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Dorien Tulner

Heart in Mind Mind in Heart

Neurobiological aspects of depression post myocardial infarction.

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HEART IN MIND
MIND IN HEART

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PROLOGUE

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AFFECTIVE DISORDER AND CARDIAC DISEASE

In 1937, Malzberg described for the first time that depression is related to cardiac mortality [1]. After that, it took several decades before a growing number of both population and clinical studies onfirmed this relationship and tried to elucidate it. In 1993 Frasure Smith et al demonstrated that major depression in patients hospitalized for myocardial infarction (MI) was an independent risk factor for cardiac mortality at 6 months [2]. They showed that the impact was at least equivalent to that of left ventricular dysfunction and a history of previous MI. Since then, numerous studies have examined the relation between depressive disorder and MI. Summarizing these data, meta analyses of prognostic studies showed that minor and major depressive disorder in the year post-MI affect 8- 30 % of the patients depending on the assessment method [3] and are associated with a 1.8 to 2.6 fold increased risk for all-cause mortality, cardiovascular mortality and cardiovascular events [4,5]. However, substantial numbers of depressive episodes associated with MI begin long before MI [6] and this questions the quantitative and qualitative contribution of pre-MI depressive disorder to index MI and the subsequent "depression related" cardiac events. Moreover, it questions the etiological role of depressive disorder in the development of coronary heart disease (CHD). The various ways in which cardiac dysfunctioning and afffective dysfunctioning might be related are summarized in Figure 1.

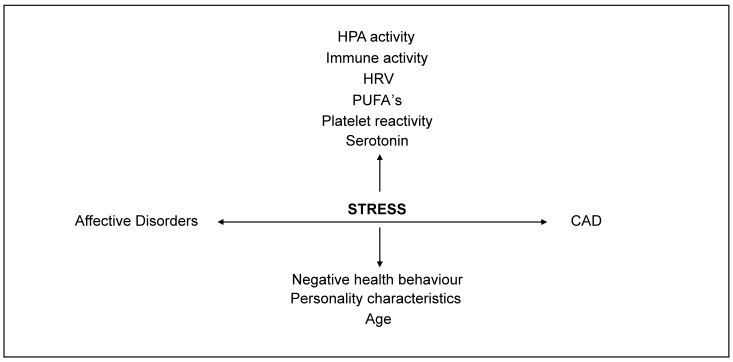


Figure 1. Pathogenesis of affective disorders and coronary heart disease. Abbreviations. HPA: hypothalamic-pituitary-adrenal axis. PUFA's: polyunsaturated fatty acids. HRV: Heart Rate Variability.

Three main issues have to be elucidated before more definite conclusions can be drawn about the exact nature of these mutual influences. These are the etiological role of depression in CHD, the role of "reversed causality" and the possibility that MI and depressive disorder are not causally related but associated by sharing the same pathophysiology (Fig 2).

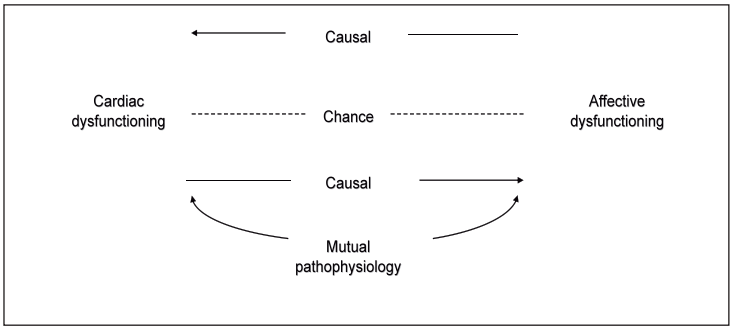


Figure 2. The relationship between cardiac dysfunction and affective disorders.

Etiological role of depression in CHD.

Three affective dispositions (emotions), i.e. depression, anxiety and anger/hostility, have been identified as putative risk factors for CHD [7]. In general population studies depressive symptoms and disorders have been found to be independent risk factors for CHD with an odds ratio of 1.6 to 3.9. [5,8,9].

Other psychological states that are characterized by affective dysregulation are associated with an unfavourable course of CHD as well. Among these are first of all the type D personality profile which is characterized by a tendency to experience distress and social inhibition [10,11] and secondly the vital exhaustion syndrome which is associated with severe somatic disease and has a symptom profile quite similar to depressive disorder but without the "classic" depressive cognitions as quilt and sadness [12,13,14]. There is mounting evidence that anxiety disorders, often present as a co-morbid disease in depressive disorders, affect the course of CHD in a negative way as well [15,16,17].

Research indicates that depressive symptoms may have their deleterious effects especially in the earlier stages of the development of CHD [5,18,19] while in more advanced stages of CHD co-morbid anxiety disorder [20] and/or the synergistic interaction between depression and anxiety [21] might have a relatively greater impact on the negative course of CHD and incidence of cardiac adverse events. To date, methodological problems of study designs and especially the limited quality of psychometric instruments in case of somatic co-morbidity prohibit definite conclusions about the etiological role of depression and anxiety in the course and adverse events of CHD [5,7,22].

The role of "reversed causality."

The second issue concerning the relationship between depression and MI that has to be elucidated is the role of "reversed causality", meaning that depressive symptoms in some circumstances could be caused by CHD or MI itself [5]. People with severe CHD may be more likely to report depressive symptoms and this may confound the association between depression and MI especially when psychometric instruments cannot discriminate between overlapping disease symptoms. There is some evidence for the hypothesis of "reversed causality" as in a subgroup of MI patients, rate of depression and severity of depressive symptoms were significantly related to severity of left ventricular dysfunction [23] whereas in other studies this relation could not be established [11,24,25]. Furthermore, numerous studies have reported a disproportionally high prevalence of depression among CHD patients with the highest rates seen among those who recently experienced a cardiac event: 15-20% versus 7% in the stabilized phase [3,25]. Also, anxiety and depression measured two months after an acute coronary syndrome in stabilized CHD patients predict greater risk on major adverse cardiac events i.e. cardiac death, myocardial infarction, cardiac arrest, or non-elective revascularization in the 2 years after the index event [25]. It might be hypothesized that anxiety and depression scores measured shortly after an acute cardiac event reflect an autonomic stress response induced by a physical life-threatening situation. Another explanation is that severity of anxiety and depression scores partially reflects severity of cardiac disease as scientific psychometric symptom scales for depression and anxiety often include a set of somatic items [22].

Mutual pathophysiology linking MI and depressive disorder

The third issue to be considered in the relation between cardiac and affective dysfunctioning is the possibility that MI and depressive disorder are not causally related but associated by sharing the same pathophysiology (fig 1). Moreover, recently some evidence

was found that genetic variation related to endothelial dysfunction might predict depressive symptoms in cardiac patients. This suggests that biological mechanisms linking depression with CHD are based on shared genetic factors [26,27]. Irrespective of the causal relationship, several biological, psychological and behavioural mechanisms have been suggested to account for the higher than expected prevalence of depression in cardiac patients.

MECHANISMS OF ASSOCIATION

Biological factors

Biological factors that are considered to mediate the association between depressive disorder and cardiovascular disease are changes in functioning of the hypothalamic pituitary adrenal axis, heightened platelet activity, endothelial dysfunction, changes in omega-3/6 fatty acid metabolism and central serotonin neurotransmission. Cerebral alterations, inflammatory processes and changes in autonomic nervous system functioning are thought to play a role as well and will be discussed more in detail.

Neuro-imaging supports the existence of an association between depressive symptoms and white matter lesions, a form of subtle structural cerebral damage [28]. This association is especially prevalent in patients with a late life depression [29]. The dominant view is that white matter lesions reflect cerebrovascular disease predisposing a subset of older patients to the development of depressive disorder by disrupting fibre tracts connecting cortical and subcortical structures including the frontostriatal circuits that are involved in the regulation of mood [30]. This view is also known as the "vascular depression hypothesis" [31]. As MI usually occurs at older age, in most cases (incident) post MI depression can probably be considered as late life depression and might be associated with white matter lesions and therefore fits in the vascular depression hypothesis.

In experimental animal studies, MI was associated with acute subtle brain damage in the mood regulating limbic regions most likely through immune mediated processes with a prominent role for the pro-inflammatory cytokine TNF-α [32]. Analogous to these preclinical findings brain damage might occur in humans as well as a result of regular TNF-α release post MI [33,34] with the development of depressive symptoms as a possible result.

Activation of the pro-inflammatory cytokines might be involved in another way as well: it might be one of the shared pathofysiological mechanisms in both the pathogenesis of MI and (post-MI) depression. In chronic inflammation peripherally produced pro inflammatory cytokines induce expression of the same cytokines in the brain. These brain cytokines are responsible for the development of sickness behavior [35]. Symptoms of sickness behavior include depressed mood, altered cognition, fatigue and sleep disorders. These observations suggest that depression in the medically ill including severe CHD and MI may be considered a psychoneuroimmunological disorder: "the cytokine hypothesis of depression" [36]. Post MI depression might be a variant of cytokine induced sickness syndrome and according to this hypothesis effective antidepressant treatment would be accompanied by changes in signs of inflammation.

Changes in autonomic nervous system activity due to pathophysiologic changes and/or structural brain damage represent one of the potential mechanisms contributing to the higher than expected cardiac death rate in depressed post MI patients as co-occurrence of depression and arrhythmia is one of the identified high risk factors for mortality post MI [37]. Heart Rate Variability (HRV) is the normal beat-to-beat variation and represents a reproducible non-invasive method of autonomic function measurement. Over the recent

years a large body of evidence has demonstrated that reduced HRV has bad prognostic value in patients with coronary artery disease. Depressive disorder is associated with reduced HRV and has been suggested to increase the risk of arrhythmic events, due to dysregulation of the autonomic nervous system [38]. Post MI depression might be associated with reduced HRV and according to this hypothesis effective antidepressant treatment would be accompanied by changes in HRV with a tendency to normalization. Both MI and depressive disorder are associated with a reduced HRV, a negative prognostic factor on cardiac outcome. In cardiac patients, depression is related to both [39,40,41]. This relationship might be mediated by inflammation as correlations between reduced HRV and increased cytokines are found. Moreover, this negative correlation appeared to be stronger in depressed as compared to non-depressed cardiac patients [42,43].

Psychological factors

The psychological factors include stress of poor prognosis and certain personality traits. Furthermore, negative health behaviour often seen in depressive patients may account for some of the findings (Fig 3).

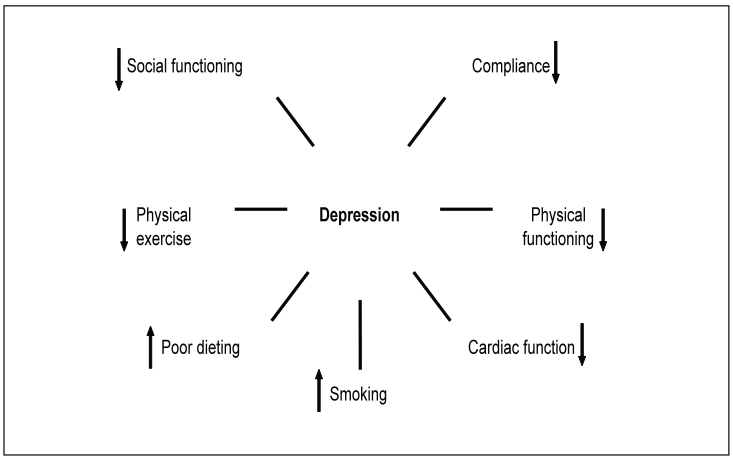


Figure 3. Depression and negative health behaviour.

TREATMENT STUDIES

During the last decades the connection between mood states and cardiovascular diseases was studied in several large-scale studies as ENRICHD [44], SADHART [45] and CREATE [46] These studies have addressed the issue whether antidepressant treatment alleviates post MI depression and reduces mortality. Most of these studies demonstrated beneficial effects among more severe and recurrent post MI major depressive disorders with efficacy rates similar to non-somatically compromised depression. In minor post MI depression antidepressant treatment demonstrated little difference in antidepressive effect compared to placebo and a relative lack of effect on cardiac mortality.
The ENRICHD study showed that Cognitive Behavioural Treatment for post-MI depression and social isolation did not have an effect on cardiac prognosis compared to Care as Usual (CAU) [44]. Neither did Interpersonal Psychotherapy affect post MI depression significantly as was demonstrated by the CREATE study [46]. In SADHART [45] and the study by Strik et al 2000 [47], antidepressant treatment with a Selective Serotonin Reuptake Inhibitor (SSRI) caused a non-significant reduction in depressive symptoms. However, since in these studies only limited effects of treatment on depression itself were reported, the question remains whether effective antidepressant treatment affects cardiovascular prognosis.
From the non-experimental studies on the cardiovascular effects of antidepressant medication, rather conflicting results emerge, with studies suggesting cardio-protective effects [48,49], no effects [50], or even cardio-toxic effects of modern antidepressant drugs [51].

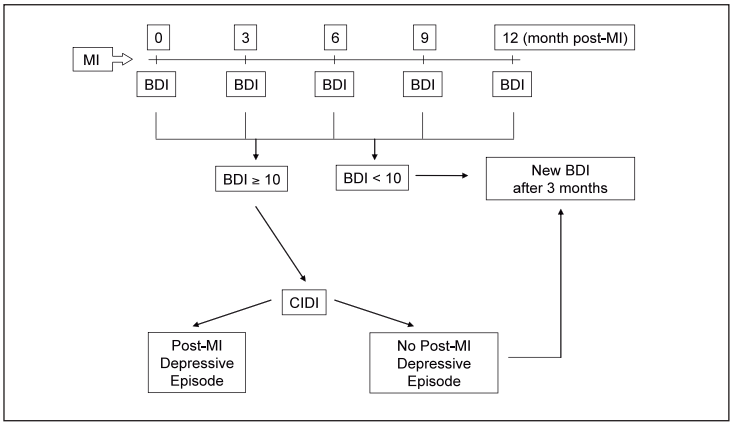
ETIOLOGICAL SUBTYPES OF POST MI DEPRESSION

Considering the observations above, the question rises whether post MI depression is a different type of depression usually seen in general psychiatry, a collection of several sub types of depressive disorder with different etiologies or merely a mix of somatic and psychological symptoms induced by cardiovascular diseases and which are difficult to differentiate from depressive disorder. The pathophysiological mechanisms underlying the association between MI and (states related to) depressive disorder are not fully known. As stated, research indicates that several mechanisms might play a role. This thesis is meant to contribute to the possible neurobiological processes in the heart brain axis that may play a role in the pathogenesis of post MI depression. Research was performed as part of a large multicenter study. Before resuming the different chapters in this thesis, background information is provided about this multicenter study.

BACKGROUND OF THE MIND-IT STUDY

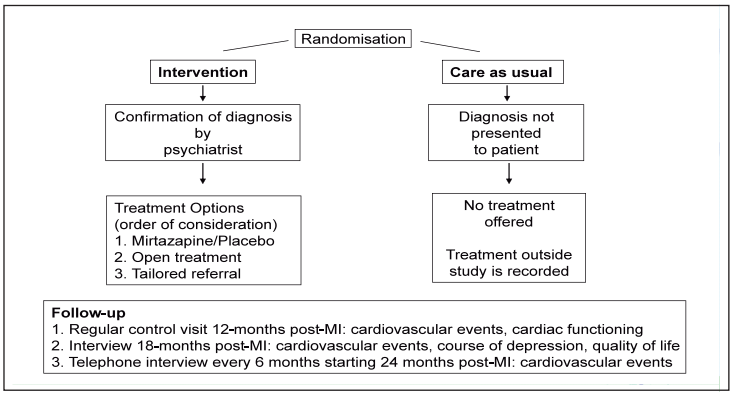
It is the aim of the Netherlands Heart Foundation's Myocardial INfarction and Depression-Intervention Trial (MIND-IT) to evaluate the influence of antidepressive treatment versus care-as-usual for post-MI depression on cardiac prognosis [52]. The MIND-IT study is a multicenter randomized clinical trial. An outline of the study is presented in Figures 4 and 5. Patients admitted with an MI are screened for depressive symptoms during hospitalization and 3, 6, 9, and 12 months after the MI with the Beck Depression Inventory (BDI) [53]. Those with symptoms (ie, a BDI score ≥10) have an additional psychiatric evaluation with a standardized psychiatric interview, the Composite International Diagnostic Interview (CIDI) [54] (Fig 4).

Figure 4. Flow chart of the MIND-IT study: screening procedure.



Patients with a research diagnosis of "post-MI depressive episode" according to ICD-10 criteria [55] on the CIDI interview are randomized to intervention or care-as-usual. In the intervention arm, the research diagnosis is to be confirmed by a psychiatrist, to permit pharmacologic intervention. First-choice treatment consists of a double-blind placebo-controlled treatment with the antidepressant mirtazapine, an antidepressant with dual action, enhancing both serotonin and noradrenaline neurotransmission. In case of refusal or nonresponse after 8 weeks, open treatment with the antidepressant citalopram, a selective serotonin re-uptake inhibitor is offered. Treatment will not start within 3 months after MI, to allow natural recovery of a transient depressive reaction. In the CAU arm, the patient is not informed about the research diagnosis. Psychiatric treatment outside the study is recorded, but no additional treatment is offered (Fig. 5). Both arms are followed for end points during an average period of 27 months. The primary end point of the MIND-IT study is the combined time-related incidence of new cardiac events (cardiac death or hospital admission for documented nonfatal MI, unstable angina, heart failure, or ventricular tachyarrhythmia). Secondary analyses will evaluate the effect of psychiatric treatment versus CAU on cardiac functioning 18 months after MI, the course of post-MI depression, and quality of life. The institutional committees on human research approved the study. All data presented in this thesis are derived from patients participating in the MIND-IT study.

Figure 5.
Flow chart of the MIND-IT study: randomisation to intervention and Care as Usual.



AIMS AND OUTLINES OF THE THESIS

In the first part of this thesis (chapter 1, 2 and 3) the effects of antidepressant treatment on post MI depression are investigated. First, the results of the 24-week, double blind, placebo-controlled trial with mirtazapine in post MI depressive patients are shown. Second, the effects of antidepressant treatment on cardiac outcome measures in the same patient cohort are described. Third, a post hoc analysis on the effects of antidepressant treatment on depressive symptoms and cardiac measures was performed and the results presented.

In the following parts the results of additional neurobiological sub studies are presented. In part 2 (chapter 4 and 5) the association between measures of cerebral damage and post MI depression is investigated. First, results on the relation between S100B, an established protein marker of cerebral damage, and depressive symptoms in the year post MI are given. Second, data from research on the association between WML and post MI depression are presented.

In part 3 (chapter 6 and 7) the association between various parameters of immune activation, post MI depression and antidepressant treatment is investigated.

In part 4 (chapter 8) data of research on the association between various parameters of heart rate variability, post MI depression and antidepressant treatment are presented.

The Epilogue gives a summary of findings and a general discussion of combined results.

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PART 1

CHAPTER 1

Treatment of Post-Myocardial Infarction Depressive Disorder: A Randomized, Placebo-Controlled Trial With Mirtazapine

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ABSTRACT

Objective. To examine the antidepressant efficacy of a dual-acting antidepressant (mirtazapine) in patients with post-myocardial infarction (MI) depressive disorder. Antidepressants used in post MI trials with a randomized, double-blind, placebo-controlled design have been restricted to selective serotonin reuptake inhibitors (SSRIs). Antidepressant effects have been limited.

Methods. In a prospective multicenter study, 2177 patients with MI were evaluated for depressive disorder during the first year post MI. Ninety-one patients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for major or minor depressive disorder were randomized to a 24-week, double-blind, placebo-controlled trial. Antidepressant efficacy was tested using last-observation-carried-forward procedure and repeated measurements analysis using the SPPS mixed models approach, with as primary outcome reduction in depressive symptomatology on the 17-item Hamilton-Depression Rating Scale (Ham-D), and secondary outcomes the Beck Depression Inventory (BDI) and depression subscale of the Symptom Check List 90 items (dSCL-90) as well as the Clinical Global Impression (CGI) scale.

Results. Using the "last observation carried forward" (LOCF) method, mirtazapine did not show to be superior to placebo on the Ham-D, but did on the BDI, dSCL-90, and CGI scale over the acute treatment phase of 8 weeks (n= 91). Using mixed models analysis over the entire 24 weeks of treatment (n= 40), we did find a significant difference favoring mirtazapine to placebo on the Ham-D, BDI, and CGI, but on the dSCL-90, this difference was not significant.

Conclusion. This trial shows efficacy of mirtazapine on primary and secondary depression measures. Mirtazapine seems to be safe in the treatment of post-MI depression.

INTRODUCTION

About 20% of post myocardial infarction (MI) patients experience a major depressive episode and an equal percentage experience a minor depressive episode in the first year post MI [1,2]. Recent data suggest that minor depressive disorder is not evanescent, and may occur independent of, or in the course of, a major depressive disorder [3,4]. Both major and minor depressive disorders post MI are associated with an increased risk of all-cause mortality, cardiac mortality, and new cardiovascular events [2]. Also, post-MI depressive disorder predicts slow recovery and poor quality of life [5–9]. Treatment refractoriness of major and minor depressive disorders is associated with increased risk for mortality after the first 6 months post MI [10]. Up to now, the efficacy of psychotherapeutic or antidepressant treatments in published randomized placebo or care as usual controlled trials in post-MI depressive disorder has been limited.

Three randomized controlled trials (RCTs) that did show at least some beneficial and statistically significant change on affective outcome parameters only included patients fulfilling the current Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for major depressive disorder, but the efficacy results are not convincing; one study showed superiority of an antidepressant over placebo on a global assessment scale [11,12] and one on hostility [13]. In a recent study in patients with coronary artery disease (CAD) and major depression, the efficacy of a selective serotonin reuptake inhibitor (SSRI), citalopram, was found to be superior to placebo in reducing 12-week Hamilton-Depression Rating Scale (Ham-D) scores [14]. However, the outcome of this study, positive as it is, refers to a different population of patients with moderate-to-severe depression at late stage after hospitalization for cardiac reasons (range = 3 weeks to 31 years; median = 18.9 months).

The choice of antidepressant drug class may well be related to efficacy, as all published placebo-controlled RCTs in post-MI depressive disorder only involved SSRIs. SSRIs are preferred because of the relative cardiotoxicity of tricyclic antidepressants (TCAs).

One might postulate that a noncardiotoxic antidepressant with both serotonergic and noradrenergic properties might be more efficacious than an SSRI in depressive disorder in the physically ill. In a comparative study of an SSRI and a TCA in depressed patients with CAD, both were found to be effective [15]. However, adverse cardiac events occurred more often in the patients treated with a TCA. Using an RCT design, the newer dual-acting antidepressants have not yet been studied in depressed patients with CAD. In an open study, mirtazapine, a nontricyclic antidepressant with presynaptic α2-antagonist properties, which enhance both noradrenergic and serotonergic neurotransmission, is well tolerated and showed no cardiotoxic effects in cardiovascular compromised patients [16].

Accordingly, we conducted a placebo-controlled RCT with mirtazapine in patients with a major and minor depressive disorder post MI. Patients could not be included during the first 3 months post MI to rule out transient adjustment disorder with depressed mood directly related to the MI. Subjects were included between 3 to 12 months post acute MI and were free of other life-threatening medical conditions. The selected patients had to fulfill the criteria for DSM-IV major or minor depressive disorder. In a 24-week trial, the primary objectives were to evaluate the safety and efficacy of mirtazapine treatment of major or major and minor depressive disorder post MI.

METHODS

The intervention study is a multicenter, randomized, placebo-controlled trial, "nested" (nested RCT) in the Myocardial Infarction and Depression-Intervention Trial (MIND-IT) [17]. The MIND-IT study is designed to evaluate the effect of psychiatric treatment versus "care as usual" in patients with a post-MI depressive disorder on the combined time-related incidence of cardiac events over an average 27-month follow-up period. More specifically, for this study, only the data on patients in the psychiatric treatment arm were evaluated. Data on "care as usual" patients were not part of this study. The Institutional Review Board at each clinical center approved the study protocol, and study patients provided written informed consent before enrollment.

Subjects

The MIND-IT study was conducted at the academic hospital of Maastricht, Amsterdam, Groningen, and seven general hospitals. Patients hospitalized with an MI were included in the study. The inclusion criteria were a) age >18 years; b) signed informed consent for study; c) a clinical picture typical for MI; d) an increase of cardiac enzymes: elevation of CK-MB of more than once the upper normal range and CK-MB/CK ratio above the local normal limit, or in case CK-MB not available, elevation of total CK of twice the upper limit range; e) electrocardiographic (ECG) changes: new significant Q waves in at least 2 of 12 leads or new in V1 with R/S ratio >1; and/or g) chest pain for >20 minutes of new or markedly increased chest pain. Exclusion criteria were a) occurrence of MI while hospitalized for another reason, except for unstable angina pectoris; b) lacking capability to participate in study procedures; c) any disease likely to influence short-term survival; d) already receiving psychiatric treatment for depressive disorder; and e) participation in any clinical trial that might intervene with the study. Patients were screened for depressive symptoms 0, 3, 6, 9, and 12 months after MI using the Beck Depression Inventory (BDI). A trained research assistant evaluated patients scoring above the cut-off on the BDI (≥10 for both men and women), which is found to be optimal in this population [18]. In case of a BDI score of ≥10, patients were invited for a standardized psychiatric interview (Composite International Diagnostic Interview, CIDI) [19]. Patients diagnosed with a post-MI depressive episode were randomized to the intervention or "care as usual" group. Patients scoring below the BDI cut-off continued to be screened for depressive symptoms. Patients randomized to intervention could only be included in the pharmacological intervention in case a psychiatrist confirmed the CIDI-research diagnosis. Exclusion criteria involved other psychiatric treatment, including psychotherapy, hypothyroidism, and suicidality. After confirmation by the psychiatrist, the first treatment option offered to patients was the doubleblind, placebo-controlled treatment with mirtazapine. The use of an RCT design worked two-fold: a) the safety and effects of mirtazapine in this population could be assessed; and b) the effect of psychiatric intervention on the cardiac prognosis in post-MI depressed patients could be evaluated with both pharmacotherapy and psychological support as separate factors. Subjects were recruited from November 1999 to November 2002. A total of 4780 subjects were assessed for eligibility, of which 2177 (46%) patients met the inclusion criteria and agreed to participate. During the screening period of 1 year post hospitalization for the index MI, 375 patients fulfilled the research diagnosis of depressive episode. From these patients, 28 were excluded due to suicide risk and 16 due to end of randomization date. In total, 331 patients were randomized (2:1, to meet the required sample sizes): 209 to the intervention group and 122 to the "care as usual" arm. Of those 209 patients, 37 refused to visit a psychiatrist, nine patients were excluded due to start of antidepressant treatment by general practitioner; in 28 patients,

a diagnosis of depressive disorder could not be confirmed by the psychiatrist and 41 patients refused participation. Three patients initially started in the nested study but dropped out after the baseline visit. Of these 108 excluded patients, depressive symptom profile and somatic characteristics did not differ from the 91 patients, who were included in the nested study. Significantly more women were excluded (Table 1).

Table 1. Baseline characteristics of study participants.

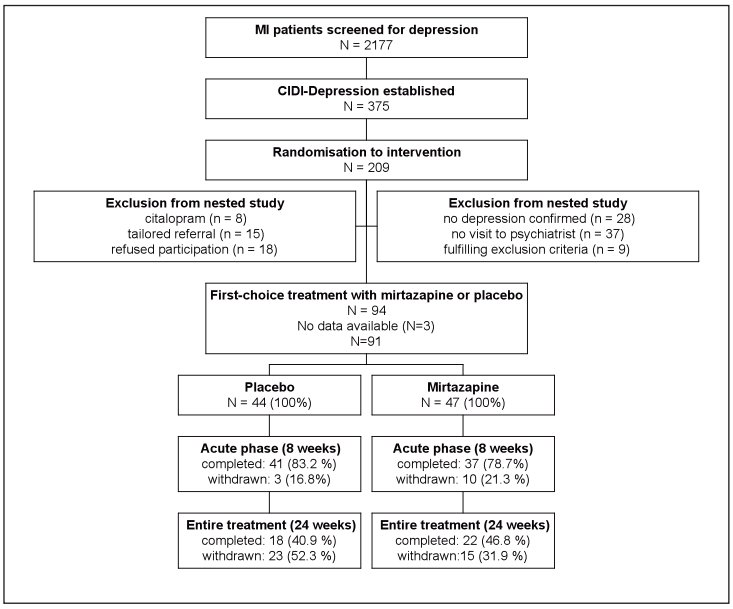
Characteristic	Included in Nested Study (n = 84)	Not Included in Nested Study (n = 121)	p[a]
Gender			
Male	86.9%	65.5%	
Female	13.1%	33.1%	.001
Age	59.16 (11.1)	57.9 (9.7)	.54
ASAT	201.8 (156.9)	198.2(178.2)	.92
CPK	1700.2 (1530.8)	1757.0 (1773.8)	.88
Ham-D	18.6 (5.2)	16.8 (3.6)	.05
Heart rate	63 (11.9)	62.8 (12.9)	.94
Killip			
Class1	91.5%	86.4%	
Class2	6.4%	11.4%	
Class3	2.1%	0%	
Class4	0%	2.3%	.75
LVEF			
> 60%	13.0%	15.4%	
45-60%	41.3%	51.3%	
30-45%	28.3%	23.1%	
< 30%	17.4%	10.3%	.45
PR interval (ms)	162.7 (31.2)	159.8 (43.7)	.72
QRS interval	93.2 (19.1)	93.1 (26.8)	.97
QT interval	404.9 (30.3)	386.5 (90.7)	.23

Values for all characteristics except for gender, Killip and LVEF are mean ± standard deviation.
[a] Baseline differences between both groups where not statistically significant, except for Ham-D.

This finding is consistent with other trials (1). Eventually, 91 patients were included in the nested RCT, having a diagnosis of DSM-IV depressive disorder, confirmed by the psychiatrist. Of these, 44 patients (39 major depressive disorder, 5 minor depressive disorder) were randomized to placebo and 47 (41 major depressive disorder, 6 minor depressive disorder) were randomized to mirtazapine (Fig 1).

Figure 1.

Flow chart of the intervention trial.



Intervention

The efficacy of mirtazapine was studied using a double blind, placebocontrolled design. Patients were randomly assigned to receive either mirtazapine or placebo. The antidepressant was prescribed for a maximum period of 24 weeks, divided in an acute treatment period of 8 weeks and a continuation treatment period of 16 weeks. Pills contained either 15 mg of mirtazapine or matching placebo. Two pills were prescribed on days 1 to 14 in the acute treatment phase. In case of severe side effects, the dose could be lowered to 1 pill, i.e., 15 mg/day. If the clinical response was insufficient (i.e., the reduction of the Ham-D total score less than 50% as compared with baseline), the investigator could decide to increase the daily dose by one additional tablet, i.e., 45 mg/day. If response was sufficient, the same dosage was given until the end of the study (day 168). Tapering down of study medication followed at the end of the trial. The oral daily dose (30 to 45 mg) of the study drug was prescribed as single nighttime dose (i.e., 30–60 minutes before bedtime). The first dose of study medication had to be taken in the evening of day 1 of treatment. At every visit, drug accountability was assessed. In case of noncompliance, patients were withdrawn from the trial. Efficacy of mirtazapine was measured for the acute phase (8 weeks, n = 78) and the entire treatment phase (24 weeks, n = 40). Responders were defined as patients with a reduction of at least 50% on the 17-item Ham-D score [20] or a Ham-D score ≤ 9. Remission was defined as Ham-D score ≤7.

Data Collection

In the first visit to the psychiatrist (week 1), the in-/exclusion criteria for treatment were evaluated. The assessment included a DSM-IV checklist for depressive disorders, medical history taking on relevant somatic and psychiatric disorders, and pretrial medication. Laboratory screening involved electrolytes, blood cells and thyroid function. Further vital signs such as blood pressure, heart rate, body weight, and height were measured. During the trial, seven visits were scheduled at baseline, 1, 2, 4, 8, 16, and 24 weeks after ran-

domization. Depression, adverse events, side effects, concurrent medication, vital signs, and Clinical Global Impression (CGI) scale were assessed every visit. Depression severity was assessed using the Ham-D. All psychiatrists were trained in assessing the Ham-D to enhance rating quality. Secondary outcome was measured with the BDI and the depression scale of the Symptom Check List 90 items (dSCL-90) [21]. The CGI was used to evaluate global clinical impression and improvement. To determine safety of treatment, ECG variables were used. Twelve lead ECG variables were heart rate, PR interval, QRS interval, and QT interval. These measures were assessed at baseline, 8, and 24 weeks. As an extra compliance monitoring, in the second week of drug treatment, a blood sample was taken for measurement of mirtazapine level. The analyses of these data were not done until all patients had finished the trial, to prevent the risk of deblinding before the trial ended. Of the 47 patients randomized to mirtazapine, a blood sample was taken on 33 patients. Of 14 patients, the blood sample data were not available due to drop out of treatment before sampling (n= 9) or missing (n= 5). A plasma level of mirtazapine = 0.5 ng/ml (standard deviation (SD)=17.98) was detectable in all patients allocated to mirtazapine from whom a blood sample had been obtained.

Statistical Analyses

To estimate the required sample size, the method of Knapp and Miller [22] was used. In the absence of previous outcome data, these guidelines recommend to estimate the SD by dividing the range of values of the response variable by 6. The mean range of the Ham-D 17 item is 26. An effect size of 2.5-point difference between the mirtazapine and placebo group and a statistically significant difference in response rate was expected a priori. When the level of significance α is set at 0.05, the power β at 0.80, and the hypotheses are tested two tailed, the required sample size is 89. For statistical analyses, SPSS (SPSS Inc, Chicago, IL) for Windows 11.0 software (Microsoft Corp, Redmond, WA) was applied. Efficacy outcome was analyzed on an intention-to-treat basis and so 91 patients who received medication (mirtazapine or placebo) were analyzed. For patients not completing the entire trial, the "last observation carried forward" (LOCF) technique was used. Before carrying out parametric analysis, dependent variables were checked for normality (skewness/kurtosis) and the presence of outlying values, thereby following the lines described by Hair and associates [23]. GLM repeated measures were used to analyze the standardized effect size (SES) of mirtazapine in comparison to placebo. In addition, we applied a repeated measurements analysis using the SPSS mixed models approach; outcomes were assessed repeatedly during follow-up (1, 2, 4, 8, 16, and 24 weeks post randomization for Ham-D; 8 and 24 weeks post randomization for BDI and dSCL-90). Optimal use is made of the available data at the repeated assessments, which are clustered within subjects. We developed mixed models consisting of treatment allocation as a factor, and the corresponding baseline variable and timing of the assessment as covariates.

RESULTS

There were no statistically significant baseline differences between the mirtazapine and placebo groups in age, gender, size of MI (using maximum ASAT), and cardiac status (using Killip Class) (Table 2).

Table 2. Baseline Characteristics of Included Patients.

Characteristic	Mirtazapine Group (N = 47)	Placebo Group (N = 44)	p[a]
Gender			
Male	87.2%	81.8%	
Female	12.8%	18.2%	.34
Age	56.6 (11.1)	57.9 (9.7)	.54
ASAT	201.8 (156.9)	198.2(178.2)	.92
CPK	1700.2 (1530.8)	1757.0 (1773.8)	.88
Ham-D	18.6 (5.2)	16.8 (3.6)	.05
Heart rate	63 (11.9)	62.8 (12.9)	.94
Killip			
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Class3	2.1%	0%	
Class4	0%	2.3%	.75
LVEF			
> 60%	13.0%	15.4%	
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QT interval	404.9 (30.3)	386.5 (90.7)	.23

Values for all characteristics except for gender, Killip and LVEF are mean ± standard deviation.
[a] Baseline differences between both groups where not statistically significant, except for Ham-D.

During the first 8-week acute treatment phase, 10 patients from the mirtazapine group and 3 from the placebo group dropped out, which is significant (c2 4.80; df= 1; p= .03).

Concurrent Medication

Medications used concurrently were acetylsalicylic acid (n= 76; 92.7%), acenocoumarol (n= 5; 5.4%), nitrate (n=34; 37%), β-blocking agents (n= 71; 86.6%), calcium-antagonists (n= 18; 22%), digoxin (n= 1; 1.2%), diuretics (n=11; 12%), ACE-inhibitors (n= 26; 31.7%), AII-antagonists (n= 5; 6.1%), and statins (n= 70; 76.1%). The median number of cardiovascular drugs taken was 4 (range = 2–7).

Overall, there was no difference in specific drugs between groups (p= .71). However, in those receiving mirtazapine, ACE-inhibitors were significantly more frequently prescribed (p= .05). The β-blockers were prescribed significantly more frequently (p= .03) to patients receiving placebo.

