Obstructive sleep apnea and hypertension

– epidemiological, diagnostic and treatment aspects

Sven Svedmyr

Center for Sleep and Vigilance Disorders

Institute of Medicine

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg 2026

Cover illustration: *Two silent killers in the night*
by Nathalie Asom

This thesis started with a younger version of myself meeting an OSA patient with newly diagnosed hypertension in our sleep lab. The clinical question of what antihypertensive medication I should prescribe to optimize his treatment has been with me all through this thesis.

sven.svedmyr@gu.se

ISBN 978-91-8115-529-7 (PRINT)
ISBN 978-91-8115-530-3 (PDF)

Printed in Borås, Sweden 2026
Printed by Stema Specialtryck AB

Obstructive sleep apnea and hypertension

– epidemiological, diagnostic and treatment aspects

Sven Svedmyr

Center for Sleep and Vigilance Disorders, Institute of Medicine
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

Background:

Obstructive sleep apnea (OSA) and hypertension are two common disorders both strongly connected with the development of future atrial fibrillation, and major adverse cardiovascular events (MACE), such as stroke, myocardial infarction, cardiac failure and premature cardiovascular (CV) death. As both conditions share several common risk factors and OSA promotes the development of hypertension, patients often have both conditions. Early studies suggest OSA patients have a higher risk of developing these CV events.

It is known that blood pressure control is poor in patients with OSA and they are harder to treat successfully with anti-hypertensive treatment (AHT). This implies that even when patients are correctly diagnosed with both disorders (which is often not the case), adequate treatment may still not be achieved, resulting in a persistently elevated risk of MACE. To optimize management and reduce long-term risk, further information is needed to determine which patients are most likely to develop CV events and whether specific classes of AHT are particularly suitable for these individuals.

Included studies and investigated questions:

In this thesis a novel method to predict vascular function in suspected OSA patients, was addressed in *study I*. Pulse Propagation Time (PPT) as a marker of arterial stiffness measured during sleep, was studied in OSA with and without hypertension. We hypothesized that PPT information collected during routine sleep investigations may improve our ability to identify patients with high CV risk. We described for the first time the changes in PPT during different sleep stages, and vascular stiffness was consistently higher in patients with OSA and hypertension than controls without these disorders.

In *study II*, we assessed the incidence of MACE in patients with OSA and/or hypertension. We compared groups with hypertension, OSA or both disorders against normotensive controls (155,830 subjects in total).

With a median follow-up time of 6.8 years, we used COX regression models to compare hazard ratios/risks for the groups, with first MACE or death as main outcomes. We adjusted for confounding factors and investigated modifying factors like adherence to therapies in the models. In addition, the protective effects of PAP treatment were assessed.

In the adjusted model, MACE risk was highest in patients with both OSA and hypertension with HR 7.0 (6.2-7.9), followed by hypertensive controls with 3.2 (2.9-3.7) and patients with OSA alone, HR 2.6 (2.2-3.0) compared to normotensive controls. All-cause mortality had a similar pattern but lower HRs of 3.1 (2.8-3.5), 2.2 (2.0-2.4) and 1.6 (1.4-1.8) respectively.

OSA patients experience their first MACE earlier in life than hypertension status matched controls—on average 5 years earlier if normotensive and 1.6 years earlier if hypertensive. Positive airway treatment (PAP) treatment of OSA, reduces the MACE risk in a dose-response manner. PAP adherence reduced risk with 22-39% from 2-<4 to 8 hours or more per night.

In *study III* we studied AHT in 5,818 hypertensive patients diagnosed with OSA. Analyses were performed in a large pan-European database (ESADA) to investigate OSA patients with hypertension before the start of PAP treatment, identifying differences in office blood pressure (BP) control depending on what AHT class (betablocker, calcium channel blocker, diuretic, renin-angiotensin blocker (RAB) or centrally acting antihypertensives) or combination used. BP was uncontrolled in 66% of the population. There were significant differences, 2-5 mmHg in BP between

AHT groups, favouring betablocker treatment compared to other AHT classes.

In *study IV,* we studied changes in BP control in 1,935 hypertensive OSA patients from ESADA, following PAP treatment stratified by antihypertensive drug class or combination. Overall, the proportion of patients with well controlled hypertension increased by 10-15% with PAP treatment. Further improvement of BP and more favourable BP control were achieved with RAB. Mean BP improvement was 3-4 mmHg with PAP and patients with combinations including RAB had a BP reduction of 4.8-6.9 mmHg.

Conclusions:

Oximetry based beat-by-beat contour pulse wave analysis was used to assess overnight vascular stiffness (PPT) and has sleep stage specific changes. Slow wave sleep (N3, deep sleep) had the lowest vascular stiffness.

PPT also decreases with higher OSA severity and in hypertension as a marker of increasing vascular stillness. PPT may be a valuable tool to better monitor vascular ageing and predict increased CV risk, during regular sleep studies.

Patients with hypertension and OSA have markedly increased risk for earlier MACE/all-cause death than controls and even compared to patients with OSA or hypertension alone and OSA patients get their first CV event earlier in life. PAP treatment mitigated the risk in a dose-response manner with increasing PAP adherence.

AHT in hypertensive OSA patients are less likely to reach intended BP control compared to non-OSA populations. Adequate OSA control improves BP control but assessment of BP status during PAP treatment is recommended as modification and/or escalation of AHTs may improve BP control. Well-treated OSA patients seem to be more suitable for RAB while untreated OSA patients had better results from betablockers alone or in combination with diuretics. This highlights the need to consider AHT when initiating OSA treatment.

Keywords: Obstructive sleep apnea, Hypertension, cardiovascular risk management

ISBN 978-91-8115-529-7 (PRINT)
ISBN 978-91-8115-530-3 (PDF)

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Obstruktiv sömnapné (OSA) och högt blodtryck är två vanliga folksjukdomar som båda ökar risken för framtida kardiovaskulära händelser som hjärtinfarkt, stroke, hjärtsvikt och hjärtkärldöd kopplad till dessa händelser (s.k. MACE) samt för förmaksflimmer. Eftersom dessa sjukdomar har flera gemensamma riskfaktorer och OSA i sig kan orsaka hypertoni, är det vanligt att en patient har båda tillstånden samtidigt. Detta leder till kraftigt ökad risk för tidigare insjuknande i allvarliga hjärtkärlhändelser.

Högt blodtryck vid OSA sjukdom är ofta svårare att behandla framgångsrikt med läkemedel och livsstilsförbättring. Följsamheten med behandlingarna och användargraden av både OSA- och hypertonibehandling tenderar att avta över tid och behandlingsmålet att normalisera blodtrycksnivåerna, reducera andningsuppehållen och möjliggöra bra sömn, nås därför mer sällan fullt ut. Det innebär att även om patienten diagnostiserats med båda dessa tillstånd (många är okända då sjukdomarna inte alltid ger symptom) är det mindre troligt att deras behandlingar kan motverka hela den förväntade riskökningen.

För att förbättra behandlingen och reducera den kardiovaskulära risken för både OSA och hypertoni behövs bättre karaktärisering av patienter med störst risk för kardiovaskulära långtidskomplikationer och identifiering av vilka läkemedel som är effektivast för behandling av högt blodtryck och samtidig OSA-sjukdom.

Genomförda studier och resultat:

I den *första studien* undersökte vi en ny oxymeterbaserad pulsvågsmetod för att identifiera patienter med ökad kardiovaskulär risk. Vi analyserade Pulse Propagation Time (PPT) och hur denna pulsvågshastighetsvariabel som en markör för kärlstyvhet förändras under olika sömnstadier, vid OSA och vid högt blodtryck. Lägre PPT motsvarar högre kärlstyvhet. I studien, beskrev vi hur PPT förändras under olika sömnstadier hos patienter med eller utan OSA och högt blodtryck. PPT sjunker vid OSA och högt blodtryck vilket markerar ökad kärlstyvhet och är längst under djupsömn där det autonoma sympatiska inflytandet på hjärta och kärl är som lägst.

I *andra studien* undersökte vi risken för nyinsjuknande i allvarlig hjärtkärlsjukdom bland svenska patienter med OSA med och utan högt blodtryck jämfört med kontroller med och utan högt blodtryck (en total studiepopulation på 155,830 deltagare). Både OSA behandling med PAP (positive airway pressure) och blodtryckssänkande behandling, samt statinbehandling var modifierande faktorer på dessa risker, men påverkas också av hur följsamma patienterna var med sina behandlingar. Medianuppföljningstiden var 6.8 år och vi använde COX regressionsmodeller för att beräkna risk för MACE eller död som huvudutfallsvariabler. Vi justerade för störfaktorer inklusive kroppsdata, viktig samsjuklighet, socioekonomi och läkemedelsbehandling och följsamhet i våra analyser.

Den kardiovaskulära risken var mer än dubblerad i OSA och drygt 3 gånger så stor i gruppen med högt blodtryck och markant högre i gruppen med båda sjukdomarna där vi fann en sjufaldig riskökning jämfört med kontroller med normalt blodtryck.

Åldern vid första MACE har stor klinisk betydelse och vi fann att den inföll i yngre ålder hos våra OSA patienter, 5 år tidigare hos patienter med normalt blodtryck och 1.6 år tidigare hos de med högt blodtryck än motsvarande kontroller, även om de hade startat PAP behandling för sin OSA. PAP behandling minskade kardiovaskulär risk med 22-39% vid OSA med dos-respons samband med ökande behandlingsföljsamhet från 2-<4 till mer än 8 timmar/natt.

I *studie III* studerades blodtryckssänkande läkemedel hos 5,818 patienter med nydiagnostiserad OSA och hypertoni. Vi använde en europeisk sömnapnédatabas (ESADA) för att undersöka OSA patienter med högt blodtryck innan PAP behandlingsstart. Vi undersökte skillnader i blodtryckskontroll och jämförde hur olika typer av blodtryckssänkande läkemedel påverkar denna kontroll. Patienter med betablockad eller betablockad och diuretika (vattendrivande) hade bättre blodtryckskontroll och blodtrycket var 2-5mmHg längre än andra behandlingar i studien.

I *studie IV* följde vi upp 1,935 patienter med högt blodtryck i ESADA efter start av PAP behandling. Återigen jämförde vi olika blodtryckssänkande läkemedelstyper. Hos patienter med välfungerande PAP behandling hade de med Renin-angiotensinblockad (RAB) ensamt eller i kombination med annan blodtryckssänkare bättre blodtryckskontroll. PAP behandling ökade andelen som får kontroll på sitt höga blodtryck med ca 10-15%, men andelen var större hos de med RAB behandling.

Slutsatser:

Oxymeterbaserade pulsvågsparametrar som PPT ger slag-för-slag analys av kärlstyvhet som varierar med olika sömnstadier och påverkas tydligt av både OSA och högt blodtryck. PPT kan vara ett användbart verktyg för att identifiera OSA patienter med hög kardiovaskulär risk i samband med vanlig sömnregistrering.

Patienter med högt blodtryck eller OSA har ökad risk för tidigare MACE/död än kontroller utan dessa tillstånd. Risken för patienter med båda diagnoserna har ännu högre risk. Patienter med OSA får sin första hjärtkärlhändelse yngre ålder än motsvarande kontroller utan eller med högt blodtryck. PAP behandling kan minska den OSA-relaterade riskökningen, med ett dosrespons-samband kopplat till följsamheten av PAP behandlingen.

Blodtryckssänkande behandling resulterar mera sällan i önskat målvärde hos patienter med OSA jämfört med patienter med högt blodtryck utan OSA.

Välbehandlade OSA patienter har bättre effekt med RAB parallellt med PAP, medan partiellt behandlade eller obehandlade OSA patienter verkar ha bättre nytta av betablockad eller kombinationsbehandling med betablockad och vätskedrivande. Uppföljning av blodtryck och PAP behandling hos patienter som får OSA diagnos, rekommenderas då justeringar i typ eller upptrappning av den blodtryckssänkande behandlingen kan behövas för bättre blodtryckskontroll.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Svedmyr, S, Zou, D, Sommermeyer, D, Ficker, J. H, Randerath, W, Fietze, I, Sanner, B, Hedner, J & Grote, L (2016). *Vascular stiffness determined from a nocturnal digital pulse wave signal.* Journal of Hypertension, 34 (12), 2427-2433. doi: 10.1097/HJH.0000000000001111

II. Svedmyr S et al. *The synergistic effect of obstructive sleep apnea and hypertension on mortality can be reduced by positive airway pressure treatment. (Submission)*

III. Svedmyr, S, Hedner, J, Zou, D, Parati, G, Ryan, S, Hein, H, Pepin, J, Tkáčová, R, Marrone, O, Schiza, S, Basoglu, O. & Grote, L. (2021). *Superior hypertension control with betablockade in the European Sleep Apnea Database.* Journal of Hypertension, 39 (2), 292-301. doi: 10.1097/HJH.0000000000002629

IV. Svedmyr S, Hedner J, Bailly S, Fanfulla F, Hein H, Lombardi C, Ludka O, Mihaicuta S, Parati G, Pataka A, Schiza S, Tasbakan S, Testelmans D, Zou D, Grote L, the European Sleep Apnea Database (ESADA) study group (2023). *Blood pressure control in hypertensive sleep apnea patients of the ESADA cohort-effects of PAP and antihypertensive medication.* European Heart Journal Open, 2023, oead109 doi:10.1093/ehjopen/oead109

CONTENTS

Abbreviations

ABPM	Ambulatory Blood Pressure Measurement
ACEI/ARB	Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker, see also RAB
AHI	Apnea Hypopnea Index
AHT	Anti-Hypertensive Treatment
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical classification
BB	Beta Blocker
BP	Blood Pressure
CAH	Central Acting antihypertensive
CCB	Calcium Channel Blocker
CKD	Chronic Kidney Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DISCOVERY	"Course of DISease in patients reported to the Swedish CPAP Oxygen and VEntilator RegistrY"
DIU	Diuretics
EEG	Electroencephalogram
ESADA	European Sleep Apnea Database
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESS	Epworth Sleepiness Scale
GLM	Generalized Linear Model
GLP-1	Glucagon Like Peptide-1
HbA1c	Hemoglobin A1c, for long-term glycemic control measurement
HBPM	Home Blood Pressure Measurement
HDL	High Density Lipoprotein cholesterol
HMOD	Hypertension Mediated Organ Damage

HMV	Home Mechanical Ventilation, see LTMV
HR	Hazard Ratio
IQR	Inter Quartile Range
LDL	Low Density Lipoprotein Cholesterol
LVH	Left Ventricular Hypertrophy
LTMV	Long-Term Mechanical Ventilation, home ventilator treatment
LTOT	Long-Term Oxygen Therapy
MACE	Major Adverse Cardiovascular Event
MAD	Mandible Advancement Device
NREM	non-REM sleep, including light and deep sleep stages
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
pCO_2	Partial Pressure of Carbon Dioxide
PG	Polygraphy
PPT	Pulse Propagation Time
PSG	Polysomnography
RAAS	Renin-Angiotensin-Aldosterone System
RAB	Renin-Angiotensin Blocker, see also ACEI/ARB
RCT	Randomized Controlled Trial
REM	Rapid Eye Movement sleep stage, “dream sleep”
RPP	Rate Pressure Product
SaO2	Oxygen Saturation
SBP	Systolic Blood Pressure
SCORE	Systematic Coronary Risk Evaluation model
SD	Standard Deviation
SESAR	Swedish Sleep Apnea Registry
Swedevox	Swedish Ventilator and Oxygen Treatment Registry
SWS	Slow Wave Sleep, N3 “deep sleep”
TIA	Transient Ischemic Attack

DEFINITIONS IN SHORT

Apnea-Hypopnea-Index	The number of respiratory events (apneas/hypopneas) per hour of sleep.
Apnea	Apnea in adults is scored when there is a drop in the peak signal excursion by ≥ 90% of pre-event baseline for ≥ 10 seconds.
OSA severity	*Mild OSA*: AHI from 5 -< 15/hour *Moderate OSA*: AHI 15-<30/hour *Severe OSA*: AHI ≥30 /hour
Hypopnea	Hypopnea in adults is scored when the peak airflow signal excursions drop by ≥ 30% of pre-event baseline for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal (AHI3, recommended), or 4% desaturation (AHI4, accepted).
Major adverse cardiovascular event	Defined as myocardial infarction, acute heart failure, stroke or CV death.
Null hypothesis	Hypothesis that there is no difference between groups. Statistical methods attempt to disprove the hypothesis for results to be significant.
Obstructive sleep apnea	Repetitive partial (hypopnea) or total (apnea) obstruction of breath, due to collapse of the upper airways, during sleep. AHI≥5 required if symptomatic or with CV comorbidities, and ≥15 otherwise. See Apnea, Hypopnea and AHI and OSA severity entries.

