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ORIGINAL RESEARCH ARTICLE

β-Blockers and the Risk of Depression: A Matched Case–Control Study

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Abstract

Introduction Depression is a commonly cited adverse effect of β-blockers but the evidence for a causal relationship is limited.
Objective We aimed to explore whether β-blockers are associated with an increased risk of new-onset depression.
Methods We conducted a case–control study using the UK population-based Clinical Practice Research Datalink (CPRD) GOLD. We identified patients aged 18−80 years with an incident depression diagnosis between 2000 and 2016, and matched controls, and estimated the risk (odds ratio [OR]) of depression in association with use of β-blockers. We also conducted analyses of exposure, categorised by number and timing of prescriptions and by indication for β-blocker use.
Results The study encompassed 118,705 patients with incident depression and the same number of matched controls. The odds of developing depression were increased for current short-term use of any β-blocker (adjusted OR [aOR] 1.91, 95% confidence interval [CI] 1.72−2.12), whereas current long-term use was not associated with the risk of depression compared with never use. The elevated risk of depression among short-term users was mostly confined to propranolol users with a neuropsychiatric disorder (aOR 6.33, 95% CI 5.16–7.76), while propranolol users with a cardiovascular indication were only at marginally increased risk of depression (aOR 1.44, 95% CI 1.14–1.82).
Conclusions This study suggests that the association between use of β-blockers and depression may not be causal but rather a result of protopathic bias. Propranolol is often prescribed to treat neuropsychiatric symptoms, suggesting that the onset of depression may be related to the underlying indication rather than to an effect of a β-blocker therapy.

1 Introduction

β-Blockers are a widely prescribed standard treatment option for various cardiovascular diseases such as chronic heart failure [1], coronary artery disease [2], cardiac arrhythmias [3], and arterial hypertension [4]. However, despite the ample evidence supporting their efficacy in these indications, β-blockers still seem to be underutilised or prescribed at lower than recommended dosages due to concerns of both prescribers and patients regarding their safety and tolerability [5].

A potential adverse effect of β-blockers, commonly cited in the medical literature as well as in the lay press, is depression. Postulated underlying mechanisms are speculative and include blockade of adrenergic receptors in the brain with subsequent change of activity in various neuronal networks, a decrease in melatonin production, antagonistic action at serotonin receptors, and membrane-stabilising properties silencing sensitive neurons in the central nervous system (CNS) [6, 7]. Hence, it has been hypothesised that hydrophilic β-blockers (atenolol, labetolol, nadolol, practolol, sotalol) might be associated with a lower risk of depression than β-blockers of intermediate or high lipophilicity (acebutolol, bisoprolol, carvedilol, celiprolol, metoprolol, nevibolol, oxprenolol, pindolol, propranolol, timolol) due to their pharmacokinetic properties, i.e. their lower ability to penetrate the blood–brain barrier [8, 9].

In April 1967, a possible association between use of β-blockers and depression was first described. In several case reports, patients reported depressive symptoms after starting therapy with the highly lipophilic β-blocker propranolol [10–12]. Since then, several studies have investigated

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Key Points

We did not find an increased risk of depression in users of lipophilic β-blockers other than propranolol, nor in users of hydrophilic β-blockers.

The elevated risk of depression in propranolol users was restricted almost entirely to those who received propranolol for the treatment of neuropsychiatric symptoms.

Our findings suggest that the reported association between use of β-blockers and depression may not be causal but rather a result of protopathic bias.

the relationship between treatment with β-blockers and the risk of depression, yielding inconsistent results. A number of observational studies found a similar putative association between β-blockers and depression [13, 14]. Subgroup analyses suggested that the observed risk was mainly attributed to the lipophilic β-blocker propranolol [13–15]. Some of these studies were based on small sample sizes, were cross-sectional in design with unclear temporal relationship between exposure and outcome, or relied solely on the use of antidepressants as a proxy for a depression diagnosis [13, 16]. In contrast, other observational studies did not report such an association [17, 18]. The large Danish population-based register study by Kessing et al. even found possible protective effects of propranolol, atenolol, bisoprolol, and carvedilol on the risk of depression [18].

A recent systematic review and meta-analysis pooled data from randomised controlled trials investigating β-blockers in cardiovascular and non-cardiovascular indications. The analysis of psychiatric adverse events did not yield evidence for an increased risk of depressive symptoms among users of β-blockers when compared with placebo or other active treatment [19].

In view of the conflicting findings from previous research, we aimed to further explore whether use of β-blockers was associated with an altered risk of developing new-onset depression in a large case–control study based on a well-validated UK primary care database, with emphasis on the pharmacokinetic properties of β-blockers, their timing of use and their likely indication.

