Beta-Blockers are among the most prescribed drugs in the world. They are registered for a wide range of indications including hypertension, angina pectoris, arrhythmias, heart failure, and as secondary prevention after myocardial infarction (MI). They have proven benefits in decreasing morbidity as well as mortality (1). In MI patients, beta-blockers have shown to reduce mortality by 23% (2).

However, despite these beneficial effects, persistent concerns about adverse effects of beta-blockers have resulted in reluctance among clinicians in prescribing these drugs (3). Concerns especially exist about neuropsychological side effects, since Waal (4), as early as 1967, reported about a conspicuously high incidence of depression among a group of hypertensive patients using propanolol as antiarrhythmic therapy. It was assumed that particularly the more lipophylic beta-blockers, which can cross the blood–brain barrier more readily, are able to cause depression (5).

Subsequent studies were limited by small sample size (6–10), study design (e.g., cross-sectional [11], not prospective), the use of unvalidated or surrogate measures of depression (11–17), or the lack of appropriate baseline depression assessment (18). In the present study, we have tried to overcome these limitations and investigated the association between beta-blocker use and depression in a large, prospective study using standardized measures of depressive symptoms and depressive disorder. Given the strong indication for beta-blockers in post-MI patients and the profound association between post-MI depression and impaired cardiovascular prognosis (19), we decided to confine our study to MI patients.

METHODS

Patients. We used data from the DepreMI (Depression and Myocardial Infarction Study) (20) and MIND-IT (Myocardial Infarction and Depression Intervention Trial) (21). In these multicenter studies in the Netherlands, 528 and 2,177 MI patients, respectively, were screened for depression. Consecutive patients were included from September 1997 to September 2000 (DepreMI) and from September 1999 to March 2002 (MIND-IT) if they met established criteria for MI. Exclusion criteria were cognitive dysfunction, not being able to speak or read Dutch, hospital admission for other reasons than MI (except angina pectoris), and a life expectancy of <1 year due to noncardiovascular disease. In the MIND-IT study, patients currently treated for depression were excluded. Because the inclusion and exclusion criteria were highly similar for both studies and the studies were comparable on the prevalence...
of depression and several important variables (gender, left ventricular ejection fraction [LVEF], percentage of beta-blocker users; \( p \approx 0.05 \), all variables), data from both studies were combined in the present analyses. For the present study, for practical reasons, a subset of data from both studies was used. For the MIND-IT study, only patients admitted to hospitals in the northern part of the Netherlands were included (n = 846). For the DepreMI study, only patients admitted to the 2 hospitals with the largest contribution to the study sample were included (n = 400). The ethics committee review boards of all participating hospitals approved the study protocol, and all patients gave informed consent.

Matching. From the resulting sample (n = 1,246), 1,086 beta-blocker users and 160 non–beta-blocker users were identified. In order to make sure that the distribution of potentially confounding variables was equally distributed in the 2 groups, the subjects were matched using the frequency matching procedure on the following variables: hospital of admission, age (<60 or \( \geq 60 \) years), gender (male/female), LVEF (<30% or \( \geq 30\% \)), and baseline depressive symptoms (Beck Depression Inventory [BDI] score <10 or \( \geq 10 \)) (22).

In order to enable a subgroup analysis based on beta-blocker dosage, beta-blocker users were over-represented by a factor 2. If one of the match variables was missing (n = 23), the subject was matched based on the available match variables. Subjects were excluded if more than 1 of the match variables was missing. If a non–beta-blocker user could not be matched with 2 beta-blocker users, the subject was excluded from the sample. Application of these criteria resulted in a final study sample of 127 non–beta-blocker users and 254 beta-blocker users, representing 30.6% of the total sample (Fig. 1).

Beta-blocker use. Beta-blocker use during hospitalization for the index MI was recorded as a standard assessment in both studies. Further information on generic name, dose, new use versus ongoing use (including duration of the

Matching. From the resulting sample (n = 1,246), 1,086 beta-blocker users and 160 non–beta-blocker users were identified. In order to make sure that the distribution of potentially confounding variables was equally distributed in the 2 groups, the subjects were matched using the frequency matching procedure on the following variables: hospital of admission, age (<60 or \( \geq 60 \) years), gender (male/female), LVEF (<30% or \( \geq 30\% \)), and baseline depressive symptoms (Beck Depression Inventory [BDI] score <10 or \( \geq 10 \)) (22).

In order to enable a subgroup analysis based on beta-blocker dosage, beta-blocker users were over-represented by a factor 2. If one of the match variables was missing (n = 23), the subject was matched based on the available match variables. Subjects were excluded if more than 1 of the match variables was missing. If a non–beta-blocker user could not be matched with 2 beta-blocker users, the subject was excluded from the sample. Application of these criteria resulted in a final study sample of 127 non–beta-blocker users and 254 beta-blocker users, representing 30.6% of the total sample (Fig. 1).

