Received: 14 September 2022 | Revised: 26 October 2022 | Accepted: 7 December 2022

DOI: 10.1111/jsr.13811

RESEARCH ARTICLE

Hypertension treatment in patients with sleep apnea from the European Sleep Apnea Database (ESADA) cohort – towards precision medicine

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Funding information
Swedish Heart and Lung Foundation, Grant/Award Number: 20210676

Summary

We recruited 5,970 patients with hypertension with obstructive sleep apnea (OSA) on current antihypertensive treatment from the European Sleep Apnea Database (ESADA) cohort. The group was subdivided into those receiving monotherapy ($n = 3,594$) and those receiving dual combined therapy ($n = 2,376$). We studied how major OSA confounders like age, gender, and body mass index as well as the degree of sleep apnea modified office systolic and diastolic blood pressure. Beta-blockers alone or in combination with a diuretic were compared with other antihypertensive drug classes. Monotherapy with beta-blocker was associated with lower systolic blood pressure, particularly in non-obese middle-aged males with hypertension. Conversely, the combination of a beta-blocker and a diuretic was associated with lower systolic and diastolic blood pressure in patients with hypertension with moderate–severe OSA. Systolic blood pressure was better controlled in female patients using this combined treatment. Our cross-sectional data suggest that specific clinical characteristics and type of antihypertensive medication influence the degree of blood pressure control in patients with hypertension with OSA. Controlled trials are warranted.

KEYWORDS
antihypertensive treatment, beta-blocker, blood pressure control, diuretic, hypertension, obstructive sleep apnea

1 | INTRODUCTION

According to recent guidelines, obstructive sleep apnea (OSA) is an established risk factor for arterial hypertension and reduced blood pressure (BP) control (Visseren et al., 2021; Williams et al., 2018). Increased sympathetic activity, vascular endothelial dysfunction and accelerated vascular ageing, all caused by intermittent hypoxia during sleep, have been identified as pathological mechanisms

linking together arterial hypertension and sleep apnea (Ahmad et al., 2017; Del Pinto et al., 2021). Further, untreated sleep apnea is associated with long-term consequences of poorly controlled hypertension, e.g., transient ischaemic attack/stroke (Javaheri et al., 2022), as well as cardiac heart failure according to longitudinal studies (Javaheri et al., 2020; Parati et al., 2016). Adequate BP control is therefore vital in this high-risk group to reduce adverse cardiovascular health outcomes. However, several studies suggest that BP control is particularly poor in patients with OSA, when compared with the general hypertension population (Grote et al., 2000; Martínez-García et al., 2018; Svedmyr et al., 2021; Zota et al., 2018).

In a recent cross-sectional analysis of a Pan-European OSA cohort we identified significantly better BP control in patients treated with beta-blockade (monotherapy) or the combination of beta-blockade and diuretics (dual therapy) independent of confounders (Svedmyr et al., 2021). This finding is supported by several randomised interventional studies in patients with hypertension with OSA (Kasai et al., 2014; Kraiczi et al., 2000; Revol et al., 2020; Salo et al., 1999).

Patients presenting with OSA constitute a heterogenic population with respect to clinical and pathophysiological phenotypes (Bailly et al., 2016; Bailly et al., 2021; Osman et al., 2018; Saaresranta et al., 2016; Zinchuk & Yaggi, 2020). Hypertension development in OSA may also differ in terms of mechanism and susceptibility to BP elevation. However, the evidence supporting an individualised strategy to achieve optimal BP control in patients with OSA is still limited. Therefore, we performed in-depth analysis of our previously published data to identify superior BP control in OSA subpopulations defined by age, gender, body mass index (BMI), and OSA severity.