2 Methods

2.1 Study Design and Data Source

We conducted a matched case–control analysis using primary care data from the UK-based Clinical Practice Research Datalink (CPRD) GOLD obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. The database encompasses approximately 11.3 million electronic patient records from around 650 practices [20]. The data are collected by the National Health Service (NHS) as part of the routine care by general practitioners [21]. Available information includes medical diagnoses, demographics, lifestyle factors, and referrals to secondary care. Individuals registered in the CPRD are representative of the UK population in terms of age, sex and ethnicity. The data quality and completeness of the CPRD has been extensively validated [22].

The UK-CPRD study is based on data from the CPRD obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research (protocol no: 13_041) and has been made available to the journal editors. The interpretation and conclusions contained in this study are those of the author/s alone.

2.2 Study Population

We identified patients aged 18–80 years with a first-time diagnosis of depression between 1 January 2000 and 31 December 2016, defined by Read codes (coded thesaurus of clinical terms used in the NHS; see the electronic supplementary Table). The validity of depression Read codes has recently been documented for common mental disorders in the Secure Anonymised Information Linkage Databank (SAIL), with routinely collected electronic primary care data [23]. We defined cases as individuals with a recorded incident depression diagnosis and with a minimum of three prescriptions for antidepressant drugs recorded after the diagnosis date (i.e. the index date), with the first prescription being issued within 90 days after the index date. We adjusted the index date to accord with the first antidepressant prescription, if the antidepressant prescription was recorded within < 90 days before the first depression code. We excluded cases if they had more than two prescriptions for antidepressant drugs at any time prior to the index date. The first requirement to have three or more prescriptions for antidepressant drugs was implemented to exclude patients with mild and transient depression, and the latter at increasing the likelihood of capturing only patients with incident rather than prevalent depression.

We excluded patients with < 3 years of history recorded in the CPRD prior to the index date, as well as patients with a documented history of cancer, HIV infection, suicidal ideation, or alcoholism.

We randomly selected from the CPRD base population one control patient per case without recorded depression

or depression-like syndrome prior to the index date of the corresponding case. We applied the same exclusion criteria to controls as to cases. We matched controls to cases on age (± 2 years), sex, general practice, calendar time, and number of years of history in the CPRD prior to the index date (±2 years).

2.3 β-Blocker Exposure and Covariates

We assessed prescriptions for systemically used β-blockers prior to the index date and categorised exposure according to timing of use (current use: last prescription < 90 days before the index date; past use: last prescription ≥ 90 days before the index date), duration of use (short term: 1–4 prescriptions; medium-term: 5–9 prescriptions; long-term: ≥ 10 prescriptions), and physicochemical properties (lipophilic vs. hydrophilic). Current use was defined based on the assumption that one pack of β-blockers would last for approximately 90 days (many prescriptions are for large packs containing up to 100 tablets); however, we could not calculate the exact period of time covered by one prescription, because dose instructions are not comprehensively captured in the CPRD. Lipophilic β-blockers included acebutolol, bisoprolol, carvedilol, celiprolol, metoprolol, nevibolol, oxprenolol, pindolol, propranolol, and timolol, and hydrophilic β-blockers included atenolol, labetolol, nadolol, practolol, and sotalol. We further stratified use of β-blockers by active substance with relevant exposure in this study population (atenolol, bisoprolol, carvedilol, metoprolol, nebivolol, propranolol, sotalol). These analyses were restricted to patients taking only one β-blocker (one active substance) prior to the index date.

We assessed the prevalence of selected lifestyle factors (body mass index [BMI], smoking status, alcohol intake), potential indications for use of β-blockers (anxiety, arrhythmia, heart failure, hypertension, hyperthyreosis, ischaemic heart disease, myocardial infarction [MI], migraine, tremor), potential adverse effects of β-blockers (erectile dysfunction, sleeping disorders), other major internal diseases (chronic obstructive pulmonary disease [COPD], diabetes, schizophrenia, stroke), and neuropsychiatric disorders (affective disorders, anxiety, neurotic or stress-related disorders) before the index date based on Read codes.

2.4 Statistical Analysis

We explored the association between use of different β-blockers and new onset of depression by running multivariate conditional logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs), as well as adjusted OR (aOR) after controlling for confounding variables.