"When a person, especially advanced in years, is lying on his back in heavy sleep and snoring loudly, it very commonly happens that every now and then the inspiration fails to overcome the resistance in the pharynx of which stretor or snoring is the audible sign, and there will be perfect silence through two, three, or four respiratory periods, in which there are ineffectual chest movements; finally, air enters with a loud snort, after which there are several compensatory deep inspirations before the breathing settles down to its usual rhythm. In the case to which I allude there was something more than this. The snoring ceased at regular intervals, and the pause was so long as to excite attention, and indeed alarm."

First historic medical description of OSA by Dr W.H. Broadbent 1877[1].

1 INTRODUCTION

Despite one of the first observed obstructive sleep apnea (OSA) patient above, it was not until the 1970s that the diagnosis was defined[2] and later linked to hypertension[3,4]. OSA and hypertension are prevalent clinical conditions[5,6], both of which are strongly associated with an increased risk of future CV events, including stroke[7], myocardial infarction[8,9], heart failure[10,11], premature CV mortality[5,12-15], and atrial fibrillation[16]. The conditions also share several important risk factors and OSA promotes the development of hypertension[17,18]. Thus, patients often have both conditions and those that do may have a higher risk of developing these CV events as well as having them occur earlier in life. The magnitude of added risk with both conditions is not well established. It is well established that hypertensive patients with OSA are harder to treat successfully with antihypertensive medication alone[19] and blood pressure control using AHT is especially poor in such populations[20]. Suboptimal long-term adherence to primary prevention strategies for OSA[21] and hypertension[5,22] may be attributed to factors such as adverse side effects, low symptom burden, and limited patient motivation, particularly when the perceived risk is not immediate. These challenges mean that even if the patients are correctly diagnosed with both disorders (many are not) they might not achieve adequate treatment of the conditions leading to residual increased CV event risk.

To improve the management of OSA and hypertension and mitigate long-term CV risk, it is essential to identify patients at high risk of developing CV events. Furthermore, investigating whether particular classes and combinations of antihypertensive treatments (AHTs) demonstrate superior efficacy in patients with coexisting OSA and

hypertension are important to improve hypertension control. Addressing these questions requires a thorough understanding of the underlying physiology and current evidence related to CV risk, OSA, hypertension, and existing treatment guidelines. Moreover, this thesis will explore several unresolved scientific questions in the field. As there is a residual risk increase even in treated OSA and hypertension, it will be important to address additional modifiable risk factors for CV events, including smoking, obesity, hyperlipidemia, and diabetes, as part of a comprehensive prevention strategy. Additional treatment options for those not tolerating positive airway pressure (PAP) treatment or mandible advancement device (MAD) are needed as well as better subclassification of OSA to individualize OSA treatment[23], but these important research areas fall outside the scope of the current thesis.

1.1 LIFETIME CARDIOVASCULAR RISK

CV disease including coronary heart disease, stroke, peripheral artery disease, or heart failure is responsible for more than 17.5 million deaths worldwide each year[24]. It has been reported that almost 10 million of these deaths can be attributed to modifiable risk factors including unhealthy diet, inactivity, diabetes, obesity, hyperlipidemia, hypertension, smoking and poor sleep[25-27] (Figure 1). Those risk factors can contribute to varying degrees during a lifetime, for example, adequate food intake and physical exercise may be more important during childhood, other lifestyle factors such as smoking and alcohol may also become important in adulthood and co-morbidities take more prominent roles as age progresses.

There will be genetic differences in turn modifying the impact of each risk factor making predictions of CV risk even harder. The continuous development of arteriosclerosis throughout ageing, is thus often modified by several individual pathways. The importance of each risk factor can also change during different stages of the development of arteriosclerosis. By addressing modifiable risk factors, preventive intervention may delay CV morbidity and death thereby saving both quality of life and productivity while reducing suffering, as well as health costs[27]. This thesis focuses on two modifiable CV risk factors: hypertension and OSA.

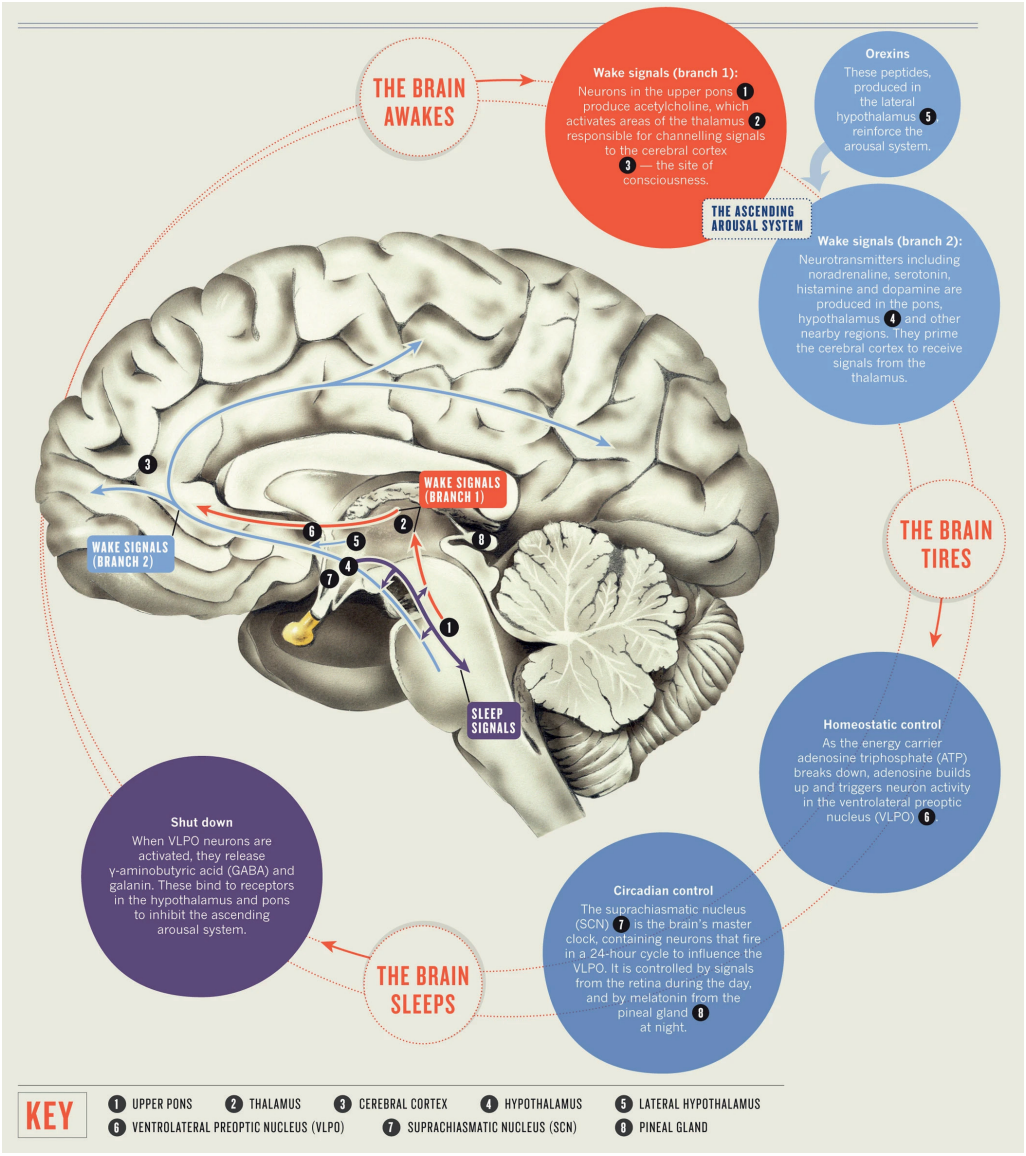
Figure 1. ***Life's Essential 8.*** *Life's Essential 8 according to American Heart Association, includes the 8 components of cardiovascular health: healthy diet, participation in physical activity, avoidance of nicotine, healthy sleep, healthy weight, and healthy levels of blood lipids, blood glucose, and blood pressure.*

https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8

1.1.1 SLEEP

Sleep is essential in all living creatures to function properly during wakefulness and to maintain health. High metabolism and intense activity lifestyle creatures tend to need to sleep for larger parts of their lifetime while slow and less active species can manage with less sleep[28,29]. Another crucial function is to be able to quickly awaken from sleep and immediately function adequately in case of emergency. Regulation of wakefulness and sleep is thus a very important factor for creature survival. Humans sleep about one third of their lifetime and disorders appearing during sleep can thus have significant impact on daily function and disease risk. During sleep, there are profound changes in brain activity and awareness, hormones, metabolism, cell function as well as modified settings for many regulatory systems and autonomic body functions like heart rate, breathing frequency and blood pressure[30,31].
Sleep is regulated by the circadian rhythm[32] (nucleus suprachiasmaticus, SCN, 7 in figure 2) and the balance between wakefulness promoting (Ascending Arousal

Figure 2. Sleep regulation and anatomy[33].

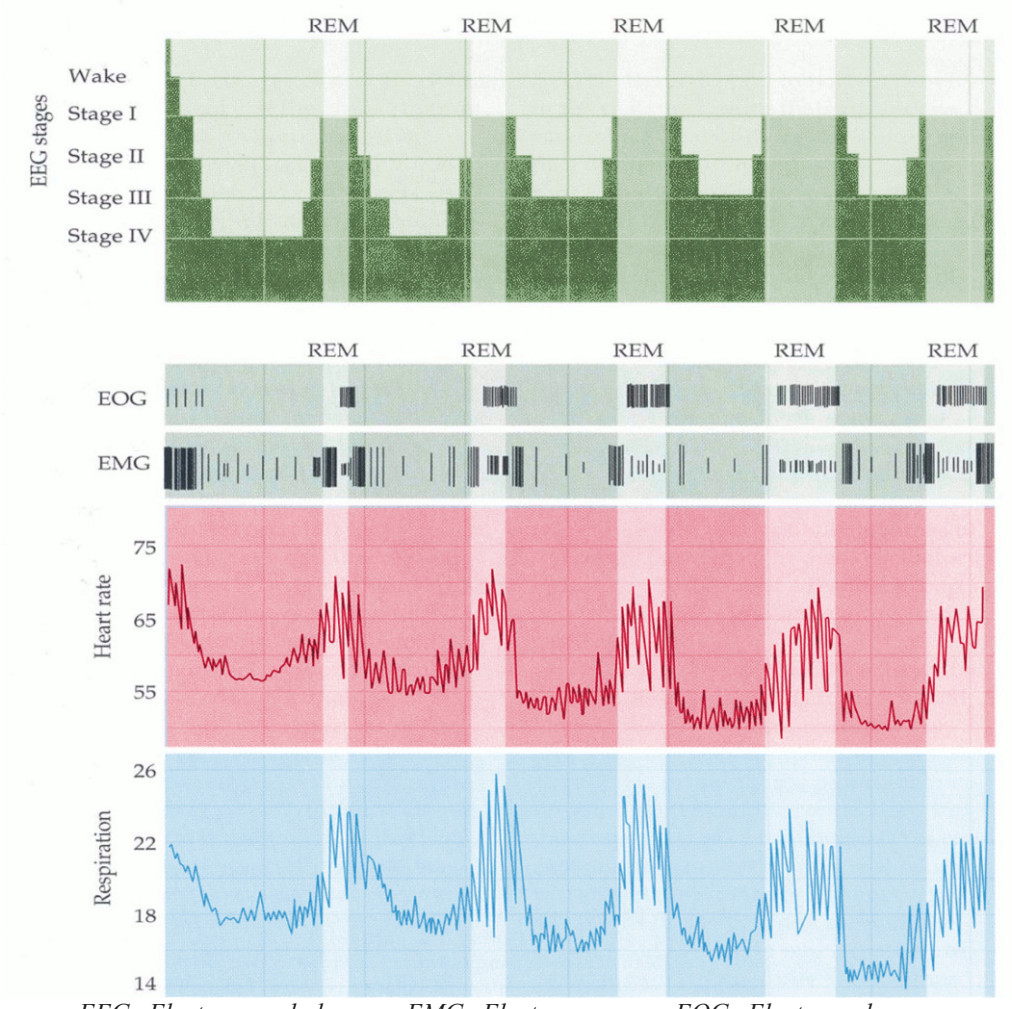


Used with permission, courtesy Springer Nature, Mark Peplow PhD.

System, 1-5 in figure 2) and sleep promoting (Ventrolateral Preoptic Nucleus, 6 in figure 2) regions of the brain[34]. The balance between wakefulness and sleep and circadian rhythm can be affected by conscious overruling when we opt to stay up late, take a daytime nap or in case of emergency. The longer we stay awake the more our sleep pressure/drive increases (Homeostatic control, 6 in figure 2) and eventually we will no longer be able to maintain wakefulness. Interestingly every cell also has its own clock

mechanism to regulate function during time of day[35]. Sleep structure is commonly described with hypnograms (green) showing sleep cycles with repeating patterns of sleep stages (Figure 3). Sleep cycles are categorized as electroencephalogram (EEG) based superficial sleep (stage 1 and 2), deep sleep (stage 3 and 4, now usually called stage N3 sleep or slow wave sleep) periods and finally rapid eye movement (REM) sleep at the end of each cycle. Early cycles have the main deep sleep periods that are essential for recovery and clearance of metabolites from the CNS[36] and rest and recovery for the body.

