SA	Sympatheticadrenomedullary system
SD	Standard Deviation
sICAM-1	Soluble Intercellular Adhesion Molecule 1
SSRI	Selective Serotonin Reuptake Inhibitor
SWEDEHEART	The Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death within men and women in Sweden today. In 2013, 37% of all deaths were attributable to CVD.[1] Acute cardiovascular disease is also the most common reason for hospital admission and represents 16% of all hospitalizations. Every year approximately 60000 patients are cared for in Swedish hospitals due to acute coronary disease to a cost of two billion Swedish crowns.[2]

Major depression disorder (MDD) is a severe and potentially incapacitating psychiatric illness described by a significant change in mood. MDD often has a recurrent or chronic course of illness and can end in substantial individual suffering and disability.[3] The lifetime incidence in the US is predicted to be 12% in men and 20% in women.[4] The three leading causes of burden of disease in 2030 are foreseen to include HIV/AIDS, unipolar depressive disorders, and ischemic heart disease.[5]

The aim of this thesis was to study the association between depression and cardiovascular morbidity and mortality in patients undergoing cardiac surgery by epidemiological methods and cross-linking of national Swedish registers.

BACKGROUND

Myocardial infarction

Myocardial infarction (MI) is a major cause of death and disability worldwide and may be the first manifestation of coronary artery disease (CAD). In patients with established disease the disease may occur repeatedly.[6] If standardized incident data is collected on MI useful information regarding the burden of CAD within and across populations can be provided.[6]

Myocardial infarction happens when the blood flow that transports oxygen to the heart muscle is severely reduced or stopped. This is due to atherosclerosis of the coronary arteries. The coronary arteries supply the heart with blood but can slowly become thicker and harder from build-up of fat, cholesterol and other substances that together are called plaque. This process is called atherosclerosis.[7] If there is an atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries, this will lead to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis.[6]

There are nine risk factors significantly associated with acute MI: abnormal lipids, smoking, diabetes, hypertension, high risk diet, physical inactivity, alcohol use, abdominal obesity and psychosocial stress.[8] Anand et al. found that women experience their first MI approximately 9 years later than men. Higher levels of risk factors including abnormal lipids, and smoking, before the age of 60 years largely explain this earlier onset among men.[8]

Coronary artery bypass grafting

For patients 40 years and over, CAD represent almost 50% of all hospital admissions in Europe and the USA. When medical treatment and percutaneous coronary intervention (PCI) do not reduce symptoms and improve the patient´s health in a satisfying way coronary artery bypass grafting (CABG) has proven to be an effective treatment for ischemic heart disease.[9] CABG is an open heart surgical procedure where one or more of the coronary arteries are bypassed.[9] The first successful human CABG was performed in the United States by Dr Goetz and Dr Rothman in 1960.[10]

After pioneering work at the Cleveland Clinics in 1967 CABG evolved over time to be a common surgical procedure.[11] The main indication for CABG surgery is to relieve angina, reduce the likelihood of future or new MIs, to prolong life-expectancy and to improve health status and quality of life.[12]

In Sweden 5787 open heart surgical procedures were performed in 2015, of these 2623 were isolated CABG.[13] During the 1990s approximately 6500 CABG procedures were performed yearly. The reason for this decrease in CABG volumes is the introduction of PCI.[1]

Depression

In a study[14] about depression, anxiety and their comorbidities in the Swedish general population, it was shown that 17.2% of all persons, at any given time point, were experiencing clinically significant depression that was likely to affect their daily lives. Approximately 5.2% experienced a current major depressive episode. Depression was more common among women than men. Co-existence of depression and anxiety increased symptom severity and affected health-related quality of life negatively.[14]

Symptoms of major depression is depressed mood or loss of interest in almost all activities for ≥ 2 weeks, together with three or more of the following symptoms: insomnia, feelings of worthlessness, excessive guilt, loss of energy, inability to concentrate, change in appetite or weight, and recurrent thoughts of death or suicide.[15]. For major depression suicidal ideation is a fundamental symptom.[16] Premature deaths in people with depression may be related to physical morbidity as well as death from unnatural causes such as suicide.[17,18] In Sweden 3 deaths per day are due to suicide.[19]

Depression related to coronary artery disease

In 1993 Frasure-Smith et al. published a study[20] demonstrating that patients who were depressed at the time of an acute MI had markedly increased mortality compared with patients who were not depressed.[20] Since then many studies[21-23] have investigated the relationship between depression and cardiovascular disease and provided evidence that depression is prevalent in 20% to 35% in populations with cardiovascular disease. Depression seems to be a predictor of cardiovascular disease, and of adverse outcomes among patients who already have cardiac disease.[23,24]

Reese et al.[25] assessed 766 patients in an Enhancing Recovery and Coronary Heart Disease ancillary. The patients were classified using the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV), as having no depression, minor depression and major depression after acute MI. The participants were followed for rehospitalizations for up to 24 months. The result revealed that patients with depressive disorders had an increased risk of rehospitalization after acute MI. Depressed patients had a higher total number of all-cause hospitalizations and visits to the emergency department during the 42 months after the initial MI. Patients suffering from depression additionally spent significantly more days in the hospital.[25]

In patients undergoing CABG, 20-25% suffer from depression.[21,23] Depression is a strong and independent risk factor for mortality, readmission and cardiac events after CABG surgery.[21] It can be challenging to detect depression in cardiac patients as some of the symptoms such as fatigue and poor appetite are the same as symptoms of other medical illnesses.[25]

Depressed patients also have the feeling of a poor quality of life and poor physical functioning.[21] The rate of major depressive disorder is 2- to 3-fold higher in patients with CVD than among the general population. Among patients suffering from CVD, depression seems to be chronic and recurrent. Studies have shown that for many patients, depression has been existing for months or years before a cardiac event rather than being a reaction to the event.[21]

Studies have also showed that between 21% and 33% of patients who survive an index hospitalization for acute coronary syndrome are rehospitalized within one year.[25] Besides high costs for society, hospital readmissions also have an impact on quality of life and for younger patients readmissions can adventure economy and employment. Therefore it is important to identify factors among patients with coronary disease that are associated with increased risk of rehospitalization.[25]

Female sex, younger age, lower education level, living alone, suffering from dyspnea and previous MI are variables strongly associated with preoperative depressive risk in patients undergoing CABG.[26]

Depression related to gender and CABG

Depression is far more common among women than men. The prevalence ratios female:male is around 2:1.[27]

It has been shown that women experience more and stronger depressive symptoms than men prior to CABG but that the depressive symptoms are at a comparable level after CABG.[28] Mitchell et al.[28] found that women with depression were significantly less likely to be married compared to men, less likely to have a paid job and more prone to unstable angina than men [28]. After surgery there was a trend for men to be sent to cardiac rehabilitation programs more often than women. Women experienced more physical recovery-related symptoms than men but reported higher levels of social support. Women were significantly more depressed and had more severe depressions compared to men before CABG but after surgery women´s symptoms were substantially improved whilst men´s symptoms improved only slightly.

Assessment of depression

More than 50% of patients with mental disorders, and depressive disorders are treated in primary care settings.[29] Less than half of the patients who are affected are accurately diagnosed. This is in part due to biases found in self-reporting screening tools used to detect depression. A patient's culture, gender or somatic symptoms can hinder the detection of depression.[29] The Beck Depression Inventory (BDI) is the most extensively used self reporting tool worldwide. It was developed in 1961, and was designed to assess the intensity of symptoms associated with psychoanalytic aspects of depression, such as sadness, feelings of failure, guilt, suicidal ideas, and social withdrawal.[30] The BDI has been criticized for being sensitive to semantically different translations of depression screening questions between countries and languages. This may decrease the specificity of scores and increase false-positive identifications of the presence of depression. It is important to remember that scores from depression screening tools cannot form a basis for diagnosis on its own.

Several studies have shown that clinical depression is a risk factor for cardiac events after CABG.[31-33] In these studies depression has been defined in different ways. Some investigators used self-assessment to define depression and some used anti-depressant use as a proxy for depression. The study of Blumenthal et al.[31] assessed depression the day before surgery according to the 20-item Center for Epidemiological Studies

Depression (CES-D) questionnaire (non-depressed (CES-D <16), mildly depressed (CES-D 16–26), and moderate to severely depressed (CES-D >27). Connerney et al.[32] used Diagnostic Interview Schedule (DIS) for MDD.[32] Tully et al.[33] used a 42-item self report instrument designed to measure the three related negative emotional states of depression, anxiety and tension/stress (DASS).[33] In a study by Xiong et al. [34] SSRI use was used as a proxy for depression.[34]. The different ways of assessing depression in the studies might affect their results and generalizability.

Behavioral factors – life style factors

There are a number of behavioral and lifestyle factors that are involved in the relationship between cardiac disease and depression. Patients suffering from depression are less likely to engage in health-promoting behaviors like keeping a healthy diet, regular exercise, adherence to medications and attendance in cardiac rehabilitation programs.[21] Depression has also been associated with increased smoking[35] use of illicit drugs and alcohol use[31]. However, controversy remains, whether it is depression that worsens outcome in patients with cardiovascular disorders or if the worse outcome is due to changes in lifestyle and behavior associated with depression.

Pathophysiology

There are numerous biological factors in patients suffering from depression that are associated with an increased risk of CVD.