Propranolol, the most commonly used β-blocker, is often prescribed to treat neuropsychiatric conditions such as nervousness and anxiety. To minimise protopathic bias, and since these conditions may be associated with depression, we conducted a sensitivity analysis restricted to patients for whom there was evidence that cardiovascular disease was the indication for use. We required these patients to have at least one recorded cardiovascular indication (arrhythmia, heart failure, hypertension, ischaemic heart disease, or MI) within 30 days before or after the first prescription of propranolol, and no record of a neuropsychiatric condition or symptom such as anxiety, stress or mood disorders within 1 year prior to the index date.

We a priori adjusted all analyses for covariates known from the literature to be associated with depression and/or use of β-blockers. These included smoking, alcohol intake, BMI, potential indications for β-blockers (anxiety, arrhythmia, heart failure, hypertension, hyperthyreosis, ischaemic heart disease, MI, migraine, tremor), selected potential adverse effects of β-blockers (sleeping disorders, erectile dysfunction), use of benzodiazepines and analogues, and use of other antihypertensive drugs (angiotensin-converting enzyme [ACE] inhibitors, angiotensin 1 [AT1]-antagonists, calcium channel blockers, diuretics). We also included a variable for neuropsychiatric disorders (affective disorders, anxiety, neurotic or stress-related disorders). Other diseases such as COPD, diabetes mellitus, hypothyroidism, stroke or schizophrenia were not included in the final model since they did not alter the ORs for the association between use of β-blockers and depression by more than 10%, when tested one at a time.

We conducted all analyses using SAS 9.4 software (SAS Institute, Cary, NC, USA), and defined statistical significance at the α-level of 0.05.

3 Results

3.1 Characteristics of the Study Population

We identified 118,705 cases with a first-time diagnosis of pharmacologically treated depression between 2000 and 2016, and the same number of matched controls. The majority of cases had a depression episode without further classification, but severe enough to be treated with antidepressant therapy. Patients had a mean age of 40.3 years (standard deviation [SD] ± 15.8 years) at the index date and the majority (61.3 %) were female (Table 1). The mean duration of active history in the database prior to the index date was 11.3 years (SD ± 5.4 years).

Compared with controls, cases were more likely to have conditions associated with β-blocker use, such as anxiety, ischaemic heart disease, migraine and tremor, as well as

having adverse effects related to their use, such as erectile dysfunction and sleeping disorders.

3.2 β-Blockers and Risk of Depression

When compared with never use, ever use of any β-blocker was associated with a slightly increased risk of depression (aOR 1.19, 95% CI 1.16−1.23). The effect was only present in new users of the therapy: current short-term use (1−4 prescriptions) of any β-blocker yielded an aOR of 1.91 (95% CI 1.72−2.12), whereas current long-term use (≥ 10 prescriptions) yielded an aOR of 0.85 (95% CI 0.85–0.94) (Table 2).

The observed elevated risk of depression among short-term users of β-blockers was, for the most part, restricted to propranolol use. The aOR for short-term users of β-blockers decreased to 1.29 (95% CI 1.12–1.50) (Table 3) when propranolol users were removed from the analysis. In contrast, the aOR for short-term users of propranolol was 2.72 (95% CI 2.32–3.18). Neither current use of lipophilic β-blockers other than propranolol nor current use of hydrophilic β-blockers was associated with an increased risk of depression (Table 3).

In the sensitivity analysis, in which we explored whether the risk of depression was associated with the underlying presumed indication for propranolol use, the aOR of depression for patients with a cardiovascular indication was only marginally increased (aOR 1.44, 95% CI 1.14–1.82), while in patients with a recorded neuropsychiatric disorder the aOR for depression was increased by more than sixfold (aOR 6.33, 95% CI 5.16–7.76) (Table 4).

4 Discussion

In this large observational study, we explored the risk of new-onset depression associated with use of β-blockers, taking into account the presumed indication for β-blocker use. Our results suggest that previous associations found between β-blockers and depression were not causal. We did not find an increased risk of depression in users of lipophilic β-blockers other than propranolol or in users of hydrophilic β-blockers [13, 14, 24]. Furthermore, the elevated risk of depression in propranolol users was restricted almost entirely to those who received propranolol for the treatment of neuropsychiatric symptoms. This finding suggests that increased risk was due to protopathic bias; that is, the underlying indication for propranolol use explained the increased risk of depression.

