Depression following myocardial infarction

– An overseen complication with prognostic importance

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THE FOUR ORIGINAL PAPERS ARE

1. INTRODUCTION
“You ought not to attempt to cure the body without the soul. The cure of many diseases is unknown to physicians because they disregard the whole.”

Hippocrates

The above quotation, written by the father of modern medicine, is highly relevant now almost 2,500 years later, in our dealing with patients with myocardial infarction (MI). Owing to 40 years of considerable improvements in prophylaxis and treatment of MI, the morbidity and mortality from this disease have decreased significantly, but a subset of patients seems not to have obtained the expected benefit of these improvements. The hypothesis has therefore been raised that some factors beyond the traditional biomedicine risk factors go unrecognized and may affect the treatment and the prognosis in the subset of patients. A growing line of research has demonstrated that depression following MI is associated with adverse outcomes, but the underlying mechanisms remain unclear. Post-MI depression is common, but studies also show that this condition is under-recognized and under-treated. The general practitioner (GP) is supposed to play a key role in the treatment of persons with coexisting physical and mental diseases because he or she serves as a care coordinator and is trained to treat both mental and physical diseases.

1. To estimate the prevalence of depression in people with MI after three months, and to estimate the provided hospital-based psychosocial rehabilitation;
2. To examine GPs’ practice of screening for depression in people with MI, and to analyse whether the screening rate varied among subgroups of people with a particularly high risk of post-MI depression;
3. To examine the association between post-MI depression and new cardiovascular events or death, taking potential mediators into account;
4. To examine the association between MI and suicide.

2. BACKGROUND

2.1 Epidemiology of depression following myocardial infarction

By 2030, depressive disorder and ischaemic heart disease are projected to be the number one and two cause of disability in developed nations and the second and third leading cause of disability in the world next to human immunodeficiency virus and AIDS.[1]

MI is a major cause of morbidity and mortality worldwide, and it is estimated that more than 7 million people suffer from MI each year.[2] In Denmark, 8,919 persons were admitted to hospital with first-time MI in 2002.[3] Considerable improvements in prophylaxis and treatment have substantially reduced mortality and physical morbidity associated with MI in 40 years of the 1970s.[4-6] In Denmark, the 30-day mortality from MI declined from 31.4% in 1984-88 to 14.8% in 2004-08 and the one-year mortality declined from 42.1% to 24.2% during the same period.[6]

About 200,000 Danes are now living with ischaemic heart disease.[3]

Major depression following MI is common and persistent. In a recent review[7] of studies using structured clinical interviews, the range of prevalence rates of major depression within two weeks after the MI was 16% to 27% and the weighted prevalence rate was 19.8% (95% CI; 19.1% to 20.6%).[7] More than three quarters...
of those were still depressed three months later and others developed depression.\textsuperscript{[8]} Symptoms of depression can exacerbate or improve, but the prevalence rate of depression seems to be rather constant at least within the first 18 months following MI.\textsuperscript{[19]}

2.2 Prognostic impact of depression following myocardial infarction

Beginning in the 1980s, a growing number of studies have reported that psychosocial stress and depression following MI are linked to prognosis. Three systematic reviews and meta-analyses\textsuperscript{[10-12]} have now investigated the association between post-MI depression and adverse outcome including all-cause mortality, cardiac mortality and new cardiovascular events. The most recent review\textsuperscript{[12]} included 29 individual studies undertaken in clinical samples of persons with MI between 1983 and 2006. A total of 16,889 MI patients were followed for a mean time of 16 months (range, 1 week to 24 months). The mean age at the time of the index MI was 61 years (range, 54 to 65 years) and 26% were women. Of the 29 studies, 18 identified depression by using screening instruments only, seven used both a screening instrument and a clinical interview, and four used a clinical interview only. The most commonly used screening instrument was the Beck Depression Inventory, although a wide range of other scales have also been used. Seventeen studies comprising a total of 10,362 patients reported on all-cause mortality and a total of 892 patients died within 2 years after the index MI. The pooled odds ratio (OR) of all-cause mortality in 3,053 depressed patients compared with 7,309 non-depressed patients was 2.25 (95% CI, 1.73-2.93).\textsuperscript{[12]} New cardiovascular events were reported in 18 studies. These studies included a total of 10,119 patients and a total of 2,247 patients had another cardiovascular event within 2 years after the index MI. The pooled OR of a new cardiovascular event after MI in 2,946 depressed patients compared with 7,173 non-depressed patients was 1.59 (95% CI, 1.37-1.85).\textsuperscript{[12]} Only two studies on mortality and five studies on new cardiovascular events provided adjusted estimates. They were too few and heterogeneous to pool by meta-analysis. In these studies, the estimates were on average 21% lower after adjustment for age, sex, comorbidity and cardiac disease severity.

2.3 Mechanisms linking depression following myocardial infarction with adverse prognosis

While the mechanisms linking post-MI depression with adverse prognosis are not well understood, a number of relationships have been suggested.\textsuperscript{[13]} A biological pathway suggests that the depressive state is associated with hyperactivity of the hypothalamic-pituitary-adrenocortical axis, disturbances in cardiac autonomic tone and low heart rate variability,\textsuperscript{[14]} disturbances in blood clotting mechanisms, vascular endothelial dysfunction of the coronary arteries, and activation of the immune system contributing to coronary artery thrombosis.\textsuperscript{[15]} A behavioural pathway suggests that patients with depression following MI are less likely to adopt a healthy lifestyle including physical activity and dietary recommendations and are less likely to adhere to recommended secondary prophylactic medication than patients without depression.\textsuperscript{[15]} Smoking rates may also be higher in people with depression and they find it more difficult to quit.\textsuperscript{[15]} A strong and consistent inverse relation has been found between the magnitude of social support and the adverse prognostic outcome in those with MI. Factors such as living alone, being socially isolated and low perceived social support have all been found to impair the prognosis.\textsuperscript{[16-18]} Furthermore, some evidence indicates that the effect of depression is confounded by worse underlying cardiac disease, i.e. persons with more severe cardiac disease may have a higher risk of developing post-MI depression than persons with less severe cardiac disease.\textsuperscript{[19]}

2.4 Diagnosis and severity of depression following myocardial infarction

The diagnostic criteria of depression following MI are the same as those of depression in persons with no history of MI. Based on good clinical practice, the guideline of depression from the Danish College of General Practitioners\textsuperscript{[20]} recommends screening with the three core symptoms of depression according to the International Classification of Diseases, 10\textsuperscript{th} Revision (ICD-10) (Table 2.1, questions 1-3). The screening is considered positive if the patient has at least two of the three core symptoms.\textsuperscript{[20]} Based on the literature, the yes/no version of the 2-item Patient Health Questionnaire (PHQ-2) (Figure 2.1) has proven to be the most effective screening tool for identifying major depressive disorder in primary care patients according to the Diagnostic and Statistical Manual of Mental Disorders, 4\textsuperscript{th} edition (DSM-IV). The PHQ-2 takes less than 1 minute to complete and score.\textsuperscript{[21,22]}

Figure 2.1

A "yes" response to one or both questions is 96% sensitive and 57% specific for major depressive disorder when administered in the form of a self-report questionnaire\textsuperscript{[22]} and 97% sensitive and 67% specific when asked verbally.\textsuperscript{[21]} A "no" response to both questions almost rules out depression. The advantage of using the PHQ-2 is that by using only two questions that take less than one minute to complete, the PHQ-2 rules out depression in more than half or two thirds of persons.\textsuperscript{[21]} However, the low specificity and positive predictive value of the PHQ-2 means that fewer than half or one third of persons with a positive screen ultimately meet the criteria for major depressive disorder. Thus, any positive screen must be followed by a clinical interview to confirm the diagnosis.

In addition to a clinical interview, the guideline of depression from the Danish College of General Practitioners\textsuperscript{[20]} recommends diagnostic assessment by the self-reporting questionnaire, the Major Depression Inventory (MDI) (Table 2.1).\textsuperscript{[24]} In an international context, the 9-item Patient Health Questionnaire (PHQ-9)\textsuperscript{[25,26]} is more commonly used. Both are self-report instruments. The MDI has been developed with reference to the ICD-10, and the PHQ-9 has been developed with reference to the
The PHQ-9 also measures how much of the time over the past two weeks a person has been bothered by each of the depressive symptoms. The wording of the items in the PHQ-9 is slightly different from the wording of the items in the MDI, and the PHQ-9 contains one item less than the MDI (item 4 in the MDI). The most important difference between the PHQ-9 and the MDI is, though, that the PHQ-9 holds only two core symptoms because lack of energy is considered only an accompanying symptom. According to the DSM-IV, a major depressive episode is considered present, when at least five symptoms from the PHQ-9 are present including at least one of the core symptoms.