Stress

One possible hypothesis is related to emotional stress. Stress has been shown to be a potent trigger or inducer of depression.[36] Stress activates the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenomedullary (SA) system. When stress is removed, these 2 systems should return to their basal states. But due to genetic predisposition, such as specific serotonin transporter gene polymorphisms, coupled with gene-environment interaction some individuals may recover from life stressors and others may not and later develop depression.[37] Depressed patients are in a constant state of perceived stress, with continuous upregulation of the HPA axis and the SA system. It has been shown in animal models that stress triggers serotonin dysregulation which leads to decreased brain monoaminergic activity and the state of depression.[38,39]

Inflammation

Chronic inflammation has been demonstrated to play a key role in the pathogenesis of several chronic disorders including CVD. Noxious stimuli such as cigarette smoke, low-density lipoprotein cholesterol and hypertension damage the arterial wall and causes a state of subacute inflammatory condition.[40]. Important for arterial repair is activation of the platelet clotting cascade.[41] With increasing age repair competent cells are not always available, artery repair fails and the inflammatory state increases.[42]

The most reliable biomarkers of increased inflammation in patients with depression are inflammatory cytokines interleukin-6 and tumor necrosis factor (TNF), as well as the acute-phase reactant C-reactive protein (CRP).[43,44]

CRP is a biomarker of inflammation and several studies have shown elevated concentrations in patients suffering from depression.[45,46] This inflammatory state might play a major role in explaining the increased risk of CAD in patients suffering from depression, although the literature is somewhat inconsistent. Bankier et al.[47] studied 72 patients with CAD of whom 30 were diagnosed as having MDD. They found a significant association between MDD and CRP levels.[47] In a much larger study by Lesperance et al.[48] plasma levels of soluble intercellular adhesion molecule 1 (sICAM-1) and interleukin-6 (IL-6) and the serum level of CRP were measured in 481 patients 2 months after hospitalization for acute coronary syndromes. Depression was measured using the Structured Clinical Interview for DSM-IV. Depressed patients were diagnosed with higher levels of sICAM-1, but there was no association with IL-6.[48]. Frasure-Smith et al. used Beck Depression Inventory – II (BDI-II) to define depression and found that patients with elevated depression symptoms had higher levels of CRP, but not IL-6, as compared with non-depressed cardiac patients.[49,50]

However, there are other studies not supporting this observation. In a case-control study of depressed (n=57) and non-depressed (n=46) patients with MI there was no difference between the groups in levels of IL-6, TNF-α or CRP.[51]

Endothelial dysfunction and oxidative stress

Endothelial dysfunction has been hypothesized to mediate the increased risk of CAD in patients with depression.[52-54]

A weakness of previous studies is that they have primarily focused on adults who were 50 years and older, and it is reasonable to believe that underlying atherosclerosis may be contributing to these effects, as it is known to alter mental state as well as compromise vascular function.[55] This hypothesis was supported by Thomfohr et al.[56] who investigated a sample of healthy, active young women, and found that, symptoms of depression were associated with diminished nitric-oxide-mediated vasodilation, which is a reflection of endothelial dysfunction.[56]

Heart-rate variability

Reductions in the hearts ability to respond to physiological demand are associated with growing risk of cardiovascular disorders and sudden cardiac death.[57] Heart-rate variability is reduced in patients suffering from depression and could be an explanation to increased mortality in patients with depression.[58]

AIMS OF THE THESIS

The overall aim of this thesis was to study the relationship between depression, cardiovascular disease and mortality, in patients who undergo coronary artery bypass grafting using epidemiological methods and cross-linking of national registers.

The specific aims were:

- To study the association between preoperative antidepressant use and survival following CABG (Study I)
- To analyze the association between preoperative depression and guide-line directed medications after CABG (Study II)
- To study the association between preoperative depression and long-term survival following primary isolated CABG (Study III)
- To study the importance of socio-economic status for long-term survival after CABG in patients with depression (Study IV)
- To analyze long-term survival after CABG in patients with depression through systematic review and meta-analysis of cohort studies (Study V)

PATIENTS AND METHODS

Registers

SWEDEHEART

The Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)[2,59] is a national registry including all patients who underwent coronary angiography, PCI, or cardiac surgery or were cared for at any cardiac intensive care unit in Sweden.[2] Agreement between information in the register and the medical records is described to be between 93% and 97%. SWEDEHEART aims to improve patient care by making it possible for hospitals to compare results and to provide basis for research. All hospitals treating patients with CAD report to SWEDEHEART on a yearly basis. SWEDEHEART include five different registers: RIKS-HIA – the register of information and knowledge about Swedish Heart Intensive Care Admissions, SEPHIA – Secondary prevention after Heart Intensive Care Admission, SCAAR – Swedish Coronary Angiography and Angioplasty Registry, Swedish Heart Surgery Registry – started in 1992 and covers 100% of all cardiac operations performed in all eight hospitals performing cardiac surgery in Sweden.

The Swedish National Patient Register

In 1964 the Swedish National Board of Health and Welfare started the National Patient Register (NPR).[60] The NPR covers all diagnoses for all patients hospitalized in Sweden since 1987. It covers more than 99% of all somatic and psychiatric hospital discharges including patient data, geographical data, administrative data of the hospital stay, and medical data. Discharge codes used in the NPR are based on the International Classification of Diseases (ICD). The validity of the register has frequently shown to be high, with a 95% validity for a primary diagnosis of heart failure, 98.6% for stroke and 98 to 100% for MI.[60,61]

The Cause of Death Register

Under the supervision of the Swedish National Board of Health and Welfare the Cause of Death Register was started in 1952. The registry contains data of all deceased persons registered in Sweden since 1961, regardless if the person died in Sweden or abroad. Information about cause of death and date of death can be obtained from the registry.

The diagnoses are coded according to the ICD and since 1997 causes of death are classified according to the international version of ICD-10. About 1-2 % of registered deaths have missing cause of death and are coded as without known cause of death.[62]

Total Population Register

The Total Population Register is a national register maintained by Statistics Sweden. The registry covers all people registered in Sweden since 1968 and is updated continuously. The registry contains information regarding name, place of birth and residence, sex, age, civil status, citizenship, immigration and relationships such as married couples and child-parent. Hundred percent of all deaths are reported to Statistics Sweden within one month.[63]

The Prescribed Drug Register

The Prescribed Drug Register, maintained by the Swedish National Board of Health and Welfare, contains information on dispensed prescriptions in all out-patient care covering the entire population of Sweden since July 2005. The register includes the ATC-code and the date of dispensing.[64]

Longitudinal integration database for health insurance and labor market studies (LISA)

The LISA register is a national register maintained by Statistics Sweden that holds annual registers since 1990 and includes all individuals above 16 years of age. The database provides information about employment, income, country of birth and place of residency, parental countries of birth and educational status. The primary objective in LISA is the individual, but connections to family, companies and places of employment are also available.[65]

The Swedish Personal Identification Number

Since 1947 all Swedish citizens have a unique personal identity number. It consists of the date of birth, a three-digit birth number and a check digit. When an individual reside in Sweden on a permanent basis, and is recorded in the Total population register, he or she is assigned a personal identity number. The unique personal identity number is of great importance in Swedish health care as well as in medical research. It facilitates linkage between registers and makes large-scale medical register-based research possible.[66]

Overview of study design and methods in Study I-IV

	Study I	Study II	Study III	Study IV
Design	Nationwide population-based cohort study			
Data source	The SWEDEHEART register The National Patient Register The Prescribed Drug Register Cause of Death register			LISA in addition to registers used in Study I-III
Cohort	Adults undergoing primary isolated CABG in Sweden			
Period	2006 to 2008			2006 to 2013
Follow-up	Until Feb, 2011 for survival. Until Dec 31, 2009 for AMI. Until Dec 31, 2008 for heart failure and stroke	Until one year after surgery.	Until Feb, 2011 for survival. Until Dec 31, 2009 for AMI. Until Dec 31, 2008 for heart failure and stroke	Until Mar, 2014 for survival
Exposure	Antidepressant use		Diagnosis of depression in the National Patient Register	Antidepressant use
Outcome	*Primary:* All-cause mortality *Secondary:* rehospitalization for AMI, heart-failure or stroke, and a composite endpoint of all-cause mortality or rehospitalization	At least 2 dispensed prescriptions <1 year after CABG in all 4 medication classes: antiplatelet agents, ACEI, beta-blockers, statins	*Primary:* All-cause mortality *Secondary:* a combination of all-cause mortality and rehospitalization for AMI, heart failure or stroke	All-cause mortality
Statistical method	Multivariable survival analysis (Cox regression)	Modified Poisson regression	Multivariable survival analysis (Cox regression)	
Confounders	Age, sex, diabetes mellitus, COPD, LVEF, acute kidney injury, postoperative antidepressant use	Age, sex, smoking, atrial fibrillation, diabetes, hyperlipidemia, hypertension, COPD, PVD, AMI, stroke, LVEF, heart failure	Age, sex, renal function, LVEF, diabetes, COPD, PVD, acute kidney injury, stroke, heart failure	Age, sex, cardiovascular risk factors, marital status, income. education, region of birth

ACEI = angiotensin converting enzyme inhibitors, AMI = acute myocardial infarction, COPD = chronic obstructive pulmonary disease, LISA = the longitudinal integration database for health insurance and labor market studies, LVEF = left ventricular ejection fraction, PVD = peripheral vascular disease

Ethics

All studies were approved by the regional Human Research Ethics Committee in Stockholm, Sweden.

Data collection

Study I-III

The Swedish National Board of Health and Welfare used the unique Swedish personal identity number to link information regarding CABG patients from 1995-2008 from the SWEDEHEART register with the National Patient Register, The Prescribed Drug Register and the Cause of Death register with follow-up until February 2011. Information about baseline patient characteristics was extracted from SWEDEHEART, and from the Swedish National Patient Register (Swedish National Board of Health and Welfare).

Study IV

In this study, the data extraction procedure was repeated using the same registers as in Study I-III and additionally, data linking was performed using The Longitudinal integration database for health insurance and labor market studies (LISA) managed by Statistics Sweden, to obtain information about socioeconomic status. Again, the Swedish National Board of Health and Welfare used the Swedish personal identity number to link information regarding patients who underwent cardiac surgery from the SWEDEHEART register, and now with inclusion time until 2013 and follow up until March 2014.

Study population

Study I

From the SWEDEHEART register, we identified 14032 patients who underwent CABG between January 2006 and December 2008. We excluded 227 patients who had previous cardiac surgery, and 2261 patients who had another cardiac procedure in addition to CABG. Finally, we excluded 660 patients who underwent emergency surgery defined as surgery within 24 hours of decision. The final study population consisted of 10884 patients who underwent primary isolated non-emergent CABG, of these patients 1171 had a dispensed prescription of antidepressants before they underwent CABG.

Study II

From the SWEDEHEART registry 14032 patients who underwent CABG between January 2006 and December 2008 were identified. We excluded 227 patients who had previous heart surgery, 2261 patients who had another cardiac procedure than isolated CABG, 660 patients who were operated within 24 h from decision, and 298 patients who had a shorter follow-up time than one year. The final study population included 10586 patients (1132 depressed and 9454 non-depressed) who underwent primary isolated non-emergent CABG.

Study III

We identified 69243 patients who underwent CABG from 1997 to 2008 from the SWEDEHEART register. We excluded 1234 patients who had previous cardiac surgery and 9509 patients who had another cardiac procedure in addition to CABG. Finally, we excluded 2436 patients who underwent emergency surgery defined as surgery within 24 hours of decision to operate. The final study population consisted of 56064 patients who underwent primary isolated non-emergent CABG. We identified 324 patients with a preoperative diagnosis of depression from the National Patient Register. The remaining 55740 patients were categorized as the control group

Study IV

We included 22930 patients who had undergone primary isolated non-emergent CABG between January 2006 and December 2013, from the SWEDEHEART register. Patients were excluded if they had undergone previous cardiac surgery or had concomitant procedures in addition to CABG or if they underwent surgery within 24 hours of decision to operate. Finally, we excluded patients who died within one year of surgery, because the outcome of interest was dispensed prescriptions after a minimum of one year of follow-up. We identified 3078 (13%) patients who had at least one dispensed prescription of antidepressants before they underwent CABG.