Propranolol is frequently used in patients with neuropsychiatric symptoms, reducing anxiety and unspecific stress-related symptoms. In addition, it is used to reduce tremor or migraine severity but is rarely used for cardiovascular indications. In this study population, only 3.2% of patients received propranolol treatment for a cardiovascular indication, whereas 18.5% had a neuropsychiatric indication. Anxiety, nervousness, tremor and other neuropsychiatric symptoms can also be early manifestations of depression, raising the possibility that the previously reported increased risk of depression among users of propranolol was the result of protopathic bias and not an adverse effect of propranolol. That is, early symptoms of depression could have led to the prescribing of propranolol. When we stratified our analyses by presumed indication for propranolol use, we found strong support for this hypothesis; the aOR for current propranolol use with a cardiovascular indication was 1.44 (95% CI 1.14–1.82), while it was 6.33 (95% CI 5.16–7.76) for those who had a reported CNS indication. The slightly, but statistically significantly, increased aOR in patients with a presumed cardiovascular indication can be explained by residual confounding (for example, it is possible that some of these patients additionally had neuropsychiatric symptoms that were not recorded in the database, but led the physician to choose propranolol), although we cannot completely rule out a small risk increase in the sense of a true adverse effect.

Several previous studies found a higher risk of incident depression for lipophilic compared with hydrophilic β-blockers [15, 25, 26]. The authors suggested that a higher concentration of lipophilic β-blockers in brain tissue compared with hydrophilic agents could explain the higher incidence of adverse effects. In our study, propranolol, bisoprolol and atenolol were the most commonly used β-blockers, but only propranolol use was associated with an increased risk of depression, especially among current short-term users. The lipophilic profile of bisoprolol is similar to that of propranolol, but atenolol is highly hydrophilic [8, 9]. Thus, the postulated mechanism for an increased risk based on the physicochemical properties does not explain our findings [14, 27]. Similarly, the cardioselectivity does not seem to play a role as we did not observe an altered risk of depression in patients taking carvedilol, the other examined non-cardioselective β-blocker beside propranolol.

Our population-based study to evaluate the risk of incident depression in association with use of β-blockers is based on a well-validated primary care database. We required that all cases receive at least three prescriptions for an antidepressant to be included as a case to limit case misclassification. Cases with a first time diagnosis of depression were predominantly middle aged and female, which is consistent with prior findings [28]. Cases were also more likely to have been smokers and to drink alcohol compared with controls.

There are limitations of this study that should be taken into consideration. First, the onset of depression is often a poorly defined point in time, as the disease may develop slowly. Thus, the index date may not always have been accurately defined. Second, we cannot rule out some case

Table 1 Characteristics of the study population (cases with incident depression and matched controls)

	Cases, $n = 118{,}705$ [n (%)]	Controls, $n = 118{,}705$ [n (%)]	OR crude	(95% CI)
Sex				
Males	45,915 (38.7)	45,915 (38.7)	–	
Females	72,790 (61.3)	72,790 (61.3)	–	
Age at diagnosis, years				
Mean (SD)	40.3 years (± 15.8)	40.3 years (± 15.8)	–	
<30	35,894 (30.2)	35,876 (30.2)	–	
30–59	67,267 (56.7)	67,272 (56.7)	–	
≥60	15,544 (13.1)	15,557 (13.1)	–	
BMI, kg/m^2				
<18	2084 (1.8)	1606 (1.4)	1.31	(1.22−1.40)
18−24.9	41,149 (34.7)	42,073 (35.4)	1.00	(Reference)
25−29.9	28,519 (24.0)	28,102 (23.7)	1.05	(1.03−1.07)
≥30	22,214 (18.7)	19,275 (16.2)	1.20	(1.17−1.23)
Unknown	24,739 (20.8)	27,649 (23.3)	0.87	(0.85−0.89)
Smoking status				
Non	51,129 (43.1)	63,029 (53.1)	1.00	(Reference)
Current	34,336 (28.9)	22,773 (19.2)	1.90	(1.86−1.94)
Ex	24,974 (21.0)	22,644 (19.1)	1.38	(1.35−1.42)
Unknown	8266 (7.0)	10,259 (8.6)	0.94	(0.91−0.98)
Alcohol intake				
Non	16,738 (14.1)	16,090 (13.6)	1.00	(Reference)
Current	79,417 (66.9)	77,079 (64.9)	0.99	(0.97−1.02)
Women	48,678 (41.0)	47,941 (40.4)	0.96	(0.93−0.98)
Men	30,739 (25.9)	29,138 (24.6)	1.08	(1.04−1.12)
Ex	1920 (1.6)	1205 (1.0)	1.56	(1.45−1.69)
Women	1024 (0.9)	774 (0.7)	1.26	(1.14−1.39)
Men	896 (0.8)	431 (0.4)	2.20	(1.95−2.49)
Unknown	20,630 (17.4)	24,331 (20.5)	0.76	(0.73−0.78)
GP visits				
<5	32,422 (27.3)	34,723 (29.3)	1.00	(Reference)
5−20	60,974 (51.4)	62,053 (52.3)	1.46	(1.41−1.52)
≥20	25,309 (21.3)	21,929 (18.5)	2.23	(2.13−2.34)
Comorbidities				
Anxiety	9241 (7.8)	3960 (3.3)	2.52	(2.42−2.62)
Arrhythmia	2019 (1.7)	1942 (1.6)	1.04	(0.98−1.11)
Heart failure	795 (0.7)	736 (0.6)	1.09	(0.98−1.21)
Hypertension	14,261 (12.0)	15,279 (12.9)	0.90	(0.87−0.92)
Hyperthyreosis	1112 (0.9)	1076 (0.9)	1.03	(0.95−1.13)
Ischaemic heart disease	3751 (3.2)	3318 (2.8)	1.16	(1.11−1.23)
Migraine	11,352 (9.6)	8176 (6.9)	1.44	(1.40−1.49)
Myocardial infarction	1613 (1.4)	1430 (1.2)	1.14	(1.06−1.23)
Tremor	1013 (0.9)	624 (0.5)	1.64	(1.48−1.81)
Erectile dysfunction	3675 (3.1)	2704 (2.3)	1.41	(1.34−1.49)
Sleeping disorders	11,130 (9.4)	4620 (3.9)	2.69	(2.59−2.79)
COPD	1728 (1.5)	1177 (1.0)	1.52	(1.41−1.64)
Diabetes mellitus	5058 (4.3)	5127 (4.3)	0.98	(0.94−1.03)
Schizophrenia	268 (0.2)	378 (0.3)	0.71	(0.61−0.83)
Stroke/TIA	2275 (1.9)	1505 (1.3)	1.58	(1.48−1.69)