The differential diagnosis of depression includes metabolic disorders, bipolar disorder, normal grief reaction, stress, problem drinking, substance abuse and medication toxicity. When managing depression in MI patients, it is important to emphasize that the anecdotal belief that β-blocker therapy causes depressive symptoms is not supported by data from clinical trials. The underlying rationale requires a clinical decision to consider the cost (both monetary and personal) along with the cost of the illness, both monetary and personal, of the test and the errors that arise when it does not classify patients accurately will be exceeded by the costs of the illness had the test not been done. A positive test result can entail the introduction of therapy when it might not otherwise have been considered. Alternatively, a negative test can give rise to the decision not to initiate therapy when it otherwise would have been given. Opponents against screening for post-MI depression argue that there is no direct evidence that screening for depression leads to improved outcomes in cardiovascular populations. It is resource-intensive and treatment for depression is currently not effectively delivered.

The most likely outcome of a positive screen would be further treatment for depression in primary care, but it is estimated that only 20% to 30% of depressed people being treated exclusively in primary care are receiving adequate care and follow-up. Moreover, depression is highly prevalent, it impairs quality of life and the overall prognosis, valid screening tests are available and treatment of depression improves depressive symptoms. The American Academy of Family Physicians recommends screening with the PHQ-2 of all patients with coronary heart disease. The guideline does not provide information on when and how often the patients should be screened. The American Academy of Family Physicians has provided a specific guideline for the detection of post-MI depression and recommends that patients having an MI should be screened for depression using standardised depression symptom check-lists at regular intervals during the post-MI period, including during hospitalisation. In the UK, the National Institute of Clinical Excellence (NICE) recommends screening for depression in a broad group of patients with chronic physical health problems, though with particular attention to cancer, heart diseases, musculoskeletal disorders, respiratory disorders, neurological disorders and diabetes. The NICE guideline recommends that physicians be alert to possible depression and that they consider using the PHQ-2 in patients who may have depression. These recommendations have been integrated into the primary care system in the UK through the Quality and Outcomes Framework (QOF), which provides GPs with financial incentives for asking case identification questions to persons with ischaemic heart disease or diabetes. The Danish Health and Medicines Authority also recommends screening of all persons with heart disease and 12 other patient groups (patients with a history of depression, stroke, pain disorders, diabetes mellitus, chronic obstructive pulmonary disease, cancer, Parkinson’s disease, epilepsy, women during pregnancy and after childbirth, refugees and immigrants). The guideline of depression from the Danish College of General Practitioners follows the recommendations from the Danish Health and Medicines Authority, and the working group recommends screening in the above-mentioned risk groups as good clinical practice by using the core symptoms of depression according to the ICD-10.

Even if routine screening for depression following MI is recommended, its rationale is widely discussed. The term screening refers to a test performed in persons without symptoms or signs of an illness. The underlying rationale requires a judgment that among persons to whom the test is administered, the cost of the illness, both monetary and personal, along with the cost (both monetary and personal) of the test and the errors that arise when it does not classify patients accurately will be exceeded by the costs of the illness had the test not been done. A positive test result can entail the introduction of therapy when it might not otherwise have been considered. Alternatively, a negative test can give rise to the decision not to initiate therapy when it otherwise would have been given. Opponents against screening for post-MI depression argue that there is no direct evidence that screening for depression leads to improved outcomes in cardiovascular populations. It is resource-intensive and treatment for depression is currently not effectively delivered. The most likely outcome of a positive screen would be further care for depression in primary care, but it is estimated that only 20% to 30% of depressed people being treated exclusively in primary care setting are receiving adequate care and follow-up. Moreover, depression is highly prevalent, it impairs quality of life and the overall prognosis, valid screening tests are available and treatment of depression improves depressive symptoms.

### 2.5 Screening for depression following myocardial infarction

Routine screening for depression following MI is recommended by the guidelines of various Western countries. The guideline from the American Heart Association and the American Psychiatric Association recommends screening with the PHQ-2 of all patients with coronary heart disease. The guideline does not provide information on when and how often the patients should be screened. The American Academy of Family Physicians has provided a specific guideline for the detection of post-MI depression and recommends that patients having an MI should be screened for depression using standardised depression symptom check-lists at regular intervals during the post-MI period, including during hospitalisation. In the UK, the National Institute of Clinical Excellence (NICE) recommends screening for depression in a broad group of patients with chronic physical health problems, though with particular attention to cancer, heart diseases, musculoskeletal disorders, respiratory disorders, neurological disorders and diabetes. The NICE guideline recommends that physicians be alert to possible depression and that they consider using the PHQ-2 in patients who may have depression. These recommendations have been integrated into the primary care system in the UK through the Quality and Outcomes Framework (QOF), which provides GPs with financial incentives for asking case identification questions to persons with ischaemic heart disease or diabetes. The Danish Health and Medicines Authority also recommends screening of all persons with heart disease and 12 other patient groups (patients with a history of depression, stroke, pain disorders, diabetes mellitus, chronic obstructive pulmonary disease, cancer, Parkinson’s disease, epilepsy, women during pregnancy and after childbirth, refugees and immigrants). The guideline of depression from the Danish College of General Practitioners follows the recommendations from the Danish Health and Medicines Authority, and the working group recommends screening in the above-mentioned risk groups as good clinical practice by using the core symptoms of depression according to the ICD-10.

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### 2.6 Treatment of depression following myocardial infarction

The PHQ-9 also measures how much of the time over the past two weeks a person has been bothered by each of the depressive symptoms. The wording of the items in the PHQ-9 is slightly different from the wording of the items in the MDI, and the PHQ-9 contains one item less than the MDI (item 4 in the MDI). The most important difference between the PHQ-9 and the MDI is, though, that the PHQ-9 holds only two core symptoms because lack of energy is considered only an accompanying symptom. According to the DSM-IV, a major depressive episode is considered present, when at least five symptoms from the PHQ-9 are present including at least one of the core symptoms.

The differential diagnosis of depression includes metabolic disorders, bipolar disorder, normal grief reaction, stress, problem drinking, substance abuse and medication toxicity. When managing depression in MI patients, it is important to emphasize that the anecdotal belief that β-blocker therapy causes depressive symptoms is not supported by data from clinical trials.
The treatment of depression following MI follows the overall treatment of depression, though with a few precautions as to the use of pharmacotherapy. GPs have four evidence-based approaches at their disposal for treatment of depression: self-management including physical activity, psychotherapy, pharmacotherapy, or a combination of these approaches. The choice of therapy depends on the severity of the depression and patient’s preference (Table 2.2).

### Table 2.2

<table>
<thead>
<tr>
<th>Severity of depression</th>
<th>Self-management, including physical activity</th>
<th>Psychotherapy including talk therapy</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Moderate</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Severe</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Self-management is fundamental and should be encouraged through patient education and brief counselling. A meta-analysis of randomized controlled trials has shown that exercise improves depressive symptoms (effect size, 0.40; 95% CI, 0.14-0.66) in patients with chronic illnesses [41] and a recent randomized trial has shown that this is also seen in people with stable coronary heart disease (effect size, 0.56; 95% CI, 0.37-0.73). [42] No interventional studies have examined the effect of exercise on depressive symptoms in patients with a recent MI. [43] In MI patients, physical exercise should be preceded by a treadmill stress test for patient security and to reassure the patient that his or her heart is stable enough to withstand regular exercise training. [44] Like all adults, MI patients should do at least 150 minutes of moderate-intensity exercise (e.g. walking or cycling) per week, at least 75 minutes of vigorous-intensity exercise (e.g. running) per week or an equivalent combination. [45] For patients with mild to moderate depression, structured psychotherapy along with self-management should be considered as first-line treatment. [46] A randomized trial [47] found that cognitive behavioural therapy improves depressive symptoms in persons with MI, although the relative improvement in the intervention group compared with the usual care group was moderate. Cognitive behavioural therapy helps patients gain positive experiences and focus on their accomplishments rather than dwell on negative life experiences. Patients with moderate to severe depressive symptoms usually benefit from pharmacotherapy (effect size, 0.66; 95% CI, 0.38-0.94), [48] and randomized trials have documented the safety of selective serotonin re-uptake inhibitors (SSRIs) [49,50] and found that they [48,50] improve depressive symptoms in persons with MI. The decision about which antidepressant medication to prescribe should be based on the patients’ preferences, adverse effects including prolonged QT interval and possible interactions with other medications. Tricyclic antidepressants should not be used as first-line agents because of their association with adverse cardiovascular events. [51,52] Treatment of post-MI depression improves depressive symptoms, but it remains unknown whether it also improves the adverse cardiovascular outcomes. Only few trials [48,49,53] have investigated the effect of antidepressants on cardiovascular events or death and they have been underpowered to detect a potential effect. However, one observational study has suggested that antidepressants reduce death and recurrent MI in patients with post-MI depression. [54]

### 2.7 Health care organization of rehabilitation following myocardial infarction in Denmark

Denmark’s publicly funded health care system provides all Danish citizens with free access to general practice, outpatient clinics and hospital care. [55] Nearly all Danish citizens are registered with a GP and the average GP list encompasses approximately 1,600 persons. The Danish Health and Medicines Authority has developed generic instructions for the management of persons with chronic illnesses. Having the primary responsibility for Danish healthcare services, the five Danish Regions have further developed specific guidelines for rehabilitation of patients with acute coronary syndrome. [56] All persons suspected of MI should be admitted to hospital. Patients with MI should be provided with cardiac rehabilitation which implies a multidisciplinary professional approach. Cardiac rehabilitation has been divided into three phases: (I) an in-hospital acute phase lasting for a few days, (II) a reconditioning phase in an out-patient ambulatory setting lasting 8-12 weeks, and (III) a lifelong community-based improvement and maintenance phase. [56-58] Phase II rehabilitation guidelines among others recommend screening for depression by questionnaire about six weeks after the patient’s discharge from hospital, a talk about the screening result; and if the screening result indicates depression, the patient should be referred to the GP for further diagnostics and potential treatment. [56,57] Most patients with depression are treated in general practice. Since 2007, the GP has had the opportunity to refer patients aged 18-37 years (from 1 July 2012, >18 years) with mild to moderate depression to a psychologist for 12 sessions of psychotherapy with a self-payment of about one third of the total prize.