Study V

Study V was a systematic review and meta-analysis. We included all cohort studies investigating the association between depression prior to CABG and long-term survival. We excluded all studies that were not cohort studies, and studies focusing on postoperative depression. A total of 1357 unique records were recognized through the literature search. Of these, 1209 were excluded due to title or abstract content, 80 due

to wrong population or outcome and 24 were review articles. The remaining 44 full-text articles were assessed for eligibility and 7 studies met the inclusion criteria. Studies included in the systematic review and meta-analysis were published between 2003 and 2015, and included data for 89490 patients from the USA, Sweden and Australia. Preoperative depression was existing in 4215 patients. The number of patients in each study ranged from 309 to 56064 with median or mean follow-up ranging from 3 to 9.3 years.

Definition of depression

In study I, II and IV we used antidepressant use as a proxy for depression. We used the national Prescribed Drug Register (Anatomical Therapeutic Chemical (ATC) code N06A, except for the following substances: N06AX02 and N06AX12). Preoperative antidepressant use was defined as having had at least one dispensed antidepressant prescription before the date of surgery.
In study III we used the National Patient Register to identify patients with a diagnosis of depression ICD-10 code: F3 and ICD-9 codes: 296, 311, 300.4, 309.0, and 309.1.

Outcome measures

All-cause mortality was the primary end-point in study I, III and IV. Information about death was obtained from the national Total Population Register. The primary outcome measure in study II was medication use defined as at least two dispensed prescriptions with the following ATC-codes: B01AC (antiplatelet agents), C09 (ACEI/angiotensin receptor blockers (ARB)), C07 (beta-blockers), and C10AA (statins) from the national Prescribed Drug Register after at least one year of follow-up, and at least four years of follow-up, respectively.
In study I, secondary outcome measures were rehospitalization for MI, heart failure or stroke, and a composite endpoint of all-cause mortality or rehospitalization for MI, heart failure or stroke.
In study III, the secondary outcome measure was a combined end-point of all-cause mortality or rehospitalization for MI, heart failure or stroke.

Statistical analysis

Study I
Baseline characteristics were described using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. The

Kaplan–Meier method was used to calculate cumulative survival and construct survival curves for the exposed and unexposed group, and the log-rank test to compare differences between the curves. We used Cox proportional hazards regression with and without multivariable adjustment to model survival. In a further effort to reduce selection bias, propensity score methods for stratification and regression adjustment was used. Stata version 12.1 (StataCorp LP, College Station, TX, USA.) was used for all analyses

Study II

To describe baseline characteristics means and standard deviations were used for continuous variables and frequencies and percentages for categorical variables. We used modified Poisson regression with a robust estimator of variance to calculate risk ratios (RR) for the use of each medication class for depressed patients with non-depressed patients as reference category. We reported unadjusted and multivariable adjusted RR with 95% CI. We also analyzed the distribution of medication class and medication use in men and women separately. Finally, we investigated the time trend in secondary prevention medication by comparing the distribution of medication class for patients who underwent surgery in 2006 to that of patients who underwent surgery during 2008. Stata version 13.0 (StataCorp LP, College Station, TX) was used for all data management and statistical analysis.

Study III

The Kaplan-Meier method was used to calculate cumulative survival and construct survival curves for the exposed and unexposed group and the log-rank test to compare differences between the curves. We used Cox proportional hazards regression to model survival. We created several multivariate models considering all baseline characteristics. Stata, version 12.1 (StataCorp LP, College Station, Texas), was used for all analyses.

Study IV

Baseline characteristics were described with frequencies and percentages for categorical variables and means and standard deviations for continuous variables. The crude incidence rates and 95% confidence intervals (CIs) were calculated and the Kaplan–Meier method was used to calculate cumulative survival. We used Cox proportional hazards regression with and without multivariable adjustment to model

survival. Age and body mass index were modeled as restricted cubic splines, and all other variables were included as categorical terms. We calculated propensity scores for each patient by logistic regression, with antidepressant use as the dependent variable and all baseline characteristics as independent variables. The propensity scores were first used for regression adjustment and were included in the multivariable Cox regression model as a continuous variable, and then divided into quintiles and a separate Cox regression model was stratified by propensity score quintile. We also constructed a 1:1 propensity score-matched cohort by nearest neighbor matching without replacement, and a caliper width equal to 0.2 of the SD of the logit of the propensity score. Standardized differences for variables were calculated to investigate post-match balance. Data management and statistical analyses were performed using Stata 13.1 (Stata Corp LP, College Station, TX,USA) and R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Study V

Adjusted HR and 95% CI was extracted from the selected articles. Fixed and random effects models were used to compute the pooled HR and 95% CI. The random effects model was used to take into account the possible clinical diversity and methodological variation amongst studies. The random and fixed effect models showed similar results. Additional tests included: Q-test to test heterogeneity between trials; I^2 to estimate the percentage of total variation across studies due to heterogeneity rather than chance. I^2 can be calculated as follows: $I^2 = 100\%*(Q-df)/Q$ (where Q represents Cochrane´s measure of heterogeneity and the degrees of freedom), and can be categorized into low (<50%), moderate (51-75%), or high (>75%) according to predefined criteria [67]. Sources of heterogeneity were further investigated by sensitivity analyses in which the pooled estimates were calculated omitting one study at a time using a random effects model. Data management and statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Missing data

Multiple imputation by chained equations was used to handle missing data.[68,69] The event indicator and the Nelson–Aalen estimator of the cumulative baseline hazard were included in the imputation model.[70] The objective of imputation was to retain statistical power and reduce selection bias that may occur when deleting observations with missing covariates.

RESULTS

Study I

Patient characteristics

Baseline characteristics of the study population in study I are shown in Table 1. The incidence of antidepressant use was 11% in the study population. Patients in the exposed group were more likely to be women, smokers and suffer from diabetes mellitus.

Primary outcome measure

The primary outcome measure was all-cause mortality. During a mean follow-up of 3.5 years 116 patients (9.9%) died in the exposed group and 765 patients (7.9%) in the non-exposed group. In the unadjusted Cox regression analysis, antidepressant use was associated with increased mortality (HR 1.36; 95% CI 1.12–1.65), compared with non-use of antidepressants. In the final multivariable model, antidepressant use was associated with increased mortality (HR 1.45; 95% CI 1.18–1.77), compared with non-use of antidepressants. The final multivariable model included the following covariates: age, sex, diabetes mellitus, chronic obstructive pulmonary disease, preoperative left ventricular function, acute kidney injury (>0.3 mg/dL (26 μmol/L) increase in postoperative creatinine), and postoperative antidepressant use (Table 2 and Figure 1).

Secondary outcome measures

Secondary outcome measures included rehospitalization for MI, heart-failure or stroke, and a composite endpoint of all-cause mortality or rehospitalization (Table 3).

Table 1
Baseline characteristics of the study population by antidepressant use.

	All patients	Antidepressant use	
		No	Yes
Number of patients	10,884	9713	1171
Percent of study population	100	89	11
Age, mean (SD), years	67 (9.2)	67.5 (9.1)	65.4 (9.4)
Female sex (%)	20	19	34
Estimated GFR, mean (SD), (mL/min/1.73 m^2)	82 (35)	82 (36)	83 (24)
Diabetes mellitus (%)	25	24	32
Hypertension (%)	59	59	62
Hyperlipidemia (%)	60	59	65
Peripheral vascular disease (%)	8	8	10
Current smoking (%)	18	17	28
COPD (%)	6	6	10
Prior MI (%)	46	46	48
Prior stroke (%)	6	5	10
Left ventricular function			
Ejection fraction >50% (%)	70	71	69
Ejection fraction 30–50% (%)	25	26	25
Ejection fraction <30% (%)	4	4	5
Acute perioperative kidney injury (%)	14	14	17
Internal thoracic artery use (%)	94	94	93
CABG without cardiopulmonary bypass (%)	2	2	2

GFR = glomerular filtration rate, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, SD = standard deviation. Acute perioperative kidney injury was defined as >0.3 mg/dL (26 μmol/L) increase in postoperative creatinine values.

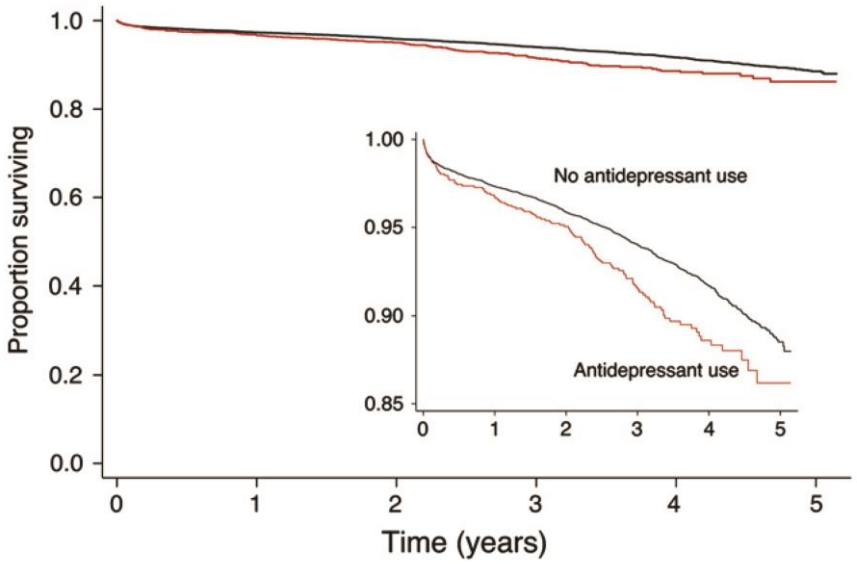

Figure 1
Overall survival from an unadjusted analysis of 1171 patients who were treated with antidepressants compared with 9713 patients with no antidepressant use before primary isolated coronary artery bypass surgery. The inset shows the same data on an enlarged y axis.

Table 2
Crude and multivariable adjusted associations between antidepressant use and all-cause mortality.

	Antidepressant use	
	No	Yes
Number of patients	9713	1171
Number of events (%)	765 (7.9)	116 (9.9)
	Hazard ratio (95% confidence interval)	
Crude	1.00	1.36 (1.12–1.65)
Adjusted for age and sex	1.00	1.57 (1.28–1.91)
Multivariable model[a]	1.00	1.45 (1.18–1.77)

CI = confidence interval.