Table 1 (continued)

	Cases, $n = 118{,}705$ [n (%)]	Controls, $n = 118{,}705$ [n (%)]	OR crude	(95% CI)
Drug use				
Systemic corticosteroids	2940 (2.5)	2548 (2.2)	1.23	(1.16−1.30)
Benzodiazepines and analogues	8348 (7.0)	1663 (1.4)	6.63	(6.26−7.02)
ACEi	6581 (5.5)	6881 (5.8)	0.94	(0.91−0.98)
ARB	2181 (1.8)	2438 (2.1)	0.89	(0.84−0.94)
CCB	4998 (4.2)	5298 (4.5)	0.94	(0.90−0.98)
Diuretics	6763 (5.7)	7126 (6.0)	0.96	(0.93−1.00)

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *CCB* calcium channel blocker, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *GP* general practitioner, *OR* odds ratio, *SD* standard deviation, *TIA* transient ischaemic attack

Table 2 Use of β-blockers and risk of depression: β-blockers overall, propranolol, and β-blockers without propranolol

	Cases, $n = 118{,}705$ [n (%)]	Controls, $n = 118{,}705$ [n (%)]	OR crude	(95% CI)	aOR[a]	(95% CI)
BB overall						
Never use of any BB	100,417 (84.6)	104,414 (88.0)	1.00	(Reference)		
Ever use of any BB	18,288 (15.4)	14,291 (12.0)	1.39	(1.36−1.43)	1.19	(1.16−1.23)
Current use of any BB (<90 days before ID)	6955 (5.9)	6123 (5.2)	1.24	(1.20−1.29)	1.19	(1.13−1.24)
1−4 Rx	1891 (1.6)	635 (0.5)	3.17	(2.90−3.47)	1.91	(1.72−2.12)
5−9 Rx	661 (0.6)	563 (0.5)	1.26	(1.12−1.41)	1.04	(0.92−1.19)
≥10 Rx	4403 (3.7)	4925 (4.2)	0.96	(0.92−1.01)	0.89	(0.85−0.94)
Past use of any BB (≥ 90 days before ID)	11,333 (9.6)	8168 (6.9)	1.49	(1.44−1.53)	1.31	(1.26−1.35)
BB without propranolol						
Never use of any BB	110,144 (92.8)	109,637 (92.4)	1.00	(Reference)		
Ever use of any BB	8561 (7.2)	9068 (7.6)	0.99	(0.95−1.02)	0.98	(0.93−1.02)
Current use of any BB (< 90 days before ID)	4393 (3.7)	5201 (4.4)	0.88	(0.84−0.92)	0.87	(0.83−0.92)
1−4 Rx	527 (0.4)	404 (0.3)	1.38	(1.21−1.57)	1.42	(1.23−1.64)
5−9 Rx	424 (0.4)	460 (0.4)	0.98	(0.86−1.12)	1.02	(0.88−1.18)
≥10 Rx	3442 (2.9)	4337 (3.7)	0.85	(0.81−0.89)	0.84	(0.79−0.89)
Past use of any BB (≥ 90 days before ID)	4168 (3.5)	3867 (3.3)	1.13	(1.08−1.18)	1.11	(1.06−1.18)
Propranolol only						
Never use of any BB	108,978 (91.8)	113,482 (95.6)	1.00	(Reference)		
Ever use of propranolol	9727 (8.2)	5223 (4.4)	1.98	(1.91−2.06)	1.42	(1.37−1.48)
Current use of propranolol (< 90 days before ID)	2148 (1.8)	638 (0.5)	3.59	(3.28−3.93)	1.89	(1.71−2.09)
1−4 Rx	1369 (1.2)	230 (0.2)	6.21	(5.38−7.16)	2.72	(2.32−3.18)
5−9 Rx	197 (0.2)	78 (0.1)	2.58	(1.98−3.35)	1.23	(0.91−1.67)
≥10 Rx	582 (0.5)	330 (0.3)	1.80	(1.57−2.07)	1.31	(1.12−1.52)
Past use of propranolol (≥ 90 days before ID)	7579 (6.4)	4585 (3.9)	1.76	(1.68−1.82)	1.34	(1.30−1.42)