Efficacy During the Acute Phase

The mean Ham-D score in the acute phase (8 weeks) decreased 7.29 points (SES = 1.30) in the mirtazapine group and 5.31 points (SES = 0.96) in the placebo group. At baseline, there was a difference of 1.85 points on the Ham-D scale, the mirtazapine group showing a higher score. After correcting for baseline difference in depression scores, the difference of 1.98 points between both groups was not statistically significant (F = 2.86; df = 1; p =.09). Twenty-seven patients in the mirtazapine group (n = 47) and 18 patients in the placebo group (n = 44) were responders. This difference was not statistically significant

(χ^2 = .78; df=1; p=.18). Sixteen patients taking mirtazapine showed remission (Ham-D score = 7) in comparison to seven patients taking placebo. This difference was not significant (χ^2 = 3.17; df= 1; p= .08) (Table 4). The mean BDI score during the acute phase decreased 4.6 points (SES = 0.68) for the mirtazapine group and 1.72 points (SES = 0.39) for the placebo group. This difference was statistically significant (F = 5.51; df = 1; p = .02). The mean dSCL-90 depression score for the mirtazapine group decreased with 6.6 points (SES = 0.67). The depression score for the placebo group decreased 2.23 points (SES = 0.38). The difference between the mirtazapine and placebo group was statistically significant (F= 6.48; df =1; p= .01). The CGI severity during the first 8 weeks decreased 1.41 points (SES = 1.69) for the mirtazapine group and 0.72 points (SES = 0.89) for the placebo group. This difference was statistically significant (F = 6.67; df = 1; p = .012) The CGI improvement score decreased for subjects receiving mirtazapine 1.03 points (SES = 1.34) during the acute phase and 0.45 points (SES = 0.51) for subjects receiving placebo. This difference was not significant (F = 3.65; df = 1; p = .06).

Efficacy During the Entire Treatment Phase

From baseline to week 24, the Ham-D score decreased 8.0 points (SES = 1.21) for the mirtazapine group and 5.56 points (SES = 0.78) for the placebo group.

Table 3.
Scores on the Depressive Symptom Rating Scales and Clinical Global Impression Scale During the Entire Trial Using LOCF and Mixed Models

Week	0	1	2	4	8	16	24	mm [a]
Mean Ham-d score								
Mirtazapine	18.66	15.82	13.68	12.23	11.37	11.15	10.66	10.38
Placebo	16.81	14.22	13.35	11.91	11.50	10.99	11.25	11.77
Mean BDI score								
Mirtazapine	14.61				10.01		9.79	9.68
Placebo	13.44				11.72		11.47	12.29
dSCL-90 score								
Mirtazapine	34.32				27.72		27.41	23.70
Placebo	30.29				28.06		28.47	26.00
Mean CGI score								
Mirtazapine	4.0	3.73	3.34	3.07	2.59	2.59	2.50	2.79
Placebo	3.79	3.53	3.44	3.07	3.07	2.95	2.91	3.06

LOCT _ "last observation carried forward"; BDI _ Beck Depression Inventory; dSCL-90 _ Symptom Check List 90 items, depression subscale; CGI _ Clinical Global Impression. a Overall follow-up means based on mixed models

Table 4.
Difference in SES Using LOCF and Mixed Models Analyses.

Scale	Effect Size Mirtazapine	Effect Size Placebo	Difference in s.e.s	p
Mirtazapine versus placebo (8 weeks) using LOCF				
Ham-D	1.30	0.96	0.34	.09
BDI	0.68	0.39	0.28	.02
SCL-90	0.67	0.38	0.33	.01
CGI	1.23	0.55	0.49	.10
Mirtazapine versus placebo (24 weeks) using LOCF				
Ham-D	1.21	0.78	0.43	.36
BDI	0.64	0.36	0.28	.07
SCL-90	0.65	0.32	0.33	.02
CGI	1.80	1.09	0.71	.05
Mirtazapine versus placebo (24 weeks) using LOCF				
Ham-D	1.60	1.40	0.20	.003
BDI	0.73	0.15	0.58	.05
SCL-90	1.08	0.73	0.35	.11
CGI	1.45	0.90	0.55	.007

Figure 2. Effects of mirtazapine versus placebo in post-myocardial infarction depressive disorder, measured with Hamilton-Depression Rating Scale (Ham-D 17) (entire treatment phase).

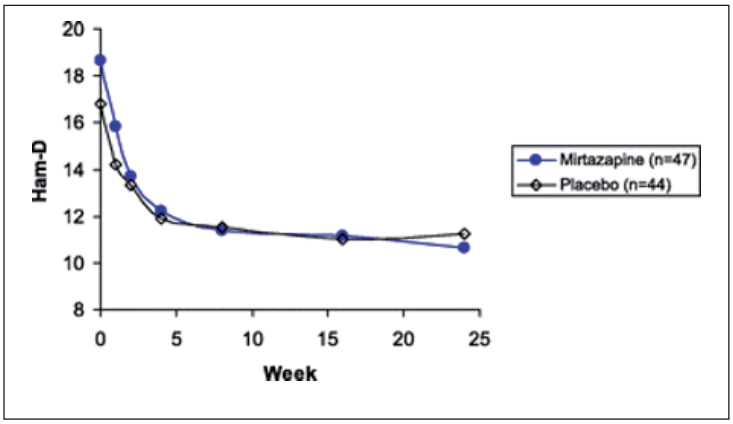
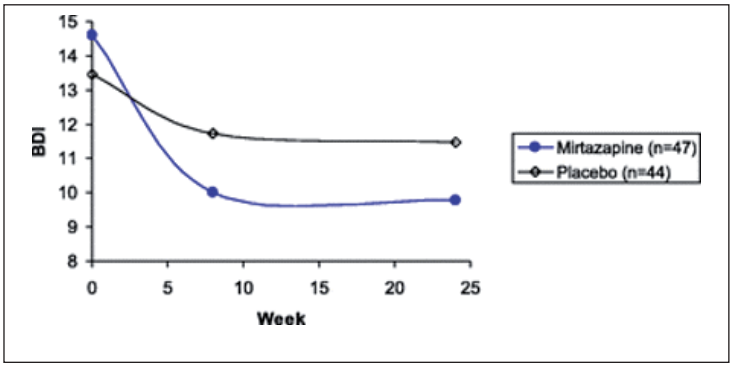


Figure 2. Effects of mirtazapine versus placebo in post-myocardial infarction depressive disorder, measured with Beck Depression Inventory (BDI) (entire treatment phase).



This difference of 2.44 points was not significant (F =1.11; df = 1; p =.36). Over the entire treatment phase, 23 patients receiving mirtazapine and 17 receiving placebo responded. A _2 test showed no significant difference (p = .22). Twenty patients taking mirtazapine showed remission (Ham-D score of =7), compared with 15 patients taking placebo. This difference was not significant (p = .27). Mean BDI scores showed a trend toward a decrease (F=2.73; df =1; p = .07) for the mirtazapine (4.82 points; SES =0.64) and placebo group (1.97 points; SES = 0.36). The mean dSCL-90 depression scores over 24 weeks decreased 6.91 points (SES = 0.65) for the mirtazapine and 1.82 points (SES = 0.32) for the placebo group. Comparable with the acute phase, this difference was found to be significant (F = 3.88; df = 1; p = .02). The CGI severity during the entire treatment decreased 1.5 points (SES = 1.80) for the mirtazapine group and 0.88 points (SES = 1.09) for the placebo group. This difference was significant (F = 3.87; df =1; p = .05) The CGI improvement score decreased for subjects receiving mirtazapine 1.03 (SES = 1.34) points during the entire treatment phase and 0.42 points (SES = 0.47) for subjects receiving placebo. This difference was not statistically significant (F =3.27; df = 1; p = .074)

Mixed models analysis revealed a significant difference of 3.24 points on the Ham-D (F = 9.039; p = .003) favoring mirtazapine to placebo, controlling for baseline Ham-D and timing of the outcome assessment. The estimated Ham-D follow-up means were 10.38 (standard error 0.33) for patients receiving mirtazapine and 11.77 (standard error 0.33) for patients receiving placebo.

This analysis also showed a significant difference on the BDI (F = 4.026; p= .05) favoring mirtazapine to placebo, controlling for baseline Ham-D and timing of the outcome assessment. The estimated BDI follow-up means were 9.68 (s.e. 0.89) for patients receiving mirtazapine and 12.29 (s.e. 0.94) for patients receiving placebo. Using mixed models analysis, however, there was only a nonsignificant difference on the dSCL-90 depression score (F = 2.6; p =.11) controlling for baseline Ham-D and timing of the outcome assessment. The estimated dSCL-90 depression follow-up means were 23.7 for patients receiving mirtazapine and 26.0 for patients receiving placebo. Mixed models shows a significant difference on the CGI (F = 7.4; p =.007). Follow-up means were 2.79 in patients receiving mirtazapine and 3.06 in patients receiving placebo.
In our study, treatment effects did not differ when controlled for history of depression (acute phase: F=3.9; df=1; p=.052; entire treatment phase: F = 2.01; df =1; p= .16).

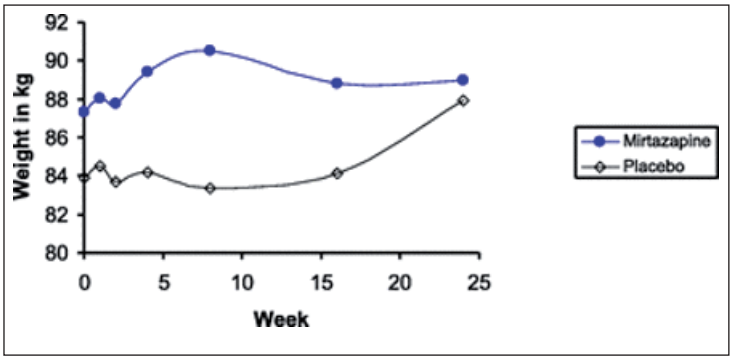
Adverse Effects and Events During the Entire Treatment

Patients from both the mirtazapine (n = 47) and placebo groups (n = 44) reported adverse effects. Most reported complaints were fatigue, appetite changes, dizziness, and headache. These adverse events are comparable with adverse events reported for mirtazapine in psychopharmacological manuals. Serious adverse events reported were heart failure (n = 1), angina pectoris (n = 1), and atrial fibrillation (n = 1) in the mirtazapine group and angina pectoris (n= 1) in the placebo group. No patients were excluded from the study because of cancer, drug overdose, or death during the study. Reasons for hospitalization were unstable angina pectoris, shortness of breath, palpitations, and revascularization (coronary angioplasty or bypass surgery). Number of hospitalizations was 10 in the placebo group and 8 in the mirtazapine group, which was not statistically significant (p = .34) (Table 5). Blood pressure and heart rate did not differ between the two groups. Mirtazapine increased the mean weight by 1.7 kg (p =.0001) within the first 8 weeks; in the placebo group, the weight did not change significantly; there was a slight decrease at 16 weeks (Fig. 4).

Table 5. Number of Adverse Events and Hospitalization of Mirtazapine Versus Placebo.

Adverse effect	Mirtazapine Group (N = 47)	Placebo Group (N = 44)	p
Fatigue	21	9	.016
Appetite Changes	13	3	.015
Dizziness	5	8	.31
Headache	7	2	.612
Other	69	67	
Hospitalization	8	10	.34

Figure 4. Weight curves mirtazapine versus placebo.



Adverse Cardiovascular Effects

The ECG variables heart rate, PR duration, QRS duration, and QTc interval did not show any significant changes during the treatment phase.

DISCUSSION

This trial, embedded in the MIND-IT study, is, to our knowledge, the first randomized, placebo-controlled trial on the efficacy of a novel dual-acting antidepressant (mirtazapine) compared with placebo in patients with post-MI minor and major depressive disorder. Randomization resulted in comparability of both groups as far as demographic data, physical health status, number of major and minor depression diagnoses, severity of MI, and somatic characteristics are concerned. At baseline, there was a difference of 1.85 points on the Ham-D scale, the mirtazapine group showing a higher score. In this study, the primary measure used to compute effect sizes was Ham-D. Using LOCF statistical procedures after correcting for baseline differences in Ham-D, we did not find statistically significant changes in the Ham-D scores at 8 and 24 weeks of treatment (primary outcome measure). On secondary measures, however, we did find statistically significant improvement on self-report rating scales (BDI 21-item, depression subscale of the dSCL-90, and CGI). Mirtazapine compared with placebo resulted in a significant greater decrease in BDI and dSCL-90 scores over 8 and 24 weeks of treatment and after 8 weeks on the CGI. To increase statistical power of the study, we also applied mixed models statistical procedure. After correcting for baseline differences in Ham-D, we did find a significant difference favoring mirtazapine to placebo on the Ham-D, BDI, and CGI, but not on the dSCL-90.

The effect size of mirtazapine in this patient population exceeds that in patients with similar mild depression in physically healthy depressed patients [24]. Judd et al. described an SES at 12 weeks of 1.19 versus 1.70 at 8 weeks of our study. Our effect size is also comparable with the recently reported effect size in major depressed patients with CAD [14]. This may indicate that a dual-acting antidepressant is at least as effective as an SSRI. Our placebo effect size, however, was much higher than that of Judd's group (1.59 versus 0.61). This high placebo effect is comparable with other studies in post-MI depression [9,12]. The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study [10] investigated whether treating post-MI depression and social isolation by means of cognitive behavioral therapy affected cardiac prognosis.

Only small effects on depressive symptoms after 6 months (SES = 0.2– 0.3) were reported. Moreover, although treated patients had a significant improvement in depressive symptoms at 6 months, usual care patients improved almost as much. Similarly, the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) study [12] reported that sertraline treatment for patients with post-MI depression had no or only small short-term antidepressive effects compared with placebo (SES = 0.1– 0.2). Differences in effect sizes, comparing treatment versus placebo, were between 0.3 and 0.5 in the nested RCT of the MIND-IT study. Our efficacy findings are at least comparable with those of the SADHART and ENRICHD studies.

There are some limitations in this study that might have resulted in the modest efficacy outcome. First, the inclusion of different subtypes of depression (minor depressive disorder and mild major depressive disorder) might have affected the statistical significance of the improvement on the 17-item Ham-D. Second, despite specific training in the use of the Ham-D to minimize interrater variability, a significant difference in Ham-D responder scores at 24 weeks between sites was found ($c2 = 6.84$; $df = 2$; $p= .03$). Because there is no reason to expect a difference in the severity of depression between the participating centers, we believe that both differences in Ham-D scores and moderate significant effect size may be related to interrater variability.

Third, because of the long duration of our trial (24 weeks), patients in both drug and placebo groups tended to improve with time, which may have obscured differences at the end of 24 weeks. Since the mirtazapine group had a 2 point higher HAMD-score than the placebo-group at baseline, potential regression to the mean might be responsible for the significant effect at 24 weeks favoring mirtazapine. However, correcting for baseline difference in all efficacy analyses, as we have done, may have dealt with this problem appropriately. Furthermore, although included and excluded patients did not differ on most parameters, they differed in gender. Significantly more women were excluded. This might hamper generalizability of our findings.

Concurrent medication use between groups was not different except that patients in the mirtazapine group were prescribed significantly more ACE-inhibitors compared with the placebo group during the trial. The placebo group used b-blocking agents more often. Based on our data, a clear pharmacological rationale for these differences in use of ACE inhibition and b blockers prescribed in the course of treatment cannot be given.

Mirtazapine proved to exhibit no significant cardiac changes as far as ECG variables was concerned. Weight increased 1.7 kg in the first 8 weeks of treatment with mirtazapine. Patients from both groups reported adverse effects.

The difference in number of hospitalizations was not statistically significant. Mirtazapine is found to be safe in the treatment of this patient population. Besides SSRIs that have proven efficacy and safety in other trials, mirtazapine should be considered in the treatment of patients with major or minor depression in the first year post MI. These data may help the clinician to safely reduce depression in the post MI period and aim for improvement of cardiac outcome.

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PART 1

CHAPTER

2

Effects of antidepressant treatment following myocardial infarction.

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ABSTRACT

Objective. Depression following myocardial infarction is associated with poor cardiac prognosis. It is unclear whether antidepressant treatment improves long-termdepression status and cardiac prognosis. In this study it was the aim to evaluate the effects of antidepressant treatment compared with usual care in an effectiveness study.
Methods. In a multicentre randomised controlled trial, 2177 myocardial infarction patients were evaluated for ICD-10 depression and randomised to intervention (n=209) or care as usual (n=122). Both armswere evaluated at 18 months post-myocardialinfarction for long-termdepression status and new cardiac events.
Results. No differenceswere observed between intervention and controlgroups In mean scores on the Beck Depression Inventory (11.0, s.d.=7.5 v.10.2, s.d.=5.1,P=0.45) or presence of ICD-10 depression (30.5 v. 32.1%, P =0.68).The Cardiac event rate was 14% among the intervention group and 13% among controls (OR=1.07,95% CI 0.57-2.00).
Conclusion. Antidepressant treatment did not alter long-term depression post-myocardial infarction status or improve cardiac prognosis.

INTRODUCTION

Depression is one of the most potent psychosocial risk factors for a poor cardiovascular prognosis after myocardial infarction [1]. A recent meta-analysis [2] showed that depression postmyocardial infarction was associated with a 2- to 2.5-fold increased risk for all-cause mortality, cardiovascular mortality and cardiovascular events. In addition, depression post-myocardial infarction is a major cause of incomplete recovery [3], poor quality of life [4], delayed return to work [5], non-adherence [6], and non-attendance at cardiac rehabilitation [7]. It is estimated that approximately 1 out of 5 patients has depression post-myocardial infarction [8]. Two intervention studies have assessed the effects of treatment of depression postmyocardial infarction. In the Enhancing Recovery in Coronary Heart Disease study (ENRICHD), the effects of cognitive–behavioural therapy (CBT) on depression and cardiac prognosis was evaluated [9]. In this large trial, no significant difference in cardiac outcomes was found between the intervention and the care as usual arms. Although substantial improvement in depression status was observed 6 months after initiation of CBT, the difference between the arms diminished over time and was no longer present after 30 months. The SADHART study [10] found sertraline to be a safe treatment for depression post-myocardial infarction, but there was little difference in depression status between groups receiving sertraline and placebo after 24 weeks of treatment. However, the effect of sertraline was greater in the patients with severe and recurrent depression. The study was not designed to assess the effects of treatment on cardiovascular prognosis, but severe cardiovascular events during the 6-month treatment tended to be less frequent in the sertraline group. The effects of sertraline on long-term depression status were not evaluated. Thus, little is known about the effects of treatment for depression post-myocardial infarction on either long-term depression status or cardiac prognosis. We have conducted the Myocardial INfarction and Depression – Intervention Trial (MIND–IT) in order to determine, using a randomised controlled design, whether antidepressant treatment for depression post-myocardial infarction improves long-term depression status and cardiovascular prognosis [11]. The MIND–IT is an effectiveness study rather than an efficacy study, and compares the effects of an active treatment strategy with usual care.

METHODS

Study participants

The inclusion and exclusion criteria for this trial have been described previously [11]. In brief, consecutive patients (September 1999 to November 2002) hospitalised for acute myocardial infarction were recruited from ten hospitals (including three tertiary centres) located in different parts of The Netherlands. Patients were enrolled if they met the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (WHO MONICA) criteria [12] for definite myocardial infarction: increased cardiac enzymes and either electrocardiographic changes or chest pain. Patients were excluded if the index myocardial infarction occurred during a hospitalisation for another medical condition (except for unstable angina pectoris), if they were unable to participate in study procedures (e.g. unable to communicate or not available for follow-up), had any other disease likely to influence short-term survival, were already receiving psychiatric treatment for depression, or were participating in another clinical trial.

The institutional review board at each clinical centre approved the study protocol and all patients provided written informed consent before enrolment. In the study information pack it was emphasised that, although all participating patients were to be screened for depression, antidepressant treatment would be offered only to a random sample of patients and all were -free to seek help for mood problems.

Design of the study

Patients admitted with an acute myocardial infarction were screened for depressive symptoms during hospitalisation and at 3, 6, 9 and 12 months post-myocardial infarction, using the Beck Depression Inventory (BDI) [13]. Those with depressive symptoms (i.e. BDI score 510) underwent a psychiatric evaluation using the WHO Composite International Diagnostic Interview (CIDI auto version 2.1;World Health Organization, 1990) [14]. The first CIDI interviews were performed at least 3 months post-myocardial infarction to allow natural recovery of depressive symptoms following a major life event. Both screening tools are widely used and their feasibility and reliability have been described elsewhere [15,16]. Patients with a research diagnosis of 'current depressive episode' [17] according to ICD–10 (further: 'depression') were randomised (1:1) to antidepressant treatment or care as usual. The assignment was carried out at the Trial Coordination Centre in Groningen with the use of computer-generated permuted blocks of four, stratified according to clinical site and time of onset of depression (within 6 months v. 6 months or more post-myocardial infarction). Because the number of patients actually treated with antidepressants was lower than expected, the randomisation ratio was changed to 2:1 on 14 March 2001. Patients with a significant risk of suicide were excluded from randomisation and referred for treatment outside the study. To compare both strategies, we used the Zelen design [18]: patients allocated to the 'care as usual' arm were not informed about their research diagnosis of depression to avoid influencing usual care. Data management was independently performed at the Trial Coordination Centre, Groningen, The Netherlands.

Baseline variables

Data were collected on demographics, medical history, clinical variables and medication use during hospitalisation for the index myocardial infarction. The cumulative burden of medical comorbidity was assessed with a modified version of the Charlson Comorbidity Index [19]. Higher scores on this scale indicate more comorbidity. To account for a possible relationship between depression post-myocardial infarction and cardiac disease severity, the following parameters of risk stratification were assessed: Killip class at

admission, maximum values of serum aspartate transaminase during hospitalisation, left ventricular ejection fraction (as measured by either echocardiography or radionuclide ventriculography) and wall motion score index (WMSI) according to the recommendations of the American Society of Echocardiography [20]. Independent analysis was performed at the core echocardiography laboratory by technicians who were unaware of the patients' randomisation status.

Antidepressant intervention

The MIND–IT study was designed as an effectiveness study comparing active antidepressant treatment with usual care. In the intervention arm, the research diagnosis provided by the CIDI interview was confirmed by a psychiatrist prior to the patient starting antidepressant treatment. Several treatment modalities were possible. Flexibility in treatment was permitted because the main research question was whether implementing any active depression treatment strategy would be associated with better outcomes than usual care in which antidepressant treatment is almost negligible [21]. However, allocation to these modalities was strictly defined in the protocol. First-choice treatment was double-blind placebo-controlled treatment with the selective noradrenaline reuptake inhibitor mirtazapine (a nontricyclic, presynaptic a2-antagonist, which enhances both noradrenergic and serotonergic neurotransmission [22]. In case of refusal or insufficient treatment response after 8 weeks, open treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram was offered [23]. Sufficient treatment response was defined as at least 50% reduction on the Hamilton Depression Rating Scale (HDRS) [24] compared with baseline score or a HDRS score at 8 weeks of 49. Thus, patients who were initially treated with placebo and who did not improve within 8 weeks were subsequently treated with an SSRI. The third option was 'tailored treatment' which was at the discretion of the clinical psychiatrist (e.g. SSRI, psychotherapy, etc.). Patients were scheduled to visit the psychiatrist on average once a month during the treatment period of 6 months. In the care as usual arm, psychiatric treatment outside the study was recorded but no treatment was offered by the MIND–IT investigators. Whether the patient was referred for cardiac rehabilitation was left to the discretion of the patient's cardiologist (who was masked to the psychiatric screening results).

Long-term depression status and quality of life

At approximately 18 months postmyocardial infarction, the course and outcome of the depressive episode was assessed in a CIDI interview. The BDI was administered to evaluate the severity of depressive symptoms. In addition, health-related quality of life was assessed with the RAND 36-item Health Survey, which consists of 36 items organised into eight scales [25,26]. Somatic health complaints were assessed with the Health Complaints Scale (HCS), a self-report measure to assess common health complaints in patients with coronary heart disease [27]. Disability was assessed according to Broadhead et al (1990) [28]. Patients were asked to indicate with a time frame of the past month: 'how many days were you not able to do your daily activities (for example your work, housework, studies, leisure activities) owing to physical or emotional problems?' and 'apart from the above, on how many days were you able to do your daily activities for less than half of the time owing to physical or emotional problems?' Both complete and partial disability were categorised as having been present for either less than 1 week or for 1 week or more during the previous month.

Cardiac events

The occurrence of any significant cardiac event served as the primary end-point for the study. Cardiac events included cardiac death or hospital admission for documented non-fatal myocardial infarction, myocardial ischaemia, coronary revascularisation (coronary angioplasty or bypass surgery), heart failure or ventricular tachycardia occurring in the time between randomisation and 18 months postmyocardial infarction. Time to follow-up (6–15 months) depended on the time of randomisation (range 3 months to 12 months post-myocardial infarction). Other cardiac-related hospital admissions (defined as admissions with an initial evaluation by a cardiologist or hospitalisations at the cardiology ward) were considered as secondary end-points. Potential end-points were recorded at 12 months and 18 months post-myocardial infarction, and were reviewed and classified according to prespecified, established criteria [29] by an independent end-point committee that was unaware of patients' treatment assignments. Discrepancies were discussed until agreement was reached.

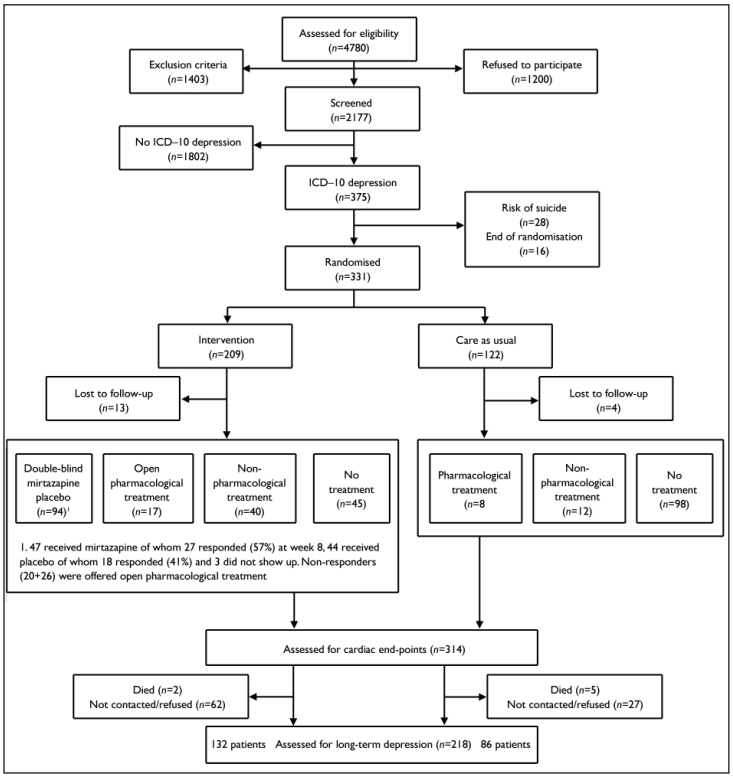
Statistical analysis

Study power was calculated for long-term depression outcomes and cardiac events. With respect to the long-term depression status, a sample of 320 randomised patients would result in a study power of 80%, assuming a drop-out rate of 20% and a small-to-medium effect size (0.35). With respect to cardiac events, we expected a 12-month incidence of 38% for patients with depression and 19% for patients without depression [30]. If psychiatric treatment could reduce the risk for patients with depression from 38 to 25% (i.e. reduction of the attributable risk by two-thirds), 190 patients in the intervention arm and 130 in the care as usual arm would give a statistical power of 0.84 to detect this effect with a log-rank test (a=0.05). t-tests were used to compare normally distributed continuous variables and the c2-test was used to compare categorical data. Time-to-event data were analysed with the Kaplan–Meier method and differences between care as usual and intervention groups in the incidence of cardiac events were assessed with the log-rank test. Outcome data were considered at 18 months post-myocardial infarction, the time of last contact, withdrawal from the study, or at the time of a primary endpoint. All P values were two-tailed.

RESULTS

A total of 4780 myocardial infarction patients were assessed for eligibility (Fig.1). Of these, 1403 (29%) met one or more exclusion criteria, and of the excluded patients, 104 were receiving treatment for depression (see Table 1 for reasons for exclusion). Of the 3377 remaining patients, 1200 refused to participate and 2177 were included (64%).

Figure 1. CONSORT diagram.



During the screening period from 3 to 12 months post-myocardial infarction, 375 patients (17.2%) met the ICD–10 criteria for depression. After exclusion of potentially suicidal patients (n=28) and patients who were diagnosed with depression after randomisation was closed (n=16), 331 patients were available for randomisation. The intervention (n=209) and care as usual (n=122) arms did not differ with respect to demographics, depressive symptoms during hospitalisation (BDI score), risk factors for coronary artery disease and important prognostic variables such as WMSI and comorbidity (Table 2). In addition, there were no differences with respect to ICD–10 depression characteristics (Table 3). Seventeen patients (5%) were lost to follow-up.

Table 1. Reasons for exclusion of 1403 patients from trial.

Reason for exclusion	n
Myocardial infarctionwhen patientwas hospitalised for another reason	82
Patient not able to communicate	99
Decreased cognitive function	112
Patient not available for follow-up/transfer to other hospital	243
Other reasons	379
Any disease likely to influence short-termsurvival	87
Already receiving psychiatric treatment for a current depression episode	104
Participation in other clinical trial	297

Table 2. BMI, bodymass index (kg/m^2);CAD, coronary arterydisease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary arterybypass grafting; LVEF1/4Leftventricular ejection fraction; ASAT, serumaspartate transaminase; WMSI, WallMotion Score Index; ACE, angiotensin converting enzyme.

[1] Current smoker or stopped smoking less than 3months.

Variable	Intervention group (n=209)	Care as usual group (n=122)
Age, yearsmean: (s.d.)	58.6 (11.5)	57.5 (10.6)
Male gender, n (%)	159 (76)	90 (74)
BMI ≥ 25, n (%)	129 (62)	75 (63)
BDI score during hospitalisationmean: (s.d.)	11.9 (7.2)	11.7 (6.4)
Diabetesmellitus, n (%)	30 (14)	15 (12)
Hypertension, n (%)	73 (35)	43 (35)
Dyslipidemia, n (%)	174 (84)	103 (84)
Family history of CAD, n (%)	104 (51)	62 (52)
Smoking, n (%) [1]	113 (54)	63 (52)
Previousmyocardial infarction, n (%)	32 (15)	22 (18)
Killip class52, n (%)	28 (13)	18 (15)
Charlson (21) category ≥3, n (%)	30 (15)	15 (12)
Qwavemyocardial infarction, n (%)	135 (65)	81 (68)
Resuscitation, n (%)	18 (9)	17 (14)
Thrombolysis, n (%)	72 (35)	55 (46)
PTCA, n (%)	96 (46)	60 (49)
CABG, n (%)	10 (5)	5 (4)
Medication at discharge, n (%)		
Acetylsalicylic acid	172 (83)	109 (90)
Acenocoumarol	28 (14)	4 (12)
Nitrate	74 (36)	48 (40)
Beta-blocker	178 (86)	102 (84)
Calciumantagonist	39 (19)	24 (20)
Diuretics	39 (19)	16 (13)
ACE inhibitor	79 (38)	53 (44)
Statin	162 (78)	98 (81)
ASATmax ,mmol/lmean: (s.d.)	203 (175)	240 (235)
LVEF ≥60%, n (%)	28 (15)	17 (15)
LVEF 45-60%, n (%)	79 (42)	49 (44)
LVEF 30-45%, n (%)	49 (26)	28 (25)
LVEF <30%, n (%)	32 (17)	18 (16)
WMSImean: (s.d.)	1.53 (0.46)	1.57 (0.43)

Table 3. Characteristics of depression in the intervention and care as usual groups.

	Intervention group (n=209) n (%)	Care as usual group (n = 122) n (%)
Early-onset depression[1]	167 (80)	96 (80)
Recurrent depression	45 (22)	28 (23)
Severity according to ICD-10 criteria		
Mild	65 (31)	36 (30)
Moderate	98 (47)	58 (48)
Severe	46 (22)	28 (23)

[1] Within 3months of myocardial infarction.

Table 4. Depression status and quality of life at18months post-myocardial infarction.

	Intervention group	Care as usual group
ICD-10 depressive disorder, %	30.5	32.1
BDI score: mean (s.d.)	11.0 (7.5)	10.2 (5.1)
Complete disability (57 days during pastmonth), %	30.5	33.3
Partial disability (57 days during pastmonth), %	28.2	26.7
HCS score: mean (s.d.)	13.4 (9.1)	14.6 (9.8)
Physical health (RAND-36) score: mean (s.d.)	39.5 (6.0)	39.5 (5.7)
Mental health (RAND-36) score: mean (s.d.)	44.5 (8.1)	43.4 (8.0)

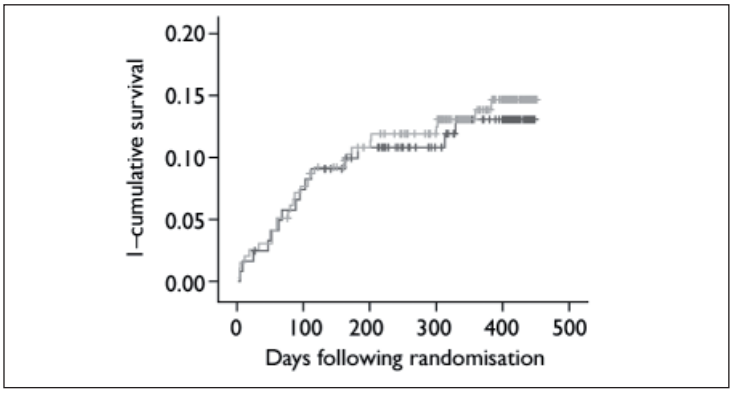
BDI, Beck Depression Inventory; HCS, Health Complaints Scale

Table 5. Cardiac events at 18months post-myocardial infarction.

	Intervention group (n=209)	Care as usual group (n = 122)
	n (%)	n (%)
Cardiac death	1 (1)	3 (3)
Recurrentmyocardial infarction	6 (3)	0 (0)
Revascularisation (PTCA/CABG)	11 (6)	8 (7)
Heart failure	7 (4)	1 (1)
Myocardial ischaemia	1 (1)	2 (2)
Ventricular arrhythmia	1 (1)	1 (1)
Total	27 (14)	15 (13)

PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

Figure 2. Kaplan-Meier curves of cumulative probability of cardiac events formyocardial infarction patientswith depression allocated to antidepressant intervention or care as usual.__, care as usual; __, intervention; vertical ticks indicate censored data.



Antidepressant intervention

Of the 196 patients assigned to the intervention and not lost to follow-up, 45 (23%) did not receive antidepressant treatment, either because they refused to accept the proposed therapy or because the psychiatrist did not confirm the diagnosis of depression at the time of the visit. The median length of time from the randomisation date to the first visit to the psychiatrist was 13 days (interquartile range 7–21 days). The majority of patients in the intervention arm received clinical management of depression and 94 (45%) were enrolled in the double-blind placebocontrolled medication treatment sub-study. Of these patients, 47 initially received mirtazapine and 44 initially received placebo. Three patients received no treatment because they failed to keep their appointment. Twenty patients originally treated with mirtazapine and 26 who received placebo subsequently received 16 weeks of open-label treatment with citalopram because of an insufficient response after 8 weeks of the initial treatment. The remaining patients continued to receive their original

treatment. Seventeen (8%) received immediate open-label antidepressant treatment with citalopram and 40 (19%) received non-pharmacological antidepressant treatment (i.e. psychotherapy, counselling, etc.). Patients in the intervention arm who received these different treatments did not significantly differ on severity of depressive symptoms during hospitalisation (mean BDI score for those receiving doubleblind treatment 11.6, s.d.=6.9; open label treatment 13.8, s.d.=8.7); other treatment 11.6, s.d.=46.6; no treatment 11.0, s.d.= 6.7; F=0.66; P=0.58). Moreover, these patient groups did not differ significantly on ICD–10 depression characteristics. In contrast, only 8 patients (7%) in the care as usual arm received antidepressant medication and 12 (10%) received nonpharmacological treatment for their depression (Fig. 1).

Effects on long-term depression status

Of the 307 patients who were alive at 18 months and available for follow-up, depression assessments were obtained for 218 patients (71%), which was comparable for patients in the intervention (69%) and care as usual arm (74%). The prevalence of ICD–10 depression was 30.5% in the patients assigned to the intervention and 32.1% in the care as usual arm (P=0.68; Table 4). No significant differences were observed between patients assigned to intervention or care as usual with respect to depressive symptoms, health complaints, disability and quality of life.

Treatment effect on cardiac outcome

The total event rate between randomisation and 18 months post-myocardial infarction was 42 out of 314 (13%, Table 5). The incidence of events did not differ among the two treatment strategies (13% in the care as usual and 14% in the intervention arm, log-rank test 0.09, P=0.76). Similarly, no differences were observed in Kaplan–Meier curves (Fig. 2). The Cox regression analyses also revealed no differences between the treatment arms (OR=1.07, 95% CI 0.57–2.00). In addition, there were no differences in the incidence of cardiac events between patients in the intervention arm who received antidepressant medication (mirtazapine n=47; open pharmacological treatment n=17) and non-responders to placebo who received citalopram (n=26) (total n=90) compared with those patients in the care as usual arm who received no antidepressant treatment (n=98; OR= 0.84, 95% CI 0.38–1.84; 14% v. 12% event rate). Within the intervention arm, the event rate for patients receiving pharmacological treatment was 13%, whereas this was 15% for patients who did not receive pharmacological treatment in the intervention arm (OR=0.80, 95% CI 0.35–1.80). There were no differences in event rates between intervention (n=144) and care as usual (n = 86) patients with moderate-to-severe ICD–10 depression (OR=1.15, 95% CI 0.56–2.38). Similarly, although this analysis may be underpowered, there were no differences in event rate between intervention (n=45) and care as usual (n=28) patients with an ICD–10 diagnosis of recurrent depression (OR=1.75, 95% CI 0.46–6.59). The total rate for cardiac-related hospitalisations between randomisation and 18 months post-myocardial infarction was 127 out of 314 (40%). The incidences of these secondary end-points were comparable between patients allocated to intervention and care as usual 77 of 196, 39% v. 48 of 118, 41%, P=0.34).