### 3. METHODS

This thesis consists of a cohort study (Papers I-III) and a case-control study (Paper IV). The cohort study was based on information from registers and questionnaires sent to patients and their GP. The case-control study was based solely on information from registers (Table 3.1).

### Table 3.1

<table>
<thead>
<tr>
<th>Characteristics of Papers</th>
<th>Study design</th>
<th>Study population</th>
<th>Data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Population-based cohort study</td>
<td>All patients with first time MI in 2009 and living in the Central Denmark Region</td>
<td>Registers: DNPR, CRIS, Patient questionnaire.</td>
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<td>All patients with first time MI in 2009 and living in the Central Denmark Region</td>
<td>Registers: DNPR, CRIS, DNBCR, CRIS, DNBCR, IDA, Patient questionnaire.</td>
</tr>
<tr>
<td>IV</td>
<td>Population-based case-control study</td>
<td>Cases: All Danish persons aged 40-80 years recorded with suicide from 1981 to 2006.</td>
<td>Controls: age and sex matched persons alive on the day the case committed suicide.</td>
</tr>
</tbody>
</table>

1. The Danish National Patient Register
2. The Civil Registration System
3. The National Health Service Register
4. The Danish National Diabetes Register
5. The Central Denmark Region Prescription Database
6. The Danish Integrated Database for Labour Market Research
7. The Cause of Death Register
8. The Danish Psychiatric Central Register

### 3.1 Data sources

#### 3.1.1 Registers

#### 3.1.1.1 The Danish National Patient Register (DNPR)

The DNPR [50] contains information on all patients admitted to any Danish somatic hospital since 1977 and emergency departments and outpatient clinics since 1995. It includes discharge diagnoses and procedure codes, coded by the physician in charge, and classified according to the Danish version of the International Classifi-
established in 1875 and computerised since 1970, the CDR in IDA are based on other registers in Statistics Denmark like the status, for the entire population from 1980 and onward. The data on income, employment status, educational level, and marital status of all Danish citizens.

3.1.1.2 The Civil Registration System (CRS)
The CRS\cite{61} was established in 1968. The CRS registers all persons alive and living in Denmark with a unique personal identification number. All new-borns have subsequently been provided with a unique number that follows people from cradle to grave. The personal identification number allows unambiguous linkage between all Danish public registers at the level of the individual. The CRS also holds information on day of birth, sex, residence, and vital status of all Danish citizens.

3.1.1.3 The National Health Service Register (NHSR)
The NHSR\cite{61} contains information on services provided by primary health care providers such as general practitioners, psychologists and other specialists. As a prerequisite for reimbursement, the individual provider is responsible for registering any given health care service.

3.1.1.4 The Danish National Diabetes Register (DNDR)
The DNDR\cite{62} includes all Danish diabetes patients according to an algorithm based on the CRS, the DNPR (discharge diagnose of diabetes), the NHSR (chirropy, blood-glucose measurements) and the Danish National Prescription Register (oral anti-diabetic drugs, insulin).

3.1.1.5 The Central Denmark Region Prescription Database (CDRPD)
The CDRPD\cite{63} holds data collected by community pharmacies on all prescriptions redeemed by out-patients and forwarded to the Central Denmark Regional Health Service section on a monthly basis. The database provides information on all reimbursed drugs according to the Anatomical Therapeutic Chemical Classification System (ATC), dispensing date, and the total number of tablets dispensed.

3.1.1.6 The Danish Integrated Database for Labour Market Research (IDA)
IDA\cite{64} holds information on socioeconomic data, including data on income, employment status, educational level, and marital status, for the entire population from 1980 and onward. The data in IDA are based on other registers in Statistics Denmark like the person register and the tax authorities register.

3.1.1.7 The Cause of Death Register (CDR)
Established in 1875 and computerised since 1970, the CDR\cite{65} covers all deaths of citizens dying in Denmark. The classification of causes of death is in accordance with the WHO’s rules, from 1968 to 1993 as specified in the ICD-8 and since 1994 as specified in the ICD-10.

3.1.1.8 The Danish Psychiatric Central Register (DPCR)
The DPCR\cite{66} stores information on all patients admitted to any psychiatric hospital and psychiatric ward in hospitals in Denmark. The register includes inpatient data since 1969 and outpatient data since 1995. It includes discharge diagnoses coded by the physician in charge and classified according to the ICD-8 from 1977 to 1993 and the ICD-10 since 1994.

3.1.2 Questionnaires
Two questionnaires were developed: one for patients and one for the patients’ GP (Appendices V-VII).

3.1.2.1 Development of questionnaires
A thorough literature search was performed using the following search terms: cardiac rehabilitation, heart disease, myocardial ischemia, depression, anxiety disorder, screening, general practice, primary care, and family practice in different combinations. The reference lists of key papers were studied. Many were identified, specific hypothesis were constructed for each topic and we chose the most relevant variables based on the literature. We used existing scales whenever possible; otherwise, ad hoc questions were constructed.

The themes in the patient questionnaire included: health services received for cardiac rehabilitation, cardiac disease severity, anxiety and depression, and health behaviours. The following validated scales were used: the British Medical Research Council (MRC) dyspnoea scale,\cite{67} the Short-Form 12 version 2 (SF-12v2),\cite{68} and the Hospital Anxiety and Depression Scale (HADS)\cite{69}. We chose the HADS because it is frequently used, extensively validated, short, easy to respond to and to calculate, measures both anxiety and depression, and was designed to be valid in clinical populations with symptoms of physical disease. It thus avoids items that might be endorsed by physical rather than mental states.\cite{69,70} The HADS is a self-report instrument that consists of a depression scale (HADS-D) and an anxiety scale (HADS-A) both with seven items that are each answered on a four-point verbal rating scale with a score of 0-3 (total score 0–21). The HADS has been validated in MI patients\cite{71,72} and has been proved to have satisfactory reliability (HADS-D, Cronbach’s α = 0.80).\cite{72} Compared with a physician-administered structured clinical interview for the DSM-IV, which is the golden standard, a HADS-D≥8 identified possible cases of depression in a GP population with a sensitivity of 80% and a specificity of 88%\cite{73} and among MI patients with a sensitivity of 65% and a specificity of 90%.\cite{72} Health behaviours were self-reported and classified according to the general recommendations of the Danish Health and Medicines Authority. We defined cardiac rehabilitation and asked the patients whether they had participated in phase II rehabilitation and in the core components of cardiac rehabilitation.

The themes in the GP questionnaire included individual information on each patient according to somatic comorbidity, previous psychiatric illness and screening for depression, and individual information on GP characteristics.

3.1.2.2 Pilot testing
The patient questionnaire was pilot-tested for comprehension and ability to discriminate answers by interviewing five MI patients and reviewing the questionnaires of 30 MI patients admitted to hospital in December 2008. The pilot test gave rise only to minor linguistic changes. The GP questionnaire was reviewed by GP colleagues from the scientific staff at the Department of Public Health, Aarhus University. Based on their comments, the GP questionnaire was adjusted and a regular pilot test was performed by interviewing six GPs and reviewing the GP questionnaires of seven MI patients. This pilot test gave rise to changes in the order of the questions and minor rewording.

3.1.2.3. Data entry
The questionnaires were designed and processed in the computer programme Teleform Enterprise version 8.0 (Cardiff software Inc., San Marcos, CA, USA) for data capture by optical scanning. An assistant scanned all returned questionnaires; and whenever the Teleform programme was in doubt of an answer, the question-
naire was thoroughly examined by the assistant and KKL. A previous study has documented the accuracy of the data processing.\textsuperscript{[74]} Data were transferred to the statistical program Stata (Statacorp LP, College Station, TX, USA) and checked for errors. If errors were encountered, the original questionnaire was inspected and the database entry corrected.

