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Impact of beta-blockers on mortality and cardiovascular disease outcomes in patients with obstructive sleep apnoea: a population-based cohort study in target trial emulation framework



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Summary

Background There is no real-world evidence regarding the association between beta-blocker use and mortality or cardiovascular outcomes in patients with obstructive sleep apnoea (OSA). We aimed to investigate the impact of beta-blocker use on all-cause mortality and cardiovascular diseases (CVDs) in patients with OSA.

Methods We conducted a target trial emulation study of 37,581 patients with newly diagnosed OSA from 1st January 2000 to 30th November 2021 using the IMRD-UK database (formerly known as the THIN database). We compared the treatment strategies of initiating beta-blocker treatment within one year versus non-beta-blocker treatment through the method of clone-censor-weight. Covariates, including patients' demographics, lifestyle, comorbidities, and recent medications, were measured and controlled. Patients were followed up for all-cause mortality or composite CVD outcomes (angina, myocardial infarction, stroke/transient ischaemic attack, heart failure, or atrial fibrillation). We estimated the five-year absolute risks, risk differences and risk ratio with 95% confidence intervals (CIs) with standardised, weighted pooled logistic regression, which is a discrete-time hazard model for survival analysis. Several sensitivity analyses were performed, including multiple imputation addressing the missing data.

Findings The median follow-up time was 4.1 (interquartile range, 1.9–7.8) years. The five-year absolute risk of all-cause mortality and CVD outcomes were 4.9% (95% CI, 3.8–6.0) and 13.0% (95% CI, 11.4–15.0) among beta-blocker users, and 4.0% (95% CI, 3.8–4.2) and 9.4% (95% CI, 9.1–9.7) among non-beta-blocker users, respectively. The five-year absolute risk difference and risk ratio between the two groups for all-cause mortality and CVD outcomes were 0.9% (95% CI, –0.2 to 2.1) and 1.22 (95% CI, 0.96–1.54), and 3.5% (95% CI, 2.1–5.5) and 1.37 (95% CI, 1.22–1.62), respectively. Findings were consistent across the sensitivity analyses.

Interpretation Beta-blocker treatment was associated with an increased risk of CVD and a trend for an increased risk of mortality among patients with OSA. Further studies are needed to confirm our findings.

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Keywords: Beta-blocker; Obstructive sleep apnoea; Cohort study; Trial emulation

Research in context

Evidence before this study

We searched PubMed on 15th Mar 2023 using the following search terms without language restriction ((obstructive sleep apnoea OR obstructive sleep apnea) AND (beta blocker)). 83 publications were screened. Concerns about the safety of beta-blockers in obstructive sleep apnoea (OSA) were initially suggested in case reports. Early small-scale studies have investigated the effect of beta-blockers on blood pressure and heart rate. There is no large epidemiological evidence regarding the association between beta-blockers and mortality or cardiovascular outcomes in patients with OSA.

Added value of this study

To our knowledge, we have conducted the first study investigating the effects of beta-blockers on mortality and

cardiovascular outcomes in patients with OSA. We applied a target trial emulation approach to minimise bias in the study design. We found that beta-blocker treatment in patients with OSA was associated with an increased risk of cardiovascular outcomes and a trend for an increased risk of mortality.

Implications of all the available evidence

This study supports the concerns that beta-blockers may not be safe or effective in patients with OSA. Therefore, beta-blocker treatment in patients with OSA may need to be closely monitored. Further studies are needed to confirm our findings in different populations and settings.

Introduction

Obstructive sleep apnoea (OSA) is becoming increasingly common. It is estimated that a total of 1.5 million adults in the UK suffer from OSA, and the majority of cases remain undiagnosed and untreated.¹ OSA can cause obstructions in the upper airways by temporarily relaxing the muscles that support the throat, tongue, and soft palate, which can disrupt normal breathing during sleep and lead to episodes of hypoxia with varying frequencies from more than once per minute to once every 12 min.² OSA has been linked to several severe health conditions including systemic hypertension,³ diabetes mellitus,⁴ ischaemic heart disease,⁵ and stroke.⁶ Notably, OSA is associated with both ventricular arrhythmias and bradyarrhythmias which could be driven by sympathetic and parasympathetic over-activity, respectively.⁷ These arrhythmias may explain why the risk of myocardial infarctions (MIs) and sudden cardiac death peak during the night in patients with OSA.⁵

As OSA is usually comorbid with many cardiovascular diseases for which beta-blockers are indicated, beta-blocker use is very common in patients with OSA and may serve as an effective therapy for sympathetically mediated tachyarrhythmias.⁸ It was reported that 35% of patients with both hypertension and OSA use beta-blockers and over 80% of patients with AF and OSA used beta-blockers.^{9–11} A number of studies found that beta-blocker is a favourable drug class for better blood pressure control in patients with OSA and hypertension.^{12–14} However, beta-blockers may have the opposite effect in bradyarrhythmias, converting bradycardia to ventricular asystole.¹⁵ There could be a real prospect that the presence of OSA could enhance the likelihood that beta-blockers will precipitate ventricular asystole and sudden death in such patients. On the other

hand, beta-blockers, especially lipophilic ones, are associated with nightmares because of the impact of drugs on the central nervous system and nightmares are linked to heart disease.¹⁶ It is key to understand how effective and safe beta-blockers are among patients with OSA.

