ESC European Society of Cardiology

European Heart Journal Open (2023) **3**, 1–10
https://doi.org/10.1093/ehjopen/oead109

ORIGINAL ARTICLE
Hypertension

Blood pressure control in hypertensive sleep apnoea patients of the European Sleep Apnea Database cohort - effects of positive airway pressure and antihypertensive medication

Sven Svedmyr [1,2,*], Jan Hedner [1,2], Sebastien Bailly[3], Francesco Fanfulla[4], Holger Hein[5], Carolina Lombardi[6,7], Ondrej Ludka[8], Stefan Mihaicuta[9], Gianfranco Parati [6,7], Athanasia Pataka [10], Sophia Schiza[11], Sezai Tasbakan [12], Dries Testelmans [13], Ding Zou [1,2], and Ludger Grote [1,2], the European Sleep Apnea Database (ESADA) study group[†]

[1]Department of Sleep Medicine, Sahlgrenska University Hospital, Blå stråket 5, 413 45 Gothenburg, Sweden; [2]Center for Sleep and Vigilance Disorders, Sahlgrenska Academy, Gothenburg University, Medicinaregatan 8B, Box 421, 405 30 Gothenburg, Sweden; [3]Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France; [4]Unità Operativa di Medicina del Sonno, Istituto Scientifico di Pavia IRCCS, Pavia, Italy; [5]Sleep Disorders Center, St.Adolf Stift, Reinbeck, Germany; [6]Cardiology Unit, Sleep Center, IRCCS Istituto Auxologico Italiano, Milan, Italy; [7]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [8]Department of Internal Medicine, University Hospital Brno, Brno, Czech Republic; [9]Center for Research and Innovation in Precision Medicine and Pharmacy, 'Victor Babes' University of Medicine and Pharmacy, Timisoara, Romania; [10]Respiratory Failure Unit, G. Papanikolaou Hospital, Aristotle University of Thessalonikii, Thessalonikii, Greece; [11]Sleep Disorders Unit, Department of Respiratory Medicine, School of Medicine, University of Crete, Crete, Greece; [12]Department of Chest Diseases, Ege University, Izmir, Turkey; and [13]Sleep Disorders Centre, University Hospital Gasthuisberg, Leuven, Belgium

Received 21 April 2023; revised 27 September 2023; accepted 10 October 2023; online publish-ahead-of-print 17 October 2023

Aims

We analysed longitudinal blood pressure (BP) data from hypertensive obstructive sleep apnoea (OSA) patients in the European Sleep Apnea Database cohort. The study investigated the interaction between positive airway pressure (PAP)-induced BP change and antihypertensive treatment (AHT).

Methods and results

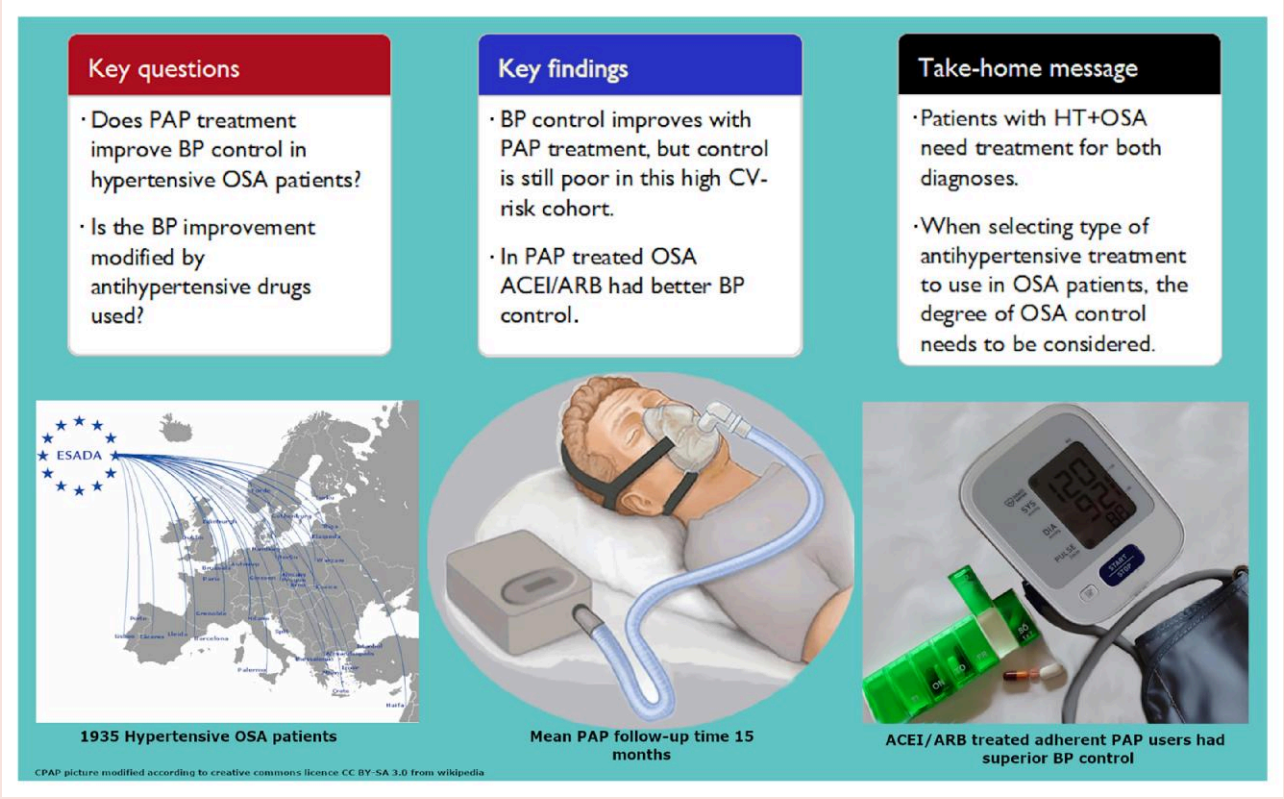
Hypertensive patients with AHT [monotherapy/dual therapy $n = 1283/652$, mean age 59.6 ± 10.7/60.6 ± 10.3 years, body mass index (BMI) 34.2 ± 6.5/34.8 ± 7.0 kg/m^2, apnoea–hypopnoea index 46 ± 25/46 ± 24 n/h, proportion female 29/26%, respectively] started PAP treatment. Office BP at baseline and 2- to 36-month follow-up were assessed. The interaction between AHT drug classes and PAP on BP was quantified and the influences of age, gender, BMI, co-morbidities, BP at baseline, and study site were evaluated. Following PAP treatment (daily usage, 5.6 ± 1.6/5.7 ± 1.9 h/day), systolic BP was reduced by −3.9 ± 15.5/−2.8 ± 17.7 mmHg in mono/dual AHT and diastolic BP by −3.0 ± 9.8/−2.7 ± 10.8 mmHg, respectively, all $P < 0.0001$. Systolic and diastolic BP control was improved following PAP treatment (38/35% to 54/46% and 67/67% to 79/74%, mono/dual AHT, respectively). PAP treatment duration predicted a larger BP improvement in the monotherapy group. Intake of renin–angiotensin blockers [angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)] alone or in any AHT combination was associated with better BP control. The AHT-dependent BP improvement was independent of confounders.