3.2 The cohort study (Papers I-III)

3.2.1 Study population

We consecutively invited all patients above 18 years, discharged from hospital with a first time MI from 1 January 2009 to 31 December 2009 and living in the Central Denmark Region (1,250,000 inhabitants). Data on patients discharged with an MI (ICD-10 code I21)\textsuperscript{[75]} were received from the DNPR on a monthly basis. Patients who had been discharged with an MI between 1994 and 2008 were excluded to identify first-time cases. Information on name, address, and vital status was obtained from the CRS, which also provided the unique personal identification number used to link data between the registers and questionnaires (Figure 3.1).

3.2.2 Data collection

The patient questionnaire was mailed to all patients between 14 and 16 weeks after their discharge from hospital. Non-responders received a reminder after 19 and 29 days.

The GP questionnaire was mailed to the GP, one for each patient, 12-13 months after the patient’s discharge from hospital. Non-responders received a reminder after 21 days.

Drug prescription data were obtained from the CDRPD,\textsuperscript{[63]} socio-demographic data from IDA,\textsuperscript{[64]} information on comorbidity from the DNPR,\textsuperscript{[59]} the DNDR,\textsuperscript{[62]} and the CDRPD,\textsuperscript{[63]} and new cardiovascular events and death from the DNPR\textsuperscript{[59]} and the CRS\textsuperscript{[60]}.

3.2.3 Statistical analyses

Responders and non-responders were compared using \(t\) tests and \(\chi^2\) tests. \(P<.05\) was considered statistically significant.

3.2.3.1 Paper I

The participation in phase II cardiac rehabilitation including screening for depression and psychosocial support within three months following MI, the prevalence of depression, drug treatment three months after the MI and the sociodemographic characteristics the year before MI were presented as numbers (proportions with 95% CIs) for categorical data and as means, standard deviations (SDs) and ranges for normally distributed continuous data.

3.2.3.2 Paper II

GPs’ practice of screening for depression in MI patients within one year after the patient’s discharge from hospital was analysed as numbers and proportions with 95% CIs. We used \(\chi^2\) test to study whether the screening rate was independent of the patients’ and the GPs’ characteristics.

3.2.3.3 Paper III

Baseline differences in characteristics between MI patients with and without depressive symptoms were compared using \(t\) tests and \(\chi^2\) tests. We calculated the event-free survival time as the time from three months after the MI (baseline evaluation of depressive symptoms) to the first cardiovascular event or death. If no event or death occurred, the patient was censored on 31 July 2012. Two persons emigrated during the follow-up period and they were censored at the time of their emigration. Owing to nationwide registers, we had complete follow-up of all patients. We estimated the risk of cardiovascular events or death associated with depressive symptoms using Cox proportional hazards models. We evaluated whether the hazard ratios (HR) of depressive symptoms following MI varied by subgroups by testing for interaction using the Wald test in an age-adjusted model. The covariates for the multivariate model (age, history of stroke, diabetes, or heart failure, cardiac disease severity, smoking, secondary prophylactic medication and physical activity) were chosen on the basis of the results from Whooley et al.\textsuperscript{[76]} No variable had more than 3.1% missing data.

Figure 3.1

Flowchart for the study populations in Papers I-III

3.2.4 Approval and ethics

The cohort study was approved by the Danish Data Protection Agency (J no. 2009-41-3018) and the Scientific Research Evaluation Committee of the Danish Academy of General Practitioners (ref no. 03-2009). Written informed consent was obtained from the patients.

3.3 The case-control study (Paper IV)

3.3.1 Study population

The case-control study was nationwide (5.5 million inhabitants in Denmark). As cases, we selected persons aged 40-89 years and recorded with suicide in the CDR from 1 January 1981 to 31 December 2006. From 1981 to 1993, the cases were identified by the ICD-8 (E950-E959) and from 1994 to 2006 by the ICD-10 (X60-X84). As controls, we randomly selected 25% of the persons who had the same sex, were born on the same day as the case and were alive on the day the case committed suicide (incidence density sampling). Cases and controls were included only if they...
had been residing in Denmark throughout the preceding year. This sampling method allowed us to estimate the incidence rate ratio (RR) and 95% CIs for a case-control study.[77]

### 3.3.2 Data collection

Data on the exposure variable, MI, were retrieved from the DNPR.[59] Potential confounders and mediators were retrieved from the CRS (day of birth, sex, and vital status (alive or dead)), the DNPR (stroke and diabetes), the DPCR (schizophrenia, affective illnesses and other psychiatric illnesses), and the IDA (marital status, labour market status, annual income and education). We extracted data on MI, stroke, diabetes and history of psychiatric contact for both cases and controls until the day where the case committed suicide (index day). Socioeconomic data were retrieved for the calendar year before the index day.

### 3.3.3 Statistical analyses

The RR of suicide among patients discharged from hospital with a diagnosis of MI was estimated by use of conditional logistic regression. RRs were adjusted for day of birth, sex, and date of suicide by stratification. RRs were adjusted for marital status, labour market status, annual income and history of psychiatric contact, stroke or diabetes by regression analysis. In sub-analyses, we also adjusted for education. The interaction between the variables was assessed by the Wald test. Owing to the nationwide nature of the registers, we had complete registration of the main variables (MI and suicide), the matching variables (sex, age and index day), marital status, annual income, labour market status, stroke and diabetes. Information on education was missing for 24% of the study population, primarily due to lack of information on people older than 60 years. We therefore adjusted for education in sub-analyses only and used sensitivity analyses in which people with missing information were categorised in the lowest and the highest educational group, respectively. P<.05 was considered statistically significant.

### 3.3.4 Approval and ethics

The study was approved by the Danish Data Protection Agency.

### 4. RESULTS IN SUMMARY

#### 4.1 The cohort study (Papers I-III)

Among a total of 1,288 eligible patients with first-time MI, 908 (70.5%) completed a questionnaire (Paper I). Information on HADS was available for 897 (69.6%) of the patients (Paper III). Compared with responders, non-responders were more often women, older, with fewer socioeconomic resources and had more comorbid conditions (Paper III, Supplemental Table). Within one year after the MI, 33 of the responders had died. The GPs of 589 (64.9%) patients returned their questionnaires (Paper II). The tendency of the GPs to respond did not depend on the patient’s sex, age, or socioeconomic resources.

#### 4.1.1 Paper I

The patients’ social and demographic characteristics are outlined in Table 4.1. Using the HADS, we found that 167 (18.6%; 95% CI, 16.1-21.2%) persons had depression three months following MI (Paper I, Table 3). Compared with the responders, non-responders were more often women, older, with fewer socioeconomic resources and had more comorbid conditions (Paper III, Supplemental Table). Within one year after the MI, 33 of the responders had died. The GPs of 589 (64.9%) patients returned their questionnaires (Paper II). The tendency of the GPs to respond did not depend on the patient’s sex, age, or socioeconomic resources.

#### 4.1.2 Paper II

Overall, 161 (27.3%; 95% CI 23.7%-30.9%) of the patients’ GPs stated that they had screened the patient for depression within the first year after their discharge from hospital (Table 4.2). Except for six, all MI patients were registered with at least one face-to-face consultation with their GP within this year.
The screening rate was higher among patients with a history of mental illness (50.0%; 95% CI, 39.5-60.5%; \(P<0.001\)) and among patients with anxiety (37.0%; 95% CI, 28.8-45.1%; \(P=0.002\)) or depression (37.5%; 95% CI, 28.0-47.0%; \(P=0.007\)) than among patients without these conditions three months after the MI (Table 4.2). The screening rate tended to increase with increasing HADS score (HADS-A<8: 23.8%; HADS-A≥8: 37.0%; HADS-A≥11: 44.9%) (HADS-D<8: 24.6%, HADS-D≥8: 37.5%, HADS-D≥11: 41.2%). None of the GP characteristics were associated with the screening rate (Paper II, Table 3).

Most of the GPs performed screening for post-MI depression according to routine procedures (n=68 (42.5%)) or upon clinical suspicion of depression (n=62 (38.8%)). The GPs screened the patients for depression by asking about specific depressive symptoms (n=95 (59.0%)), using a symptom checklist (n=19 (11.8%)) or by using other methods (n=23 (14.3%)). Most of the GPs (n=19 (82.6%)) who used other methods stated that they used their clinical judgment as a basis for their evaluation of the patient during the consultation.

**Figure 4.1**

Association between baseline depressive symptoms and subsequent cardiovascular events or death for patients with myocardial infarction and specific characteristics.

Abbreviation: MRC, Medical Research Council dyspnoea score.