Currently, there is a lack of evidence about the effects of beta-blocker treatment on all-cause mortality and cardiovascular disease (CVD) outcomes among patients with OSA. Therefore, this study aimed to investigate whether the use of beta-blockers is harmful or beneficial to patients with OSA.

Methods

Data source

We used the IQVIA Medical Research Data (IMRD-UK; formerly known as the THIN database) for this study. The IMRD-UK is a nationwide database of primary care records in the UK that contains around 6% of the total UK population in 2015. A previous study in 2011 demonstrated the validity of the database for pharmacoepidemiologic studies and its generalisability to the UK population.¹⁷ The IMRD-UK includes data on demographic information, lifestyle information (including smoking and alcohol consumption), medical diagnosis and procedures (recorded in Read codes), and prescribing information. This study was approved by the IMRD Scientific Review Committee (22SRC041).

Study design and eligibility criteria

We conducted a population-based cohort study by applying the target trial emulation framework (i.e., an observational study emulating a pragmatic clinical trial),¹⁸ with the clone-censor-weight approach,

comparing the impact of beta-blockers on mortality and cardiovascular outcomes in patients with OSA. The specification and emulation of the target trial are presented in [Supplementary Table S1](#).

Patients aged >18 years who had a diagnosis of OSA in the medical records between 1st January 2000 and 30th November 2021 were included. Read codes were used to identify patients with OSA. Only patients who were in the “up-to-standard” general practices, with data quality standards predefined by IMRD-UK, were included in the study. The baseline (T_0) was defined as the date of the first diagnosis of OSA during the study period. We excluded patients who had less than one year of record history with the current GP practice, and who used beta-blockers within 180 days before the first OSA diagnosis. All patients were followed up from baseline until an occurrence of the outcomes, transfer out of the current practice, end of data collection, or administrative end of the study period (30th November 2021), whichever occurred first. A diagram illustrating key aspects of the study design, including treatment definition, covariate definition, exclusion and observation period can be found in [Supplementary Figure S1](#).

Treatment strategies

We compared the treatment strategies of initiating oral beta-blocker treatment to not starting beta-blocker treatment in OSA patients. Initiation of beta-blocker treatment was defined as receiving a beta-blocker treatment at any dose within 12 months (i.e., a grace period) after the first record of the OSA diagnosis. Patients who did not receive a beta-blocker during the grace period were considered non-users of beta-blocker treatment.

Study outcomes

The study outcomes were all-cause mortality or a diagnosis of CVD, which was defined as a composite event of angina, MI, stroke/transient ischaemic attack (TIA), heart failure (HF), or atrial fibrillation (AF).

Covariates

Covariates included age, sex, smoking status (current smoker, ex-smoker, non-smoker), alcohol consumption (current drinker, non-drinker, and ex-drinker), body mass index (BMI) in categories (underweight— <18.5 kg/m², normal weight— 18.5 to 24.9 kg/m², overweight— 25 to 29.9 kg/m², and obese— ≥ 30 kg/m²), socioeconomic status measured as Townsend score, other medical conditions, recent positive airway pressure (PAP) therapy (within 180 days before T_0), and recent drug prescriptions (within 180 days before T_0). Other medical conditions included a history of systemic hypertension, dyslipidaemia, MI, angina, HF, stroke/TIA, AF, cancer, chronic kidney disease, diabetes mellitus, bronchial asthma, and chronic obstructive pulmonary disease (COPD). Disease history was defined as a record of disease at any time before the T_0 point using

the relevant read codes. We used the measures the closest to the baseline data for smoking status, alcohol consumption, and BMI. Individuals with missing data on smoking status, alcohol consumption, BMI and Townsend score were reported as a separate data category. All diagnoses and PAP therapy were identified by using the read code lists from the CALIBER platform.¹⁹ Recent prescriptions (within 180 days before T_0) included antiplatelet medications, antidiabetic medications, non-steroidal anti-inflammatory drugs (NSAIDs), calcium-channel blockers (CCBs), diuretics, lipid-lowering medications, and renin-angiotensin system inhibitors (RASIs), which were identified by using Multilex drug codes. The calendar year of study entry (stratified in 2000–2006, 2007–2013, and 2014–2021) was described among patient cohorts.

Statistical analysis

Emulation of the target trial

To emulate a target trial, we applied cloning, censoring, and weighting^{18,20} approach with a grace period of 12 months to screen for treatment initiation ([Supplementary Table S1](#)). We created a dataset with two copies of each eligible individual (i.e., cloning) and assigned each of the replicates to one of the treatment strategies at the start of follow-up (T_0). Thereafter, at monthly intervals, we assessed whether replicates adhered to their assigned treatment strategy; replicates were censored if and when their actual treatment deviated from their assigned treatment strategy, thereby ensuring that replicates followed their assigned strategy. That is, if a replicate was assigned to start beta-blocker treatment, but did not receive a prescription by the end of 12 months, they would be censored at that point. Conversely, if a replicate is assigned to no beta-blocker treatment, but initiated beta-blockers at any time during the follow-up, they would be censored at that point. To adjust for the potential selection bias induced by this censoring, each individual received a time-varying inverse probability weight. The denominator of the weights was the probability that a replicate remained on the assigned treatment strategy conditional on baseline characteristics. The weights created two pseudo-populations in which treatment initiation was independent of measured prognostic factors. We estimated the time-varying weights by fitting a pooled logistic model for the monthly probability of remaining uncensored, including variables for time (in its linear and quadratic terms) and the baseline covariates as mentioned. To avoid undue influence of outliers, weights were truncated at the 99.5th percentile. Further details of the clone-censor-weight approach are available in [Supplementary Method S1](#).

