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## Research report

## Beta blocker therapy is associated with reduced depressive symptoms 12 months post percutaneous coronary intervention

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## ABSTRACT

**Background:** Beta blocker therapy may induce depressive symptoms, although current evidence is conflicting. We examined the association between beta blocker therapy and depressive symptoms in percutaneous coronary intervention (PCI) patients and the extent to which there is a dose–response relationship between beta blocker dose and depressive symptoms.

**Methods:** Patients treated with PCI (N=685) completed the depression scale of the Hospital Anxiety and Depression Scale 1 and 12 months post PCI. Information about type and dose of beta blocker use was extracted from medical records.

**Results:** Of all patients, 68% (466/685) were on beta blocker therapy at baseline. In adjusted analysis, beta blocker use at 1 month post PCI (OR: 0.82; 95% CI: 0.53–1.26) was not significantly associated with depressive symptoms. At 12 months post PCI, there was a significant relationship between beta blocker use and depressive symptoms (OR: 0.51; 95% CI: 0.31–0.84), with beta blocker therapy associated with a 49% risk reduction in depressive symptoms. There was a dose–response relationship between beta blocker dose and depressive symptoms 12 months post PCI, with the risk reduction in depressive symptoms in relation to a low dose being 36% (OR: 0.64; 95% CI: 0.37–1.10) and 58% (OR: 0.42; 95% CI: 0.24–0.76) in relation to a high dose.

**Conclusions:** Patients treated with beta blocker therapy were less likely to experience depressive symptoms 12 months post PCI, with there being a dose–response relationship with a higher dose providing a more pronounced protective effect.

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### 1. Introduction

Beta blocker therapy has clear survival benefits in patients with chronic heart failure (Javed and Deedwania, 2009), in patients following a myocardial infarction (MI), and in patients

with hypertrophic obstructive cardiomyopathy (Bangalore et al., 2007). Beta blockers are also used in the treatment of supraventricular arrhythmias, to control ventricular arrhythmias related to sympathetic activation, and to prevent postoperative cardiac complications during noncardiac surgery (Bangalore et al., 2007). Beta blockers are prescribed not only for cardiovascular disease but also for migraine prophylaxis, various anxiety disorders, tremor, and aggressive disorders secondary to organic brain illnesses (Elliott, 1977; Jankovic and Fahn, 1980).

There has been a long-standing concern, however, that beta blocker use might be associated with neuropsychological side effects, such as depression. In 1967 Waal already reported a 50% incidence of depression in patients prescribed more than 120 mg/day of propranolol for hypertension, although this

*Abbreviations:* AP, angina pectoris; CAD, coronary artery disease; CNS, central nervous system; HADS, Hospital Anxiety and Depression Scale; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention

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finding was largely based on anecdotal evidence (Waal, 1967). Experts have suggested that the inhibitory actions of beta blockers on the beta receptors and serotonin receptors in the central nervous system may be involved in the pathophysiology of depressive disorders (1977). However, subsequent publications have reported conflicting results (Avorn et al., 1986; Bright and Everitt, 1992; Ko et al., 2002; Krantz et al., 1982; Patten and Love, 1993; Schleifer et al., 1991; Thiessen et al., 1990). These conflicting results may in part be attributed to differences in study design and case definition, and in part to confounding disease states (Ried et al., 1998). A more recent and well conducted study that used a prospective design showed no relationship between beta blocker use and depression – neither depressive symptoms nor depressive disorder (van Melle et al., 2006). A review by Verbeek et al. did not rule out that specific types of beta blockers might have a depressogenic effect but this weak evidence should not be decisive to prescribe beta blockers to patients (Verbeek et al., 2011).

Given that depression is associated with a 2-fold risk of mortality in patients with coronary artery disease (CAD) (Nicholson et al., 2006), and even minimal symptoms of depression have been shown to predict short-term prognosis in patients treated with percutaneous coronary intervention (PCI) with drug eluting stenting (Pedersen et al., 2009), it is important to know whether beta blocker therapy is linked to depression.

We examined the association between beta blocker therapy and depressive symptoms in patients treated with PCI and the extent to which there is a dose–response relationship between beta blocker dose and depressive symptoms.