[a] Multivariable adjustment was made for age, gender, diabetes mellitus, chronic obstructive pulmonary disease, preoperative left ventricular function, acute kidney injury, and postoperative antidepressant use.

Table 3
Crude and multivariable adjusted associations between antidepressant use and rehospitalization for heart failure, myocardial infarction or stroke, and the composite endpoint of all-cause mortality or rehospitalization.

	Antidepressant use	
	No	Yes
Number of patients	9713	1171
Rehospitalization[a]		
Number of events (%)	1248 (13)	185 (16)
	Hazard ratio (95% confidence interval)	
Crude	1.00	1.32 (1.13–1.54)
Adjusted for age and sex	1.00	1.37 (1.17–1.60)
Multivariable model[b]	1.00	1.40 (1.19–1.65)
Composite endpoint[c]		
Number of events (%)	1793 (18)	265 (23)
	Hazard ratio (95% confidence interval)	
Crude	1.00	1.36 (1.20–1.55)
Adjusted for age and sex	1.00	1.45 (1.27–1.65)
Multivariable model[b]	1.00	1.44 (1.26–1.64)

[a] Rehospitalization for heart failure, myocardial infarction or stroke.

[b] Multivariable adjustment was made for age, gender, diabetes mellitus, chronic obstructive pulmonary disease, preoperative left ventricular function, acute kidney injury, and postoperative antidepressant use.

[c] Composite endpoint of all-cause mortality or rehospitalization for heart failure, myocardial infarction or stroke.

Study II

Patient characteristics are presented in Table 4. Female sex, current smoking, a history of stroke, and diabetes were more common in patients with depression.

Table 4
Characteristics of the study population.

	All patients	Antidepressant use	
		No	Yes
Number of patients	10,586	9454	1132
Percent of study population	100	89	11
Age (years)	67.1 (9.2)	67.3 (9.1)	65.2 (9.4)
Female sex (%)	20	19	34
Estimated GFR (mL/min/1.73 m^2)	82 (25)	82 (25)	83 (24)
Diabetes mellitus (%)	24	23	33
Atrial fibrillation (%)	3	3	2
Hypertension (%)	59	58	62
Hyperlipidemia (%)	60	59	64
Peripheral vascular disease (%)	8	8	10
Current smoking (%)	18	17	28
COPD (%)	6	6	10
Prior myocardial infarction (%)	46	45	47
Prior heart failure (%)	3	3	4
Prior stroke (%)	5	5	10
Left ventricular function			
Ejection fraction >50% (%)	71	71	70
Ejection fraction 30–50% (%)	25	25	26
Ejection fraction <30% (%)	4	4	4

GFR = glomerular filtration rate, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease. Age and GFR are given as means with standard deviations. All other values are percentages.

Primary outcome measure

During the first year after CABG, 93% of all non-depressed patients had at least two dispensed prescriptions for an antiplatelet agent, 68% for an ACEI/ARB, 91% for a beta-blocker, and 92% for a statin. Fifty-seven percent of all non-depressed patients had prescriptions for all four medication classes. Among depressed patients 94% had at least two dispensed prescriptions for an antiplatelet agent, 72% for an ACEI/ARB, 90% for a beta-blocker, and 93% for a statin. Fifty-eight percent of all depressed patients had prescriptions for all four medication classes. (Figure 2). During the fourth year after CABG, compliance was generally lower. Among non-depressed patients, 44% used all four medication classes, compared to 46% among depressed patients (Figure 3).

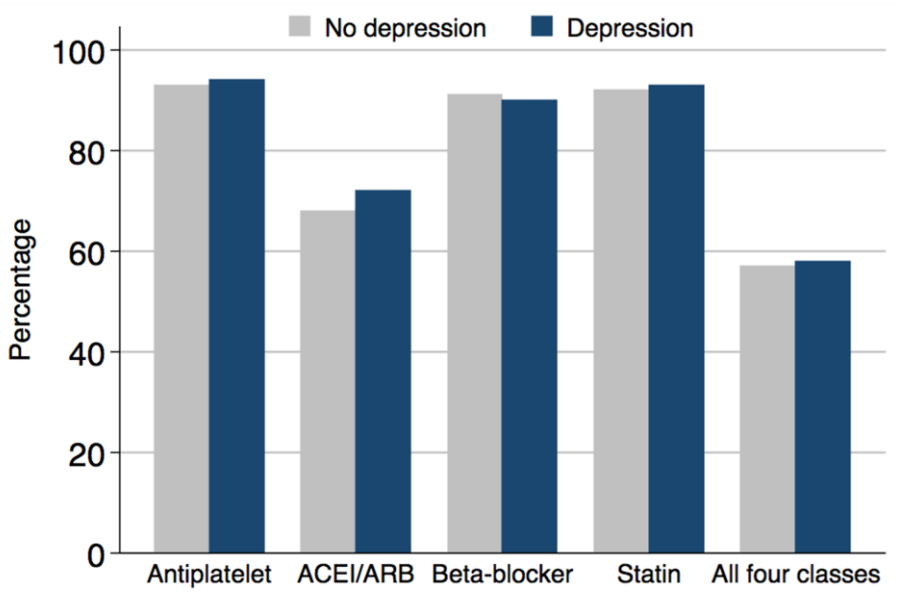

Figure 2. Distribution of medication use one year after surgery in 10,586 patients who underwent primary isolated CABG between 2006 and 2008 in Sweden. ACEI =angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CABG = coronary artery bypass grafting.

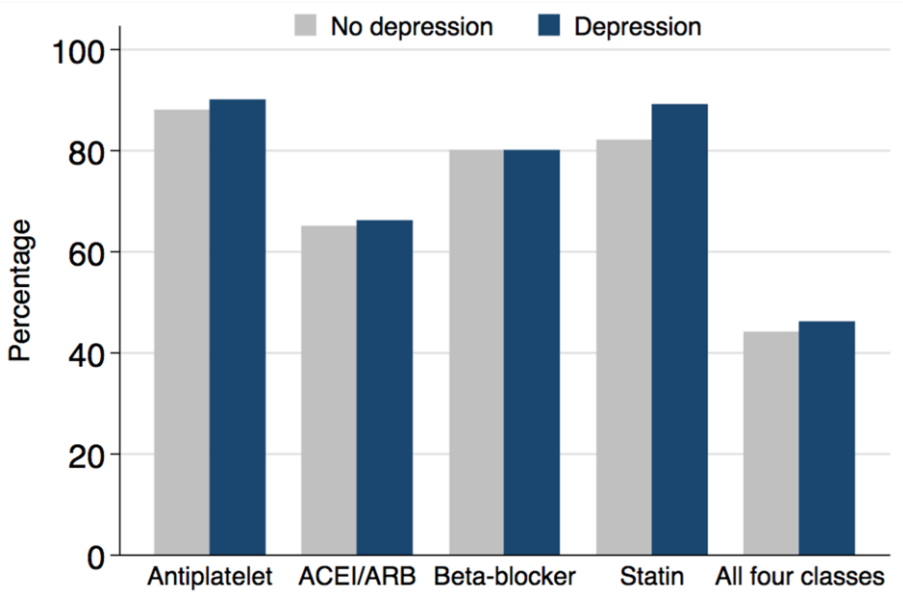

Figure. 3. Distribution of medication use four years after surgery in 4034 patients who underwent primary isolated CABG between 2006 and 2008 in Sweden. ACEI =angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CABG = coronary artery bypass grafting.

After multivariable adjustment, there was no significant association between depression and all four classes of guideline-directed medical therapy for secondary prevention (RR 0.97, 95% CI: 0.86 to 1.09) four years after surgery (Table 5 and 6).

Table 5
Crude and multivariable adjusted associations between antidepressant use and guideline-directed medical therapy for secondary prevention in 10,586 patients after CABG between 2006 and 2008 in Sweden. Risk ratios (95% confidence interval).

	Antidepressant use	
	No[a]	Yes
Number of patients	9454	1132
Antiplatelet agent		
Unadjusted	1.00	1.00 (0.99–1.02)
Multivariable adjusted[b]	1.00	1.00 (0.98–1.02)
ACEI/ARB		
Unadjusted	1.00	1.06 (1.02–1.10)
Multivariable adjusted[b]	1.00	1.02 (0.98–1.06)
Beta-blocker		
Unadjusted	1.00	0.99 (0.97–1.01)
Multivariable adjusted[b]	1.00	0.99 (0.97–1.01)
Statin		
Unadjusted	1.00	1.00 (0.99–1.02)
Multivariable adjusted[b]	1.00	1.00 (0.99–1.02)
All four classes		
Unadjusted	1.00	1.03 (0.97–1.08)
Multivariable adjusted[b]	1.00	0.98 (0.93–1.03)

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker.
[a] Reference category.
[b] Multivariable adjustment was made for age, gender, current smoking, atrial fibrillation, diabetes mellitus, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, prior myocardial infarction, prior stroke, left ventricular ejection fraction, and preoperative heart failure.

Table 6
Adjusted[a] associations between antidepressant use and guideline-directed medical therapy for secondary prevention in 4034 patients four years after CABG. Risk ratios (95% confidence interval).

	Antidepressant use	
	No[b]	Yes
Number of patients	3698	336
Antiplatelet agent	1.00	1.01 (0.97–1.05)
ACEI/ARB	1.00	0.97 (0.90–1.05)
Beta-blocker	1.00	0.99 (0.94–1.05)
Statin	1.00	1.08 (1.03–1.12)
All four classes	1.00	0.97 (0.86–1.09)
All four classes during four consecutive years	1.00	0.91 (0.77–1.07)

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker.
[a] Multivariable adjustment was made for age, gender, current smoking, atrial fibrillation, diabetes mellitus, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, prior myocardial infarction, prior stroke, left ventricular ejection fraction, and preoperative heart failure.
[b] Reference category.

Time trends

Antiplatelet agent and beta-blocker use was similar for patients going through surgery in 2006 as compared to those who underwent surgery in 2008. During the same time period, a small increase in the use of ACEI/ARB and statins was noted (Figure 4).