We estimated the effect of beta-blockers on all-cause mortality and CVD outcomes using standardised, weighted pooled logistic regression, including an indicator for treatment strategy, time (in its linear and quadratic terms), and their interactions to allow for non-

proportional hazards. Pooled logistic regression is a discrete-time hazard model that is commonly used in causal survival analysis. We use the pooled logistic regression model to estimate the probability of outcome occurrence during each follow-up time interval, and the overall cumulative probability of outcome over the entire follow-up time.²¹ The doubly robust estimate was computed by adjusting for the inverse probability weights and all measured baseline covariates in the outcome model. The predicted probabilities from this model were used to estimate the adjusted predicted probability of the outcomes under each treatment strategy and produce standardised, weighted survival probability curves. We estimated the five-year absolute risks, risk differences, and risk ratios with pointwise 95% confidence intervals (CIs) using a non-parametric bootstrap of 300 samples. We also approximated hazard ratios (HRs) from a Cox regression using odds ratios from the pooled logistic regression and 95% CIs with the robust variance estimator, given that the outcome is rare during each follow-up interval.²²

Baseline characteristics with the information before and after weighting were presented as median (IQR) for continuous variables and as numbers (%) for categorical variables. Standardised mean difference (SMD) was used to evaluate the difference in patient characteristics between two treatment groups before and after weighting. A SMD of <0.1 is considered of good balance between the treatment groups. Findings were considered to be statistically significant when the 95% confidence intervals for risk on a relative scale did not cross 1 or when the 95% confidence interval for risk difference on an absolute scale did not cross zero.

We also performed several sensitivity analyses to test the robustness and consistency of our results. Firstly, we shortened the grace period from 12 months to 6 months, which reduced the number of beta-blocker initiators and also the patient-time overlaps between the two treatment groups. Secondly, we compared the results using untruncated weights. Thirdly, by assuming the data are missing at random, we used multiple imputation with chained equation method to deal with the missing data at baseline such as smoking status, alcohol intake, and BMI. The multiple imputation models included all variables (beta-blocker use status, all covariates, GP practice, and outcome status) and generated 15 imputed datasets. Separate models were fit for the treatment and no treatment groups. The inverse probability of weights and effect estimates were calculated in each imputed dataset and combined using Rubin's rules to obtain the overall estimates. Fourthly, we stratified the analysis based on the lipophilicity of the beta-blocker treatment (classifications in [Supplementary Methods S2](#)). Fifthly, we performed subgroup analyses by age (below 65 years versus 65 years or above), sex, presence of diabetes mellitus, and presence of a history of CVD.

Sixthly, we stratified by the calendar year of cohort entry to explore heterogeneity in treatment effect over time. All statistical analyses were carried out using SAS (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 68,777 patients with newly diagnosed OSA were identified from the database during the study period. Of these, 37,581 patients met the eligibility criteria and were included in the analysis. The eligible patients were duplicated and assigned to one of the two treatment strategies ([Fig. 1](#)). The median follow-up time was 4.1 (IQR, 1.9–7.8) years for all-cause mortality and 3.8 (IQR, 1.7–7.3) years for the composite CVD outcome. Among the included patients, 1,236 (3.3%) patients initiated beta-blocker treatment and 36,345 (96.7%) patients did not over a 12-month grace period following the OSA diagnosis. The pattern of beta-blocker treatment initiation over the grace period is presented in [Supplementary Table S2](#). After censoring due to treatment deviation over the grace period, 1129 beta-blocker initiators and 31,868 non-beta-blocker initiators remained in the cohort, and the other 4,584 patients experienced outcomes or were administratively censored during the grace period. [Table 1](#) shows the characteristics of the patients before and after censoring over the grace period. The mean age at baseline was 51.6 years (SD, 12.5) and the mean BMI was 30.7 kg/m² (SD, 7.1) among patients with a numerical value of the BMI (n = 34,520). Patients who initiated beta-blockers during the grace period tended to be older at baseline and had more baseline CVDs. After weighting, there was a good balance for all covariates at the end of the grace period between the two treatment groups ([Supplementary Table S3](#)). Distributions of the inverse probability weights are summarised in [Supplementary Table S4](#). Truncation at the 99.5th percentile did not change the overall distribution of the weight or the covariate balance.