2 | METHODS

For this cross-sectional analysis we recruited 5,970 patients with hypertension from the European Sleep Apnea Database (ESADA) cohort before starting OSA treatment. The design of the ESADA (Hedner et al., 2011), as well as the studied population has been described elsewhere in detail (Svedmyr et al., 2021). Briefly, patients with hypertension with ongoing antihypertensive treatment at baseline were separately analysed into those receiving monotherapy (n = 3,594) and those receiving dual combined therapy (n = 2,376). The main results on BP levels stratified for antihypertensive drug classes have been published recently (Svedmyr et al., 2021). In the present analysis, we focused on different patient subgroups defined by patient characteristics (age, gender, and BMI) as well as the severity of OSA (mild Apnea–Hypopnea Index (AHI) 5–15, moderate AHI 15–30, and severe AHI ≥30 events/h). Hypertension diagnosis was defined from medical history together with ongoing antihypertensive medication. Office BP was measured according to contemporary recommendations by auscultatory or oscillometric techniques after at least 5 min of rest.

2.1 | Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 27 (IBM Corp., Armonk, NY, USA). Variable values outside the clinically expected range were considered missing values (<1% of data). Missing data on covariates in the main cohort was 6.1% (n = 219) for the monotherapy group and 7.2% (n = 161) in the combined therapy group. Thus, we performed imputation of missing data (BMI, systolic BP [SBP], diastolic BP [DBP], AHI), with the Full Conditional Specification procedure considering site effects (using Proc MI by SAS, version 9.4 [SAS Institute, Cary, NC, USA], Liu & De, 2015). Means and standard deviations (SDs) or percentages are reported for the group differences for clinical data, as well as p values (t test).

We used multiple generalised linear models with estimated means and standard errors (SEs). Each subgroup model was controlled for the remaining three potential confounders of age, BMI, gender, and OSA severity. SBP and DBP constituted the dependent variable. Anthropometric factors and sleep apnea frequency, as well as the type of antihypertensive medication were used as explanatory variables. The controlled estimated mean difference for beta-blocker versus non-beta-blocker in mono- and beta-blocker and diuretic versus other combinations for dual therapy, were subsequently compared using standard t test for age classes, gender, BMI classes, and OSA severity classes. Mean differences and SEs are reported (mean difference and 95% confidence interval [CI] for Figures 1 and 2). A $p < 0.05$ was considered as statistically significant. In sensitivity analysis we excluded patients with uneven distribution of comorbidities between groups.

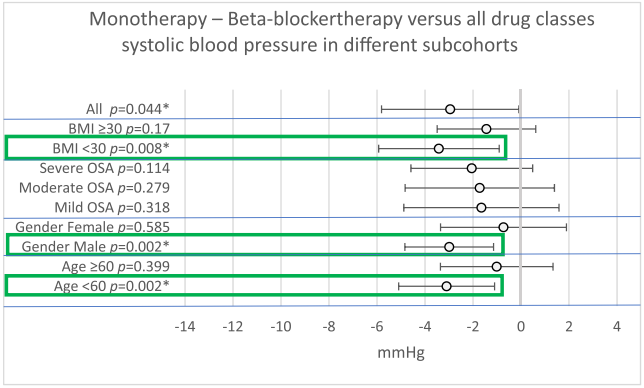
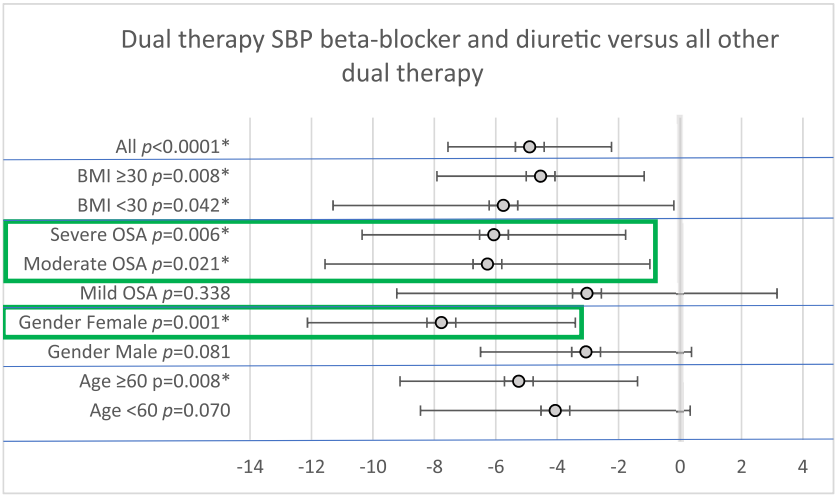