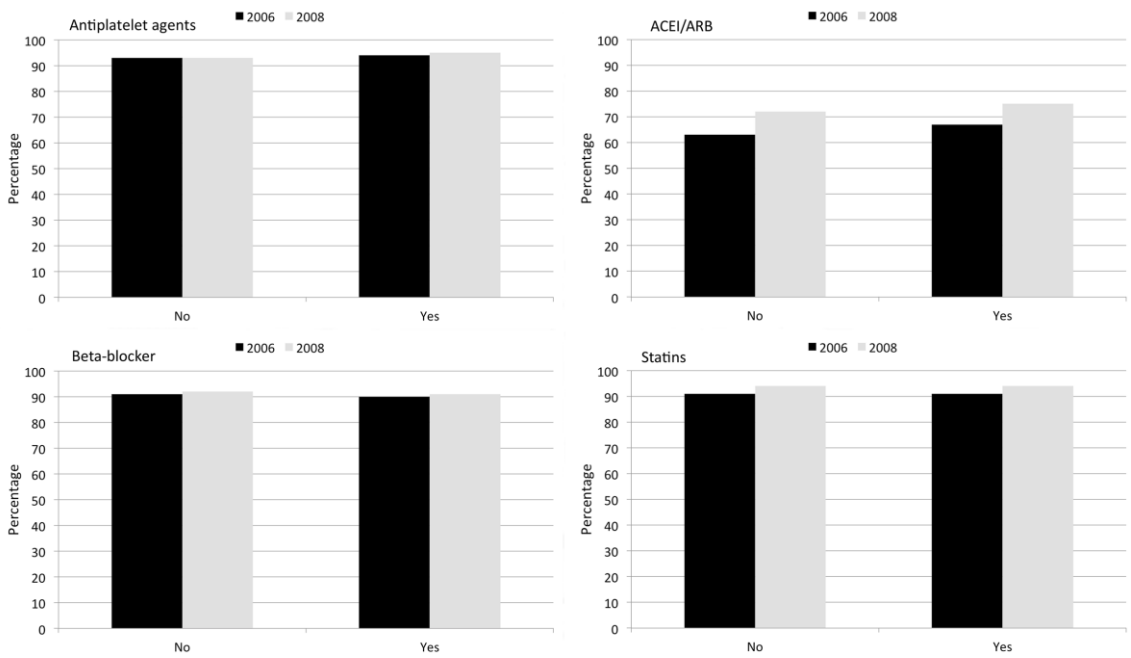

Figure. 4. Distributions of medication use in patients with or without depression who underwent CABG in 2006 compared to 2008. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CABG = coronary artery bypass grafting.

Study III

Baseline characteristics of the study population are listed in Table 7. Patients with depression and the control group were not balanced regarding several potentially confounding factors, most importantly, female gender, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, and a history of stroke.

Table 7
Baseline characteristics

Variable	All Patients	Depression	
		No	Yes
	n = 56064	n = 55740	n = 324
Percent of study population	100%	99.4%	0.6%
Age, mean (SD), (years)	66.6 (9.3)	66.7 (9.3)	66.1 (9.8)
Women	22%	22%	42%
Estimated GFR, mean (SD), (mL/min/1.73 m^2)	75 (21)	75 (21)	70 (26)
Diabetes mellitus	22%	22%	41%
Hypertension	56%	56%	56%
Hyperlipidemia	58%	58%	62%
Peripheral vascular disease	7%	7%	14%
Current smoker	19%	19%	24%
Chronic obstructive pulmonary disease	5%	5%	11%
Prior myocardial infarction	42%	42%	52%
Prior stroke	4%	4%	12%
Prior heart failure	4%	4%	9%
Left ventricular ejection fraction			
>50%	74%	74%	68%
30–50%	23%	23%	29%
<30%	3%	3%	3%
Acute perioperative kidney injury	13%	13%	20%
Internal thoracic artery use	92%	92%	91%
Coronary bypass without cardiopulmonary bypass	8%	8%	10%

Acute perioperative kidney injury was defined as >0.3 mg/dl (26 µmol/L) increase in postoperative creatinine values.
SD = standard deviation.

Primary outcome measure

In the unadjusted Cox regression analysis, depression was associated with increased mortality HR 1.94, 95% CI 1.61 to 2.33 (Figure 5). The unadjusted 1-, 5-, and 12-year survival was 93%, 80%, and 41% in depressed patients and 97%, 89%, and 63% in the control group (p <0.001), respectively. In the final multivariate Cox regression model, depression was significantly associated with increased mortality: HR 1.65, 95% CI 1.37 to 1.99 (Table 8).

Secondary outcome measure

In the unadjusted Cox regression analysis, depression was significantly associated with the combined end point: HR 2.01, 95% CI 1.73 to 2.35 (Figure 6). Depression was significantly associated with the combined end point in the multivariate-adjusted model: HR 1.61, 95% CI 1.38 to 1.89 (Table 9).

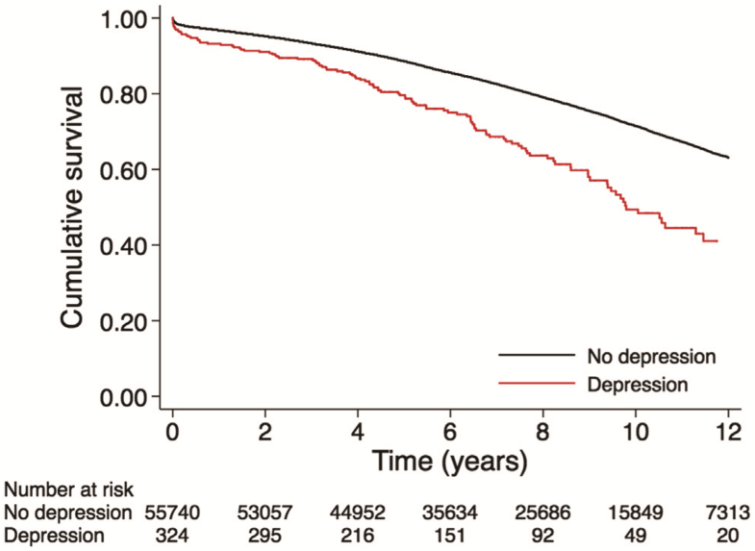

Figure 5. Kaplan-Meier estimated survival in 56064 patients with or without depression diagnosis before primary isolated CABG from 1997 to 2008 in Sweden.

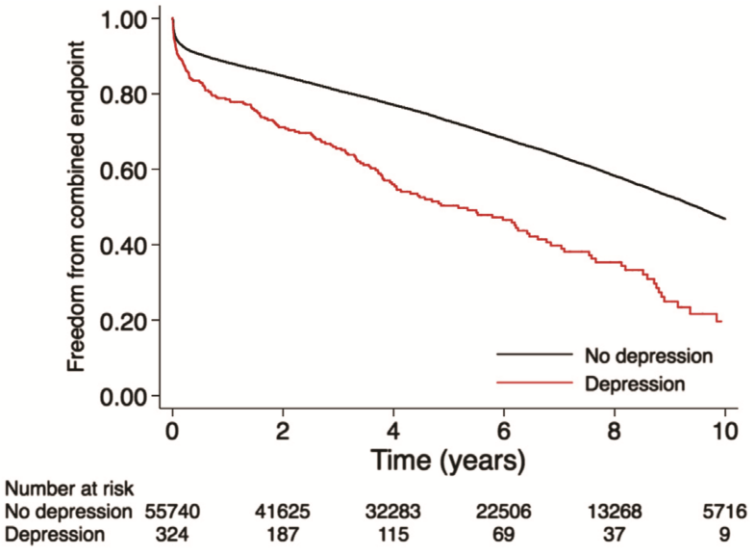

Figure 6. Kaplan-Meier estimated freedom from the combined end point of death or rehospitalization for myocardial infarction, heart failure, or stroke in 56064 patients with or without depression diagnosis before primary isolated CABG from 1997 to 2008 in Sweden.

Table **8**
Crude and multivariate-adjusted association between depression and all-cause mortality

	Depression	
	No*	Yes
Number of patients	55740	324
Number of events	13767 (25%)	114 (35%)
	Hazard ratio (95% confidence interval)	
Crude	1.00	1.94 (1.61−2.33)
Adjustment for age and sex	1.00	2.04 (1.70−2.46)
Multivariable model†	1.00	1.65 (1.37−1.99)

* Reference category.

† Multivariate adjustment was made for age, gender, estimated glomerular filtration rate, preoperative left ventricular function, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, acute kidney injury, previous stroke, and previous heart failure.

Table **9**
Crude and multivariate-adjusted association between depression and the composite end point of all-cause mortality or rehospitalization for heart failure, myocardial infarction, or stroke. Hazards ratios and 95% confidence intervals

	Depression	
	No*	Yes
Number of patients	55740	324
Composite endpoint†		
Number of events	20896 (37%)	166 (51%)
Crude	1.00	2.01 (1.73−2.35)
Adjustment for age and sex	1.00	2.07 (1.78−2.41)
Multivariable model‡	1.00	1.61 (1.38−1.89)

* Reference category.

† Composite end point of all-cause mortality or rehospitalization for heart failure, myocardial infarction, or stroke.

‡ Multivariate adjustment was made for age, gender, estimated glomerular filtration rate, preoperative left ventricular function, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, acute kidney injury, previous stroke, and previous heart failure.

Study IV

Baseline characteristics are shown in Table 10. Patients with antidepressant use were more often women, had a history of alcohol dependency and chronic obstructive pulmonary disease, and had a lower family disposable income.

Table 10
Baseline characteristics in 22,930 patients who underwent primary isolated CABG in Sweden 2006–2013 in relation to antidepressant use.