DISCUSSION

We found that an active treatment strategy for depression post-myocardial infarction did not improve the long-term depression status or cardiac prognosis compared with usual care. At 18 months post-myocardial infarction, about one-third of the intervention and control patients continued to have ICD–10 depression. With respect to whether cardiac prognosis can be improved by treating depression effectively, the trial is inconclusive. Our findings are consistent with the results of the ENRICHD study [9] that showed no overall effect of CBT on the risk of all-cause mortality and reinfarction in myocardial infarction patients with depression and/or a low level of social support, and small differences in depression between the intervention and care as usual groups.

Limitations

The lack of positive results in our trial might be a result of either suboptimal antidepressant treatment in the intervention arm or better than expected treatment in the care as usual arm. This possibility is not supported by our secondary analyses because comparing treated patients in the intervention arm with untreated patients in the care as usual arm still yielded no differences in the incidence of cardiac events. However, the data needed to determine whether optimal dosage and continuation of antidepressant treatment were provided in the intervention arm were not collected. It could also be argued that perhaps these findings are the result of a large rate of spontaneous recovery from depression, which has been observed previously in both ENRICHD and SADHART clinical trials. Although this is plausible, our study was not designed to evaluate this possibility in detail since we used a Zelen design in which the care as usual patients were not informed about their depression and randomisation status. The advantage of this design is that usual care was truly representative but the disadvantage is that we cannot evaluate the (short-term) spontaneous recovery. However, the fact that both arms were comparable in depression outcomes at 18 months does support this possibility. This stresses the need to improve the identification of patients with persistent depression post-myocardial infarction in future clinical trials.

An important limitation is the power of the study. When the trial was initiated the results of the ENRICHD and SADHART trials had not been published and we had to rely on data that in retrospect may have been too optimistic e.g. Frasure-Smith et al, 1995 [30]. First, the expected incidence of cardiac events was substantially higher than the observed incidence. Second, the association between depression and cardiac outcomes might have been overestimated and third, the anticipated effects of treatment on depression were overly optimistic. As a result, we believe that our study had sufficient power to detect differences in longterm depression outcomes (standardised effect size 40.35) but was underpowered to detect differences in cardiac outcomes. However, the nearly identical long-term depression status in the two arms and the similar rates of cardiac events offer little evidence that a significant difference would have emerged if more patients had been included. Thus, although we believe that our trial was underpowered, the observation that there were no consistent differences suggests that more study power would very likely not have yielded different conclusions.

Implications

The MIND–IT produced null findings in terms of long-term depression outcomes and was inconclusive about the effects of depression treatment on cardiac outcomes. We were unable to substantially alter long-term depression status, and as a result we still do not know whether effective treatment of depression would result in a better cardiac

prognosis. Future efforts should focus on the identification and effective treatment of patients with depression post-myocardial infarction with different antidepressant treatment modalities. In the absence of such knowledge, we did not choose one specific antidepressant therapy but rather compared an active psychiatric intervention arm with care as usual. Unfortunately, this has resulted in a considerable proportion of patients that did not receive antidepressant medication although being in the intervention arm. When the efficacy of one antidepressant treatment has been proven, the next step should be to investigate whether that treatment might improve the impaired cardiac prognosis in this patient group. Some recent findings suggest that particular subtypes of depression postmyocardial infarction might be specifically related to impaired prognosis. We have found that only somatic/affective symptoms are associated with a worsened cardiac prognosis [31]. Other studies have found that only incident postmyocardial infarction depression [32,33] is related to poor cardiac outcomes, and that even minimal symptoms can have an effect [34]. We believe that the validity and homogeneity of the diagnosis and treatment of depression in acute coronary syndromes need to be reconsidered [35] might lead to treatment strategies that might be quite different from treatment for depression in the general population [36] but be better adapted to cardiac care.

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PART 1

CHAPTER

3

Nonresponse to treatment for depression following myocardial infarction: association with subsequent cardiac events.

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ABSTRACT

Objective. Depression following myocardial infarction is associated with an increased risk of cardiac events, but attempts to alter cardiovascular prognosis by providing antidepressive treatment have not been successful. This may be because of the limited effects of antidepressive treatment on depression itself. The authors assessed whether nonresponse to treatment of post-myocardial infarction depression is associated with new cardiac events.

Methods. The authors made a subgroup analysis of a multicenter randomized clinical trial on the effects of antidepressant treatment for post-myocardial infarction depression. Patients were enrolled in double-blind, placebo-controlled treatment with mirtazapine (30 mg/day) and in the case of insufficient treatment response after 8 weeks, open treatment with citalopram. Patients were classified as responders to antidepressants (at least 50% reduction in Hamilton Depression Rating scale [HAM-D] score or HAM-D score <9 at 24 weeks) (N=43), as nonresponders (N=27), and compared to untreated control subjects (N=98) on cardiac events (cardiac mortality or cardiac-related hospital admission) after 24 weeks post-random assignment and within 18 months after index infarction.

Results. The event rate was 25.6% among nonresponders, 11.2% among untreated control subjects, and 7.4% among responders. In relation to untreated comparison subjects, nonresponders had a hazard ratio of 2.66 for new cardiovascular events, which remained after the authors controlled for potential confounders (hazard ratio=2.92).

Conclusion. This study provides further preliminary evidence that nonresponse to treatment of post-myocardial infarction depression may be associated with cardiac events. Efforts should be dedicated to develop more effective treatments for depressed patients with myocardial infarction.

INTRODUCTION

Depression following myocardial infarction affects about 20% of patients with myocardial infarction and is associated with a 2–2.5-fold increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events [1]. Whether these effects can be prevented by antidepressant treatment remains unclear. From the observational studies on the cardiovascular effects of antidepressant medication, inconsistent results emerge, with studies suggesting cardioprotective effects [2, 3], no effects [4, 5], or even cardiotoxic effects of modern antidepressant drugs [6].

The experimental evidence for a protective cardiovascular effect of antidepressant treatment is equally inconclusive. In the Enhancing Recovery in Coronary Heart Disease Patients study (ENRICHD), it was found that cognitive behavior treatment (for post-myocardial infarction depression and social isolation) did not have an effect on cardiac prognosis compared to care as usual [7]. Similarly, in the Myocardial Infarction and Depression—Intervention Trial (MIND-IT), no effects of antidepressant pharmacological treatment on cardiovascular prognosis were found [8, 9]. However, because in these studies no strong effects of treatment on depression itself were reported, the question remains whether effective antidepressant treatment affects cardiovascular prognosis. In ENRICHD compared to usual care, cognitive behavior therapy resulted in a modest relative decrease in Hamilton Depression Rating Scale (HAM-D) score at 6 months (1 to 2.5 points on the HAM-D) that was no longer present at the 30-month follow-up [7]. In MIND-IT, antidepressant medication (mirtazapine) was significantly better than placebo after 8 weeks of treatment [9], but no differences in depression status were found between patients in the intervention arm of the study versus the care as usual arm at 18 months post-myocardial infarction [8]. In two other studies, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) [10] and a study by Strik et al. [11], a nonsignificant reduction in depressive symptoms as scored with the HAM-D was found in depressed patients with acute coronary syndromes that were treated with a selective serotonin reuptake inhibitor (i.e., sertraline and fluoxetine, respectively) compared to patients with placebo. Of interest, in the SADHART, significant improvements in depressive symptoms were observed in patients with severe depression, in depression with an onset before the acute coronary syndrome, and in patients with a history of depression [10, 12], a finding that needs to be further explored. An exploratory analysis using ENRICHD data of depressed patients with a myocardial infarction was performed by Carney et al. [13]. They reported that patients whose depression is refractory to cognitive behavior therapy and sertraline are at high risk for late mortality after myocardial infarction (occurring after 6 months). These results may be explained by the beneficial effects of antidepressant treatment but also by the possibility that a subtype of depression is associated with both a poor response to antidepressant treatment and a high risk for mortality. In the present study, we will evaluate the cardiovascular prognosis of depressed patients post-myocardial infarction who were enrolled in a randomized, controlled trial comparing placebo-controlled medication treatment for post-myocardial infarction depression (the MIND-IT). We hypothesized that responders after 24 weeks of antidepressive treatment would experience fewer new cardiovascular events than nonresponders. To evaluate if differences were due to the protective effects of antidepressant medication itself or to the presence of treatment-resistant depression with a poor cardiac prognosis, we added a comparison with untreated control subjects. These analyses, like the ones by Carney et al. [13] should be seen as preliminary because they were not based on random allocation and, as a result, one cannot rule out the possibility that the findings were produced by the presence of (unmeasured) confounders. Still,

these analyses may help to clarify the importance of short-term response to antidepressant medication in preventing cardiovascular events.

METHODS

The data were derived from MIND-IT, a multicenter, randomized, controlled study on the effects of antidepressant therapy for post-myocardial depression on cardiovascular prognosis [14]. For the present analyses, data from patients included in the "nested study," the placebo-controlled efficacy study of mirtazapine [9], were combined with data from the overall study (8). In- and exclusion criteria have been described previously [14]. In brief, we recruited consecutive patients (September 1999 through November 2002) who were hospitalized for acute myocardial infarction in 10 hospitals in the Netherlands. Patients were enrolled if they met World Health Organization (WHO) Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) criteria for definite myocardial infarction [15]. Exclusion criteria were the occurrence of myocardial infarction while the patient was hospitalized for another reason, being unable to participate in the study procedures, having a disease likely to influence short-term survival, already receiving psychiatric treatment for depression, and participation in another clinical trial. The institutional review board at each clinical center approved the study protocol, and all patients provided written informed consent before enrollment. In the study information it was emphasized that although all participating patients were screened for depression, antidepressive treatment was offered only to a random sample of the depressed patients and that all patients were free to seek help for mood problems.

Procedure

The patients were screened for depressive symptoms during hospitalization and at 3, 6, 9, and 12 months post-myocardial infarction with the Beck Depression Inventory [16]. Those with depressive symptoms (i.e., a Beck Depression Inventory score ≥10) underwent a psychiatric evaluation using the WHO Composite International Diagnostic Interview (CIDI), auto version 2.1 [17,18]. The first CIDI interviews were performed not earlier than 3 months post-myocardial infarction to allow for natural recovery of depressive symptoms. Patients with a diagnosis of "depressive episode" according to the ICD-10 were randomly assigned to intervention or care as usual except for patients with a significant risk of suicide. We used a Zelen design [19]; i.e., the patients allocated to the care-as-usual arm were not informed about their research diagnosis of depression in order to make sure that patients in the care-as-usual arm were truly representative of patients in usual care. The patients in the intervention arm were offered antidepressant treatment if the study psychiatrist confirmed a DSM-IV research diagnosis of major or minor depression.

Subjects

In MIND-IT, 4,780 subjects were assessed for eligibility, of which 2,177 (46%) of the patients met the inclusion criteria and agreed to participate. Of these, 375 patients developed a post-myocardial infarction depression, of whom 331 patients were randomly assigned to the intervention and the care-as-usual arm. At the start of the trial, we used a 1:1 ratio, but this was changed into a 2:1 ratio because the number of patients actually treated with antidepressants in the intervention arm was lower than expected. This resulted in 209 patients in the intervention arm and 122 in the care-as-usual arm. Of the 209 patients in the intervention arm, 37 refused to visit a psychiatrist, nine patients were

excluded because of the start of antidepressant treatment by the general practitioner and in 28 patients, the psychiatrist did not confirm the research diagnoses of a depressive disorder. A total of 41 patients did not agree to receive double-blind, placebo-controlled treatment and were given open-label treatment with an antidepressant (N=8) and a referral to counseling or psychotherapy (N=15), whereas 18 patients refused any treatment. These 115 subjects were excluded from the present data analyses because no follow-up assessment of depression status at 24 weeks post-random assignment was conducted in these groups. The remaining 94 were offered doubleblind mirtazapine/placebo treatment (i.e., the "nested study") and used for the present analyses. Of the 122 patients in the usual-care arm, we selected the postmyocardial infarction depressed patients who did not receive antidepressive treatment based on patient self-reports at 18 months post-myocardial infarction and reports from the patients' general practitioners. In Figure 1, the flowchart of the study is shown.

Intervention

Double-blind, mirtazapine/placebo was prescribed for a maximum period of 24 weeks, divided into an acute treatment period of 8 weeks and a continuation treatment period of 16 weeks. Mirtazapine is a nontricyclic, presynaptic α2-antagonist that enhances both noradrenergic and serotonergic neurotransmission and is well tolerated by patients with coronary artery disease [20,21]. The starting dose was 30 mg/day, which could be increased to 45 mg/day and in case of severe side effects was lowered to 15 mg/day. After 8, 16, and 24 weeks, response to treatment was evaluated with the Hamilton Depression Rating Scale (HAM-D) [22]. If after 8 weeks, the HAM-D score was reduced by at least 50% or the HAM-D score was less than or equal to 9, treatment was continued. Otherwise, a switch to open treatment with citalopram (20mg/day–40 mg/day) was made [23]. For those of whom HAM-D scores were not available at 8 weeks (N=16), the effects were estimated based on the last-observation-carried-forward technique.

After 24 weeks of treatment, the subjects were classified as responders (a reduction of at least 50% in HAM-D score or a HAMD score less than or equal to 9) or nonresponders.

Baseline Variables

We collected demographic and cardiovascular data during hospitalization for the index myocardial infarction. The cumulative burden of medical comorbidity was assessed with a modified version of the Charlson Comorbidity Index [24]. Further cardiovascular data included the left ventricular ejection fraction (assessed by either echocardiography or radionuclide ventriculography), the Killip class, and a series of cardiovascular risk factors (e.g., the presence of diabetes mellitus, cerebrovascular disease, hypertension). Depression characteristics were based on CIDI interviews with ICD-10 criteria and self-report data (the Beck Depression Inventory). With the CIDI, we assessed whether the onset of the post-myocardial infarction depression was within 3 months postmyocardian infarction or after and whether the post-myocardial infarction depression was a first-ever episode or a recurrent one.

Cardiac Events

The main outcome was a combined time-related variable consisting of cardiac death or hospital admission with an initial evaluation by a cardiologist (e.g., for nonfatal myocardial infarction, myocardial ischemia, revascularization, heart failure, or ventricular arrhythmia). Potential cardiac events were recorded at 12 months post-myocardial infarction (cardiac outpatient clinic, as part of usual cardiac care) and 18 months post-myocardial infarction (during the "outcome" CIDI interview session or through contact with the patient's general practitioner). Potential cardiac events were reviewed and classified according to prespecified, established [24] criteria by an independent endpoint committee whose members were unaware of the patients' treatment assignments. Discrepancies were discussed and decisions were taken by unanimity. All cardiac events occurring after random assignment were collected. However, the event had to occur after 24 weeks following random assignment and within 18-months post-myocardial infarction in order to prevent bias (i.e., the event resulting in nonresponse to antidepressant treatment).

Depression Status at 18 Months Post-Myocardial Infarction

At approximately 18 months post-myocardial infarction, the CIDI Interview was administered to determine whether the patients had a diagnosis of "depressive episode" according to the ICD-10. The CIDI interviews were conducted by trained research assistants, who were kept unaware of the patients' random assignment status.

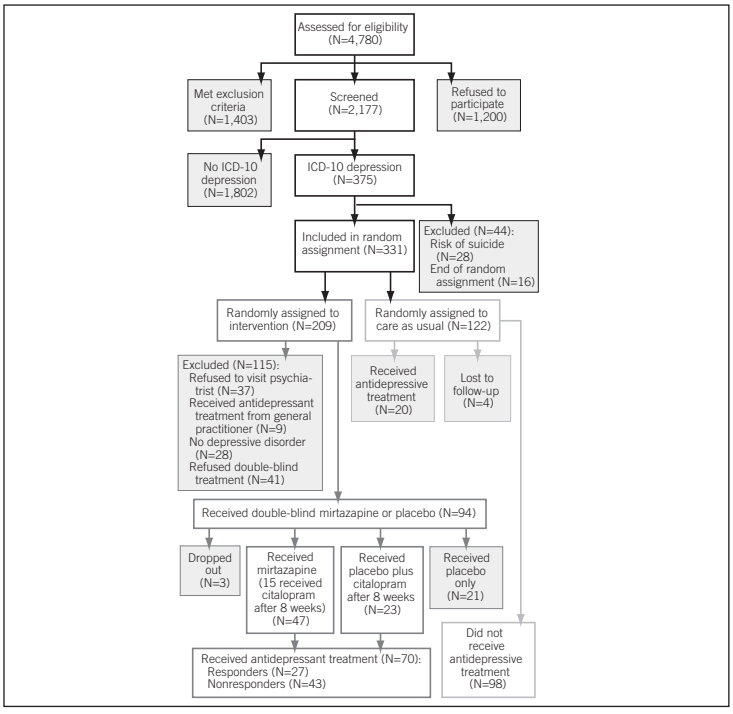
Statistical Analyses

Responders, nonresponders, and untreated control subjects were compared on baseline characteristics, including sociodemographic data, cardiac risk factors, cardiac status, and depression characteristics by means of Fisher's exact test, the Kruskal-Wallis test, and the Mann-Whitney U Test where appropriate. Differences between the groups on cardiac events were analyzed with Kaplan-Meier curves, with outcome data censored at 18 months post-myocardial infarction, the time of last contact, withdrawal from the study, or the time of an event. Univariate and multivariate comparisons between responders, nonresponders, and untreated comparison subjects were conducted with Cox regression analysis, with untreated control subjects used as a reference group. All p values were two-tailed.

RESULTS

Of the 94 patients referred to the study psychiatrists in the nested study, 91 received actual double-blind mirtazapine/placebo treatment (47 mirtazapine and 44 placebo) (96.8%) (Fig.1). Of the 47 patients who received mirtazapine, 15 (32%) were classified as nonresponders at 8 weeks and given an open treatment with citalopram during weeks 8 through 16. Of the 44 placebo patients, 23 (52%) were nonresponders and received open treatment with citalopram during weeks 8 through 16. Therefore, of the 94 patients included in the nested study, 70 (47 mirtazapine patients and 23 placebo patients who were switched to citalopram) received actual antidepressant medication. At 24 weeks after random assignment, of these 70 patients, 27 (38.6%) were classified as responders and 43 as nonresponders (61.4%) (see Fig 1).

Figure 1. Flowchart of the Study Design.



Of the 122 patients randomly assigned to usual care, 98 received no formal care for their depression and were used as untreated comparison subjects. Table 1 shows a comparison between responders, nonresponders, and untreated control subjects on baseline sociodemographic data, cardiovascular risk factors, cardiac status, and depression characteristics. The groups did not differ significantly on any of the baseline data. The mean Beck Depression Inventory scores were relatively low for all groups (i.e., between 12.0 and 14.4) compared to, for example, depressed patients in the ENRICHD (i.e., between 17.7 and 18.0) [7]. However, mean baseline HAM-D scores in our group (17.0 and 18.4) were comparable to those in the ENRICHD study (17.7 and 17.8).

Table 1. Demographic and Clinical Characteristics of Depression Responders, Nonresponders, and Untreated Control Subjects with Myocardial Infarction at Baseline.

Variable	Responders at 24 Weeks (N=27)		Nonresponders at 24 Weeks (N=43)		Untreated Control Subjects (N=98)		Analysis
	N	%	N	%	N	%	p
Sociodemographic characteristics							
Female sex	4	14.8	8	18.6	29	29.6	0.17[a]
	Mean	SD	Mean	SD	Mean	SD	p
Age (years)	59.2	10.4	56.4	11.1	58.4	10.7	0.48[b]
	N	%	N	%	N	%	p
Cardiac risk factors							
Diabetes mellitus	3	11.1	5	11.6	12	12.2	0.99
Family history of CAD	15	55.5	21	48.8	45	46.9	0.73
Cerebrovascular disease	1	3.8	2	4.7	4	4.1	0.99
Body mass index ≥25	17	63.0	29	67.4	61	62.9	0.87
Peripheral vascular disease	1	3.8	4	9.3	12	12.4	0.43
History of CABG	0	0.0	2	4.7	6	6.2	0.41
History of percutaneous transluminal coronary angioplasty	1	3.7	3	7.0	9	9.2	0.63
Hypertension	7	25.9	10	23.3	35	35.7	0.28
Hypercholesterolemia	24	88.9	37	88.1	82	83.7	0.69
Current smoker	12	44.4	28	65.1	53	54.1	0.22
Previous myocardial infarction	2	7.7	3	7.7	19	19.6	0.09
Baseline cardiac data							
LVEF <30%	4	14.8	6	12.8	16	16.7	
LVEF 30%–45%	7	44.4	11	43.6	22	41.1	
LVEF 45%–60%	12	25.9	17	28.2	37	24.4	
LVEF ≥60%	4	14.8	5	12.8	15	16.7	0.99[a]
Killip class 1	24	88.9	39	90.7	82	84.5	
Killip class 2	2	7.4	3	7.0	11	11.3	
Killip class 3	0	0.0	1	2.3	1	1.0	
Killip class 4	1	3.7	0	0.0	3	3.1	0.79[a]
Charlson Comorbidity Index							
Score=0	15	57.7	25	58.1	53	54.6	
Score=1–2	9	34.6	14	32.6	31	32.0	
Score=3–4	2	7.7	1	2.3	8	8.2	
Score ≥5	0	0.0	3	7.0	5	5.2	0.75[a]
Depression characteristics	Mean	SD	Mean	SD	Mean	SD	p
BDI score at week 0	14.1	7.3	14.4	7.0	12.0	6.0	0.12[b]
HDRS score at week 0	17.2	4.9	18.7	4.8	—	0.21[c]	
	N	%	N	%	N	%	p
Onset of depression <3 months							
Post MI	22	81.5	36	83.7	85	86.7	0.76[a]
Recurrent depressive episode	9	33.3	7	16.3	22	22.4	0.25[a]

a Fisher's exact test.
b Kruskal-Wallis test.
c Mann-Whitney U test.

This may be because of differences in study design; in the ENRICHD study, cognitive behavior therapy was started soon after the myocardial infarction, whereas in the MIND-IT, treatment was started after only 3 months post-myocardial infarction, which possibly resulted in fewer somatic depressive symptoms, such as fatigue (which are prominent in the Beck Depression Inventory). Of interest and in line with findings from the SADHART [12], the prevalence of recurrent depression seemed considerably higher in the responders group. However, a pairwise comparison between the responders and the nonresponders was not significant ($p<0.10$). We used sex, age, recurrence of depression, severity of depressive symptoms (the Beck Depression Inventory), myocardial infarction history, cur-

rent smoking, and occurrence of early cardiac events (i.e., occurring within 24 weeks after random assignment) as potential confounders in the multivariate analyses. Forty-eight cardiac events occurred between random assignment and 18 months after myocardial infarction, of which 24 were after the end of the 24-week antidepressant treatment. A total of 25.6% (95% confidence interval [CI]=14.8–40.3) of the nonresponders (11 of 43) experienced a cardiac event after 24 weeks; this percentage was 7.4% (95% CI=1.7–20.8) for the responders (two of 27) and 11.2% (95% CI=6.2–19.2) for the untreated control subjects (11 of 98). These percentages represented a significant overall difference among the groups (log rank=8.58, p=0.01) and specifically between the responders and the nonresponders (log rank=5.20, p=0.02). In Figure 2, the event-free survival for responders, nonresponders, and untreated control subjects is plotted.

A comparison of the event rates between untreated control subjects, responders, and nonresponders in a Cox regression analysis (Table 2) resulted in the following findings. First, an increased risk of cardiac events for nonresponders compared to untreated control subjects was found (hazard ratio=2.66, 95% CI=1.15–6.16, p=0.02), which remained after we controlled for age, sex, previous myocardial infarction, baseline Beck Depression Inventory score, history of depression, smoking, history of coronary artery bypass graft and percutaneous transluminal coronary angioplasty, and presence of peripheral vascular disease and after we controlled additionally for early cardiac events (hazard ratio=2.92, 95% CI=1.08–7.87, p=0.03). Second, no significant difference between responders and untreated control subjects was found (hazard ratio=0.52, 95% CI=0.12–2.37, p=0.41), which was unaltered after we controlled for confounders. Third, when directly comparing nonresponders to responders, we found an increased risk for nonresponders (hazard ratio=4.89, 95% CI=1.08–22.10, p=0.04), which remained similar after we controlled for confounders but was no longer statistically significant (hazard ratio=4.47, 95% CI=0.51–39.77, p=0.18). Of the 168 (70 treated and 98 untreated) patients, a CIDI interview at 18 months was performed in 124 (73.8%). Of the responders at 24 weeks of treatment, 9.5% had a ICD-10 depressive episode at 18 months post-myocardial infarction. These percentages were 58.8% for the nonresponders and 33.3% for the untreated control subjects and were significantly different among the groups (Fisher's exact test=14.2, p=0.001).

DISCUSSION

The primary finding of this study was that incomplete response to antidepressant treatment for post-myocardial infarction depression was associated with more prospective cardiac events even when compared to untreated control subjects. This suggests that by providing a standard antidepressant treatment, a subtype of treatment-resistant post-myocardial infarction depression with an im impaired cardiovascular prognosis may be identified [13].

Figure 2. Event-Free Survival for Responders, Nonresponders, and Untreated Control Subjects (Events After 24 Weeks Post-Random Assignment).

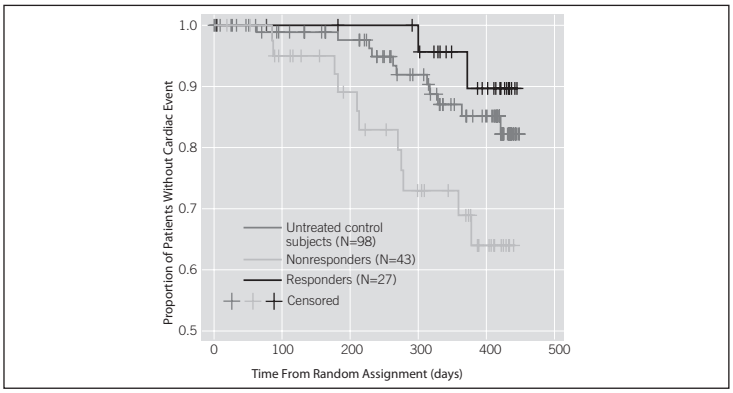


Table 2. Hazard Ratios for New Cardiovascular Events for Depression Responders and Nonresponders Compared to Untreated Control Subjects, All With Myocardial Infarction.

	Model 1[a]			Model 2[b]			Model 3[c]		
Group	Hazard Ratio	95%CI	p	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Nonresponders – untreated control subjects	2.66	1.15–6.16	0.02	2.81	1.13–6.96	0.03	2.92	1.08–7.87	0.03
Responders – untreated control subjects	0.52	0.11–2.33	0.39	0.29	0.03–2.45	0.25	0.41	0.05–3.58	0.42
Nonresponders – responders	4.89	1.08–22.10	0.04	5.85	0.70–48.85	0.10	4.47	0.51–39.77	0.18

a Univariate.

b With control for sex, age, previous myocardial infarction, baseline Beck Depression Inventory score, history of depression, smoking, history of coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and peripheral vascular disease.

c Model 2 plus cardiac events within 24 weeks of post-random assignment.

This finding corroborates with several lines of research on the association between depression and cardiac mortality. First, the importance of depression persistence on prognosis is stressed by most of the mechanisms supposed to be responsible for the association (e.g., reference 25). Whether because of increased sympathetic activation of the autonomous nervous system, elevated platelet reactivity, or increased immune system reactions, all mechanisms require a persistent depressive state in order to produce cardiovascular events. In line with this, we have recently shown elsewhere that among post-myocardial infarction depressed patients, a subgroup can be identified with persistent post-myocardial infarction depressive symptoms that, in addition, had the highest risk for new cardiac events in a period of 2.5 years, which was not explained by baseline cardiac impairments or the presence of additional risk factors [26]. Second, despite large efforts in this field, there is no consistent evidence of pleiomorphic effects of antidepressant treatment, i.e., effects on cardiac prognosis irrespective of their effects on depression itself; in the ENRICHD trial, no evidence of cardiovascular effects attributed

to antidepressant treatment was found in the absence of relevant antidepressant efficacy [7]. Because the 95% CI of the cardiovascular event rates of the untreated control subjects (6.2%–19.2%) was clearly in between the rates found for the responders (7.4%) and the nonresponders (25.6%), no support was found either for a pleiomorphic effect or for a cardiotoxic effect of antidepressant treatment. Post-myocardial infarction depressed patients whose depression is refractory to treatment thus seem to be at increased risk for new cardiac events. Of interest, of the early responders, only 9.5% were depressed at 18 months postmyocardial infarction compared to 58.8% of the nonresponders. This finding suggests that it is persistent depression that is the key variable and that resistance to acute treatment may be a marker for that. Our findings thus stress the importance of early response to post-myocardial infarction antidepressant treatment and the need to develop more effective treatments for depression in the context of a myocardial infarction, such as stepped care in case of early nonresponse. We did not find support for the presence of a subgroup of patients with a treatment-resistant "vascular depression" [27, 28] because responders and nonresponders did not differ on any of the cardiac risk factors at baseline. Among the strengths of our study was the random allocation to usual care versus active treatment. In contrast to earlier studies [2], we prevented bias due to baseline differences among these groups. Second, we randomly assigned patients only if their post-myocardial infarction depression was still present in the period 3–12 months post-myocardial infarction. This inclusion criterion has reduced the number of adjustment disorders with a depressed mood occurring relative early after the event with a high rate of spontaneous recovery. Because it may be argued that in adjustment disorders recovery is less a function of treatment response, the results from our study more closely resemble a true treatment effect. Third, by counting cardiac events only if they occurred after 24 weeks post-random assignment, we reduced the chance that the postulated relation between events and treatment response is bidirectional or even the reverse. Of interest, differences among the responders and nonresponders, in fact, emerged after only 3–4 months of treatment (Fig. 2). Fourth, by comparing the cardiac prognosis of responders and nonresponders to an untreated control group, we were able to distinguish whether the "pleiomorphic hypothesis" or the "persistent depression hypothesis" could explain our findings. A comparison of responders versus nonresponders alone could not have demonstrated or refuted the pleiomorphic hypothesis. This hypothesis can only be confirmed if exposure to antidepressive medication per se is associated with fewer cardiac events. On the other hand, comparing subjects treated with antidepressive medication to untreated patients alone without consideration of response to treatment would not have allowed us to study the possibility that the persistence of depression is of interest. The present findings should be considered with caution because of the following study limitations as well. First and most important, the numbers of patients in the different groups were small, and because the data analysis was a secondary analysis of a complex trial, the patients had reached the relevant groups (responders and nonresponders) by different routes and no prior power calculation had been possible. Second, the number of cardiac events was small partly because we counted events only when they occurred after termination of the antidepressant treatment. However, because similar results have been reported before [13], we do not expect this to be an accidental finding. Third, because we do not know why some patients responded to antidepressant treatment and others did not, we cannot conclude that depression is a causal risk factor for new cardiovascular events. Fourth, the fact that we used a stepped protocol for the provision of antidepressive medication—mirtazapine as the first treatment of choice and citalopram in case of insufficient treatment

response after 8 weeks— hindered us from further breaking down nonresponse to a specific antidepressant. Fifth, of the untreated control
patients we did not have data on early (spontaneous) recovery, and as a consequence, these patients could not be further divided as responders or nonresponders as we did for the treated patients. By monitoring the outcomes of post-myocardial infarction depression treatment, we may identify patients with refractory depression and an impaired cardiovascular prognosis. The challenge is thus to develop more effective treatments for post-myocardial infarction depression to further reduce insufficient treatment response.
Second, we need to identify risk factors for nonresponse to antidepressant treatment. Recent work has shown that important predictors of response to sertraline are depression related and include onset, recurrence, and severity of postmyocardial depression [12]. In our study, we found that depression recurrence but not severity was related to nonresponse.
Our present findings leave the possibility open that post-myocardial depression may be causally involved in cardiovascular prognosis. However, the actual test for causality has to wait until the long-term course of postmyocardial infarction depression can be altered by more effective treatment.

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PART 1

CHAPTER

4

Circulating cerebral S100B protein is associated with depressive symptoms following myocardial infarction.

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ABSTRACT

Objective. Prevalence of depressive symptoms in the post-myocardial infarction (MI) period varies from 8 to 30%. Cerebral damage after MI, caused by transient ischemia, an inflammatory response or both, may contribute to development of post-MI depression. S100B is an established protein marker of cerebral damage. In a pilot study, the authors assessed whether S100B serum levels are: (1) increased during the week after MI, and (2) related to depressive symptoms during index hospital admission and the year following MI.
Methods. This pilot study is a substudy of the Myocardial Infarction and Depression Intervention Trial (MIND-IT). In 48 patients, serum levels of S100B were available at 1, 2, 3, 4 and 8 days following MI. Subsequently, in 27 patients, depressive symptoms were measured at 0, 3, 6, 9 and 12 months following MI with the Beck Depression Inventory (BDI). In 21 of the initial 48 patients, BDI data were lacking due to refusals to fill out BDI forms or missing data.
Results. Significant and transient increases in serum S100B were observed in 81.3% of the 48 patients: 37.5% reached S100B serum levels comparable to serum levels found in acute brain injury (> 0.20 µg/l) and 43.8% reached mildly elevated S100B serum levels comparable to serum levels found in depressive disorder (0.10–0.20 µg/l). In 18.7%, no S100B was detected in serum. Using nonparametric Spearman rank correlation tests, a trend towards an association was found between serum S100B and depressive symptoms during the post-MI year (r values between 0.16 and 0.53) in 27 patients who completed both the S100B serum study and the BDI study.
Conclusion. Transiently elevated levels of S100B are suggestive of minor acute cerebral damage in the first days following MI and associated with depressive symptoms in the year following MI. Cerebral damage could be an important mechanism in the pathogenesis in a subtype of post-MI depression.

INTRODUCTION

Depressive symptoms following myocardial infarction (MI) have been associated with arrhythmic events and an increased risk of cardiac death up to 5 years after MI [1]. In a recent meta-analysis, the odds ratios for allcause mortality and cardiac mortality were estimated to be 2.38 and 2.59, respectively [2]. The prevalence of depressive symptoms varies from 8 to 30% depending on the assessment method [3]. Cerebral damage, caused by transient ischemia, an inflammatory response or both, may contribute to induction of post-MI depression. Proinflammatory cytokines, including TNF-α, affect blood-brain barrier (BBB) integrity [4], and in experimental animal studies MI was associated with brain damage, most likely through immune-mediated processes [5]. Brain damage might also occur in human MI patients as a result of regular TNF-α release after MI [6]. Neuroimaging supports the association between subtle cerebral damage and depressive symptoms, since in clinically depressed but physically healthy patients cerebral white matter lesions (WML) are found [7]. WML in the elderly are associated with a 3- to 6-times higher risk of depressive symptoms compared to patients without WML [8]. Moreover, it was shown that MI and WML are related to each other [9]. Certain proteins in blood circulation may serve as markers of central nervous system (CNS) injury. Such an established marker is S100B, a calcium-binding protein of the S100 family that comprises 21 members. It is present in high concentrations in astroglial and oligodendroglial cells in the CNS, and is normally not detected in peripheral blood. Increased serum S100B levels may indicate glial alterations, either due to brain damage or functional secretion of S100B by astrocytes. Disruption of the BBB is mandatory to allow for cerebral efflux [10]. Extracellular S100B exerts a dual effect on neurons depending on its concentration, i.e. a pro-survival effect on neurons and stimulation of neurite outgrowth at nanomolar doses and a toxic effect at micromolar doses [11,12] Circulating S100B has a biological half-life of 25 min [13]. Following acute structural cerebral damage, S100B leaks into the bloodstream either directly from damaged tissue or indirectly via extra-cellular space. S100B efflux due to acute significant cerebral damage leads to a characteristic curve of S100B serum levels. Usually, the highest serum levels of S100B are observed 2–4 days after acute brain damage and normalize thereafter within 1–3 weeks [14]. S100B serum levels reflect S100B Cerebro Spinal Fluid levels [15]. After acute cerebral injury, serum S100B levels > 0.30 µg/l at 48 h have predictive value for long-term anxiety [16] , serum S100B > 0.50 µg/l for persisting neuronal damage [17] and serum S100B > 0.70 µg/l for death [18]. In several (neuro) psychiatric disorders, e.g. melancholic depression, elevation of S100B in serum is rather subtle (0.10–0.20 µg/l) and over time becomes more pronounced [12, 19–21]. S100B can also be found in serum after exercise with high cardiac output when activities included repetitive jarring movements or contact with the head (running), but not after exercise on a stationary bicycle, probably reflecting astroglial and/or BBB reaction in the first group [10]. However, in certain circumstances S100B is released from extra-cerebral tissues, e.g. after trauma, melanoma and cardiac surgery [22–24]. Therefore, it could be argued that serum S100B is not solely a marker for cerebral damage, but also a marker of cardiac damage. Fortunately, due to the short half-life of S100B and human renal clearance of 2 h, release of S100B from different damaged tissues leads to different time curves of the (peak) appearance of S100B in serum [14, 25]. This makes it possible to discriminate between different tissue origins of S100B, as was done in studies on cardiac surgery with cardiopulmonary bypass procedure (CPB) where both cerebral and cardiac sources of serum S100B were established [25]. During CPB, S100B was found in special reservoirs for cardiac surgical wound blood not contaminated by cerebral blood flow [26] and S100B serum levels measured immediately after cardiac surgery did correlate with measures of

cardiac injury and not with neuropsychological outcome, which points to a cardiac source of S100B [27]. However, several other studies found a strong positive correlation between increased S100B serum levels and cerebral dysfunction after cardiac surgery, pointing to a cerebral origin of S100B in CPB [28–30]. The combination of these results suggested that in CPB two different pathophysiological mechanisms are responsible for S100B release in serum. Therefore, later on, the clinical significance of early and late release of S100B after CPB were analyzed separately [28]. Timing of its appearance in the circulation indicated that serum S100B has an early peak (immediately at the end of surgery) associated with cardiac damage measured by creatine kinase (CK) [27] or troponin I [25], and a late peak (5–48 h after surgery) associated with neurological dysfunction after cardiac surgery [25, 28]. As far as we know, data on the relation between S100B and MI are lacking. To validate the hypothesis that cerebral damage may occur after MI and may contribute to induction of post-MI depression we investigated: (1) whether S100B serum levels are increased during the week after MI, (2) the timing of its appearance in serum to discriminate between cardiac and cerebral sources, and (3) whether S100B serum levels in the first week after MI are related to depressive symptoms during hospital admission and the year following MI.