Figure 3. ***Sleep structure and changes in respiration and heart rate during sleep*** [37]



EEG=Electroencephalogram, EMG=Electromyogram, EOG=Electrooculogram, REM=Rapid-eye-Movement sleep stage

Unless we are sleep-deprived, deep sleep will be reduced in the latter half of the sleep period. The REM periods get longer in the later parts of the night and are important for memory consolidation, and sorting, emotional regulation as well as scenario training[38]. Electrooculography (EoG) captures the motor activity underlying the rapid eye movements that define REM sleep. Electromyography (EMG) primarily monitors motor activity in chin and the legs and is useful for diagnosing sleep-disrupting muscle activity. EMG also aids in distinguishing wakefulness from REM sleep, as heart rate, respiration, and EEG patterns can appear quite similar in these states. During REM sleep, muscle activity is markedly reduced (REM atonia), preventing individuals from physically acting out dream-related behaviours. During non-REM sleep, and particularly during deep sleep, the body rests with reduced ventilatory demand, heart rate, blood pressure, muscle activity, and metabolism. REM sleep, however, is physiologically more variable, characterized by pronounced fluctuations in ventilation, heart rate, and BP, resembling wakefulness but with suppressed muscle activity. In this thesis, the regulation of breathing, blood pressure, and heart rate during sleep are of primary relevance. (Figure 3, BP not shown). Due to reduced body metabolism and activity, less oxygenation and transportation of metabolites is needed during sleep. Reduced activity during sleep is important for recovery and repair both on cell and organ level. Reduced BP during sleep is important for preserving heart and blood vessel health and function and BP should have a dipping pattern on 24-h measurements with 10-15% lower BP during sleep. In fact, non-dipping BP[39], reduced sleep times and poor sleep quality[40] have been shown to be risk factors for CV disease[41,42].

1.1.1.1 SLEEP DIAGNOSTIC PROCEDURES

Sleep evaluation is commonly conducted using polysomnography (PSG) or indirectly from oximeter-based pulse wave-derived sleep classification. For the diagnosis of OSA, however, polygraphy (PG) is typically sufficient to confirm or exclude the condition (Table 1). PG captures many of the same physiological signals as PSG, with the notable exception of EEG parameters and EoG, necessary for sleep stage classification and scoring of arousals. Key signals recorded during PG include airflow, thoracic and abdominal respiratory effort, body position, and oximetry parameters such as oxygen saturation and pulse rate. Due to the absence of EEG and EoG, PG does not provide any hypnogram, nor does it allow for the detection of arousals or accurate measurement of total sleep time during the recording period. In straightforward cases like Figure 4, PG alone is adequate for OSA diagnosis. However, in borderline presentations, such as mild but sleep fragmenting OSA, disruptive snoring, or suspected comorbid sleep disorders, comprehensive evaluation with PSG may be warranted to ensure diagnostic accuracy and guide appropriate management.

Novel oximeter-derived signals like the pulse wave signals including Pulse Propagation Time (PPT) investigated in study I and used in pulse wave-derived sleep stage scoring are normally filtered away during basic PG but may provide additional information on CV status in future clinical investigations.

Table 1. ***Classification of sleep study types. Adapted from American Society of Sleep Medicine guidelines[43].*** *Although advanced sleep studies offer richer insights, they are resource-intensive in terms of both execution and interpretation. Most sleep studies are now done at the patient's home, unless interventions during the night is called for, but PSG especially with video is still often in house at a sleep clinic.*

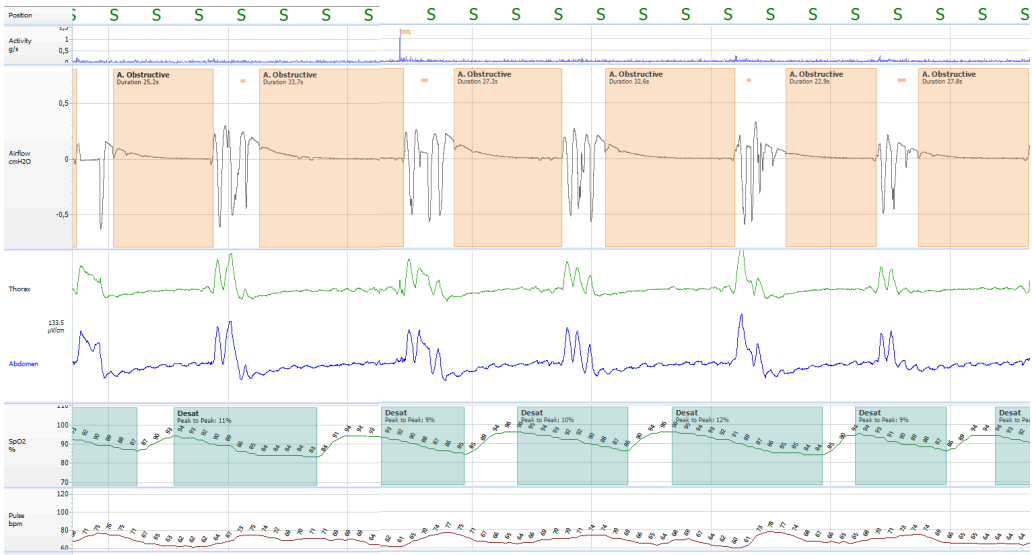
Level	Setting	Physiological Parameters Monitored	Purpose and Clinical Application	Resource Intensity
1	In-laboratory	Electroencephalography (EEG), Electrooculography (EOG), Electromyography (EMG), Electrocardiography (ECG), Oxygen Saturation (SpO2), Respiratory Effort, Leg Movements (15-20 sensors) Airflow, position	Comprehensive sleep architecture analysis, evaluation of complex sleep disorders, neurological comorbidities	Highest
2	Home-based	Equivalent to Level 1, without on-site technical supervision	In-depth sleep analysis, elucidation of equivocal sleep disturbances, pediatric patients, and individuals preferring a home environment	High
3	Home-based	Respiratory Effort, SpO2 , Heart Rate, Snoring, Body Position (4-7 sensors) Airflow	Diagnosis of obstructive sleep apnea (OSA), assessment of respiratory-related sleep disorders	Moderate Low
4	Home-based	Heart Rate and Oxygen Saturation (SpO2) (1-2 sensors)	Initial screening for sleep-disordered breathing, risk stratification for sleep apnea, rapid preliminary assessment	Low

Advantages of Level 1 Studies	Advantages of Level 3 Studies	Advantages of Level 4 Studies
Provides the most granular physiological data, enabling detection of the full spectrum of sleep disorders. Benefits from professional on-site monitoring and expert interpretation.	Offers an optimal balance between diagnostic accuracy and patient convenience. Highly effective for the diagnosis of obstructive sleep apnea in a comfortable home setting, incurring lower costs compared to laboratory-based studies. Lacks information on sleep stages.	Characterized by ease of application, facilitating rapid preliminary screening. Cost-effective and suitable for serial monitoring to assess treatment efficacy or disease progression.

1.1.2 OBSTRUCTIVE SLEEP APNEA

OSA is a prevalent disorder with a global prevalence varying between 5-50% for clinically relevant adult OSA and total prevalence reaching even higher in some countries[6]. In OSA, collapse of the upper airway leads to disrupted breathing during sleep. Complete collapse leads to apneas with increasing hypoxia linked to apnea length, and eventually a stress reaction causing an arousal and restoration of breathing. Partial obstruction of the upper airway can lead to turbulent airflow and vibrations causing snoring and if flow reduction is > 30% to hypopneas, with similar breathing pattern but often less hypoxic burden compared to apneas (see definitions for full description). The severity of the hypoxia and duration is also affected by body mass index (BMI), lung function, age and comorbidities. Apneas and hypopneas often return directly when the patient falls asleep again, leading to patterns with repeated apneas/hypopneas and arousals with a few undisturbed breaths between them (see figure 4). OSA leads to poor sleep quality linked to varying degrees of daytime sleepiness. The repetitive hypoxia and stress reactions promote high blood pressure, sympathetic activation and accelerated atherosclerosis (section 1.1.2.4 and Figure 6). Thus, OSA can eventually lead to CV disease[15].

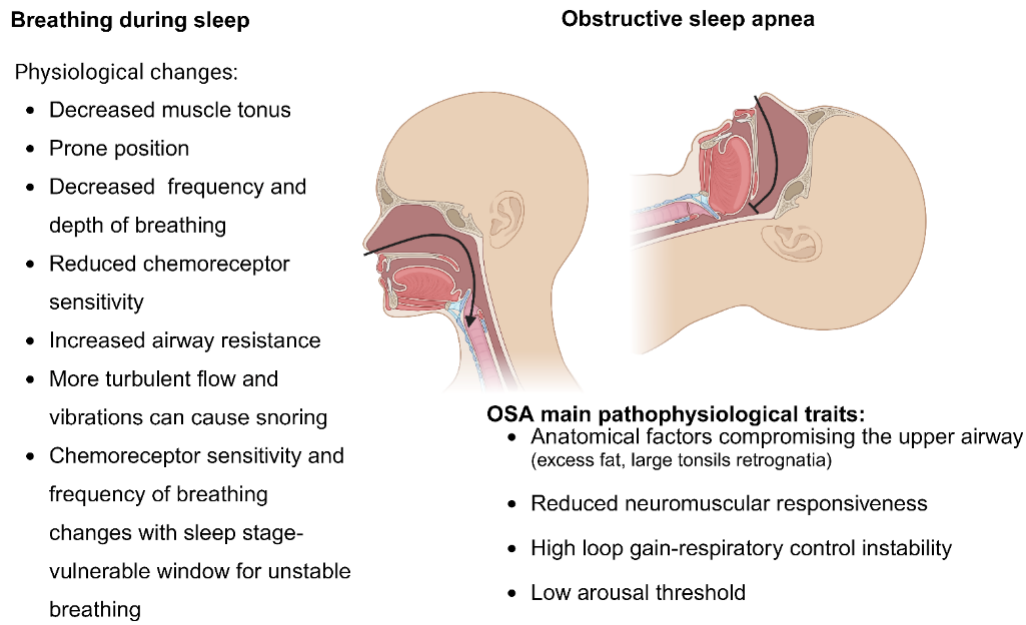
Figure 4. ***Severe sleep apnea on polygraphy.*** *Repetitive apneas followed by periods of hyperventilation (flow signal) with consecutive episodes of intermittent hypoxia and heart rate surges (oximetry, oxygen saturation and pulse).*



Signals from top to bottom: Position, Activity, Airflow, Thorax and Abdominal belts for respiratory effort, oxygen saturation and pulse. In obstructive apneas respiratory effort remains but no airflow passes the upper airway leading to increasing hypoxia and pulse increases.

The pathophysiology of OSA[44] is manifold (Figure 5). There are substantial changes in drive to breathe, muscle function and chemoreceptor sensitivity during sleep and even between sleep stages[45,46]. Chemosensitivity changes are most pronounced during REM sleep. The gravitation pull in the prone position will cause changes in airway shape and collapsibility and a fluid shift to tissues around the neck from the lower body in prone position, has been described to contribute to a reduced airway diameter[47,48]. Anatomical factors such as retrognathia, tonsil or tongue hypertropia and fat deposits around the airway increase risk of sleep disordered breathing but OSA can be present without such factors[48,49]. Reduced pharyngeal, and tongue muscle tonus during sleep is another key component in OSA and differ between individuals but can also change depending on current drive to breath during sleep[48,50] (Figure 5).

Figure 5. ***Sleep related changes and sleep apnea traits.***



Created in BioRender. Svedmyr, S. (2025)

Obstructive apneas are distinct from central apneas, which are characterized by a lack of respiratory effort due to unstable respiratory drive. Central sleep apnea (CSA) is commonly observed in patients with atrial fibrillation or chronic heart failure, where delayed circulation and increased chemosensitivity leads to fluctuations in respiratory drive. This can result in cyclical patterns of hyperventilation alternating with central apneas, a phenomenon known as Cheyne–Stokes respiration[48,51]. CSA may also emerge during the initiation of PAP therapy for OSA[52], or because of respiratory inhibitory medications[53]. Further complicating

the clinical picture, fluctuations in respiratory drive and effort also influence upper airway muscle tone, potentially contributing to obstructive events. These obstructive events, in turn, may exacerbate respiratory instability[48].

1.1.2.1 ENDOTYPES

Endotypes are subpopulations within a disorder with different specific pathomechanisms causing the disease. OSA is not considered a homogeneous disorder. Several endotypes have been described with different mechanisms leading to repetitive apneas/hypopneas[54,55]. Most patients seem to express the characteristics of several endotypic traits (Figure 5) that contribute to their OSA. Not all OSA patients are obese or have compromised upper airway anatomical structures causing their disrupted breathing. Frequent arousals and shifts in sleep stage may cause instability in respiratory control causing variations in drive for breathing and muscle tonus, which means low arousal threshold plays an important part in some patients[54,55]. Patients with very strong reactions to breathing events are also vulnerable to instable breathing as they tend to hyperventilate more intensely after an event. The overreaction leads to reduced pCO_2 and high saturation which can cause subsequent apneas due to the decreased drive of breathing. The complicated mechanisms behind this phenomenon are referred to as high loop gain[56]. The upper airway neuro-muscular compensation to an apnea can also be impaired in some patients. Integration of endotyping in routine OSA diagnosis is expected to make individualized treatment in OSA feasible in OSA patients[10,23]. It is not yet known whether certain endotypes are associated with increased CV risk, but high collapsibility tends to give more hypoxic burden during sleep and can therefore be suspected to have higher risk.

1.1.2.2 ASYMPTOMATIC OSA AND SYMPTOMATIC OSAS

While this thesis focuses on CV risk as indication for treatment, it is important to recognize that the main reason to treat OSA is to provide better sleep and quality of life in patients with symptomatic OSA syndrome (OSAS)[57]. However, perhaps surprisingly, not all OSA patients suffer from poor subjective sleep quality and increased daytime sleepiness[58]. Depending on arousal threshold and chemosensitivity, varying degrees of sleep apnea can occur without impacting sleep structure and quality of sleep. On the other hand, patients who sleep with maintained sleep structure despite severe sleep apnea often have more severe hypoxic burden. Patients with disturbed sleep have very diverse degree of daytime symptoms in OSA[59]. Cognitive functions such as concentration and memory may be affected, and fatigue and sleepiness are common in symptomatic OSA. Excessive daytime sleepiness can have a major impact on quality of life, social function, productivity and increased risk of accidents[57]. Stressful awakenings with shortness of breath and palpitations are sometimes present, but surprisingly rare, likely due to how memory function works in humans in transition from sleep to wake.

For the long-term memory to awaken you often need to be awake for more than a minute. As most OSA related awakenings are very short, patients seldom remember them after a night's sleep. In fact, often bedpartners are more disturbed by the patients snoring and apneas than the patient themselves. It has been suggested that symptomatic OSA patients have a CV risk and a degree of adherence to PAP that differs from that of asymptomatic patients[60].