FIGURE 1 Monotherapy. Difference in systolic blood pressure in patients using beta-blocker compared with all other monotherapies. Shown are the difference in the standardised means and 95% confidence intervals, for all patients (all) and for the subgroups defined by BMI, apnea severity, gender, and age. Clinical characteristics which modified BP difference are highlighted. p values are the difference between beta-blocker/other for each subgroup. BMI, body mass index; OSA, obstructive sleep apnea. Mild OSA, Apnea–Hypopnea Index (AHI) 5–15; moderate OSA, AHI 15–30; severe OSA, AHI >30 events/h



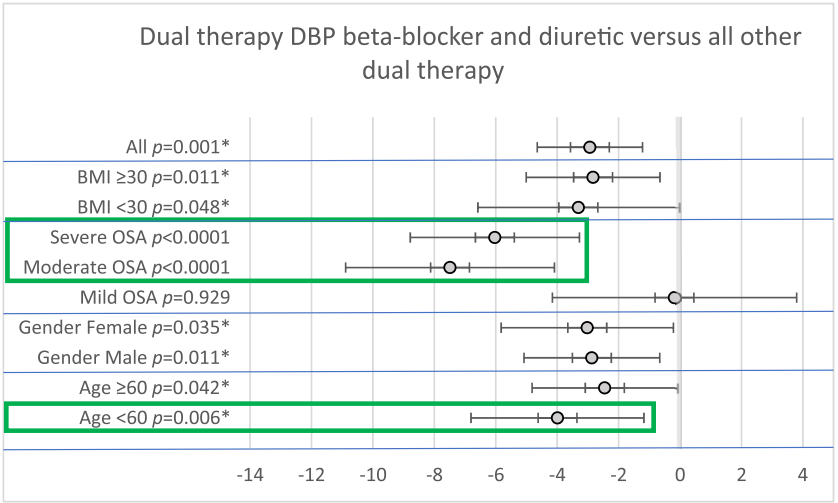


FIGURE 2 (a, b) Dual therapy. Difference in systolic blood pressure (a) and diastolic blood pressure (b) in patients using beta-blocker plus diuretics compared with all other dual therapies. Shown are the difference in the standardised means and 95% confidence intervals, for all patients (all) and for the subgroups defined by BMI, apnea severity, gender, and age. Clinical characteristics that modified BP difference are highlighted. *p* values are the differences between beta-blocker plus diuretic/other for each subgroup. BMI, body mass index; DBP; diastolic blood pressure; OSA, obstructive sleep apnea; SBP, systolic blood pressure. Mild OSA, Apnea–Hypopnea Index (AHI) 5–15; moderate OSA, AHI 15–30; severe OSA, AHI >30 events/h

3 | RESULTS

3.1 | Monotherapy

Patients treated with a beta-blocker ($n = 632$) were slightly less obese and had a slightly lower AHI than those on other drugs ($n = 2,962$) (Table 1). Monotherapy with a beta-blocker, compared to all drug classes, was associated with lower SBP in males, with a mean (SE) difference of −3.0 (0.9) mmHg ($p = 0.002$); in young to middle-aged patients (aged <60 years), with a mean (SE) difference of −3.1 (1.0) mmHg ($p = 0.002$); and in patients with OSA with a BMI of <30 kg/m^2, with a mean (SE) difference of −3.4 (1.3) mmHg ($p = 0.008$; Figure 1). Sleep apnea severity was not associated with BP levels in the beta-blocker-treated subgroup. Further, DBP level did not differ for any of the investigated subgroups.