		Antidepressant use		
	All patients	No	Yes	p-Value
Number of patients	22,930	19,852	3078	
Age, years, mean (SD)	67.4 (9.2)	67.7 (9.1)	65.9 (9.7)	<0.001
Female sex	4558 (19.9%)	3547 (17.9%)	1011 (32.8%)	<0.001
Birth region				<0.001
Nordic countries	20,452 (89.2%)	17,846 (89.9%)	2606 (84.7%)	
Other	2478 (10.8%)	2006 (10.1%)	472 (15.3%)	
Body mass index (kg/cm^2)				<0.001
1st tertile (lowest)	6960 (33.4%)	6117 (33.9%)	843 (30.3%)	
2nd tertile	6947 (33.3%)	6054 (33.5%)	893 (32.1%)	
3rd tertile	6924 (33.2%)	5882 (32.6%)	1042 (37.5%)	
Diabetes mellitus	6202 (27.0%)	5199 (26.2%)	1003 (32.6%)	<0.001
Hypertension	10,513 (45.8%)	8953 (45.1%)	1560 (50.7%)	<0.001
Hyperlipidemia	5856 (25.5%)	4965 (25.0%)	891 (28.9%)	<0.001
Peripheral vascular disease	2334 (10.2%)	1947 (9.8%)	387 (12.6%)	<0.001
Chronic pulmonary disease	1881 (8.2%)	1486 (7.5%)	395 (12.8%)	<0.001
eGFR (mL/min/1.73 m^2)				0.34
>60	17,863 (81.4%)	15,504 (81.6%)	2359 (80.4%)	
45 to 60	2609 (11.9%)	2231 (11.7%)	378 (12.9%)	
30 to 45	937 (4.3%)	812 (4.3%)	125 (4.3%)	
15 to 30	191 (0.9%)	169 (0.9%)	22 (0.7%)	
<15[a]	334 (1.5%)	284 (1.5%)	50 (1.7%)	
Prior myocardial infarction	12,911 (56.3%)	11,099 (55.9%)	1812 (58.9%)	0.002
Prior PCI	4389 (19.1%)	3691 (18.6%)	698 (22.7%)	<0.001
Heart failure	2290 (10.0%)	1924 (9.7%)	366 (11.9%)	<0.001
Stroke	2067 (9.0%)	1661 (8.4%)	406 (13.2%)	<0.001
Atrial fibrillation	1399 (6.1%)	1218 (6.1%)	181 (5.9%)	0.58
Left ventricular ejection fraction				0.33
>50%	15,989 (70.6%)	13,870 (70.8%)	2119 (69.5%)	
30 to 50%	5660 (25.0%)	4866 (24.8%)	794 (26.0%)	
<30%	992 (4.4%)	856 (4.4%)	136 (4.5%)	
Alcohol dependency	595 (2.6%)	391 (2.0%)	204 (6.6%)	<0.001
Cancer	1549 (6.8%)	1297 (6.5%)	252 (8.2%)	<0.001
Education				0.55
<10 years	9291 (41.2%)	8014 (41.0%)	1277 (42.1%)	
10–12 years	8981 (39.8%)	7788 (39.9%)	1193 (39.3%)	
>12 years	4295 (19.0%)	3729 (19.1%)	566 (18.6%)	
Civil status				<0.001
Married	15,132 (66.0%)	13,253 (66.8%)	1879 (61.0%)	
Not married	3163 (13.8%)	2702 (13.6%)	461 (15.0%)	
Divorced	3651 (15.9%)	3048 (15.4%)	603 (19.6%)	
Widowhood	984 (4.3%)	849 (4.3%)	135 (4.4%)	
Family disposable income (quintiles)				<0.001
Q1 (lowest)	4587 (20.0%)	3812 (19.2%)	775 (25.2%)	
Q2	4585 (20.0%)	3920 (19.7%)	665 (21.6%)	
Q3	4586 (20.0%)	4002 (20.2%)	584 (19.0%)	
Q4	4586 (20.0%)	4016 (20.2%)	570 (18.5%)	
Q5	4586 (20.0%)	4102 (20.7%)	484 (15.7%)	

Data are n (%) unless otherwise noted.
eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention, SD = standard deviation.
[a] This category includes patients on preoperative dialysis.

Primary outcome measure

In the unadjusted Cox regression analysis, antidepressant use was associated with increased mortality (HR 1.33; 95% CI 1.19–1.50), compared with non-use of antidepressants (Figure 7).

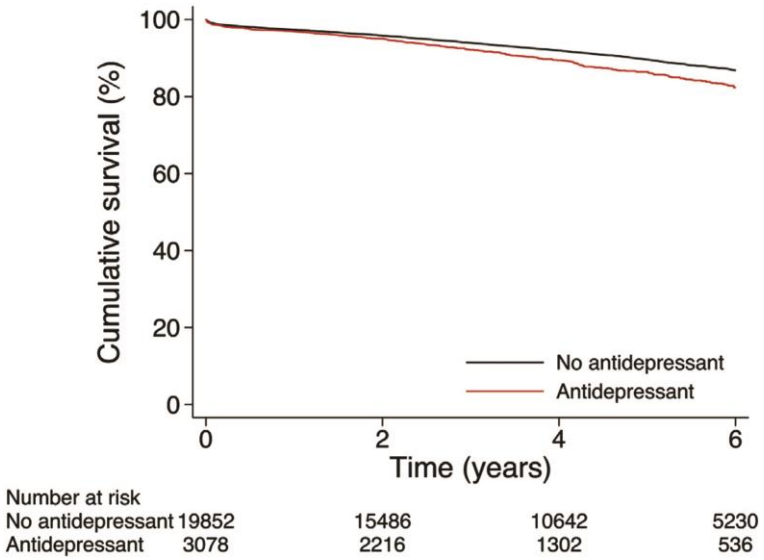

Figure 7. Kaplan-Meier estimated survival in 22930 patients who underwent coronary artery bypass surgery in Sweden 2006-2013 according to preoperative antidepressant use.

After multivariable adjustment for cardiovascular risk factors, antidepressant use was associated with increased mortality (HR 1.27; 95% CI 1.13–1.43). The addition of SES variables educational level, family disposable income, and civil status to the model resulted in a very small change in the estimated risk for death: HR 1.25; 95% CI 1.11–1.41 (Figure 8).

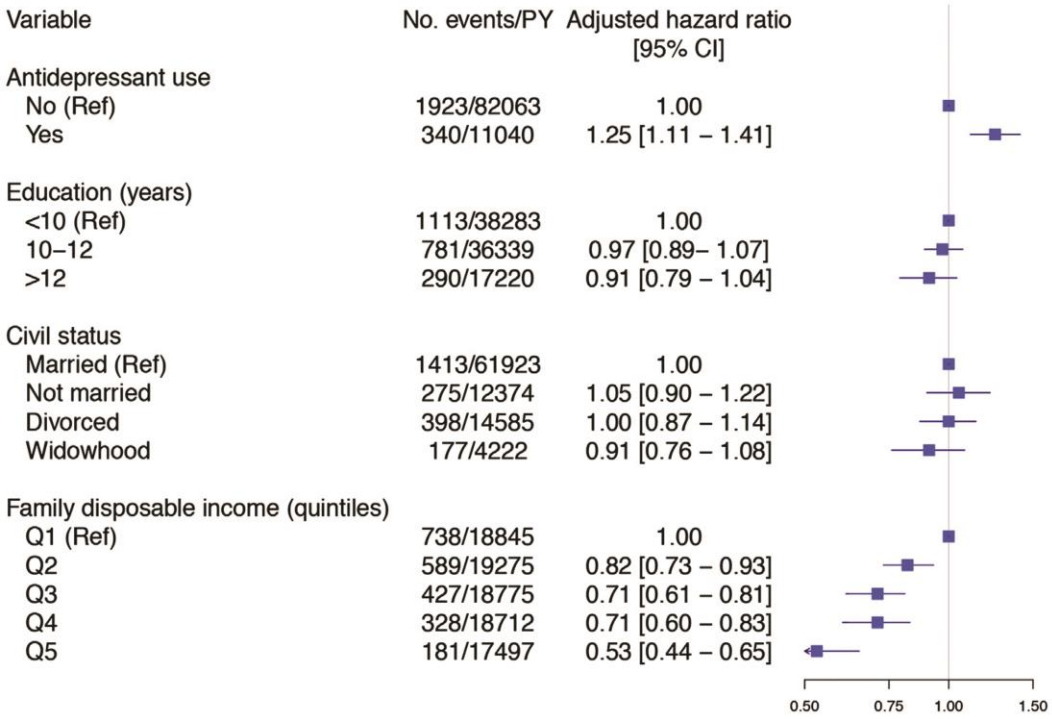

Figure 8. Multivariable adjusted hazard ratios and 95% confidence interval for all-cause mortality in 22930 patients who underwent coronary artery bypass surgery in Sweden 2006-2013.

The association between antidepressant use and all-cause mortality was investigated in selected subgroups. The increased risk for mortality in patients with preoperative antidepressant use was similar in patients younger vs. older than 70 years, men vs. women, and in tertiles of family disposable income, levels of education, and civil status (Figure 9).

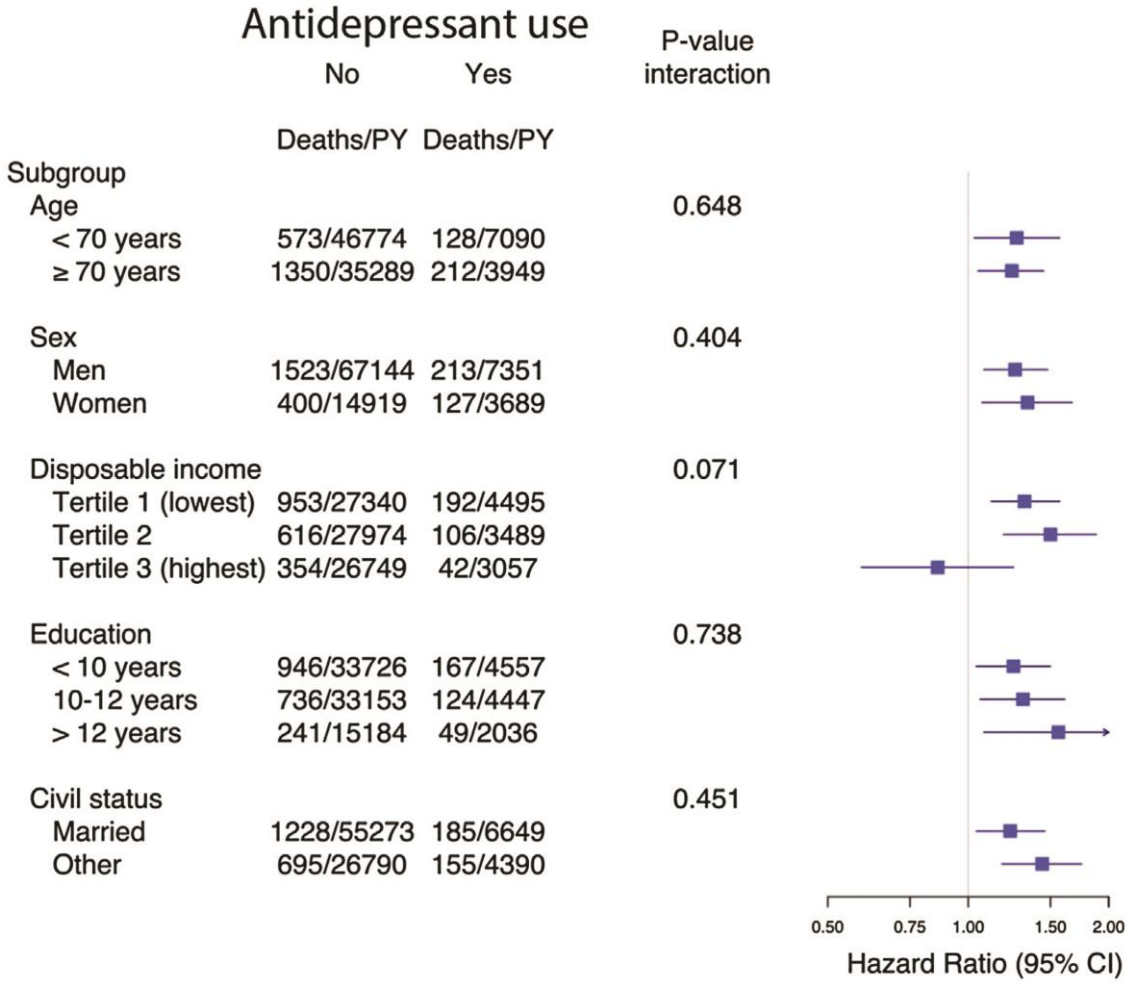

Figure 9. Hazard ratios for all-cause mortality in 22930 patients who underwent coronary artery bypass surgery in Sweden 2006-2013 according to preoperative antidepressant use in selected subgroups.