There were 398 and 1733 cases of all-cause mortality in the treatment strategies of beta-blocker treatment and non-beta-blocker treatment groups, respectively. The standardised, weighted 5-year absolute risk was 4.9% (95% CI, 3.8–6.0) among beta-blocker users and 4.0% (95% CI, 3.8–4.2) among non-beta-blocker users. The was a small increase in absolute risk difference of 0.9% (95% CI, –0.2 to 2.1) and risk ratio of 1.22 (95% CI, 0.96–1.54), albeit being statistically non-significant. The approximated HR was 1.21 (95% CI, 0.96–1.51), which was highly consistent with the risk ratio ([Table 2](#), [Fig. 2A](#)).

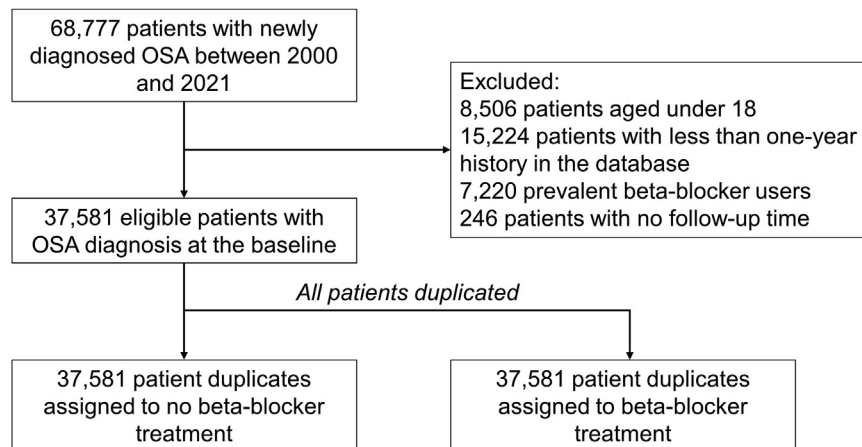


Fig. 1: Process of patient cohort selection.

There were 1252 and 3670 cases of composite CVD events among the beta-blocker treatment and non-beta-blocker treatment groups, respectively. The standardised, weighted five-year absolute risk for composite CVD was 13.0% (95% CI, 11.4–15.0) for beta-blocker treatment group and 9.4% (95% CI, 9.1–9.7) for non-beta-blocker treatment group. Beta-blocker treatment was associated with a higher risk for CVD outcomes with a five-year absolute risk difference of 3.5% (95% CI, 2.1–5.5) and risk ratio of 1.37 (95% CI, 1.22–1.62). The approximated HR was 1.35 (95% CI, 1.17–1.56) (Table 2, Fig. 2B). Secondary analysis of the individual CVD outcomes showed that beta-blocker treatment was associated with an increased risk of angina with a 5-year risk difference of 2.1% (95% CI, 1.1–3.4) and risk ratio of 2.11 (95% CI, 1.55–2.82). We also observed an increased risk of MI, HF, AF or stroke/TIA among beta-blocker users when compared to non-blocker users. However, it did not reach statistical significance (Supplementary Table S5, Supplementary Figure S2A–E).

All results from the sensitivity analyses and subgroup analyses are summarised in Supplementary Figures S3 and S4. When we changed the grace period from 12 months to six months, there were 701 patients who initiated beta-blocker treatment and remained in the cohort after the grace period. The characteristics of the patients after censoring due to treatment deviation over the grace period are presented in Supplementary Table S6; all measured characteristics were balanced after weighting. Beta-blocker treatment initiated within six months was associated with higher risks of composite CVD outcomes (five-year absolute risk difference, 3.5%; 95% CI, 1.8–5.8) and all-cause mortality (five-year absolute risk difference, 1.7%; 95% CI, 0.3–3.5) (Supplementary Table S7, Supplementary Figure S5A and B), which are materially the same as the results of the main analysis. Results on individual

CVDs are also consistent with those of the main analysis (Supplementary Table S8). Analyses with untruncated weights and multiple imputation showed consistent results to the main analysis. When the analysis was stratified by the lipophilicity of the beta-blockers, there were 1005 patients initiated lipophilic beta-blockers and 231 patients initiated hydrophilic beta-blockers within 12 months. Both types of beta-blockers were associated with similar risks of CVDs. Lipophilic beta-blockers, but not hydrophilic ones, may be associated with an increased risk of all-cause mortality. Other stratified analyses by patients' baseline age, sex, prior CVD, diabetes mellitus status, and calendar year did not find significant interactions between patient subgroups.

Discussion

In this target trial emulation of 37,581 newly diagnosed OSA patients, we found that compared to those who did not take beta-blockers, those who used beta-blockers had a 37% higher risk of CVDs. Beta-blocker therapy was also associated with a trend of increased risk of all-cause mortality, but this did not reach statistical significance.