3.2 | Dual combined therapy

Patients with combination of a beta-blocker and a diuretic ($n = 193$) were slightly older and had a slightly higher proportion of females than those on other antihypertensive combined therapies ($n = 2,183$) (Table 1). For the entire group the combination of beta-blocker and diuretic treatment was associated with lower SBP, at a mean (SE) of −4.9 (1.4) mmHg ($p < 0.0001$), and DBP of −2.9 (0.9) mmHg ($p = 0.001$; Figure 2a,b).

In the subgroup analysis, female gender was associated with a significantly lower SBP (mean [SE] −7.8 [2.2] mmHg, $p = 0.001$) during beta-blocker + diuretic treatment compared with other combined therapies. The difference in males was modest and showed only a statistical trend (mean [SE] −3.1 [1.8] mmHg, $p = 0.081$). Moderate (AHI 15–30 events/h), as well as severe OSA (AHI ≥30 events/h), were associated with a lower SBP, at a mean (SE) of −6.3 (2.7) mmHg ($p = 0.021$) and −6.1 (2.2) mmHg ($p = 0.006$), respectively. There was a stronger association in the older age group (aged ≥60 years, mean [SE] −5.25 [2.0] mmHg, $p = 0.008$; Figure 2a), compared to those aged <60 years. There was a slight advantage in non-obese patients (BMI <30 kg/m^2), but more obese patients on beta-blocker + diuretic treatment also had significantly better SBP than patients with other combinations.

Lower DBP levels were significantly associated with young to middle age patients (aged <60 years, mean [SE] −4.0 [1.4] mmHg, $p = 0.006$), but

TABLE 1 Clinical characteristics of the two cohorts with monotherapy and combined therapy

Antihypertensive monotherapy	Beta-blocker $n = 632$	Other therapies $n = 2,962$	Total $n = 3,594$	p
Anthropometrics and comorbidities				
Age, years, mean (SD)	56.9 (10.4)	57.3 (10.5)	57.2 (10.5)	0.362
BMI, kg/m^2, mean (SD)	31.9 (6.3)	32.9 (6.7)	32.8 (6.7)	<0.0001
Gender male, %	66.0	69.5	68.9	0.079
IHD (%)	14.7	6.6	8.0	<0.0001
Previous stroke or TIA, %	4.1	3.0	3.2	0.170
Cardiac failure, %	0.5	1.5	1.3	0.035
Hyperlipidaemia, %	31.0	31.6	31.5	0.814
Diabetes I or II, %	17.9	21.3	20.7	0.052
Current smoking, %	21.9	20.9	21.1	0.590
Sleep apnea variables, mean (SD)				
AHI	30.3 (24.1)	34.2 (26.8)	33.5 (26.4)	<0.0001
Haemodynamic variables, mean (SD)				
Systolic BP, mmHg	135.9 (17.3)	138.5 (17,7)	138.0 (17.6)	0.001
Diastolic BP, mmHg	83.7 (11.5)	83.6 (11.7)	83.7 (11.6)	0.844
Antihypertensive combined therapy	**Beta-blocker + diuretic $n = 193$**	**Other combinations $n = 2,183$**	**Total $n = 2,376$**	**p**
Anthropometrics and comorbidities				
Age, years, mean (SD)	61.4 (10.3)	59.1 (10.4)	59.3 (10.4)	0.004
BMI, kg/m^2, mean (SD)	33.5 (6.3)	33.5 (6.9)	33.5 (6.8)	0.984
Gender male, %	60.1	71.0	70.1	0.02
IHD, %	22.3	19.3	19.5	0.343
Previous stroke or TIA, %	4.7	3.9	4.0	0.567
Cardiac failure, %	10.9	4.3	4.8	<0.0001
Hyperlipidaemia, %	30.6	32.8	32.6	0.575
Diabetes I or II, %	29.5	27.2	27.4	0.501
Current smoking, %	13.5	18.9	18.5	0.08
Sleep apnea variables, mean (SD)				
AHI, events/h	34.3 (24.9)	33.8 (25.7)	33.9 (25.6)	0.791
Haemodynamic variables, mean (SD)				
Systolic BP, mmHg	134.6 (18.5)	139.2 (18.1)	138.8 (18.2)	0.001
Diastolic BP, mmHg	79.9 (12.4)	83.4 (11.8)	83.2 (11.9)	<0.0001