ACEi angiotensin-converting enzyme inhibitor, *aOR* adjusted odds ratio, *ARB* angiotensin receptor blocker, *BB* β-blockers, *BMI* body mass index, *CCB* calcium channel blocker, *CI* confidence interval, *ID* index date, *OR* odds ratio, *Rx* prescription drug

[a]Adjusted for a history of potential indications for β-blockers (heart failure, hypertension, myocardial infarction, ischaemic heart disease, arrhythmia, migraine, tremor, anxiety, hyperthyreosis), potential adverse effects of β-blockers (erectile dysfunction, sleeping disorders), current use of other cardiovascular drugs (ACEi, ARB, CCB, diuretics), current use of benzodiazepines and analogues, neuropsychiatric indications (affective disorders, anxiety, neurotic or stress-related disorders), smoking status (non, current, ex, unknown), alcohol status (non, current, ex, unknown), and BMI (<18, 18–24.9, 25–29.9, ≥30 kg/m^2)

Table 3 Use of β-blockers and risk of depression by active substance and pharmacokinetic properties

Use of BB	Cases, $n = 118{,}705$ [n (%)]	Controls, $n = 118{,}705$ [n (%)]	OR crude	(95% CI)	aOR[a]	(95% CI)
Never use of any BB	100,417 (84.6)	104,414 (88.0)	1.00	(Reference)		
Current use of any BB (< 90 days before ID), overall	6955 (5.9)	6123 (5.2)	1.24	(1.20−1.29)	1.19	(1.13−1.24)
Current use of lipophilic BB only:	3633 (3.1)	2211 (1.9)	1.79	(1.69−1.89)	1.29	(1.21−1.38)
Bisoprolol only	1185 (1.0)	1235 (1.0)	1.01	(0.93−1.10)	0.95	(0.86−1.05)
Carvedilol only	62 (0.1)	77 (0.1)	0.83	(0.59−1.16)	0.69	(0.48−1.01)
Metoprolol only	145 (0.1)	149 (0.1)	1.02	(0.81−1.28)	0.91	(0.70−1.18)
Nebivolol only	73 (0.1)	71 (0.1)	1.07	(0.76−1.49)	0.94	(0.65−1.37)
Propranolol only	2148 (1.8)	638 (0.5)	3.60	(3.29−3.94)	1.89	(1.71−2.10)
Current use of hydrophilic BB only	3109 (2.6)	3580 (3.0)	0.93	(0.88−0.97)	0.92	(0.86−0.97)
Atenolol only	2924 (2.5)	3347 (2.8)	0.91	(0.86−0.96)	0.89	(0.84−0.95)
Sotalol only	147 (0.1)	178 (0.2)	0.88	(0.70−1.09)	0.84	(0.65−1.08)

We did not display use of acebutolol, celiprolol, esmolol, labetalol, nadolol, oxprenolol, pindolol, and timolol because of low frequency of use

ACEi angiotensin-converting enzyme inhibitor, *aOR* adjusted odds ratio, *ARB* angiotensin receptor blocker, *BB* β-blockers, *BMI* body mass index, *CCB* calcium channel blocker, *CI* confidence interval, *ID* index date, *OR* odds ratio