Comparison of beta-blocker use with existing studies

Few studies have investigated the use of beta-blockers among OSA patients. However, no other study has investigated the long-term cardiovascular mortality effects of beta-blockers in treating patients with OSA. A number of studies have reported that beta-blockers are effective in controlling blood pressure in patients with OSA.^{12–14} Another two recent studies reported that beta-blockers were not associated with deteriorating nocturnal bradyarrhythmias among OSA patients.^{10,23} However, these studies are limited by their relatively small sample size and short follow-up which may explain the non-significant findings. Severe iatrogenic

	All patients at baseline (n = 37,581)	Beta-blocker users after the grace period (n = 1,129) ^a	Beta-blocker non-users after the grace period (n = 31,868) ^a
Age (years) (SD)	51.6 (12.5)	54.0 (12.3)	51.5 (12.2)
Male sex (%)	27,137 (72.2)	829 (73.4)	23,161 (72.7)
Calendar year (%)			
2000–2006	7473 (19.9)	268 (23.7)	6853 (21.5)
2007–2013	15,681 (41.7)	448 (39.7)	14,176 (44.5)
2014–2021	14,466 (38.5)	413 (36.6)	10,839 (34.0)
BMI (kg/m²) (%)			
Underweight (<18.5)	159 (0.4)	4 (0.4)	129 (0.4)
Normal weight (18.5–24.9)	3144 (8.4)	74 (6.6)	2663 (8.4)
Overweight (25–29.9)	8265 (22.0)	240 (21.3)	7076 (22.2)
Obese (≥ 30)	23,263 (61.9)	744 (65.9)	19,600 (61.5)
Missing	2750 (7.3)	67 (5.9)	2400 (7.5)
Smoking status (%)			
Current smoker	7914 (21.1)	230 (20.4)	6802 (21.3)
Ex-smoker	11,445 (30.5)	393 (34.8)	9627 (30.2)
Non-smoker	17,339 (46.1)	484 (42.9)	14,624 (45.9)
Missing	883 (2.4)	22 (2.0)	815 (2.6)
Alcohol status (%)			
Current drinker	26,629 (70.9)	807 (71.5)	22,640 (71.0)
Ex-drinker	1137 (3.0)	33 (2.9)	926 (2.9)
Non-drinker	5652 (15.0)	174 (15.4)	4702 (14.8)
Missing	4163 (11.1)	1156 (10.2)	3600 (11.3)
Townsend score (%)			
1 (affluent)	7496 (19.9)	230 (20.4)	6439 (20.2)
2	7133 (19.0)	220 (19.5)	6121 (19.2)
3	7575 (20.2)	235 (20.8)	6379 (20.0)
4	6837 (18.2)	196 (17.4)	5829 (18.3)
5 (deprived)	4885 (13.0)	155 (13.7)	4097 (12.9)
Missing	3655 (9.7)	93 (8.2)	3,003 (9.4)
PAP therapy (%)	376 (1.0)	15 (1.3)	322 (1.0)
Comorbidities (%)			
Systemic hypertension	15,993 (42.6)	653 (57.8)	13,437 (42.2)
Dyslipidaemia	14,216 (37.8)	512 (45.4)	11,841 (37.2)
Angina	1219 (3.3)	93 (8.2)	990 (3.1)
MI	596 (1.6)	48 (4.3)	472 (1.5)
Stroke/TIA	1035 (2.8)	45 (4.0)	834 (2.6)
HF	648 (1.7)	55 (4.9)	486 (1.5)
AF	947 (2.5)	84 (7.4)	721 (2.3)
Cancer	1394 (3.7)	55 (4.9)	1113 (3.5)
CKD	1363 (3.6)	66 (5.9)	1101 (3.5)
Diabetes mellitus	4844 (12.9)	199 (17.6)	4042 (12.7)
Bronchial asthma	8113 (21.6)	168 (14.9)	6857 (21.5)
COPD	2056 (5.5)	49 (4.3)	1711 (5.4)
Recent medications (%)			
NSAIDs	5952 (15.8)	204 (18.1)	5131 (16.1)
Antidiabetic agents	4290 (11.4)	165 (14.6)	3569 (11.2)
Antiplatelet agents	4241 (11.3)	206 (18.3)	3574 (11.2)
Lipid-lowering drugs	8845 (23.5)	360 (31.9)	7449 (23.4)
CCBs	5924 (15.8)	257 (22.8)	4880 (15.3)
Diuretics	5938 (15.8)	268 (23.7)	4977 (15.6)
RASIs	9489 (25.3)	290 (25.5)	7981 (25.0)

SMD, standardised mean difference; SD, standard deviation; BMI, body mass index; PAP, positive airway pressure; MI, myocardial infarction; TIA, transient ischaemia attack; HF, heart failure; AF, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NSAID, non-steroidal anti-inflammatory drug; CCB, calcium-channel blocker; RASI, renin-angiotensin system inhibitor. ^aThese numbers do not add up to the total number of patients as some patients experienced study outcomes or administrative censoring over the grace period.

Table 1: Patient characteristics before and after censoring over the 12-month grace period.

Treatment	No. of patients	No. of patient-years	No. of outcomes	5-year absolute risk (%) (95% CI)	5-year risk difference (%) (95% CI)	5-year risk ratio (95% CI)	Hazard ratio (95% CI)
All-cause mortality							
No beta-blocker	37,581	196,142	1733	4.0 (3.8–4.2)	Reference	Reference	Reference
Beta-blocker	37,581	41,576	398	4.9 (3.8–6.0)	0.9 (–0.2 to 2.1)	1.22 (0.96–1.54)	1.21 (0.96–1.51)
Composite CVD							
No beta-blocker	37,581	186,004	3670	9.4 (9.1–9.7)	Reference	Reference	Reference
Beta-blocker	37,581	38,856	1252	13.0 (11.4–15.0)	3.5 (2.1–5.5)	1.37 (1.22–1.62)	1.35 (1.17–1.56)

CI, confidence interval; CVD, cardiovascular disease.