Conclusion

In this pan-European OSA patient cohort, BP control improved following initiation of PAP. Longer PAP treatment duration, was associated with a favourable effect on BP. Our study suggests that ACEI/ARB, alone or in combination with other drug classes, provides a particularly strong reduction of BP and better BP control when combined with PAP in OSA.

* Corresponding author. Tel: +46 31 342 7978, Email: sven.svedmyr@gu.se
† See full collaborator list in the Appendix.

Graphical Abstract



Keywords Hypertension • Obstructive sleep apnoea • Antihypertensive treatment • Precision medicine • ESADA

Introduction

Obstructive sleep apnoea (OSA) and hypertension are common disorders associated with an increased risk of major cardiovascular events (stroke, myocardial infarction, and cardiac failure), and patients with both disorders are common as they share several important risk factors. Longitudinal studies have identified untreated sleep apnoea as a risk factor for adverse long-term consequences including systemic hypertension, poorly controlled hypertension,[1–3] heart failure,[4,5] and transient ischaemic attack/stroke.[6] The proposed pathomechanisms behind the development of hypertension and cardiovascular disease in OSA include increased sympathetic activity,[7–9] vascular endothelial dysfunction, and accelerated vascular ageing,[10] all caused by intermittent hypoxia during sleep[11] and frequent arousals.[12] Positive airway pressure (PAP) treatment of OSA can effectively eliminate the immediate consequences of repetitive apnoeas and can reduce office blood pressure (BP), but only by a modest mean reduction of 2–3 mmHg.[13] This highlights the need for optimized antihypertensive medication in these patients even when treated successfully for OSA with PAP. Indeed, several studies suggest that BP control is particularly poor in hypertensive patients with OSA.[14–16]

We have recently identified superior office BP control in hypertensive OSA patients taking beta-blockade (monotherapy) or the combination of beta-blockade and diuretics (DIU) (dual therapy). OSA was yet untreated in this analysis.[14] Our data have strong support from randomized interventional studies showing a high efficacy of beta-blockade and DIU for BP-reducing capacity in OSA.[17–20] There are also some limited data suggesting that blockade of the renin–angiotensin system (RAS) may have favourable BP-reducing effects in untreated OSA patients.[21–23] However, when clinically significant OSA is identified in hypertensive patients, PAP treatment is the primary choice to improve both quality of life and BP control. It remains unclear if a specific antihypertensive drug class may have a superior influence on BP control in the PAP-treated OSA condition.

In the current analysis, we therefore aimed to quantify changes in BP control after initiation of PAP treatment and especially any modifying effect of different antihypertensive treatments (AHTs). Hypertensive patients with mainly severe OSA were analysed in the large multi-centric European Sleep Apnea Database (ESADA) cohort. We hypothesized that renin–angiotensin blockers [angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)] alone or in combination were associated with better BP control in patients with well-treated OSA.

Methods

The design of the ESADA,[24] as well as the studied population, have been described elsewhere in detail.[14] In brief, unselected adult patients with suspected OSA were recruited into the database from 28 sleep centres in Europe from March 2007 to December 2021. Patient anthropometrics, co-morbidities, and concomitant medication were captured in a standardized manner. For this

longitudinal analysis, we recruited all ($n = 1935$) adult hypertensive OSA patients with current mono- or dual combination AHT and simultaneous PAP treatment in the ESADA cohort. Patients had follow-up data from at least 2 months up to 3 years after the baseline visit. Latest follow-up visit within 3 years was used in case of multiple visits. Oral and written informed consent was obtained from all patients after approval from the local ethics committee at each study site (DNR 386–09, for Gothenburg, Sweden). Patients were divided into those receiving monotherapy ($n = 1283$) and those with dual combination therapy ($n = 652$). Patients receiving three or more antihypertensive drugs ($n = 354$) were excluded from the analysis due to the large number of small groups with different multiple drug combinations. PAP adherence (hours of use/day collected from machine counter) as well as duration of treatment were assessed.

Hypertension diagnosis was determined by positive 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. The mean of the two last measures of BP and heart rate were used in the analysis. All medications were characterized according to the Anatomical Therapeutic Chemical (ATC) classification system. Antihypertensive drug classes were classified as follows: beta-blockers (BBs; ATC code C07), DIU (ATC code C03), renin–angiotensin blockers (ACEI/ARBs; ATC code C09), calcium channel blockers (CCBs; ATC code C08), and centrally acting antihypertensives (CAHs; ATC code C02).

Changes in BP and degree of BP control following PAP treatment were assessed. In case of multiple follow-up visits, the most recent visit with complete BP data was used. We excluded patients with less than 2 months of follow-up time. We computed the percentage of BP under control according to systolic and diastolic cut-off values defined by the ESC/ESH 2018 guidelines[2] both at baseline and follow-up.

Statistical analysis

Statistical analysis was performed in SPSS (version 27, IBM, Armonk, NY, USA). Variable values outside the clinically expected range were considered missing values (<1% of data). Means and standard deviations (SDs) and percentage, as well as *P*-values (*t*-test) are reported for the group differences for clinical data. Unadjusted and adjusted changes of BP following PAP treatment were analysed. For dual therapy, the most frequently used five drug combinations are shown as well as each drug as part of any dual combination.

We used multiple mixed linear models adjusting for major confounders (see Supplementary material online) including gender, age, body mass index (BMI) at follow-up, co-morbidities (cardiac failure, ischaemic heart disease, and diabetes mellitus), follow-up duration, and BP at baseline. The study site was included as a random factor in the final model to adjust for differences in local patient populations, variation in BP assessments, and AHT traditions. Changes in systolic BP (SBP) and diastolic BP (DBP) constituted the dependent variable. Changes in BP control were compared using McNemar's test. *P*-values less than 0.05 were considered statistically significant.

Sensitivity analyses

Separate mixed linear model analyses were performed after excluding patients with any change in AHT medication during follow-up. An increase in antihypertensive medication was observed in 3% of patients for monotherapy. Corresponding changes for dual therapy were a decrease in 3% and an increase of medication in 4% of patients.

Results

Clinical data at baseline

A total of 1935 hypertensive OSA patients were included (mono/dual $n = 1283/652$). Patients with dual therapy had more cardiovascular co-morbidities and were more frequently diabetic when compared with patients receiving monotherapy (*Table 1*). Anthropomorphic data, OSA at screening, and prevalence of hyperlipidaemia and smoking were comparable between the two therapy groups. Baseline SBP was slightly lower in the monotherapy group (*Table 1*).

