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Journal of Psychosomatic Research 61 (2006) 493–499

Journal of Psychosomatic Research

Decreased impact of post-myocardial infarction depression on cardiac prognosis?

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Received 6 May 2005; received in revised form 13 February 2006; accepted 16 February 2006

Abstract

Objective: A recent meta-analysis suggests that the impact of post-myocardial infarction (MI) depression on cardiac prognosis has decreased over the last decade. We tested whether depression still significantly affects prognosis in the present health care situation. **Methods:** Four hundred ninety-four MI patients were screened for depression. Patients with depression were compared with patients without on cardiovascular events (fatal or nonfatal) during an average follow-up of 2.5 years. Demographic characteristics and cardiac risk factors were controlled for. **Results:** We found that depression was associated with the occurrence of cardiovascular events in both univariate [hazard ratio (HR), 1.84; 95% confidence interval, 1.24–2.72] and multivariate analysis (HR, 1.56; 1.02–2.38). **Conclusions:** Depression still has an independent impact on cardiac prognosis after MI, but this influence is smaller than found in early studies. Improvements in general care for MI and better recognition and treatment of post-MI depression may have decreased the impact of depression on prognosis.

Keywords: Depression; Myocardial infarction; Cardiac prognosis; Cardiac events; Cardiac mortality; Risk factors

Introduction

In 1993, Frasure-Smith et al. [1] reported that depression after a myocardial infarction (MI) increases the risk of cardiac mortality in the 6 months post-MI with a factor 3. These alarming results—found in a Canadian sample of MI patients—were backed up at that time by similar findings of studies conducted in the United States [2] and Germany [3], and put depression on the agenda for cardiologists.

The cardiac prognosis following MI is highly dependent on the acute and follow-up care provided for MI patients. This care has changed greatly over time. The WHO MONICA project, for example, showed that the chance to survive after MI was approximately 10% greater in the mid-1990s than in the mid-1980s, and that this better prognosis was related to improvements in MI care over that period [4]. In addition, care for MI patients shows large differences between countries because of, for example, differences in budget, the way health care is organized, and local circumstances such as the vicinity of hospitals. These differences and changes over time may not only affect the cardiac prognosis of MI patients in general, but also the additive effect of having a post-MI depression. A recent meta-analysis [5] suggested such a change over time in impact of post-MI depression, from a mean increased mortality risk of 3.22 [95% confidence interval (CI), 2.14–4.86] for studies that included patients before 1993, to a mean increased risk of 2.01 (95% CI, 1.45–2.78) for studies that included patients after 1993, although this difference did not reach statistical significance (P=.08). Some recent studies cannot confirm an impact of post-MI

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doi:10.1016/j.jpsychores.2006.02.016

depression on cardiac prognosis (e.g., Ref. [6,7]), whereas others do (e.g., Ref. [8,9]).

We aim to investigate whether depressive symptoms after MI still significantly affect cardiac prognosis in the present Dutch health care situation. The impact on fatal and nonfatal cardiovascular events will be studied in order to exclude on the one hand mortality unrelated to cardiac prognosis (e.g., suicides and traffic accidents without a cardiac cause), and to include on the other hand cardiovascular events that proved nonfatal more because of the adequacy of the response to the event than because of the underlying morbidity. We believe that the combined fatal and nonfatal cardiovascular events provide the theoretically clearest outcome measure to study the extent and nature of the impact of post-MI depression on cardiac prognosis.

Methods

Design

The present Depression after Myocardial Infarction (DepreMI) study is a naturalistic follow-up study of the impact of depression on cardiac prognosis in MI patients. Patients were eligible if they were admitted for MI between September 1997 and September 2000 in one of four participating hospitals in the north of the Netherlands. Depression (i.e., the presence of significant depressive symptoms) was assessed during or shortly after hospitalization. The follow-up time was variable and lasted for all patients until April 2002. Patients received usual aftercare for their MI. No information on the results of depression screening was provided to those treating the patient. Study endpoints were cardiovascular complications (either mortality or new morbidity) during follow-up. Potential endpoints were evaluated by a panel of cardiologists.

The study protocol was approved by the institutional review boards of the participating hospitals. All participating patients signed an informed consent form.