METHODS

Study Population

Data were derived from the Myocardial Infarction and Depression Intervention Trial (MIND-IT), a multi-center randomized controlled study on the effects of antidepressant therapy for post-MI depression on cardiovascular prognosis. Inclusion and exclusion criteria have been described previously [31]. In brief, we recruited consecutive patients (September 1999–November 2002) hospitalized for acute MI in 10 hospitals across the Netherlands. Patients were enrolled if they met WHO MONICA criteria for definite MI. The patients for the S100B sub-study were all inpatients at the Coronary Care Unit of Medical Centre, Leeuwarden, the Netherlands, 1 of the 10 participating hospitals of the MIND-IT study. Exclusion criteria were: occurrence of MI while the patient was hospitalized for another reason, inability to participate in study procedures, a disease likely to influence short-term survival, receiving psychiatric treatment for depression already and participation in another clinical trial.

Procedures

Fifty-three consecutive patients (35 men and 18 women; age range 47–76 years) entered the S100B study. After written informed consent for participation in the S100B study, blood was collected by means of a venous puncture 5 times during the week after MI. Blood samples (6 ml) for S100B assays were taken on the day of admittance as soon as diagnosis of MI was given, before the start of thrombolytic therapy. Time interval between time of admittance for MI and the first S100B measurement varied between 1 and 3 h (mean 1.8 h). According to changes in the electrocardiograph, reperfusion was obtained 2–12 h after admittance for MI (mean 5 h). Information was obtained from clinical records by the participating cardiologist. Subsequently, on days 2, 3, 4 and 8, a fixed schedule was used and all venous punctures were performed at 8 a.m. After blood for S100B determination was collected, patients were asked to participate in the MIND-IT study. As part of this study, patients with MI were screened for depressive symptoms during initial hospitalization (0 months) and 3, 6, 9 and 12 months after MI with the 21-item Beck Depression Inventory (BDI) questionnaire, an established method for screening depressive

disorders in cardiac patients [32]. Demographic and medical information were obtained from the patients' medical records (table 1).

Table 1. Baseline and treatment characteristics for S100B.

Variable	%
Male sex	58.3 (28)
Age >60 years	56.3 (27)
Anterior MI	33.3 (16)
Cardiac history (MI, PCI, CABG)	12.5 (6)
CK-MB (mean 8 SD), U/l	197± 164
Peak CK (mean 8 SD), U/l	2,080±1,650
LVEF <45%	20.9 (10)
Medication at hospital admittance	
Acenocoumarol	2.1 (1)
b-Blockers	14.6 (7)
Diuretics	12.5 (6)
Calcium antagonists	8.3 (4)
Statins	12.5 (6)
ACE inhibitors	8.3 (4)
Medication during acute treatment phase	
Thrombolysis	100.0 (48)
Nitrates	100.0 (48)
Heparin	100.0 (48)
Ascal	100.0 (48)
Medication at day 8	
Nitrates	20.8 (10)
Ascal	83.3 (40)
Acenocoumarol	18.8 (9)
β-Blockers	85.4 (41)
Diuretics	22.9 (11)
Calcium antagonists	35.4 (17)
Statins	77.1 (37)
ACE inhibitors	27.1 (13)

Values are percentages with the numbers of subjects given in parentheses, unless otherwise indicated. PCI = Percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; ACE = angiotensin-converting enzyme.

From the 53 patients participating in the S100B study, 30 agreed to continue in the MIND-IT study and fill in BDI forms, whereas 23 refused. After BDI forms were completed, missing data were calculated for S100B only (n = 3), BDI only (n = 1) and both S100B and BDI (n = 2). Finally, complete data on S100B were available for 48 patients. Additionally, for 27 of these 48 patients, complete BDI data were available (Fig.1). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the local ethical committees approved the design of the MIND-IT study. A separate informed consent was required by the local ethical committee of the Medical Centre of Leeuwarden for the collection of the S100B data. All participants were fully informed, and gave written informed consent.

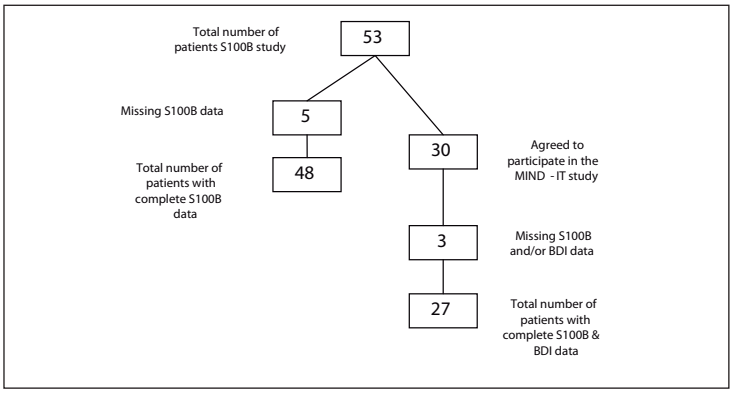

Figure 1. Flow chart of patients in the S100B and subsequently the MIND-IT study. Missing data: S100B only (n = 3), BDI only (n = 1) and both S100B and BDI (n = 2).

Infarct Size

CK/CK-MB was used as a marker of the presence of MI, not for infarct size, as all patients received thrombolytic therapy after admission [33]. Left ventricular ejection fraction (LVEF) was used as a more reliable marker of infarct size. Details on the measurement of CK and LVEF were described previously [31,34].

Biochemistry

Heparinized serum samples were centrifuged within 2 h at 2,300 g ; aliquots were taken and frozen at –20 ° C until analysis. S100B was determined with an immunofluorometric sandwich assay using a monoclonal anti-S100B chain antibody (LIA-mat R Sangtec Kit and Magic Little Analyzer 2, version 4.0; Sangtec, Bromma, Sweden). The Sangtec 100 LIA immunol-uminometric assay uses tubes coated with 2 monoclonal antibodies as solid phase, and a monoclonal antibody for detection. The assay measures concentrations of S100B protein over the range of 0.02–20 µg/l. Measurements were performed according to the instructions of the manufacturer. Details about linearity, a description of the analytical technique, the accuracy and precision, and limit of quantification of the kit were described earlier [35] . The assay's threshold for detecting S100B is 0.02 µg/l. To minimize inter-assay variations, S100B was determined after all samples were collected.

Statistical Analysis

No sample size calculation was performed due to the exploratory nature of the trial. S100B data are expressed as medians and interquartile ranges, which are less affected by outliers in a small sample than means and standard deviations. Missing S100B data (6.7%) and missing data on the BDI (4.4%) were estimated by means of 2-way imputation [36]. The method was only used for patients with 2 or fewer missing values. As a consequence, 5 patients were excluded from further analyses on S100B, and 3 patients were excluded from analyses involving the BDI (Fig.1). Brain damage was expressed as both S100B peak value between day 2 and 4, and S100B area under the curve (AUC). AUC was calculated for each participant by integrating simple linear functions, which were set up using S100B at days 1, 2, 3, 4 and 8. The course of S100B during the first week after MI was evaluated with non-parametric pairwise comparisons between S100B at day 1,S100B peak value (days 2–4) and S100B at day 8 (Wilcoxon signed rank test). The relationships of S100B peak values and S100B AUC with BDI scores and LVEF, respectively, as

a measure of MI severity, were evaluated with non-parametric Spearman rank correlation tests (ρ). Given the small sample size, a was set at 0.10 to increase statistical power. With regard to the peak levels of serum S100B, 3 subcategories of patients were made in order to allow comparison (especially in the low range) with (neuro) psychiatric diseases in which elevated S100B concentrations are known to occur and are related to clinical symptoms. The first group was defined as having no S100B serum levels above 0.10 µg/l, which is comparable with healthy controls [37]. The second group was defined according to mildly elevated S100B levels between 0.10 and 0.20 µg/l, comparable with levels found in melancholic depression [21]. The third group was defined according to serum S100B levels > 0.20 µg/l measured in various degrees of acute neurological pathology ranging from minor traumatic head injury [38] to stroke with unfavorable outcomes [10, 14, 17, 23, 28, 30, 38].

RESULTS

Subjects (n = 30) who filled out a BDI did not differ from those who refused (n = 23) with respect to age, gender, co-morbidity, renal function, MI severity (LVEF) or S100B values.

Serum S100B Levels and Time Course

Non-parametric pairwise comparisons revealed significant differences for the sample as a whole between S100B at day 1 and S100B peak value (Z = –4.01; p< 0.001).
No significant difference was found between S100B at day 1 and S100B at day 8 (Z = –1.14; p = 0.25).

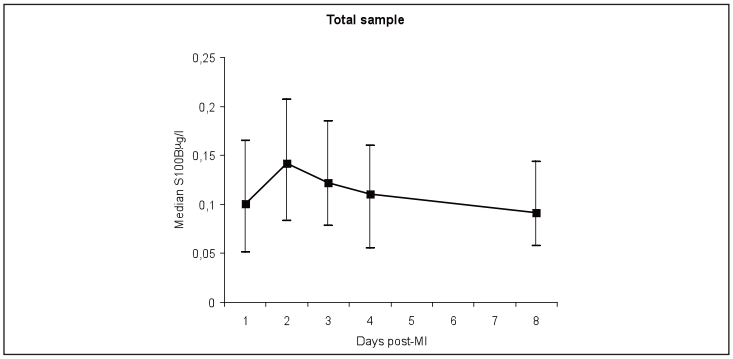

Figure 2. Time course of median S100B serum levels of the whole sample following MI (n= 48). The error bars represent the interquartile range.

Table 2. Spearman's ρ correlation coefficients for S100B (peak value and AUC) and depressive symptoms at baseline and follow up.

Depressive symptoms	S100B peak value	S100B AUC
First week after MI	0.07	0.16
3-month follow-up	0.47**	0.34*
6-month follow-up	0.30	0.23
9-month follow-up	0.53***	0.34*
12-month follow-up	0.36*	0.16

* p < 0.10; ** p < 0.05; *** p < 0.01.

Figure 2 shows the temporal pattern of the median S100B levels and in- terquartile range of the whole group (n = 48). Nine patients (18.7%) had no serum S100B levels above 0.10 µg/l. The second group of 21 patients (43.8%) had mildly elevated serum S100B levels between 0.10 and 0.20 µg/l, comparable with levels found in melancholic depression [21]. In the third group of 18 patients (37.5%), serum S100B levels were significantly elevated and reached levels > 0.20 µg/l as measured in acute neurological pathology. Five of these reached values analogous to values seen in the range of severe cerebral pathology, e.g. stroke (> 0.35 µg/l; Fig. 3).

Serum S100B and Infarct Size

S100B peak value ($\rho = -0.14$; P= 0.49) and S100B AUC ($\rho = 0.03$; P = 0.90) were not associated with LVEF (n =48).

Serum S100B and Depressive Symptoms

Depressive symptoms assessed at initial hospitalization were not related to serum S100B peak value and serum S100B AUC (Fig. 3; n = 27). However, serum S100B peak values and serum S100B AUC were both associated with the BDI score of depressive symptoms at follow-up (Fig. 3). As shown in table 2, a consistent pattern of significant correlations and trends was found for depressive symptoms assessed at 3, 6, 9 and 12 months after MI (n = 27).

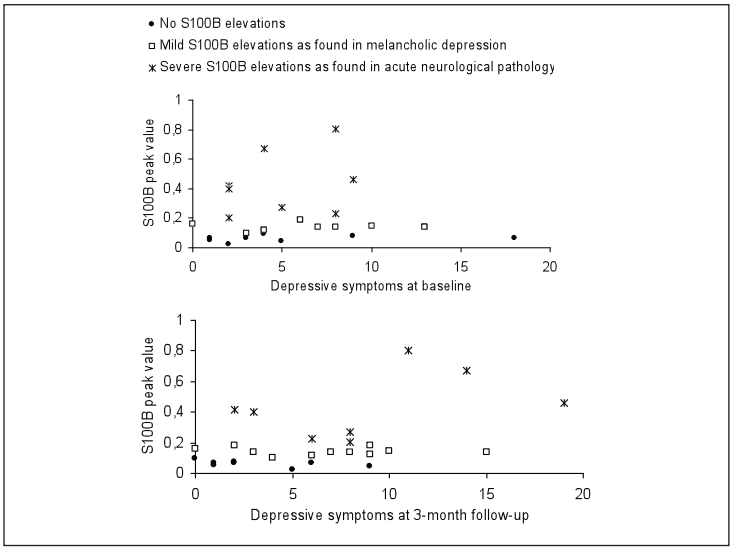

Figure 3: Scatter plots: relation between serum S100B peak value (µg/l) and BDI score.

DISCUSSION

This pilot study is the first to report that S100B serum levels may be increased in the first week after MI in a time and peak pattern comparable with serum S100B release after acute cerebral damage (Fig. 2). Moreover, a trend towards an association was found between serum S100B levels and depressive symptoms during the first year after MI, especially at the later measurement points 3–12 months after MI (table 2). S100B serum levels were not associated with infarct size as derived from LVEF. These data indicate that cerebral damage may play a role in the development of post-MI depression. Although we measured plasma CK/CK-MB, it was not used as a marker of infarct size as early thrombolytic therapy is a confounder in this situation [33]. Therefore, we preferred LVEF as a marker for infarct size.

The results are consistent with previous studies on the association between the late increase in S100B serum levels and cognitive/neurological dysfunction after CPB [25,28]. In late release, defined as the first 5–48 h after CPB, S100B serum contamination from cardiac sources is presumed to be insignificant [24, 28]. Our study results are also in line with the observation that heightened S100B serum levels (>0.30 µg/l) 48 h after CPB might predict long-term (3–6 years) anxiety [16] demonstrating that a single cardiac event might result in long lasting psychiatric symptoms. In light of these studies it is not surprising that another single cardiac event as MI may result in long-lasting depressive symptoms.

As the relation between S100B serum levels and MI is unknown, the question to be considered here is whether the S100B serum levels after MI have a cerebral, cardiac or mixed origin. Several arguments favor a predominantly cerebral origin of the S100B serum levels we found in this pilot study. The isolated ischemic rat heart releases S100B, but only for a maximum of 60 min after myocardial ischemia [39]. As yet no data are available in man.

Considering the short biological half-life of S100B of 25 min and human renal clearance of 2 h [13] the supposed early but transient cardiac release of S100B due to MI will probably only last from some minutes to an hour. This rise will probably remain unnoticed when examining serum samples taken at least several hours following MI, as was the case in this study. As the average time between hospital admittance for MI and the first serum S100B measurement point was 1.8 h, and time between admittance for MI and reperfusion 5 h, we cannot completely rule out that cardiac S100B added to the amount of serum S100B, especially in the serum S100B measurements on day 1. For the measurements of serum S100B on days 2–8 this is highly unlikely, considering the half-life of 25 min. Moreover, we did not find any association between LVEF and S100B serum levels, which also points to an extracardiac origin of S100B.

In addition, the cerebral origin of serum S100B is strongly backed up by the time course, with a peak of median S100B serum levels on days 2–3 after MI (Fig. 2). The pattern is the same as seen after primary acute cerebral injury [14] and also corresponds with the time pattern of late-release serum S100B associated with cerebral damage after CPB [25, 28]. The observed S100B serum levels (Fig. 3) are also comparable to S100B levels found in various neurological and psychiatric study populations. In order to estimate the clinical significance of the measured S100B serum levels, we divided our study population into 3 subgroups. This made comparison possible with previous study populations in which a relation was established between serum S100B and the clinical disease examined. The first group (18.7%) had no S100B elevation at all, therefore the conclusion that MI does not automatically lead to late (5–48 h) release of serum S100B is justified. The second group (43.8%) was defined according to S100B levels found in depressive disorder (0.10–0.20 µg/l) [21]. The third group (37.5%) had levels >0.20 µg/l that can be found in

various forms of cerebral damage ranging from minor traumatic head injury to stroke [10, 14, 17, 23, 28, 30, 38]. This last comparison adds to the preliminary conclusion that the serum S100B levels we found might have clinical relevance.

The variation in S100B levels between the 3 groups is probably due to individual variation in cerebral vulnerability for changes after MI, which is consistent with the observation that patients with a previous history of stroke or transient ischemic attack had higher levels of S100B directly after CPB than those who did not [28]. We presume that the incidental high serum S100B levels > 0.35 µg/l in the range of serious neurological damage [10, 30] may point to small non-progressive brain lesions, formed shortly before blood was collected as none of the patients experienced physical neurological symptoms. Consistent with the latter is that in a serum S100B serial measurement study of head trauma, values of 0.9 µg/l were measured with a rapid decline to 0.2–0.4 µg/l during the first 12 h after the trauma [40]. None of the patients in our study had persistently high serum S100B values. The clinical relevance of glial protein S100B in depressive disorder has not yet been established. Histopathological post-mortem studies showed consistent reductions in glial cell density in prefrontal brain regions of depressive patients [41]. A relation between elevated serum S100B levels and melancholic major depression (a subtype of depressive disorder) was established in physically healthy patients [19]. It was replicated for other but not all types of depressive disorder [19, 21]. In case of association between depressive disorder and S100B serum levels, the levels were consistently between 0.05 and 0.2 µg/l [21]. Antidepressant drugs influence secretion of S100B by astrocytes via the serotonergic system [42]. S100B may induce neurogenesis [43] that is required for behavioral effects of antidepressants [44]. Four treatment studies showed that S100B decreases after successful antidepressant treatment [20, 21, 45, 46]. Patients with increased S100B levels had a better therapeutic response than those with normal S100B levels [46]. However, the effect sizes differ [21], and this may have its origin in the fact that depressive disorder is a heterogeneous group of psychiatric disorders with different neurobiological and psychological characteristics. It is a spectrum disorder with at one-end characteristic predominant psychological symptoms, possibly reflecting only a 'psychological' reaction to stressful circumstances including a life-threatening disease; the other end is characterized by severe somatic symptoms combined with a typical cognitive profile, and related to somatic diseases such as brain damage, MI and severe LV dysfunction in which it is difficult to assess whether the depression is a 'biological' consequence of the illness itself or not [8, 47]. The MIND-IT study provided evidence for the same heterogeneity in post-MI depression [47] . Moreover, it was found that a significant number of patients were depressed before MI, and impaired cardiovascular prognosis and heightened mortality were found only in patients with incident post-MI depression. Incident post-MI depression might be a depressive subtype that is a pathophysiological consequence of cardiovascular illness itself [48] .

The association of elevated S100B levels in the first week after MI with depressive symptoms at 3- to 12-month follow-up indicates that de novo cerebral damage may contribute to the development of post-MI depression. This is also indicative of a specific (biological) subtype of post-MI depression, and in line with earlier reports on cardiac events and induction of psychopathology [16]. Although there seems to be a connection, the small number of patients causes a statistical weakness of association between S100B and depressive symptoms.

Large-scale studies are necessary to gather more in-depth insight into the connection between S100B levels and depressive symptoms.

As different subtypes of post-MI depression have a different response to treatment and non-response is associated with more cardiac events [48], it is important to obtain knowledge about possible mechanisms in the association between depressive symptoms and MI in the several subtypes of post-MI depression in order to develop prophylactic and therapeutic regimens, both in terms of quality of life and prognosis.

Given the dual (survival and toxic) effect on neurons and its wide variety of intra- and extra-cellular functions, it remains to be proven if the increase in S100B serum concentration in our study is due to substantial destruction of CNS tissue or to an active release of S100B from intact astrocytes attempting to repair neuronal damage.

The present findings need to be interpreted with caution, given the small number of subjects, the absence of neuropsychological tests to assess cognitive impairment and the lack of inflammatory data. Nor do we exclude the possibility that brain damage was caused by complications of thrombolytic therapy [49]. Nonetheless, the results do warrant further research to discern the interrelation of post-MI depression, MI-related brain damage, inflammation and coronary heart disease.

In conclusion, our data are the first to show a release of S100B in serum during the first week after MI, and a positive correlation between serum S100B and depressive symptoms at 3- to 12-month follow-up. Although we do not entirely rule out the influence of cardiac S100B, several arguments favor cerebral damage as the main source of the serum-derived S100B. The arguments include the positive correlation between S100B and depressive symptoms at 3- to 12-month follow-up, the time course of the curve of S100B in the first week after MI and the absence of S100B elevation in 18% of the patients during the initial hospitalization for MI. The present data may imply that post-MI cerebral damage is associated with a subtype of post-MI depression.

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PART 1

CHAPTER

5

White matter lesions and occurrence of depressive symptoms in post myocardial infarction patients: data from the MIND-IT.

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Submitted

ABSTRACT

Objective. Several studies suggest that late life depression is associated with the presence of white matter lesions (WML). Post myocardial infarction (MI) depression can be considered as late life depression. The aim of this study was to investigate whether presence and severity of WML was associated with depressive disorder or in a lesser degree to depressive symptoms in the year post MI.

Methods. All participants of this Magnetic Resonance Imaging (MRI) sub-study of the Myocardial Infarction and Depression -Intervention Trial (MIND-IT) were screened for depressive symptoms with the Beck Depression Inventory (BDI) in the year post MI. Complete BDI data were available for measurement points 0 and 3 months post MI. Brain MRI scans were performed in 34 post-MI patients after clinically examination by a psychiatrist. Of these, 16 were diagnosed with a DSM IV depressive disorder (and BDI≥10) and 18 were clinically not depressed (and BDI <10). Severity of DSM IV depressive disorder was assessed with the Hamilton Rating Scale and BDI.

Results. Severity of sub-cortical WML was associated with the severity of depressive symptoms, as assessed by BDI, the first week post MI ($t=4.01$, $df=31.1$, $p<.001$). Average levels of depressive symptoms were higher in the WML group at both time points as compared to the non-WML group. DSM IV depressive disorder was not statistical significantly associated with presence of WML (OR=4.52; 95%CI 0.60-34.09, $p=.14$) and severity of WML ($Z= -.31$, $p=.76$).

Conclusion. Presence of subcortical WML is associated with severity of depressive symptoms on the BDI during the in hospitalization phase for MI. No statistically significant association was found between WML and DSM IV depressive disorder post MI, in part due to the small number of patients included in this substudy.

INTRODUCTION

Minor and Major Depressive disorder in the year post Myocardial infarction (MI) affect 8 to 30 % of the patients depending on the assessment method [1] and are associated with a 2-2.5 fold increased risk for all-cause mortality, cardiovascular mortality and cardiovascular events [2] Although substantial numbers of depressive episodes associated with MI begin long before MI [3], especially incident depression post MI is associated with an increased risk for further cardiac events [4,5]. Whatever the relationship between the pre-MI and the post-MI psychiatric status, the MI patient is vulnerable for depression, which may be mediated by discrete vascular lesions in several regions of the brain. White Matter Lesions (WML) are ischemia related lesions in cerebral white matter that are regarded as manifestations of poor perfusion. They are seen as bright areas in brain parenchyma on a T2 weighted magnetic resonance imaging (MRI) scan, without demonstrating clear infarcts. Established risk factors for the development of WML are aging and vascular risk factors such as hypertension, atrial fibrillation and measures of atherosclerosis [6]. WML can be subdivided in peri-ventricular WML (PVWML) and deep or sub-cortical white matter WML (SCWML). PVWML have been associated with cognitive dysfunction while SCWML have a stronger association with depressive symptoms [7]. Reports on the association between the localization of WML and depressive disorder differ. The occipital and temporal areas are mentioned as most prevalent sides for WML [8] as well as frontal and temporal regions [9,10]. In contrast to SCWML, PVWML predict both ischemic stroke and myocardial infarction in patients with established atherosclerotic disease [11]. Despite differences in risk factors and outcome parameters the prevalence of PVWML and SCWML is highly correlated [6]. Studies on WML in depressive disorder have suggested that more frequent and severe WML are associated with Late Onset or Late Life Depression (LLD). The dominant view is that WML reflect cerebrovascular disease that predisposes a subset of older patients to the development of depressive disorder by disrupting fibre tracts connecting cortical and subcortical structures including the frontostriatal circuits that are involved in the regulation of mood [9,10]. This view is also known as the "vascular depression hypothesis" [12].

As MI usually occurs at older age, in most cases (incident) post MI depression can be considered as LLD. Post MI depressive disorder consists of several subtypes [3,4,13]. In a previous study we demonstrated that transiently elevated levels of serum S100B in the first week post MI were associated with depressive symptoms in the year post MI [14]. S100B is a marker for cerebral damage [15]. Therefore, cerebral damage could be an important mechanism in the pathogenesis in a subtype of post-MI depression. In patients with heart failure a significant correlation was found between the severity of frontal WML and severity of depressive disorder [16].

To date the association between WML and depressive symptoms in the post MI period has not been assessed. The aim of this study was to test the hypothesis that presence and severity of cerebral white matter lesions in post MI patients are associated with depressive disorder or, in a lesser degree, depressive symptoms. Considering the age and cardiovascular status of the study sample a high prevalence of WML was expected. Therefore it was decided to assess the association between WML and post MI depressive disorder in two ways. At first, we choose a dichotomous comparison. The patient sample with a depressive disorder fulfilling Diagnostic and Statistical Manual -IV (DSM IV) criteria was compared to the non depressed group with regard to presence and severity of total WML, PVWML and sub-cortical WML. Then, in a second analysis we abandoned the dichotomous depressed/non depressed categorization of the study sample. Next, we studied the sever-

ity of depressive symptoms on a continuous severity rating scale in relation to presence and severity of WML in the patient sample as a whole and independent of their DSM IV diagnosis of depressive disorder.

METHODS

SubjectsData were derived from the Myocardial Infarction and Intervention Trial (MIND-IT). The MIND-IT is a multicenter, randomized controlled study on the effects of antidepressant therapy for post-MI depression on cardiovascular prognosis.The study design of the MIND-IT study has been described previously in detail [17]. In brief, we recruited consecutive patients (September 1999-November 2002), hospitalized for acute MI, in 10 hospitals in The Netherlands. Patients were enrolled if they met WHO MONICA criteria for definite MI. Exclusion criteria were: the occurrence of MI while the patient was hospitalized for another reason, unable to participate in study procedures, a disease likely to influence short-term survival, patients already receiving psychiatric treatment for depression, and participation in another clinical trial. The MRI sub-study included only patients admitted to Medical Centre Leeuwarden, one of the participating hospitals of the MIND-IT study. Additional exclusion criteria for the MRI sub study were contraindications for MRI scanning like claustrophobia or metallic objects.Patients were screened for depressive symptoms during hospitalization for MI (0 months) and at 3, 6, 9 and 12 months post-MI, using the Beck Depression Inventory (BDI) a rating scale for subjective depressive symptoms [18]. Those with BDI score ≥ 10 underwent a psychiatric evaluation by trained research nurses using the WHO Composite International Diagnostic Interview (CIDI) auto version 2.1[19] (Fig. 1).

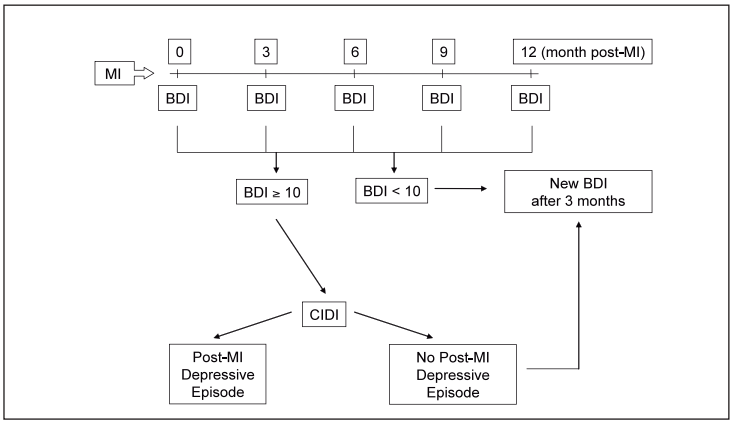


Figure 1. Flow chart of the MIND-IT study: screening procedure.

Patients with a diagnosis of 'Depressive Episode' according to the CIDI were randomised to Intervention or Care as Usual. Those randomised to intervention had a clinical interview with a psychiatrist for assessment of clinical diagnosis according to DSM IV (Fig. 2). Patients meeting clinical criteria for a depressive disorder according to DSM-IV were asked to participate in the presented MRI sub-study of the MIND-IT (n=16) and severity of depressive symptoms was assessed with the Hamilton Rating Scale (HAM-D 17) and the BDI. MRI scans were made with a range from 5-15 months post MI.

The non-depressed control group (n=18) was also recruited from the MIND IT cohort during their follow-up screening period in the year post MI (Fig.1). They were selected when BDI < 10 and matched with the DSM IV depressed patients for age, gender, time to MI. Next, all control patients had a clinical assessment by a psychiatrist to exclude a psychiatric disorder before they entered MRI scanning.

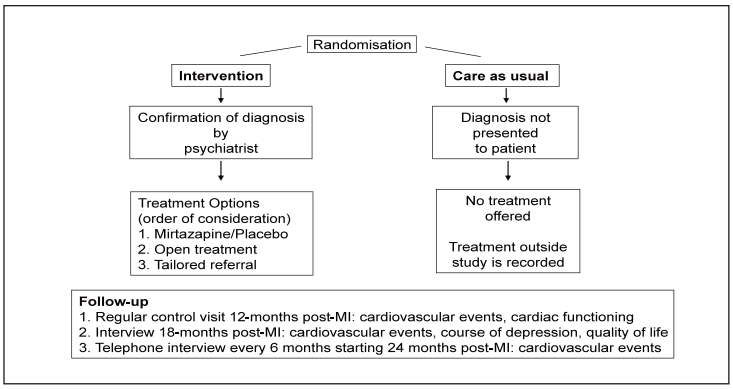


Figure 2. Flow chart of the MIND-IT study: randomisation to intervention and Care as Usual.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the local ethical committees approved the study design. All participants were fully informed and gave written informed consent.Imaging analysis Cranial MRI scanning (Siemens Magnetom Impact 1.5T) was performed in all 34 patients using a transverse (anterior-posterior commisure line) plane with 4-5mm slice thickness and a 20% gap covering the whole brain and acquiring T2 spin-echo (TR 2250 ms, TE 19 ms) and Fluid Attenuated Inversion Recovery (FLAIR) (TR 9000 ms, TE 100 ms, TI 1900 ms) images. The information was coded and stored anonymous on a digital disk.
White Matter Lesion Rating ScaleAn experienced neuro-radiologist, blinded to participant's category and clinical data, rated the presence, size and number of white matter lesions on a workstation. White matter lesions were considered present if hyper-intense on FLAIR and T2-weighted images and not as hypo-intense as liquor on a T1-weighted image. A WML severity score was used to assess the extent of increased white matter signal intensity on FLAIR images for the subcortical area as described previously [20]. Briefly, for subcortical WML an index for their total volume was approximated (based on number and size of all subcortical lesions (range 0 - 0.4 mL). The size of subcortical WML was rated according to their largest diameter in categories of small (< 3 mm), medium (3-10 mm), or large lesions (> 10 mm). Considering them spherical with a fixed diameter per size category, a total approximated volume of subcortical WML was calculated. Periventricular Lesions were rated as none, pencilthin (1), slightly extending into the periventricular white matter (2), or extensively extending into the periventricular white matter (3).
Statistical analysis
The aim of this study was to test the hypothesis that presence and severity of cerebral white matter lesions in post MI patients are associated with DSM IV depressive disorder or, in a lesser degree, to depressive symptoms. Considering the complex relation between WML, cardiovascular disease and depressive disorder it was decided to assess the association between WML and post MI depressive disorder in two ways. First, we split the study population in a DSM IV depressed and DSM IV non-depressed group.

Subcortical WML and periventricular WML were dichotomized as respectively 'subcortical WML present' vs. 'subcortical WML not present', and 'periventricular WML present' vs. 'periventricular WML not present'. In addition, an approximation for subcortical WML volume was used as described in the previous paragraph. One case was identified as outlier (WML severity >3SD), and was excluded for analyses involving subcortical WML volume. The relationship between the presence of WML and DSM IV depressive disorder was tested by using the contingency coefficient (f) in univariate analysis, and by using logistic regression in multivariate analysis controlling for sex and age. Finally, the association between subcortical WML volume and clinical DSM IV depression was examined using the Mann-Whitney U test.

In the second analysis scores on the BDI were related to presence and severity of total WML and SCWML in the patient sample as a whole, that is both the DSM IV depressed and non depressed group. Next, a group comparison was made between patients with and without WML independent of their DSM IV diagnosis and for both groups severity of depressive symptoms on the BDI was assessed.

A t-test or Mann-Whitney U test (depending on normality of data) was used to determine the association between the presence of WML and depressive symptoms. Multivariate regression analysis was adopted to test the same association while controlling for sex and age. To test the association between subcortical WML volume and depressive symptoms, Spearman's rho correlations (ρ) were employed.

RESULTS

Baseline characteristicsThe majority of subjects were male (Table 1). There was no difference between the depressed and non-depressed patients with regard to localization and history of MI, LVEF, and prevalence of diabetes and hypertension. Depressed patients were more likely to have hypercholesterolemia (81.2% vs. 55.6%, p= .05) as compared to non-depressed patients. Ascal, beta-blockers, and statins were the most prescribed medications. Depressed patients were more likely to be on calcium antagonists (31.1% vs. 5.6%, p=.05) and statins (87.5% vs. 55.6%, p=.04) as compared to non-depressed patients.

WML were present in 79.4% (n=27) of the patients. Small (< 3 mm), medium (3-10 mm), and large subcortical lesions were observed in 76.5% (n=26), 50% (n=17), and 14.7% (n=5) of all patients respectively. Only in 11.8 % (n=4) of patients confluent lesions were found. Of the patients with WML, 41.2% (n=14) had periventricular lesions.

*Table 1. Baseline and treatment characteristics stratified by depressed vs. non-depressed patients.**

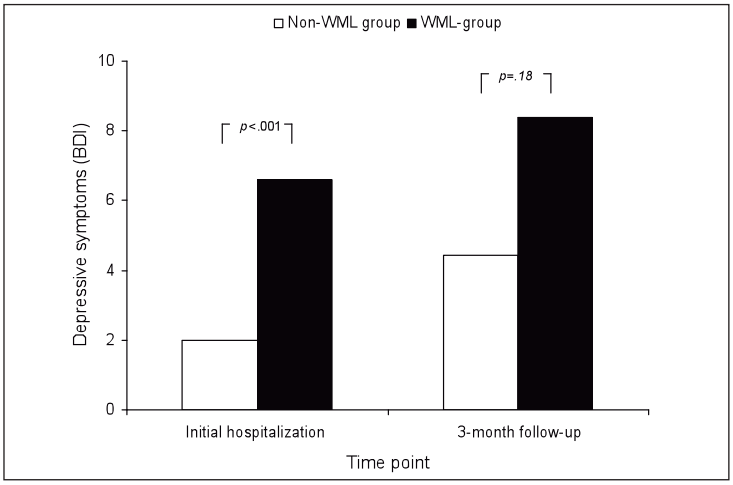
Variable	Total group (n=34)	Depressed (n=16)	Non-depressed (n=18)	p-value
Male sex	82.4 (28)	75.0 (12)	88.9 (16)	.29
Age, mean in years (SD)	62.7 (12.0)	60.1 (12.7)	64.9 (11.2)	.26
Anterior MI	29.4 (10)	25.0 (4)	33.3 (6)	.60
History of MI	8.8 (3)	12.5 (2)	5.6 (1)	.48
LVEF<45%	44.1 (15)	64.3 (9)	37.5 (6)	.14
Diabetes	17.6 (6)	25.0 (4)	11.1 (2)	.29
Hypertension	38.2 (13)	50.0 (8)	27.8 (5)	.18
Hypercholesterolemia	67.6 (23)	86.7 (13)	55.6 (10)	.05
Medication at discharge				
Nitrates	26.5 (9)	31.3 (5)	22.2 (4)	.55
Ascal	79.4 (27)	87.5 (14)	72.2 (13)	.27
Acenocoumarol	17.6 (6)	12.5 (2)	22.2 (4)	.46
Beta blocker	85.3 (29)	81.3 (13)	88.9 (16)	.53
Diuretics	23.5 (8)	18.8 (3)	27.8 (5)	.54
Calcium antagonists	17.6 (6)	31.3 (5)	5.6 (1)	.05
Statins	70.6 (24)	87.5 (14)	55.6 (10)	.04
ACE-inhibitors	23.5 (8)	18.8 (3)	27.8 (5)	.54

*numbers represent % (n), unless stated otherwise

WML and DSM IV depressive disorder Presence of WML was not associated with presence of depressive disorder according to DSM IV in the year post MI in both univariate (ϕ=.19, p=.27) and multivariate analysis (OR=4.52; 95%CI 0.60-34.09, p=.14). Additionally, the severity of subcortical WML was not associated with depressive disorder according to DSM IV in the year post MI (Z= -.31, p=.76).