[a]Adjusted for a history of potential indications for β-blockers (heart failure, hypertension, myocardial infarction), ischaemic heart disease, arrhythmia, migraine, tremor, anxiety, hyperthyreosis), potential adverse effects of β-blockers (erectile dysfunction, sleeping disorders), current use of other cardiovascular drugs (ACEi, ARB, CCB, diuretics), current use of benzodiazepines and analogues, neuropsychiatric indications (affective disorders, anxiety, neurotic or stress-related disorders), smoking status (non, current, ex, unknown), alcohol status (non, current, ex, unknown), and BMI (<18, 18–24.9, 25–29.9, ≥30 kg/m^2)

misclassification if depression was incorrectly coded or diagnosed. However, misclassification is unlikely to be a major source of concern as we required cases to have a recording of major depression followed by three newly prescribed antidepressants. Third, we cannot rule out the possibility that β-blocker users experience mild mood disorders in the early phase of therapy, not requiring further medical work-up and pharmacological treatment; such mild forms were not the focus of this study. Fourth, by excluding patients with a history of alcoholism, we may have limited the generalisability of our findings; we did this to increase the likelihood of including only idiopathic depression cases, which may have been triggered by β-blockers, as opposed to include cases who were already at high risk of depression based on an underlying alcohol addiction.

5 Conclusion

This population-based observational study provides evidence that neither lipophilic nor hydrophilic β-blockers are associated with a clinically meaningful increased risk of depression. The reported high risk of new onset of depression after use of propranolol may be explained by protopathic bias and not by a pharmacological effect of propranolol.

Table 4 Sensitivity analysis: risk of depression among propranolol users by indication for use: cardiovascular indication or neuropsychiatric disorder[a]

	Cases, $n = 118{,}705$ [n (%)]	Controls, $n = 118{,}705$ [n (%)]	OR crude	(95% CI)	aOR[b]	(95% CI)
No propranolol use	108,978 (91.8)	113,482 (95.6)	1.00	Reference		
Users with cardiovascular indication						
Propranolol use	1223 (1.0)	860 (0.7)	1.51	(1.38–1.65)	1.35	(1.22–1.49)
Current use (< 90 days before ID)	216 (0.2)	144 (0.1)	1.59	(1.28–1.96)	1.44	(1.14–1.82)
Past use (≥ 90 days before ID)	1007 (0.9)	716 (0.6)	1.49	(1.35–1.64)	1.33	(1.19–1.48)
Users with neuropsychiatric indication						
Propranolol use	2129 (1.8)	418 (0.4)	5.47	(4.92–6.09)	3.63	(3.24–4.07)
Current use (< 90 days before ID)	984 (0.8)	118 (0.1)	9.10	(7.49–11.05)	6.33	(5.16–7.76)
Past use (≥ 90 days before ID)	1145 (1.0)	300 (0.3)	4.07	(3.58–4.63)	2.63	(2.29–3.02)

ACEi angiotensin-converting enzyme inhibitor, *aOR* adjusted odds ratio, *ARB* angiotensin receptor blocker, *BMI* body mass index, *CCB* calcium channel blocker, *CI* confidence interval, *ID* index date, *OR* odds ratio

[a]Recorded 30 days before/after first prescription

[b]Adjusted for a history of potential indications for β-blockers (heart failure, hypertension, myocardial infarction, ischaemic heart disease, arrhythmia, migraine, tremor, anxiety, hyperthyreosis), potential adverse effects of β-blockers (erectile dysfunction, sleeping disorders), current use of other cardiovascular drugs (ACEi, ARB, CCB, diuretics), current use of benzodiazepines and analogues, smoking status (non, current, ex, unknown), alcohol status (non, current, ex, unknown), and BMI (<18, 18–24.9, 25–29.9, ≥30 kg/m^2)

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Declarations

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Conflicts of interest/competing interests Delia Bornand, Daphne Reinau, Susan S. Jick, and Christoph R. Meier declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Availability of data and material For reasons of confidentiality, we are not allowed to make the data available.

Code availability Most analyses were conducted using standard procedures without special code development. Codes can be obtained upon request to the corresponding author.

Ethics approval Not applicable.

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Consent for publication Not applicable.

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References

1. National Institute for Health and Care Excellence. Chronic heart failure in adults: diagnosis and management: NICE guideline [NG106]. 2018. https://www.nice.org.uk/guidance/ng106. Accessed 21 Jul 2019.