Patients

Patients were eligible if they met at least two of the following three criteria for acute MI: (1) chest pain for at least 20 min, (2) creatine phosphokinase value 100% higher than normal or creatine phosphokinase MB value greater than 10%, or (3) presence of new pathological Q wave on the electrocardiogram in at least two leads.

The number of patients that met the inclusion criteria was 1166. Of these, 284 (24%) were excluded: 13 (1%) because they had a life expectancy less than 1 year due to noncardiovascular reasons, 57 (5%) because they had poor cognitive functions, 14 (1%) because they were unable to speak or read Dutch, 7 (1%) because they had visual or auditory problems that precluded participation, 60 (5%) because they had MI during hospital admission for other reasons, 44 (4%) because they were scheduled for follow-up visits in a nonparticipating hospital, 60 (5%) because they had a too poor physical condition, and 29 patients (2%) because they died before they could be approached or decide about participation.

Eight hundred eighty-two patients were eligible and were approached for participation in the study. Of these, 528 (60%) gave informed consent. The participants were significantly younger than those who refused (mean, 60.7 years; S.D. 11.7 vs. 66.7; S.D. 12.8, t=7.14, P<.01) and were more often male (81% vs. 60%, χ^2=43.56, P<.01).

Assessment of depression

The presence of depressive symptoms was assessed with the Beck Depression Inventory (BDI) [10] during or shortly after hospitalization for the index infarction. The BDI is a widely used 21-item self-report measure of the presence and severity of symptoms of depression. A cutoff score of 10 or higher was used because this is generally accepted as indicating the presence of significant depressive symptoms [10] and is in keeping with many previous studies [1–3,6–8,11,12]. Some patients insisted on filling in the BDI after discharge from the hospital. Their data were included in the analyses if the BDI was returned within 75 days of the index MI, and no endpoint had occurred before filling in the questionnaire.

Endpoints

Study endpoints were cardiovascular events (either mortality or new morbidity) after discharge from the hospital. Cardiovascular was taken to refer to a new MI, (un)stable angina, heart failure, arrhythmia, peripheral cardiovascular disease, or CVA. Potential endpoints (in particular, readmissions to hospital) were identified in regular post-MI control visits (usually 1, 3, and 12 months post-MI) and patient interviews at 3 and 12 months post-MI (face-to-face interviews) and thereafter every 6 months until end of follow-up (telephone interviews). Information on potential endpoints was gathered from hospital records, treating physician, and patient's primary care physician, if necessary. Two cardiologists independently evaluated whether sufficient information was available and classified the nature (in particular, whether cardiovascular or not), onset (i.e., developed after discharge from the hospital for the index MI), and clinical relevance of the event (i.e., necessitating hospitalization). Discrepancies were discussed and decisions were taken by unanimity. The panel members were blind to the depression status of the patient.

The follow-up period was defined as the time from index MI until (1) the occurrence of a panel-confirmed cardiovascular event, (2) death of the patient for noncardiovascular reasons, (3) refusal of the patient to participate in further outcome assessments, in which case, the date of the last outcome assessment was taken as end of the follow-up period, or (4) end of study.

Analysis

Cox regression (i.e., survival analysis) was used to test whether the presence of depressive symptoms after MI increases the risk [as expressed by the hazard ratio (HR)] of new cardiovascular events. The effect of depression was tested both before and after controlling for confounding. Confounding was controlled for by first entering all control variables listed below and then testing the remaining predictive power of post-MI depression.

Control variables

Variables controlled for as potential confounders included demographic characteristics, characteristics of the index MI, complications during hospital admission, history of cardiovascular disease, and cardiovascular risk factors.

The demographic characteristics controlled for consisted of age, gender, living alone, and level of education. Living alone and level of education were assessed in a face-to-face patient interview 3 months post-MI. Level of education distinguished whether the patient finished some form of secondary education or only had primary school.

Characteristics of the index MI, complications during admission, history of cardiovascular disease, and cardiovascular risk factors were obtained from hospital charts. Characteristics of index MI included site of MI (anterior vs. otherwise), size of MI (as indicated by the maximum level of creatine phosphokinase assessed during admission, the distribution of which was highly skewed and had to be normalized for the analyses by taking its logarithm, log max CPK), and heart failure as indicated by Killip class at admission (i.e., a standardized four-point clinical assessment of the degree of heart failure, based on pulmonary rales and X-ray; divided as ≥class II or not) and left ventricular ejection fraction (LVEF; assessed by either nuclear method, gated SPECT, wall motion score index, MRI, angiography, or clinical assessment and dichotomized at ≥40% or <40%).