### 4.1.3 Paper III

A total of 288 composite outcomes (239 new cardiovascular events and 49 deaths) occurred during 1,975 person-years of follow-up (mean 2.2 years; SD 1.0); 76 (45.5%) events occurred among persons with HADS≥8, and 212 (29.0%) events occurred among persons with HADS<8. Overall, the HR of cardiovascular events or death for MI patients with depression three months after MI was 1.76 (HR, 1.76; 95% CI, 1.36-2.29; \(P<0.001\)) compared with MI patients without depression (Table 4.3). Adjustments for cardiac disease severity and comorbid conditions attenuated the HRs, but the association remained statistically significant (HR, 1.43; 95% CI, 1.08-1.88; \(P=0.01\); Table 4.3). Additional adjustment for physical activity further attenuated the association; and in the final adjusted model, MI patients with depression had a 35% higher rate of cardiovascular events or death (HR, 1.35; 95% CI, 1.13-1.60; \(P=0.003\); Table 4.3) than MI patients without depression.

In the final model, post-MI depression was associated with an increased rate of death (HR, 2.07; 95% CI, 1.32-3.25; \(P=0.001\)), but not of new cardiovascular events (HR, 1.18; 95% CI, 0.86-1.62; \(P=0.302\); Table 4.3).

We found no statistically significant difference in the HR between subgroups of MI patients (Figure 4.1). However, the association between depression and new cardiovascular events or death tended to be smaller among person who took antidepressants (\(P=0.35\) for interaction) or were physically active (\(P=0.12\) for interaction).

**Table 4.3**

<table>
<thead>
<tr>
<th>Adjusted variables</th>
<th>Any CVD event</th>
<th>Any event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.32 (1.32-1.33)</td>
<td>1.32 (1.32-1.33)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.42 (1.32-1.54)</td>
<td>1.32 (1.32-1.54)</td>
</tr>
<tr>
<td>History of stroke, diabetes mellitus, or heart failure</td>
<td>1.40 (1.04-1.88)</td>
<td>1.73 (1.07-2.73)</td>
</tr>
<tr>
<td>Smoking status (current)</td>
<td>1.03 (0.92-1.15)</td>
<td>1.03 (0.92-1.15)</td>
</tr>
<tr>
<td>Secondary prophylactic medication</td>
<td>1.01 (0.92-1.11)</td>
<td>1.01 (0.92-1.11)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>1.18 (0.86-1.63)</td>
<td>1.18 (0.86-1.63)</td>
</tr>
</tbody>
</table>

**4.2 The case-control study (Paper IV)**

We identified 19,857 persons who committed suicide during the study period from 1981 to 2006 and 190,058 controls (for characteristics of the matching criteria, see Paper IV, Table 1). Among the individuals who committed suicide, 851 (4.3%) had a history of MI compared with 5,537 (2.9%) controls. Overall, the adjusted RR of suicide for persons with MI compared with persons without MI was 1.24 (95% CI, 1.14 to 1.35). The RR of suicide was the same for men (RR, 1.24; 95% CI, 1.13 to 1.36) and women (RR, 1.32; 95% CI, 1.09 to 1.60) (\(P=0.64\) for interaction with sex). The RR remained virtually the same throughout the study period (\(P=0.79\) for interaction with calendar year) (Table 4.4).

**Table 4.4**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate ratio&lt;sup&gt;1&lt;/sup&gt; (95% CI)</th>
<th>Adjusted rate ratio&lt;sup&gt;2&lt;/sup&gt; (95% CI)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.41 (1.13-1.75)</td>
<td>1.43 (1.18-1.74)</td>
<td>.064</td>
</tr>
<tr>
<td>Sex</td>
<td>1.42 (1.32-1.54)</td>
<td>1.41 (1.32-1.54)</td>
<td>.064</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.01 (1.00-1.02)</td>
<td>1.01 (1.00-1.02)</td>
<td>.564</td>
</tr>
<tr>
<td>History of MI</td>
<td>1.24 (1.03-1.49)</td>
<td>1.24 (1.03-1.49)</td>
<td>.564</td>
</tr>
<tr>
<td>Status at matching</td>
<td>1.24 (1.03-1.49)</td>
<td>1.24 (1.03-1.49)</td>
<td>.564</td>
</tr>
</tbody>
</table>

1 Adjusted for sex, age and calendar time by matching.
2 Adjusted for sex, age and calendar time by matching and further adjusted for marital status, labour market status, annual income, psychiatric illness, stroke, and diabetes mellitus by regression analyses.

The risk of suicide was highest within the first month after discharge for MI persons with RR, 64.05, 95% CI 13.36 to 307.06) and without (RR, 3.25; 95% CI, 1.61 to 6.56) a psychiatric
illness, but remained high throughout the entire study period (Table 4.5).

The association between MI and suicide was strongest for the youngest persons (age 40-59) whether they suffered psychiatric illness (RR, 13.85; 95% CI, 10.68 to 17.98) or not (RR, 1.51; 95% CI, 1.22 to 1.87), and the RR tended to decrease with age (p=0.119 for trend) (Table 4.4 + Paper IV, Table 4).

As expected, psychiatric illness was strongly associated with suicide (Table 4.5 + Paper IV, Table 4 and 5). The association between MI and suicide was modified by the type of psychiatric illness (p<0.001 for interaction). Persons with an affective disorder had the highest risk. The RR of suicide was high the first year after discharge for MI for persons with an affective disorder, whereas it remained high until 5 years after discharge for MI for persons with schizophrenia and other psychiatric illnesses. Overall, the risk of suicide after MI remained high (RR, 1.39; 95% CI, 1.26 to 1.53) even among those without psychiatric illness and after adjusting for diabetes, stroke, marital status, labour market status and annual income (Paper IV, Table 5).

### Table 4.5

<table>
<thead>
<tr>
<th>Association between MI and suicide according to psychiatric illness and time since MI</th>
<th>Cases</th>
<th>Controls</th>
<th>Rate ratio</th>
<th>Adjusted rate ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No psychiatric illness</td>
<td>N=10,671</td>
<td>13,155</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>Acute MI, 1 month</td>
</tr>
<tr>
<td>MI, 1 month to 1 year</td>
<td>50</td>
<td>540</td>
<td>1.89 (1.46-2.43)</td>
<td>1.80 (1.39-2.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI, 1.5 years</td>
<td>206</td>
<td>1,992</td>
<td>1.50 (1.30-1.74)</td>
<td>1.44 (1.24-1.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI, 5 years</td>
<td>239</td>
<td>2,517</td>
<td>1.29 (1.21-1.38)</td>
<td>1.23 (1.07-1.43)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1Adjusted for sex, age and calendar time by matching.
2Adjusted for sex, age and calendar time by matching and further adjusted for marital status, labour market status, annual income, psychiatric illness, stroke, and diabetes mellitus by regression analyses.

5. DISCUSSION OF RESULTS

### 5.1 Prevalence of depression three months after myocardial infarction and hospital-based psychosocial rehabilitation (aim 1)

According to the HADS, 18.6% (95% CI, 16.1-21.2%) of the MI patients in our study had depression three months after having suffered MI. During the first three months post MI, only 3.3% (95% CI, 2.1-4.5%) were screened for depression and less than one-third participated in the hospital-based psychosocial rehabilitation offered in this period.

Depression is about three times more common in patients having suffered MI than in the general community. Assessments conducted in the hospital indicate that one in five patients with MI has depression; and even more patients show levels of depressive symptoms. Less is known about the prevalence of depression in outpatient samples. A review from 2006 assessed the prevalence of depression in patients hospitalised for MI and the relation between assessment modality and prevalence (Section 2.2). In eight studies using structured clinical interviews, prevalence rates of depression within two weeks following MI ranged from 16% to 27%, and the weighted prevalence was 19.8% (95% CI, 19.1-20.6%). In four studies using a HADS-D score of ≥8, prevalence rates ranged from 11% to 17%, and the weighted prevalence was 15.5% (95% CI, 13.2-18.0%). Only two of the studies, using structured interviews and none of the studies using HADS addressed the persistence of depression in patients diagnosed during hospitalization for MI. Schleifer et al. reported that about three quarters continued having depression three months later; Lesperance et al. et al. reported that this was the case for about half of the patients after 6 months and, in addition, 16% of those who did not have depression during admission had depression after 6 months. A recent Norwegian study reported a depression prevalence (HADS-D≥8) at three months after MI of 13.4%. However, all three studies have major limitations in that the study populations were small (N=283, N=227, N=413), the participation rates in the follow-up were only moderate (60%), (54%) or low (40%) and non-participants were older and more often female than participants. These limitations may have led to inaccurate estimates and underestimation of the depression prevalence. No previous studies have reported on patient-specific participation in psychosocial rehabilitation during the hospital-based rehabilitation following MI, but a European survey described the contents of hospital-based rehabilitation programs throughout Europe. In this survey, the providers of rehabilitation in all the European countries (except Denmark and Luxembourg) identified from the national organizations or a national contact person, and a self-report questionnaire was sent to the providers. The questionnaire evaluated the duration of the rehabilitation programs, staffing, contents and cost. The survey reported that about half of the hospital-based rehabilitation programs encompassed psychological tests and psychosocial follow-up, but it did not report whether tests and follow-up were provided to the patients or if they participated. In general, it is well-known that mental illnesses including depression are under-recognised and under-treated worldwide. In Europe, it is estimated that mental illnesses affects 27.9% of the population every year, 74% of whom receive no treatment. A A WHO review of 37 studies worldwide showed that the proportion of people who are untreated for depression is 56%.