2. Montalescot G, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949–3003. https://doi.org/10.1093/eurheartj/eht296.
3. National Institute for Health and Care Excellence. Atrial fibrillation: diagnosis and management: NICE guideline [NG196]. 2021. https://www.nice.org.uk/guidance/ng196. Accessed 19 Nov 2021.
4. Mancia G, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219. https://doi.org/10.1093/eurheartj/eht151.
5. Kiel RG, Deedwania P. The safety and tolerability of beta blockers in heart failure with reduced ejection fraction: is the current underutilization of this evidence-based therapy justified? Expert Opin Drug Saf. 2015;14(12):1855–63. https://doi.org/10.1517/14740338.2015.1102225.
6. Verbeek DE, et al. A review on the putative association between beta-blockers and depression. Heart Fail Clin. 2011;7(1):89–99. https://doi.org/10.1016/j.hfc.2010.08.006.
7. Stoschitzky K, et al. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol. 1999;55(2):111–5.
8. Poirier L, Tobe SW. Contemporary use of beta-blockers: clinical relevance of subclassification. Can J Cardiol. 2014;30(5 Suppl):S9–15. https://doi.org/10.1016/j.cjca.2013.12.001.
9. Frishman WH. The beta-adrenoceptor blocking drugs. Int J Cardiol. 1982;2(2):165–78.
10. Oppenheim G. Propranolol-induced depression: mechanism and management. Aust N Z J Psychiatry. 1983;17(4):400–2. https://doi.org/10.1080/00048678309160022.
11. Waal HJ. Propranolol-induced depression. Br Med J. 1967;2(5543):50.
12. Nolan BT. Acute suicidal depression associated with use of timolol. JAMA. 1982;247(11):1567.
13. Avorn J, Everitt DE, Weiss S. Increased antidepressant use in patients prescribed beta-blockers. JAMA. 1986;255(3):357–60.
14. Thiessen BQ, et al. Increased prescribing of antidepressants subsequent to beta-blocker therapy. Arch Intern Med. 1990;150(11):2286–90.
15. Johnell K, Fastbom J. The association between use of cardiovascular drugs and antidepressants: a nationwide register-based study. Eur J Clin Pharmacol. 2008;64(11):1119–24. https://doi.org/10.1007/s00228-008-0541-3.
16. van Melle JP, et al. Treatment of depression in acute coronary syndromes with selective serotonin reuptake inhibitors. Drugs. 2006;66(16):2095–107.
17. van Melle JP, et al. Beta-blockers and depression after myocardial infarction: a multicenter prospective study. J Am Coll Cardiol. 2006;48(11):2209–14. https://doi.org/10.1016/j.jacc.2006.07.056.
18. Kessing LV, et al. Antihypertensive drugs and risk of depression: a nationwide population-based study. Hypertension. 2020;76(4):1263–79. https://doi.org/10.1161/HYPERTENSIONAHA.120.15605.
19. Riemer TG, et al. Do beta-Blockers Cause Depression? Systematic review and meta-analysis of psychiatric adverse events during beta-blocker therapy. Hypertension. 2021;77(5):1539–48. https://doi.org/10.1161/HYPERTENSIONAHA.120.16590.
20. Herrett E, et al. Data resource profile: clinical practice research datalink (CPRD). Int J Epidemiol. 2015;44(3):827–36. https://doi.org/10.1093/ije/dyv098.
21. Wolf A, et al. Data resource profile: clinical practice research datalink (CPRD) Aurum. Int J Epidemiol. 2019;48(6):1740–1740g. https://doi.org/10.1093/ije/dyz034.
22. Herrett E, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4–14. https://doi.org/10.1111/j.1365-2125.2009.03537.x.
23. John A, et al. Case-finding for common mental disorders of anxiety and depression in primary care: an external validation of routinely collected data. BMC Med Inform Decis Mak. 2016;16:35. https://doi.org/10.1186/s12911-016-0274-7.
24. Patten SB. Propranolol and depression: evidence from the antihypertensive trials. Can J Psychiatry. 1990;35(3):257–9.
25. Gleiter CH, Deckert J. Adverse CNS-effects of beta-adrenoceptor blockers. Pharmacopsychiatry. 1996;29(6):201–11. https://doi.org/10.1055/s-2007-979572.
26. Ko DT, et al. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA. 2002;288(3):351–7.
27. Luijendijk HJ, et al. Beta-blockers and the risk of incident depression in the elderly. J Clin Psychopharmacol. 2011;31(1):45–50. https://doi.org/10.1097/JCP.0b013e31820482c4.
28. Thapar A, et al. Depression in adolescence. Lancet. 2012;379(9820):1056–67. https://doi.org/10.1016/S0140-6736(11)60871-4.