Occurrence of any of the following complications during admission for the index MI was recorded: recurrence of angina after the patient had been free of chest pain, new MI (according to the same criteria as the index MI), arrhythmic event (atrial fibrillation, ventricular fibrillation, or ventricular tachycardia more than 48 h post-MI, or cardioversion for ventricular fibrillation or ventricular tachycardia within 48 h post-MI), or heart failure, as indicated clinically by the initiation of treatment.

History of cardiovascular disease included previous MI, history of cerebral vascular disease, and history of peripheral vascular disease. Cardiovascular risk factors included history of hypertension, history of diabetes, family history of cardiovascular disease, smoking, and overweight (i.e., a Quetelet Index of 30 or more) at time of index MI.

Results

Baseline characteristics

Of the 528 patients who gave informed consent, 494 (94%) filled in the BDI; 227 did this during hospitalization for their index MI and 267 after discharge (mean, 19.2 days after discharge; S.D., 15.7; median, 17; range, 1–68). The average BDI score was 6.73 (S.D., 6.18; median, 5; range, 0–48), with 117 patients (23.7%) having a score of 10 or higher, indicating significant symptoms of depression. The patients that filled in the BDI during hospitalization and those who completed it after discharge did not differ on average BDI score or percentage with a score of 10 or higher (6.42 vs. 7.00, P=.30, and 21.1% vs. 25.8%, P=.22, respectively).

In Table 1, baseline characteristics of the total study sample are presented, and differences between patients with and without post-MI depressive symptoms are tested. The table shows that patients with depressive symptoms are somewhat older, more often female, live alone, are less educated, and more often have a history of cardiovascular disease (cerebral, peripheral, or previous MI) than patients

Table 1
Baseline characteristics of the study sample and differences between patients with and without post-MI depressive symptoms

Characteristic	Total sample (n=494)	Depressed patients (n=117)	Nondepressed patients (n=377)	Difference (P)
Age, mean (S.D.)	60.5 (11.7)	62.4 (12.6)	60.0 (11.4)	.05
Female	18.6%	29.9%	15.1%	<.01
Living alone	16.2%	28.1%	12.5%	<.01
Primary school only	19.1%	25.7%	17.1%	.05
Anterior site of MI	31.6%	35.9%	30.2%	.25
Log max CPK, mean (S.D.)	2.92 (0.43)	2.86 (0.44)	2.94 (0.42)	.09
Killip class≥II	14.5%	19.7%	12.8%	.07
LVEF<40%	23.3%	25.6%	22.6%	.50
Complications during admission	20.2%	20.5%	20.2%	.93
History of MI	13.6%	18.8%	11.9%	.06
History of cerebral vascular disease	4.3%	7.7%	3.2%	.04
History of peripheral vascular disease	5.9%	12.0%	4.0%	<.01
History of hypertension	26.9%	28.2%	26.5%	.72
History of diabetes	10.1%	12.8%	9.3%	.27
Family history of cardiovascular disease	37.2%	32.5%	38.7%	.22
Smoking at time of index MI	53.3%	55.9%	52.5%	.55
Quetelet Index≥30	16.5%	12.5%	17.7%	.23
BDI depression score, mean (S.D.)	6.73 (6.18)	15.74 (5.68)	3.93 (2.65)	<.01

without depressive symptoms. We examined the relationship between patient characteristics and having post-MI depressive symptoms elsewhere [13].

Follow-up and endpoints

Of the 117 patients with depressive symptoms, 64 (55%) discussed the emotional problems with a (mental) health professional during the post-MI year (in hierarchical order: 19 with a psychiatrist or a psychologist, 26 with a primary care physician, 8 with a cardiologist, 5 with a nurse, 3 with a social worker, and 3 with another professional). Twenty-three of these patients (20%) received some form of treatment for the problems. The treatment consisted of antidepressant medication for 10 patients, of counseling for 7, of a combination of antidepressant medication and counseling for 5, and an unspecified treatment for 1 patient. As stated, no information on the results of the depression screening as part of the study was provided to either the patients or to those treating the patients.