Beta-blocker use. Beta-blocker use during hospitalization for the index MI was recorded as a standard assessment in both studies. Further information on generic name, dose, new use versus ongoing use (including duration of the

**Figure 1.** Flow chart: selection of study subjects. DepreMI = Depression and Myocardial Infarction Study; MIND-IT = Myocardial INfarction and Depression-Intervention Trial.
beta-blocker use before admission) was obtained by chart review. If beta-blockade was not prescribed, we checked the reasons for non-prescription. For every patient, the whole year post-MI was screened for changes in beta-blocker use (withdrawal, change in type of beta-blocker, or change in dosage). The prescribed beta-blockers were marked as lipophilic or hydrophilic. Dosages were marked as above or below the median dosage.

**Depressive symptoms and major depressive episode.** Depressive symptoms were assessed at baseline (during hospitalization for index MI), and at 3, 6, 12 months after MI, using the BDI (22). The presence of a depressive disorder was assessed with a standardized interview according to International Classification of Diseases-10 criteria, the Composite International Diagnostic Interview (CIDI) (23). In the DepreMI study, all patients underwent the CIDI at 3 and 12 months after MI. In the MIND-IT study, patients underwent a CIDI only after a “positive” BDI (i.e., BDI score ≥10). This procedure is justified due to the high negative predictive value of the BDI (i.e., 98%) (24).

**Potential confounding variables.** Four pre-specified categories of potential confounders on the relationship between beta-blockers and depression were considered: 1) contraindications for beta-blocker use; 2) indicators and risk factors for cardiac disease; 3) baseline depressive symptoms; and 4) benzodiazepine use.

The following (relative) contraindications for beta-blocker use were registered: hypotension, bradycardia, chronic obstructive pulmonary disease (defined as: for which daily medication is necessary), diabetes mellitus (defined as: for which medication is necessary), and known peripheral vascular disease of the lower extremities.

Variables concerning indicators and risk factors for cardiac disease were LVEF, previous MI, Killip class, smoking, hypertension, and revascularizations.

The presence of depressive symptoms during hospitalization (i.e., BDI ≥10) was considered. Finally, the use of benzodiazepines either before, during, or after the hospitalization for MI was taken into account.

**Statistical analysis.** In previous analyses in the same population (25), the prevalence of depression was found to be 18%. Considering a relative risk of 2.0 for beta-blocker users as compared with non–beta-blocker users to develop a depressive disorder as clinically relevant, a total of 381 patients would yield a power of 0.84 to demonstrate an effect. Using this sample size of 381 patients, a difference in BDI score of 2 points can be detected with a power 83%.

Comparison of baseline characteristics was tested by means of logistic regression analysis. All statistical comparisons were 2-tailed, and a value of p ≤ 0.05 was considered as statistically significant.

**RESULTS**

**Subjects.** The sample consisted of 381 patients; 127 patients without a beta-blocker and 254 matching patients with a beta-blocker at discharge (Fig. 1). Patient characteristics are presented in Table 1. Inherent to the matching procedure, the variables age, gender, LVEF, baseline depression, and hospital of admission were equally balanced across the 2 groups. Non–beta-blocker users differed from beta-blocker users in chronic obstructive pulmonary disease (p < 0.01), digitalis use (p = 0.05), and pre-MI beta-blocker use (p = 0.01).

**Beta-blocker prescriptions.** Metoprolol was the most prescribed beta-blocker (77%). Only 7% of all prescribed beta-blockers were hydrophilic. Bradycardia was the most important (28%) reason for non-prescription, followed by chronic obstructive pulmonary disease (4%). In 64% of the cases, the reason for not prescribing a beta-blocker was not documented. Of the patients who did not have a beta-blocker at discharge, 19% as yet received beta-blockade in the year after MI (9% within 3 months after MI, 15% within half a year after MI). Of the patients who did have a beta-blocker at discharge, the beta-blocker was withdrawn after discharge in 12% (4% within 3 months, 8% within half a year post-MI). Dose adjustments during the first year post-MI occurred in 23% of the patients; changes in type of beta-blocker occurred in 6% of the patients.