## 2. Methods

### 2.1. Patient population and design

The study population (N=685) consisted of two cohorts, all were treated with the Taxus stent. Patients were enrolled in the study if they were at least 18 years of age, had stable or unstable angina or provokable ischemia, and were undergoing PCI for a single, previously untreated lesion in a native coronary artery (Stone et al., 2004). The exclusion criteria were PCI for a lesion involving a previously implanted stent or patients receiving only BMS in the DES era (Stone et al., 2004). Depressive symptoms were assessed within 1 month post PCI (referred to as baseline in the remainder of the article) and 12 months post PCI in both cohorts.

The first consecutive cohort (cohort I) was comprised of 406 patients treated with PCI between July 1, 2003 and July 1, 2004. These patients completed the Hospital Anxiety and Depression Scale (HADS) at baseline and 12 months post PCI. Only patients who completed the HADS at baseline as well as 12 months post PCI were included in this study. Differences on baseline characteristics between responders and excluded/non-responders were found on age and diabetes. Excluded and non-responders were more likely to be older (mean age =  $64 \pm 10$  vs.  $62 \pm 11$ ) but less likely to have diabetes (15% versus 19%). No other systematic differences were found on baseline characteristics, including cardiac medication.

The second consecutive cohort (cohort II) included 279 patients treated with PCI between January 2006 and August 2006, who completed the HADS at baseline and 12 months post PCI. Only patients who completed the HADS at baseline

as well as 12 months post PCI were included in this study. Differences on baseline characteristics between responders and excluded/non-responders were found on age and prior PCI. Excluded and non-responders were more likely to be younger (mean age =  $61 \pm 11$  vs.  $63 \pm 11$ ) but less likely to have undergone a prior PCI (23% versus 28%). No other systematic differences were found on baseline characteristics, including cardiac medication.

Differences between Cohorts I and II were the following. Patients enrolled in cohort I were more likely to have hypercholesterolemia, a prior MI, a PCI indication for stable AP, and they were more likely on a beta blocker, calcium antagonist, ACE inhibitor and diuretics. Furthermore, there were fewer smokers in Cohort I.

### 2.2. Demographic and clinical variables

Information on demographic and clinical variables was obtained from the patients' medical records or from purpose-designed questions in the questionnaire. Demographic variables included age and gender. Clinical variables included cardiac history (i.e., previous MI, PCI or coronary artery bypass graft surgery (CABG)), indication for PCI (MI, stable or unstable angina), stent type (sirolimus eluting stent or paclitaxel-eluting stent) smoking status, hypertension, hypercholesterolemia, diabetes, familiar cardiac history and multivessel disease. Cardiac medication included aspirin, beta blockers, calcium antagonists, nitrates, ACE inhibitors, and statins. Information on all the clinical variables was collected during and immediately after the procedure.

Given the objective of the study, we collected detailed information on both the type of beta blocker used and the dose. Types of beta blockers prescribed included bisoprolol, metoprolol, atenolol, carvedilol, nebivolol, propranolol, labetalol, pindolol, sotalol, and celiprolol. Dose of beta blocker therapy was divided into low versus high, with a low dose defined as patients using less than 25% of the maximum recommended therapeutic dose, whereas a high dose was defined as exceeding or equal to 25% of the maximum recommended therapeutic dose (van Gestel et al., 2008). For bisoprolol, a maximum recommended therapeutic dose of 20 mg was used, for metoprolol 400 mg, for atenolol 100 mg, for carvedilol 50 mg, for nebivolol 10 mg, for propranolol 320 mg, for labetalol 800 mg, for pindolol 30 mg, for sotalol 320 mg, and for celiprolol 400 mg.

### 2.3. Depressive symptoms

Depressive symptoms were assessed with the 7-item depression subscale of the Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002). All items are answered on a four-point Likert scale from 0 to 3 with a score range of 0–21, with a higher score indicating more depressive symptomatology. Depressive symptoms were dichotomized using the standardized cut-off  $\geq 8$ . The HADS is a valid and internally consistent measure, as indicated by Cronbach's  $\alpha = 0.68$ – $0.93$  for anxiety and Cronbach's  $\alpha = 0.67$ – $0.90$  for depressive symptoms (Bjelland et al., 2002). An advantage of using HADS in cardiac patients is that the scale contains no somatic items, decreasing the likelihood that scores are confounded by disease severity (Herrmann-Lingen et al., 2001).