Abbreviations: AHI, Apnea–Hypopnea Index; BMI, body mass index; BP, blood pressure; IHD, ischaemic heart disease; TIA, transient ischaemic attack.

older patients also had significantly better DBP on the beta-blocker + diuretic combination (mean [SE] −2.8 [1.2] mmHg, $p = 0.042$) and moderate–severe OSA (AHI 15–30 events/h, mean [SE] −7.5 [1.7] mmHg, $p < 0.0001$; AHI ≥30 events/h, mean [SE] −6.0 [1.4] mmHg, $p < 0.0001$; Figure 2b).

3.3 | Sensitivity analysis

Analysis excluding patients with unevenly distributed comorbidities (ischaemic heart disease for monotherapy and cardiac failure and current smoking in dual therapy) as well as investigation of possible confounding by creatinine levels confirmed our results (data not shown).

4 | DISCUSSION

Our study identified OSA patient characteristics where use of beta-blocker treatment alone or in combination with diuretics was associated with significantly better BP when compared with patients using other antihypertensive medication. In particular, we report for the first

time that easily identifiable factors like gender, age, non-obesity, and sleep apnea intensity are associated with lower BP in patients with these treatments.

Our findings suggest that beta-blockers have an advantage in younger, not yet treated patients with OSA. One potential explanation includes findings in previous studies showing that the early stages of hypertension development are characterised by a circulatory state associated with high SBP as a consequence of increased heart rate and cardiac output (Mancia & Grassi, 2014; Palatini & Julius, 2009). It may be speculated that the reduction of heart rate by beta-blockade is a sympatholytic consequence that results in a better effect on BP control in patients with OSA, compared for instance with a compound acting through vasodilatory action. At a later stage of hypertension with OSA comorbidity, arteriosclerosis and hypertension may mediate permanent vascular remodelling, which may be better addressed with drugs acting on other mechanisms such as modulation of the renin–angiotensin system.

For dual therapy, the combination of diuretic treatment and beta-blockade was associated with substantially lower SBP and DBP levels when compared to other, even more frequently used combined therapies such as angiotensin receptor blocker (ARB) and diuretic or ARB and calcium channel blockers (CCB). Mechanism including a reduced cardiac sympathetic activity, reduced blood volume, and direct vasodilatory properties following a drug with diuretic properties may explain why this combined therapy was particularly useful in patients with OSA. Female patients with OSA appeared to benefit in terms of better SBP control following this combined therapy. Some diuretic agents are also known to have mild carbonic anhydrase inhibitory properties, which are known to dampen a high respiratory loop gain, a pathophysiological phenotype reported in a subgroup of patients with OSA (Eckert et al., 2013). This mechanism may have a stronger impact on female compared to male patients. It has been shown that diuretics reduce the severity of OSA by reducing rostral fluid shift during sleep but to date it is unknown if this effect has gender differences that could partly explain our findings. In post-menopausal women with hypertension diuretics have been shown to result in better BP control than other monotherapies (Wassertheil-Smoller et al., 2000); however, a separate analysis on diuretics in monotherapy did not show any clear advantage in our population.