Table 1 Clinical characteristics of the two cohorts with monotherapy and dual combination therapy

	Monotherapy $n = 1283$	Dual therapy $n = 652$	*P*-value
Anthropometrics and co-morbidities			
Age	59.6 ± 10.7	60.6 ± 10.3	0.047
BMI	34.2 ± 6.5	34.8 ± 7.0	0.083
BMI at follow-up	34.0 ± 6.2	34.4 ± 6.7	0.175
Gender male (%)	71	74	0.164
IHD (%)	7	32	<0.0001
CHF (%)	3	9	<0.0001
TIA/stroke (%)	3	5	0.272
Atrial fibrillation (%)	1	3	0.005
Diabetes (%)	26	33	0.001
Hyperlipidaemia (%)	44	45	0.403
COPD (%)	14	14	0.553
Smokers (%)	25	24	0.631
Sleep apnoea variables			
AHI	45.6 ± 25.0	45.9 ± 24.4	0.754
ODI	42.2 ± 26.7	42.6 ± 26.9	0.756
Mean SaO_2	91.5 ± 3.2	91.1 ± 4.0	0.028
ESS	10.4 ± 5.1	10.0 ± 5.2	0.115
BP and heart rate			
Baseline SBP	135.2 ± 16.0	138.1 ± 16.9	<0.0001
Baseline DBP	80.0 ± 10.9	80.8 ± 11.4	0.102
Baseline heart rate	74.1 ± 11.4	74.8 ± 13.0	0.287
Follow-up SBP	131.3 ± 15.4	135.3 ± 16.7	<0.0001
Follow-up DBP	77.0 ± 10.4	78.1 ± 10.9	0.028
Follow-up heart rate	74.1 ± 10.8	73.6 ± 12.3	0.400
Antihypertensive medication (%)			
BB	12	59	<0.0001
CAH	3	6	0.002
CCB	5	27	<0.0001
DIU	3	29	<0.0001
ACEI/ARB	77	78	0.618
PAP treatment information			
Daily PAP usage (h/night)	5.6 ± 1.6	5.7 ± 1.9	0.467
Treatment duration in months	15.8 ± 10.1	14.9 ± 9.5	0.059

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; AHI, apnoea–hypopnoea index; BB, beta-blocker; BMI, body mass index; BP, blood pressure; CAH, central acting antihypertensives; CCB, calcium channel blockers; CHF, cardiac heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic BP; DIU, diuretics; ESS, Epworth Sleepiness Scale; IHD, ischaemic heart disease; ODI, oxygen desaturation index; PAP, positive airway pressure; SaO_2, oxygen saturation; SBP, systolic BP; TIA, transient ischaemic attack.

Blood pressure change following positive airway pressure treatment: unadjusted analyses

Mean PAP adherence was high and treatment duration was long; both did not differ significantly between the mono- or dual therapy groups (*Table 1*). Following the PAP treatment, SBP was improved by −3.9

± 15.5/−2.8 ± 17.7 mmHg in mono/dual AHT; corresponding changes in DBP were −3.0 ± 9.8/−2.7 ± 10.8 mmHg (*Table 2*, all $P < 0.0001$).

Most patients on monotherapy received ACEI/ARB treatment (77%, *Table 1*). SBP and DBP improved more during PAP (−4.7 ± 14.0 mmHg and −3.3 ± 9.5 mmHg), and BPs were significantly lower in patients treated with ACEI/ARB compared with patients using other drug classes in the unadjusted model (*Table 3*).

The ACEI/ARBs were also the most commonly prescribed medications among dual combination therapy followed by BB, DIU, and CCB (*Table 1*). In the uncontrolled analysis, BB + ACEI/ARB resulted in better reductions of SBP and DBP, and combinations containing ACEI/ARB had a significantly stronger effect on DBP (*Table 3*). When comparing the change of BP from baseline for each drug class as part of any combination, ACEI/ARB, BB, and DIU resulted in a significantly stronger SBP and DBP improvement compared with the remaining drug classes (*Table 3*).

Table 2 Changes in blood pressure and heart rate following positive airway pressure treatment

Unadjusted mean changes in blood pressure and heart rate following PAP treatment				
	Mono	***P*-value**	**Dual**	***P*-value**
Systolic blood pressure (mmHg)	−3.9 ± 15.5	<0.0001*	−2.8 ± 17.7	<0.0001*
Diastolic blood pressure (mmHg)	−3.0 ± 9.8	<0.0001*	−2.7 ± 10.8	<0.0001*
Heart rate (bpm)	−0.1 ± 9.4	0.753	−1.3 ± 11.5	0.013*

bpm, beats per minute; PAP, positive airway pressure. *used to mark statistically significant results.

Independent predictors of blood pressure change following positive airway pressure

PAP adherence was generally good (*Table 1*). Baseline BP was a significant predictor for all observed changes following PAP treatment in the controlled mixed models. In addition, treatment duration was a predictor for BP reduction following PAP in monotherapy ($P < 0.0001$; Supplementary material online, *Table S3*) but not in dual therapy.

With regard to drug classes, a combination therapy including ACEI/ARB provided a significantly stronger SBP improvement (−4.76 ± 1.82, −4.94 ± 2.13, and −6.90 ± 2.29 mmHg (estimate and standard error) for BB + ACEI/ARB, CCB + ACEI/ARB, and DIU + ACEI/ARB, respectively) than those combinations without ACEI/ARB drug (*Table 4*). The change of DBP following PAP was not independently influenced by any specific antihypertensive drug combination (see Supplementary material online, *Table S3*).

Control of hypertension before and after PAP treatment

In monotherapy, SBP control improved with PAP treatment from 38 to 54% ($p < 0.0001$) and improvement was particularly visible in patients treated with ACEI/ARB (*Figure 1A*). Still, in monotherapy, only 57% of the ACEI/ARB-treated patients reached adequate SBP control. In general, DBP control was better (all groups near 80% DBP control) compared with SBP control, particularly when ACEI/ARB, CCB, and BB were used (*Figure 1B*).

Table 3 Unadjusted changes in blood pressure by antihypertensive treatment

	n=	**Baseline SBP**	**ΔSBP with PAP**	***P*-value**	**Baseline DBP**	**ΔDBP with PAP**	***P*-value**
Monotherapy *n* = 1283							
Mean changes in blood pressure with PAP by antihypertensive drug class							
BB	156	136.4 ± 17.3	−1.8 ± 20.1	0.264	81.7 ± 12.0	−2.1 ± 10.7	0.013*
CAH	40	133.6 ± 16.5	−0.9 ± 16.4	0.745	84.0 ± 11.3	−2.8 ± 10.4	0.100
CCB	62	135.2 ± 19.3	−1.6 ± 20.8	0.548	79.0 ± 10.4	−1.8 ± 10.9	0.188
DIU	33	135.8 ± 17.1	0.8 ± 20.6	0.827	80.8 ± 12.5	0.3 ± 10.8	0.873
ACEI/ARB	992	135.0 ± 15.5	−4.7 ± 14.0	<0.0001*	79.5 ± 10.6	−3.3 ± 9.5	<0.0001*
Dual therapy *n* = 652							
Mean changes in blood pressure with PAP by antihypertensive drug class combination and class in dual combination							
BB + CCB	19	138.9 ± 13.8	5.8 ± 18.3	0.181	83.6 ± 12.1	−2.9 ± 16.4	0.452
BB + DIU	29	139.9 ± 19.8	0.2 ± 18.3	0.960	82.2 ± 11.0	−3.9 ± 12.2	0.099
BB + ACEI/ARB	152	137.4 ± 15.5	−3.0 ± 15.6	0.02*	81,1 ± 10.5	−2.0 ± 10.6	0.024*
CCB + ACEI/ARB	55	145.9 ± 19.8	−5.1 ± 22.4	0.096	84.8 ± 10.6	−5.0 ± 10.3	0.001*
DIU + ACEI/ARB	49	137.4 ± 16.8	−4.2 ± 19.2	0.130	84.0 ± 9.4	−4.4 ± 10.2	0.004*
BB	383	136.9 ± 15.9	−2.1 ± 15.7	0.010*	79.3 ± 11.1	−2.0 ± 10.4	<0.0001*
CAH	41	138.4 ± 18.2	−3.0 ± 21.5	0.386	84.2 ± 12.4	−2.0 ± 12.0	0.281
CCB	178	141.2 ± 17.6	−2.6 ± 19.6	0.079	82.6 ± 11.2	−3.5 ± 12.0	<0.0001*
DIU	189	138.0 ± 18.0	−2.7 ± 18.8	0.049*	81.3 ± 12.5	−3.0 ± 11.1	<0.0001*
ACEI/ARB	511	138.0 ± 16.7	−3.5 ± 17.6	<0.0001*	80.9 ± 11.1	2.9 ± 10.5	<0.0001*