The average follow-up time for the 494 patients was 2.5 years (S.D., 0.9; range, 0.1–4.6). One hundred twelve patients (22.7%) experienced a cardiovascular event (fatal or nonfatal) severe enough to warrant hospitalization according to the panel of cardiologists. This included 61 cases (12.3%) of angina pectoris, 19 (3.8%) of recurrent MI, 12 (2.4%) of sustained arrhythmia, 11 (2.2%) of heart failure, and 9 (1.8%) of other cardiovascular events (i.e., CVA, peripheral arterial disease, pericarditis, rupture of cerebral aneurysm). Of the patients with depressive symptoms, 38 (32.5%) experienced a cardiovascular event, and of the patients without symptoms, 74 (19.6%). A fatal cardiovascular event occurred in 21 (4.3%) patients (sometimes after a previous nonfatal event listed above). This included one death during a CABG procedure for angina pectoris, six deaths due to recurrent MI, four due to sustained arrhythmia, five due to heart failure, and five due to other cardiovascular events (i.e., CVA and sudden death outside the hospital). Of the patients with depressive symptoms, 9 (7.7%) had a fatal cardiovascular event, and of those without, 12 (3.2%). In addition, 12 patients (2.4%) died of noncardiovascular causes: 3 (2.6%) of those with depressive symptoms and 9 of those without (2.4%).

Impact on prognosis

In the left part of Table 2, the univariate associations between baseline characteristics and cardiovascular events are presented. The strength of the associations is expressed by the HR, which may be understood as the relative risk of an event for patients with different levels on the predictor variable (e.g., presence vs. absence of a condition or increase of risk per year of age) but with the same follow-up time. The table shows that, before controlling for other variables, having depressive symptoms post-MI increases the subsequent risk of a cardiovascular event (fatal or nonfatal) by a factor of 1.84 (95% CI, 1.24–2.72). This does not depend on whether the depression was assessed before or after discharge from the hospital (1.60 [0.88–2.91] vs. 2.07 [1.22–3.51], P=.54). Other predictors of a poor cardiac prognosis post-MI are being older, an anterior site of the MI, a Killip class of two or more, an LV ejection fraction less than 40%, complications during admission, a previous MI, a history of peripheral vascular disease, and a history of diabetes. The influence of post-MI depression on the occurrence of cardiovascular events is displayed in the Kaplan-Meier curves, presented in Fig. 1. Shown are the survival probabilities without a cardiovascular event for patients

Table 2
Univariate and multivariate associations of baseline characteristics with cardiovascular events (n=494)

	Univariate			Multivariate		
Characteristics	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.02	1.01–1.04	<.01	1.02	1.00–1.04	.08
Female	0.91	0.55–1.48	.69	0.79	0.45–1.38	.41
Living alone	1.16	0.71–1.90	.55	1.04	0.60–1.79	.89
Primary school only	1.13	0.70–1.82	.63	1.08	0.65–1.81	.77
Anterior site of MI	1.70	1.17–2.47	<.01	1.59	1.03–2.45	.04
Log max CPK	1.21	0.78–1.87	.39	1.31	0.82–2.09	.26
Killip class≥II	2.11	1.37–3.26	<.01	1.36	0.83–2.22	.22
LVEF<40%	1.67	1.12–2.49	.01	0.93	0.58–1.51	.78
Complications during admission	1.78	1.18–2.67	<.01	1.81	1.15–2.86	.01
History of MI	2.21	1.42–3.43	<.01	1.63	0.96–2.79	.07
History of cerebral vascular disease	1.69	0.79–3.65	.18	1.26	0.54–2.90	.59
History of peripheral vascular disease	2.57	1.47–4.51	<.01	1.49	0.79–2.82	.22
History of hypertension	0.93	0.61–1.42	.74	1.07	0.69–1.67	.76
History of diabetes	2.30	1.43–3.70	<.01	2.53	1.49–4.30	<.01
Family history of cardiovascular disease	1.08	0.74–1.58	.69	1.44	0.95–2.19	.09
Smoking at time of index MI	1.06	0.71–1.57	.77	1.33	0.85–2.08	.22
Quetelet Index≥30	0.73	0.41–1.32	.30	0.78	0.41–1.49	.45
Depressive symptoms (BDI≥10)	1.84	1.24–2.72	<.01	1.56	1.02–2.38	.04

with and patients without post-MI depressive symptoms. The curves are trimmed at 3 years post-MI because the total number of patients at risk dropped below 100 beyond this point, making the curves unreliable. The figure shows a consistently lower and gradually diverging survival probability for patients with post-MI depression compared with those without.