Table 2: Risks of all-cause mortality and CVD between beta-blocker treatment versus no beta-blocker treatment in patients with OSA.

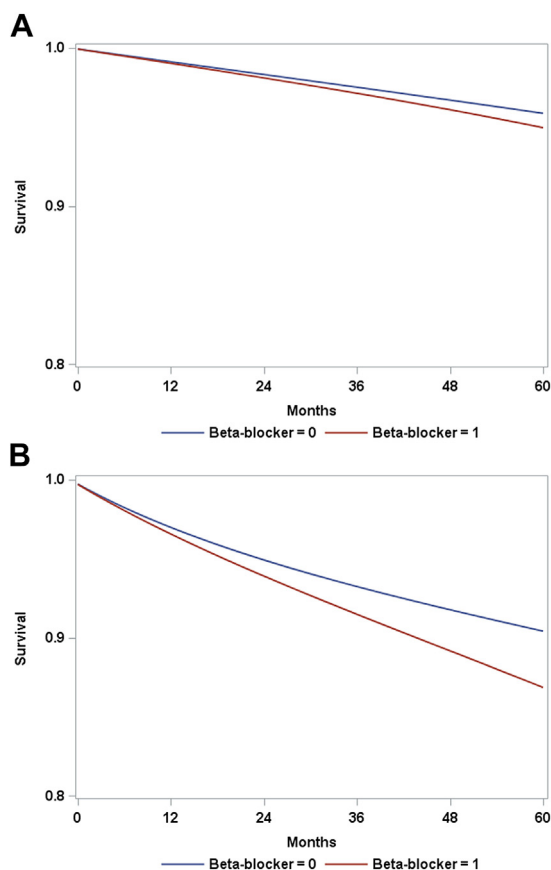


Fig. 2: Standardised, weighted survival probability curves for (A) all-cause mortality, (B) composite CVD with beta-blocker treatment and no beta-blocker treatment after OSA diagnosis.

bradycardia related to the combined use of beta-blocking agents and sodium channel blockers has been reported in a study by Kawabata et al.¹⁵ We observed a 70% elevated risk of angina, aligning with prior reports of bradycardia-induced angina.²⁴

This relationship between beta-blocker treatment and higher CVD or mortality risks is not only limited to OSA populations. There have been previous observations on an increase in the risks for cardiovascular

events and mortality in beta-blocker-treated than non-beta blocker-treated patients with diabetes mellitus.^{25–27} Similarly, beta-blocker was not associated with improved cardiovascular or mortality outcomes in patients without recent MI.^{28–30} However, due to the difference in patient profiles and the unique pathophysiology of OSA, our findings should be interpreted within the context of patients with OSA and caution against their generalisation to other populations.

There are reasons that may lead to the non-prescribing of beta-blockers in our study cohort, such as comorbid COPD or asthma, as the use of beta-blockers in patients with respiratory conditions remains a contentious issue due to potential side effects.³¹ While our analysis indicated a lower rate of beta-blocker prescription among OSA patients with COPD or asthma, a more thorough exploration of these subgroups was constrained by the limited sample sizes. Future research with larger sample sizes is warranted to clarify the impact of these comorbidities on beta-blocker prescription and subsequent cardiovascular outcomes in patients with OSA.

Potential mechanisms of action and future work

The increased risk of CVD events observed in beta-blocker users may be explained by a few reasons. Firstly, the association of beta-blockers with neurohormonal and electrophysiological abnormalities may increase the risk of cardiac ischaemia and fatal arrhythmias³² which leads to cardiovascular events. Secondly, the high prevalence of bradycardia among OSA patients³³ can lead to a higher risk of CVD events such as MI and heart failure as evidenced by the systematic review and meta-analysis study.³⁴ Furthermore, beta-blockers targeting the sympathetic nervous system having negative chronotropic and inotropic effects could slow down the heart rhythm to an unexpected degree.¹⁵ Therefore, beta-blockers may have additional impacts on OSA patients who already have a high prevalence of bradycardia. Several observational studies found the prevalence of AF, atrial arrhythmias, bradycardia, and ventricular arrhythmias to be higher among individuals with OSA.^{33,35,36} In addition, lipophilic beta-blockers,

which have been linked with an increased risk of nightmares, were associated with increased risks of CVD in our study.¹⁶ Conversely, hydrophilic beta-blockers exhibited no association with all-cause mortality or CVD outcomes. However, caution is advised in interpreting these results due to the small sample size of hydrophilic beta-blocker users in our study. Further investigation in diverse populations is warranted to corroborate these findings.