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; BB, beta-blocker; BP, blood pressure; CAH, central acting antihypertensives; CCB, calcium channel blockers; DBP, diastolic BP; DIU, diuretics; PAP, positive airway pressure; SBP, systolic BP. *used to mark statistically significant results.

Dual therapy SBP control during PAP treatment improved in all combinations except for BB + DIU. However, the proportion of patients reaching SBP control was still low with only the BB + ACEI/ARB combination providing more than 50% SBP control (*Figure 2A*). The degree of DBP control with PAP treatment increased in all combinations and was proportionally stronger than the SBP control. Combinations including BB led to slightly better DBP control, and the proportion of patients with DBP control was highest in the BB + ACEI/ARB combination group (*Figure 2B*).

Table 4 Multiple mixed linear models

Cardiovascular changes during PAP	Estimate	Standard error	*P*-value
Delta SBP dual $n = 652$			
BB + DIU	−0.162	2.37	0.752
BB + CCB	0.842	2.875	NA
BB + ACEI/ARB*	−4.76	1.82	0.036*
CCB + ACEI/ARB*	−4.94	2.13	0.043*
DIU + ACEI/ARB*	−6.90	2.29	0.010*

Antihypertensive drugs modification of BP change after PAP treatment, for mono- or dual treatment after control for age, BMI at follow-up, gender, IHD, CHF, diabetes, treatment duration, and baseline pressure. Site included as random variable in all models. No significant modification was apparent for monotherapy. For full results, please see Supplementary material online, *Table S3*.
ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blockers; CHF, cardiac heart failure; DIU, diuretics; IHD, ischaemic heart disease; SBP, systolic BP.
**P*-values from comparison with BB + CCB.

Sensitivity analyses excluding patients with any change in AHT medication

In the monotherapy group, a total of 1197 patients had the same medication at follow-up. The corresponding number in the dual therapy group was 529. Analyses in these groups, excluding patients with any change in medication during follow-up, showed similar results (see Supplementary material online, *Tables S1* and *S2*).

Discussion

Our study shows clinically meaningful improvements in BP control following PAP initiation in drug-treated hypertensive OSA patients. Positive airway pressure treatment duration was strongly associated with improved BP in the monotherapy group. The ACEI/ARB treatment, with and without combination with BB, was associated with a superior BP control in this group of hypertensive OSA patients compliant with PAP. Importantly, our data show that BP control in hypertensive patients with OSA is still very poor even in compliant PAP users. Only when PAP treatment is combined with ACEI/ARB treatment, the degree of BP control is comparable with hypertensive non-OSA patients.[25]

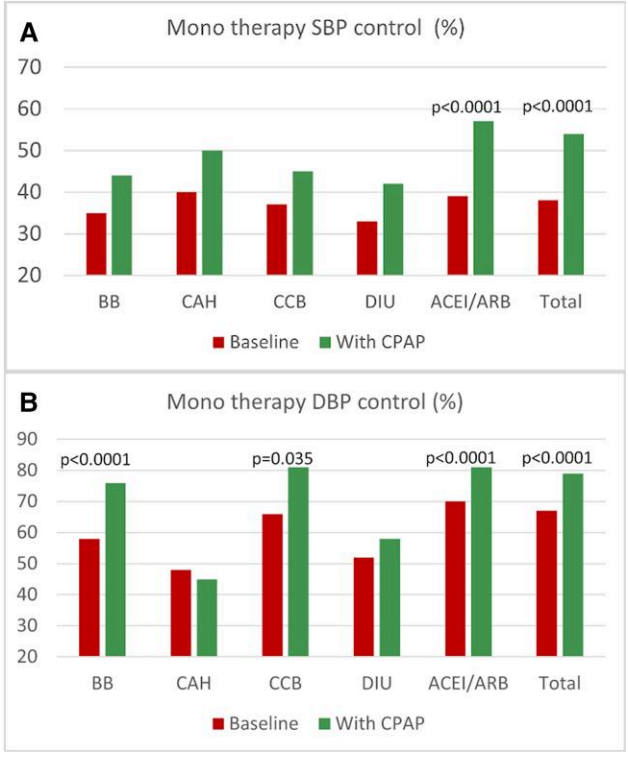


Figure 1 (*A* and *B*) Monotherapy, systolic blood pressure, and diastolic blood pressure control percentage before and after positive airway pressure treatment. ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CAH, central acting antihypertensives; CCB, calcium channel blockers; DBP, diastolic BP; DIU, diuretics; PAP/CPAP, positive airway pressure; SBP, systolic BP.

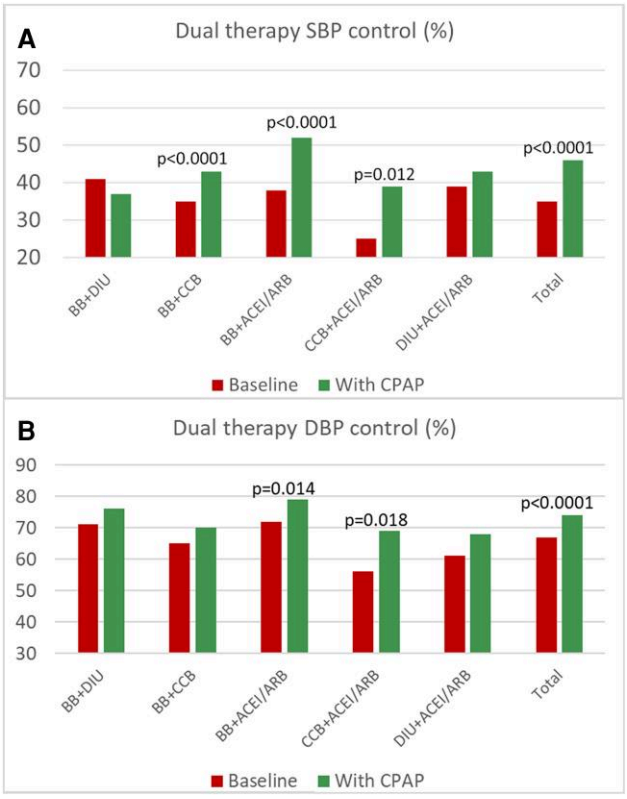


Figure 2 (*A* and *B*) Dual therapy, systolic blood pressure, and diastolic blood pressure control before and after positive airway pressure treatment. ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BB, beta-blocker; BP, blood Pressure; CAH, central acting antihypertensives; CCB, calcium channel blockers; DBP, diastolic BP; DIU, diuretics; PAP/CPAP, positive airway pressure; SBP, systolic BP.