## 2.4. Statistical analysis

Prior to statistical analyses, Cohorts I and II were pooled as depressive symptoms were measured with the HADS in both cohorts. Discrete variables were compared with the  $\chi^2$  test (Fisher's exact test when appropriate) and continuous variables with the Student's *t*-test for independent samples. Univariable and multivariable logistic regression analyses were performed to evaluate the influence of beta blocker use on depressive symptoms at baseline and at 12 months post PCI. In multivariable logistic analysis, we adjusted for age, gender, prior MI, prior PCI, prior CABG, current smoking, hypertension, hypercholesterolemia, diabetes, multivessel disease, indication for PCI, and family history. The results of the regression analyses are presented as odds ratios (OR) with the corresponding 95% confidence intervals (CI). All statistical analyses were performed with SPSS for Windows version 15.0.

## 3. Results

### 3.1. Patient baseline characteristics stratified by beta blocker therapy

Of all patients, 68% (466/685) of patients were prescribed beta blocker therapy. Baseline characteristics for the total sample and stratified by beta blocker therapy are displayed in Table 1. Patients who were on beta blocker therapy were more likely to be younger (62 vs 65 years,  $p=0.02$ ), to have a prior MI (39 vs 30,  $p=0.02$ ), to have a PCI indication for unstable angina pectoris (40 vs 31,  $p=0.02$ ) and to be prescribed aspirin (66% vs 40%,  $p<0.001$ ), calcium antagonists (36% vs 26%,  $p=0.05$ ), ACE inhibitors (20 vs 17,

$p=0.02$ ) and statins (91 vs 85,  $p=0.01$ ) but were less likely to have a PCI indication for acute MI (12 vs 18,  $p=0.02$ ) and stable angina pectoris (48 vs 52,  $p=0.02$ ) as compared with patients who were not on beta blocker therapy.

### 3.2. Prevalence of depressive symptoms

The prevalence of depression (cut-off of  $\geq 8$  on the HADS depression scale) in Cohort I was 19.7% at baseline and 12.1% at 12 months post PCI, and in Cohort II 12.2% at baseline and 11.8% at 12 months post PCI.

### 3.3. Depressive symptoms and beta blocker use at baseline and at 12 months

At baseline, beta blocker use was not associated with depressive symptoms (OR: 0.85; CI: 0.55–1.29) in unadjusted analysis, while at 12 months post PCI, there was a statistically significant association between beta blocker use and depressive symptoms (OR: 0.53; CI: 0.33–0.84). The association between beta blocker use and depressive symptoms (OR: 0.51; CI: 0.31–0.84) 12 months post PCI remained after adjustment for potential demographic and clinical confounders, with patients on beta blocker therapy having a 49% risk reduction in depressive symptoms (Table 2). When we add baseline HADS in the multivariable model the odds ratio is even more significant at 12 months post PCI namely OR: 0.46 (CI: 0.25–0.83).

When we only adjust for baseline HADS and the use of beta blocker therapy the outcome is comparable namely OR: 0.46 (CI: 0.26–0.82).

**Table 1**  
Patient baseline characteristics (merged Cohorts I and II) stratified by beta blocker therapy\*.

	Total (n = 685)	Beta blocker (n = 466)	No beta blocker (n = 219)	p-value
Demographic characteristics				
Age, years (SD)	63 (11)	62 (10)	65 (11)	0.02
Male (%)	76	359 (77)	162 (74)	0.4
Cardiac history				
Prior MI	36	39	30	0.02
Prior CABG	11	11	13	0.3
Prior PCI	25	25	27	0.5
Risk factors				
Current smoking	17	17	19	0.5
Hypertension	48	49	46	0.4
Diabetes	19	18	20	0.5
Family history	48	47	50	0.5
Multivessel disease	56	56	55	0.9
PCI indication				
Stable angina pectoris	49	48	52	0.02
Unstable angina pectoris	37	40	31	0.02
Acute MI	14	12	18	0.02
Cardiac medication				
Aspirin	58	66	40	<0.001
Calcium antagonist	33	36	26	0.05
Nitrates	19	20	17	0.3
ACE inhibitors	38	41	31	0.02
Statins	89	91	85	0.01
Diuretics	8	12	11	0.1

\*Results are presented as % unless otherwise indicated.

\*MI = myocardial infarction; CABG = coronary artery bypass grafting; and PCI = percutaneous coronary intervention.

**Table 2**

Association between beta blocker therapy and depressive symptoms at baseline and at 12 months post PCI.

Beta blockers		% Depressive symptoms	Mean (SD) depressive symptoms	Depression (univariable) OR [95% CI]	Depression (multivariable) OR [95% CI]
Baseline	BBL+	15.9	4.32 (3.7)	0.85 [0.55–1.29]	0.82 [0.53–1.26]
	BBL–	18.3	4.59 (3.9)		
12 months	BBL+	9.7	3.71 (3.2)	0.53 [0.33–0.84]	0.51 [0.31–0.84]
	BBL–	16.9	4.62 (3.6)		

BBL = Beta Blocker; OR = Odds ratio; and CI = Confidence interval.