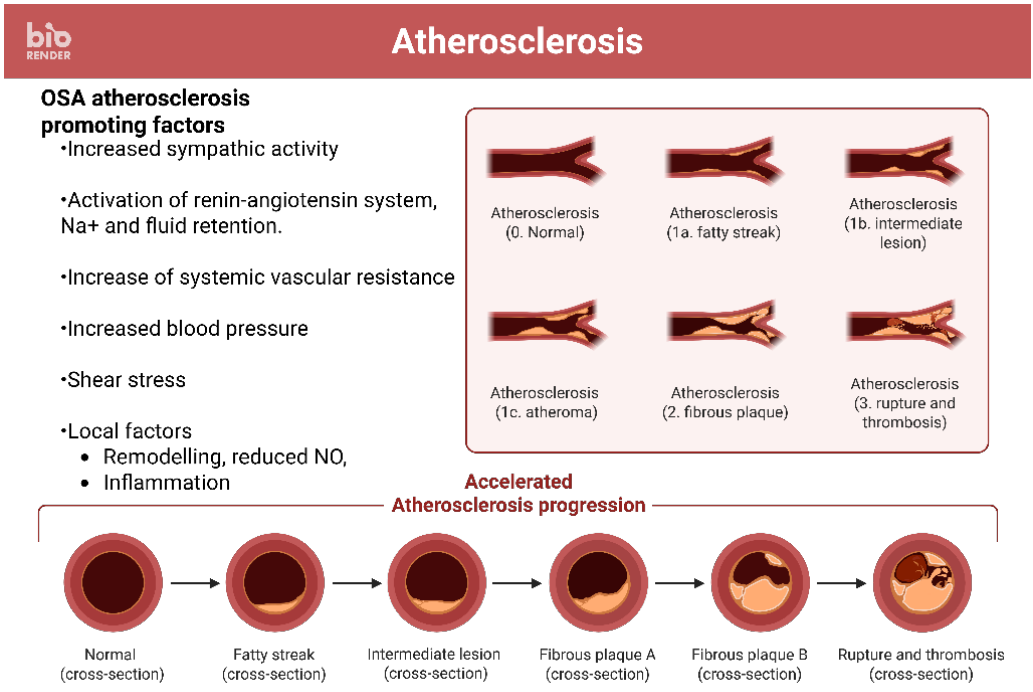
1.1.2.3 OSA AS A MEDIATOR FOR HYPERTENSION

Several mechanisms have been described for how OSA promotes the development of hypertension[61]. Poor sleep quality, repeated hypoxia, increased sympathetic drive, negative intrathoracic pressure swings and long-term negative effects of adaptive defence mechanisms, such as activation of the renin-angiotensin system and fluid retention, all contribute to increased and maintained high blood pressure[19,62]. The high blood pressure leads to increasing shear pressure that affects the blood vessels, activates local factors that promote inflammation and arterial remodelling which tends to maintain hypertension (Figure 6). OSA also causes insulin resistance[63] and increased harmful lipids[64,65], further increasing atherosclerosis and raising CV risk. Increased pulse, cardiac output and peripheral vasoconstriction may lead to accelerated vascular ageing and increased pulse pressure, which is linked to increasing end organ damage (kidney and brain especially, see also Figure 10). Resistant hypertension (see section 1.1.3.7) is common in hypertensive patients with untreated OSA[66]. One important step in hypertension development in OSA is the development of a non-dipper pattern in 24h BP measurements[67]. The normal dip in BP during sleep no longer occurs and BP might even increase. Soon the cascade of hypertension promoting pathways (see 1.1.3.1) lead to persistent hypertension even if morning pressure may remain more elevated than mean BP.

1.1.2.4 ACCELERATOR FOR ARTERIOSCLEROSIS AND MEDIATOR FOR CV RISK

All the mechanisms described above accelerate the development of arteriosclerosis and hypertension and lead to manifest CV disease earlier in life for many OSA patients. In particular, intermittent hypoxia activates low grade inflammation as a key factor promoting accelerated atherosclerosis. This is supported by high sensitivity CRP and pro-inflammatory cytokines and by reduction in anti-inflammatory markers in OSA[68]. Functional studies showed reduced vasodilatation[69] and imaging data thickened intima-media thickness of large vessels in OSA[70]. Many of these changes in OSA has also been shown to be reversable by PAP treatment[71].

Figure 6. ***Atherosclerosis and hypertension development and accelerating factors in OSA***



Created in BioRender. Svedmyr, S (2025)

1.1.2.5 OSA RELATED RISK FOR ACCIDENTS AND CANCER INCIDENCE

OSA has several other important consequences where our scientific knowledge about pathomechanism and magnitude of risk varies. It is well documented that OSA patients have an increased risk for traffic and work-related accidents[72,73] and PAP treatment has been shown to reduce these risks[74]. The highest risk is in monotonous situations with single drivers. Regulations for driver's license holder, especially in occupational drivers, have been reinforced in order to reduce the risks related to sleepy driving (Figure 7). Similar actions are taken among other occupations with dire consequences in case you fall asleep or lose vigilance[75]. Finally, OSA is linked to increased incidence of malignant cancers of several types on a population level[76].

Figure 7. ***Reduced vigilance can have major consequences!***

Regulations for occupations with high demands on vigilance and responsibility have stricter regulations. Uncontrolled hypersomnia, characterized by irresistible short sleep episodes in monotonous situations, is the most common cause of accidents. Even without full sleep episodes, impaired vigilance and slowed reaction times can be sufficient to trigger accidents. Picture AI-generated by gamma.app, by Sven Svedmyr 2025.

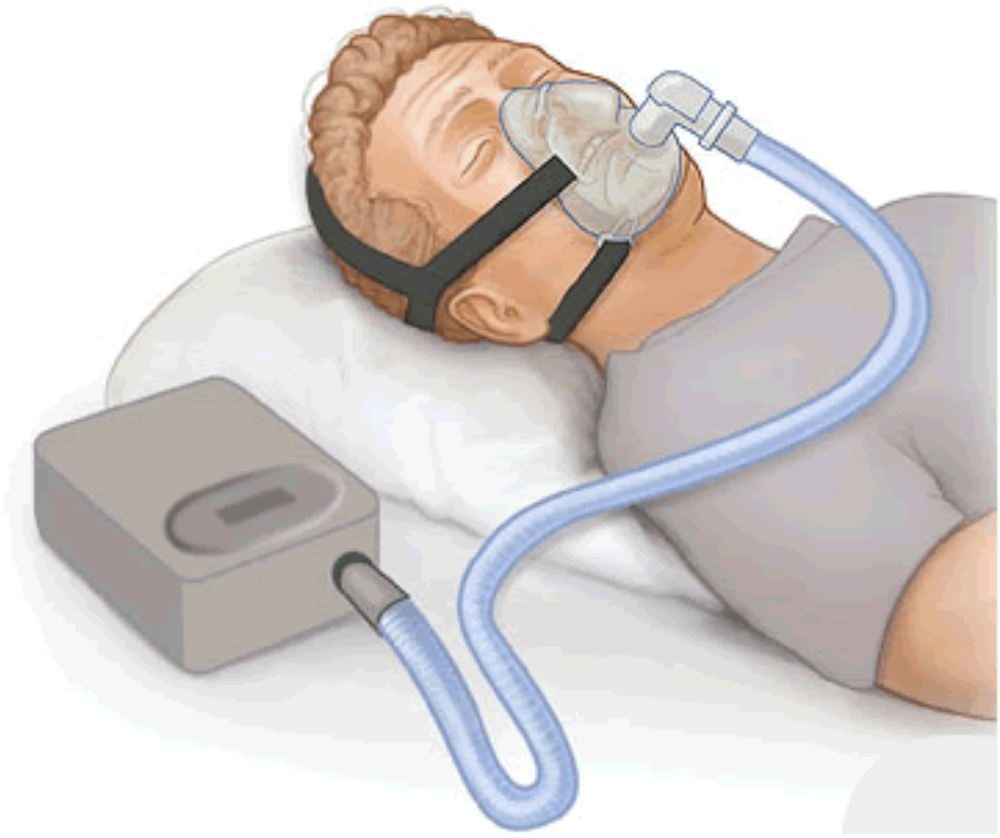
1.1.2.6 OSA TREATMENTS

OSA is a treatable disease that impacts both quality of life and future health. There is no doubt on indication for treatment in symptomatic OSA and these patients are often highly motivated. Which asymptomatic OSA patients need treatment is still under discussion. Patients with primary preventive indication for treatment may be less motivated and their adherence may be poorer.

1.1.2.6.1 Positive airway pressure

Positive airway pressure was originally invented in Australia 1980 by Colin Sullivan and published in *Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares.* Lancet 1981, Sullivan et al. [77]. Though technical advancement has improved PAP devices making them smarter, less noisy and less burdensome, the basic principle of applying a pressure to stabilize the upper airway, remains the same. For many symptomatic OSA patients the treatment causes significant improvements in quality of life and health benefits. PAP therapy was initially delivered at a fixed pressure, with each patient's optimal level determined through overnight titration in a hospital setting.

Figure 8. ***PAP treatment.***



Used with permission, courteous creative commons licence Wikipedia.

Today, most PAP devices are autoregulated (APAP), automatically adjusting pressure to optimize treatment for each patient. This approach minimizes recurrent disruptions in therapy, such as those occurring when a patient shifts to a prone sleeping position or enters a REM sleep period, where the patient often requires higher pressures[78]. Many algorithms for APAP control have been developed[79]. Less pressure reduces the risk of leaks and makes the treatment more tolerable in most patients. If well tolerated, the PAP treatment is very effective and results in almost complete resolution of all relevant sleep apnea and snoring. There is still a rational to use fixed PAP pressure in some patients, for example in mixed apneas or treatment emergent CSA[52] due to instable respiratory regulation or if patients do not tolerate higher pressures. Recently it has also been suggested fixed PAP may provide better CV risk prevention than APAP[80]. However, regardless of fixed or APAP, many patients struggle with accepting the PAP mask or

pressure needed or experience other side effects like swallowing air. Adherence to the treatment is limited with about 55% still using the treatment after 10 years[21] or even quicker decline in adherence in a French study where 50% still used their PAP after 3 years[81]. Adherence is strongly linked to patients' motivation, improvement of subjective symptoms, bedpartner demand, and perceived improvements in CV health. It is difficult to motivate asymptomatic patients to undergo a somewhat burdensome treatment that offers no immediate benefit, but only potential—though not guaranteed—health advantages years later. The minimum daily use of PAP to be considered adherent is still unclear, but at least 4 hours each night, at least 5 nights each week, is usually recommended.

1.1.2.6.2 Mandible advancement devices

Mandible advancement devices (MAD) aim to maintain upper airway patency during sleep by advancing the lower jaw and the tongue preventing it from falling back into the hypopharynx. In general, MADs are often better tolerated than PAP[82], but side-effects like teeth- or jaw joint pain or bite changes and drooling may limit the acceptance of MAD therapy. It is recommended first line therapy in mild and moderate OSA, but in severe OSA residual disordered breathing, may occur. The overall mean effects size in severe OSA is an approximate 50% reduction of AHI, with reported improvement of residual oxygenation and sleep quality[83]. Patients often report remarkable subjective improvements comparable to PAP-treatment. MAD treatment is associated with blood pressure improvements in hypertensive patients. The effect size on blood pressure is comparable to PAP treatment, and the combination of PAP and MAD has recently shown superior blood pressure reducing effects[84,85].

1.1.2.6.3 Weight loss regimes

While not all OSA patients are overweight or obese, weight reduction may be the most effective way that OSA patients can reduce nocturnal breathing problems and degree of OSA[86]. Reductions in degree of OSA severity by weight loss are well documented[87] with a mean AHI decrease of 2.6% per 1% weight reduction. For PAP treated patients this will lead to lower pressure demand and reduced leaks which can improve PAP comfort and adherence. Weight loss and maintenance of weight provide a challenge for most people. Dietary advice and lifestyle changes to promote more activity and exercise may be effective and are often paramount also in OSA patients with PAP or MAD to prevent worsening of OSA degree by weight gain. Surgical weight loss has been shown to be effective in reducing weight and OSA in obese patients but has perioperative risks as well as risk of long-term side-effects like malabsorption[88]. Recently several drugs (GLP-1 agonists) have shown strong reduction in body weight (-20%) and AHI (-50%)[89-91]. Subsequently, the combined GLP-1 and GIP agonist tirzepaptide has been approved as the first drug treatment labelled for OSA treatment in the US[92].

1.1.2.6.4 Upper airway surgery

OSA is frequently linked to anatomical factors such as enlarged tonsils, hypertrophic uvula or the soft palate which act to obstruct the upper airway[93]. Several surgical techniques have been applied in OSA patients, including tonsillectomy and uvulopalatopharyngoplasty as the most frequently applied ones. Surgery along with adenoidectomy are still first-line treatment in children with OSA[94]. Randomized trials in adults have shown beneficial effects in patients with enlarged tonsils after 6 months[95]. These positive results maintained even at long-term follow up in patients without weight gain over time. Relapses of OSA occur with concomitant weight gain within a few years[96]. Moreover, side-effects such as difficulties to swallow and pain, have been described, and these surgical methods are no longer first line treatments in adults. However, they may help in select cases or improve results of treated OSA with residual breathing and disrupted sleep, or be the only treatment option if PAP, MAD and weight reduction are ineffective or not tolerated. Moreover, more conservatory surgical methods are recommended to reduce the risk of side-effects[97]. Tracheostomy remains a drastic but effective way to treat the most severe cases of symptomatic OSA where all other treatments have failed[98].

1.1.2.6.5 Pharmacological treatment

Along with more knowledge of different OSA endotypes, several suggested pharmacological treatment approaches have been suggested[23]. Weight loss treatment with GLP-1 agonists was mentioned above. Other strategies include a combination of Atomoxetine and Oxybutynin (Ato/Oxy)[99] and Carbonic anhydrase inhibitors (CAI)[100] and both are currently studied in OSA. CAI has been previously used in high altitude sickness and appears to modify loop gain via an inhibition of the enzyme carbonic anhydrase, which modifies pH and pCO_2 as well as the respiratory drive. High respiratory loop gain is linked to high chemosensory drive and hyperventilation in approximately one-third of patients with OSA[101,102]. A high loop gain is therefore linked to unstable breathing, and this pathomechanism may provide a potential therapeutic target[55,103]. The placebo corrected AHI reduction for the CA inhibitor Sulthiame, was between 30 and 49% in a recent phase 2 trial[100].

Ato/Oxy or CAI are not yet clinically available but will likely be a complement to traditional treatments where residual OSA and symptoms are found or in patients who do not tolerate PAP and MAD.

1.1.2.6.6 Nerve stimulation

Electric stimulation of the hypoglossus nerve (HNS) to increase muscle activity of the tongue can improve airway stability and reduce apneas. So far, treatments are expensive and require careful selection of suitable patients[104]. There are few studies exploring HNS in hypertensive OSA with negative or inconclusive result[105]. This treatment modality is not clinically available in Sweden yet.

1.1.2.6.7 Positional training

Position dependent OSA incorporates patients with a dominant sleep apnea in the supine position. Avoiding sleeping on their back can significantly reduce their OSA. Several variants of devices to make patients avoid the supine position have been introduced starting with strapping of a tennis ball or a "backpack" to the back or using buzzers to interrupt sleep each time the patient turns to the supine position. Results vary and the main problems are negative impact on sleep quality and low tolerance. However, careful selection of patients is needed to obtain a clinically useful effect[106].