Pathomechanic links between obstructive sleep apnoea and hypertension

Proposed pathomechanisms behind the association between OSA and hypertension include intermittent hypoxia/hypercapnia,[9,26–29] intra-thoracic pressure swings,[30,31] and frequent arousals.[12,32] Chronic activation of the sympathetic nervous system,[9,33–35] upregulation of the RAS,[36–38] and increased oxidative stress all may promote vascular inflammation, endothelial dysfunction,[39] and accelerated development of atherosclerosis.[40] Several of these mechanisms constitute the target in AHT drug treatment that aims to reduce the pressure level and thereby to protect the cardiovascular system from end-organ damage. It is anticipated that the elimination of OSA by PAP substantially changes the hemodynamic conditions. Given the mechanisms of BP elevation in OSA and on the background of these expected changes by PAP, it is expected that some AHT drug classes are associated with more effective BP reductions in treated OSA patients.

Related meta-analyses and studies

One of the most recent comprehensive meta-analyses of randomized trials evaluating the BP-reducing effects of PAP reported a reduction of SBP by −2.85 (−5.55 to −0.24) and a −1.87 (−2.86 to −1.23) mmHg reduction for DBP. Improvement of 24-h BPs was slightly higher, SBP −3.13 (−5.10 to −1.66) and DBP −2.88 (−4.46 to −1.55) mmHg.[13] Improvement of daytime SBP and DBP (6 a.m. to 10 p.m.) varied between −2.27 to −2.7 and −1.78 to −2.4 in previous meta-analyses.[41–43] These BP reductions observed in controlled trials are comparable with the changes in office BP observed in our large clinical real-life OSA patient cohort where PAP use with high adherence was associated with a SBP and DBP reduction of approximately 3–4 mmHg in unadjusted analysis. However, different from those randomized controlled trials (RCT), the majority of patients in our study were adherent to PAP treatment, and we could not demonstrate any dose-response relationship between PAP adherence and the size of BP reduction (data not shown). On top of these confirmatory data, we were able to show that AHT drug class modified the improvement of BP control following PAP. Interestingly, one study[23] evaluated ACEI/ARB treatment in newly diagnosed hypertensive OSA patients. They reported that ACEI/ARB treatment had favourable effects on BP in OSA patients but did not see any added effect of PAP treatment on top of ACEI/ARB AHT on BP. Some notable differences between the studies have to be mentioned. First, our study investigated patients with established hypertension on previously established AHT. Second, the sample size was significantly larger in our study, which provided power to detect significant changes in BP. Third, PAP treatment duration differed between studies, 6 + 6 weeks in the RCT compared with approximately 16 months in monotherapy and 15 months in dual therapy in our study. Indeed treatment duration was an independent predictor for favourable BP response to PAP treatment, confirming previous results by Bouloukaki *et al.*[44] Our data suggest that long-lasting, rather than instant adaptive, processes are operative in OSA-associated hypertension.

The ACEI/ARB was associated with lower BP values in one study[21] when compared with BBs, CCB, and DIU. Stronger BP lowering properties for ACEI/ARB were observed in monotherapy with a similar

trend for dual therapies in hypertensive OSA patients. Interestingly, BP assessments were performed prior to the start of PAP treatment in that study. These findings support our results for PAP-treated patients in the monotherapy group and in patients treated with the AHT combination of ACEI/ARB and BB. This is in line with a very recent systematic review[38] showing that the renin–angiotensin–aldosterone system is significantly upregulated in OSA with higher levels of renin–angiotensin–aldosterone system hormones. Superior BP control using ACEI/ARB AHT in our study suggests that upregulation of the RAS persists even in PAP-treated patients.

Blood pressure control

Several studies have shown poor BP control in patients with OSA and established hypertension.[14–16,45] Most of these cohorts studied patients with suspected OSA and were made before PAP treatment. To the best of our knowledge, our current analysis illustrates, for the first time, how BP control improved significantly in long-term PAP-treated patients by 7–16%. Furthermore, we can demonstrate that the improvement of BP control was modified by AHT.

Hypertension development

Several different phases in the development of hypertension have been described. Early stages of hypertension development have been characterized as a circulatory state associated with high SBP as a consequence of increased heart rate and cardiac output.[46] These cardiovascular changes may theoretically respond particularly well to BBs and DIU[14] and, as suggested in the present study, by PAP treatment. At later stages of hypertension with OSA co-morbidity, atherosclerosis and hypertension may mediate permanent vascular remodelling that is better addressed with drugs acting on other mechanisms. PAP therapy, in this stage, may require a longer time to promote an improvement in BP control. Earlier stages of hypertension may therefore be more susceptible to therapy, as indicated by studies showing that early initiation of treatment might lead to better cardiovascular risk reduction and cardiovascular protection.[47]

Differences between treated and untreated obstructive sleep apnoea on hypertension

In the untreated OSA condition, we were able to show in the same cohort that AHT with BB was associated with favourable BP control.[14] This is expected due to elevated sympathetic activity in untreated or poorly treated OSA. In the current study, we followed those patients with a high degree of PAP adherence. Considering that PAP will remove repetitive hypoxia, most arousals, and the chronic sympathetic activation, it is likely that other mechanisms may play a dominant role following OSA treatment. Indeed, patients receiving ACEI/ARB showed a stronger reduction of BP and an improved overall BP control suggesting that this regulatory system remains activated and specifically responsive to drug treatment. It remains unknown what degree of residual OSA determines the favourable effect of BB or ACEI/ARB drug treatment on BP control in OSA patients. There are data suggesting that a daily PAP usage over 4 h is at least needed to achieve BP-lowering effects, but recent meta-analyses suggest an even higher degree of daily PAP adherence.[48] Yet, so far most AHT studies in OSA tend to ignore the degree of OSA treatment success and mix all OSA patients in one group, which may in part explain the inconsistent results shown previously.

Strength and limitations of the study

Strengths and limitations of our study need to be discussed. First, this is one of the largest studies so far on the topic of BP control in PAP-treated OSA patients. The multi-centric and multi-national study design increases the generalizability of our findings. All patients followed a pre-defined study protocol that increased the validity of data. The information on medication was obtained in 20 different European countries and labelled according to ATC coding. The power of our study allowed for advanced statistical analysis including a large number of confounders (see *Table 4* and the Supplementary material online). We controlled for baseline BPs to reduce the impact of regression towards the mean effects. Finally, the follow-up in the current study was significantly longer (2–36 months) compared with 2–12 weeks reported in the majority of AHT RCT trials published so far.[17,18,49] Considering that our study includes a sleep apnoea cohort without systematic exclusion of patients with multiple co-morbidities or high age, it may in fact be more representative of the clinical setting compared with many RCTs.

