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CORRESPONDENCE

# What is the best treatment strategy for obstructive sleep apnoea-related hypertension?

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Obstructive sleep apnoea (OSA) is characterized by the repetitive occurrence of complete (apnoea) and incomplete (hypopnea) pharyngeal collapse inducing chronic intermittent hypoxia (CIH) and sleep fragmentation. The prevalence of hypertension in OSA patients reaches 50% [1] with a high rate of uncontrolled and resistant hypertension [1, 2], both leading to cardiovascular diseases [3]. CIH leads to intermediary mechanisms such as increased sympathetic activity [4] and/or dysregulation of the renin–angiotensin aldosterone system [1], which can be targeted by specific classes of antihypertensive agents. Additional data suggest that fluid accumulated in the legs during the day is shifted during sleep from the legs to the upper body, reducing upper airway size, increasing upper airway collapsibility and aggravating OSA [5]. This suggests that diuretics could play a critical role in reducing OSA severity and treating OSA-related hypertension. For primary hypertension, the main classes recommended for treatment initiation in monotherapy are thiazide diuretics, beta-blockers (BB), long-acting calcium channel blockers (CCB) and renin–angiotensin blockers (angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB, also known as sartans)). In the general population, these drug classes have been shown to be equally effective. Owing to the specific underlying mechanisms of OSA-related hypertension some of these classes might be anticipated to be better candidates, but a head-to-head comparison between BB, CCB, ACE and ARB is still lacking in the sleep apnoea literature.

To address this question, we exploited the baseline data of the OPTISAS$_2$ multicentre randomized controlled trial (NCT: 01505959), in which 213 OSA patients at high cardiovascular risk had measured self-home blood pressure (BP) (three measurements each morning and evening for 3 days). Our aim was to identify individual classes or combinations of anti-hypertensive medications associated with the best blood pressure control in this OSA population. The method of inverse probability of treatment weight (IPTW) estimator is well adapted to address this question using observational data. Briefly, this causal inference method balances patients according to their baseline characteristics by creating pseudo-populations in which each patient is weighted by the inverse of the probability of receiving his/her treatment. In the final pseudo-population, treatment exposure is independent of the measured confounders. In this way, the average treatment effect of each antihypertensive strategy could be assessed with a validity and strength of demonstration close to that of a randomized controlled trial [6, 7]. We used two approaches: (1) a multinomial IPTW estimator to assess the respective impact of different antihypertensive monotherapies on BP control; (2) a standard IPTW estimator to assess the impact of different dual therapies, including diuretics, on BP control. For both methods, we used stabilized weight and a robust estimator of the variance. A weight truncation at the 95th percentile was performed to reduce the risk of violation of the positivity assumption. All statistical analyses were performed by using SAS v9.4 (SAS Institute Inc., Cary,

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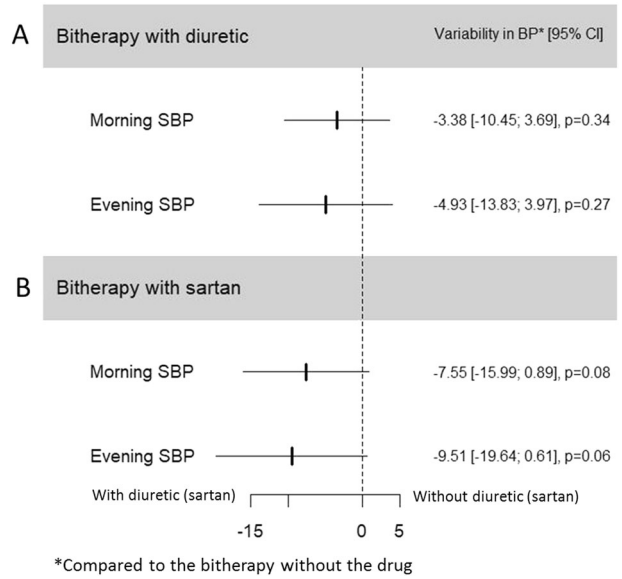


**Fig. 1** Effect of antihypertensive bitherapy with or without diuretic (**a**) and with or without sartan (**b**) on SBP. Asterisk: compared to the bitherapy without the drug

NC, USA). A $p$-value of <0.05 was considered as significant.