### 5.2 Screening for post-myocardial infarction depression by general practitioners (aim 2)

Within one year after MI, 27.3% (95% CI, 23.7-30.9%) of the patients in our study had been screened for depression by their GP. The screening rate was higher among patients with previous mental illness (50.0%; 95% CI, 39.5-60.5%) and those who had depression according to the HADS three months after MI (37.5%; 95% CI, 28.0-47.0%) than among patients without these conditions. Most of the GPs screening for post-MI depression asked about specific depressive symptoms without using symptom checklists. Routine screening for depression in patients with MI is recommended in national guidelines in various Western countries, but little is known about to which extent such guidelines are actually being implemented. In Paper I, we found that during the first three months post first-time MI, only 3.3% of the patients reported that they had been screened for depression during the hospital-based psychosocial rehabilitation offered in this period. GPs manage the long-term rehabilitation of MI patients and are in a key position to recognize and treat depression in this population. A Canadian cross-sectional study evaluated 163 (response rate 63%) GPs’ practice patterns for managing depression, including screening. About 40% of the GPs reported that they performed routine screening of all adults, and about 60% reported that they screened only patients at high risk of depression. Most GPs screened the patient by interview rather than by using a symptom checklist. These discrepancies between the Canadian study and our study with regard to screening rates may stem from the fact that Canadian study evaluated general behaviour,
whereas we evaluated patient-specific behaviour. Moreover, the responders in the Canadian study may have had a particular interest in depression that caused the study to overestimate the proportion of GPs who performed routine screening. In the UK, screening for depression by means of the PHQ-2 in patients with diabetes mellitus and/or ischaemic heart disease was included in the QOF in 2006. The QOF was introduced into UK general practice in 2004 and it provides financial incentives to improve the quality of chronic disease management.[86] In the 2009/10 QOF, 88.3% of the patients recorded with diabetes mellitus and/or ischaemic heart disease had been screened for depression within the past 15 months by means of the PHQ-2.[12] Like in the UK, Danish GPs are remunerated partly on a fee-for-service basis, and they are given a financial incentive to use depression symptom checklists, but not to screen for depression. Moreover, in Danish general practice, the screening recommendations are not promoted by quality development or systematic and automatic electronic tools. This may partly explain the difference in screening rates between the UK and Denmark. A recent qualitative study[88] from the UK showed that GPs find that implementation of the screening instruments has helped them overcome barriers of mentioning mood during a consultation about coronary heart disease.[89]

In general, a recent meta-analysis[87] of 41 studies revealed that GPs identified depression in 47% of the patients who had depression according to an interview. Many of the studies covered by this meta-analysis are cross sectional. They have therefore been criticised because, unlike primary care itself, they do not have a longitudinal perspective. Complying with this issue, the studies were separated in the meta-analysis. This led to an improved diagnostic sensitivity (53%) with prospective examination over an extended period (3-12 months) compared to cross-sectional data (34%).[87] We found that screening for depression within one year following MI had neither been systematically implemented in the hospital-based rehabilitation nor in Danish general practice. Our results indicate that in the absence of systematic screening, a significant part of those with depression or diabetes mellitus and/or ischaemic heart disease may have a higher risk of developing depression than persons with less severe cardiac disease (Section 2.3).[95] A meta-analysis[95] from 2011 found that patients with post-MI depression had a 2.25 (95% CI, 1.73-2.93) times higher risk of all-cause mortality (17 studies) and a 1.59 (95% CI, 1.37-1.85) times higher risk of new cardiovascular events (18 studies) (Section 2.2) than patients without post-MI depression. Only eight studies[96-99] provided adjusted estimates and they were too heterogeneous to pool by meta-analysis. Five of the studies (two on all-cause mortality[34,97] and three on new cardiovascular events[34,96]) adjusted for cardiac disease severity. The adjusted associations were smaller than the unadjusted associations, but remained statistically significant for four of them.[94-96] The attenuation was 3%,[96] 4%[96] and 10%[96] in the studies on cardiovascular events and 7%[96] and 65%[96] in the studies on all-cause mortality. Caution is warranted when interpreting the results of the latter study[97] due to its limited statistical power because of low numbers which results in large CIs. In a recent study, Zuidersma et al.[96] found that one third to half of the association between post-MI depressive symptoms and cardiovascular events or death was explained by cardiac disease severity and previous MI. In patients with stable coronary heart disease, Whooley et al.[76] found that cardiac disease severity and a history of MI, stroke, diabetes and heart failure attenuated the association with 13%; after further adjustment for physical inactivity, there was no longer a significant association between depression and cardiovascular events or death in these patients.

Our findings support the hypothesis that the association between depressive symptoms and adverse outcome is confounded by the severity of the underlying cardiac disease and they add that physical inactivity also plays an important role. However, persons with depressive symptoms had a higher risk of new cardiovascular events or death than persons without depressive symptoms, even after adjusting for these potential confounders. Physical inactivity three months after MI may hence be a step on the causal pathway from depressive symptoms to the adverse outcome and should therefore not be adjusted for.[95] Sub-analyses were performed to adjust for other potential confounders (sex, marital status, education, labour market status, body mass index, antidepressant use, and participation in hospital-based rehabilitation) but this did not change the estimates. In one sub-analysis, we also excluded patients with the more severe underlying physical disease (MRC≥3, previous stroke, heart failure or diabetes mellitus) and found that patients with depressive symptoms had a 1.48 (95% CI, 0.95-2.32) times higher risk of cardiovascular events or death than patients without depressive symptoms. These findings support that post-MI depressive symptoms seem to be an independent prognostic risk factor for new cardiovascular events or death in our study.

We examined the association between post-MI depressive symptoms and adverse outcome in several subgroups, but identified no factors that modified the risk. However, the sample size was small in some of the subgroups, and we found a tendency towards a lower association with increasing physical activity and among users of antidepressants. Larger studies are needed to clarify the impact of these potential modifiers of the association and to evaluate how such modifiers may be catered for in the treatment of post-MI patients with symptoms of depression.
Meanwhile, general recommendations are that clinicians should recognize and treat post-MI depression. Randomized trials have found that antidepressants and cognitive behavioral therapy reduce depressive symptoms in persons with MI. Physical exercise reduces depressive symptoms in patients with stable coronary heart disease, but no interventional studies have examined the effect of exercise on depressive symptoms in patients with a recent MI. In these patients, physical exercise should be supervised and preceded by a treadmill stress test for patient security and to reassure the patients that their hearts are strong enough to withstand regular exercise training. Furthermore, it remains unknown whether treatment of depression improves the adverse cardiovascular outcomes of persons with coronary heart disease. Previous trials have been underpowered to detect any such effect on cardiovascular events or death, but one observational study suggested that antidepressants reduced death and recurrent MI in patients with post-MI depression. Mounting evidence shows that comprehensive and collaborative care is effective in managing persons with depression and co-existing physical illness including MI. Such care includes components like education about the condition, interventions to encourage physical exercise and systematic monitoring of patients’ adherence to medication. Initiatives should be taken to implement comprehensive and collaborative care, and future studies should evaluate whether these strategies also improve the overall prognosis.

5.4 Myocardial infarction and risk of suicide (aim 4)
MI was strongly associated with an increased risk of suicide. This risk was particularly high immediately after the MI but remained much elevated for more than five years, notably, among persons with a history of psychiatric illness.

MI is a severe life event that is accompanied by an increased risk of anxiety, depression and decreased quality of life. However, no previous studies have examined whether the mental burden of MI is so heavy that it increases the risk of suicide. Previous studies, though, found a positive correlation between the incidence of death from suicide and death from ischaemic heart disease in Brazil, and a positive association between the life-time prevalence of coronary artery disease and suicide attempts has been reported in an elderly population in the South of France. A small study from Baltimore in the USA found that 7.3% of patients had suicidal plans following the acute and threatening physical illnesses such as MI and stroke. Two studies examined the association between several physical illnesses and the risk of suicide in elderly people and found no association between cardiovascular disease and suicide. The difference between their results and ours may be attributed to their smaller sample sizes, their broader diagnostic categories, and the fact that they did not take time since diagnosis into account.