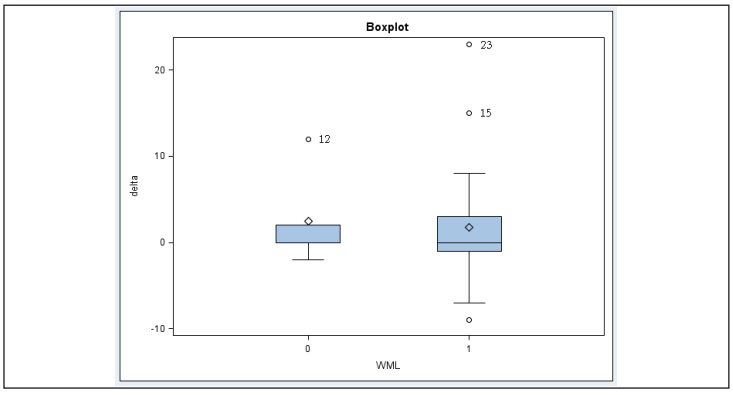
WML and depressive symptoms measured with the BDIIn univariate analyses no association was found between the total number of WML and severity of depressive symptoms on the BDI at 0 and 3 months post MI. The presence of sub-cortical WML was highly significantly associated with severity of depressive symptoms during initial hospitalization (t=4.01, df=31.1, p<.001). This association remained significant (β=.39, p=.03) after controlling for gender and age (both p>.05). Nor did controlling for prescription of calcium antagonists and statins alter this association. Presence of subcortical WML was not associated with severity of depressive symptoms at 3-month follow-up (t=1.22, df=32, p=.23). Average levels of depressive symptoms were higher in the WML group at both time points as compared to the non-WML group (fig 3).

Figure 3. Average level of depressive symptoms stratified by WML-group.



In the WML group 2 patients could be defined as having extreme values on the BDI as compared to he remaining patients in the same group; in the non-WML group 1 patient could be regarded as an outlier (Fig. 4). Abandonning these three values from analyses changed the association between WML and depressive symptoms on 3 months in the direction of significance (p=0.053). However, from a clinical point of view both the BDI and WML have a wide range of distribution. Therefore, omission of outliers would influence the study results in an essential way. For that reason it was decided not to abandon outliers.

Figure 4. Changes in BDI scores (delta) between 0 and 3 months post MI in the non-WML group (0) and WML group (1).



Periventricular WML were not associated with depressive symptoms during initial hospitalization (t=1.80, df=32, p=.08) or at 3-month follow-up (t=.77, df=32, p=.45). Furthermore, volume of subcortical WML was not associated with depressive symptoms during initial hospitalization (ρ=.12, p=.51) and at 3-month follow-up (ρ= -.06, p=.76).

DISCUSSION

This investigation documents for the first time that WML are associated with depressive symptoms in the post MI period. However, this relationship is complicated which is reflected by the study data showing the presence of WML in the majority of the patients and a variable association over time between WML and depressive symptoms.
WML were present in about 80% of both the depressed and non- depressed post MI patients. This high prevalence of WML is reasonable due to the age and cardiovascular status of the study sample but may be a confounding factor in establishing the relation between WML and depressive disorder, especially when the small sample size is considered. Therefore we investigated the relationship between WML and post MI depression in two ways.
When the study population was dichotomized in a DSM IV depressed versus non depressed group no statistic significantly association was found between severity of total WML, SCWML and PVWML and presence of DSM IV depressive disorder in the year post MI (OR=4.52; 95%CI 0.60-34.09, p=.14). Considering the OR of 4.52 and the relatively small sample size a power problem might be responsible for this lack of association.

However, depression consists of a continuum of symptoms that has to reach a certain threshold in symptom severity before it fullfills the criteria of DSM IV depressive disorder. Many non-depressed post MI patients have sub-threshold depressive symptoms that can be measured by the BDI.
So, in the second analysis the association between severity of depressive symptoms and WML was investigated in the patient sample as a whole and independent of their DSM IV diagnosis of depressive disorder. With this approach the hypothesized relation between WML and depressive symptomatology became more evident.
The presence of SCWML was strongly associated with severity of depressive symptoms on the BDI during initial hospitalization for MI, but not significantly associated with severity of depressive symptoms at 3-month follow-up. This association lost its statistical significance at 3 months post MI (p=.23) as between 0-3 months the non-WML group had a higher incidence of depressive symptoms on top of baseline depressive symptoms as compared to the WML group.
The average levels of depressive symptoms were higher in the WML group as compared to the non-WML group at both 0 and 3 months post MI (Fig. 3).
PVWML were not associated with severity of depressive symptoms at any time point, which is in accordance with previous reports [7].
Besides the power problem, comparing these results with previous studies has its limitations as research diagnosis and severity of (late life) depression in MRI studies are defined by a wide range of different diagnostic criteria, assessments methods and subjective rating scales [10]. Despite these limitations, the results of this study are consistent with numerous cross-sectional studies on WML and depression demonstrating that especially SCWML are associated with late life depressive symptoms [7,8,9, 21].
The studies with a longitudinal prospective design [21, 22, 23, 24] show more conflicting results concerning the predictive value of WML on the development of depressive symptoms at follow up. The results of our study are in line with the only longitudinal large scale study on patients with cardiovascular disease demonstrating that WML were not predictive for the development of depressive symptoms at follow up [22]. In contrast to the findings in the cardiovascular population, WML did have predictive value for the development of depressive disorder at follow up in a general population study [23].

In order to explain our results we hypothesize that post MI depression consists of several subtypes of depressive disorder [4,25,26] and only some of them are associated with WML. The association between depressive symptoms and WML at 0 months may indicate that the stressful period in the hospitalization phase for MI has more impact on subjects with less capacity for compensation due to lesions in the sub-cortical brain structures such as WML. This could explain why, during hospitalization, patients with WML compared to those without WML, experience stronger affective and somatic symptoms as measured with the BDI. Moreover, part of the observed association between depressive symptoms and sub-cortical WML at 0 months could be due to pre-MI depressive symptoms as a substantial number of depressive episodes associated with MI begin long before MI [3].
Between 0 and 3 months post MI the number of depressive symptoms rises in both the WML and non WML group but only with a mean of two points on the BDI (Fig. 3). This pattern suggests that the vast majority of patients with both WML and a vulnerability for development of depressive symptoms are already depressed at 0 months.
As no association was found between the presence of WML and the development of depressive disorder in the year post MI, additional factors might play a role in the development of depressive symptoms in the year post MI.
In order to explain this finding we hypothesize that some subtypes of post MI depression are de novo depressive disorders that need some months to develop to reach a clinical threshold for depression. For instance, as a consequence of severe heart disease [4,13], activation of the immune system and sickness symptoms [26] or de novo cerebral damage as reflected by transiently increased serum S100B levels in the first week post MI [14]. The finding that S100B blood levels post MI are not associated with depressive symptoms during hospitalization but were associated with those at 3-12 month follow-up supports this hypothesis [14].

Among the strong aspects of our study is first at all its novelty, as there are no other reports on the association between WML and post MI depressive disorder. Secondly, all patients were free of antidepressants and thirdly the multiple approaches to assess possible relationships. This study shows that with a dichotomous categorial analysis valuable information is lost while with a dimensional approach the subtle relationship between WML and depressive symptoms becomes apparent.
Some negative findings such as the lack of association between depression defined by DSM-IV diagnostic criteria and WML might be attributed to the limited size of the study. On the other hand we found highly significant association between depressive symptoms in the acute phase of MI and sub-cortical WML indicating that the size is sufficient to reach possibly clinically relevant conclusions.

Limitations of the study should also be addressed. MRI scans were performed at variable times (5-15 months) post MI. We related the WML scores several months post MI retrospectively to the BDI scores at 0 and 3 months. One might question whether MRI assessment of WML at several months post MI gives reliable information about the WML status of the patient during hospital admission and 3 months post MI. Two arguments are in favour to do so. First: previous studies demonstrated that progression of WML is very slow [22]. Therefore, it seems justified to make the assumption that the WML status of the patients was the same during hospital admission and the year after. Moreover, previous research demonstrated that progression of study baseline WML during 33 months is not associated with the development of new depressive symptoms [22]. Second: MRI scan-

ning during hospital admission for MI and repeated MRI during the depressive episode would have been more reliable but was ethically and clinically not feasible.In sum, we found an association between presence of WML and severity of depressive symptoms during the hospitalization phase that was lost at 3 months post MI although depressive symptoms increased in both the WML and non WML group. The present findings need to be interpreted with caution, given the small number of subjects and the absence of rating of WML location. Another limitation is the absence of longitudinal "repetitive follow up" MRI scanning. Nonetheless, the relationship between the early post MI depressive symptoms and SCWML was highly significant. The results do warrant further longitudinal research to discern the interrelation of post-MI depression, MI-related brain damage and coronary heart disease.

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PART 1

CHAPTER

6

Inflammatory markers in depressed post-myocardial infarction patients.

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ABSTRACT

Objective. Depressive disorder in the post-myocardial infarction (MI) period has been associated with increased cardiac morbidity and mortality. Possible pathophysiological mechanisms behind this association are not clear. Major depression in physically healthy subjects has been related to immune abnormalities including increased plasma levels of interleukin-6 (IL-6), tumor necrosis factor alfa (TNF-α) and C-reactive protein (CRP). In patients with MI, increased inflammatory markers, such as CRP and TNF-α, have been associated with increased cardiovascular events. It was the aim of this study to test the hypothesis that depression in post-MI patients is associated with increased inflammation as compared to non-depressed post-MI patients.

Methods. The cytokines IL-6 and TNF-α; the soluble cytokine receptors sIL-6R, sTNF-RI and sTNF-R2; neopterin; and the inflammation-sensitive plasma proteins (ISPs) CRP and haptoglobin were assessed in a group of 57 patients with a diagnosis of depression post-MI and in a control group of 46 non-depressed post-MI patients, matched for age, gender and time elapsed since MI.

Results. Cytokine, neopterin and ISP levels were not statistically different in the depressed post-MI group as compared to the non-depressed post-MI group. Several inflammatory markers were however elevated in both cohorts when compared with levels reported in healthy subjects, indicating persistent inflammation several months after MI.

Conclusion. There was no indication of increased inflammation in depressed post-MI patients as compared to non-depressed post-MI patients.

INTRODUCTION

Depression is an important independent risk factor for cardiovascular events in both medically healthy individuals and cardiac patients [1,2] Possible pathophysiological mechanisms behind this association have not yet been elucidated. Interestingly, in somatically healthy patients with major depression, increased levels of cytokines, such as IL-1b, IL-2, IL6 and TNF-α, have been reported [3-9]. Also, increased levels of neopterin and inflammation-sensitive plasma proteins (ISPs) such as CRP and haptoglobin have been found [10-13].

On the other hand, growing evidence suggests that atherosclerosis, as one of the main causes of cardiovascular events, is fundamentally an inflammatory disease [14] and that inflammatory markers are predictors of coronary events [15,16]. In patients with MI, a major clinical complication of atherosclerosis, increased levels of TNF-α [16] and CRP [15] were associated with increased risk of recurrent coronary events. And in a prospective study involving 14 916 apparently healthy men, elevated levels of IL-6 were associated with increased risk of future MI [17]. Recently neopterin, which is produced by activated macrophages and serves as a marker for the activation status of monocytes/macrophages, was shown to be a predictor of adverse coronary events in patients who experienced a non-Q-wave MI [18].

In summary, recent evidence suggests that both depression as well as atherosclerosis associated diseases such as MI, are characterized by elevated levels of various circulating proinflammatory mediators. Some of these proinflammatory markers have additionally been associated with increased risk of cardiac events. If both MI and depression are associated with inflammation, it may be hypothesized that depressed post-MI patients have an additional inflammation on top of MI-related inflammation. Higher levels of proinflammatory mediators, which are at the same time risk markers for coronary artery disease (CAD), might then be a possible link between post-MI depression and increased cardiac morbidity and mortality. In this study we tested the hypothesis that depressed post-MI patients have increased markers of inflammation as compared to nondepressed post-MI patients. For this reason cytokines IL-6 and TNF-α; soluble cytokine receptors sIL-6R, sTNF-R1 and sTNF-R2; neopterin and the ISPs CRP and haptoglobin were assessed in depressed and non-depressed post-MI patients.

METHODS

Patients

From September 2001 to December 2002, as part of their participation in the multicenter Myocardial Infarction and Depression – Intervention Trial (MIND-IT) [19], patients admitted with an MI were screened for depressive symptoms during hospitalisation and 3, 6, 9 and 12 months after MI with a 21-item Beck Depression Inventory (BDI) questionnaire. Those with symptoms (ie a BDI score ≥10) had an additional psychiatric evaluation with a standardized psychiatric interview, the structured Composite International Diagnostic Interview (CIDI-auto) by a research assistant. Patients with a research diagnosis of "post-MI depressive episode" had a clinical interview by a psychiatrist. Depression was defined as meeting DSM-IV criteria for major or minor depression. If the diagnosis depression was confirmed, patients were asked for blood collection as part of the present substudy. A consecutive cohort of 57 depressed MI patients (31 patients in Maastricht, 12 in Leeuwarden, 9 in Amsterdam and 8 in Groningen) gave informed consent for additional blood collection. None of these patients had antidepressant treatment at the time blood was collected.

The control group consisted of non-depressed post-MI patients participating in the MIND-IT study. These patients were recruited from the MI patients who had BDI scores of 9 or less. The control group, matched for age, gender and time elapsed since MI, consisted of 46 non-depressed post-MI patients (23 patients were recruited in Maastricht, 13 in Leeuwarden, 7 in Amsterdam and 3 in Groningen). MI diagnoses were made by a cardiologist based on to the following criteria: clinical presentation, electrocardiographic signs typical of an acute MI, creatinine kinase (CK) levels of ≥480 U/l (twice the upper limit of normal) and enzyme aspartate aminotransferase (ASAT) levels of ≥80 U/l (twice the upper limit of normal). Blood samples were taken between 9.00 and 11.00 a.m. after an overnight fast. A venapuncture was performed in the antecubital vein. Blood samples were collected and stored in sterile Vacutainer tubes without additives (Becton–Dickinson, Basel, Swiss) and samples centrifuged at 2200g for 5 min. Serum samples were stored at -70° until analysis. Exclusion criteria for this substudy were: presence of other psychiatric diagnoses, receiving anticoagulant medication except aspirin, presence of acute infections and presence of chronic illnesses known to affect the immune status (e.g. rheumatoid arthritis, inflammatory bowel disease).

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the study design was approved by the local ethical committee. All participants were fully informed and gave written informed consent.

Laboratory analyses

Serum concentrations of various inflammatory markers were measured using commercially available enzymelinked immunosorbent assays (ELISA). Kits for sIL-6R, TNF-α sTNF-RI and sTNF-R2 were obtained from Bender MedSystems (Vienna, Austria), and kits for neopterin from IBL (Hamburg, Germany). CRP was measured using a high-sensitive ELISA-kit from ICN Pharmaceuticals (Orangeburg, NY, USA). All assays were performed according manufacturer instructions. The detection limits in our laboratory were: 0.08 ng/ml (sIL-6R, sTNF-R 60 kDa), 0.16 ng/ml (sTNF-R 80 kDa), 8 pg/ml (TNF-α) and 0.005 mg/l (CRP). IL-6 concentrations were measured with ELISA-kits from Dia-Med-Eurogen (Turnhout, Belgium) using a modified protocol to increase the sensitivity of the ELISA. Modifications were: longer incubation times for standard/sample and detection-antibody incubation (2 and 1 h,respectively); incubation of standard/sample and detection-antibody at room temperature while shaking at 600 rpm on a microtiterplate shaker;

and further dilution of standards. The detection limit in our laboratory was 0.5 pg/ml. Hp concentrations were determined by means of fixed-time immunonephelometry with a BNII nephelometer (Behringwerke AG, Marburg, Germany), calibrated against the international CRM 470 standards [20].

Statistical analysis

First, baseline characteristics were investigated of the depressed and the non-depressed groups. Chi-square in case of dichotomous variables and t-test in case of continuous variables were applied. Next, multivariate linear regression analyses were performed with each individual immune parameter as dependent variables and post-MI depression (0–1) as predictor. Age, smoking on admission, dummy variables for quit smoking after MI, continue smoking after MI and never smoked, body mass index (BMI), hypertension, positive family history for CAD, months elapsed since MI and cholesterol plasma levels were tested for their potential confounding effects. Since it was a multicenter study, it was tested whether there were in-between center effects. Analyses were also performed with (a continuous) mean BDI score as predictor instead of (a dichotomous) depressive state. Cook's distance was used to identify influential cases according to the lines described by [21]. The significance level was set at $\alpha = 0.05$ (two-tailed). Statistical analyses were performed with SPSS 10.0 for Windows.

RESULTS

Demographic data

Patients' ages ranged from 36 to 79 (mean 57.3) in the group with a depressive disorder post-MI and from 34 to 80 (mean 56.1) in the post-MI group without depression. As part of their participation in the MIND-IT study, patients could not be included earlier than 3 months after MI and not later than 12 months post-MI (mean 5.8; SD 3.3). Mean BDI score of depressed patients was 13.5 (SD 6.8) and of non-depressed patients 3.4 (SD. 2.4); the difference was significant ($p < 0.001$). There were no significant differences between the groups with regard to BMI ($t = -0.3$; $p = 0.7$) or cholesterol plasma levels ($t = -0.1$; $p = 0.9$) (Table 1). Other conventional risk factors for CAD such as hypertension, smoking, CAD in the family and diabetes mellitus were not significantly different between the groups. As can be seen in Table 1, prevalence of diabetes mellitus was low in both groups (6–7%). This was due to the fact that these patients refused additional blood collection more often and because some patients with diabetes had exclusion criteria for this substudy such as receiving anti-coagulant medication except aspirin, presence of acute infections and presence of chronic illnesses known to affect the immune status (e.g. rheumatoid arthritis, inflammatory bowel disease). Infarction size, as measured by left ventricle ejection fraction (LVEF), creatinine kinase (CK) and enzyme aspartate aminotransferase (ASAT) levels were not statistically different between the groups. Treatment of MI, defined as thrombolysis, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG), was also not statistically different between the groups. Nearly all patients were prescribed aspirin (>89%), a beta-blocker (>84%) and a statin (>82%). Prescription of ace-inhibitors (ACE-I) was higher in the non-depressed group as compared to the depressed group (35% and 25% respectively) but the difference was not significant. Prescription of calcium channel blockers (CCB) was 15% and 21% respectively ($p = 0.6$).

Table 1. Demographic and cardiovascular characteristics of depressed and non-depressed post-MI patients on admission to hospital for MI and at discharge.

	Non-depressed MI-patients n = 46	Depressed MI-patients n = 57	p-Value
Gender (m/f)	41/5	49/8	NS
Age	56.1 (12.0)	57.3 (11.1)	NS
BMI	26.7 (3.7)	27.0 (4.2)	NS
BDI	3.4 (2.4)	13.5 (6.8)	p < 0.001
CKmax (U/l)			
(normal range 40–240 U/l)	1995 (1897)	1895 (1735)	NS
ASATmax (U/l) (n: 5–40 U/l)	239 (157)	226 (169) NS	
Cholesterol (mmol/l) (n: 4–6 mmol/l)	5.3 (1.1)	5.3 (1.1) NS	
Smoking on admission (%)	65.2	61.4	NS
Hypertension (%)	21.7	22.8	NS
Diabetes mellitus (%)	6.5	7.0	NS
Previous MI (%)	4.4	8.8	NS
Family history for CAD (%)	52.6	42.2	NS
Peripheral vascular disease (%)	10.9	7.0	NS
At discharge			
Thrombolysis (%)	43.5	38.6	NS
PTCA (%)	45.7	42.1	NS
CABG (%)	6.5	5.3	NS
LVEF (%) ≥60%	31.8	13.2	NS
45–60%	38.6	50.9	NS
30–45%	27.3	26.4	NS
<30%	2.3	9.4	NS
Aspirin (%)	95.7	89.5	NS
Beta-blocker (%)	84.8	87.7	NS
Statin (%)	82.6	91.2	NS
ACE-inhibitor (%)	34.8	24.6	NS
Calcium antagonist (%)	15.2	21.1	NS

p-Value = two-tailed level of significance; Values are means (SD); NS: not statistically significant; BMI: body mass index; LVEF: left ventricular ejection fraction; MI: myocardial infarction; CKmax: maximum levels of creatinine kinase during hospitalisation for MI, ASATmax: maximum levels of aspartate aminotransferase during hospitalisation for MI; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting; CAD: coronary artery disease; BDI: Beck Depression Inventory.

Immune activation

The mean values of eight immune parameters for the depressed and the non-depressed group are listed in Table 2. As can be seen from the data, no meaningful increase can be observed in the depressed group, as compared to non-depressed patients. For each parameter a bivariate regression model was tested with the immune parameter as dependent variable and group (depressed versus non-depressed) as predictor variable. None of these models was significant (all p-values > 0.29). Since no bivariate model reached significance, an additional correction for multiple testing was not carried out. In a second step, for each immune parameter a multiple regression analysis was carried out including potential confounding variables (such as smoking, BMI, etc). Also in these multivariate models the group effect was not significant. A trend (p = 0.053) was visible for the group effect in the neopterin model. However, this finding is highly disputable since correction for multiple testing indicates that only p-values less than 0.0063 (0.05/8 in case of a Bonferroni method) can be considered as statistically significant.

Table 2. Inflammatory markers (mean, SD) in depressed and non-depressed post-MI patients.

	Non-depressed MI-patients n = 46	Depressed MI-patients n = 57	p-Value
sTNF-R2 (ng/ml) (ev 3.4–10.8 ng/ml)	12.7 (11.0)	15.3 (13.0)	NS
sTNF-R1 (ng/ml) (ev 1.4–4.16 ng/ml)	0.96 (0.4)	0.89 (0.4)	NS
TNF-α (pg/ml) (ev < 66 pg/ml)	38.2 (8.3)	38.1 (9.5)	NS
Il-6 (pg/ml) (ev 1.4–14.1 pg/ml)	1.96 (1.6)	2.2 (2.5)	NS
sIl-6R (ng/ml) (ev 65.9–202.7 ng/ml)	230 (81.3)	213 (90.9)	NS
CRP (mg/l) (ev < 5 mg/l)	3.3 (3.2)	3.8 (4.3)	NS
Neopterine (nmol/l) (ev < 10 ng/ml)	6.4 (2.3)	7.4 (2.6)	NS
Haptoglobine (g/l) (ev 0.27–2.14 g/l)	1.7 (0.7)	1.5 (0.7)	NS

A regression analysis was performed for each immune parameter. ev = expected value for healthy individuals according to manufacturer. Haptoglobin was assessed in a sample of 33 depressed and 23 non-depressed post-MI patients.

In post-hoc analyses, smoking on admission to hospital predicted sTNF-R2 ($p = 0.002$, $\beta = -7.8$) and quit smoking after MI predicted sTNF-RI ($p = 0.045$, $\beta = -2.3$). After excluding three outliers based on Cook's distance, quit smoking predicted CRP levels with $p = 0.03$ ($\beta = -1.8$) and still smoking after MI with $p = 0.012$ ($\beta = 2.2$). A positive family history for CAD was a significant predictor for sTNF-RI ($p = 0.04$, $\beta = -0.2$). Time elapsed since MI was a significant predictor for both sTNF-R2 ($p = 0.03$, $\beta = 0.9$) and sTNFRI ($p = 0.03$, $\beta = 0.03$).
When BDI score was used as predictor instead of depressive state, no significant association of depression scores with any cytokine, cytokine receptor or ISP was found.
A significant model was found with neopterin as dependent variable ($F = 6.1$, $df = 2.94$, $p = 0.003$, $R^2 = 0.11$) with BDI score significantly predicting neopterin levels ($p = 0.01$, $\beta = 0.09$) as well as smoking on admission ($p = 0.01$, $\beta = -1.4$).

DISCUSSION

Both depressed and MI patients have been associated with an increased activation status of the immune system. This augmented activation status is reflected among others by elevated plasma levels of various inflammatory markers such as CRP, TNF-α, IL-6 and neopterin [3,8,9,15,16]. In line with these findings, we hypothesized that an additional depression may further increase systemic levels of inflammatory markers in post-MI patients as compared to non-depressed post-MI patients. Nonetheless, no significant difference in inflammatory status between depressed post-MI patients as compared to non-depressed post-MI patients for any cytokine, cytokine receptor or ISP could be detected although there was a trend for higher neopterin levels ($p = 0.053$) in depressed post-MI patients. Fifteen percent of all depressed patients had levels >9.7 mmol/l, compared to 9% in the non-depressed group. Levels higher than 9.7 mmol/l have been associated with increased risk of recurrent MI or cardiac death in non-Q wave MI patients [18]. If depression in post-MI patients is related to higher neopterin levels, there might be a possible pathophysiological link between neopterin levels and increased cardiac events in depressed post-MI patients. In the study of van Haelst et al. a strong correlation was found between levels of neopterin determined within 48 h after admission for MI and levels of neopterin one year post MI. No such correlation was found in that study for levels of CRP, indicating that neopterin reflected another inflammatory processes than CRP [18]. In the present study, time elapsed since MI ranged from 3 to 12 months (mean 6.0; SD 3.3). In post-hoc analyses, time elapsed since MI predicted levels of sTNF-R2 and sTNF-RI, but not of sIL-

6R, IL-6, neopterin, TNF-α or CRP. The effect of depression however, remained unaltered in these regression models, indicating that time elapsed since MI was not a confounding parameter.

When compared with data reported in somatically healthy individuals [3,10,13,11,22,23] in the present study mean levels of sIL-6R and sTNF-R2 were elevated in both depressed and nondepressed post-MI patients despite the fact that all patients were prescribed at least three types of cardiovascular treatment regimens. Because of the relation between elevated inflammatory cytokine levels and detrimental effects on cardiac functioning, interest in the various effects of cardiovascular treatments on inflammatory parameters is increasing. Statins have been shown to reduce parameters of inflammation independent of their cholesterol level [24]. Mechanisms by which statins reduce inflammation are not fully understood, but it has been reported that some decrease secretion of CRP, IL-1, IL-6, neopterin and TNF-α [25,26]. A beta-blocker was shown to lower levels of TNF-α in patients with dilated cardiomyopathy in one study [27] and in patients with chronic heart failure, ACE inhibitor treatment was associated with a reduction of IL-6 levels and an increase in sIL-6R levels [28]. Mohler et al. have shown that a calcium antagonist lowered plasma IL-6 levels in patients with chronic heart failure [29]. No anti-inflammatory effect of aspirin 325 mg/day given for a period of eight weeks was found in healthy subjects [30], but a reduction was observed in patients with chronic stable angina [31]. It is therefore interesting to note that data from the present study show that in spite of treatment during a mean period of 6 months after MI with at least three prescriptions of cardiac medications that may lower inflammatory status, several inflammatory markers were still elevated when compared with values reported in somatically healthy individuals. Ongoing inflammation in post-MI patients implicates that more research is necessary to assess the extent of immunoregulatory effects of cardiovascular treatment regimens. In spite of mounting data on the relation between depression and inflammation, until now it remains unclear whether depression promotes an inflammatory response or whether inflammation induces depression. Several studies have shown that administration of cytokines can induce depression in humans [32-35]. Increased inflammation related to MI might then be a risk factor for development of depression in the post-MI period. Indeed, prevalence of depression after MI is 13–20% [36,37], raising to 20–30% one year post-MI [38,39]. Increased inflammation might be the consequence of indirect mechanisms such as induced by health behavior. Higher BMI, smoking status and hyperlipidaemia, which are also strongly associated with atherosclerosis, have been shown to increase inflammatory parameters [10,11,13]. In the present study the significant regression model with neopterin as dependent variable showed a significantly predictive effect of smoking. Besides health behavior, stressful psychosocial factors have been shown to induce inflammation [40-42]. Appels et al. demonstrated an association between mental state of coronary patients and inflammation with significantly higher levels of IL-1b and TNF-α in exhausted patients with stable angina pectoris as compared to non-exhausted patients with stable angina pectoris [43]. Recently, in a group of 35 depressed patients undergoing a coronary angiogram for a suspected acute MI or episode of high-risk unstable angina, significantly increased levels of soluble intercellular adhesion molecule-1 were found as compared to 446 non-depressed patients undergoing a coronary angiogram [44]. No significant difference between the groups was found for levels of IL-6 (1.24, SD = 0.39 and 1.20,SD = 0.52 pg/ml in depressed and non-depressed patients respectively). Serum CRP levels were 1.33 (SD = 0.77) and 1.23 (SD = 0.73) mg/l respectively. Although the difference was not significant when comparing depressed versus non-depressed, the difference became significant

when only depressed patients not taking statins were included in the analysis [44]. In the present study effect of depressed state on levels of inflammatory markers of post-MI patients was assessed. In both cohorts of the present study, prescription of a statin was present in more than 82% of patients. It can therefore not be excluded that due to statin therapy, the difference in levels of inflammatory markers between the two groups was not detectable anymore. There are several limitations of the study that have to be considered. First, measurement of inflammatory markers was done only once. A reference cytokine blood level on admission to hospital might have shed more light on the significance of the absolute cytokine blood level on the moment depression was assessed. Second, because immune status is influenced by many factors, the number of subjects may have been too low to detect a difference in immune status due to depressive state alone. And third, the high use of statin therapy may have biased outcome. Accurate registration of prescribed dosages is necessary to control for potential confounding effects.

Conclusion

Based on earlier observations that both MI and depression are associated with inflammation, we hypothesized that depression in post-MI patients is associated with increased inflammatory status as compared to non-depressed post-MI patients. If so, increased inflammatory parameters – more specifically increased CAD-related inflammatory markers – in depressed post-MI patients might contribute to increased cardiac morbidity and mortality observed in depressed post-MI patients. Data from the present study showed no additional inflammation in the depressed post-MI group as compared to the non-depressed post-MI group. It might therefore be concluded that immune activation in this cohort was not the most likely candidate in the pathophysiological relationship between depression and MI. Larger cohorts with more information about patient characteristics such as accurate registration of medications (and dosages), co-morbidity, and a more accurate quantification of the extension of atherogenic disease, are necessary in order to know more about the relative contribution of different factors (such as depressive state) to inflammatory status in MI patients. Results from research on inflammatory status in MI patients, will contribute to therapeutic strategies, which aim at reducing symptoms of depression on the one hand and risk of cardiac events on the other.

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PART 3

CHAPTER

7

Antidepressive effect of mirtazapine in post-myocardial depression is associated with soluble TNF-R1 receptor increase: data from the MIND-IT.

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ABSTRACT

Objective. Depressive disorder post-myocardial infarction (MI) is associated with increased cardiac morbidity and mortality. Immune activity such as inflammation might be implicated as an underlying mechanism. The purpose of this study is to investigate whether response to an antidepressant in post MI depression is associated with changes of inflammatory markers in serum.

Methods. In a double blind placebo-controlled study with mirtazapine 30 mg/d (50 patients), antidepressant effect was related to immune activation parameters. Cytokines IL-6 and TNF-α, soluble cytokine receptors sIL-6R, sTNF-RI and sTNF-R2, inflammation-sensitive plasma proteins C-reactive protein (CRP) and neopterin were assessed.

Results. Subgroup analyses revealed a highly significant correlation of pronounced sTNF-RI increase with a decrease of depressive symptoms in antidepressant-responders.

Conclusion. Significant effects on inflammation accompany therapeutic efficacy of mirtazapine in contrast to therapeutic efficacy of placebo and non-therapeutic efficacy of mirtazapine.

INTRODUCTION

Prevalence of depressive symptoms during hospitalization in the post myocardial infarction (MI) period varies from 8-30% depending on the assessment method [1]. Several studies have addressed the issue whether antidepressant treatment (ADT) alleviates post MI depression [2,3,4,5]. Most of these studies demonstrated effects among more severe and recurrent post MI major depressive disorders. In minor post MI depression ADT demonstrated little difference in effect compared to placebo. The Myocardial INfarction and Depression – Intervention Trial (MIND-IT), showed that an incomplete response to ADT of post-MI depression is associated with increased cardiac events [6].
Activation of the immune system including pro-inflammatory cytokines might be one of the shared biological mechanisms in both the pathogenesis of MI and (post-MI) depression.
In chronic inflammation peripherally produced pro inflammatory cytokines induce expression of the same cytokines in the brain. These brain cytokines are responsible for the development of sickness behaviour [7]. Symptoms of sickness behaviour include depressed mood, altered cognition, fatigue and sleep disorders. Sickness symptoms are largely the result of increased IL-1 and TNF-α which serve as neurotransmitters and neuromodulators [8]. These observations suggest that depression in the medically ill (including MI) may be considered a psychoneuroimmunological disorder: 'the cytokine hypothesis of depression' [9].
In experimental conditions 'sickness behaviour' induced by liopolysacharide administration was reversed by antidepressants (AD) [9,10]. In humans, effects of ADT on the immune system are diverse [11].

A previous MIND-IT sub study on antidepressant drug naïve patients in the year post MI, revealed that there was no indication of increased inflammation in depressed post-MI patients as compared to non-depressed post-MI patients [12]. However, this inflammation sub study or "baseline study" revealed that in post MI patients inflammation markers such as TNF-α and s TNF-R2 were elevated whereas sTNF-R1 was lowered as compared to normal controls or depressed non post MI patients [11,13,14]. Even when compared to depressed and non depressed heart failure patients [15,16] TNF-α values were elevated [12]. We hypothesize that in a subset of patients susceptible for depressive disorder, these persistent elevated levels of pro-inflammatory cytokines are a pathogenetic factor in post MI depressive disorder. It is hypothesized that especially in these patients successful ADT could be accompanied by effects on inflammation.
The presented study reveals the effects of 8 weeks ADT on inflammation parameters in depressed post MI patients, a subset of the patient cohort of our previous baseline study [12]. We tested the hypothesis that successful ADT for 8 weeks is associated with changes in serum levels of TNF-α, IL-6, neopterine, CRP, sTNF-R1&2, sIL-6R. We selected these inflammation parameters as they may all be involved in the disease processes of both MI and depressive disorder [12]. TNF-α is elevated during the year post MI and individuals with the highest levels have 3-fold increase in the risk of recurrent cardiac events [17]. TNF-α exerts its effect through TNF-binding proteins, such as the (soluble) TNF receptors 1&2 (sTNF-R1&2). TNF receptor 1 is expressed in most cell types, and can be activated by binding of either soluble TNF or transmembrane TNF, with a preference for soluble TNF [18,19]. STNF-R1 functions as a physiologic inhibitor of systemic inflammatory TNF-α activity [20,21]. TNF-R2 is expressed primarily by cells of the immune system (including microglia) and by endothelial cells, and is preferentially activated by transmembrane TNF, both of these characteristic are likely to result in fewer biological effects compared to the effects of TNF-R1-dependent signaling [18]. Overall, TNF-R2 activation is believed to initi-

ate primarily pro-inflammatory and pro-survival signaling [18]. Elevated levels of CRP, IL-6, sTNF-R1 and neopterin have been found to be a risk factor for future MI in apparently healthy men [22, 23, 24] and are associated with depressive disorder [25,26,27,28].
There are only a few studies on the effects of mirtazapine on the TNF system [13,29]. The plasma levels of TNF-alpha and both soluble TNF receptors increased during treatment with mirtazapine in a non-cardiac patient sample [13]. Preclinical research revealed that mirtazapine has effect on endocrine and signaling related factors in human monocytic blood cells [29].

Both our previous and present investigation was derived from the MIND-IT, a multicenter, randomized controlled study on the effects of ADT for post-MI depression on cardiovascular prognosis [4,6]. The inflammation data of the depressed patients in our previous study [12] were used as baseline data for the presented study.

METHODS

Sample

In,- and exclusion criteria of the MIND-IT were previously described [4]. In short, we recruited consecutive patients (September 1999-November 2002), hospitalized for acute MI, in 10 hospitals in The Netherlands. Patients were enrolled if they met WHO MONICA criteria for definite MI. Exclusion criteria were occurrence of MI when hospitalization took place for another reason, disorders affecting inflammatory systems apart from Coronary Heart Disease patient's inability to participate in study procedures, a disease likely to influence short-term survival, patients already receiving psychiatric treatment for depression or using psychotropic medication, and participation in another clinical trial. Concommitant psychotropic medication was not allowed during the study, including benzodiazepines, except 1) if the eligible subject was using bezodiazepines (no more than 50 mg oxazepam per day or an equivalent) for at least 2 weeks before screening and this cannot be changed during the study, unless there is a need to taper the dose or 2) if absolutely necessary during the study period, a maximum of 30 mg oxazepam per day was allowed as concomitant medication.

Patients were screened for depressive symptoms during hospitalization and at 3, 6, 9 and 12 months post-MI, using the Beck Depression Inventory (BDI). Those with depressive symptoms (i.e. BDI score ≥ 10) underwent a psychiatric evaluation using the WHO Composite International Diagnostic Interview (CIDI) auto version 2.1. The first CIDI interviews were conducted not earlier than 3 months post-MI to allow for natural recovery of depressive symptoms. Patients with a diagnosis of 'Depressive Episode' according to the International Classification of Diseases (ICD-10) were randomized to Intervention or Care As Usual.
Patients who were randomized to Intervention had a clinical interview with a psychiatrist for assessment of DSM IV diagnosis. Patients meeting criteria for a major or minor depressive disorder according to DSM-IV were offered treatment in the double blind placebo controlled trial with Mirtazapine.
Mirtazapine is a non-tricyclic, presynaptic α2-antagonist [30] that enhances both noradrenergic and serotonin neurotransmission and is well tolerated by patients with coronary artery disease [4,6].
Severity of depressive symptoms were assessed with the Hamilton Rating Scale (HAM-D 17) Patients were asked for blood collection as part of the present sub study of the MIND-IT.