The right part of Table 2 presents the multivariate prediction model of cardiovascular events by post-MI depression and the control variables combined. It shows that, after controlling for the confounding influences of the control variables, a post-MI depression still increases the risk of a cardiovascular event by a factor of 1.56 (1.02–2.38). Again, this is independent of assessment of depression during hospitalization or after discharge (1.41 [0.70–2.84] vs. 1.75 [0.98–3.14], P=.33). The table also shows that, beside post-MI depression, the occurrence of cardiovascular events is predicted by an anterior site of the MI, complications during admission, and a history of diabetes.

Other studies looked at cardiovascular or all-cause mortality as outcome measure (e.g., Ref. [1–3,6–8,11,12]). We find in univariate analysis that post-MI depression increases the risk of cardiovascular mortality by a factor of 2.53 (1.07–6.02, P=.04), of all-cause mortality by a factor of 1.95 (0.96–3.97, P=.06), and of a nonfatal cardiovascular event by a factor of 1.66 (1.08–2.54, P=.02). After controlling for confounding by multivariate analysis, the associations among depression and cardiovascular mortality, all-cause mortality, and nonfatal cardiovascular events are no longer significant, with HR=2.11 (0.81–5.51, P=.13), 1.65 (0.77–3.54, P=.20), and 1.49 (0.95–2.34, P=.08), respectively.

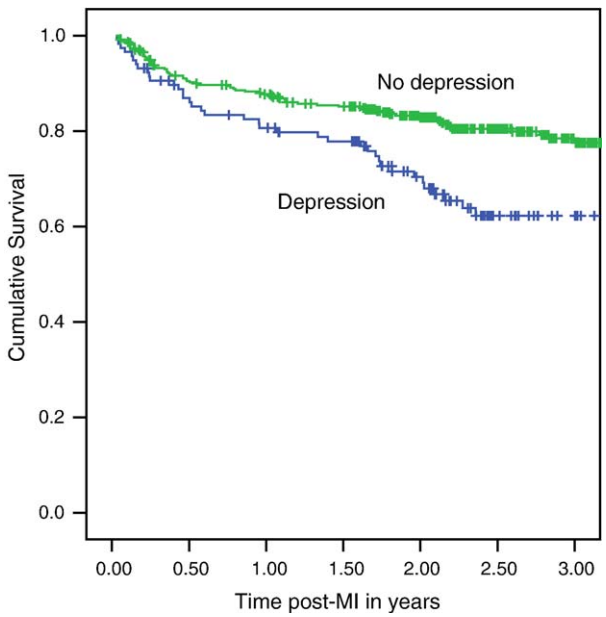

Fig. 1. Kaplan-Meier curves of cumulative survival without cardiovascular event for patients with and without post-MI depression.

4. Discussion

We studied the impact of post-MI depression on cardiac prognosis in today's cardiac care in the Netherlands. A decrease of this impact was suggested by a meta-analysis [5], which compared studies that included patients before 1993 (the year the alarming findings of Frasure-Smith et al. were published) with studies that included patients thereafter. The early studies showed an increased mortality risk of 3.22 (95% CI, 2.14–4.86) for depression, whereas this was 2.01 (95% CI, 1.45–2.78) for more recent studies. Our findings confirm that (1) depression following MI has a negative impact on cardiac prognosis, (2) part of this impact is independent of other post-MI risk factors, (3) it is found for cardiovascular events—fatal or nonfatal—as well as for cardiovascular or all-cause mortality, and (4) the impact indeed appears to have decreased over the past decade, but this should be formally tested in meta-analysis. Our estimate of the impact—an additional risk of 1.84 (95% CI, 1.24–2.72) for cardiovascular events, of 2.53 (1.07–6.02) for cardiovascular mortality, and of 1.95 (0.96–3.97) for all-cause mortality before correction for other risk factors, and of 1.56 (1.02–2.38) for cardiovascular events, of 2.11 (0.81-5.51) for cardiovascular mortality, and 1.65 (0.77–3.54) for all-cause mortality after correction—is in close agreement with the findings of other recent studies, but substantially smaller than found in the early studies.