1.1.2.7 PARTIAL TREATMENT/RESIDUAL OSA

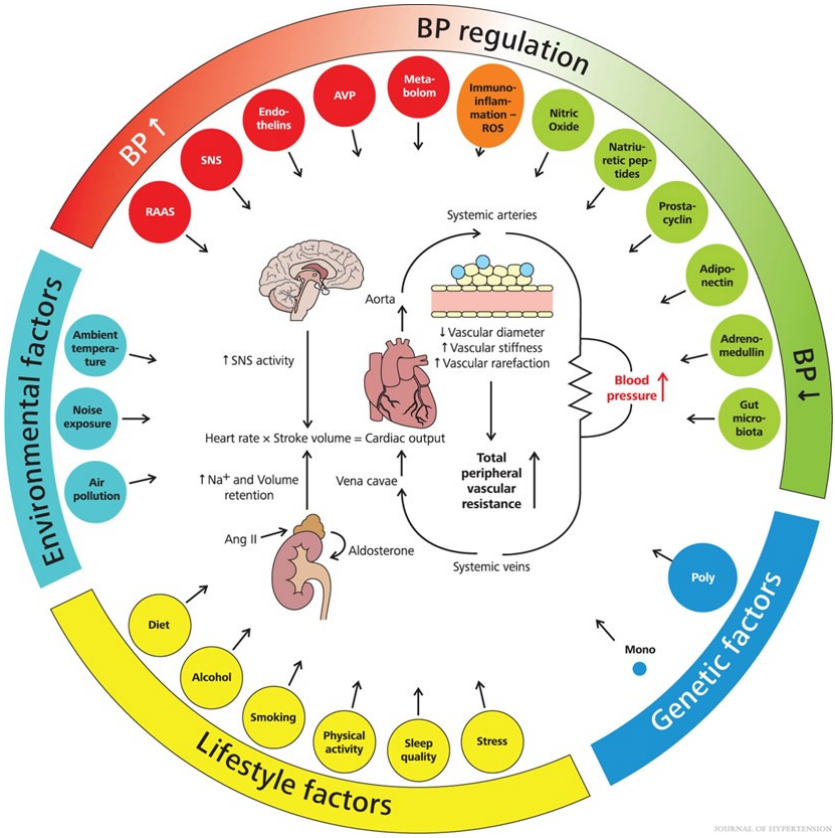
Many OSA patients do not tolerate PAP and MAD and may not be suitable for the less conventional treatments above. The degree of OSA alleviation[107] in patients treated with PAP or MAD is around 50% when considering the adherence, due to patients using the treatment only for part of the night or not using it every night. Thus, it cannot be assumed that all OSA and hypertension patients will have adequate OSA control. Varying degrees of residual daytime symptoms are also not unusual in treated OSA patients, despite having objectively well controlled breathing during sleep[108]. It is unclear if these residual symptoms affect residual CV risk.

1.1.3 HYPERTENSION

1.1.3.1 DEFINITION AND DEVELOPMENT OF HYPERTENSION.

Heart rate and blood pressure are highly variable throughout the day depending on physical demand, psychological factors, as well as the state of wakefulness and sleep. In fact, pulse and blood pressure variability are a sign of a healthy CV system[109]. There has been lots of interest into different bio signals using variability measures to assess CV function[110-112]. However, if blood pressure remains elevated for longer periods of time these short-term positive adaptions can have negative consequences, and the individual may develop sustained hypertension with negative long-term consequences for the entire CV system. Lifestyle factors, genetics, environmental factors, and co-morbidities affect the pathophysiology of hypertension, and these complex contributors have been highlighted by the European Society of Hyåertension (ESH) (Figure 9). Initially high cardiac output and increased vascular resistance lead to elevated systolic blood pressure (SBP)[113]. In this dynamic phase of hypertension long-term adaptation and consequences of the high blood pressure like ventricular hypertrophy or vascular stiffening may not yet have developed and may even be prevented if treatment starts early.

Figure 9. ***Mechanisms involved in BP regulation and the pathophysiology of hypertension***[22].



RAAS=Renin-Angiotensin-Aldosterone-System, SNS= Sympathetic Nervous System, AVP= Arginine VasoPressin ROS= Reactive Oxygen Species and Ang II= Angiotensin II. Used with permission, courtesy Wolters Kluwer, 2023 ESH Guidelines for the management of arterial hypertension.

Eventually the strain of continuously high pressures together with physiological ageing will trigger several mechanisms promoting CV remodelling and increased arterial stiffness[114]. In a vicious circle, such remodelling process promotes further rise in blood pressure and end organ damage - primarily in the brain, heart, and kidneys. The risk for major CV events such as stroke, myocardial infarction, cardiac failure, and atrial fibrillation increases over time[22]. It is likely that reversing these manifest changes in the CV system becomes more difficult and require longer periods of successful treatment. Some changes may even be irreversible. There is convincing evidence from both epidemiological and interventional studies, that blood pressure lowering antihypertensive medication as well as lifestyle changes drastically can reduce the risk

of early major adverse CV events[22,115]. Recommendations for hypertension diagnosis (Table 2), treatment strategies and target BPs have been defined and updated. Certain co-morbidities such as diabetes, should prompt even lower BP targets.

Table 2. ***European guideline recommendations. Monitoring Blood Pressure & Actions***[21]**.** *For AHT please see section 1.1.3.5.*

Category	BP Range (mmHg)	Recommended Action
Optimal BP	<120 / <80	• Repeat BP at least every 5 years
Normal BP	120–129 / 80–84	• Repeat BP at least every 3 years
High-Normal BP	130–139 / 85–89	• Consider masked hypertension • Repeat BP annually • Consider ABPM or HBPM
Hypertension	≥140 / ≥90	• Confirm diagnosis via: → Repeated office BP measurements → Out-of-office BP (ABPM or HBPM)

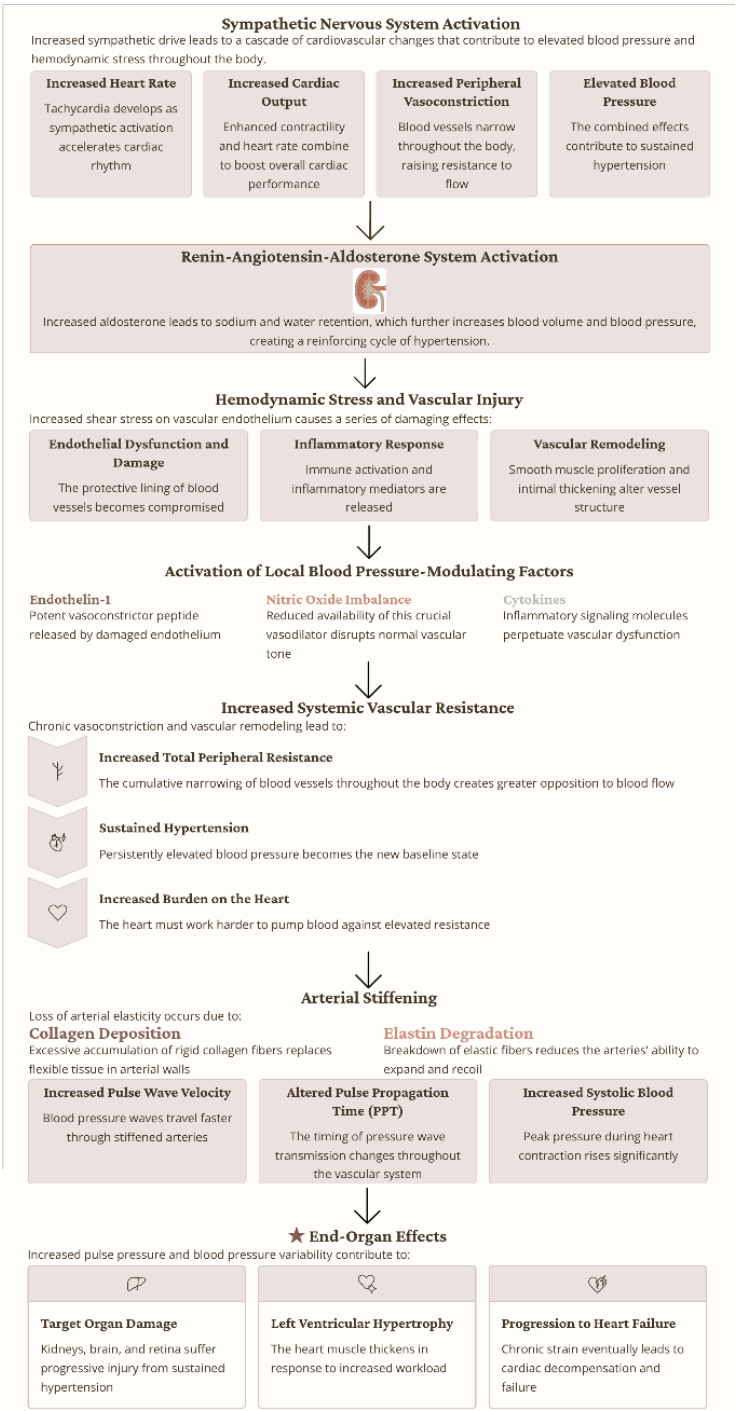
ABPM: Ambulatory Blood Pressure Monitoring, HBPM: Home Blood Pressure Monitoring, BP: Blood Pressure

1.1.3.2 PATHOFYSIOLOGY OF HYPERTENSION

Development of hypertension and atherosclerosis includes multiple risk factors contributing to increased blood pressure and vascular remodelling (Figure 1 and 9). Genetic factors[116] modify the impact of these risk factors or can in some cases lead to these changes in the absence of other risk factors. Some risk factors are relatively constant, while others may vary during life. Further, short-term adaptive mechanisms to these changes tend to have negative long-term effects. Hypertension is divided into primary (also called essential hypertension) and secondary hypertension. Secondary hypertension described in 1.1.3.5 has specific causes and often more severe hypertension with earlier age of onset. Hypertension promotes more advanced changes in the CV system through multiple pathways. While some changes can be considered part of the natural ageing process, but occur earlier in life with additional risk factors, other mechanisms are more clearly pathological.

The sympathetic nervous system (SNS) is strongly activated by repetitive hypoxia in OSA (section 1.2) but may also be due to other causes. The increased sympathetic drive affects the heart with increased heart rate and cardiac output and the peripheral vessels

Figure 10. ***Pathophysiology of Hypertension and Atherosclerosis.***



OSA is involved in all steps. In particular, repetitive hypoxia and reoxygenation and disrupted sleep activates a potent activation of the SNS, raises RAAS activity, amplifies inflammatory response in the vessels and activates local BP elevating factors. Along with accelerated atherosclerosis, these pro-hypertensive factors contribute to high pressure pulse waves and end organ damage (section 1.2).

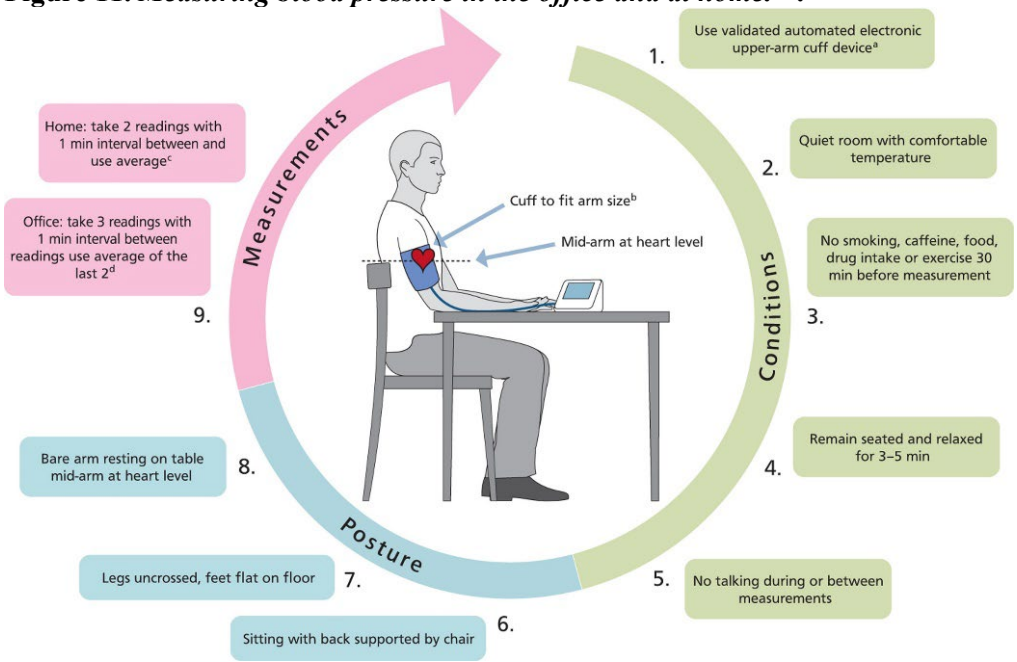
with vasoconstriction, all leading to elevated BP[117]. The renin-angiotensin-aldosterone system (RAAS) in the kidneys and adrenal gland helps regulate salt and water homeostasis and BP is normally activated by low BP or blood volume[118]. However, the system can also be activated by stress and comorbid OSA[119,120]. Activation of the RAAS leads to increased sodium and water retention and causes vasoconstriction promoting increased blood volume and BP[119]. Angiotensin is converted into Ang II by angiotensin-converting-enzyme (ACE) mainly in the endothelium in the lungs and kidneys. Ang II leads to increased oxidative stress, smooth vascular muscle contraction, endothelial dysfunction and fibrosis and RAAS is implicated in the pathogenesis of not only hypertension but also atherosclerosis, heart failure and kidney disease. Aldosterone is also elevated in patients with obesity[121], a major risk factor for both hypertension and OSA. On top of Ang II activating local factors on the blood vessels, the high blood pressure itself causes shear stress on the endothelium, which causes endothelial dysfunction and damage[122]. The inflammatory response to the damage in turn promotes vascular remodelling and nitric oxide imbalance and cytokine activation[123]. At this point removing the initial triggering mechanisms for hypertension may no longer lead to rapid normalization of BP. Chronic vasoconstriction from increased sympathetic drive, RAAS activation and vascular remodelling contributes to increased peripheral resistance and sustained hypertension that in turn, leads to additional vessel damage, atherosclerosis acceleration, and increased burden for the heart. As inflammation, vascular remodelling and atherosclerosis progress the arteries lose elasticity leading to arterial stiffening which reduces the dampening effect in the vessel for the pulse wave[114]. The pulse pressure thereby increases which promotes end-organ damage (Figure 10). Progressive atherosclerosis also leads to the development of plaques that may rupture and cause major adverse CV events such as stroke or myocardial infarction[124] (Figure 6).

1.1.3.3 DIAGNOSIS: MEASURING BLOOD PRESSURE

"Measurement of blood pressure was first made by an English clergyman, Stephen Hales, in 1708 and was published 1733. Having previously experimented on dogs, he used a brass pipe connected to a 9 feet hollow glass tube applied into an artery in the left crural artery of a horse and recorded a resultant rise of the column of blood of 8 feet 3 inches and noticed a rise and fall of 2-5 inches every heartbeat. In 1881 Ritter von Basch introduces a clinically useful instrument for the non-invasive measurement of blood pressure in humans and in 1896, Scipione Riva-Rocci developed the prototype of the now commonly used manual sphygmomanometer based on the von Basch's model".

Haemostaticks, Statistical essays Vol 2, Stephen Hales 1733, Jeremy Booth 1977[125]

Figure 11. ***Measuring blood pressure in the office and at home.*** [22].



Used with permission, courtesy Wolters Kluwer, 2023 ESH Guidelines for the management of arterial hypertension.

Measuring blood pressure has been standardized to evaluate BP in a controlled setting for more consistent and comparable results over time (Figure 11). Thus, we can reduce misinterpretation of temporary BP changes such as white coat hypertension[126]. However, even with standardized procedure for office BP measurement, we need to be aware of that BP can vary considerably due to the method of analysis, from office BP

to home measurements as well as through other factors including the circadian cycle/time of day. 24-hour home measurements should be considered in unclear cases[22]. Results from 24-h BP has been shown to have best predictive values for later outcomes[127] and can identify nighttime BP hypertension i.e. "non-dippers"[67,128,129].

1.1.3.4 DIAGNOSIS: STAGING OF HYPERTENSION AND THE EUROPEAN RISK SCORING MATRIX

Based on epidemiological and clinical studies, hypertension is graded by BP levels (Table 3). The ESH 2023 guidelines recommend CV risk assessment in patients with hypertension. Two widely used and implemented European CV risk matrix, the SCORE[130] (Systemic Coronary Risk Estimation) and the updated SCORE 2[131] are included in the ESH risk evaluation.