In our study, the association between MI and suicide remained stable throughout the study period, although many other factors changed. During the study period, the acute treatment of MI was improved by thrombolysis and percutaneous coronary angioplasty, and the subsequent treatment was improved by drugs and comprehensive rehabilitation. Furthermore, the number of days spent at hospital after MI decreased significantly. These factors might have affected the mental condition of persons with MI in different ways but the association between MI and suicide remained virtually unchanged even if overall suicide rate declined markedly in the Danish population for men (from 22/100.000 in 1980 to 7/100.000 in 2001) and women (from 10/100.000 in 1980 to 4/100.000 in 2001).

We found that the risk of suicide after MI decreased slightly when we adjusted for previous admission due to stroke or diabetes mellitus, annual income and labour market status; and the risk increased slightly when we adjusted for marital status. However, the results did not change significantly. This, our results imply that MI per se is a risk factor for suicide even after adjustment for physical comorbidity and various socioeconomic factors known to increase the risk of suicide in the general population.

Several risk factors contribute to suicide. The stress-diathesis model suggests that a stress-full life event combined with a genetic predisposition may entail a suicidal act. MI is known to be significantly associated with psychological distress, and many patients are affected by depression following MI (Paper I). Components of the diathesis include hopelessness, aggression and impulsivity due to low hormonal activity (serotonin, noradrenaline). Recently (March 2012), a large case-control study also examined the association between several physical illnesses and the risk of suicide and found that coronary heart disease was associated with a 1.53 times increased risk of suicide which was largely explained by clinical depression. Combined with our results, these findings emphasise the mental burden of MI and support that it is important to address the mental health following MI.

DISCUSSION OF METHODS
In assessing the validity of the findings from the four studies in this thesis, one needs to address bias in selection or measurement, confounding and chance (Figure 6.1).

Figure 6.1
Association and cause. From Clinical Epidemiology – The Essential.

6.1 Selection bias
Observational studies are vulnerable to selection bias, which may stem from the procedures used to select subjects and from factors influencing study participation. In the cohort study (Papers I, II, III), the response rate among patients was good (70%). However, the non-responding patients were older, more often women, had fewer socioeconomic re-
sources and more comorbid conditions than the responders (Paper III, Supplemental Table). In the cross-sectional analysis in Paper I, we may therefore have underestimated the depression prevalence and overestimated the participation rate in psychosocial rehabilitation. If non-responders have a higher depression prevalence than responders, we may have underestimated the overall screening rate in Paper II, because the screening rate was higher in patients with depression than in patients without. However, the screening rates according to specific patient characteristics would not be affected because age, sex and socioeconomic resources did not impact the GPs’ screening rates. Non-responding GPs could affect the estimated screening rates both ways. However, the GP response rate was fair (65%), the tendency of GPs to respond did not depend on the patient’s age, sex or socioeconomic resources, and no GP characteristics were associated with the screening rate (Paper II, Table 3). In Paper III, we used antidepressant consumption as a proxy for depressive symptoms as has also been done in previous studies. The estimates of these analyses of the association between antidepressants and new cardiovascular events or death in both responders (HR, 1.49; 95% CI, 1.09–2.05) and non-responders (HR, 1.40; 95% CI, 1.05–1.87) were the same and they were comparable to that of HADS in responders, which reduces the risk of selection bias. The risk of selection bias is further reduced by the fact that we had complete follow-up owing to our use of nation-wide registers.

In the case-control study, complete information was available on all persons in Denmark registered with suicide during the study period and a random sample of control persons with the same age and sex alive on the day the case person committed suicide. No loss to follow-up occurred, and selection biases are unlikely explanations for our findings.

6.2 Information bias
Information bias may arise when the information collected is erroneous. Misclassification of the exposure, the outcome or any confounding factors can cause such errors. Misclassification can be differential or non-differential. Differential misclassification can either exaggerate or underestimate the true association, whereas a non-differential misclassification tends to produce a bias towards the null.

Information on MI was registered prospectively in both the cohort study and the case-control study. It therefore did not rely on the participants’ or the relatives’ memory. The MI diagnosis in the DNPR was based on current European Society of Cardiology criteria for MI, coded by the physician in charge of the discharge. The diagnosis is known to have a high sensitivity (90%) and specificity (92%), which is unrelated to age.

In the cohort-study, the specificity of the MI diagnosis was even higher than in the DNPR because we asked the patients to confirm their diagnosis and we reviewed the discharge summary. We excluded 47 patients due to misclassification of the MI diagnosis and eight due to lacking information on diagnosis and lacking permission to retrieve the discharge letter (Figure 3.1). When developing the questionnaires, we used both single factual items and psychometric tests, such as the HADS. Both were included based on an extensive literature search and our clinical experience. Whenever possible, we used questions from previous surveys and previously translated and validated scales. Health behaviours were classified according to the Danish Health and Medicines Authority. The questionnaires were pilot-tested for comprehension (content validity) by interviewing MI patients and GPs, and for the respondents’ ability to discriminate answers (construct validity) by reviewing the MI patients’ and the GPs’ questionnaires. For most single items, a test against a golden standard (criterion validity) made no sense, as no such true value could be found. Allocating a diagnosis of depression is based ideally on a diagnostic interview. However, the diagnostic usefulness of HADS-S has a high quality with specificity of 90% in MI patients when compared with the golden standard, a physician-administered structured clinical interview for DSM-IV. In Paper II, the retrospective nature of the information on screening for depression makes it prone to recall bias, which could affect the overall screening rate. To minimize this, the GPs were provided with the patient’s personal identification number in order to be able to consult their electronic patient files when completing the patient-specific questionnaire. We also reduced the risk of information bias by using high-quality register data, such as socioeconomic data, whenever possible.

Concerns about information bias were minimal in the case-control study, which was based solely on registers. Registration errors do occur; yet, they are most likely non-differential. The overall necropsy rate declined from 44% in 1971 to 9% in 2011, but medico legal inquest is statutory when suicide is suspected. We included only suicide cases for which the coroner’s verdict was “suicide”. This ensures a high specificity of the outcome, which is important in case-control studies. The quality of a suicide diagnosis is likely to be the same for those with and without a previous MI diagnosis, although we cannot exclude that some suicides may have been misclassified as sudden cardiac death if they occurred shortly after the MI. If so, we might have underestimated the true association between MI and suicide.

6.3 Confounding
A confounder is a factor related to both exposure and outcome. However, it cannot be a factor in the pathway between exposure and outcome, and its presence must be unbalanced between groups. In other words, it must be an independent risk factor. There are several methods to account for confounders in observational studies. We used matching, restriction, stratification and adjustment in multivariate regression analyses.

We examined associations in Papers III and IV. Data were available on a wide range of covariates. Thus, it was possible to account for a number of potential confounders, including, age, sex, socioeconomic resources and comorbidity; for Paper III, it was also possible to account for severity of disease, health behaviour and health care interventions. However, our observational studies carried an inherent risk of residual confounding. This risk arises in the analysis of an association when confounding remains present after adjustment, when confounding comes from factors that are not controlled at all, or when the possible confounder is measured inaccurately. In Paper III, we were unable to evaluate whether the association between post-MI depression and adverse outcome was explained by potential biological mechanisms such as heart rate variability and inflammatory mechanisms because we had no information on these issues. In the study by Wholey et al., inflammation as measured by C-reactive protein explained a small part of the association, but it is unclear whether inflammation acted as a mediator between depressive symptoms and cardiovascular events or death or as a marker of more severe disease. In Paper IV, unrecorded psychiatric illness could confound the association between MI and suicide. Psychiatric outpatients were not included before 1995, and patients with milder psychiatric illnesses, such as mild depression, may not be in the register. However, the risk of suicide after MI was the same during the study period 1981-1995 as during 1996-2006, which...
indicates that the association was not affected by the inclusion of less severe cases. Furthermore, the association decreased only slightly when we adjusted for psychiatric illness as registered in the DPCR.

6.4 Chance

Chance, or random error, is closely related to precision, because the mean of a large number of unbiased observations tends to approximate the true value in the population, even though the individual samples may vary considerably.\textsuperscript{39} Large studies are therefore more precise and contain less random estimation error than smaller studies. However, random variation can never be totally eliminated, so precision and chance should always be considered in assessments of clinical observations. In Papers I-IV, the precision was reflected by the width of the 95\% CIs. In all our main analyses, the large study populations gave a high level of statistical precision. However, in some of the analyses, the statistical precision of the estimates was lower due to either fewer included observations or further stratification of the main study. Examples are the analyses of the GPs’ screening procedures (Section 4.1.2) and the association between MI and suicide according to type of psychiatric illness and time since MI (Paper IV, Table 5). Some caution is therefore warranted when interpreting the findings of these analyses as they were more sensitive to chance.