### 3.4. Prevalence of depressive symptoms stratified by beta blocker dose

There was a clear dose–response relationship between beta blocker dose and depressive symptoms, with the pattern being more clear at 12 months post PCI than at baseline (Fig. 1). A higher dose of beta blocker therapy was associated with a reduced risk of depressive symptoms, in particular at 12 months, with the risk reduction in depressive symptoms in relation to a low dose being 36% (OR: 0.64; 95% CI: 0.37–1.10) and 58% (OR: 0.42; 95% CI: 0.24–0.76) in relation to a high dose (Table 3).

### 3.5. Lipophilic and hydrophilic beta blocker use

In statistical analyses, we could not take into account the potential influence of the type of beta blocker (i.e., hydrophilic versus lipophilic) due to the majority (89%) of patients using a lipophilic beta blocker. Of the patients using a beta blocker, 89.0% at baseline and 89.3% 12 months post PCI in cohorts I and II used a lipophilic beta blocker against 11.0% and 10.7% at baseline and 12 months post PCI who used a hydrophilic beta blocker. Based on percentages, lipophilic beta blocker users experience depressive symptoms more frequently, compared with hydrophilic beta blocker users (16.0% versus 8.0% at baseline and 10.3 versus 4.0 at 12-months post-PCI, respectively).

### 3.6. Sensitivity analyses

In order to ensure that the results on merged data were not driven by a relationship between beta blocker therapy and depressive symptoms in only one of the cohorts, we also examined the two cohorts separately. In unadjusted analysis, there was no significant relationship between beta blocker therapy and depressive symptoms at baseline in Cohort I (OR: 0.71; CI: 0.41–1.24) nor in Cohort II (OR: 0.72; CI: 0.35–1.34). Similarly, in adjusted analysis there was no significant association between beta blocker therapy and depressive symptoms at baseline in Cohorts I (OR: 0.61; CI: 0.34–1.10) and II (OR: 0.82; CI: 0.38–1.78).

Furthermore, linear regression was applied to investigate the association between beta blocker therapy and depressive symptoms when the dichotomous depression scale was replaced by the continuous scale of the HADS in the analysis. At baseline and 12 months post PCI, the results of the unadjusted (p-value 0.38 and 0.001) and adjusted (p-value 0.50 and 0.002) analysis was in accordance with the prior analysis.

When stratifying beta blocker use by dose (i.e., low versus high) and no beta blocker therapy as the reference category, there were no statistically significant differences at baseline for low beta blocker dose (OR: 0.90; CI: 0.49–1.65) nor high beta blocker dose and depressive symptoms in Cohorts I (OR: 0.55; CI: 0.29–1.04) and II (OR: 0.97; CI: 0.42–2.23) (OR: 0.51; CI: 0.19–1.34). However, at 12 months post PCI

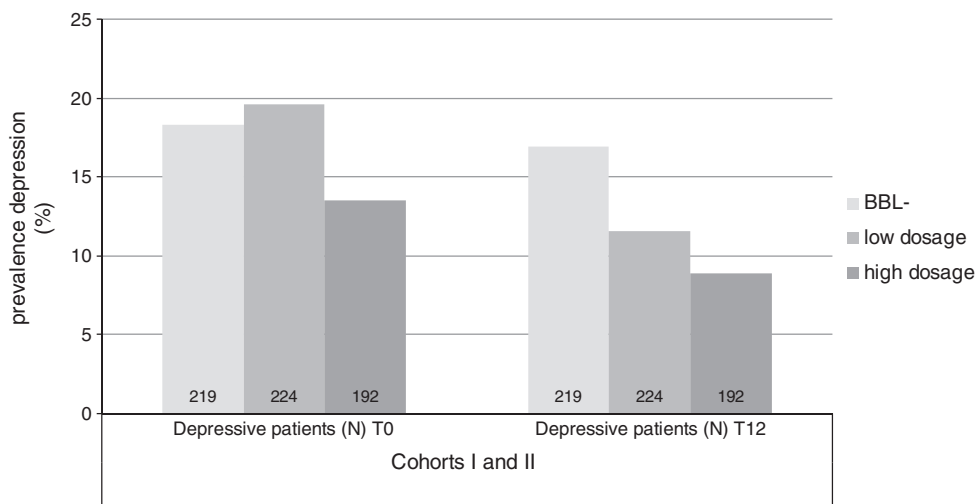


Fig. 1. Prevalence of depressive symptoms stratified by cohort and dose of beta blocker therapy.