Strengths and limitations

This is the first study estimating the causal effect of beta-blocker treatment on survival and CVD events in patients with OSA. The study is strengthened by a relatively large sample size, long follow-up, and the target trial emulation approach with comprehensive analyses. We have provided the effect estimates in terms of both relative risks and absolute risks to facilitate a clear interpretation of the results. Since beta-blockers are indicated for a wide range of underlying CVDs that commonly co-exist with OSA,^{9–11} it poses difficulty in selecting an appropriate active comparator treatment to reduce the risks of bias in observational data in traditional epidemiological study designs.³⁷ This motivated us to use the trial emulation framework with the clone-censor-weight approach proposed by Hernàn et al.¹⁸ Such an approach has been applied to studies using large electronic health records and successfully reduces the risk of bias.³⁸

Our study has limitations. Firstly, despite the implementation of a target trial emulation framework to reduce bias, the observational nature of the data implies that the treatment assignment was not truly randomised. We cannot rule out the impact of potential residual confounding. Secondly, the one-year grace period in our study may appear to be long. However, this is necessary as beta-blockers are not directly indicated for OSA but for the underlying cardiovascular risks or other conditions associated with the OSA diagnosis. This grace period would be needed for prescribers to screen for the indications for beta-blockers following the OSA diagnosis in these patients. The potential influence of a long grace period in this design is including more “misclassified” patient-time in the treatment group thus biasing the results towards the null. However, the follow-up time of patients in our study was long (median follow-up time was around four years and five-year outcomes were assessed), and the proportion of the grace period relative to total follow-up time in our study is similar to previous studies using the clone-censor-weight design.³⁹ Nevertheless, the results in the sensitivity analysis with a short grace period of six-months yielded consistent findings. Thirdly, some other covariates, such as genetic abnormality or ethnicity, leading to the development and progression of OSA, or other treatments for OSA, were poorly recorded or not available in the database, which may also potentially affect the decision of initiating beta-

blocker treatment and the risks of death or CVDs. Nevertheless, in our subgroup analysis stratified by the recorded baseline CVDs, we found consistent results between the subgroups, which supports the robustness of our results. Certain OTC medications were also not recorded, but most of the study medications are not available from OTC (except for short-term NSAIDs, low-dose aspirin and low-dose statin, which were controlled as covariates), the risk of misclassification bias is low. Fourthly, the study was subjected to limited statistical power for certain subgroups and sensitivity analyses, which prevented us from making definitive interpretations of the subgroup analysis results. Fifthly, our study does not have information on cardiovascular mortality, and the symptoms or severity of OSA. As a result, we are unable to investigate potential differences in cardiovascular mortality among these subgroups. This is a noteworthy consideration because the presence or absence of symptoms such as excessive daytime sleepiness could influence cardiovascular outcomes and treatment approaches. While our database analysis could not delve into this distinction, it represents a critical area for future research. Consequently, our findings should be interpreted in light of this limitation, and it underscores the need for more comprehensive patient data in future investigations. Finally, the OSA diagnosis and PAP therapy are likely under-recorded in the primary care setting in the UK as the condition is formally diagnosed in a specialist secondary or tertiary care settings.⁴⁰ Further prospective studies are needed to confirm the generalisability of our findings.

Conclusions

Our study revealed an association between beta-blocker use and elevated CVD risks and a statistically non-significant trend for increased mortality risk in OSA patients, with clinical ramifications. Given the frequent use of beta-blockers as first-line treatment for arrhythmias and the high prevalence of comorbid bradyarrhythmias in OSA patients, vigilant monitoring of beta-blocker therapy is essential. Healthcare professionals should evaluate the suitability of beta-blocker therapy for OSA patients.

Contributors

AS, ISM, TMM and LW contributed to the study conception. CJ, LW and KM designed the study and contributed to data acquisition. AC and CJ conducted the literature review, performed the data analysis, drafted the first version of the manuscript and contributed equally to this work. AC, CJ, ISM, TMM, ADS, LW and KM contributed to interpretation of data and critically revised the manuscript for important intellectual content. All authors approved the final version. KM is the guarantor.

Data sharing statement

No additional data available.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at <https://www.thelancet.com/for-authors/forms?section=icmje-coi>. ISM reports research grant income to her institution from Menarini, EMA,

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanepc.2023.100715>.