Design

A consecutive cohort of 60 depressed MI patients gave informed consent for blood collection. The procedure and inclusion and exclusion criteria for this "inflammation sub-study" were previously described [12]. In short, patients who used medication or suffered from diseases that were likely to influence inflammatory blood markers were excluded. After the first blood collection patients entered the double blind mirtazapine/placebo study. Patients were randomly assigned to receive either mirtazapine (30 mg/d) or placebo. After 8 weeks, the second blood collection took place. Response to treatment was evaluated at 8 and 24 weeks treatment. Responders were defined as patients with a reduction of at least 50% on the HAM-D 17 score or HAM-D score <9 at 8 and 24-weeks of treatment. For various reasons 10 patients (4 on placebo and 6 on mirtazapine) dropped out of the mirtazapine/placebo treatment. So, 50 pre- and a post-treatment blood samples were available: placebo n=26; mirtazapine n=24. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and local ethical committees approved of the study design. All participants were fully informed and gave written informed consent.

Laboratory analyses

Venous blood samples were collected between 9.00 and 11.00 a.m. after an overnight fast. Blood was collected in sterile Vacutainer tubes without additives (Becton-Dickinson, Basel, Switzerland). Samples were centrifuged at 2200g for 5 minutes and serum was stored at -70º until analysis. Serum concentrations of various inflammatory markers were measured using commercially available enzyme-linked immunosorbent assays (ELISA). Kits for sIL-6R, TNF- α, sTNF-R1 and sTNF-R2 were obtained from Bender Med Systems (Vienna, Austria), and that for neopterin from IBL (Hamburg, Germany). All assays were performed in accordance with manufacturer's instructions. CRP was measured using a high-sensitive ELISA-kit from ICN Pharmaceuticals (Orangeburg, NY, USA).
Detection limits in our laboratory were: 0.08 ng/ml (sIL-6R, sTNF-R 55 kDa = sTNF-R1), 0.16 ng/ml (sTNF-R 75 kDa = sTNF-R2), 8 pg/ml (TNF-α) and 0.005mg/l (CRP). IL-6 concentrations were measured with ELISA-kits from DiaMed-Eurogen (Turnhout, Belgium) using a modified protocol to increase the sensitivity of the ELISA. Modifications were longer incubation times for standard/sample and detection-antibody incubation (2h and 1h, respectively); incubation of standard/sample and detection-antibody at room temperature while shaking at 600 rpm on a micro titer plate shaker; and further dilution of standards. The detection limit in our laboratory was 0.5 pg/ml.

Statistical Analysis

Baseline characteristics were collected of the mirtazapine and placebo group. Data are presented as mean (+ sd or range). Chi-square in case of dichotomous variables and t-test in case of continuous variables were applied. The assumption for normal distribution of the data was checked and met by means of Kolmogorof-Smirnov test.
Immune response was calculated by means of residualized change scores (e.g. ΔIL-6_{res}). Residualized change scores were also computed for the Hamilton depression rating scale (ΔHamiltonres). These measures reflect the degree in which an individual increased or decreased more than would be expected given baseline status. Residualized change scores are preferred over simple change scores because they eliminate auto correlated error and regression to the mean effects.

A series of regression analyses was performed [31] to test the mediation model in which the association between antidepressant treatment and $\Delta Hamilton_{res}$ is explained by immune response. First, associations between treatment group and immune response were examined. Second, effect of intervention on $\Delta Hamilton_{res}$ was evaluated. Finally, the joint effect of treatment and immune response on $\Delta Hamilton_{res}$ was estimated. If the immune response mediated the association between treatment and $\Delta Hamilton_{res}$, it was expected that immune response would eliminate or sizably attenuate the relationship between treatment and $\Delta Hamilton_{res}$ in the final step.

RESULTS

General patient characteristics

Demographic characteristics and medication of the cohort are summarized in table 1. Patients' ages ranged from 36 to 79 (mean 57.3) Patients were not included earlier than 3 months and not later than 12 months post-MI (mean 6.0; sd 3.3). There were no significant differences between the mirtazapine and placebo groups with regard to infarction size and the ASAT levels. Treatment of MI with PTCA or CABG was also not statistically different between the groups. There were no significant differences between the mirtazapine and placebo groups with regard to use of medication except for the use of β blocker, for which there is no clear cardiac explanation. Finally, there were no statistically significant baseline differences between the mirtazapine and placebo groups in severity of depression (measured with HAM-D) and severity of MI (measured with maximum CK, ASAT and LVEF).

Table 1. Baseline comparison of the mirtazapine and placebo patients

	Mirtazapine (n=24)	Placebo (n=26)	Test
Socio-demographic:			
Gender (male)	93.3%	82.8%	$\chi 2$=1.6; p=.21
Weight (kg)	82.3 (14.5)	82.4 (18.1)	Z=-0.02; p=.99
Length (cm)	176 (8.7)	175 (8.4)	Z=0.47; p=.64
MI severity:			
LVEF >60 %	13.3%	11.5	
LVEF 45-60 %	43.3%	57.7	
LVEF 30-45 %	30.0%	23.1	
LVEF <30 %	13.3%	7.7	$\chi 2$=1.3; p=.74
Killip class 1	93.3%	89.7	
Killip class 2	3.3%	10.3	
Killip class 3	3.3%	0	$\chi 2$=2.1; p=.36
ASATmax (U/L)	218.0 (156.2)	206.5 (158.1)	Z=0.28; p=.78
CKmax (U/L)	1673.0 (1487.2	1968.0 (1950.4	Z=-0.63; p=.53
Co-medication:			
Acetylsalicylacid	86.7%	96.6%	$\chi 2$=1.9; p=.17
Acenocoumarol	10.0%	3.4%	$\chi 2$=1.0; p=.32
Betablocker	80.0%	100%	$\chi 2$=6.5; p=.01
Calcium antagonist	26.7%	17.2%	$\chi 2$=0.8; p=.38
Digoxin	0%	0%	-
Diuretics	16.7%	10.3%	$\chi 2$=0.5; p=.48
Ace-inhibitor	33.3%	20.7%	$\chi 2$=1.2; p=.28
All-antagonist	3.3%	3.4%	$\chi 2$=0.0; p=.98
Statin	93.3%	86.2%	$\chi 2$=0.8; p=.37

LVEF: left ventricular ejection fraction; MI: myocardial infarction; CKmax :maximum levels of creatine kinase during hospitalization for MI; ASATmax: maximum levels of aspartate aminotransferase during hospitalization for MI

Mediating effects of immune response

The serum levels of 7 immune parameters are listed in table 2. To correct for multiple comparisons, a Bonferroni correction was applied here yielding a significance level of .05 / 7 = .007. The increase of sTNF-R1 was significantly higher in patients who received mirtazapine treatment (β=.39; p= .005). This effect was independent from using β-blockers (β=-.09; p= .53), and changes in body mass index (β=.03; p=.87). Since only change in sTNF-R1 was related to treatment, other immune parameters were not included in subsequent statistical analyses.

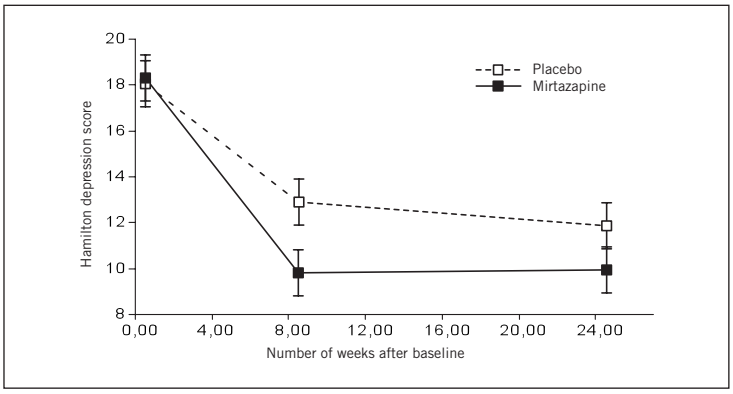
Table 2. Mean (SD) levels of immune parameters for placebo and mirtazapine patients at baseline and 8-week follow-up

		Placebo n=26	Mirtazapine n=24	β*	p-value
TNFα pg/ml	Week 0	36.79 (7.69)	39.32 (10.29)		
	Week 8	38.76 (7.47)	44.40 (10.26)	.22	.12
sTNF-R1 ng/ml	Week 0	0.91 (0.63)	0.98 (0.47)		
	Week 8	0.86 (0.58)	1.15 (0.50)	.39	.005
sTNF-R2 ng/ml	Week 0	18.17 (25.38)	18.99 (15.37)		
	Week 8	15.70 (20.30)	16.84 (11.77)	-.15	.32
IL-6 pg/ml	Week 0	1.77 (1.32)	2.51 (3.18)		
	Week 8	3.54 (5.44)	2.93 (3.05)	-.07	.63
sIL-6R ng/ml	Week 0	215.74 (90.04)	214.56 (83.56)		
	Week 8	240.02 (72.13)	201.01 (66.64)	-.34	.019
Neopterine ng/l	Week 0	7.63 (3.53)	7.34 (2.52)		
	Week 8	7.90 (3.61)	7.08 (2.14)	-.20	.16
CRP mg/l	Week 0	4.81 (6.45)	3.91 (3.10)		
	Week 8	5.52 (7.20)	6.33 (4.79)	.07	.67

Standardized regression coefficient of the association between treatment and residualized change scores of immune parameters

As shown in Figure 1 the HAMD scores between baseline and 8 weeks follow-up decreased more in the mirtazapine group as compared to the placebo group (β= -.32; p= .023). HAM-D ratings did not significantly change between 8 and 24 weeks follow-up in both the placebo (p=.28) and treatment group (p=.90) [4].

Figure 1. Effect of treatment on Hamilton Depression Rating Scale.



Defining responders as patients with a reduction of at least 50% on the HAM-D or HAM-D score <9 at 8 and 24-weeks of treatment, post-hoc analysis revealed that there was only a remarkable increase of sTNF-R1 in the responders of the mirtazapine group (fig. 2), but not in the placebo responders, nor in any of the other immune parameters.

The previous analyses revealed that (1) mirtazapine treatment was associated with immune responses in sTNF-R1 and sIL-6, and (2) that mirtazapine treatment was associated with improved depression scores. As a final step, the joint effect of treatment and immune response on change in depression scores ($\Delta Hamilton_{res}$) was estimated. If the immune response mediated the association between treatment and $\Delta Hamilton_{res}$, it was expected that immune response would eliminate or sizably attenuate the relationship between treatment and $\Delta Hamilton_{res}$. Therefore, we tested the following model: $\Delta Hamilton_{res}$ =treatment + $\Delta sTNF\text{-}R1_{res}$. After controlling for change in sTNF-R1 ($\Delta sTNF\text{-}R1_{res}$; β= -.42; p= .004), treatment with mirtazapine (β= -.14; p= .34) did not remain significantly associated with change in depression scores ($\Delta Hamilton_{res}$). Hence, the effect of mirtazapine on change in depression scores was fully accounted for by the sTNF-R1 response (β= -.42; p= .004).

These statistical analyses together support the idea that the antidepressant effect of mirtazapine is predominantly if not exclusively explained by sTNF-R1.

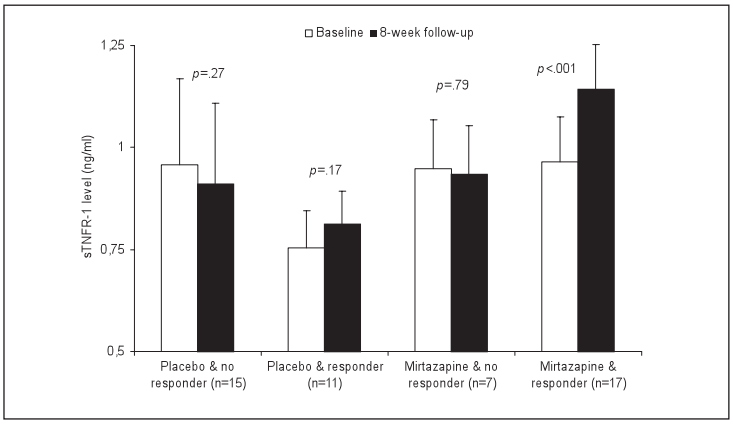


Figure 2. Changes in the levels sTNF-R1 stratified by treatment and anti-depressive response to treatment.

DISCUSSION

Successful response to treatment in post MI depression is associated with a highly significant effect on inflammation in mirtazapine responders but not in placebo responders. Neither non-response in mirtazapine nor in placebo shows any effect on inflammation. These findings suggest that placebo and mirtazapine cause remission of post MI depression through different mechanisms, which is in accordance with the results of ADT continuation studies that demonstrate that relapse rates are much higher for placebo compared to ADT [32,33].

Although statistically highly significant, the association between therapeutic efficacy of mirtazapine and inflammation parameters was limited to an increase of sTNF-R1 only. Remarkably there was an obvious treatment-induced change in IL-6 levels in the placebo group. Although one could argue that this may be related to an overall improvement also in the placebo-condition, literature on this topic shows conflicting results [34]. This limits interpretation of this correlation.

Changes in sIL-6R were marginal, whereas no significant differences were found between baseline/pre-treatment and post-treatment plasma levels of CRP, Neopterin, TNF-α and sTNF-R2 . With heightened inflammation parameters at baseline [12] and no changes in inflammation parameters except for sTNF-R1, it can be concluded that signs of chronic inflammation associated with MI and /or atherosclerosis persist after 8 weeks of ADT.

In accordance with other reports [26,35] we found no association between sTNF-R1 and weight gain (p=0.87). Nor was the change in inflammation a side effect of mirtazapine itself as non-responders on mirtazapine did not show this effect while blood levels did not differ between the two groups. Further statistical analysis emphasized the mediating role of sTNF-R1 in the antidepressant effect of mirtazapine.
As the increase of sTNF-R1 seems to reflect one of the essential parts of successful ADT, the discussion will focus on the question to what extent changes in sTNF-R1 serum levels might reflect cerebral changes involved in remission of post MI depressive disorder.

TNF-α initiates its effects by binding to distinct cellular surface receptors: TNF-R1 and TNF-R2 [36]. Also, soluble TNF-R1&2 in serum may play a key role in inflammation, immune responses, cellular proliferation, and apoptosis. STNF-R1&2 might be formed by shedding of surface receptors, following the activation of intracellular TNF-α converting enzyme, or by intracellular formation of precursor proteins missing a trans-membrane domain [37]. Unlike most other cytokines, TNF-α has a facilitated influx system from blood to brain and can cross the Blood Brain Barrier (BBB) by TNF-R1&2 mediated endocytosis. This transport is up regulated under conditions such as recovery after central nervous system (CNS) trauma and inflammation. The temporal and spatial patterns indicate that TNF-α transport across the BBB is mediated by tissue and soluble factors. The BBB is intimately involved in communication between peripheral cytokines and the CNS [36]. For TNF-α, there is no efflux system from the CNS to blood other than re-absorption of CFS with bulk flow [38].

In addition to inducing sickness behaviour and depressive symptoms, TNF-α plays a role in (the degree of) regaining remission of depressive symptoms. Higher serum levels of TNF-α predict non-response to ADT with selective serotonin reuptake inhibitors [11] and relapse of depressive disorder after remission [35,39]. Successful ADT is associated with 1) changes in the interaction between TNF-α and the HPA axis and 2) TNF-α modulated functioning of the noradrenergic α receptor [33,40].
In order to explain our results we hypothesize that the increase of plasma sTNF-R1 could be a peripheral marker pointing to changes in cerebral TNF-α activity, associated with the restorative process in inflammation related subtypes of post MI depressive disorder. Elevation of sTNF-R1 could exert its effect on mood by blocking the effect of serum TNF-α. TNF-α serum levels were unaffected by successful ADT and remained elevated which points to ongoing inflammation due to the atherosclerotic process usually associated with MI. In the ADT responders, TNF-α levels were about 40 pg/ml and sTNF-R1 levels about 1000 pg/ml and therefore 25 times higher than TNF-α. Although mathematical modeling is difficult; the stoichiometric ratio of TNF versus its high affinity receptor suggests that cytokine action might be antagonized by an sTNF-R1 increase and therefore attenuate depressive and/or sickness symptoms induced by this cytokine [8]. We propose two possible mechanisms. Firstly, sTNF-R1 might block the effect of the peripherally produced pro inflammatory cytokine TNF-α thereby reversing the chronic inflammation related process of inducing expression of TNF-α in the brain [7].
Secondly, local protective activity of the elevated sTNF-R1 at the level of the BBB might be present, as shown by Taylor et al [41]. They demonstrated that a single dose of recombinant sTNF-R1 was accompanied by initial inhibition of both BBB permeability and CNS inflammation leading to diminishing of disease symptoms for 5 days. This mechanism might be relevant as in a previous study we demonstrated an increased permeability of

the BBB during the first week post MI [42], which might have long lasting effects on the up regulated transport of TNF-α [38].
Similar to TNF-α, sTNF-R2 is already elevated on baseline in this cohort of post MI depressed patients when compared to depressed but somatically healthy patients [13]. We presume that successful ADT is not able to induce an additional increase on top of this baseline elevation [12] which is in contrast with earlier studies on mirtazapine [13].
In contrast, sTNF-R1 is decreased in pre-treatment post MI depression compared to depressed but somatically healthy patients [12,13]. This probably explains why ADT has only effect on sTNF-R1 and not on sTNF-R2. In a cohort of heart failure (HF) patients with co-morbid depression comparable results were found: significantly elevated levels of sTNF-R1 (1.6ng/l) in formerly depressed patients on ADT compared to lower sTNF-R1 levels (1.1 ng/l) in non- depressed HF patients. As in our study, no AD treatment effects on levels of TNF-α, sTNF-R2, IL-6, sIL-6R and CRP were found [28].

Although high serum levels of sTNF-R1 [24 ng/l] are prognostic indicators of mortality [24], it is unlikely that sTNF-R1 levels of 1.15 ng/l during ADT affect cardiac mortality risk negatively as confirmed in the MIND-IT [6].
In conclusion, in post MI depression we found a strong correlation between the increase of sTNF-R1 and treatment response on ADT with mirtazapine in contrast to therapeutic efficacy of placebo and non-therapeutic efficacy of mirtazapine.
Further research is necessary to assess whether this relationship is confined to mirtazapine and post-MI patients and to establish which depressive symptoms or profile are associated to the cytokine response. Limitations of the present study are the small sample size and the limited power.

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PART 4

CHAPTER

8

Heart Rate Variability and treatment of depressed post-myocardial infarction patients. A pilot study.

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Submitted.

ABSTRACT

Objective. Studies show negative correlations between heart rate variability (HRV) and inflammatory markers. In cardiac patients, depression is related to both. We investigated the link between HRV and inflammatory markers in relation to antidepressant treatment in the year post Myocardial Infarction (MI).

Methods. In a substudy of a double blind placebo-controlled study with mirtazapine 30 mg/d (MIND-IT), antidepressant effect was related to parameters of heart rate variability and immune activation in 20 depressed post MI patients. Both longer-range HRV parameters VLF, LF and SDANN and the inflammatory markers TNF-α and its soluble receptor sTNF-RI were assessed in patients who responded or not responded to mirtazapine vs placebo treatment. In addition, the association between cytokines and HRV in relation to antidepressant treatment was assessed.

Results. No differences were observed in HRV measures between patients treated with mirtazapine vs placebo, nor between antidepressant responders and non-responders on mirtazapine vs placebo. With regard to inflammatory markers, change in inflammation markers was more pronounced in patients that responded to mirtazapine.

Due to limited response on HRV, and the small numbers in this pilot, we were not able to further explore the hypothesized cross-sectional and longitudinal relationships between the effect of antidepressant therapy, the HRV parameters and inflammation markers.

Conclusion. Treatment with mirtazapine did not affect any of the HRV measures. Mirtazapine appears to be a safe antidepressant in the treatment of post MI depression.

INTRODUCTION

Depression is associated with an increased risk of cardiac morbidity and mortality in the post myocardial infarction (MI) period [1]. Non-response to antidepressive therapy is associated with high risk for late mortality after myocardial infarction up to 7 years [2]. Several mechanisms contribute to this phenomenon and one of them might be the dysregulation of the autonomic nervous system. Heart rate variability (HRV) provides a non-invasive index of autonomic nervous function. Both reduced heart rate variability and elevated heart rate are caused by withdrawel of parasympathic control or increased sympathetic control over the heart. During MI HRV drops and then recovers substantially though incompletely during especially the next three months. Between 3 and 12 months post MI HRV values reach a quite stable level. [3].

It is well established that decreased HRV is associated with an increased risk of cardiovascular and arrhythmic death in patients with stable coronary heart disease (CHD) [4]. Major Depressive disorder is associated with reduced HRV as well [5]. Depression in the post MI period exaggerates the post MI reduction of HRV as compared to non-depressed post MI patients [6,7,8, 9, 10]. In contrast to normal recovery, the expected increase of HRV is absent in post MI depressed patients. Instead, a further decrease of HRV is measured in depressed post MI patients not using antidepressants [9,11]. A twin study demonstrated that a shared genetically influenced pathway underlies the association between depression and lower HRV [12]. Other etiological factors may play a role as well as not all studies have shown significant results on the relation between depression, reduced HRV and stable CHD [13]. In fact, a recent meta-analysis [14] reported that depression predicts only about 2% of the variance in HRV in both CHD and non-CHD samples. Moreover it was found that only somatic depressive and not the cognitive depressive symptoms were associated with lower HRV, which was largely explained by differences in comorbidities and lifestyle factors [10]. Conflicting results on the effects of antidepressant treatment on HRV are reported as well [9,15].

One potential reason for inconsistencies among studies is that depression- related differences in HRV may vary depending on the patients' inflammation status. There is a growing body of literature demonstrating that both major depressive disorder (MDD) and sub-threshold elevations of depression are related to increases in inflammatory processes in those with and without CHD [16,17]. In the post MI period several cytokine levels are increased. Tumor Necrosis Factor- α (TNF-α) is elevated during the year post MI and individuals with the highest levels have 3-fold increase in the risk of recurrent cardiac events [18]. Increased inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6) are associated with cardiovascular mortality as well [19,20]. An inflammation substudy of the Myocardial Infarction and Depression-Intervention trial (MIND-IT) revealed that there were no differences in increased inflammation in depressed post-MI patients as compared to non-depressed post-MI patients. However, TNF-α and the soluble TNF-receptor-2 (sTNF-R2) were elevated whereas sTNF-R1 was lowered as compared to normal controls and depressed non-post MI patients. Even when compared to depressed and non depressed heart failure patients TNF-α values were elevated [21]. Antidepressant response on mirtazapine was associated with a highly significant increase of sTNF-R1.

In CHD patients with MDD only a few studies investigated the relation between HRV and inflammation. Measures of low frequency power of HRV were related to IL-6 [22]. The negative association between HRV measures and inflammatory markers are stronger among depressed than non-depressed cardiac patients [23].

In fact, to our knowledge, no studies have evaluated how antidepressant treatment influences HRV, inflammation and their mutual relationship. In this pilot study we examined

the relationship between the effect of 8 weeks of antidepressant therapy with mirtazapine or placebo on the HRV parameters and cytokines. As the longer-range parameters are most strongly related to post-MI depression, we selected VLF, LF and SDANN [8,22]. Regarding the cytokines, we evaluated serum levels of TNF-α and sTNF-R1 as these were identified as associated with treatment reponse in post-MI depression [24]. We hypothesized, that in responders of anti-depressant therapy an improvement in autonomic function (i.e. reflected by an increase in HRV) could be responsible for this better cardiac prognosis than in non-responders. Furthermore we hypothesized that an improvement in HRV would be mediated by changes in cytokine levels.

METHODS

Design

The present study was a predefined substudy of the MIND-IT that was initiated to evaluate the influence of antidepressive treatment versus care-as-usual for post-MI depression on cardiac prognosis. In-, and exclusion criteria of the MIND-IT were previously described [24]. In short, we recruited consecutive patients (September 1999-November 2002), hospitalized for acute MI, in 10 hospitals in The Netherlands. Patients were enrolled if they met WHO MONICA criteria for definite MI. Exclusion criteria were occurrence of MI when hospitalization took place for another reason, disorders affecting inflammatory systems apart from Coronary Heart Disease, patient's inability to participate in study procedures, a disease likely to influence short-term survival, patients already receiving psychiatric treatment for depression or using psychotropic medication, and participation in another clinical trial. Concommitant psychotropic medication was not allowed during the study, including benzodiazepines, except 1) if the eligible subject was using bezodiazepines (no more than 50 mg oxazepam per day or an equivalent) for at least 2 weeks before screening and this cannot be changed during the study, unless there is a need to taper the dose or 2) if absolutely necessary during the study period, a maximum of 30 mg oxazepam per day was allowed as concomitant medication.

After discharge of the hospital patients were followed for 18 months. At 18 months depression status and cardiac event rate was assessed. Patients were screened for depressive symptoms during hospitalization and at 3, 6, 9 and 12 months post-MI, using the Beck Depression Inventory (BDI) [26]. Those with depressive symptoms (i.e. BDI score ≥ 10) underwent a psychiatric evaluation using the WHO Composite International Diagnostic Interview (CIDI) auto version 2.1 (fig1).

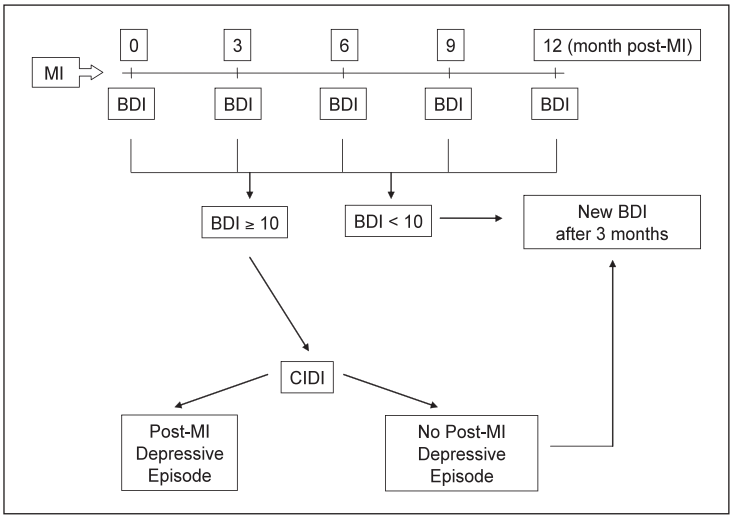

Figure 1. Flow chart of the MIND-IT study: screening procedure.

The first CIDI interviews were conducted not earlier than 3 months post-MI to allow for natural recovery of depressive symptoms. Patients with a diagnosis of 'Depressive Episode' according to the International Classification of Diseases (ICD-10) were randomized to Intervention or Care As Usual. Patients who were randomized to Intervention had a clinical interview with a psychiatrist for assessment of DSM IV diagnosis. Patients meeting criteria for a major or minor depressive disorder according to DSM-IV were offered treatment in the double blind placebo controlled trial with Mirtazapine for 8 weeks with continuation in case of response. Patients were randomly assigned to receive either mirtazapine (30 mg/d) or placebo (fig. 2).

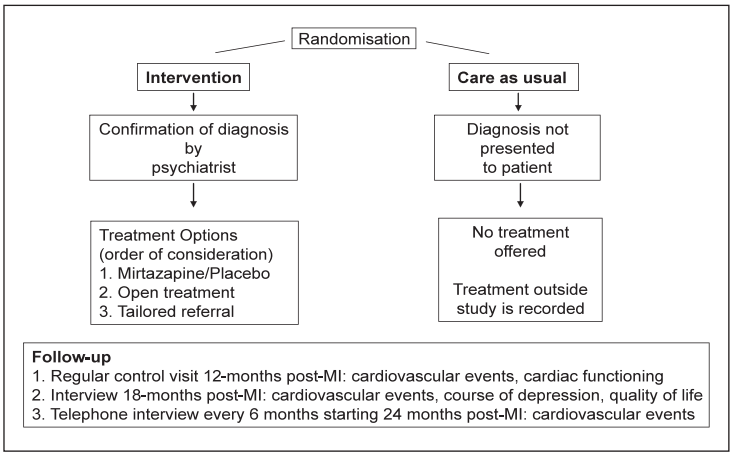

Figure 2. Flow chart of the MIND-IT study: randomisation to Intervention and Care as Usual.

Mirtazapine is a non-tricyclic, presynaptic α2-antagonist [27] that enhances both noradrenergic and serotonin neurotransmission. Severity of depressive symptoms was assessed with the Hamilton Rating Scale (HAM-D 17) and the BDI. Response to treatment was evaluated at 8 and 24 weeks treatment. Responders were defined as patients with a reduction of at least 50% on the HAM-D 17 score or HAM-D score <9 at 8 and 24-weeks of treatment.

For this pilot study, we selected all patients from the "MIND-IT inflammation sub-study", in whom both cytokines were assessed and 24-hour ambulatory electrocardiographic (Holter) monitoring was performed before the start of Mirtazpine/placebo at 0 weeks and at 8 weeks ADT. In total, a cohort of 20 depressed post MI patients completed both blood collection and Holter monitoring; Mirtazapine n=12; Placebo n=8.
The procedure, in,-exclusion criteria and results for the predefined MIND-IT "inflammation sub-study" were previously described [21,24]. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and local ethical committees approved of the study design. All participants were fully informed and gave written informed consent.

Heart Rate Variability

Methods have been detailed previously and followed the recommendations of the Task Force of the European Society of cardiology and the North American Society of Pacing and Eletrophysiology [28]. In brief, Holter monitoring was performed using a Marquette Holter recorder (GE Medical system holter recorde, series 8500, Milwaukee, WI, US). Three electrocardiographic leads were used: modified leads V1, V5 and aVF. The recordings were analysed in a core laboratory (Groningen University Hospital) on a GE Medical system Mars 8000 analyser and reviewed by an experienced analyst. Recordings with >5 % noise or ectopic beats, including atrial fibrillation, were excluded from analysis. The following time domain parameters were analysed: mean normal-to-normal (NN) RR interval, standard deviation of the means of NN intervals in all five-minute segments (SDANN) and square root of the mean of the squares of differences between adjacent NN intervals (RMSSD). Discrete Fourier transformation was used for the analysis of the frequency (spectral) domain parameters. The following parameters were calculated: very-low-frequency power (VLF, 0.0033-0.04Hz) low frequency power (LF, 0.04-0.15 Hz), high frequency power (HF, 0.15-0.40 Hz) and the ratio of low-frequency power and high frequency power (LF/HF).

Data analysis

Assessments made at baseline were summarized by treatment and served to identify any imbalances between the randomized treatment groups. For quantitative parameters, descriptive statistics were mean ± standard deviation (SD). In case of a skewed distribution, a log transformation was performed to achieve a normal distribution. For qualitative parameters (categorical or ordered), frequency counts and percentages of each category were calculated.
For quantitative parameters differences between the treatment groups will be evaluated using a T-test for two independent samples. For qualitative parameters, group differences will be evaluated using either a Fisher's exact test or Chi-square test.
Analysis of covariance was used to assess to association between depression and the change in HRV parameters as well as for the inflammatory markers, also taking into consideration the baseline status and antidepressant treatment. The same approach was used to assess the association between inflammatory markers and HRV.
The analyses performed in the pilot study were all exploratory. So, any significant finding must be viewed with due caution in light of their status as exploratory analyses. For all analyses, commercially available computer software (Statistical Analysis System version 9.2; SAS Institute, Cary, NC, USA) was used.

RESULTS

Fifty patients participated in the inflammation substudy [24]. Twentyfour of these patients underwent Holter monitoring before and after 8 weeks of antidepressant treatment with mirtazapine or placebo. In four of these patients the Holter recording was inadequate, due to technical failure, noise or ectopy. The remaing 20 constitute the present group who completed 8 weeks antidepressant treatment with complete inflammation and Holter data available.

Demographic characteristics and medication of the cohort are summarized in table 1. As shown in Table 1, apart from the BDI, no differences were observed between patients treated with mirtazapine versus placebo. With regard to the BDI, a subjective assessment of the severity of depression, in patients treated with mirtazapine, the baseline BDI was 16, whereas in patients treated with placebo this was 10 (p=0.02). The more objective assessment using the Hamilton rating scale did not show a significant difference in the severity of depression at baseline, with 19 vs 16, in mirtazapine and placebo, respectively (p=0.12).

Table 1. General patient characteristics

		Mirtazapine (n=12)	Placebo (n=8)	P-value
Socio-demographic:				
Age (years) [1]		58 ± 13	63 ± 10	0.51
Gender (male %)		83	88	1.00
Weight (kg) [1]		84 ± 13	80 ± 13	0.37
Length (cm) [1]		174 ± 9	173 ± 5	1.00
Body Mass Index (kg/m2) [1]		24.3 ± 3.2	23.2 ± 4.7	0.37
MI severity:				
LVEF (%)	>60 %	33.3	14.3	
	45-60 %	25	14.3	
	30-45 %	33.3	42.8	
	<30 %	8.3	29.6	0.55
Killip class (%)	1	83.3	75	
	2	8.3	12.5	
	3	8.3	0.	0.51
	4	0	12.5	
$ASAT_{max}$ (U/L) [1]		246 ± 155	349 ± 249	0.30
CK_{max} (U/L) [1]		1740 ± 1563	2963 ± 3050	0.46
Co-medication (%):				
Acetylsalicylacid		83	75	0.10
Acenocoumarol		8	25	0.54
Betablocker		67	88	0.60
Calcium antagonist		50	38	0.67
Digoxin		0	13	0.40
Diuretics		17	25	1.00
Ace-inhibitor		33	25	1.00
ATII-antagonist		8	0	1.00
Statin		100	100	1.00
Depression severity				
Ham-D [1]		19 ± 3.5	16 ± 3.8	0.12
BDI [1]		16 ± 4.8	10 ± 3.5	0.02

[1] mean ± standard deviation

As shown in Table 2, with regard to HRV and inflammation markers at baseline, patients treated with mirtazapine versus placebo were comparable.

Table 2. HRV and inflammation markers at baseline

	Mirtazapine (n=12)	Placebo (n=8)	P-value
HRV:			
LnSDANN (ms) [1]	4.87 ± 0.30	4.85 ± 0.40	0.91
Ln LF (ms) [1]	6.07 ± 0.79	6.11 ± 1.36	0.67
Ln VLF (ms) [1]	7.23 ± 0.65	7.05 ± 0.75	0.56
Inflammation:			
TNFα (pg/ml) [1]	36.60 ± 6.34	36.53 ± 7.28	0.56
sTNF-R1 (ng/ml) [1]	1.00 ± 0.51	1.32 ± 1.08	0.65
sIL-6R (ng/ml) [1]	170.8 ± 64.1	163.9 ± 97.0	0.72

[1] mean ± standard deviation

HRV change in mirtazapine and placebo

In patients treated with mirtazapine versus placebo, no significant changes were found on the HRV parameters, lnSDANN, lnLF, and lnVLF before and after 8 weeks antidepressant treatment (Table 3). In the patients treated with mirtazapine, the change in lnSDANN, lnLF, and lnVLF was -0.22 ms, -0.38 ms and -0.42 ms, respectively, whereas in placebo, this was -0.20 ms (p = 0.90), -0.26 ms (p = 0.60) and -0.19 ms (p = 0.26).

Table 3. HRV and inflammation markers at 8 weeks

	Mirtazapine (n=12)	Placebo (n=8)	P-value[2]
HRV:			
LnSDANN (ms) [1]	4.64 ± 0.37	4.60 ± 0.45	0.90
Ln LF (ms) [1]	5.74 ± 0.98	5.50 ± 1.17	0.60
Ln VLF (ms) [1]	6.80 ± 0.81	6.77 ± 0.86	0.26
Inflammation:			
TNFα (pg/ml) [1]	41.17 ± 8.19	36.73 ± 7.89	0.065
sTNF-R1 (ng/ml) [1]	1.13 ± 0.57	1.39 ± 1.02	0.20
sIL-6R (ng/ml) [1]	165.1 ± 52.1	192.4 ± 62.3	0.31

[1] mean ± standard deviation; [2] p-value based on change from baseline;

In addition, when considering the response to mirtazapine and placebo, defined as a reduction in Hamilton rating score > 50% or an absolute value < 9, no differences were observed in either of the four subcategories of responding and non-responding patients treated with mirtazapine or placebo (Fig 1).

Furthermore, when assessing the relationship between the change in HRV and the change in depression by Hamilton rating score, no association was observed (lnSDANN p = 0.48, ln LF p = 0.19 and ln VLF p = 0.36).