**Table 3**

Association between beta blocker dose (low versus high) a no beta blocker use at baseline and at 12 months post PCI.

	Depression multivariable OR (95% CI)
Baseline <sup>a</sup>	
No beta blocker (reference)	1.00
Low dose beta blocker	1.08 [0.67–1.74]
High dose beta blocker	0.64 [0.38–1.07]
12 months <sup>a</sup>	
No beta blocker (reference)	1.00
Low dose beta blocker	0.64 [0.37–1.10]
High dose beta blocker	0.42 [0.24–0.76]

Low dose beta blocker = <25% of the maximum recommended therapeutic dose.

High dose beta blocker = ≥25% of the maximum recommended therapeutic dose.

<sup>a</sup> Depressive symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS). OR = Odds ratio; CI = Confidence interval.

in Cohort I patients with a low (OR: 0.83; CI: 0.40–1.73) and a high dose (OR: 0.56; CI: 0.26–1.22) were less likely to have depressive symptoms than patients with no beta blocker therapy, although the associations were not statistically significant. At 12 months in Cohort II, there was also not a statistically significant association between a low dose and depressive symptoms (OR: 0.41; CI: 0.16–1.06), although this was the case for a high dose of beta blocker therapy (OR: 0.25; CI: 0.08–0.74), with this effect being higher than in combined analyses on Cohorts I and II.

In order to rule out the potentially confounding influence of other types of cardiac medications and indication for PCI, we examined their association with depressive symptoms in Cohorts I and II merged together. None of the other types of cardiac medications or PCI indication was associated with depressive symptoms neither at baseline nor at 12 months follow-up (*p*-values > 0.05; results not shown).

We examined whether beta blocker therapy was associated with anxiety at baseline and at 12 month post PCI in Cohorts I and II merged together (Table 4). In unadjusted analysis, there was no significant relationship between beta blocker therapy and anxiety at baseline (OR: 0.72; CI: 0.40–1.32) nor at 12 months post PCI (OR: 0.51; CI: 0.25–1.02). In adjusted analysis there was no significant association between beta blocker therapy and anxiety at baseline (OR: 0.66; CI: 0.36–1.23) but at 12 months post PCI there was significant association (OR: 0.42; CI: 0.20–0.87).

#### 4. Discussion

The objective of the current study was to examine the association between beta blocker therapy and depressive

**Table 4**

Association between beta blocker therapy and anxiety at baseline and at 12 months post PCI.

	Anxiety (univariable) OR (95% CI)	Anxiety (multivariable) OR (95% CI)
Baseline <sup>a</sup>	0.72 [0.40–1.32]	0.66 [0.36–1.23]
12 months <sup>a</sup>	0.51 [0.25–1.02]	0.42 [0.20–0.87]

<sup>a</sup> Anxiety was assessed with the Hospital Anxiety and Depression Scale (HADS); OR = Odds ratio; CI = Confidence interval.

symptoms in patients treated with PCI and the extent to which there is a dose–response relationship between beta blocker dose and depressive symptoms. Compared to the study by van Melle et al. (2006), we focused not only on post MI patients but also on patients with stable and unstable angina as indication for PCI.

We found that beta blocker therapy was not associated with depressive symptoms at baseline, while at 12 months post PCI patients on beta blocker therapy had a 47% risk reduction in depressive symptoms in unadjusted analysis and a 49% risk reduction in adjusted analysis. We also found a dose–response relationship, particularly at 12 months post PCI, with a higher dose of beta blockers being associated with a more significant risk reduction in depressive symptoms. The risk reduction in depressive symptoms for a low dose was 36% and 58% for a high dose, respectively, compared to no beta blocker therapy.

We can only speculate why beta blocker therapy may have protective effects against depressive symptoms in patients after PCI. Previous animal studies with fear as the main outcome have shown that these memories can change when recalled (Kindt et al., 2009), and also that behavioral expression of fear in humans can be erased before memory reactivation with the beta adrenergic receptor antagonist propranolol (Kindt et al., 2009). Maybe beta blockers are potent not only with respect to erasing fear but also with respect to reducing depressive symptoms. When looking at the heart rate variability literature, there might be a link between depression and reduced heart rate variability (Grippe and Johnson, 2002). However, beta blocker use, such as metoprolol and atenolol, has been shown to increase heart rate variability in CAD (Niemela et al., 1994). Hypothetically, if heart rate variability increases with beta blocker therapy, and if heart rate variability is causally related to depressive symptoms, our findings support this hypothesis.