Some strengths of our study may include the following: this is one of the largest studies to date on this topic. The statistical power in the analysis allowed us to perform the subgroup analysis in the study. In addition, the study design of a multicentre and multinational study cohort increases the generalisability of our findings. All patients followed a pre-defined study protocol, which increases the validity of data. The information about medication from 20 different European countries was collected according to Anatomical Therapeutic Chemical (ATC) code in order to avoid misclassification. Statistical analysis used the most powerful confounders for OSA. The sensitivity analyses of other confounders confirmed our results. We used imputation of missing data to maximise the statistical power in our analysis. On the other hand, a number of limitations are also recognised. First, the cross-sectional study design does not allow any firm statement on the causal relation between hypertension control and medication use and we were not able to examine changes in BP from baseline or investigate treatment duration of the antihypertensive drugs. Second, BP assessments did not include 24-h BP measurement as the 'gold standard' and this, together with a potential between-centre variability weakens the exactness of our BP values. However, we identified highly significant differences in BP despite this potential risk of imprecise BP assessment. In fact, the true differences may be even higher, especially during sleep. Third, despite multiple confounder adjustments, referral bias to the ESADA and confounders not addressed in this study may explain part of the observed findings. Fourth, we recognise that some groups contain small numbers of patients compared to the full cohort, especially for the beta-blocker + diuretic treatment. Nevertheless, comparisons in these groups were significant. Therefore, our study may serve as a trigger for future interventional studies of the subject matter. Finally, we performed a hypothesis-driven post hoc analysis of our data, which may have increased the risk of by-chance findings. Therefore, our data cannot be used for clinical practice recommendations.

4.1 | Clinical implications and future studies

The readily available characteristics applied in our analysis may be used in prospective studies to develop precision medicine-based algorithms for improved BP control in patients with hypertension with OSA. The current European recommendations for hypertension treatment (Williams et al., 2018) stress that BP control is still generally poor in patients with OSA. The most recent treatment recommendations state that the start of treatment should be performed with a combined therapy in newly detected arterial hypertension. If BP remains uncontrolled, additional antihypertensive drugs should be added. However, our results in the previous study, suggest that the hypertension and OSA overlap population may be less suitable for standard antihypertensive combinations (mainly ARB + CCB or ARB + diuretic) and that poorly compliant as well as unsuccessfully treated patients with OSA with hypertension would benefit from a beta-blocker and diuretic combined treatment. These findings need to be investigated further as prospective data are needed. Studies evaluating the impact of combined continuous positive airway pressure treatment and antihypertensive treatment on BP control are ongoing.

5 | CONCLUSIONS

We identified subtypes of untreated patients with OSA with hypertension with better BP control. In monotherapy, beta-blockers were more successful in controlling SBP in non-obese middle-aged males with hypertension. For dual therapy, the combination of beta-blocker and diuretic treatment was associated with favourable BP control in patients with moderate–severe OSA. SBP was better controlled in female patients using this combined treatment.

AUTHOR CONTRIBUTIONS

Sven Svedmyr, corresponding author, planning, data management, analysis and writing of the first manuscript draft. **Jan Hedner**, data collection, planning and writing. **Maria Rosaria Bonsignore**, data collection, discussion and reviewing. **Carolina Lombardi**, data collection, discussion and reviewing. **Gianfranco Parati**, data collection, discussion and reviewing. **Ondrej Ludka**, data collection, discussion and reviewing. **Ding Zou**, data collection, data management, analysis, discussion and reviewing. **Ludger Grote**, data collection, planning, analysis, writing. All authors approved the final submission.

ACKNOWLEDGMENTS

Collaborators in the ESADA project (E-supplement).

CONFLICT OF INTEREST

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Svedmyr, S., Hedner, J., Bonsignore, M. R., Lombardi, C., Parati, G., Ludka, O., Zou, D., Grote, L., & on behalf of the European Sleep Apnea Database (ESADA) study group (full collaborator list in E-supplement) (2022). Hypertension treatment in patients with sleep apnea from the European Sleep Apnea Database (ESADA) cohort – towards precision medicine. *Journal of Sleep Research*, e13811. https://doi.org/10.1111/jsr.13811