Limitations of the study include the use of office BP assessments rather than 24-h ambulatory BP measurements, which did not allow us to assess changes in 24-h BP profile induced by treatment or the degree of nocturnal BP reduction. There might have been differences between centres that weakened the accuracy of BP measurements. However, we attempted to minimize such influences by introducing study site as random factor in our mixed models. As our study was not a RCT, we cannot exclude that part of the observed BP reduction can be attributed to the regression towards the mean effect. However, the main focus of our analysis was to detect if specific drug classes were associated with superior BP control and any regression towards the mean effect is expected to be similar between drug classes. Moreover, we did not have information on daily dose of AHTs, and ATC classes were only classified to the first decimal. This allowed us to analyse BP change in drug class but not individual drugs within AHT drug class. In addition, our data did not allow for the evaluation of BP changes at multiple visits over time. Finally, despite multiple confounder adjustments, referral bias to the ESADA itself and PAP compliance-related selection bias in our current patient subcohort may have limited the possibilities to assess the full effect of PAP treatment on BP control.

Clinical implications and future studies

There are currently no specific clinical recommendations on what antihypertensive drugs should be used in hypertensive OSA patients. The latest 2018 European recommendations on hypertension treatment[2] reported that BP control, in general, is low among hypertensive patients in Europe. They also recommended that the start of treatment should incorporate a combination therapy in newly detected arterial hypertension. If BP remains uncontrolled, an additional drug should be added. As BP control is even poorer in hypertensive OSA patients, these recommendations are especially important to follow and to reassess BP control over time in hypertensive patients with OSA. Our current results suggest that ACEI/ARB + BB, ACEI/ARB + CCB, and ACEI/ARB + DIU are the most efficient combination therapies in hypertensive treated OSA patients, which is in line with current treatment guidelines.[2] In addition, our data also suggest that some standard AHTs may be less suitable for the treatment of hypertension with OSA co-morbidity. Previous results suggest that poorly compliant as well as unsuccessfully treated OSA patients with hypertension may benefit from a BB and DIU combination treatment.[14] In this study, we show that AHTs containing ACEI/ARB were associated with lower BP values and better BP control in highly compliant PAP-treated OSA patients. On top of existing guidelines for the choice of AHT, the degree of control of OSA by treatment will thus need to be considered. Our data suggest that for better BP control, hypertensive patients with uncontrolled OSA may benefit from BB or BB/DIU combination whereas hypertensive patients with compliant PAP-treated OSA may benefit from ACEI/ARB or BB + ACEI/ARB combination. Importantly, these hypotheses need to be verified in prospective RCTs. This gap of knowledge is also highlighted in a very recent review article on the management of hypertension in OSA.[50] Furthermore, the present study suggests that future RCTs on arterial hypertension

treatment in OSA patients should also investigate PAP-treated cohorts. Patients with resistant hypertension are highly prevalent in OSA cohorts and need to be addressed separately in future studies.

Conclusion

BP levels and the degree of BP control improve by a clinically meaningful degree (7–16%) after initiation of PAP treatment in OSA, but BP control remains poorer than in non-OSA hypertensive patients. These favourable changes are further improved by antihypertensive drugs and become more evident over time. Our study suggests that ACEI/ARB, alone or in combination with other drug classes, provides a particularly strong reduction of BP and better BP control when combined with PAP in OSA. Prospective long-term trials are needed to confirm these findings and to guide future personalized AHT in OSA—treated or untreated—for better overall BP control.

Lead author biography

Dr Sven Svedmyr is a specialist in internal medicine currently working at the Sleep clinic at the Pulmonary Department, Sahlgrenska University Hospital in Gothenburg, Sweden. He has since 2017 been working mainly with sleep disorders, while doing his PhD studies part time since 2016. He is also clinically involved in starting a Center of Excellence for HHT/Mb Osler at Sahlgrenska and teaches sleep disorders for medical students, colleagues, and future sleep specialists. His thesis is focused on OSA and CV risk prevention.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

The ESADA network has received support from the European Union COST action B26 (2005-2009) and the European Respiratory Society (ERS) funded Clinical Research Collaboration (CRC; 2015 to present). Unrestricted seeding grants from the ResMed Foundation and the Philips Respironics Foundation for establishment of the database in 2007 and 2011 are gratefully acknowledged. The ESADA has a scientific collaboration with Bayer AG (2018–22). Non-financial support was provided by the European Sleep Research Society (ESRS) and the European Respiratory Society (ERS) in terms of logistics for communication, meetings, and data presentations for the ESADA collaborators.

Funding

Dr Svedmyr used funding from his grant from the Swedish Heart and Lung Foundation to perform the study.

Conflict of interest: The ESADA study group received unrestricted funding grants from Respironics and Resmed Foundations (2008–11) and an unrestricted collaboration grant from Bayer AG (2018–22). S.S., corresponding author, reports no COI. He has grants from the Swedish Heart and Lung Foundation. J.H. reports no COI related to the content of the manuscript. He has institutional grants from Gothenburg University, Swedish Government Research and Educational grant LUA/ALF and grants from the Swedish Heart and Lung Foundation. Outside of the current manuscript, he has EU grants Horizon 2020, Eureka, and Inter Funding: Sleep Across Waters. He has consulting fees from SomnoMed (advisory input), has received research equipment from Itamar, and owns stock in Cereus Pharma. S.B. reports no COI. F.F. reports no COI. H.H. reports no COI. C.L. reports no COI. O.L. reports no COI. S.M. reports no COI. G.P. reports no COI; he has honoraria for lectures from Merck. A.P. reports no COI. S.S. reports no COI. S.T. reports no COI. D.T. reports no COI; he has payment to his Institution for lectures from Nyxoah. D.Z. reports no COI. L.G. reports no COI related to the content of the manuscript. He has institutional grants from LUA/ALF and the Swedish Heart and Lung Foundation. Outside the current manuscript, he provided lectures for Resmed, Philips, Astra Zeneca, and Lundbeck; and he has ownership in a patent licensed to Desitin GMBH related to sleep apnoea therapy.