7. MAIN CONCLUSIONS

Main conclusions for aim 1-4

1. Post-MI depression was common; persons with MI were rarely examined for depression and few of them received psychosocial support during the three-month post-MI hospital-based rehabilitation phase;

2. GPs’ screening for depression during the first year after MI was neither complete among persons with MI nor in subgroups of such patients at particularly high risk of post-MI depression. When screening, the GPs followed guidelines asking about specific depressive symptoms;

3. Depressive symptoms following MI were associated with an increased risk of new cardiovascular events or death. Half of this association was explained by cardiac disease severity, comorbidity and physical inactivity, but depressive symptoms remained an independent prognostic risk factor. The effect of depression did not vary between subgroups of MI patients;

4. MI was strongly associated with an increased risk of suicide. This risk was particularly high shortly after the MI, but remained high for more than five years after the MI.

8. PERSPECTIVES FOR THE CLINIC AND FUTURE RESEARCH

Modern management of MI rests on a clinical evidence base drawn from many studies undertaken over the past four decades. The evolution in clinical practice has substantially reduced mortality and morbidity associated with MI.\textsuperscript{16} The key to this success is the effective introduction of secondary prophylactic medication combined with timely reperfusion. This evolution has been underpinned by better risk stratification and optimised systems of care.\textsuperscript{2} Remaining challenges include evidence-based management of depression following MI. This thesis demonstrates that depression following MI is common, under-recognised and has a major impact on prognosis.

Screening for depression following MI has not been systematically implemented either in the hospital-based rehabilitation or in Danish general practice. In the absence of systematic screening, a significant part of those who suffer from depression or are at an increased risk of depression go unrecognised. The Danish program for clinical quality development in cooperation with a working group from the Danish Society of Cardiology have recently described quality indicators for phase II rehabilitation and established a database for registering such quality indicators. Screening for depression is one of the quality indicators, and reporting to the database begins in the spring of 2013. Future studies should examine whether this strategy improves the screening rate and the subsequent treatment undertaken in general practice. Like international guidelines,\textsuperscript{29-31} the Danish College of General Practitioners\textsuperscript{30} recommends screening for depression in patients with MI. However, none of the guidelines provide instructions on when and how often the patient should be screened for depression, and the guidelines are not promoted by system support in Danish general practice. We may improve the detection rate of depression and improve the cost-effectiveness of the screening program if more specific guidelines for the screening for depression are developed and initiatives are taken to further their implementation.\textsuperscript{117} These guidelines should provide information on management of patient groups at particularly high risk of depression and should suggest when and how often they should be screened. Besides interactive educational strategies,\textsuperscript{122} screening for depression may be helpful, particularly when screening is coupled with system changes that help ensure adequate treatment and follow-up.\textsuperscript{34,123}

MI increases the risk of suicide, mediated by depression,\textsuperscript{117} and depression following MI impairs the overall prognosis. We examined the association between post-MI depressive symptoms and adverse outcome in several subgroups, but identified no factors that modified the risk. Larger studies are needed to clarify the impact of potential modifiers of this association and to evaluate how such modifiers may be catered for in the treatment of post-MI depression. Randomized trials have found that antidepressants\textsuperscript{102,104} and cognitive behavioural therapy\textsuperscript{94} reduce depressive symptoms in persons with MI. However, it remains unknown whether treatment of depression improves the adverse cardiovascular outcomes in these persons. Previous trials have been underpowered to detect a potential effect on cardiovascular events or death,\textsuperscript{46,48,49,53} but one observational study has suggested that antidepressants reduce death and recurrent MI in patients with post-MI depression.\textsuperscript{54} Mounting evidence shows that comprehensive and collaborative care is effective in managing persons with depression and co-existing physical illness\textsuperscript{102,103} including MI\textsuperscript{104} such collaborative care includes components like education about the condition, interventions to encourage physical exercise and systematic monitoring of the patient’s adherence to medication.\textsuperscript{105} Initiatives should be taken to implement comprehensive and collaborative care,\textsuperscript{103,105,108} and future studies should evaluate whether these strategies also improve the overall prognosis.

9. SUMMARY

Background and aims

Myocardial infarction (MI) is a severe life event that is accompanied by an increased risk of depression. Mounting evidence suggests that post-MI depression is associated with adverse outcomes, but the underlying mechanisms of this association remain unclear, and no previous studies have examined whether the mental burden of MI is so heavy that it increases the risk of sui-
Conclusions and perspectives

This thesis demonstrated that post-MI depression is common, under-recognized and has a strong prognostic impact. About one in five patients have depression three months after MI. Guidelines recommend screening for depression, but the guidelines have not been systematically implemented either in the hospital-based rehabilitation or in Danish general practice. In the absence of systematic screening, we found that a significant part of those who had depression were not recognized. MI increases the risk of suicide, and depression following MI impairs the overall prognosis. The thesis indicates that physical activity and antidepressants modify the adverse prognosis in patients with post-MI depression, but larger studies are needed to clarify the impact of these potential modifiers and to evaluate how they may be catered for in the treatment of post-MI patients with depression.

10. LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Source</th>
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<tr>
<td>ACT</td>
<td>Anatomical Therapeutic Chemical Classification System</td>
<td>KD-8 = International Classification of Diseases, 8th Revision</td>
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<tr>
<td>BE</td>
<td>Beck Depression Inventory</td>
<td>KD-10 = International Classification of Diseases, 10th Revision</td>
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<tr>
<td>CDR</td>
<td>The Cause of Death Register</td>
<td>MDD = Major Depression Disorder</td>
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<tr>
<td>CDRCR</td>
<td>The Central Regions Register - Prescription Database</td>
<td>NM = Major Depression Inventory</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
<td>MI = Myocardial Infarction</td>
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<tr>
<td>CRU</td>
<td>The Civil Registration System</td>
<td>MRC = Medical Research Council (UK)</td>
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<tr>
<td>DNR</td>
<td>The Danish National Registry</td>
<td>NHS = The National Health Service Registers</td>
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<td>DNRN</td>
<td>The Danish National Patient Register</td>
<td>DCI = The National Institute of Clinical Excellence (UK)</td>
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<tr>
<td>DOPK</td>
<td>The Danish Psychiatric Central Register</td>
<td>OR = Odds Ratio</td>
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<tr>
<td>DRMF</td>
<td>Diagnosis and Statistical Manual of Mental Disorders, 5th Edition</td>
<td>PDH = Patient Health Questionnaire, 2 items</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
<td>PDQ-9 = Patient Health Questionnaire, 9 items</td>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
<td>QOF = Quality and Outcomes Framework</td>
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<tr>
<td>HADS-A</td>
<td>Hospital Anxiety and Depression Scale anxiety score</td>
<td>MI = Mortality</td>
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<td>HADS-D</td>
<td>Hospital Anxiety and Depression Scale depression score</td>
<td>SD = Standard Deviation</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
<td>SSS = Selective Serotonin Reuptake Inhibitors</td>
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<tr>
<td>SISA</td>
<td>The Danish Integrated Database for Labour Market Research</td>
<td>MF-3104 = Most Form 13 version 2</td>
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11. REFERENCES


42. Blumenthal JA, Sherwood A, BABYMA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: Results from the UPBEAT understanding the prognostic benefits of exercise and anti-
60. Pedersen CB. The Danish Civil Registration System. 2012;60(12):1053-1063.


59. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient

58. Ades PA. Cardiac rehabilitation and secondary prevention of

54. Taylor CB, Youngblood ME, Catellier D, et al. Effects of antide-

53. Baumeister H, Hutter N, Bengel J. Psychological and pharma-

52. Roose SP, Miyazaki M. Pharmacologic treatment of depression

51. Roose SP. Treatment of depression in patients with heart

48. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treat-

47. Rayner L, Price A, Evans A, et al. Antidepressants for depres-

46. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The enhancing recovery in coro-

45. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The enhancing recovery in coro-


53. Baumeister H, Hutter N, Bengel J. Psychological and pharma-

54. Taylor CB, Youngblood ME, Catellier D, et al. Effects of antide-


56. Piepoli MF, Corra U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: From knowledge to implementa-


59. Lynge E, Sandegaard JL, Reboli M. The Danish National Patient


62. Carstensen B, Kristensen JK, Marcussen MM, et al. The Na-

63. Gaist D, Sorensen HT, Hallas J. The Danish prescription regis-


70. Johnston M, Pollard B, Hennessy P. Construct validation of the hospital anxiety and depression scale with clinical popula-


72. Thoms BD, Magr-Fashsett G, Bass EB, et al. Performance characteristics of depression screening instruments in survi-


74. Jorgensen CK, Karlsbomese B. Validation of automated forms processing. A comparison of Teleform with manual data en-


78. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: Its nature and con-


81. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: Its nature and con-


84. Jorgensen CK, Karlsbomese B. Validation of automated forms processing. A comparison of Teleform with manual data en-

85. Taylor CB, Youngblood ME, Catellier D, et al. Effects of antide-

86. Baumeister H, Hutter N, Bengel J. Psychological and pharma-


89. Lynge E, Sandegaard JL, Reboli M. The Danish National Patient


118. Fletcher RW, Fletcher SW. Clinical epidemiology. the essentials. 4th ed. USA: Lippincott Williams & Wilkins; 2005.