Some limitations of the study should be considered. First of all, 40% of the eligible patients did not give informed consent, and these patients tended to be somewhat older and more often female. This may have affected the number of patients with post-MI depression. But whether it also affected the association between depression and cardiac prognosis is unclear. However, the association found in multivariate analysis was corrected for the influences of age and gender. Second, more than half of the patients completed the BDI after discharge from the hospital, although within 75 days of their MI. This group may have included patients whose depression only started some time after the MI, and this may have reduced the association between depression and cardiac prognosis, if late onset depression is less predictive of cardiovascular events than depression in the hospital. However, both in univariate and multivariate analysis, we find that the impact of depression on cardiac prognosis is somewhat more pronounced in the group of patients who filled in the BDI after discharge than among those who completed it in hospital, although this difference is not significant. Therefore, if anything, including patients whose depression only was assessed shortly after discharge will have raised our estimate of the impact of post-MI depression, compared with other studies, instead of reducing it. Nevertheless, we find an association between post-MI depression and cardiac prognosis that is substantially less than found in early studies, but that is in line with the trend found in meta-analysis [5].

Now, how can the impact of post-MI depression decrease over time? First, the alarming findings of Frasure-Smith et al. [1,11] may have alerted cardiologists and primary care physicians to evaluate the presence of depressive symptoms in MI patients, and may thus have increased (referral for) treatment of the depression. Second, psychosocial problems after MI are increasingly addressed in cardiac rehabilitation programs, both in general programs for unselected MI patients and in special programs for indicated patients (see, e.g., Ref. [14]). But can treatment of post-MI depression improve the cardiac prognosis following MI? A meta-analysis of randomized controlled studies on cardiac rehabilitation programs for CAD patients showed that patients enrolled in programs that included psychosocial interventions (such as stress management and counseling) experienced less mortality [odds ratio (OR), 0.59; 95% CI, 0.38–0.92] and less recurrent cardiac events (OR, 0.54; 0.33–0.89) than patients enrolled in programs without such interventions [15]. Evidence for an effect of psychiatric treatment for post-MI depressive disorder on cardiac prognosis is less compelling, however. The ENRICHD study [16] showed no effect of cognitive behavior therapy for post-MI depression on survival or recurrent infarction (HR, 1.01; 0.86–1.18). The SADHART study [17] found a trend of somewhat fewer adverse events (death or rehospitalization for a cardiovascular disorder) in post-MI depression patients treated with the antidepressant sertraline (17.2%) compared with those receiving a placebo (22.4%), but this difference was not statistically significant (relative risk, 0.77; 0.51–1.16). Finally, in the MIND-IT study [18], we are currently investigating the effect of antidepressive treatment on cardiac prognosis in MI patients who are (still) depressed more than 3 months post-MI. Whether the decrease in impact of post-MI depression on cardiac prognosis, confirmed by the present study, can be explained by an increased alertness for and treatment of post-MI depression, therefore, remains unclear for the time being.

Is screening for and treatment of depression in MI patients nevertheless warranted? Yes, because depression is associated with a considerable reduction in functioning and quality of life in MI patients [7,19,20], as in noncardiac patients [21–23]. Furthermore, depression can be safely and effectively treated [24], although improvements found in MI patients on psychosocial outcomes are limited [16,25–28]. Finally, post-MI depression is a common and important risk factor for cardiac prognosis, comparable in strength to and only partly overlapping with established risk factors post-MI, such as LV ejection fraction, anterior site of MI, diabetes, and previous MIs. These factors, including post-MI depression, warrant the attention and special care of cardiologists and primary care physicians.

Acknowledgments

We thank the following participating hospitals, cardiologists, and researchers:

Universitair Medisch Centrum Groningen: TA Spijkerman, RHS van den Brink, JF May, JB Winter, JHC Jansen, HJGM Crijns, J Ormel.

Martini Ziekenhuis Groningen: JH Bennekers, F van den Berg, PJLM Bernink, RB van Dijk, MG Niemeyer, JL Postma, LEJM Schrijvers, LH Takens.

Refaja Ziekenhuis Stadskanaal: K de Vries, LM van Wijk.

St. Lucas Ziekenhuis Winschoten: TR Bouwmeester, A van der Galien.

The study was funded by a grant from the Netherlands Organization for Scientific Research (ZonMw, grant 904-57-106).

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