Table 3. ***Classification of Office BP and Hypertension Grades.***[22]

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	< 120	< 80
Normal	120–129	and/or 80–84
High Normal	130–139	and/or 85–89
Grade 1 Hypertension	140–159	and/or 90–99
Grade 2 Hypertension	160–179	and/or 100–109
Grade 3 Hypertension	≥ 180	and/or ≥ 110
Isolated Systolic Hypertension	≥ 140	and < 90

BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated. The same classification is used for all ages from 16 years.

Assessments are recommended in apparently healthy patients with stage 1 hypertension to assess an individual's 10-year risk of fatal and nonfatal CV events (Figure 12). It is not recommended in patients *already at high or very high risk* (hypertension stage 2 and 3) due to established CVD or chronic kidney disease (CKD), long-lasting or complicated diabetes, severe hypertension mediated organ damage (HMOD, e.g. left ventricle hypertrophy-LVH) or a markedly elevated single risk factor (e.g. cholesterol, albuminuria).

Sex, SBP, non-HDL cholesterol level, age and smoking determine a patient's ten-year CV risk in SCORE 2. Similar adjusted matrixes are available for elderly patients (SCORE-OP and SCORE2-OP) and regional versions exist considering differences in CV risk in European regions. Note however that the European Society of Cardiology (ESC) starts with SCORE 2 (or appropriate modified version) for the general

population, for those who do not have manifest CV disease (LVH not counted), diabetes or severe comorbidities.

The ESH risk matrix considers comorbidities, number of risk factors (Table 4), hypertension mediated organ damage (HMOD), manifest kidney disease or diabetes or manifest CV disease on top of the grade of hypertension. Stage 1 comprises varying grades of hypertension without kidney disease, diabetes or CV disease, stage 2 includes patients with HMOD, diabetes or kidney disease (grade 3). Stage 3 defines patients with manifest CV disease or grade 4 kidney failure. The hypertension stage is referenced against the hypertension grade to give an estimation of low, moderate, high or very high CV risk over the upcoming 10 years, with an increasingly stronger indication for treatment with higher risk. Risk stratification is particularly crucial in individuals with high-normal blood pressure or grade 1 hypertension, as it may influence clinical decisions regarding the initiation of antihypertensive pharmacotherapy.

Figure 12. ***ESH CV risk according to grade and stage of hypertension***.[22].

Hypertension disease staging	Other risk factors, HMOD, CVD or CKD	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1	No other risk factors[a]	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2	HMOD, CKD grade 3, or diabetes mellitus	Moderate to high risk	High risk	High risk	Very high risk
Stage 3	Established CVD or CKD grade ≥4	Very high risk	Very high risk	Very high risk	Very high risk

	<50 years	60–69 years	≥70 years	
	<2.5%	<5%	<7.5%	Complementary
	2.5 to <7.5%	5 to <10%	7.5 to <15%	risk estimation in Stage 1
	≥7.5%	≥10%	≥15%	with SCORE2/SCORE2-OP

HMOD-hypertension mediated organ damage, CKD-chronic kidney disease, CVD-cardiovascular disease, BP-blood pressure (DBP-diastolic, SBP-systolic). Used with permission, courtesy Wolters Kluwer, 2023 ESH Guidelines for the management of arterial hypertension.

Table 4. ***Risk factors increasing CV risk*** *(ESH guidelines)*[22]**.**

Category	Risk Factors
Demographic	- Age SCORE 2 - Male gender SCORE 2
Lifestyle	- Smoking SCORE 2 - Sedentary lifestyle - Overweight or obesity - Healthy diet
Clinical Measurements	- Systolic blood pressure SCORE 2 - Non-HDL cholesterol SCORE 2
Psychosocial & Environmental	- Psychological or socioeconomic factors - Environmental factors (air pollution, noise) - Depression
Metabolic & Endocrine	- Diabetes (Type 1 or 2)
Sleep & Respiratory	- Sleep disorders (especially OSA) - Chronic obstructive pulmonary disease (COPD)
Inflammatory & Infectious	- Chronic inflammatory diseases - Chronic infections
Family & Genetic	- Family history of early hypertension or CVD
Geographic	- Regional risk
Previously Manifest Event or Diagnosis	- Increased large artery stiffness - Established cardiovascular or kidney disease

1.1.3.5 SECONDARY HYPERTENSION

When hypertension is caused by specific mechanism outside of primary hypertension, it is be referred to as secondary hypertension which may require specific diagnostic approaches, that allow us to detect their specific causes and to select effective drug treatment or specific interventional treatment. Severe or true resistant hypertension is often a sign of secondary forms of hypertension as are worsening of previously controlled hypertension or increased severity of complications, especially if disproportionate to the duration of hypertension. Secondary hypertension should be suspected especially in younger patients (<40yrs) with severe or treatment resistant hypertension, although some forms appear in older patients as well (Table 5).

Traditional secondary hypertension causes are renal artery stenosis or other renal disorders, endocrine disorders such as primary aldosteronism, pheochromocytoma, Cushing syndrome or hyperthyroid disorders. Secondary hypertension can also occur in pregnant women with eclampsia for example.

Table 5. ***Clinical indicators for suspecting secondary hypertension***[22]

Clinical Scenario	Rationale
Patients <40 years with grade 2 or 3 hypertension or any childhood hypertension	Early-onset hypertension often suggests underlying pathology
Sudden onset of hypertension in previously normotensive individuals	May indicate an acute secondary cause (e.g., renal or endocrine)
Acute worsening of BP control in previously well-controlled patients	Suggests new or progressing secondary condition
Resistant hypertension	Defined as uncontrolled BP despite ≥3 medications, including a diuretic
Hypertensive emergency (grade 3 or malignant hypertension)	Severe elevation may reflect secondary etiology
Severe/extensive HMOD disproportionate to BP duration or severity	Organ damage out of proportion to BP history suggests secondary cause
Clinical presentation of typical endocrine disorders	Symptoms like hypokalemia, palpitations, or adrenal masses warrant evaluation
Suspected obstructive sleep apnea (OSA)	OSA contributes to hypertension via sympathetic activation, hypoxia and disrupted sleep

Whether OSA is a kind of secondary hypertension is debated as it is often described as a strong accelerator of primary hypertension instead. Even if the downstream hypertension mechanisms activated in OSA are the same as in primary hypertension, initial mechanisms are not. Repetitive hypoxia and very high sympathetic activation are specific for OSA and might therefore qualify as secondary hypertension. 24-hour BP measurement is recommended in suspected secondary hypertension and may help identify OSA by "non-dipper pattern" (see 1.1.1) with absence of normal BP reduction during sleep or even raised nighttime BP. Non-dipper pattern in has been shown to increase CV risk independently from hypertension grade[132].

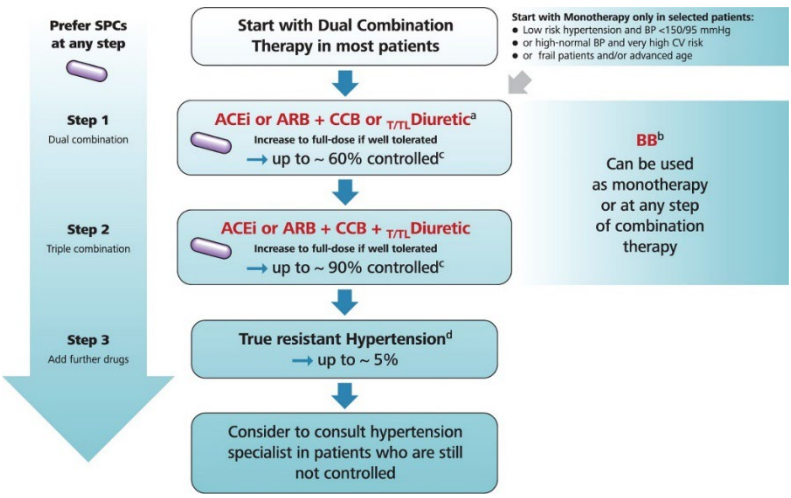
1.1.3.6 ANTIHYPERTENSIVE TREATMENT

When hypertension is diagnosed, patients are strongly advised to make improvements in lifestyle, like increased exercise, improved diet, smoking cessation and reduction of stress. Depending on the initial grade of hypertension, most patients also require pharmacological treatment. In low CV risk, low grade hypertension lifestyle improvement can sometimes be adequate alone, but follow-up visits to verify BP control are important. Current European guidelines[22] recommend starting with two antihypertension drugs for most patients (Figure 13). Type of AHT is often ACEi/ARB combined with CCB or diuretic, but some comorbidities can affect drug class choice. ACEi/ARB is even more important in diabetes patients to protect the kidneys, ACEi/ARB is often combined with betablockers and diuretics in heart failure, and betablockers also play a role in cardiac arrythmias for example.

The new ESC 2024 hypertension guidelines were updated 2025[133] and focus on high-risk patients. They suggest some changes to hypertension classification, but treatment recommendations are only marginally different. Reaching the recommended hypertension control is still challenging as most hypertensive patients do not have any symptoms motivating them to be adherent in pharmacological treatments. Adherence to AHT is around 75-90%, but is generally lower in lower socioeconomic patients, complex medication regimes and patients with poorer lifestyle factors[134]. Taking multiple pills with possible side effects and cost now to prevent potential future problems may not be of highest priority for the individual in question. Clinical inertia, defined as the failure of clinicians to appropriately intensify antihypertensive therapy, represents another major barrier to blood pressure control. This phenomenon may contribute more to uncontrolled hypertension than patient nonadherence to prescribed pharmacological regimens. Thus, improving AHT is still a major challenge with only about 50% of patients reaching optimal BP control[135].

Using combination pills has been advocated as one option to improve compliance along with motivational approaches. Current European ESC/ESH hypertension guidelines both recommend combination treatment for most patients with newly diagnosed hypertension and continuous re-evaluation of BP control with additional medication added until BP is well controlled. As hypertension tends to progress with increasing age repeated checks for hypertension control are important and likely improve AHT compliance. There is often a need to add additional AHTs to maintain BP control.

Figure 13. ***Starting anti-hypertensive treatment***[22].



SPC: single-pill combinations, ACEi: angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, CCB; calcium channel blocker, BB; betablocker. Used with permission, courtesy Wolters Kluwer, 2023 ESH Guidelines for the management of arterial hypertension.

1.1.3.7 RESISTANT HYPERTENSION

When target blood pressure levels are not reached despite using three or more AHTs, this severe hypertension is called resistant hypertension[22]. Apart from poor AHT adherence, OSA is the most common reason for resistant hypertension and among patients with resistant hypertension 80% have been shown to have OSA[66,136]. Treatment of OSA has been shown to improve BP control in resistant hypertension[39,137]. Secondary hypertension and particularly OSA, should thus be considered in patients with resistant hypertension.

1.2 OSA AND ARTERIAL HYPERTENSION: PATHOPHYSIOLOGICAL INTERPLAY

OSA and arterial hypertension frequently coexist, creating a clinically significant overlap with profound CV consequences. Epidemiological evidence indicates that 30–50% of individuals with hypertension exhibit OSA[138-141], with prevalence exceeding 80% among those with resistant hypertension[66,136]. Conversely, 40–60% of patients with moderate-to-severe OSA present with arterial hypertension[139,142-144], underscoring a robust bidirectional association. Although this relationship is most pronounced in obese, middle-aged men, it remains clinically relevant across sexes and age groups. Hypertension and OSA share many risk-factors including age, obesity[89,145], smoking[146,147] and alcohol use[148]. OSA often appear earlier in life in males than in females. OSA becomes more prevalent after menopause[149,150] and with increasing age. The shared risk factors along with OSA promoting hypertension frequently leads to an overlap between these disorders. It is important to recognize that OSA and hypertension can co-occur in different ways. In some patients, hypertension might be caused by OSA and would not be present if OSA had not been present. In other patients, hypertension might be due to other factors not mainly related to the OSA. In many of the patients, hypertension may be explained on OSA along with other risk factors. In other words, hypertension can be a mediator for OSA on CV risk but also be an independent risk factor separately. It is evident that the impact of OSA treatment may differ between patients with these clinical differences.

The connection between OSA and hypertension is mediated by multiple, interrelated mechanisms:

Intermittent Hypoxia and Increased Sympathetic Overactivity (OSA specific)

Recurrent apnoeic episodes induce cyclical hypoxia and reoxygenation, stimulating peripheral chemoreceptors and sustaining sympathetic nervous system activation[151-153]. This leads to nocturnal and daytime blood pressure elevations through increased catecholamine release and augmented vascular tone.

Endothelial Dysfunction and Oxidative Stress

Hypoxia–reoxygenation cycles generate reactive oxygen species, fostering oxidative stress and systemic inflammation. These processes impair nitric oxide bioavailability, resulting in endothelial dysfunction and diminished vasodilatory capacity[154].

Renin–Angiotensin–Aldosterone System (RAAS) Activation

OSA activates RAAS via sympathetic pathways and hypoxia-driven renal mechanisms, elevating angiotensin II and aldosterone levels. This promotes sodium retention, vascular remodelling, and sustained hypertension[119,120].

Baroreflex Impairment and Vascular Stiffness

Chronic sympathetic stimulation attenuates baroreflex sensitivity[155], while inflammatory mediators and oxidative stress accelerate arterial stiffening, perpetuating hypertensive states[156,157].

Sleep Fragmentation and Neurohumoral Dysregulation

Frequent arousals disrupt slow-wave sleep, altering hypothalamic–pituitary–adrenal axis activity and increasing cortisol secretion[158]. This neurohumoral imbalance synergizes with sympathetic overdrive to further elevate blood pressure. As previously described, most of these mechanisms are present in OSA or hypertension alone but get amplified and sustained in patients with both disorders. The cumulative impact of these mechanisms explains why OSA is a major contributor to resistant hypertension and why blood pressure reduction with PAP therapy is often modest, particularly in normotensive or mildly hypertensive individuals. These observations highlight the need for integrated therapeutic strategies targeting sympathetic activity, RAAS, and endothelial function alongside upper airway stabilization.

A comprehensive understanding of these mechanistic pathways is essential for designing tailored interventions aimed at mitigating CV risk in this high-risk population.

1.3 GAPS OF KNOWLEDGE

Despite the extensive body of knowledge regarding OSA and its association with hypertension, and the strong evidence indicating that OSA not only contributes to the development of hypertension and CV[19,159] complications but also activates and sustains all known pathological mechanisms of hypertension (as outlined in Figure 10)[119,120,151-154,156,157], disseminating this information to general practitioners and cardiologists remains a significant challenge.

Hypertension and CV risk are major areas of medical research, attracting substantial interest and investment from pharmaceutical companies. This has led to the execution of very large-scale, well-funded RCTs focusing on pharmacological interventions. In contrast, sleep medicine—and OSA in particular—represents a smaller and less commercially supported field. The lack of pharmacological treatment options specifically for OSA has also contributed to limited financial resources, restricting much needed research to RCTs in smaller selected populations and cohort studies that often face methodological limitations, as previously discussed.

Consequently, many cardiologists have not fully acknowledged the role of OSA in CV disease. Initially, there was considerable scepticism, with many attributing the risks observed to obesity rather than to OSA itself[160]. Debates surrounding causality and confounding factors in cohort studies persist[161,162]. However, the consistent findings linking OSA to increased CV risk are gradually gaining recognition, and OSA is now acknowledged as a significant risk factor in guidelines for hypertension[22] and CV risk prevention[27].