An alternative explanation for the conflicting findings with respect to the association between beta blocker therapy and depression to date could be the definition of depression used in previous studies, with some studies having used antidepressant prescription as a marker for depression (Avorn et al., 1986; Thiessen et al., 1990). Because antidepressant medication is prescribed not only for psychiatric indications but also for pain management and induction of sleep, this is not an optimal proxy for depressive symptoms (Gerstman et al., 1996). Furthermore, fatigue, a common beta blocker side effect, may have been misinterpreted as depression, which could lead to an overestimation of depression (Goble, 1992; Patten and Barbui, 2004).

Previous studies have also demonstrated that pindolol has a significant affinity for the 5-HT<sub>1A</sub> receptor (Plenge and Mellerup, 2003). The inhibition of 5-HT-uptake results in an antidepressant effect. Therefore, pindolol is comparable to the working mechanism of selective serotonin reuptake inhibitors (SSRIs). Especially the combination of paroxetine (an SSRI) with pindolol creates a nearly complete blockade of the 5-HT transporter already after the first dose (Plenge and Mellerup, 2003). This, in combination with beta blocker therapy, could be an explanation for the borderline significance of the positive trend toward lower depressive symptoms at 12 months post PCI. Unfortunately, in the current study we did not have information on the use of antidepressant medication.

Our findings showed a considerable risk reduction in depressive symptoms at 12 months in patients on beta blocker therapy while van Melle et al. (2006) found a trend to less depressive symptoms already at 3 months in post MI patients. In part, these results may be attributed to type of beta blocker (Ried et al., 1998), as several studies have suggested that the risk of central nervous system (CNS) adverse effects is greater for lipophilic than for hydrophilic beta blockers (Drayer, 1987; Gengo et al., 1987; Theodoresen and Brors, 1989) due to lipophilic drugs more readily crossing the blood–brain barrier than hydrophilic drugs (Ried et al., 1998). Hence, if the hypothesis is true that beta blocker use increases the risk of depression, propranolol is the most likely offender because it is the most lipophilic type (Steffensmeier et al., 2006). However, for atenolol and nadolol there is only minimal evidence that they lead to depression (McNeil et al., 1982). Ko et al. (2002) even found a non significant trend toward a higher risk of depressive symptoms in low to moderate lipid solubility beta blockers compared with beta blockers that have a high lipid solubility. von Kanel and Begre (2006) demonstrated that in the meta-analysis of Ko et al. (2002) the overall prevalence of depressive symptoms in patients who used and who did not use beta blockers was similar. They also noticed that neither the lipophilic nor the hydrophilic beta blocker compounds did have a part in this. In the current study, we were not able to examine whether the type of beta blocker (i.e., lipophilic versus hydrophilic) influenced the results, as the majority of patients (90%) on beta blocker therapy were prescribed a lipophilic beta blocker.

The results of the current study should be interpreted with some caution. First, we used two independent cohorts of post PCI patients, with the sample size ranging between 279 and 406 in the two registries. Furthermore, it is possible that a selection bias might have occurred, given that some patients did not return the questionnaire, or were unable to complete the questionnaire due to insufficient knowledge of the Dutch language. In addition, patients who died within the first 1 month post PCI or between 1 month and 12 months post PCI were not able to complete the HADS, which might potentially have biased the results. Second, we did not have data on psychoactive drug use or psychological support of the patients before they were enrolled in the study. Third, in statistical analyses we were not able to take into account whether the type of beta blocker (i.e., hydrophilic versus lipophilic) had an influence on depressive symptoms, given that the majority of patients on beta blocker therapy were prescribed a lipophilic beta blocker. Fourth, it is uncertain whether patients, who had a prescription for a beta blocker, actually took their medication, or complied with their dosing regimen.

In conclusion, the results of the current study showed that patients on beta blocker therapy had a considerable risk reduction in depressive symptoms 12 months post PCI, with there being a general dose–response relationship with a higher dose providing a more pronounced protective effect. Further studies are warranted to confirm these findings, as to our knowledge this is the first study to show that beta blocker therapy may have a protective effect against depressive symptoms in cardiac patients.

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#### Conflict of interests

We have no conflicts of interest to disclose.

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