**Beta-blocker use at discharge and prospective depressive symptoms.** There were no significant differences in BDI scores at 3, 6, and 12 months after MI between both groups (Table 2). After controlling for baseline depressive symptoms, subjects taking a beta-blocker at discharge scored significantly lower (p = 0.04) on the 3 months BDI as compared with non–beta-blocker users (Table 3). However, there was no significant difference on the 6- and 12-month BDI. Moreover, when controlling for the other clinical variables, this difference on the 3-month BDI disappeared. Also, in a sensitivity analysis in patients without depressive symptoms at baseline (BDI < 10), we found no difference in the BDI score at any of the 3 time points (i.e., 3, 6, and 12 months post-MI) between the beta-blocker group and
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Match variables</th>
<th>No Beta-Blocker (n = 127)</th>
<th>Beta-Blocker (n = 254)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (mean ± SD)</td>
<td>64.6 ± 11.5</td>
<td>64.0 ± 11.2</td>
<td>0.61*</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>99 (78.0%)</td>
<td>198 (78.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>LVEF ≥30%</td>
<td>105 (92.9%)</td>
<td>239 (95.6%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Baseline depressive symptoms (BDI ≥10)</td>
<td>29 (24.4%)</td>
<td>64 (25.3%)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Other clinical variables

| COPD                                 | 29 (23.0%)                | 18 (7.1%)              | <0.01   |
| Diabetest                             | 13 (10.4%)                | 25 (9.9%)              | 0.89    |
| Peripheral vascular disease           | 10 (7.9%)                 | 10 (4.0%)              | 0.10    |
| Beta-blocker use at admission         | 7 (6.0%)                  | 34 (15.2%)             | 0.01    |
| Hypertension                         | 35 (28.5%)                | 89 (36.8%)             | 0.11    |
| Digitalis use                        | 12 (9.7%)                 | 11 (4.4%)              | 0.05    |
| Benzodiazepine use                   | 17 (13.8%)                | 32 (13.0%)             | 0.82    |
| History of MI                        | 17 (13.4%)                | 49 (19.3%)             | 0.15    |
| Killip class I                       | 106 (83.5%)               | 218 (86.2%)            | 0.48    |
| Current smoker                       | 61 (50.4%)                | 119 (48.2%)            | 0.69    |
| PTCA during hospitalization          | 33 (28.0%)                | 65 (27.7%)             | 0.95    |
| CABG during hospitalization          | 5 (4.2%)                  | 18 (7.7%)              | 0.22    |

All variables were tested with chi-square test, unless specified otherwise. *Student t test.

BDI = Beck Depression Inventory; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

non–beta-blocker group (4.8 vs. 5.6 [p = 0.16], 4.9 vs. 5.1 [p = 0.66], and 4.8 vs. 4.8 [p = 0.98], respectively).

Actual beta-blocker use and prospective depressive symptoms. In Table 4, the relationship between actual beta-blocker use and depression is presented. Again, no significant differences in unadjusted BDI scores between beta-blocker users and non–beta-blocker users were found at the various time points. A trend toward less depressive symptoms at 3 months post-MI among beta-blocker users was present. Beta values increased at each time point in the year post-MI: at 3 months they became less negative, and at 12 months they were all positive.

Beta-blocker use and depressive disorder. No differences were found between beta-blocker users and non–beta-blocker users regarding the occurrence of depressive disorder. In patients using a beta-blocker at discharge, 20.5% were diagnosed with depressive disorder. In patients using a lipophilic beta-blocker at discharge, the prevalence was 21.3% (p = 0.86). When controlling for other clinical variables, no significant differences were found between non–beta-blocker users and beta-blocker users.

Subgroup analyses. Within the group of beta-blocker users, no significant differences were found in BDI scores during the year post-MI between those using a hydrophilic and those using a lipophilic beta-blocker at discharge: mean BDI scores at 3, 6, and 12 months for hydrophilic versus lipophilic beta-blocker users were 7.8 vs. 6.3 (p = 0.29), 8.7 vs. 6.3 (p = 0.13), and 7.0 vs. 6.7 (p = 0.86), respectively.

Of the patients who used a beta-blocker at discharge, 52 patients (20%) already used a beta-blocker before admission (“ongoing use”). This group scored higher on the baseline BDI assessment than those who were new users of beta-blockers (p < 0.001). The average duration of beta-blocker use before admission was 27 months.

Patients receiving high dosages of beta-blockade at discharge did not differ on the mean 3-month BDI score as compared with patients using low-dose beta-blockade (6.8 vs. 6.1, p = 0.34). At 6 months, however, patients who were prescribed high-dose beta-blockade scored significantly higher on the BDI (7.2 vs. 5.6, p = 0.03). The same was seen at 12 months (7.4 vs. 5.8, p = 0.05).

DISCUSSION

In the present study in MI patients, using standardized methods of depression, no significant associations between the use of beta-blockers and the development of depression were found. After adjustment for baseline depression, beta-blocker users even had somewhat lower depression scores than non–beta-blocker users at 3 months post-MI (p = 0.06). Thus, despite current beliefs about the potential side effects of beta-blockade, we found no support for short-term effects on prospective depression in an MI population. No
difference was found in depressive symptomatology between lipophilic and hydrophilic beta-blockers; however, due to small numbers, this finding needs to be interpreted cautiously.