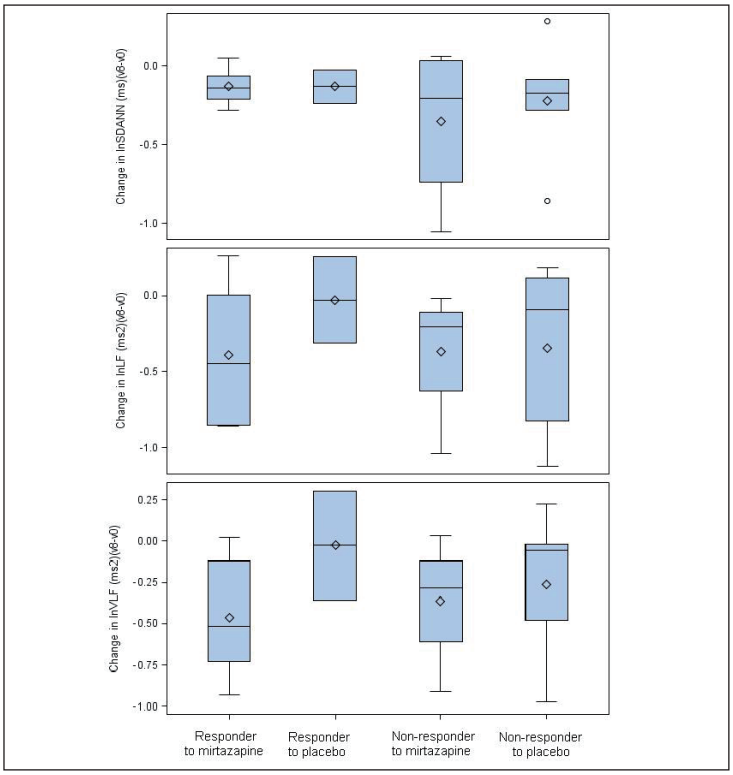

Figure 1. Absolute change from baseline of HRV in responders and non-responders on mirtazapine and placebo.

Change in inflammation markers in mirtazapine and placebo

As presented in Table 3, a marginal difference in the inflammation marker TNFα was observed in patients treated with mirtazapine versus placebo. In the patients treated with mirtazapine the change in TNFα was 4.57 ± 5.31 pg/ml, whereas in placebo, this was 0.21 ± 2.92 pg/ml ($p = 0.065$). For sTNF-R1 were 0.13 ± 0.18 ng/ml in mirtazapine versus -0.01 ± 0.24 ng/ml ($p = 0.20$) in placebo.

When also taking the response to mirtazapine and placebo into account, the change in inflammation markers was the most pronounced in those patients that responded to mirtazapine (Fig 2). Due to very small numbers in these subgroups, ability to perform statistical testing was very limited. However, when assessing the association between the change in Hamiton score and the change in TNFα and sTNF-R1, the change in TNFα was marginally related to a change in Hamilton score ($p= 0.057$). For sTNF-R1 p value was 0.048. Of note, the significance must be viewed with due caution in light of the very small numbers and the setting of an exploratory analysis.

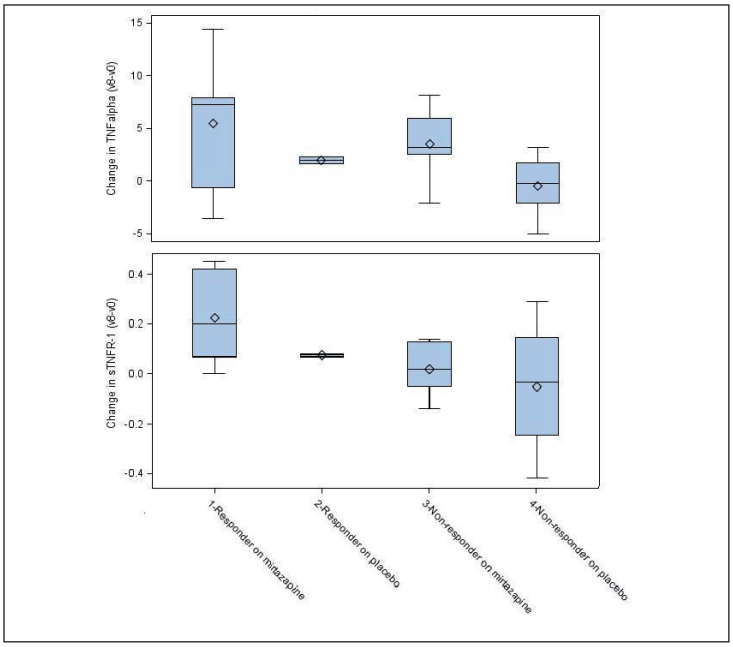

Figure 2. Absolute change from baseline of inflammation markers in responders and non-responders on mirtazapine and placebo.

DISCUSSION

Regarding the inflammation parameters, an association was found between sTNF-R1 increase and resonse to treatment in the mirtazapine group. Statistical signifance was not reached due to a power problem. These findings are in line with our previous inflamation sub-study of the MIND-IT demonstrating a highly significant correlation of pronounced sTNF-RI increase with a decrease of depressive symptoms in mirtazapine-responders [24].
In the presented pilot study on 20 depressed post MI patients we observed no differences in time domain or frequency domain measures of HRV before and after 8 weeks of antidepressant treatment. HRV measures were not affected differentially by mirtazapine and placebo nor were there any differences between responders and non- responders.
For the HRV parameters, differences were of such small magnitude that our pilot was to small to draw any meaningfull conclusions.
In addition, due to the absence of HRV differences, we could not assess the hypothesized cross-sectional and longitudinal relationships between the effect of antidepressant therapy, HRV parameters and cytokines. Further research on a larger group of post MI patients with depression might provide more insight in the mutual relationship of autonomic control, inflammation and their relation to post MI depression.

The most important finding of this pilot study is that mirtazapine seems to be a safe antidepressant in this cardiac compromised patient group. These results are in accordance with previous reported MIND-IT data concerning the use of mirtazapine and cardiac effects [29,30]. We presume that if mirtazapine has (serious) negative effects on HRV it would have been demonstrated in this pilot as in a previous equally small pilot study effect of mirtazapine on HRV could be demonstrated. Mirtazapine (n=10) was compared to the tricyclic antidepressant (TCA) imipramine (n=10) with regards to its effect on HRV and heart rate (HR) in depressed patients without cardiovascular disease. Both drugs demonstrated a suppression of mid- and high-frequency fluctuations of HRV but this was larger

for imipramine than for mirtazapine. It is suggested that the increase in HR and decrease in HRV may be attributed to the anticholinergic properties of imipramine (strong) and mirtazapine (weak), resulting in cardiac vagal inhibition [31].
We assume that the HRV decrease post MI hides the small HRV reducing effect of mirtazapine and that mirazapine causes no extra reduction of HRV on top of the MI induced HRV reduction.
This finding is of importance for the clinical decision making process in choosing the right antidepressant in post MI depression as contradicting results are reported on the clinical (side) effects of antidepressants on HRV. Recent results from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study conducted in 2981 subjects aged 18–65 years, indicate that the use of all classes of antidepressants (TCA, SNRI, or SSRI) has a significant negative impact on HR and HRV in non cardiac compromised patients. TCAs had the strongest effect, followed by SNRIs and SSRIs whereas discontinuing antidepressant use systematically increased cardiac vagal control [32].

However, unlike other antidepressants, mirtazapine does not inhibit the reuptake of norepinephrine or serotonin (5-HT) but acts as an antagonist at noradrenergig presynaptic alpha2-receptors, at postsynaptic 5-HT2, 5-HT3 and histamine H1-receptors with possible differential effects on the cardiovascular system. Beneficial effects of 5-HT3 antogonists on HRV are reported [33] even as cortisol decreasing effects of mirtazapine [34].

Besides this pilot, only limited data are available concerning the effects of antidepressant treatment on HRV in post MI depression and the negative findings of the NESDA are not replicated in these studies.

In 2001 the first report on antidepressant treatment of post MI depression and its effects on HRV was published. In depressed post MI patients, sertraline (SSRI) facilitates the rate of recovery of SDNN, a potent predictor of cardiac mortality. For the sertraline-treated group the trend toward restoring autonomic balance paralleled that of the nondepressed group [11]. Another study on depressed patients with an acute coronary syndrome (unstable angina and MI) demonstrated that sertraline significantly increased ultra low–frequency power, while improvement in mood was associated with higher low-frequency power independent of treatment [9]. These results however were primarily caused by a relatively greater decrease in HRV in the depressed comparison groups but not fully comparable because unstable angina has other pathophsiological characteristics as compared to MI.

In conclusion, this pilot study showed no HRV reducing effects of mirtazapine in post MI depression and mirtazapine appears to be safe regarding that aspect. Whether positive or at least stabilizing effects of mirtazapine on HRV in post MI depression can be expected has to be explored in a larger scale study.

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EPILOGUE

Putting the pieces together……

The aim of this thesis was to provide knowledge that contributes to the understanding of neurobiological characteristics of post MI depression and their consequences for treatment. Data used in this thesis were derived from sub-studies of the Myocardial Infarction and Depression–Intervention Trial (MIND-IT).

In this chapter, the main findings of these studies will be discussed. This discussion includes the clinical implications as well as some methodological issues. Finally, based on the data some general conclusions will be formulated and suggestions for further research given.

BACKGROUND

The World Health Organization (WHO) predicts that in 2030 depression and heart disease become numbers 1 and 2 respectively on the list of diseases with the greatest loss of "disability adjusted life years" in high income countries and numbers 2 and 3 worldwide [1]. In the highly industrialized countries rapid progress is made in acute intervention cardiology leading to decreasing mortality related to acute coronary syndromes such as myocardial infarction (MI). As a result of the consequently higher survival rate, prevalence of chronic cardiac disease with associated psychiatric co-morbidity increases: the cumulative incidence rate of depression in the general population is 5-10%, while the 1-year cumulative incidence of major and minor depression in post MI patients has found to be 20-30% [2,3]. Currently, the estimated prevalence of mood disorder in older patients with cardiovascular disease is 23 % [4].

These data suggest an important gain in public health and disease burden when depression, heart disease and especially their co-morbidity could be recognised and treated timely and adequately. Therefore, healthcare programs that focus on the prevention of cardiovascular disease and depressive disorder are of major importance. Of equal importance is the development of effective healthcare programs for the co-morbidity of these two disabling diseases.

Up to the landmark studies of Frasure-Smith et al. in 1993 the importance of the effects of depression on cardiac prognosis in the post MI period was not recognized [5].

Since then, large-scale studies were performed to examine the association between depressive disorder and myocardial infarction with regard to epidemiological, etiological, clinical and treatment issues. These studies confirmed that depression is not only accompanied by a decrease in quality of life in patients that suffer already the consequences of MI, but depression has also been identified as a significant risk factor for recurrent cardiac events or death in patients with heart disease [6,7]. Moreover, both cross-sectional and prospective analyses have demonstrated that depression is not only an important cardiovascular risk factor for cardiac patients, but also for individuals without cardiovascular morbidity [8,9,10].

These data and developments highlight both the virulent combination of MI and depression as well as the extensiveness of the problem worldwide.

In this thesis we explored the neurobiological relationship between MI, depression and psychopharmacological intervention. The presented studies all involve patients suffering from depressive symptoms or depressive disorder in the first year after an acute myocardial infarction. These studies had different designs (observational study, post hoc analysis, randomized controlled trial, case control) with a wide range of topics (efficacy of antidepressant treatment in post MI depression, cardiac adverse events in the post MI period, sub-typing in post MI depression, inflammation, cerebral damage, heart rate variability and MRI scanning). So, several aspects of post MI depression were evaluated.

MAIN FINDINGS

Three chapters deal with efficacy of antidepressant treatment in post MI depression, two chapters focus on brain damage and three chapters are devoted to the mutual relationship between inflammation, heart rate variability and antidepressant treatment effects.

Efficacy

In Chapter 1, we presented the results of the first large scale randomized, placebo-controlled trial on the efficacy of the dual-acting antidepressant mirtazapine in patients with post-MI depressive disorder.

In previous studies the efficacy of tricyclic antidepressants (TCAs) was established but the cardiac side effects limits their use in post MI patients [11,12,13]. The efficacy results of RCTs with SSRIs were not convincing [2,14]. In the MIND-IT study, we postulated that mirtazapine, a non-tricyclic antidepressant with presynaptic α2-antagonist properties, which enhance both noradrenergic and serotonergic neurotransmission, might be more efficacious than an SSRI in post MI depressive disorder.

The standardized effect size of mirtazapine in this post MI patient group (1.70) exceeded the standardized effect size in physically healthy patients with similar mild depression (1.19) [15] and is comparable with the recently reported standardized effect size of an SSRI in major depressed patients with CAD [16]. The placebo standardized effect size in this mirtazapine study (1.59), however, was much higher than reported in physically healthy patients with similar mild depression (0.61) [15] although comparable with other studies in post-MI depression [14,17]. The results of our study indicate that mirtazapine is at least as effective as an SSRI.

In chapter 2 we presented the results of an active case finding strategy and subsequent antidepressant treatment of depression in the year post MI with the expectation that this strategy would lead to a decrease of depression and related cardiac events on the long term.

When the effects of antidepressant treatment in the MIND-IT intervention group were compared with the Care as Usual group at 18 months post-MI it appeared that about one-third of both the intervention and Care as Usual patients continued to have ICD–10 depression whereas the cardiac event rate was 14% among the active antidepressant intervention group and 13% among Care as Usual.

The 18 months depression status of the antidepressant treatment group and the small differences in antidepressive effect between placebo and mirtazapine during the acute treatment phase suggests a limited pharmocological effect of antidepressant treatment. Moreover, these results questioned the issue whether screening on depressive disorder in post MI patients and subsequent antidepressant therapy is useful [18]. In considering these clinical dilemmas the interpretation of our study results has to be placed in a larger perspective.

There is a growing awareness that the a-theoretical purely descriptive definition of depressive disorder according to the Diagnostic and Statistical Manual (DSM) resulting in a polymorphic and widely diagnosed disease will not reflect one single underlying process in terms of vulnerability, etiology and patho-physiology. It is reasonable to assume that in the large multicenter projects like the MIND-IT, SADHART [14], ENRICHED [17] and CREATE [16] subgroups are lumped as all patients fulfill descriptive criteria for depressive disorder. These studies therefore harbour depressive disorder of different etiologies and probably also various courses of disease.

As described in Chapter 1 and 2 in the MIND-IT as well as in other studies [2,14,16,17] no strong effects of antidepressant treatment on post MI depression itself were reported. This raised the question whether subgroups of depressed post MI patients could be identified that would benefit from antidepressant treatment and whether effective antidepressant treatment influences cardiovascular prognosis in these subgroups.
Therefore we performed several subgroup analyses of the MIND-IT study.

Subgroup analyses

The first sub-study, presented in Chapter 3, showed that incomplete response to antidepressant treatment for post-myocardial infarction depression was associated with an increased risk of cardiac events (25%) when compared to responders (7.4%) and untreated Care as Usual subjects (11.2%). ENRICHD and SADHART data show similar findings, as non-response to cognitive behavior therapy and SSRI was associated with high risk for late mortality after myocardial infarction [19,20].
These results may be explained by the beneficial effects of antidepressant treatment but also by the possibility that a subtype of depression is associated with both a poor response to antidepressant treatment and a high risk for mortality. Evidence for a more somatically compromised subtype of post MI depression is demonstrated by studies revealing that only somatic/affective and not cognitive/affective symptoms of depresssive disorder are associated with disease severity, and all-cause mortality in MI patients [21]. Furthermore, van Melle et al. established an association between lower LVEF and higher rate of depression from 3-12 months post-MI [22]. However, as reported by Frasure-Smith, this relationship between severity of cardiac dysfunction and occurrence of depression is not generally recognized [23,24]. The complexity of the relationship is further illustrated by Martens et al., who demonstrated that although more severe somatic/affective symptoms were associated with lower LVEF, after controlling for LVEF, severity of somatic/affective symptoms remained significantly predictive of cardiac death/recurrent MI [25].

Further evidence that post MI depression harbours depressive disorder of different etiologies was found in the neurobiological sub-studies presented in the chapters 4 -8.

Brain Damage

In Chapter 4 and 5 we presented the results of 2 studies on the association between post MI depression and signs of cerebral damage. We assumed that part of the etiology of post MI depression fits in the “vascular depression hypothesis”, based on the assumption that cerebro-vascular disease predisposes a subset of older patients to the development of depressive disorder by disrupting fibre tracts connecting cortical and sub-cortical structures including the fronto-striatal circuits that are involved in the regulation of mood.
This thesis established that both structural and transient brain damage contribute to the presence of depressive symptoms in the post MI period. A transient release of S100B, a glial marker for cerebral damage, in serum during the first week after MI was associated with the development of depressive symptoms 3-12 months post MI. Serum S100B was not associated with depressive symptoms during hospitalization phase of MI. In contrast to the findings as regards to S100B, depressive symptoms in hospitalization phase for MI were significantly associated with the presence of white matter lesions, a form of structural brain damage. These results point to the involvement of incidental and structural brain processes in post MI depression as one of the contributing factors which for white

matter lesions is in accordance with the vascular depression hypothesis as introduced by Alexopoulos [26]. The release of S100B points to a cerebral reaction during the acute phase of MI but it is not known whether this leads to structural or merely functional changes in the brain.

Inflammation

In Chapter 6 and 7 we presented the results of 2 studies on the association between post MI depression and inflammatory status post MI. We hypothesized that part of the etiology of post MI depression fits in the 'the cytokine hypothesis of depression' based on the assumption that in chronic inflammation peripherally produced pro inflammatory cytokines IL-1 and TNF-α induce expression of the same cytokines in the brain. Brain cytokines act as neuromodulators and are responsible for the development of sickness behaviour, which has many symptoms similar to depression [27,28].

At first we tested the hypothesis whether depressed post-MI patients had an additional inflammation on top of MI related inflammation as compared to non-depressed post-MI patients which could explain the high incidence of depressive symptoms or sickness behaviour post MI. The results presented in Chapter 6 however, showed no increased inflammatory status in depressed post MI patients.

This finding might be explained by the high percentage of patients treated with statins (82% and 92%, in non-depressed and depressed, respectively). Differences in inflammation status might not be detectable as statins suppress inflammation in depressed patients suspected for acute MI [29].

The use of statins is also associated with significant reduction (69-79%) in the risk of depression in individuals who have had a cardiac event [30]. However, statin use between both cohorts in this thesis did not differ significantly, therefore statins cannot account for the differences in prevalence of mood disorder. Hence other factors must account for the differences in the prevalence of post MI depression. Therefore, individual susceptibility in combination with relatively increased inflammation parameters could induce depressive symptoms in one individual but not in another. Arguments that favour this hypothesis are the findings that when depressed and non-depressed post MI groups were compared to healthy subjects the mean levels of sIL-6R, TNF-α, sTNF-r2 and CRP of both post MI groups were considerably elevated. Even when compared to depressed and non-depressed heart failure patients, TNF-α blood values remain elevated [31,32]. STNF-R1 was lowered as compared to normal controls or non-depressed post MI patients. In sum, in the year post MI significant changes in inflammation parameters can be found but they do not discriminate depressed from non-depressed patients. In case inflammation plays a role as an etiological factor in post MI depression it contributes as a concomitant factor in combination with other etiological and/or pathogenetic factors.

In chapter 7 we presented the results of the effects of antidepressant treatment on inflammatory markers in post MI depression. A highly significant association was found between sTNF-RI increase and a decrease of depressive symptoms in mirtazapine responders. These effects were not observed in placebo responders or mirtazapine non-responders pointing at an essential difference in antidepressive mechanisms between mirtazapine and placebo. Other immune parameters appeared not to be involved. The results indicate involvement of the TNF-α system in post MI depression. In previous studies antidepressant treatment with mirtazapine was associated with an increase of TNF-α and sTNF-RI&2 in depressed patients without somatic co-morbidity [33] but sTNF-R1 was

never before associated with antidepressant therapeutic effects. A possible explanation is that a subset of depressed post MI patients in fact experiences a chronic form of the sickness syndrome and that especially these patients benefit from the mirtazapine induced sTNF-RI increase. A recent preclinical study demonstrated that brain TNF-R1-dependent activation of the sphingomyelin-ceramide pathway is required for brain TNFα to induce sickness behavior [34]. Protective activity of sTNF-R1 against sickness symptoms was demonstrated at the level of the Blood Brain Barrier as a single dose of recombinant sTNF-R1 was accompanied by initial inhibition of both Blood Brain Barrier permeability and CNS inflammation leading to diminishing of disease symptoms for 5 days in autoimmune neuritis. [35]. This mechanism might be relevant as we demonstrated in Chapter 4 of this thesis the presence of an increased permeability of the Blood Brain Barrier during the first week post MI, which might have long lasting effects on the up-regulated transport of TNF-α [36]. These results are in accordance with the observation that the efficacy of the tricyclic antidepressant desipramine is due to its property to decrease levels of TNF in the brain, ultimately modifying noradrenergic neurotransmission [37].
So, in our inflammation studies we made three important observations: 1) there is no difference in inflammation status between depressed and non-depressed post MI patients but 2) inflammation is involved as successful antidepressant treatment is associated with effects on the TNF-α system and 3) the mechanisms of antidepressant treatment response between placebo and mirtazapine differ.

Heart Rate Variability

In Chapter 8 we presented the results of the study on the mutual relationship between inflammation, heart rate variability (HRV) and antidepressant treatment effects. We hypothesized that successful antidepressant treatment would normalize decreased HRV and that this effect might be mediated by changes in inflammation parameters. This assumption was based on the fact that both MI and depressive disorder are associated with a decrease of HRV and recent studies showing negative correlations between HRV and inflammatory markers [38,39].
The preliminary findings did not indicate towards the presence of an association between single inflammation markers and any of the HRV parameters. Mirtazapine had no measurable effects on HRV in post MI depression. These preliminary findings are in accordance with previous safety studies on mirtazapine, and are of significance as a negative role of antidepressant use in the dysregulation of the autonomic nervous system has been observed among depressed and anxious subjects [40]. In cross-sectional studies, the use of TCAs, SNRIs, and SSRIs was associated with increased heart rate and decreased HRV, whereas associations were small or even non-significant when heart rate and HRV were compared between antidepressant-naive depressed or anxious subjects and healthy control subjects [40, 41,42] These results raised the question to what extent the presence as such of depression and anxiety disorders in their own right may cause diminished functioning of the parasympathetic nervous system and increased sympathetic nervous system activity and also to what extent antidepressants contribute to the findings. Given these considerations it is of significance that mirtazapine appears to be safe in a cardiac comprised patient group. However, due to the very small sample size of our study, the findings must be interpreted with caution.

……AND CONSIDER THEM IN A LARGER PERSPECTIVE.

Medical disorders are classified on the basis of symptomatology, pathophysiology and etiology [43]. Despite psychiatry being a medical specialism, history demonstrates that diagnoses and treatment in psychiatry are heavily influenced by variable social, psychological and political views. These are reflected in the development of the subsequent editions of the DSM. The DSM was developed to facilitate reliable clinical diagnosis and research and is based on clinical consensus among experts in the field. The first edition (DSM-I) was published in 1952, and had about 60 different disorders. DSM-II was published in 1968. Both of these editions were strongly influenced by the psychodynamic approach. There was no sharp distinction between normal and abnormal, and all disorders were considered reactions to environmental events. The early editions of the DSM distinguished between a psychosis and a neurosis. A psychosis is a severe mental disorder characterized by a break with reality. A neurosis is a milder mental disorder characterized by distortions of reality, but not a complete break with reality. Neuroses typically involve anxiety and depression. In 1980, with DSM-III, the psychodynamic view was abandoned and the medical model became the primary approach, introducing a clear distinction between normal and abnormal. The DSM became "a-theoretical", since it had no preferred etiology for mental disorders. In 1987 the DSM-III-R was introduced as a revision of DSM-III. In 1994, it evolved into DSM-IV with a 'Text Revision' (DSM-IV-TR) published in 2000. DSM-V is due for publication in 2013 with more than 350 defined psychiatric disorders.
Influenced by the fast neurobiological research developments, it is only since the last decades that there is a revival of "medical" psychiatry with the concomittant readjustment of views on the medical context of psychiatric diagnoses and their neurobiological underpinnings. In this readjustment process the validity of the (DSM) criteria for psychiatric disorder is a recurrent point of discussion. Recently the National Institute for Mental Health (NIMH) stated: "diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics. The boundaries of these categories based upon presenting signs and symptoms may not capture fundamental underlying mechanisms of dysfunction. One consequence has been to slow the development of new treatments targeted to underlying pathophysiological mechanisms" [44]

Clinical Implications

This thesis underscored the problem registered by the NIMH as it showed that post MI depression harbours different etiologies and probably also various courses of disease. The latter became obvious in the increased mortality associated with non-response on antidepressant treatment as described in Chapter 3. The different etiologies in post MI depression might require different treatment modalities to achieve optimal antidepressive effect. The inflammation sub-study demonstrated clearly that remission of post MI depression could be achieved in several ways by influencing different neurobiological pathways. In contrast to placebo response, mirtazapine response was associated with influencing the TNF-α system. The clinical importance of this variety in pathways is underscored by the results of antidepressant treatment- continuation studies (24 months). These studies demonstrate that relapse rates are much higher for placebo treatment as

compared to antidepressant treatment [45,46] pointing to the necessity of long-term use of antidepressants in depressive disorders of certain etiologies.
As described in Chapter 7 it was demonstrated that TNF-α plays a role in (the degree of) regaining remission of depressive symptoms. Successful antidepressant treatment is associated with 1) changes in the interaction between TNF-α and the Hypothalamic Pituary Axis and 2) TNF-α modulated functioning of the noradrenergic a receptor. Higher serum levels of TNF-α predict non-response to antidepressant treatment with SSRIs [47] and relapse of depressive disorder after remission [48]. The increased serum TNF-α in post MI patients as compared to healthy controls in combination with the absence of the antidepressant continuation treatment in the mirtazapine responders could explain the high incidence of post MI depression at 18 months post MI. As higher TNF-α predict non-response on SSRIs and the used antidepressants in both the antidepressant treatment group and Care as Usual of the MIND-IT are more or less limited to mirtazapine and SSRIs, it is reasonable that high rates of depression are present in both groups at 18 months post MI. Therefore, from a clinical point of view a trial with a serotonin-norepinephrine reuptake inhibitor would be recommendable as we expect this class of antidepressants to have effects on the TNF-α system.
Moreover, after completion of the nested study research protocol of the MIND-IT (mirtazapine/placebo/citalopram during 24 weeks) or in case of refusal of the patient to participate in the prescribed medication of the nested study, clinicians were relatively free in the choice of antidepressant treatment during the 18 months post MI. This was done to achieve optimal antidepressant treatment and compliance in order to maximize the presumed protective effect of successful antidepressant treatment on cardiac adverse events. As a consequence, no strict antidepressant treatment protocol was followed. When examining the used antidepressants during the 18 months post MI none of the patients in both the active intervention group and the Care as Usual group completed the full depression medication protocol according the Psychiatric Guidelines (Table 1). So, it seems reasonable that for both the intervention and the Care as Usual group an increase of efficacy can be gained by additional antidepressant therapy.

Table 1. Antidepressant treatment in the MIND-IT study

	Intervention (n=208)	Care as Usual (n=122)
No therapy	33%	80%
Mirtazapine/placebo	45%	0
SSRI	7%	6%
TCA/non-SSRI	1%	2%
Psychotherapy/counseling	9%	10%
Unknown	5%	3%
Lithium	0	0
Electro Convulsive therapy	0	0
Continuation treatment	?	?

In sum, this thesis presented evidence for several distinct etiological factors contributing to post MI depression. We found evidence for recurrent depressive disorder, which is probably more genetically determined than the other subtypes; the relation with inflammation points to some evidence for the “cytokine hypothesis of depression”; the relation with white matter lesions and acute cerebral damage reflected by S100B release points to evidence for the “vascular depression hypothesis”. Moreover, there is evidence for a

somatically comprised subtype namely the antidepressant treatment non-responders with worse cardiac prognosis. However, due to small numbers in the subgroups, we could not assess the mutual relationships between the several subtypes. So it is possible that the latter belongs to one of the other "subtypes".
Considering the current discussions on the validity of the descriptive DSM IV diagnosis it can be concluded that the broad descriptive symptomatology offers sufficient possibilities for accurate clinical diagnosis. The problem in clinical diagnosis of post MI depression is merely the accurate recognition by the clinicians as symptom presentation is slightly different from the depressed but not somatically ill [3]. Another complicating factor in clinical diagnostic assessment is that both patients and clinicians are inclined to assign depressive symptomatology to somatic disease equivalents. This last factor may have been responsible for the decision not to follow the Psychiatric Guidelines for antidepressant treatment.
The refusal and exclusion research rate of the MI patients is about 55% in the Multi Center studies on post MI depression. This probably leads to underrepresentation in the study sample of the most seriously ill and to an overrepresentation of relatively mild depressive patients in which the effect sizes of antidepressant treatment are usually small. Despite this limitation the effect size of mirtazapine exceeded those found in similar non-somatically comprised depressions and a clear difference in mechanism between placebo and mirtazapine was defined.
The results of the neurobiological sub-studies suggest that depression in the context of MI may not be a homogeneous condition and that only some aspects of depression are associated with worsened cardiovascular prognosis. Nevertheless, suffering from a depressive disorder is accompanied by a significant decrease of quality of life for the patient and his/here surroudings and a major source of health care costs. Therefore it is important to screen on depressive disorder in cardiovascular high-risk groups and improve diagnostic and treatment facilities for co-morbidity.

Future Research

For 2030, the World Health Organization projected depression and heart disease to become numbers 1 and 2 on the list of diseases with the greatest loss of "disability adjusted life years" in high-income countries [1]. Studies as the MIND-IT, SADHART, ENRICHD, CREATE, Heart and Soul, and NESDA provide growing knowledge about several aspects the co-morbidity of cardiovascular diseases and mood disorders. However, many questions remain unanswered especially issues regarding clinical practice. One of the major challenges will be to translate the merely epidemiological data into research, diagnostic and treatment programs that are clinical relevant for all MI patients.
The findings of this thesis demonstrate the complexity of research in post MI depression. It showed once more that lumping and splitting produce significantly different results as several clinically relevant findings became only apparent in subgroup analyses.
Also, this thesis has shown the complexity of the processes and interactions that lead to post MI depression. Affective symptoms and cardiac dysfunction are not related directly to dysfunctioning of one physiological or organ system.
Considering individual differences in adaptation capacity, interactions between systems, and the accumulation of adversity -both cross sectional (i.e. a cascade of disturbances during MI) as well as longitudinal (previous depression, existence of WML, persistent inflammation)- could be a better concept explaining the processes involved in post MI depression.

Etiological factors in post MI depression such as e.g. inflammation have differential effects on individual patients. Some of these effects only become apparent when they are changed, as was the case in the inflammation sub-study. The increase of sTNFR-1 was highly significantly associated with the response to mirtazapine, whereas baseline sTNFR-1 did not differ between depressed and non-depressed post MI patients. Placebo response was reached in another way and no direct relationship with the measured inflammation parameters was found. Cerebral vulnerability and LVEF affect the mood states of post MI patients in their own way. All these systems are related to each other in a complex way.

As it is expected that identifying syndromes based on pathophysiology eventually will improve outcomes, the National Institute on Mental Health is launching the Research Domain Criteria [44]. The Research Domain Criteria have to create a long- term framework for research that can yield incorporating of data on pathophysiology in ways that eventually will help identify new targets for treatment development, detect subgroups for treatment selection, and provide a better match between research findings and clinical decision making. The assumptions of the Research Domain Criteria fit in future research solutions necessary for the field of cardiopsychiatry. The Research Domain Criteria regard mental disorders as disorders of brain circuits which can be detected with tools of neuroscience and in the ideal case deliver molecular and neurobiological parameters that provides help in the decision making process for the choice of the right antidepressant treatment. For instance, selection of antidepressants on basis of its pharmacological profile and properties to influence relevant cytokine systems.

From the clinicians point of view, future research on post MI depression has to focus on identifying subgroups of patients with a post MI depressive disorder as far as it concerns the differential psychological and neurobiological etiological factors that contribute to the development of post MI depression. Response prediction treatment studies that take these factors into account will provide the necessary rationale for effective tailor made treatment in which an effective match can be made between the specific characteristics of antidepressant treatment and the psychological and neurobiological characteristics of the patient with cardiac and psychiatric co-morbidity. In this thesis, we demonstrated that splitting of etiological and pathogenic pathways as well as specific symptom complexes of depression as research strategy are important. This splitting procedure identified several subtypes of post MI depressive disorder and cerebral damage being one of the etiological factors. Moreover the splitting strategy demonstrated that influencing inflammation parameters is an important factor for successful antidepressant treatment of post MI depression. This promising line of research can deliver important insights that provide tools for better treatment strategies in post MI depressive disorder.

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SAMENVATTING

De som der delen.....

Het doel van het in dit proefschrift beschreven onderzoek was om meer inzicht te krijgen in de neurobiologische factoren die een rol spelen bij het ontstaan en de behandeling van een depressie na een hartinfarct. De onderzoeksdata werden verkregen uit de Myocardial Infarction and Depression–Intervention Trial (MIND-IT).

Dit hoofdstuk geeft een overzicht van de belangrijkste bevindingen. De discussie omvat zowel de klinische implicaties als enkele methodologische problemen die bij de analyse van de onderzoeksresultaten aan het licht kwamen. Op basis van de onderzoeksdata worden tot slot enkele algemene conclusies geformuleerd en suggesties voor verder onderzoek gegeven.

ACHTERGROND

De World Health Organization (WHO) voorspelt dat in 2030 depressieve stoornissen en cardiale aandoeningen als oorzaak van het verlies aan ziekte gerelateerde productieve levensjaren in de geïndustrialiseerde landen resp. de nummers 1 en 2 zullen zijn en wereldwijd de nummers 2 en 3 [1].
In de hoog geïndustrialiseerde landen wordt op dit moment snelle vooruitgang geboekt in de acute interventie cardiologie wat leidt tot een dalende mortaliteit als gevolg van de acute coronair syndromen zoals het hartinfarct. Als gevolg van het consequent hogere overlevingspercentage stijgt de prevalentie van chronisch cardiale aandoeningen en de daarmee geassocieerde psychiatrische comorbiditeit: de cumulatieve incidentie van depressie in de algehele bevolking is 5-10%, terwijl de 1-jaars cumulatieve incidentie van een depressieve stoornis na een hartinfarct 20-30 % blijkt te zijn [2,3]. De geschatte prevalentie van stemmingsstoornissen bij oudere patiënten met een (niet acute) cardiovasculaire aandoening in de algemene populatie is 23% [4].
Deze gegevens suggereren dat er qua publieke gezondheid en ziektekosten belangrijke winst geboekt kan worden wanneer depressieve stoornissen, hartziekten en in het bijzonder hun gezamenlijk voorkomen tijdig en adequaat herkend en behandeld worden. Gezondheidszorg programma's die zich richten op de preventie van cardiovasculaire aandoeningen en depressieve stoornissen zijn van groot belang. Daarnaast is het nodig om specifieke en effectieve zorgprogramma's te ontwikkelen voor patiënten die beide aandoeningen hebben.

Met de publicaties van de baanbrekende studies van Frasure-Smith e.a. in 1993 werd voor het eerst duidelijk dat patiënten die in het jaar na een hartinfarct een depressieve stoornis krijgen een groter risico lopen om in dat jaar nieuwe cardiale problemen te krijgen of te overlijden. Nadien zijn er wereldwijd diverse grote studies verricht naar de epidemiologie, etiologie, klinische presentatie en behandeling van stemmingsstoornissen in de periode na het hartinfarct. Deze studies bevestigden dat een depressie niet alleen vergezeld gaat van een daling van de kwaliteit van leven maar ook een significante risicofactor is voor nieuwe cardiale gebeurtenissen en overlijden [6,7].
Bovendien hebben cross-sectionele en prospectieve studies aangetoond dat een depressie niet alleen een belangrijke cardiovasculaire risicofactor is voor patiënten die al een hart aandoening hebben maar ook voor mensen die geen hart en vaatziekten hebben [8,9,10].
Deze bevindingen en ontwikkelingen benadrukken niet alleen het gezondheidsrisico van de combinatie depressie en hartinfarct maar ook de wereldwijde aanwezigheid van het probleem.

In dit proefschrift onderzochten wij de neurobiologische aspecten van de relatie tussen hartinfarct, depressie en psychofarmacalogische interventies. Alle studies betreffen patiënten die lijden aan depressieve symptomen of een depressieve stoornis in het eerste jaar na het hartinfarct. De studies hadden verschillende onderzoeksdesigns (observationele studie, post hoc analyse, gerandomiseerd design (RCT), case control) met een brede variatie aan onderwerpen (effectiviteit van antidepressiva bij post MI depressie, cardiale complicaties in de post MI periode, sub typering van de post MI depressie, inflammatie, cerebrale schade, Heart Rate Variability en MRI onderzoek).

SAMENVATTING VAN DE RESULTATEN

Het proefschrift bestaat uit 8 hoofdstukken. De eerste drie hoofdstukken beschrijven de effectiviteit van antidepressiva bij de post- infarct depressie. De daaropvolgende twee hoofdstukken behandelen de relatie tussen hersenschade en de post infarct depressie. In de laatste drie hoofdstukken worden verschillende aspecten van de relatie tussen ontstekingsfactoren, Heart Rate Variability en de effecten van antidepressieve behandeling beschreven.

Effectiviteit

In hoofdstuk 1 presenteren we de resultaten van de eerste grootschalige placebo gecontroleerde studie naar de effectiviteit van mirtazapine bij de behandeling van de post infarct depressie. Mirtazapine is een niet tricyclisch antidepressivum met pre-synaptische $\alpha 2$ antagonistische eigenschappen dat zowel de noradrenerge als de serotonerge neurotransmissie stimuleert.

In eerdere studies werd de effectiviteit van tricyclische antidepressiva (TCA) al bewezen maar het cardiale bijwerkingenprofiel van de TCAs beperkt hun gebruik bij post infarct patiënten [11,12,13]. De antidepressiva behorend tot de groep van de serotonine heropname remmers (SSRIs) hebben minder cardiale bijwerkingen maar daarentegen bleek de effectiviteit van SSRIs bij de behandeling van de post infarct depressie weer niet erg overtuigend [2,14].