Nevertheless, the protective effects of OSA treatment remain under investigation, and studies evaluating AHT in patients with hypertensive OSA are still scarce. There are RCTs on PAP reversing endothelial dysfunction[163-165] in OSA and improving BP[166-168], but no convincing RCT evidence on CV protective effect in primary or secondary prevention, apart from subgroup analyses. There are few RCTs comparing different AHTs but more comparing single drug to placebo. All AHTs seem to work in hypertensive OSA but some data suggest better effects of RAAS blockers, beta blockers or mineral corticoid receptor /aldosterone antagonist (Table 6 and 7). Without clear evidence that treating OSA modifies CV risk, the clinical impact of diagnosing OSA outside of sleep clinics remains uncertain and potentially limited.

With high CV risk in OSA patients with hypertension and poor BP control, there is a need to further study AHTs and combinations to see if type of AHT matters and if any AHT or combination have superior effect in this high-risk population. Further information on PAP treatment protective effects in primary and secondary CV prevention is still needed.

There is a need for more accurate methods to identify OSA patients at the highest CV risk, as intensified management and follow-up may be most effective in those at greatest risk. Current knowledge is limited regarding differences in CV risk among patients with both OSA and hypertension compared to those with either condition alone. Furthermore, it remains unclear whether applying lower BP targets, like those recommended for patients with diabetes, could provide preventive benefits in hypertensive OSA.

Table 6. ***Randomly controlled trials on multiple AHTs in OSA.***

Study (Year)	Drugs Compared	Population & Design	BP Outcome	Key Findings
Mayer et al. (1990)	Metoprolol (betablocker) and cilazapril (ACEinhibitor)	12 patients with OSA+ hypertension.	Both treatments lower nighttime BP C stronger effect	C stronger effect in REM No effect on AHI.
Pelttari et al. (1998)	Atenolol, the calcium antagonist isradipine, hydrochlorothiazide and the ACE inhibitor spirapril	18 obese OSA patients with hypertension, RCT double blind crossover	BP lowered	Beta-blockers reduce BP variability, but all reduce BPs. Small changes in nBP.
Salo et al. 1999	Atenolol, the calcium antagonist isradipine, hydrochlorothiazide and the ACE inhibitor spirapril	RCT, OSA+ hypertension. double-blind crossover	Not main outcome	HRV and BPV resonded better to betablocker.
Kraici (2000)	Atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan	40 OSA patients with HTN, RCT crossover	All reduced BP	Beta-blocker had better DBP and nBPs than the rest.
Heitmann (2010)	Nebivolol vs Valsartan	31 OSA patients with hypertension, RCT	Comparable BP lowering	Both drugs effective for BP, betablocker gave lower pulse rate.
Zou et al. (2010)	Beta-blockers vs ACE inhibitor	16 OSA + HTN patients, RCT	Both lowered BP	ACE inhibitors and beta-blockers effective for BP, doxazosin had less effect on nBP
Kario et al. (2014)	Nifedipine, a calcium channel blocker vs carvedilol, a nonselective β - blocker/α1 - blocker	OSA-related hypertension, prospective, randomized, parallel - group crossover design	CCB had stronger nighttime BP effects but both improved nBP	Nighttime dosing of a vasodilating or a sympatholytic antihypertensive drug can be effective for OSA-related nHTN
Ziegler (2017)	Beta1-blocker vs Hydrochlorothiazide	31 OSA + HTN patients completed study, RCT	Both lowered BP effectively	Diuretics may have added benefit on OSA severity
Shi (2019)	Metoprolol vs Amlodipine	Hypertensive OSA patients, RCT	Effective BP reduction	Similar BP effects. betablocker did not reduce Pulse rate
Lucca et al. (2023)	Chlorthalidone + Amiloride vs Amlodipine	65 patients Moderate OSA + HTN, double-blind RCT	Similar BP reduction	Mainly studied BP variability and find similar results between groups.
Cicheleroet al. (2024)	Chlorthalidone/amilorid e with amlodipine	OSA patients with grade 1 hypertension	Both treatments lower BP	No effect on AHI.
Schwartz et al. (2024)	Atomoxetine+Spironolac tone vs atomoxetine alone	21 Hypertensive OSA patients, RCT	Significant BP reduction	Superior BP reduction in combination treatment

ACE=angiotensin-converting-enzyme inhibitor, CCB=Calcium channel blocker, n=nighttime, RCT= randomly controlled trial.

Table 7. Information from cohort studies and reviews on AHT in OSA.

Study (Author, Year)	Design & Population	Intervention	Key Outcomes	Major Findings
OPTISAS2 multicentre randomized controlled trial baseline data. (Revol et al., 2018)	213 French high CV risk OSA patients with hypertension	Comparative effectiveness of AHTs	Blood pressure control and antihypertensive effectiveness	ARBs (sartans) demonstrated superior blood pressure lowering effects alone or in combination with another AHT.

Review (Author, Year)	Included Studies	Focus	Main Findings	Clinical Implications
Kou et al., 2022 (J Hypertension)	49 RCTs, 4,893 patients	Effects of OSA treatments on BP	MRAs and ACEI/ARBs most effective; CPAP modest BP reduction	Combination therapy recommended for BP control in OSA

ACE=angiotensin-converting-enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=Calcium channel blocker, MRA=mineralocorticoid receptor antagonist, n=nighttime, RCT= randomly controlled trial.

Potential differences in the protective effects of PAP therapy between OSA patients with and without hypertension have not been established. High PAP adherence may be particularly important in hypertensive OSA. These hypotheses, however, have yet to be rigorously tested. We need more real-world data on different AHTs in hypertensive OSA patients to improve hypertension guidelines to aid optimal prescription and clinical results not only in BP control but future comorbidity and survival for patients with both OSA and hypertension. If the real-world data shows differences in AHT and combination of AHT efficiency in hypertensive OSA, the need for large-scale prospective RCTs becomes evident.

In this thesis, we identified an opportunity to build on previously described evidence by examining whether patients with both OSA and hypertension experience an additive—or a potentially synergistic—CV risk. We also aimed to explore the primary preventive effects of PAP in this high-risk population, leveraging the strengths of cohort methodology to address questions that are difficult to answer through RCTs alone. Finally, we used cohort study design in study 3 and 4 exploring AHT in OSA before and during PAP treatment.

2 AIM

2.1 OVERALL AIM OF THE THESIS

To enhance risk stratification and optimize treatment strategies for patients with *coexisting hypertension and OSA*. This includes identifying high-risk phenotypes, clarifying the interplay between OSA and hypertension in CV outcomes, and evaluating whether tailored interventions—such as adjusted AHTs or improved adherence to positive airway pressure therapy—can reduce CV risk in this population.

2.2 SPECIFIC AIMS

I. *Evaluation of a diagnostic method:*
To evaluate a potential pulse wave signal for simple, accessible methods for identifying patients at elevated CV risk. The reflection of the finger pulse waveform, measured as PPT, serves as a reliable indicator of arterial stiffness and can be continuously monitored during sleep. This study aimed to explore the associations between sleep architecture, sleep-disordered breathing, hypertension, and PPT in individuals with suspected OSA. We hypothesize that PPT is associated with established CV risk factors but independently predicts hypertension status. Furthermore, we expect PPT to be shorter in patients with OSA and hypertension, reflecting increased arterial stiffness in these known CV risk increasing disorders.

II. *Primary prevention of CV disease risk in OSA and hypertension:*
This study aimed to analyse long-term CV risk for patients with OSA and hypertension, by comparing patients with hypertension only, OSA only and patients with combined hypertension and OSA to controls in a prospective registry-based cohort in Sweden. Further, effects of interventions with PAP, in the OSA subgroups, were assessed as modifying factors in primary prevention of major adverse CV events (MACE)/death. We hypothesized that patients with combined hypertension and OSA diagnoses have the highest risk, which can be mitigated by PAP treatment.

III. *Evaluation of antihypertensive treatment in OSA, part 1:*
This study aimed to evaluate the degree of blood pressure control among untreated OSA patients receiving various AHTs. As OSA is promoting several pathophysiological features of hypertension, BP control is generally poor in this patient group. BP control while using both mono and dual AHT regimens in untreated OSA patients, were compared across different drug classes. Considering these mechanisms, we hypothesized antihypertensive agents with sympathoinhibitory effects, such as beta blockers, may offer superior efficacy in this population.

IV. *Evaluation of antihypertensive treatment in OSA, part 2:*
Subsequently, study IV, aimed to determine AHTs with best BP control in PAP treated OSA and to evaluate PAP related BP improvement at follow-up across AHT drug classes in mono- and dual AHT. As OSA treatment by PAP reverses many of the pathophysiological mechanisms involved in OSA including the increased sympathoadrenergic drive, and the activated RAAS, we hypothesized that AHT drug classes other than BB may be associated with improved BP control in adherent PAP treated hypertensive OSA patients.

3 PATIENTS AND METHODS

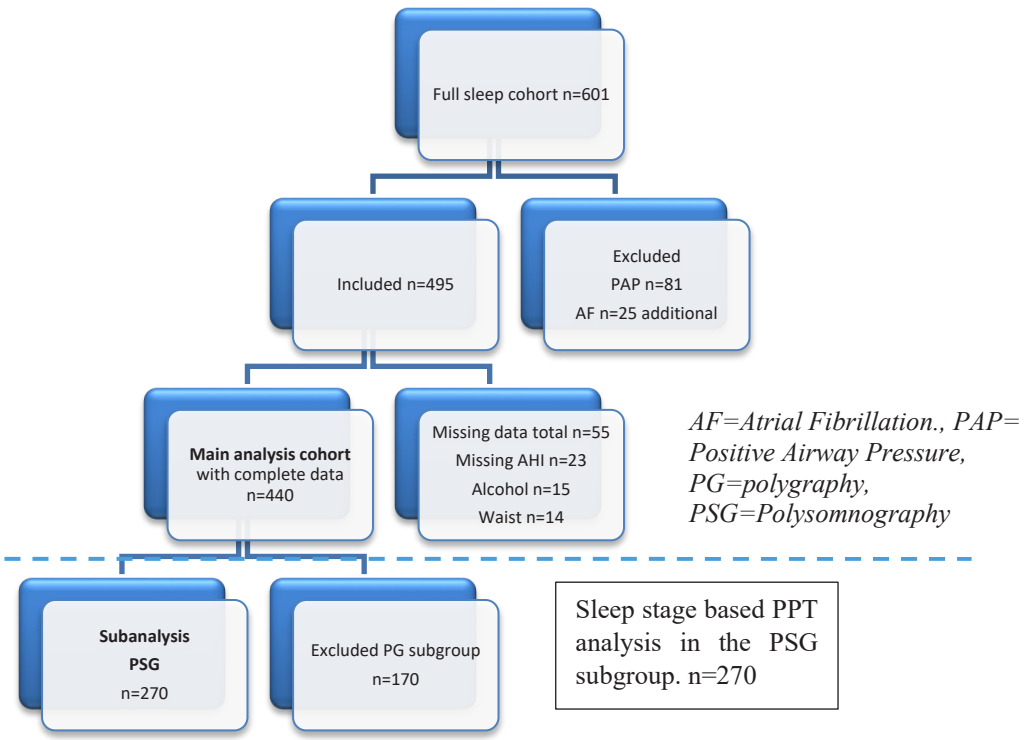
In this thesis we studied patients with suspected sleep apnea (study I) or patients with an established diagnosis of OSA (study II-IV). Table 8 contains important clinical data at baseline for all these cohorts.

3.1 PATIENT COHORTS

3.1.1 STUDY I, A MULTICENTER COHORT OF PATIENTS WITH SUSPECTED OSA.

A total of 601 subjects were recruited between November 2009 and April 2011 from five sleep centers— one in Sweden (Gothenburg) and four located in Germany (Berlin, Nuremberg, Solingen, and Wuppertal). Patients referred to sleep studies due to suspected sleep apnea or for follow-up monitoring of the condition were eligible for inclusion. The study aimed to evaluate a novel oximeter-based pulse signal analysis in routine OSA diagnosis. Due to an irregular pulse wave form and pulse rate, patients with atrial fibrillation were excluded. The final analysis included data from 440 patients.

Figure 14. ***Study I cohort.***



3.1.2 STUDY II, DISCOVERY 2.0

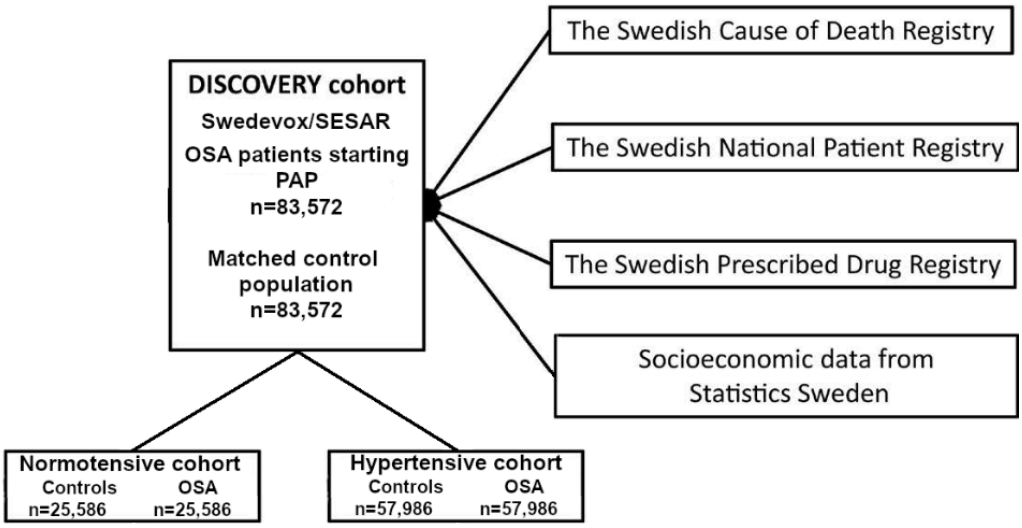
The DISCOVERY (Course of DISease in patients reported to the Swedish CPAP Oxygen and VEntilator RegistrY) 2.0 cohort[169] (Figure 15) contains anonymized data for patients with OSA and a control population without OSA, obtained by cross-referencing several Swedish quality registries with the aid of Swedish personal identification number. Data was available for diagnoses, anthropometrics, medications prescribed and delivered to patients at Swedish pharmacies, diagnostic sleep study results and OSA treatments at baseline. In addition, incident CV disease or death and OSA treatment information during the follow-up time have been gathered.

In study II four groups were defined:

OSA only, combined hypertension and OSA, hypertensive controls, and normotensive controls assembled 2008-October 2022. OSA patients were from the Swedevox and/or SESAR at PAP treatment start, while non-OSA controls were gathered from population-based control group was identified from Statistics Sweden's Living Conditions Surveys (ULF/SILC)[170], which consists of a random selection of approximately 6,000 people between the ages of 16 and 74 years in Sweden repeated every year since 1987. The control cohort is from the same time span as the study population. Data from the ULF/SILC regarding age, gender, length, weight, smoking, housing type, living area, civil status and year of study are collected for the study. The control group was divided into controls with or without hypertension diagnosis.