References

- 1 Foundation TBL. *Obstructive Sleep Apnea (OSA)*; 2015. https://www.blf.org.uk/sites/default/files/OSA_Toolkit_2015_BLF_0.pdf.
- 2 Ziegler MG, Milic M, Elayan H. Cardiovascular regulation in obstructive sleep apnea. *Drug Discov Today Dis Models*. 2011;8(4):155–160.
- 3 Pankow W, Nabe B, Lies A, et al. Influence of sleep apnea on 24-hour blood pressure. *Chest*. 1997;112(5):1253–1258.
- 4 Doumit J, Prasad B. Sleep apnea in type 2 diabetes. *Diabetes Spectr*. 2016;29(1):14–19.
- 5 Kuniyoshi FH, Garcia-Touchard A, Gami AS, et al. Day-night variation of acute myocardial infarction in obstructive sleep apnea. *J Am Coll Cardiol*. 2008;52(5):343–346.
- 6 Sharma S, Culebras A. Sleep apnoea and stroke. *Stroke Vasc Neurol*. 2016;1(4):185–191.
- 7 Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome. *Am J Med*. 1982;73(3):317–321.
- 8 Grandi E, Ripplinger CM. Antiarrhythmic mechanisms of beta blocker therapy. *Pharmacol Res*. 2019;146:104274.
- 9 Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail*. 2007;9(3):251–257.
- 10 Wolf J, Drozdowski J, Czechowicz K, et al. Effect of beta-blocker therapy on heart rate response in patients with hypertension and newly diagnosed untreated obstructive sleep apnea syndrome. *Int J Cardiol*. 2016;202:67–72.
- 11 Ziegler MG, Milic M, Sun P. Antihypertensive therapy for patients with obstructive sleep apnea. *Curr Opin Nephrol Hypertens*. 2011;20(1):50–55.
- 12 Svedmyr S, Hedner J, Zou D, et al. Superior hypertension control with betablockade in the European Sleep Apnea Database. *J Hypertens*. 2021;39(2):292–301.
- 13 Ou YH, Tan A, Lee CH. Management of hypertension in obstructive sleep apnea. *Am J Prev Cardiol*. 2023;13:100475.
- 14 Kraiczi H, Hedner J, Peker Y, Grote L. Comparison of atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan for anti-hypertensive treatment in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2000;161(5):1423–1428.
- 15 Kawabata M, Yokoyama Y, Sasaki T, et al. Severe iatrogenic bradycardia related to the combined use of beta-blocking agents and sodium channel blockers. *Clin Pharmacol*. 2015;7:29–36.
- 16 Siclari F, Valli K, Arnulf I. Dreams and nightmares in healthy adults and in patients with sleep and neurological disorders. *Lancet Neurol*. 2020;19(10):849–859.
- 17 Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of the Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*. 2011;19(4):251–255.
- 18 Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758–764.
- 19 Phenotypes H. *HDR phenotypes*; 2023. <https://phenotypes.healthdatagateway.org/>. Accessed January 25, 2023.
- 20 Maringe C, Benitez Majano S, Exarchakou A, et al. Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *Int J Epidemiol*. 2020;49(5):1719–1729.
- 21 Hernan MA. The hazards of hazard ratios. *Epidemiology*. 2010;21(1):13–15.
- 22 Green MS, Symons MJ. A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. *J Chronic Dis*. 1983;36(10):715–723.
- 23 Lombardi C, Faini A, Mariani D, Gironi F, Castiglioni P, Parati G. Nocturnal arrhythmias and heart-rate swings in patients with obstructive sleep apnea syndrome treated with beta blockers. *J Am Heart Assoc*. 2020;9(21):e015926.
- 24 Shaheen J, Wanderman A, Tzivoni D. Angina induced by excessive bradycardia. *Clin Cardiol*. 2000;23(6):460–461.
- 25 Malik AH, Shetty S, Kar K, El Accaoui R. Effect of beta-blocker therapy in diabetic patients with stable coronary heart disease: a meta-analysis. *J Geriatr Cardiol*. 2019;16(3):291–297.
- 26 Tsujimoto T, Sugiyama T, Shapiro MF, Noda M, Kajio H. Risk of cardiovascular events in patients with diabetes mellitus on beta-blockers. *Hypertension*. 2017;70(1):103–110.
- 27 Zaccardi F, Nystrup Husemoen LL, Thorsted BL, et al. Selectivity of beta-blockers, cardiovascular and all-cause mortality in people with hypoglycaemia: an observational study. *Nutr Metab Cardiovasc Dis*. 2019;29(5):481–488.
- 28 Bangalore S, Steg G, Deedwania P, et al. beta-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA*. 2012;308(13):1340–1349.
- 29 Ishak D, Aktas S, Lindhagen L, et al. Association of beta-blockers beyond 1 year after myocardial infarction and cardiovascular outcomes. *Heart*. 2023;109:1159.
- 30 Delaney JA, Daskalopoulou SS, Suissa S. Traditional versus marginal structural models to estimate the effectiveness of beta-blocker use on mortality after myocardial infarction. *Pharmacoepidemiol Drug Saf*. 2009;18(1):1–6.
- 31 Baker JG, Wilcox RG. beta-Blockers, heart disease and COPD: current controversies and uncertainties. *Thorax*. 2017;72(3):271–276.
- 32 Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*. 2005;352(12):1206–1214.
- 33 Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea. Characteristics and mechanism. *J Clin Invest*. 1982;69(6):1286–1292.
- 34 Teo YH, Han R, Leong S, et al. Prevalence, types and treatment of bradycardia in obstructive sleep apnea—a systematic review and meta-analysis. *Sleep Med*. 2022;89:104–113.
- 35 Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study. *Am J Respir Crit Care Med*. 2006;173(8):910–916.
- 36 Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Sleep-induced apnea syndrome. Prevalence of cardiac arrhythmias and their reversal after tracheostomy. *Am J Med*. 1977;63(3):348–358.
- 37 Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11(7):437–441.
- 38 Fu EL, Evans M, Carrero JJ, et al. Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. *BMJ*. 2021;375:e066306.
- 39 Trevisan M, Fu EL, Xu Y, et al. Stopping mineralocorticoid receptor antagonists after hyperkalaemia: trial emulation in data from routine care. *Eur J Heart Fail*. 2021;23(10):1698–1707.
- 40 Erridge S, Moussa O, McIntyre C, et al. Obstructive sleep apnea in obese patients: a UK population analysis. *Obes Surg*. 2021;31(5):1986–1993.