Our study is one of the first to investigate the effects of beta-blockers in a well-powered, prospective way using standardized methods. Despite non-randomization, beta-blocker users and non-beta-blocker users were comparable on almost all baseline variables. In addition, an extensive list of important confounders was taken into account. Moreover, we had a long-term follow-up, and we took into account changes in beta-blocker use. Carney et al. (26) studied patients referred for coronary angiography and reported no increased risk of depression in beta-blocker users. They used standardized instruments of depression, but, unfortunately, the study was cross-sectional. To our knowledge, only 1 prospective study has been conducted previously using a standardized diagnostic interview for depression (27). In this study, 335 patients were assessed for depression at 8 to 10 days, and 190 were re-interviewed at 3 to 4 months. It was found that the use of digitalis, and not beta-blockers, predicted the development of depression.

Two observations in our study suggest that we need to be cautious in interpreting the depressogenic effects of long-term beta-blocker use. First, patients who already used beta-blockers before admission scored significantly higher on the BDI at baseline than patients who were prescribed a beta-blocker during hospitalization for index MI (p < 0.001). Although it may be assumed that this group of patients had more comorbidity, even after controlling for important confounders, including hypertension and previous MI, prior beta-blocker users continued to have more depressive symptoms at baseline.

Second, it is noteworthy that patients with a relatively high dosage of beta-blockade did report more depressive symptoms at 6 and 12 months post-MI (p = 0.03 and p = 0.05, respectively).

Our results have to be considered in relation to the following limitations. Firstly, we were not able to control for the presence of previous episodes of depression. Secondly, the screening procedure regarding depressive disorder was not entirely identical for the cohorts. However, separate analyses on the 2 study samples revealed no differences with respect to incidence of depression. Another limitation is the predominance of male patients in our study population. Gender differences in the prevalence of depression are well-known, and it cannot be ruled out that there are differences in central nervous system sensitivity to beta-blockade between men and women. Striking in this light is that most case reports on beta-blocker–induced depression involved women. Finally, it needs to be stressed that individual susceptibility for depressant effects of beta-blockers cannot be ruled out.

Taken together, our study adds important information to the available literature and showed no relationship between beta-blocker use and the development of depression in MI patients in the first year post-MI. Therefore, because beta-blockers have proven to decrease cardiac-related morbidity and mortality, clinicians should not be reluctant in prescribing beta-blockers in MI patients for reasons of putative depressant effects. However, more research is warranted to explore the long-term and high-dose effects of beta-blockers on depressive symptomatology.

### Table 3. Beta-Blocker Use at Discharge and BDI Scores at 3, 6, and 12 Months After MI

<table>
<thead>
<tr>
<th></th>
<th>BDI 3</th>
<th></th>
<th>BDI 6</th>
<th></th>
<th>BDI 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>B</td>
<td>95% CI</td>
<td>p Value</td>
<td>R²</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.01</td>
<td>−0.95</td>
<td>−2.22, 0.32</td>
<td>0.14</td>
<td>0.00</td>
</tr>
<tr>
<td>Adjusted for baseline depression</td>
<td>0.38</td>
<td>−1.10</td>
<td>−1.88, −0.07</td>
<td>0.04</td>
<td>0.36</td>
</tr>
<tr>
<td>Adjusted for potential confounders*</td>
<td>0.36</td>
<td>−0.92</td>
<td>−2.16, 0.33</td>
<td>0.14</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*Baseline depression, age, gender, left ventricular ejection fraction, hypertension, benzodiazepine use, digitalis use, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, previous myocardial infarction (MI), Killip class, smoking, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and hospital of admission.

### Table 4. Actual Beta-Blocker Use at 3, 6, and 12 Months After MI and Corresponding BDI Scores

<table>
<thead>
<tr>
<th></th>
<th>BDI 3</th>
<th></th>
<th>BDI 6</th>
<th></th>
<th>BDI 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>B</td>
<td>95% CI</td>
<td>p Value</td>
<td>R²</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.01</td>
<td>−1.10</td>
<td>−2.27, 0.06</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted for baseline depression</td>
<td>0.37</td>
<td>−0.93</td>
<td>−1.88, 0.02</td>
<td>0.06</td>
<td>0.36</td>
</tr>
<tr>
<td>Adjusted for potential confounders*</td>
<td>0.35</td>
<td>−0.68</td>
<td>−1.79, 0.44</td>
<td>0.23</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Baseline depression, age, gender, left ventricular ejection fraction, hypertension, benzodiazepine use, digitalis use, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, previous myocardial infarction (MI), Killip class, smoking, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and hospital of admission.

Abbreviations as in Table 3.
REFERENCES