Appendix

Collaborators in the ESADA project (March 2023)

(1) Alexandroupolis, Greece
- Steiropoulos P, Sleep Unit, Department of Pneumonology, Democritus University of Thrace, Alexandroupolis, Greece

(2) Antwerp, Belgium
- Verbraecken J, Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium
- Petiet E, Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

(3) Athens, Greece
- Trakada G, Pulmonary Medicine, National and Kapodistrian University of Athens, Athens, Greece

(4) Berlin, Germany
- Fietze I, Schlafmedizinisches Zentrum, Charité—Universitätsmedizin Berlin, Germany
- Penzel T, Schlafmedizinisches Zentrum, Charité—Universitätsmedizin Berlin, Germany

(5) Brno, Czech Republic
- Ludka O, Department of Cardiology, University Hospital Brno and International Clinical Research Center, St. Ann´s University Hospital, Brno, Czech Republic

(6) Crete, Greece
- Bouloukaki I. Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece
- Schiza S, Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece

(7) Dublin, Ireland
- McNicholas WT, Department of Respiratory Medicine, St. Vincent´s University Hospital, Dublin, Ireland
- Ryan S, Pulmonary and Sleep Disorders Unit, St. Vincent's University Hospital, Dublin, Ireland

(8) Edinburgh, United Kingdom
- Riha RL, Department of Sleep Medicine, Royal Infirmary Edinburgh, Scotland

(9) Førde, Norway
- Kvamme JA, Sleep Laboratory, ENT Department, Førde Central Hospital, Førde, Norway

(10) Gothenburg, Sweden
- Grote L, Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden

- Hedner J, Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden
- Zou D, Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden

(11) Gent, Belgium
- Hertegonne K, Department of Respiratory Medicine, Ghent University Hospital, and Department of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Gent, Belgium
- Pevernagie D, Department of Respiratory Medicine, Ghent University Hospital, and Department of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Gent, Belgium

(12) Grenoble, France
- Bailly S, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France
- Pépin JL, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France
- Tamisier R, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France

(13) Hamburg, Germany
- Hein H, Sleep Disorders Center, St. Adolf Stift, Reinbeck, Germany

(14) Izmir, Turkey
- Basoglu OK, Department of Chest Diseases, Ege University, Izmir, Turkey
- Tasbakan MS, Department of Chest Diseases, Ege University, Izmir, Turkey

(15) Klecany, Czech Republic
- Buskova J, Department of Sleep Medicine, National Institute of Mental Health, Klecany, Czech Republic

(16) Kosice, Slovakia
- Joppa P, Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J. Safarik University and L. Pasteur University Hospital, Kosice, Slovakia

(17) Lisbon, Portugal
- Staats R, Department of Respiratory Medicine, Hospital de Santa Maria, Lisbon, Portugal

(18) Leuven, Belgium
- Testelmans D, Sleep Disorders Centre, University Hospital Gasthuisberg, Leuven, Belgium

(19) Mainz, Germany
- Gouveris H, ENT department at Mainz University Hospital, Mainz, Germany
- Ludwig K, ENT department at Mainz University Hospital, Mainz, Germany

(20) Milano, Italy
- Lombardi C, Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy.
- Parati G, Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy.

(21) Palermo, Italy
- Bonsignore MR, PROMISE Dept., University of Palermo, Palermo, Italy

(22) Pavia, Italy
- Fanfulla F, Unità Operativa di Medicina del Sonno, Istituto Scientifico di Pavia IRCCS, Pavia, Italy

(23) Porto, Portugal
- Drummond M, Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal
- van Zeller M, Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal

(24) Solingen, Germany
- Randerath W, Sleep Disorders Centre, Pulmonary Clinic, Solingen, Germany
- Treml M, Respiratory Research Institute, Pulmonary Clinic, Solingen, Germany

(25) Split, Croatia
- Dogas Z, Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia
- Pecotic R, Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia

(26) Thessaloniki, Greece
- Pataka A, Respiratory Failure Unit, G. Papanikolaou Hospital, Aristotle University of Thessaloniki, Greece

(27) Timisoara, Rumania
- Mihaicuta S, Center for Research and Innovation in Precision Medicine and Pharmacy, 'Victor Babes' University of Medicine and Pharmacy, Timisoara, Romania

(28) Turku, Finland
- Anttalainen U, Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland
- Saaresranta T, Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland

(29) Warsaw, Poland
- Sliwinski P, 2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland.

References

1. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, Melles RB, Bhatt DL. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med* 2019; **381**:243–251.
2. Williams LB, Mancia EG, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; Authors/Task Force Members. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018;**36**: 1953–2041.
3. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Euro Heart J* 2021;**42**:3227–3337.
4. Javaheri S, Brown LK, Abraham WT, Khayat R. Apneas of heart failure and phenotype-guided treatments: part one: OSA. *Chest* 2020;**157**:394–402.
5. Parati G, Lombardi C, Castagna F, Mattaliano P, Filardi PP, Agostoni P. Heart failure and sleep disorders. *Nat Rev Cardiol* 2016;**13**:389–403.
6. Javaheri S, Peker Y, Yaggi HK, Bassetti CLA. Obstructive sleep apnea and stroke: the mechanisms, the randomized trials, and the road ahead. *Sleep Med Rev* 2022;**61**:101568.
7. Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L, Tkacova R, Lévy P, Riha R, Bassetti C, Narkiewicz K, Mancia G, McNicholas WT; EU COST Action B26 members. Recommendations for the management of patients with obstructive sleep apnoea and hypertension. *Eur Respir J* 2013;**41**:523–538.

8. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. *Chest* 1993;**103**: 1763–1768.
9. Tamisier R, Pepin JL, Remy J, Baguet JP, Taylor JA, Weiss JW, Levy P. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. *Eur Respir J* 2011;**37**:119–128.
10. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, Lavie L, Pépin JL. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers* 2015;**1**:15015.
11. Ahmad M, Makati D, Akbar S. Review of and updates on hypertension in obstructive sleep apnea. *Int J Hypertens* 2017;**2017**:1848375.
12. Ren R, Zhang Y, Yang L, Somers VK, Covassin N, Tang X. Association between arousals during sleep and hypertension among patients with obstructive sleep apnea. *J Am Heart Assoc* 2022;**11**:e022141.
13. Kou C, Zhao X, Lin X, Fan X, Wang Q, Yu J. Effect of different treatments for obstructive sleep apnoea on blood pressure. *J Hypertens* 2022;**40**:1071–1084.
14. Svedmyr S, Hedner J, Zou D, Parati G, Ryan S, Hein H, Pepin JL, Tkáčová R, Marrone O, Schiza S, Basoglu OK, Grote L; European Sleep Apnea Database (ESADA) study group. Superior hypertension control with betablockade in the European Sleep Apnea Database. *J Hypertens* 2021;**39**:292–301.
15. Grote HL, Hedner HJ, Peter HJ. Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension. *J Hyperten* 2000;**18**:679–685.
16. Martínez-García FM-A, Navarro-Soriano MC, Torres JG, Barbé F, Caballero-Eraso C, Lloberes P, Diaz-Cambriles T, Somoza M, Masa JF, González M, Mañas E, de la Peña M, García-Río F, Montserrat JM, Muriel A, Selma-Ferrer MJ, García Ortega Ao, Campos-Rodriguez F. Beyond resistant hypertension: relationship between refractory hypertension and obstructive sleep apnea. *Hypertension* 2018;**72**:618–624.
17. Kraiczi H, Hedner J, Peker Y, Grote L. Comparison of atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan for antihypertensive treatment in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2000;**161**:1423–1428.
18. Salo TM, Kantola I, Voipio-Pulkki LM, Pelttari L, Viikari JSA. The effect of four different antihypertensive medications on cardiovascular regulation in hypertensive sleep apneic patients—assessment by spectral analysis of heart rate and blood pressure variability. *Eur J Clin Pharmacol* 1999;**55**:191–198.
19. Revol B, Jullian-Desayes I, Bailly S, Tamisier R, Grillet Y, Sapène M, Joyeux-Faure M, Pépin JL, Grillet Y, Sapène M, Pépin JL. Who may benefit from diuretics in OSA? A propensity score-match observational study. *Chest* 2020;**158**:359–364.
20. Kasai DT, Bradley GT, Friedman GO, Logan GA. Effect of intensified diuretic therapy on overnight rostral fluid shift and obstructive sleep apnoea in patients with uncontrolled hypertension. *J Hypertens* 2014;**32**:673–680.
21. Revol B, Jullian-Desayes I, Bailly S, Regnaut L, Tamisier R, Pepin JL, Joyeux-Faure M. What is the best treatment strategy for obstructive sleep apnoea-related hypertension? *Hypertens Res* 2018;**41**:1070–1072.
22. Morgan BJ, Teodorescu M, Pegelow DF, Jackson ER, Schneider DL, Plante DT, Gapinski JP, Hetzel SJ, Dopp JM. Effects of losartan and allopurinol on cardiorespiratory regulation in obstructive sleep apnoea. *Exp Physiol* 2018;**103**:941–955.
23. Thunstrom E, Manhem K, Rosengren A, Peker Y. Blood pressure response to losartan and continuous positive airway pressure in hypertension and obstructive sleep apnea. *Am J Respir Crit Care Med* 2016;**193**:310–320.
24. Hedner J, Grote L, Bonsignore M, McNicholas W, Lavie P, Parati G, Sliwinski P, Barbé F, De Backer W, Escourrou P, Fietze I, Kvamme JA, Lombardi C, Marrone O, Masa JF, Montserrat JM, Penzel T, Pretl M, Riha R, Rodenstein D, Saaresranta T, Schulz R, Tkacova R, Varoneckas G, Vitols A, Vrints H, Zielinski J. The European Sleep Apnoea Database (ESADA): report from 22 European sleep laboratories. *Eur Respir J* 2011; **38**:635–642.
25. Borghi C, Tubach F, De Backer G, Dallongeville J, Guallar E, Medina J, Perk J, Roy C, Banegas JR, Rodriguez-Artalejo F, Halcox JP. Lack of control of hypertension in primary cardiovascular disease prevention in Europe: results from the EURIKA study. *Int J Cardiol* 2016;**218**:83–88.
26. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* 2005;**112**: 2660–2667.
27. Tkacova R, McNicholas WT, Javorsky M, Fietze I, Sliwinski P, Parati G, Grote L, Hedner J. Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study. *Eur Respir J* 2014;**44**:931–941.
28. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, Lavie L, Pépin JL. Correction: obstructive sleep apnoea syndrome. *Nat Rev Dis Primers* 2015;**1**:15024.
29. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, Malhotra A, Martinez-Garcia MA, Mehra R, Pack AI, Polotsky VY, Redline S, Somers VK. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol* 2017;**69**: 841–858.
30. Somers VK, Dyken ME, Skinner JL. Autonomic and hemodynamic responses and interactions during the Mueller maneuver in humans. *J Auton Nerv Syst* 1993;**44**:253–259.
31. Umlauf MG, Chasens ER, Greevy RA, Arnold J, Burgio KL, Pillion DJ. Obstructive sleep apnea, nocturia and polyuria in older adults. *Sleep* 2004;**27**:139–144.
32. Levy P, Tamisier R, Arnaud C, Monneret D, Baguet JP, Stanke-Labesque F, Dematteis M, Godin-Ribuot D, Ribuot C, Pepin JL. Sleep deprivation, sleep apnea and cardiovascular diseases. *Front Biosci (Elite Ed)* 2012;**4**:2007–2021.
33. Hedner J, Ejnell H, Sellgren J, Hedner T, Wallin G. Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? *J Hypertens* 1988;**6**:S529–S531.
34. Somers VK, Mark AL, Zavala DC, Abboud FM. Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. *J Appl Physiol (1985)* 1989;**67**:2101–2106.
35. Narkiewicz K, Van De Borne PJH, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation* 1998;**98**: 772–776.
36. Barceló A, Piérola J, Esquinas C, de la Peña M, Arqué M, Alonso-Fernández A, Bauçà JM, Robles J, Barceló B, Barbé F. Relationship between aldosterone and the metabolic syndrome in patients with obstructive sleep apnea hypopnea syndrome: effect of continuous positive airway pressure treatment. *PLoS One* 2014;**9**:e84362.
37. Lacedonia D, Tamisier R, Roche F, Monneret D, Baguet JP, Lévy P, Pépin JL. Respective effects of OSA treatment and angiotensin receptor blocker on aldosterone in hypertensive OSA patients: a randomized cross-over controlled trial. *Int J Cardiol* 2014;**177**: 629–631.
38. Loh HH, Lim QH, Chai CS, Goh SL, Lim LL, Yee A, Sukor N. Influence and implications of the renin–angiotensin–aldosterone system in obstructive sleep apnea: an updated systematic review and meta-analysis. *J Sleep Res* 2023;**32**:e13726.
39. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia–revisited–the bad ugly and good: implications to the heart and brain. *Sleep Med Rev* 2015;**20**: 27–45.
40. Lévy P, Pépin JL, Arnaud C, Baguet JP, Dematteis M, Mach F. Obstructive sleep apnea and atherosclerosis. *Prog Cardiovasc Dis* 2009;**51**:400–410.
41. Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med* 2012;**08**:587–596.
42. Bakker JP, Edwards BA, Gautam SP, Montesi SB, Durán-Cantolla J, Aizpuru F, Barbé F, Sánchez-de-la-Torre M, Malhotra A. Blood pressure improvement with continuous positive airway pressure is independent of obstructive sleep apnea severity. *J Clin Sleep Med* 2014;**10**:365–369.
43. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 2019;**15**:301–334.
44. Bouloukaki I, Mermigkis C, Tzanakis N, Giannadaki K, Mauroudi E, Moniaki V, Kallergis EM, Schiza SE. The role of compliance with PAP use on blood pressure in patients with obstructive sleep apnea: is longer use a key-factor? *J Hum Hypertens* 2017;**31**: 106–115.
45. Zota IM, Sascau R, Statescu C, Boisteanu D, Roca M, Constantin MML, Mastaleru A. Hypertension control in patients with moderate-severe obstructive sleep apnea. *J Hypertens Res* 2018;**4**:90–98.
46. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res* 2014; **114**:1804–1814.
47. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk—overview and meta-analyses of randomized trials. *J Hypertens* 2014;**32:** 2305–2314.
48. Oh A, Grivell N, Chai-Coetzer CL. What is a clinically meaningful target for positive airway pressure adherence? *Sleep Med Clin* 2021;**16**:1–10.
49. Pelttari LH, Hietanen EK, Salo TT, Kataja MJ, Kantola IM. Little effect of ordinary antihypertensive therapy on nocturnal high blood pressure in patients with sleep disordered breathing. *Am J Hypertens* 1998;**11**:272–279.
50. Ou Y-H, Tan A, Lee C-H. Management of hypertension in obstructive sleep apnea. *Am J Prev Cardiol* 2023;**13**:100475.