Study V

Characteristics of the included studies are presented in Table 11. Preoperative depression was present in 4215 patients. The number of patients in each study ranged from 309 to 56064 with median or mean follow-up ranging from 3 to 9.3 years. The overall pooled HR for preoperative depression and mortality was 1.46; 95% CI 1.23 to 1.73, according to a random effects model with moderate heterogeneity (I^2 = 50.1% p=0.061) (Figure 10).

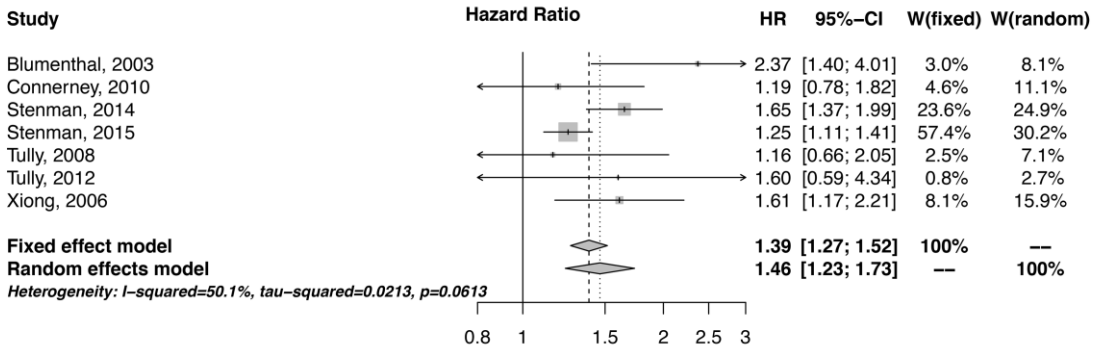

Figure 10. Forest plot of preoperative depression and survival following CABG.

Table 11. Characteristics of the included studies

Source	Country	Study period	Definition of depression	Total number of patients (depressed/non-depressed)	Follow-up time, y	Multivariable adjustment	NOS
Blumenthal,[15] 2003	USA	1989-2001	CES-D>27 (moderate to severely depressed)	817 (97/720)	Median: 5.0 y, mean: 5.2	Age, sex, EF, number of grafts, prior MI, smoking, diabetes	9
Connerney,[16] 2010	USA	1997	DIS interview for major depressive disorder	309 (63/246)	Median: 9.3 y	Age, sex, EF, diabetes	9
Stenman,[17] 2014	Sweden	1997-2008	ICD-10 codes from national hospital discharge register	56064 (324/55740)	Mean:7.5 y	Age, sex, EF, renal function, diabetes, COPD, PVD, acute kidney injury, stroke, heart failure	9
Stenman,[18] 2015	Sweden	2006-2013	Antidepressant use from national Prescribed Drug Register	22930 (3078/19852)	Mean: 4.1 y	Age, sex, and 19 other variables including co-morbidity and socio-economic factors	9
Tully,[19] 2008	Australia	1996-2006	Self-report DASS >=10	440 (89/351)	Median: 5 y and 10 months	Age, renal disease, concomitant valve procedure, CVD, PVD	9
Tully,[20] 2012	Australia	1996-2008	SSRI/SNRI use from hospital database	4136 (105/4031)	Median: 4.7 y	By propensity scores derived from: age, sex, EF, urgency, prior MI, respiratory disease, diabetes, renal disease, PVD, CVD, shock, heart failure, hypertension, smoking, OPCAB, statin, anti-platelets, anti-coagulants	9
Xiong,[21] 2006	USA	1999-2003	SSRI use from inpatient pharmacy records	4794 (246/4548)	Median: 3.0 y	Age, heart failure, shock, PVD, lung disease, hypercholesterolemia, diabetes, MI, redo CABG, race, CVD, ACEi, aspirin, iv nitrates	9

Abbreviations: CES-D = 20-item Center for Epidemiological Studies depression questionnaire, DIS = Diagnostic Interview Schedule, DASS = depression anxiety stress scales, NOS = Newcastle-Ottawa scale, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, EF = ejection fraction, MI = myocardial infarction, COPD = chronic obstructive pulmonary disease, OPCAB = off-pump coronary artery bypass surgery, PVD = peripheral vascular disease, CVD = cerebrovascular disease, ACEi = angiotensin converting enzyme inhibitor.

DISCUSSION

Methodological considerations

Epidemiologists study the occurrence of diseases, effects of treatments and compare treatments and preventive actions. Important to consider in all epidemiological studies are the corner stones: internal validity (systematic errors), precision (random errors), causality and external validity (generalizability).[71]

Cohort studies

Epidemiologic study designs can be divided into two main categories: intervention (experimental) or observational studies (descriptive or analytic). Study I-IV are analytic observational studies. A cohort is a group of individuals being followed over a period of time. The archetype of all epidemiologic studies is the cohort study. In a cohort study the occurrence of disease is measured within one or more cohorts.[71]

Internal validity (systematic errors or bias)

Bias can be classified into three broad categories: selection bias, information bias and confounding.

Selection bias occurs if the association between exposure and disease is different between those who participate in the study and those who do not.[71]

Information bias is introduced if the information collected from or about the study participants is not collected in a correct way. This kind of information is referred to as being misclassified - if it leads to a person being placed in an incorrect category. Misclassification of study participants can be divided into differential or non-differential misclassification. If the misclassification is different for patients in the exposed and the non-exposed group, the misclassification is differential. When the misclassification is unrelated to the exposure or disease it is non-differential. Differential misclassification is more problematic than non-differential as it can result in under- and overestimation of the results.[71]

Confounding is often referred to as confusion or mixing of effects. The effect of the exposure is mixed up with the effect of another variable and therefore leading to bias. A confounder is always associated with both exposure and outcome. A confounder

describes an association that is true but might be misleading and leading to incorrect interpretation. Confounders can be handled in a study protocol before starting the study by randomization, restriction, or matching, or in the statistical analysis by stratifying or multivariable statistical models.[71]

Random error is the error that remains after systematic error is eliminated or in other words, the influence of chance. It is the variation in data that cannot be explained and is to some extent present in all studies Larger studies increase precision and reduce random error and smaller studies have less precision and therefore higher risk of random error.[71]

External validity or generalizability is another important concern. That is the ability to apply results from one study to other cohorts or settings than where the study was conducted.[71]

Causality

Causation means that one thing will cause the other. "Correlation does not imply causation" is a phrase often used to emphasize that a correlation between two variables does not imply that one causes the other. August Bradford Hill (1897-1991), a British medical statistician, outlined the minimal conditions needed to establish a causal relationship between two items. He suggested the following set of criteria:[72]

Strength – the stronger the association, the more likely is a causal effect.

Consistency – if a relationship is causal we would expect consistency if the study was replicated.

Specificity – the probability of a causal relationship increases the more specific an association between a factor and an effect is.

Temporality - exposure must always precede the outcome.

Biologic gradient – refers to the presence of a dose-response relationship. A present dose-response relationship gives stronger evidence for causal relationship.

Plausibility – for causation the relationship should be plausible, in other words, the results should be biologically sensible.

Coherence – the association should be consistent with results from a number of studies.

Experimental evidence – if the factor of interest is removed the risk of disease should be reduced.

Analogy – the necessity to consider multiple hypotheses before making conclusions about a causal relationship.

Study I

We investigated the association between preoperative antidepressant use and survival following CABG, and the association between preoperative antidepressant use and rehospitalization for MI, heart failure or stroke. Patients who were treated with antidepressants before surgery had 45% higher risk for death. The risk for rehospitalization, MI, heart failure or stroke was also significantly increased among patients with anti-depressant use. The reported incidence of depression among patients with CVD varies between 31-45%. In our study only 11% of the patients had a dispensed prescription of antidepressants before the date of surgery. This is most likely an underestimation of depression and is related to our definition of depression. We defined exposure based on whether or not a patient had at least one dispensed prescription with antidepressants at any point in time from July 2005, and before the date of surgery. To investigate the effect of elapsed time between dispensing of a prescription for antidepressants and surgery, we reclassified the exposure first as a dispensed prescription within 6 months before surgery, and second, as a dispensed prescription within 1 year before surgery. The results from these analyses were practically the same as our main analysis.

A possible explanation to the higher mortality in the exposed group is that the use of SSRI inhibits platelet function and therefore increases the risk of bleeding.[73] This has been investigated in patients undergoing orthopedic surgery. An increased risk of bleeding and need for blood transfusion was found in patients who were treated with serotonergic antidepressants.[74] However, published studies are conflicting. Kim et al.[75] carried out a study in patients who had received any antidepressants before CABG and categorized the patients into SSRI users and non-SSRI users before CABG.[75] The SSRI group comprised of 1076 patients and the non-SSRI group of 304 patients. The study showed that SSRI use before CABG was not related to increased risk for bleeding or in-hospital mortality after CABG. These findings were in line with the results of a Danish population-based cohort study conducted by Andreasen et al.[76] They studied

transfusion requirements among 3454 patients undergoing CABG in Denmark between 1 January 1998 and 31 December 2003. The aim of the study was to find out if the requirement for red blood cell transfusion was increased following preoperative SSRI use among these patients.[76] Andreasen et al. came to the conclusion that SSRI use before CABG did not increase the necessity for red blood cell transfusion.[76] Additionally, they found no association between antidepressant use and re-exploration for bleeding or 30-day mortality. These findings were also supported by Tully et al.[77] They investigated 4136 patients who underwent CABG surgery. Of these patients 105 (2.5%) were SSRI/SNRI users. SSRI/SNRI users did not experience severe bleeding events or long-term mortality after CABG surgery.[77]

In our study we also performed a separate analysis in patients with at least one dispensed prescription with ATC-code N06AB (SSRI) before undergoing primary isolated non-emergent CABG. We found that SSRI use was associated with an increased risk of the different clinical endpoints (all-cause mortality, rehospitalization or the composite endpoint), compared with non-use of SSRIs.