In de MIND-IT studie onderzochten we of mirtazapine -gezien het van TCAs en SSRIs verschillende farmacologische profiel- bij de behandeling van de post infarct depressie effectiever zou zijn dan de SSRIs. De “standardized effect size” (SES) van mirtazapine bleek in de MIND-IT patiënten groep 1.70 te zijn en overtrof daarmee de SES van een SSRI behandeling bij somatisch gezonde maar vergelijkbaar milde depressieve patiënten (SES 1.19) [15]. De placebo SES in onze mirtazapine studie (1.59) was echter veel hoger dan bij deze somatisch gezonde depressieve patiënten (0.61) [15] alhoewel vergelijkbaar met andere studies bij een post infarct depressie [14,17]. De resultaten van onze studie duiden erop dat mirtazapine tenminste even effectief is als een SSRI bij post infarct depressies [16].

In Hoofdstuk 2 presenteren we de resultaten van een “active case finding strategy” dat wil zeggen: het actief opsporen en vervolgens behandelen van patiënten met een depressie in het eerste jaar na het infarct (Interventie-arm). Wij hadden de verwachting dat, in vergelijking met de Care as Usual (CAU) controle groep, de “active case finding strategy” op de langere termijn zou leiden tot een lager percentage depressies en cardiale gebeurtenissen zoals een re-infarct of dotterprocedure.

Het bleek echter dat 18 maanden na het infarct 1/3 van beide groepen depressief was en het percentage nieuwe cardiale gebeurtenissen respectievelijk op 13% en 14% lag. Deze bevindingen en de kleine verschillen in antidepressief effect tussen mirtazapine en placebo zouden de suggestie kunnen wekken dat het effect van een farmacologische interventie bij de post infarct depressie erg beperkt is. Verder roepen deze resultaten de vraag op of het wel zinvol is om patiënten te screenen op een depressie na een infarct [18]. Voor een goede beschouwing van deze klinische dilemma’s is het nodig om de interpretatie van onze studie resultaten in een breder perspectief te plaatsen.

Er is een toenemend besef dat de a-theoretische en zuiver descriptieve definitie van de depressieve stoornis volgens het wereldwijd meest gebruikte classificatie systeem de Diagnostic and Statistical Manual (DSM) leidt tot een polymorf en frequent gediagnosticeerd ziektebeeld zonder dat er sprake is van een uniform onderliggend proces qua erfelijk bepaalde kwetsbaarheid, etiologie en pathofysiologie. Het is logisch om aan te nemen dat in de grote multi-center studies als de MIND-IT, SADHART, ENRICHED en CREATE patiënten

met verschillende subtypes van depressies zijn samengevoegd die allemaal voldoen aan de descriptieve DSM criteria voor depressie. Deze multi-center studies herbergen dus depressies met een diverse etiologie en waarschijnlijk ook een daarbij passend verschillend ziektebeloop.
In Hoofdstuk 1 en 2 wordt beschreven dat in de MIND-IT en andere vergelijkbare studies geen sterke effecten van een antidepressieve behandeling op de postinfarct depressie gevonden wordt [2,14,16,17]. Dit riep de vraag op of er patiënten subgroepen gedefinieerd en geïdentificeerd konden worden die wel duidelijk baat hebben bij een antidepressieve behandeling en of/hoe een effectieve antidepressieve behandeling in deze subgroepen de cardiovasculaire prognose zou beïnvloeden. Om deze vraagstelling te kunnen beantwoorden hebben wij binnen de MIND-IT studie verschillende subgroep analyses gedaan.
De eerste subgroepanalyse - beschreven in Hoofdstuk 3- toonde aan dat een partiële remissie na antidepressieve behandeling van de post infarct depressie geassocieerd is met een verhoogd risico op nieuwe cardiale gebeurtenissen (25%) in vergelijking met responders (7.4%) en onbehandelde Care as Usual patiënten (11.2%). De onderzoeksdata uit de ENRICHD en SADHART laten vergelijkbare bevindingen zien: non-respons bij Cognitieve Gedrags Therapie en een SSRI is geassocieerd met late mortaliteit in de postinfarct periode [19,20].
De gunstige werking van de antidepressieve behandeling zelf zou hiervoor een verklaring kunnen zijn; een alternatieve verklaring is dat een subtype van de post infarct depressies specifiek geassocieerd is met zowel een slechte respons op antidepressiva als met een slechte cardiale prognose. Bewijs voor een meer ‘somatisch gecompromitteerde’ depressie wordt geleverd door studies die aantonen dat alleen de somatisch/affectieve en niet de somatisch/cognitieve symptomen van de depressieve stoornis geassocieerd zijn met de ernst van de cardiale aandoening en de overall mortaliteit in infarct patiënten [21]. Bovendien hebben van Melle e.a. een associatie aangetoond tussen een lagere Linker Ventrikel Ejectie Fractie (LVEF) – een maat voor de hartfunctie – en een hogere depressie score 3-12 maanden post infarct. De relatie tussen de ernst van cardiale disfunctie en het optreden van een depressie wordt echter niet in zijn algemeenheid bevestigd [23,24]. De complexe relatie wordt geïllustreerd door Martens e.a. die aantoonde dat er weliswaar een associatie was tussen een lagere LVEF en een hogere somatisch/affectieve score maar dat, na correctie voor de LVEF, somatisch/affectieve symptomen significant gecorreleerd bleven met een verhoogde kans op cardiale sterfte of een re-infarct [25].
Meer bewijs voor de aanname dat bij de postinfarct depressie meerdere etiologische factoren een rol spelen werd gevonden in de neurobiologische substudies die in de Hoofdstukken 4-8 gepresenteerd worden.

Hersenschade

In Hoofdstuk 4 en 5 presenteren we de resultaten van 2 studies naar de associatie tussen de post infarct depressie en tekenen van cerebrale schade. We veronderstelden dat een deel van de etiologie van de post infarct depressie verklaard kan worden vanuit de “vasculaire depressie hypothese”. Deze hypothese is gebaseerd op de aanname dat een cerebro-vasculaire aandoening een deel van de oudere patiënten kwetsbaar maakt voor het ontwikkelen van een depressieve stoornis door een beschadiging van de neuronale circuits in de hersenen. Het betreft dan m.n. verbindingen tussen de corticale en subcorticale structuren inclusief de cortico-striatale circuits die betrokken zijn bij de stemmingsregulatie.

In dit proefschrift werd conform de onderzoekshypothese aangetoond dat zowel structurele als incidentele hersenbeschadiging een bijdrage levert aan de ontwikkeling van depressieve symptomen in de postinfarct periode. De incidentele schade bleek uit het vrijkomen van S100B in het bloed gedurende de eerste week post infarct en de associatie tussen S100B en de ontwikkeling van depressieve symptomen 3-12 maanden postinfarct. S100B is een marker voor cerebrale gliacel beschadiging en normaliter niet meetbaar in het bloed. Serum S100B was niet geassocieerd met depressieve symptomen tijdens de ziekenhuisopname voor het index infarct.
Depressieve symptomen in de ziekenhuis fase waren daarentegen wel significant geassocieerd met cerebrale witte stof afwijkingen, een vorm van structurele hersenschade. Incidentele en structurele hersenbeschadiging spelen dus een rol bij de ontwikkeling van de postinfarct depressie hetgeen in overeenstemming is met de vasculaire depressie hypothese zoals die geïntroduceerd is door Alexopoulos [26]. Het vrijkomen van S100B in de bloedbaan duidt op een cerebrale reactie tijdens de acute fase van het hartinfarct maar het is niet bekend of dit tot structurele of meer functionele veranderingen in het brein leidt.

Inflammatie

In Hoofdstuk 6 en 7 beschrijven we ons onderzoek naar het verband tussen de ernst van depressieve symptomen en de hoogte van ontstekingsparameters in de post infarct periode. Uitgangspunt hierbij was dat de 'cytokine hypothese voor depressie' bij een deel van de patiënten een mogelijk verklaringsmodel zou kunnen zijn voor het ontstaan van de post infarct depressie. Cytokines zijn eiwitten die een rol spelen in het immuun afweersysteem. De 'cytokine hypothese voor depressie' is gebaseerd op de aanname dat bij een chronische ontstekingsreactie perifeer geproduceerde ontsteking stimulerende cytokines Interleukine 1 (IL-1) en Tumor Necrose Factor α expressie van deze zelfde cytokines in de hersenen induceren. Cytokines als IL-1 en TNF-α acteren in het brein als neuromodulatoren en zijn verantwoordelijk voor het 'ziektegevoel' oftewel het 'sickness syndrome' dat tijdens infecties optreedt. Het 'sickness syndrome' heeft qua symptomen veel overeenkomsten met de depressieve symptomatologie [27,28].
Als eerste onderzoeksvraag in het kader van deze 'cytokine hypothese' hebben we onderzocht of depressieve post infarct patiënten een hogere ontstekingsactiviteit (d.w.z. meer cytokines) in het bloed zouden hebben in vergelijking met niet depressieve infarct patiënten. De resultaten gepresenteerd in Hoofdstuk 6 laten zien dat dat niet het geval was. Dat wij bij de depressieve groep geen verhoogde ontstekingsactiviteit vonden, zou verklaard kunnen worden uit het feit dat in beide groepen een hoog percentage patiënten met statinen -een cholesterolverlagend medicament- behandeld werd (82% vs 92%; niet depressief vs. depressief). Verschillen in ontstekingsactiviteit kunnen hierdoor gemaskeerd worden aangezien eerder onderzoek aantoonde dat statines bij depressieve hartinfarct patiënten de ontstekingsactiviteit onderdrukten [29]. Het gebruik van statines bleek in ander onderzoek eveneens geassocieerd te zijn met een significante reductie (69-79%) van het risico op een depressie bij patiënten die een cardiale gebeurtenis doorgemaakt hebben [30].
Echter, aangezien het statine gebruik tussen de 2 groepen in ons onderzoek niet significant verschilde kunnen de statines niet de verklaring zijn voor het verschil in prevalentie van de stemmingsstoornis in de post infarct periode en moeten andere factoren een rol spelen.

Een andere verklaring zou kunnen zijn dat cytokines wel degelijk een rol spelen bij het ontstaan van de postinfarct depressie maar alleen bij die patiënten die al een bepaalde kwetsbaarheid voor het ontwikkelen van een depressie hebben. Deze hypothese wordt ondersteund door het onderzoeksgegeven dat zowel bij depressieve als niet depressieve post infarct patiënten de serum spiegels van de ontstekingsmarkers sIL-6R, TNF-α, sTNF-R2 (allen cytokines) en C-reactive proteine (algemene ontstekingsmaat) verhoogd bleken te zijn wanneer deze vergeleken werden met gezonde mensen. Ook wanneer onze studie populatie met (niet) depressieve hartfalen patiënten vergeleken werd, bleken de TNF-α waarden bij de MIND-IT patiënten hoger [31,32]. Daarentegen was de soluble Tumor Necrose Factor –Receptor 1 (sTNF-R1) bij de depressieve post infarct patiënten verlaagd in vergelijking met gezonde controle personen en niet depressieve post infarct patiënten. Samengevat kan worden gesteld dat er in het jaar post infarct significante veranderingen in ontstekingsparameters gevonden worden maar dat op basis hiervan niet voorspeld kan worden welke post infarct patiënten depressief zullen worden. Als inflammatie een rol speelt als oorzakelijke factor bij de post infarct depressie dan is het als bijkomende factor in combinatie met andere etiologische en/of pathogenetische factoren.
Als tweede onderzoeksvraag in het kader van onze 'cytokine hypothese' voor de post infarct depressie hebben we onderzocht of behandeling met antidepressiva tot een verandering van de ontstekingsactiviteit zou leiden. De derde vraag luidde vervolgens of de eventuele verandering van de ontstekingsactiviteit gepaard zou gaan met een afname van depressieve symptomen. Hoofdstuk 7 beschrijft de resultaten van het onderzoek naar de effecten van mirtazapine en placebo op ontstekingsmarkers bij de post infarct depressie. Tegen de verwachting in bleek een antidepressieve behandeling geen directe verlaging van cytokines als TNF-α te veroorzaken. Er bleek bij de mirtazapine responders wel een zeer significante associatie te bestaan tussen de stijging van sTNF-R1 en een daling van depressieve symptomen. Deze effecten werden niet gezien bij de placebo (non) responders, noch bij de mirtazapine non-responders hetgeen wijst op een essentieel verschil tussen de werkzame antidepressieve mechanismen van mirtazapine en placebo. Andere ontstekingsparameters leken niet betrokken te zijn bij de antidepressieve respons. Onze resultaten wijzen op een complexe betrokkenheid van het TNF-α systeem bij de post infarct depressie. In voorgaande studies bij depressieve patiënten zonder somatische co-morbiditeit was al gevonden dat behandeling met mirtazapine geassocieerd is met een stijging van TNF-α en sTNF-RI&2 [33]. STNF-R1 is echter nooit eerder in verband gebracht met antidepressieve therapeutische effecten. Een mogelijke verklaring voor het "antidepressieve effect" van sTNF-R1 is dat een deel van de patiënten met een post infarct depressie in feite lijdt aan een chronische vorm van het 'sickness syndrome' gezien de verhoogde inflammatie status in het jaar na het infarct. Speciaal deze subgroep zou baat kunnen hebben bij de door mirtazapine geïnduceerde stijging van sTNF-R1 en zijn ontstekingsremmende werking. Bewijs voor deze hypothese werd geleverd door een recente preklinische studie. Deze toonde aan dat een TNF-R1 afhankelijke activatie van het sphingomyeline-ceramide systeem in de hersenen een voorwaarde is voor de inductie van TNF-α 'sickness behavior' [34]. STNF-R1 heeft een beschermende werking tegen het optreden van sickness-symptomen op het niveau van de bloed-hersenbarriere. Dit werd aangetoond middels een studie waarbij een dosis recombinant sTNF-R1 bij auto-immuun neuritis werd gevold door een remming van zowel de bloed-hersenbarriere permeabiliteit als de ontstekingsreactie van het centrale zenuwstelsel. Dit leidde tot een vermindering van neuritis symptomen gedurende 5 dagen [35]. Hetzelfde mechanisme kan eveneens relevant zijn bij de behandeling van de post infarct depressie aangezien wij in Hoofd-

stuk 4 van dit proefschrift aantoonden dat er in de week post infarct bij een deel van de patiënten sprake is van een verhoogde bloed-hersenbarriere permeabiliteit. Dit kan resulteren in een langdurige stijging van het transport van TNF-α vanuit het bloed over de bloed-hersenbarriere heen het hersenweefsel in.
Onze bevinding dat beïnvloeding van het TNF-α systeem onderdeel is van de antidepressieve eigenschappen van mirtazapine is in overeenstemming met het gegeven dat de effectiviteit van het tricyclische antidepressivum desimipramine gekoppeld is aan de eigenschap om de TNF-α spiegels in de hersenen te verlagen met een daaraan gekoppelde verandering van de noradrenerge neurotransmissie.
Samengevat hebben wij in de 2 inflammatie studies drie belangrijke observaties gedaan: 1) er is geen verschil in de hoogte en aard van de ontstekingsreactie tussen depressieve en niet depressieve postinfarct patiënten 2) het inflammatie systeem is bij de postinfarct depressie betrokken aangezien succesvolle antidepressieve behandeling geassocieerd is met effecten op het TNF-α systeem en 3) de mechanismen waarlangs mirtazapine en placebo hun antidepressieve effect bereiken verschillen.

Heart Rate Variability

Hoofdstuk 8 beschrijft de resultaten van een pilot onderzoek naar de onderlinge relatie tussen inflammatie, heart rate variability (HRV) en antidepressieve behandeling. De HRV is het fysiologische fenomeen dat het tijdsinterval tussen 2 opeenvolgende hartslagen varieert. Hoe groter de variatie –binnen normale grenzen- hoe gezonder het hart. De HRV is tevens een maat voor het functioneren van het autonome zenuwstelsel. Na een hartinfarct en tijdens een depressie wordt vaak een verlaagde HRV gezien. Wij onderzochten de hypothese dat succesvolle antidepressieve behandeling de verlaagde HRV zou normaliseren en dat dit effect gemedieerd zou worden door veranderingen in ontstekingsparameters. Deze laatste aanname was gebaseerd op het feit dat er een negatieve correlatie tussen HRV en bepaalde ontstekingsmarkers bestaat [38,39].
Onze pilot resultaten lieten echter geen associatie zien tussen de inflammatie parameters en de HRV maten. Mirtazapine had evenmin een meetbaar effect op de HRV maten dat wil zeggen: het verbeterde noch verslechterde de HRV en dit is in overeenstemming met de eerdere klinische studies naar de veiligheid van het gebruik van mirtazapine bij hart patiënten.
Deze constatering is van belang aangezien onlangs is gebleken is dat antidepressiva een negatieve rol lijken te spelen bij de autonome disregulatie bij patiënten met een depressie en angststoornis [40]. In cross-sectionele studies bleek namelijk dat het gebruik van TCAs, SSRIs en SNRIs geassocieerd is met een stijging van de hartfrequentie en een daling van de HRV. Wanneer hartfrequentie en HRV van medicatievrije patiënten met een depressie of angststoornis vergeleken werden met controlepersonen werden geen significante verschillen gevonden [40,41,42]. Deze bevindingen roepen de vraag op in hoeverre de autonome disregulatie bij patiënten met een depressie en/of angststoornis door de ziekte zelf veroorzaakt wordt dan wel –deels- door het gebruik van antidepressiva. Gegeven deze overwegingen is het van belang om vast te stellen dat mirtazapine veilig lijkt te zijn in het gebruik bij postinfarct patiënten in de zin dat het de HRV niet in negatieve zin beïnvloedt. Deze conclusie kan echter slechts met de nodige voorzichtigheid getrokken worden gezien de kleine aantallen in onze studie.

……BESCHOUWD IN EEN GROTER PERSPECTIEF.

Medische ziektebeelden worden geclassificeerd op basis van symptomatologie, pathofysiologie en etiologie [43]. Ondanks dat psychiatrie een medisch specialisme is toont de geschiedenis aan dat de diagnostiek en behandeling in de psychiatrie zwaar beïnvloed wordt door sterk wisselende sociale, psychologische en politieke opvattingen. Deze niet medische wisselende opvattingen vinden hun weerslag in de ontwikkeling van de opeenvolgende edities van de Diagnostic and Statistical Manual (DSM). De DSM is een classificatiesysteem dat in eerste instantie ontwikkeld is om betrouwbare klinische diagnostiek t.b.v. onderzoek mogelijk te maken. De eerste editie (DSM I) is in 1952 gepubliceerd en kende plm. 60 verschillende psychiatrische diagnosen. De DSM II volgde in 1968. Deze beide edities werd sterk beïnvloed door de psychodynamische opvattingen. Er was geen scherp onderscheid tussen normaal en abnormaal en alle ziektebeelden werden beschouwd als zijnde een reactie op de omgeving. De vroege edities maakten wel onderscheid tussen een psychose en neurose. Een psychose is een ernstige psychiatrische stoornis waarbij de patiënt het normale contact met de - door zijn omgeving ervaren - werkelijkheid geheel of gedeeltelijk kwijt is. Een neurose is volgens de psychodynamische invalshoek een mildere psychiatrische stoornis die gekenmerkt wordt door een vervormd waarnemen van de werkelijkheid voortkomend uit onbewuste innerlijke conflicten. De depressie en angststoornis werden als typische voorbeelden van een neurotische stoornis gezien. Met het verschijnen van de DSM III in 1980 werd de psychodynamische invalshoek verlaten en het medisch model de primaire invalshoek waarbij een duidelijke scheiding werd geïntroduceerd tussen normaal en abnormaal. De DSM werd 'a-theoretisch' aangezien het geen voorkeur hanteerde voor een bepaald etiologisch model. In 1987 volgde een herziene versie: de DSM III-R die in 1994 opgevolgd werd door de DSM IV met een gereviseerde uitgave in 2000 (DSM IV TR). In 2013 wordt de DSM V uitgebracht met naar verwachting meer dan 350 gedefinieerde psychiatrische aandoeningen.
De laatste decennia is er onder invloed van de snelle ontwikkelingen op het gebied van neurobiologisch onderzoek een revival van de 'medische' psychiatrie met de bijbehorende wijzigingen in visie op de medische context van psychiatrische aandoeningen en hun neurobiologische basis. In dit ontwikkelproces vormt de validiteit van de (DSM) criteria voor psychiatrische stoornissen een terugkerend punt van discussie. Onlangs gaf het Amerikaanse National Institute for Mental Health de volgende verklaring uit: "diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics. The boundaries of these categories based upon presenting signs and symptoms may not capture fundamental underlying mechanisms of dysfunction. One consequence has been to slow the development of new treatments targeted to underlying pathophysiological mechanisms" [44].

KLINISCHE IMPLICATIES

Dit proefschrift onderstreept het door het National Institute for Mental Health gesignaleerde probleem aangezien het aantoont dat de post infarct depressie geen homogeen ziektebeeld is maar depressieve stoornissen met een verschillende etiologie en diverse beloopsvormen herbergt. Het laatste werd met name duidelijk bij de vaststelling dat non respons op een antidepressieve behandeling geassocieerd is met een verhoogde mortaliteit zoals beschreven in Hoofdstuk 3. Het is mogelijk dat de qua etiologie verschillende typen depressie een op onderdelen verschillende 'type specifieke' behandeling nodig hebben voor een optimaal resultaat. De inflammatie substudie toonde aan dat een goede respons op een antidepressieve behandeling via verschillende mechanismen bereikt kan worden daar de mirtazapine respons geassocieerd bleek te zijn met beïnvloeding van het TNF-α systeem terwijl dit bij de placebo respons niet het geval was. Het gegeven dat er verschillende mechanismen zijn past bij de uitkomst van placebo gecontroleerd onderzoek naar het effect van langdurig (2 jaar) preventief antidepressiva gebruik: in de placebo groep was het depressie recidief percentage significant hoger [45,46]. Uit onderzoek blijkt dat m.n. het TNF-α systeem een rol speelt bij het al dan niet recidiveren van een depressie. Ons onderzoek toonde aan dat juist het TNF-α systeem verschillend door mirtazapine en placebo beïnvloed wordt.
Succesvolle antidepressieve behandeling is geassocieerd met 1) veranderingen in de interactie tussen TNF-α en de hypothalamus-hypofyse- bijnier as en 2) door TNF-α gemoduleerde veranderingen in het functioneren van de noradrenerge receptor. Hogere TNF-α bloed spiegels voor aanvang van de antidepressieve behandeling voorspellen een non respons op een antidepressieve behandeling met SSRIs [47] en een grotere kans op een relapse (terugval) na remissie van een depressie.
De persisterend hoge TNF-α spiegels bij depressieve post infarct patiënten en het ontbreken van een langdurige preventieve onderhoudsbehandeling bij de mirtazapine responders maakt dat deze patiënten groep een grotere kans heeft op een (recidief) depressie zoals op 18 maanden post infarct ook vastgesteld werd. Aangezien hogere TNF-α bloed spiegels ook nog eens een non respons op SSRI's voorspellen en juist SSRI's naast mirtazapine zowel in de Interventie groep als in de Care as Usual groep de meest gebruikte antidepressiva waren, vormt dit een 2e verklaring voor het hoge depressie percentage 18 maanden post infarct. Vanuit klinisch perspectief is op basis van deze onderzoeksresultaten een vervolgstudie met een serotonine –noradrenaline heropname remmer op zijn plaats aangezien deze groep antidepressiva in tegenstelling tot de SSRIs wel invloed hebben op het TNF-α systeem

Een andere factor die mogelijk een rol speelt als oorzaak van het hoge depressie percentage 18 maanden post infarct, is het feit dat er geen strikt antidepressief medicatie protocol gevolgd is. Artsen waren relatief vrij in hun behandelbeleid met betrekking tot antidepressiva nadat het MIND-IT studie protocol (mirtazapine/placebo/citalopram gedurende 24 weken) doorlopen was of wanneer de patiënt weigerde de medicatie volgens MIND-IT protocol te nemen. De vrijheid van behandelbeleid was ingesteld op basis van de verwachting dat dit tot: 1 maximale patiënt participatie en daarmee tot 2 optimale antidepressieve behandeling en 3 maximale bescherming tegen nieuwe cardiale gebeurtenissen zou leiden. Wanneer we nu kijken naar de antidepressiva die gedurende de 18 maanden post infarct gebruikt zijn, zien we dat geen van de patiënten in de Interventie groep noch van de Care as Usual groep het volledige depressie medicatie protocol volgens de gangbare psychiatrische richtlijnen doorlopen heeft (tabel 1). Het lijkt logisch dat het

depressie percentage 18 maanden post infarct al eenvoudig verlaagd kan worden door deze richtlijnen te volgen.

Tabel 1. Antidepressieve behandeling in de MIND-IT studie

	Intervention (n=208)	Care as Usual (n=122)
No therapy	33%	80%
Mirtazapine/placebo	45%	0
SSRI	7%	6%
TCA/non-SSRI	1%	2%
Psychotherapy/counseling	9%	10%
Unknown	5%	3%
Lithium	0	0
Electro Convulsive therapy	0	0
Continuation treatment	?	?

Samengevat toont dit proefschrift aan dat verschillende etiologische factoren een bijdrage leveren aan de post infarct depressie te weten: de recidiverende depressie die mogelijk meer erfelijk bepaald is dan de andere subtypen; de relatie met inflammatie wijst in de richting de 'cytokine hypothese voor depressie' en verband met witte stof afwijkingen en acute cerebrale schade in de eerste week post infarct pleit voor de 'vasculaire depressie hypothese'. Daarnaast zijn er aanwijzingen voor een 'somatisch bepaalde' depressie waarbij non respons geassocieerd is met een slechte cardiale prognose. Aangezien de aantallen in de verschillende subgroepen klein waren konden we de onderlinge relaties tussen de verschillende subtypen niet vaststellen en kan het zijn dat het 'somatisch bepaalde' subtype tot een van de andere subtypen behoort.

Gelet op de huidige discussie over de validiteit van de descriptieve DSM IV diagnoses kan gesteld worden dat de brede descriptieve symptomatologie voldoende mogelijkheden biedt om een accurate diagnose te stellen. Het probleem bij de diagnostiek van de postinfarct depressie is eerder de goede herkenning door de clinici aangezien de symptoom presentatie iets anders is dan die bij depressies zonder een somatische aandoening [3]. Een andere complicerende factor bij de diagnostiek is gelegen in het feit dat zowel patiënten als clinici geneigd zijn om depressieve symptomen te zien als symptomen van de onderliggende cardiovasculaire ziekte. Deze laatste factor is waarschijnlijk de verklaring dat de algemeen geldende psychiatrische richtlijnen voor antidepressieve behandeling niet gevolgd zijn.

Een ander belangrijk punt bij de interpretatie van de onderzoeksresultaten is het gegeven dat bij Multi Center studies naar post infarct depressies de initiële drop out ongeveer 55% is als gevolg van weigering om te participeren en exclusiecriteria. Dit leidt waarschijnlijk tot een ondervertegenwoordiging van de ziekste patiënten in het onderzoekscohort en een oververtegenwoordiging van patiënten met een relatief milde depressie waarvan bekend is dat het meetbare antidepressieve behandel effect vaak gering is aangezien bij mildere depressies een hogere placebo respons gevonden wordt. Ondanks deze methodologische beperkingen bleek mirtazapine een goed meetbaar effect te hebben dat zelfs het effect overtrof dat doorgaans bij depressieve niet lichamelijk zieken gevonden wordt en tevens kon vastgesteld worden dat het mechanisme waarlangs mirtazapine zijn effect bereikt anders is dan van placebo.

De resultaten van de neurobiologische substudies suggereren dat een depressie in de context van een infarct geen uniforme conditie is en dat slechts enkele aspecten van de

postinfarct depressie geassocieerd zijn met een slechtere cardiovasculaire prognose. Afgezien van het feit dat niet alle postinfarct depressies geassocieerd zijn met een slechte prognose gaat het hebben van een depressie gepaard met een aanzienlijke daling van de kwaliteit van leven van de patiënt en zijn/haar omgeving en brengt het aanzienlijke maatschappelijke kosten met zich mee. Om deze redenen is het van belang dat er in cardiovasculaire risicogroepen op depressies gescreend wordt en dat de diagnostische en behandelfaciliteiten verbeterd worden.

TOEKOMSTIG ONDERZOEK

De World Health Organization voorspelt dat in 2030 in de rijke landen depressie en hart en vaatziekten nummer 1 en 2 staan als oorzaak van verlies aan 'productieve levensjaren'. Studies als de MIND-IT, SADHART, ENRICHD, CREATE, Heart and Soul en NESDA leveren een toenemende hoeveelheid kennis van de verschillende aspecten van de co-morbiditeit van cardiovasculaire aandoeningen en stemmingsstoornissen. Veel vragen blijven echter tot op heden onbeantwoord en met name betreffende de klinische praktijk. Een van de grote uitdagingen voor de nabije toekomst zal erin gelegen zijn om de hoofdzakelijk epidemiologische data te vertalen in onderzoek en diagnostische en behandel programma's die klinisch relevant zijn voor alle post infarct patiënten.
Dit proefschrift laat zien dat onderzoek bij de post infarct depressie complex is en dat de keuze van het studiedesign en met name het verschil tussen de 2 onderzoeksdesigns 'lumping' en 'splitting' de uitkomsten bepaalt. Het 'lumping' onderzoeksdesign gaat er van uit dat de gemeenschappelijke symptomen waarop geselecteerd is voldoende onderscheidend zijn om de hele groep als een min of meer homogene onderzoeksgroep te beschouwen. Bij het 'splitting' design worden er op basis van aanvullende kenmerken meer specifieke subgroepen gecreëerd. Bepaalde fundamentele klinisch relevante gegevens kwamen alleen in de subgroep analyses (= splitting) naar voren hetgeen de complexiteit aantoont van de processen die tot een post infarct depressie leiden.
Depressieve symptomen en cardiale disfunctie blijken niet direct te relateren aan het disfunctioneren van één bepaald fysiologisch systeem of één enkel orgaan systeem. Gezien de individuele verschillen in adaptatie capaciteit, interacties tussen verschillende fysiologische systemen en de opeenvolging van negatieve gebeurtenissen –zowel cross sectioneel (de cascade van ontregelingen tijdens het infarct) als longitudinaal (voorafgaande depressie, aanwezigheid van witte stof afwijkingen, persisterende inflammatie) – is het aannemelijker om het ontstaan van de post infarct depressie te verklaren vanuit een multi factorieel model.

De diverse relevante factoren hebben een per individu verschillend effect en daardoor ook een per patiënt wisselende bijdrage aan het ontstaan en de remissie van de post infarct depressie. Dit werd het meest duidelijk bij de inflammatie studie. De stijging van sTNFR-1 bleek zeer sterk te correleren met een respons op mirtazapine, terwijl er bij de baseline meting geen verschil was tussen de sTNFR-1 bij depressieve en niet depressieve post infarct patiënten. Placebo respons bleek daarentegen op een andere wijze tot stand te komen en had geen invloed op de inflammatie parameters. Een kwetsbaar brein en de Linker Ventrikel Ejectie Fractie -een maat voor de hart functie- beïnvloeden de stemming weer langs een andere weg. Al deze systemen beïnvloeden elkaar op een complexe manier.

Aangezien de huidige onderzoekstechnieken binnen de psychiatrie volgens The National Institute for Mental Health niet de resultaten opleveren die nodig zijn om een snelle

wetenschappelijke en klinische vooruitgang mogelijk te maken hebben zij onlangs de Research Domain Criteria (RDC) gelanceerd. Uitgangspunt is dat syndromen op basis van pathofysiologie gedefinieerd moeten worden en niet op basis van symptoom beschrijving. Het is de bedoeling dat de RDC een kader bieden voor lange termijn onderzoek waarbij m.n. pathofysiologsche gegevens op een zodanige wijze verzameld worden dat op basis hiervan: 1 nieuwe behandelmethoden ontwikkeld kunnen worden en 2 een betere match tussen subgroepen en specifieke behandeling mogelijk wordt en 3 er een brug geslagen wordt tussen wetenschappelijk onderzoeksresultaten en het klinisch proces. De basisgedachten die aan de RDC ten grondslag liggen passen erg goed bij de toekomstige onderzoeksrichting die voor de verdere ontwikkeling van de cardiopsychiatrie nodig is. Volgens de RDC zijn psychiatrische aandoeningen stoornissen in hersencircuits die vastgesteld kunnen worden met onderzoeksmethoden uit de neurowetenschappen en in het ideale geval moleculaire en neurobiologisch parameters leveren op basis waarvan het klinische beslisproces om tot de juiste keuze van een behandeling te komen ondersteund wordt. Vertaald naar de cardiopsychiatrie zou dit betekenen dat de keus van een bepaalde antidepressivum plaats zou moeten gaan vinden op basis van het farmacologische profiel en de mogelijkheden om specifieke cytokine systemen te beïnvloeden.

Vanuit klinisch perspectief is het nodig dat toekomstig cardiopsychiatrisch onderzoek zich met name richt op het definiëren en identificeren van subgroepen op basis van verschillende psychologische en neurobiologische factoren die een rol spelen bij het ontstaan en onderhouden van de post infarct depressie. Respons predictie onderzoek – ‘splitting’ - op basis van deze factoren zal leiden tot de ontwikkeling van de noodzakelijke rationale voor een specifieke voor de individuele patiënt op maat gemaakte therapie keuze. Met de ‘splitting’ procedure die we in dit proefschrift toegepast hebben werden al enige mogelijke subtypes van de post infarct depressie vastgesteld: bijvoorbeeld degene waarbij cerebrale schade een rol speelt. Verder bracht onderzoek op basis van subtypering aan het licht dat beïnvloeding van inflammatie parameters een belangrijke voorwaarde is voor een succesvolle antidepressieve behandeling bij een deel van de patiënten. Deze veelbelovende lijn van onderzoek kan in de toekomst belangrijke inzichten verschaffen en tot de ontwikkeling van effectievere behandelingen leiden.

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DANKWOORD

Wat zou er zijn gebeurd als ik niet mijn keuze co-schap psychiatrie in het duistere met sigarettenrook omnevelde Zoar op de terreinen van het psychiatrisch ziekenhuis Licht en Kracht had gedaan? Ik was waarschijnlijk tropenarts of internist geworden.

Echter, de bezieling waarmee dr. Cees Slooff in Zoar zijn vak als psychiater uitoefende en een wetenschappelijk onderbouwd behandelaanbod ontwierp voor een verwaarloosde groep patiënten werd voor mij een bijzonder voorbeeld.
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Met deze basis kwam ik in contact met prof.dr. Hans Ormel, prof.dr. Harry Crijns, prof. dr. Aart Schene en prof.dr. Adriaan Honig, Principle Investigators van de MIND-IT study. Dankzij hen, de maatschap en afdeling cardiologie MCL en de directie van het MCL werd het mogelijk om in het MCL een groot centrum van de MIND-IT te maken en daardoor de substudies te ontwikkelen die de kern zijn van dit proefschrift.

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Heren, er zit niets anders op: tijd voor het scherpen der geesten en een nieuwe strategie. Ik ben benieuwd!

CURRICULUM VITAE

Dorien Tulner werd geboren op 3 juni 1960 te Aduard in de provincie Groningen. Na het Praedinius Gymnasium te Groningen en een onvoltooide rechtenstudie aan de Juridische Faculteit te Groningen behaalde ze in 1989 het artsexamen in het Academisch Ziekenhuis te Groningen.

Ze begon haar loopbaan als arts assistent op de PAAZ van Medisch Centrum Leeuwarden zuid onder de enthousiaste leiding van T.C.M. Bruinen, tropenarts en psychiater. In 1991 startte ze met de opleiding psychiatrie in het UMCG te Groningen (opleider prof dr. R. van den Bosch) en werd in 1995 geregistreerd als psychiater. Tijdens het laatste jaar van de opleiding deed ze ervaring op met de combinatie van wetenschappelijk onderzoek en de ontwikkeling van een nieuwe organisatiestructuur gericht op dataverzameling voor longitudinaal onderzoek. Ze deed dit onder leiding van dr. R. Knegtering, psychiater, op de nieuw te ontwikkelen onderzoeksafdeling voor mensen met een eerste psychose. Aansluitend heeft ze als psychiater in het UMCG gewerkt op een onderzoeksafdeling voor therapie resistente psychosen.

In 1997 ging ze terug naar het Medisch Centrum Leeuwarden; aanvankelijk was ze werkzaam in de combinatie ouderenpsychiatrie/ziekenhuispsychiatrie later volledig in de ziekenhuispsychiatrie. In 1999 heeft ze in samenwerking met de MIND-IT collegae de onderzoeksstructuur voor de MIND-IT in het MCL opgezet en in samenwerking met MCL collegae een aantal aanvullende locale studies. Zij heeft tot 2011 in het MCL gewerkt en zich naast de directe patiëntenzorg met de ontwikkeling van diverse vormen van somatisch/psychiatrisch geïntegreerde zorg bezig gehouden.

Begin 2011 heeft ze de overstap gemaakt naar Cavari Clinics Groningen, een privékliniek die zich primair richt op cardiovasculaire preventie en arbo-curatieve zorg.
In de loop van 2011 is ze samen met dr. Rene van Dijk, cardioloog, gestart met de oprichting van Cavari Clinics IC, een Zelfstandig Behandel Centrum voor innovatieve somatisch/psychiatrisch geïntegreerde zorg.

Daarnaast bekleedt ze een aantal landelijke bestuursfuncties op het gebied van de ziekenhuispsychiatrie.