At baseline the 213 OSA patients, predominantly men (73.2%), with a median age of 61 [54–66] years, a median body mass index (BMI) of 32 [29–36] kg/m$^2$ and a median apnoea–hypopnea index (AHI) of 48 [36–62] events per hour were being treated with antihypertensive drugs. Among them, 99 were on monotherapy, 71 on dual therapy and 43 treated by three or more antihypertensive drugs. These groups did not differ in terms of age, sex, BMI, sleepiness and OSA severity. In OSA patients on monotherapy, there was a significant difference between BB (as reference), ARB (sartans), CCB and ACE inhibitors in reducing evening systolic BP ($p = 0.03$), in favour of sartans (−7.57 [−16.93 to 1.8] mmHg). There was no difference between drug classes in monotherapy for morning systolic BP or for diastolic BP. Only five patients were treated by a diuretic in monotherapy, which did not allow the comparison with the other classes. In the OSA patients being treated by a combination of two antihypertensive medications, the multivariate analysis failed to show any significant difference between associations of antihypertensive drugs. The presence of a sartan in the combination tended to be associated with a higher reduction in systolic BP (Fig. 1) in comparison with a dual therapy without sartan (morning: −7.55 [−15.99 to 0.89] mmHg, $p = 0.08$ and evening: −9.51 [−19.64 to 0.61] mmHg, $p = 0.06$). For the 43 patients on three or more antihypertensive drugs, the number of patients on each antihypertensive drug combination was too small for statistical analysis.

Our results indicated that sartans are the most effective drugs in monotherapy and seem to reinforce blood pressure control when dual therapy is required. Accordingly, Thunstrom et al. [8] recently showed that losartan reduces BP in OSA patients, but the range of reduction was smaller in OSA than in non-OSA patients. Physiological studies have previously demonstrated that losartan reduced oxidative stress and sympathetic nerve activity in healthy humans exposed to acute or intermittent hypoxia [9, 10]. We have previously reported, in a randomized study, that valsartan led to a fourfold higher reduction in BP compared to continuous positive airway pressure in OSA patients [11]. In view of our analysis and the existing literature, sartans should be prioritized in the antihypertensive strategy for OSA patients.

Our study has some limitations: (1) the sample size was not calculated specifically for this analysis; (2) as it was not a randomized trial, some unmeasured confounders might be missing. However, by using an IPTW estimator, which is well known for its good performances in accounting for confounders in observational studies, we significantly reduced the risk of biases in the final results. Moreover, we used another method based on Generalised Boosted Models to confirm our results [12].

Our results suggest that sartans might be the first-choice medication for sleep apnoea-related hypertension. This observational study also provides data helping to design and calculate the sample size for upcoming randomized clinical trials.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Prim. 2015;1:15015. https://doi.org/10.1038/nrdp.2015.15
2. Cai A, Wang L, Zhou Y. Hypertension and obstructive sleep apnea. Hypertens Res J Jpn Soc Hypertens. 2016;39:391–5. https://doi.org/10.1038/hr.2016.11
3. Sekizuka H, Osada N, Akashi YJ. Impact of obstructive sleep apnea and hypertension on left ventricular hypertrophy in

Japanese patients. Hypertens Res J Jpn Soc Hypertens. 2017;40:477–82. https://doi.org/10.1038/hr.2016.170
4. Tamisier R, Pépin JL, Rémy J, Baguet JP, Taylor JA, Weiss JW, et al. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. Eur Respir J. 2011;37:119–28. https://doi.org/10.1183/09031936.00204209
5. Kasai T. Fluid retention and rostral fluid shift in sleep-disordered breathing. Curr Hypertens Rev. 2016;12:32–42.
6. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008;168:656–64. https://doi.org/10.1093/aje/kwn164
7. Bailly S, Pirracchio R, Timsit JF. What's new in the quantification of causal effects from longitudinal cohort studies: a brief introduction to marginal structural models for intensivists. Intensive Care Med. 2016;42:576–9. https://doi.org/10.1007/s00134-015-3919-6
8. Thunström 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;193:310–20. https://doi.org/10.1164/rccm.201505-0998OC
9. Pialoux V, Foster GE, Ahmed SB, Beaudin AE, Hanly PJ, Poulin MJ. Losartan abolishes oxidative stress induced by intermittent hypoxia in humans. J Physiol. 2011;589:5529–37. https://doi.org/10.1113/jphysiol.2011.218156
10. Jouett NP, Moralez G, Raven PB, Smith ML. Losartan reduces the immediate and sustained increases in muscle sympathetic nerve activity after hyperacute intermittent hypoxia. J Appl Physiol. 2017;122:884–92. https://doi.org/10.1152/japplphysiol.00683.2016
11. Pépin J-L, Tamisier R, Barone-Rochette G, Launois SH, Lévy P, Baguet J-P. Comparison of continuous positive airway pressure and valsartan in hypertensive patients with sleep apnea. Am J Respir Crit Care Med. 2010;182:954–60. https://doi.org/10.1164/rccm.200912-1803OC
12. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med. 2013;32:3388–414. https://doi.org/10.1002/sim.5753