The results from our study indicate that depression should be considered an important risk marker for prognosis following CABG surgery.

Study II

Study II was conducted in the same study population as in study I. We investigated if patients with depression would have lower use of guideline-directed medications for secondary prevention of cardiovascular events following CABG than patients without preoperative depression. The purpose was to explore if this could explain the higher mortality among patients with depression. Preoperative depression was not associated with lower use of guideline-directed medications for secondary prevention of cardiovascular events. These findings suggest that the observed higher mortality following CABG among depressed patients is not explained by inadequate secondary prevention medication. Secondary prevention medications were similar between men and women. Previous research has indicated that depressed patients do not receive optimal coronary care due to failing in communication and patient cooperation.[78] Due to this, and our results in study I, we hypothesized that depressed patients could have worse secondary prevention medications compared to non-depressed patients. However, we did not find a lower use of secondary prevention medications among

patients with preoperative depression. Our results differ from the observations by Kronish et al.[79] They found that persistently depressed patients had a lower adherence to secondary prevention medications and behaviors at three months after acute coronary syndrome than persistently non-depressed patients. In our study we did not evaluate postoperative depressive status, but it has been shown that preoperative depression is associated with the highest risk for postoperative depression.[80] Depression is a risk factor for mortality after CABG[23,81] and studies have shown that improvement of depression symptoms was consistently associated with better adherence to medications in patients hospitalized with cardiac conditions.[82] This is one of the reasons to why it is important to detect and treat depression before CABG, to increase the likelihood of adequate adherence to secondary prevention medications.

Study III

In study III we wanted to study the relation of major depression to survival after CABG. We acquired information regarding depression diagnosis from the National Patient Register. In this way we were able to capture the most severely ill patients because these patients were treated in a hospital or by a psychiatrist in the specialized outpatient clinic because of their depression.

We identified 324 patients with a preoperative diagnosis of depression. During a mean follow-up of 7.5 years we found a significant association between preoperative depression and long-term survival after CABG. Preoperative depression was also associated with an increased risk of the combined endpoint of death or rehospitalization for heart failure, MI or stroke. The observed association between depression and mortality differed between men and women. Although depression was more common in women, the association between depression and long-term mortality was statistically significant only in men and not in women. This may in part be explained by the fewer number of female patients in the study or other mechanisms that we were unable to identify. One possible mechanism to why more women than men suffer from depression could be that depression can take different shapes in men and women.[83] Symptoms of anger, irritability, risk-taking behaviors, and substance abuse are more likely to be reported among men with depression over more traditional symptoms such as sleep problems and withdrawal from social occasions.[83] If only traditional symptoms are taken into account in clinical care, depression could be underdiagnosed in men.[83]

The findings in our study are supported by another Swedish study.[84] Gale et al.[84] investigated the association between different mental disorders in 1107524 Swedish young men at conscription and the risk of incident CAD. The age-adjusted HR regarding depression at conscription and incident CAD was 1.30 (95% CI 1.05 to1.60). As the participants in this study were young, it is unlikely that the association between depression and incident CAD was due to reverse causation, that is, living with cardiovascular disease causes depression.

Behavioral factors should be taken into account concerning postoperative morbidity events in patients on antidepressant medication. Depressed persons have a tendency to smoke[35], drink[85] and use illicit drugs to a larger extent than persons without depression. In our study there were more smokers in the group taking antidepressants before the operation compared to the unexposed group, which are in line with earlier findings regarding depression and smoking. A concern is that it was difficult to get reliable and correct information regarding smoking. We may have information bias regarding smoking in our study. However, we have information regarding chronic obstructive pulmonary disease which could be used as a proxy for smoking. Depressed persons are reportedly less physically active[86], have poorer diets, care less about hygiene and self-care, and are less likely to take prescribed medicine according to schedule.[87]

Study IV

A limitation in our earlier studies was the lack of information regarding socioeconomic status (SES). It is possible that SES could have an effect on the relationship between depression and prognosis. In this study we retrieved information regarding SES (marital status, education, income, region of birth). The emphasis of this study was to investigate the effect of socioeconomic factors and how these factors modify the association between depression and survival after CABG. We used the same exposure as in study I, antidepressant use. We found that among patients who underwent CABG in Sweden, preoperative antidepressant use was associated with worse survival even after controlling for socioeconomic factors. Little is known about the effect of SES in patients with preoperative depression and survival after CABG. In a study by Poole et al.[88] length of hospital stay in patients with preoperative depression undergoing CABG and the role of SES was investigated. They used yearly household income as a proxy for SES, and grouped the patients into five categories according to SES. A dose-response relationship

between depression symptoms and length of hospital stay was found, and they also found an interaction between depression symptoms and household income. The negative effect of depression was augmented by a low income while a higher income reduced the negative effect of depression on length of stay.[88] In a large Danish cohort study including 56581 patients between 2003 and 2012 the relationship between socioeconomic position and survival after stroke was investigated.[89] The authors discovered that lower income was significantly associated with worse survival after a stroke, while level of education was less important for prognosis, especially in patients older than 65 years.[89] Like in our study, socioeconomic position was measured as household income and length of education.

Lower SES has been linked to poorer health and shorter life expectancy compared with persons with higher SES.[90] Possible explanations are that persons with low SES are often less engaged in favorable lifestyle choices[91], like eating healthily[92] or taking part in physical activity during leisure time.[93] It has also been claimed that persons with low SES may have fewer social supports and networks.[94] Taken together these factors are assumed to negatively affect health outcomes in patients with cardiovascular disease.

Study V

Study V is a systematic review and meta-analysis. The aim was to provide a summary estimate of the association between preoperative depression and long-term survival in adults who underwent CABG. The pooled results from the meta-analysis showed a significant association between preoperative depression and worse long-term survival following CABG. Depression was defined by different methods in the seven studies, because of this we performed separate analyses in patients with antidepressant use before CABG and in patients with self-assessed depression through questionnaires before CABG. In the analysis with depression based on questionnaires the HR was 1.47 (95% CI 0.94 to 2.31) and in the group with antidepressant use as a proxy for depression the HR was 1.32 (95% CI 1.13 to 1.54). A sensitivity analysis was also performed to measure the influence of individual studies on the primary outcome we did a series of new meta-analyses, omitting one study at a time. The HR changed only slightly when removing the largest study by Stenman et al., HR: 1.40 (95%CI 1.16 to 1.69). A meta-analysis facilitates objective evaluation and pooling of different study populations, and makes it possible to analyze large and diverse cohorts of patients and summarize the field of interest up to a certain time. This is the first meta-analysis

investigating the association between depression before CABG and long-term mortality. There are, however, existing systematic reviews and meta-analyses on depression and CVD. [23,24] The results from our meta-analysis are in line with prior findings.

Strengths and Limitations

The strengths of study I-IV in this thesis involve the nationwide, population-based, longitudinal, cohort design; the large study population; and the complete and accurate follow-up and survival ascertainment due to the high-quality national Swedish registers. The cohorts consisted of all CABG procedures in Sweden. This gives good external validity and we believe that our results could be applied in other countries, with similar level of health care.

It is known that between 31% and 45 % of all patients with cardiac disease suffer from depression.[21,95] In our study population only 11% had at least one dispensed prescription of antidepressants before CABG surgery. Due to the observational study design it was not possible to use any kind of depression measurement. It is therefore likely that patients with a depressive disorder were present in the non-exposed group. This is in epidemiological terms referred to as information bias, when incorrect information about the study participant is collected. In study I, II and IV, we most likely have information bias due to misclassification of exposure. The Swedish Prescribed Drug Register only contains information on prescriptions since July 2005. Therefore, there are undoubtedly patients in our study who had a dispensed prescription of antidepressants before that date, and underwent surgery between 2006 and 2008. Such patients would erroneously be classified as non-exposed in our study. It is also possible that patients in the exposed group were not suffering from depressive disorder, but some other condition requiring antidepressant medication for example SSRI treatment for obsessive-compulsive disorder.

Because the design in study I-IV prevents strong conclusions about causation, we can only speculate on the explanations for our findings. For example, it is not possible to answer the question of whether it is depression in itself or treatment with antidepressants that contributes to worse survival

Another limitation is the lack of information regarding compliance, dosage and duration of antidepressant use. We only know that the antidepressant medication has been dispensed and the date of dispensing but we can only assume that the patients actually

have taken the dispensed antidepressant medication. Medical adherence generally refers to both primary adherence and secondary adherence. Primary adherence is the rate at which patients collect their newly prescribed medication from pharmacies and secondary adherence is the correct intake of a prescribed medication.[96,97] There can be several reasons to why patients do not pick up their prescribed medication. The overall adherence to antidepressants is known to be low.[98,99] In Freccero´s et al., study they found that primary adherence to antidepressants prescribed at primary health care centers in Sweden was 85%.[100]

Clinical implications

Depression is a significant, independent risk marker in patients with CVD. Depression should be considered as important as other well-known risk factors like for example heart failure and chronic kidney disease in patients undergoing CABG. It can be difficult to detect depression in patients with CVD as symptoms in both conditions many times are the same. One way to detect depression is through systematic screening. In October 2008 the American Heart Association (AHA) prevention Committee recommended that all coronary heart disease patients should be screened for depression using the 2-item Patient Health Questionnaire (PHQ-2) and that patients with a positive PHQ-2 screen would be followed up by using the 9-item PHQ-9 screen.[95] The patients who screened positive on PHQ-9 would be given a treatment referral.[101] In the US Preventive Services Task Force Recommendation Statement[102] screening for depression is recommended in the general adult population as depression is among the leading causes of disability and the magnitude of harms of screening for depression in adults is small to none.[102] This statement further stresses the importance of systematic screening for depression in patients with CVD.

Conclusions

- Antidepressant use was associated with worse long-term survival after CABG.
- Antidepressant use was also associated with an increased risk of rehospitalization for heart failure, myocardial infarction or stroke and a combination of rehospitalization or death.
- Preoperative depression was not associated with lower use of guideline-directed medications for secondary prevention of cardiovascular events.
- Preoperative major depression was associated with worse long-term survival after CABG.
- Preoperative major depression was also associated with an increased risk of the combined endpoint of death or rehospitalization for heart failure, myocardial infarction or stroke.
- Preoperative antidepressant use was associated with worse long-term survival even after controlling for socioeconomic factors.
- Depression was a significant risk marker for worse long-term survival following CABG in a systematic review and meta-analysis of 7 observational cohort studies.

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