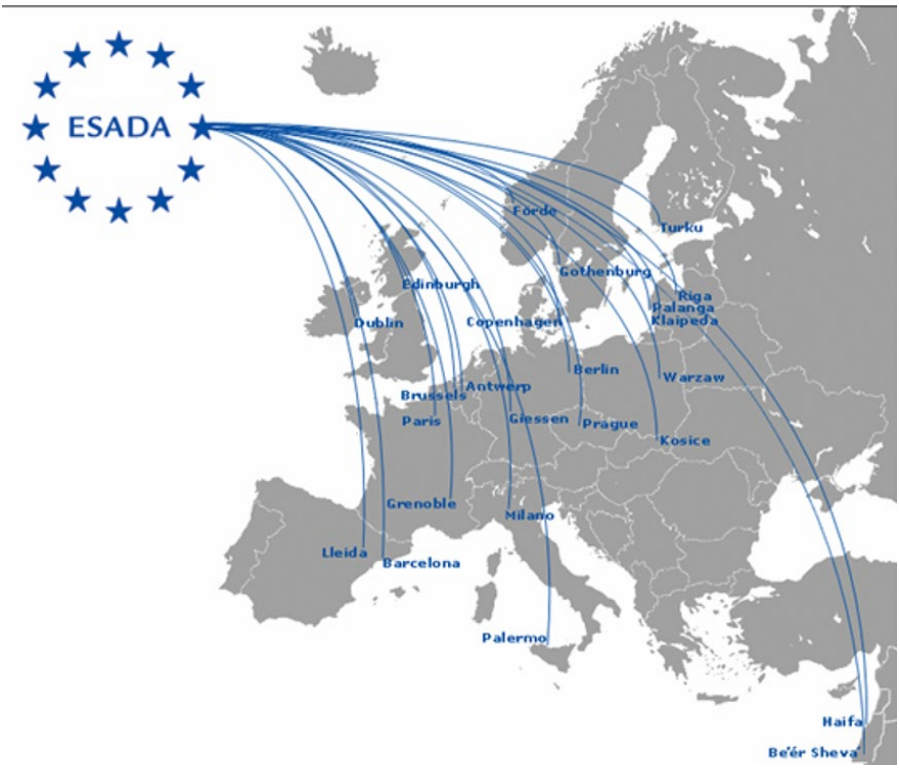
Anthropometric data (age, body mass index, sex), comorbidities (hyperlipidemia, diabetes, depression and obstructive lung disease, socioeconomic factors (education level and income), medication (AHTs, statins and adherence of these drug therapies), and number of AHTs at baseline entry were allowed as confounders.

Figure 15. ***Study II, Discovery cohort.***



PAP=positive airway pressure treatment, OSA=obstructive sleep apnea.

3.1.3 STUDY III AND IV, ESADA



The European Sleep Apnea Database (ESADA) was started in 2007 and reflects a network of 33 (study III) or 29 (study IV) sleep disorder centers in Europe enabled by a COST action B26 program[171]. This data reflects differences in standard clinical care of patients with OSA across Europe. ESADA was established as a resource for real-world data-based research in this disorder. Consecutively included patients with suspected OSA are followed up according to local clinical standards. Anthropometrics, medical history, medication, daytime symptoms and sleep data (polysomnography or cardiorespiratory polygraphy) are recorded in a structured web-based report form (Figure 16). Ethical approval and signed informed patient consent has been obtained at all involved centers including using anonymized data for sleep studies and clinical information. The data represent unselected patients referred with suspected OSA in the age≥18 years of age.

Figure 16. ***ESADA information.*** *Overview of data structure and information in ESADA.*

Used with permission, courtesy Journal of Physiology[172]*, Prof. Maria Bonsignore and Ashraf Yassen.*

Table 8. Study baseline comparison.

	Study 1	**Study 2**				**Study 3**		**Study 4**	
	Total n=440	Controls n= 25,586	Hypertension alone n= 57,986	OSA alone n= 25,586	Hypertension and OSA n= 57,986	Mono Therapy n=3594	Dual Therapy n=2224	Mono Therapy n=1283	Dual Therapy n=652
Anthropometric data									
Age (years)	55±13	49.0 (40.0-58.0)	59.0 (50.0-67.0)	49.0 (40.0-58.0)	59.0 (50.0-66.0)	57.2±10.5	59.2±10.4	59.6±10.7	60.6±10.3
Sex, female	36%	28.0%	33.3%	28.0%	33.3%	31.1%	30.1%	29%	26%
BMI, kg/m^2	30±6.1	29.4 (26.6-33.1)	31.4 (28.1-34.0)	30.0 (26.8-34.3)	31.5 (28.1-35.7)	32.8±6.7	33.5±6.8	34.2±6.5	34.4±6.7
Comorbidities									
Diabetes	16%	489 (1.9%)	7,025 (12.1%)	774 (3.0%)	8,624 (14.9%)	20.7%	27.2%	26%	33%
Hyperlipidemia	28%	620 (2.4%)	9,985 (17.2%)	1,173 (4.6%)	13,495 (23.3%)	NA (uses cholesterol instead)	NA (uses cholesterol instead)	44%	45%
Obstructive lung disease	NA (uses smoking instead)	1,059 (4.1%)	3,914 (6.8%)	1,986 (7.8%)	7,367 (12.7%)	NA	NA	14%	14%
Ischemic heart disease	8%	NA (exclusion criteria)	NA (exclusion criteria)	NA (exclusion criteria)	NA (exclusion criteria)	8%	20.1%	7%	32%

Heart failure	6%	NA (exclusion criteria)	NA (exclusion criteria)	NA (exclusion criteria)	NA (exclusion criteria)	1.3%	4.7%	3%	9%
Previous stroke/TIA	6%	NA (exclusion criteria)	NA (exclusion criteria)	NA (exclusion criteria)	NA (exclusion criteria)	NA	NA	3%	5%
Medication									
Numbers of AHTs	NA	0	2.0 (1.0-3.0)	0	2.0 (1.0-3.0)	1	2	1	2
Sleep data									
ESS	NA	NA	NA	10.0 (5.0–14.0)	9.0 (5.0–13.0)	9.8±5.2	9.5±5.1	10.4±5.1	10.0±5.2
Mean AHI	19±19					33.5±26.4	33.6±25.5	45.6±25.0	45.9±24.4
No OSA	26.1%	100.0%	100.0%	1.9%	2.1%	10,6%	7,6%	0,9%	0,7%
Mild OSA (5–<15 events/h)	30.2%	NA	NA	18.0%	13.3%	20,2%	20,7%	6,2%	6,1%
Moderate OSA (15–<30 events/h)	21.8%	NA	NA	33.8%	31.6%	23,1%	23,9%	24,5%	25,3%
Severe OSA (≥30 events /h)	21.8%	NA	NA	46.3%	53.0%	46,1%	47,3%	68,4%	67,9%

AHI=apnea-hypopnea index, AHT=antihypertensive treatment, BMI=body mass index, ESS=Epworth sleepiness scale, NA=not available/applicable, OSA=obstructive sleep apnea, TIA=transient ischemic attack.

3.2 METHODS

3.2.1 STUDY I

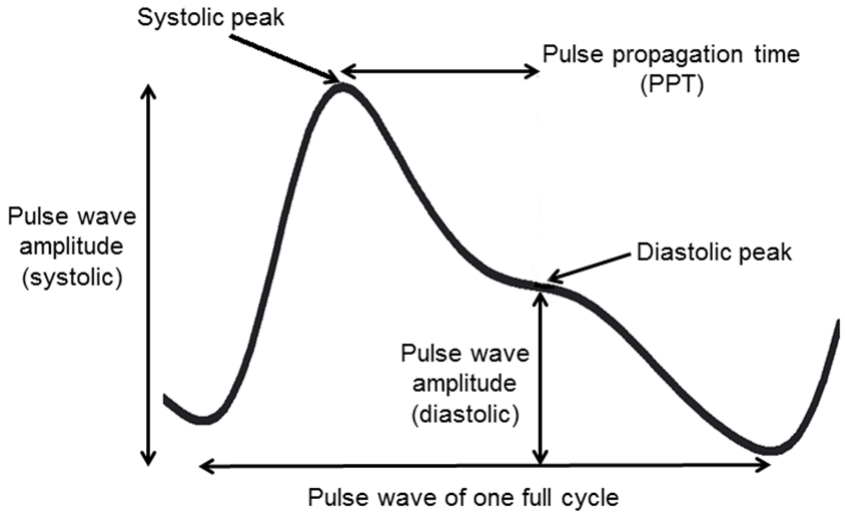
Sleep Recording

Participants underwent overnight sleep monitoring using one of the following systems: SomnoCheck II/R&K, SomnoCheck II, SomnoLab, or SomnoCheck Micro (Weinmann, Hamburg, Germany). Recordings were conducted either at the patient's home or in a hospital setting, depending on local clinical routines. Sleep data were collected between approximately 10:00 PM and 6:00 AM. For polysomnographic recordings, sleep stages and indices of sleep-disordered breathing were manually scored in accordance with the 2007 criteria of the American Academy of Sleep Medicine (AASM)[43]. The Apnea-Hypopnea Index (AHI) was calculated as the total number of apneas and hypopneas divided by the recording time (for polygraphic data) or total sleep time (for polysomnographic data).

Novel Pulse Wave Analysis

Continuous pulse wave monitoring was conducted using a specialized pulse oximeter module (ChipOx, Corescience GmbH, Germany), as previously described in detail[173,174]. The photoplethysmographic (PPG) signal was recorded unfiltered at a sampling rate of 100 Hz, with data acquisition limited to a single finger sensor. Pulse Propagation Time (PPT) was defined as the interval between the systolic peak and the diastolic peak of the pulse waveform, measured in milliseconds[175] (see Figure 17). A mean PPT value was calculated across the entire recording period, which had a minimum duration of four hours. Artifacts were automatically excluded from analysis. In a subgroup analysis comprising 125 normotensive and 145 hypertensive individuals, mean PPT values were computed for distinct sleep stages (NREM stages 1, 2, and 3; REM sleep) as well as periods of wakefulness, during the overnight recording.

Figure 17. ***Pulse propagation time.*** *PPT is the time between systolic and diastolic peaks in the pulse wave in milliseconds. Shorter PPT is associated with higher vascular stiffness.*



Used with permission, courtesy Journal of Hypertension, Sven Svedmyr et al.

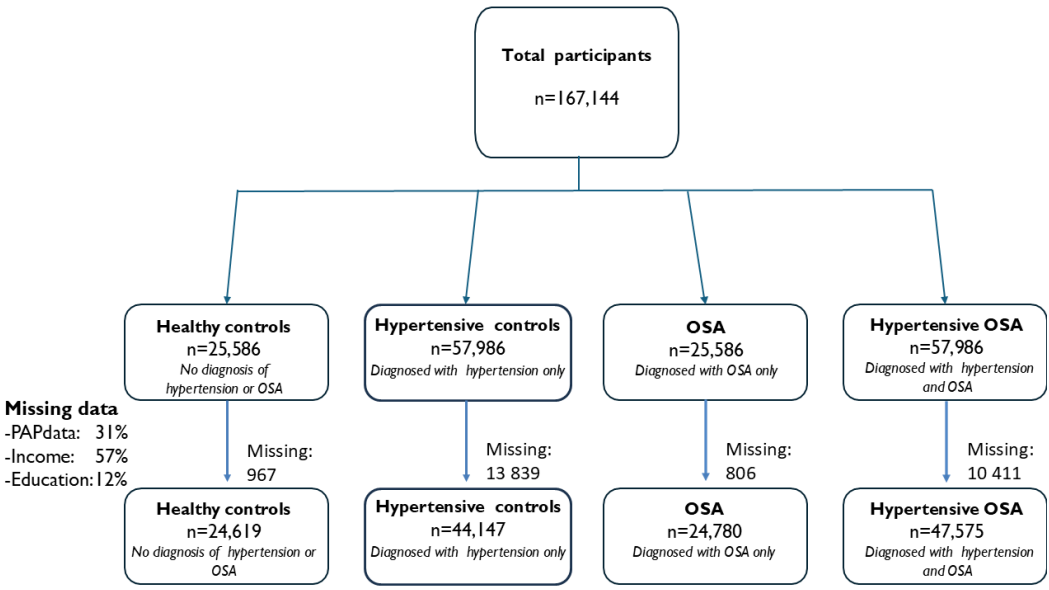
3.2.2 STUDY II

All patients diagnosed with OSA, starting PAP treatment, and without manifest CV disease, renal failure, or malignancy, in the SESAR or Swedevox registries between 2010 and 2021, were included in the study. A control population without these diagnoses was identified from the Discovery database. Both patients and controls were stratified based on hypertension status, resulting in four distinct groups (Figure 18).

Participants were followed until October 2022. Outcome data MACE and all-cause mortality were obtained from mandatory national death and diagnosis registries. Information on anthropometric confounders (age, BMI, sex), comorbidities (hyperlipidemia, diabetes, depression and obstructive lung disease), medication with AHTs and statins (including adherence information), and socioeconomic factors (education level and income) were collected. PAP data was also sourced from routine clinical care records (Swedevox and /or SESAR) included in the Discovery database. Patients with unknown adherence to PAP therapy were classified as having low or no usage, defined as 0–2 hours per day. Baseline hypertension was defined as the presence of a documented hypertension

diagnosis in combination with an active prescription for at least one antihypertensive medication. High treatment compliance was defined as having at least two dispensed prescriptions per year for at least 75% of the study period, with an active prescription status for each respective AHT class or statin. Adjusted multifactorial Cox regression models were used with MACE and all-cause death risk as main outcomes and PAP risk reduction of primary outcomes, in secondary analyses.

Figure 18. ***Study II, flow chart***

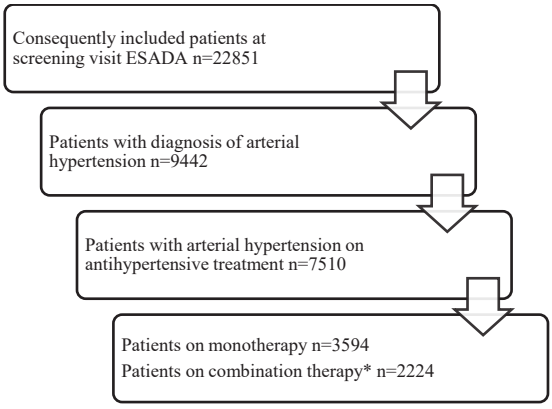


3.2.3 STUDY III

Data from 7,510 patients with OSA and hypertension treated with one or two antihypertensive medications were extracted from the ESADA, encompassing 33 participating European centers. Patients were included between 2007-2017. To focus on clinically relevant combinations and to ensure sufficient statistical power, AHT combinations represented by fewer than 100 patients were excluded. After applying these criteria, the final study population consisted of 5,818 patients (Figure 19). The cross-sectional analysis evaluated office BP by antihypertensive medication used, while adjusting for relevant confounding factors associated with BP control. These included anthropometric variables (age, sex, body mass

index), comorbidities (ischemic heart disease, heart failure, and diabetes), sleep apnea severity (apnea-hypopnea index), and study center.

Figure 19. ***Flow chart study III.*** *Patients on more than 2 AHTs were excluded.*



AHT medications were categorized into the following drug classes based on ATC codes: beta-blockers (BB; C07), diuretics (DIU; C03), renin-angiotensin system blockers (RAB; C09), calcium channel blockers (CCB; C08), and centrally acting antihypertensives (CAH; C02). Systolic blood pressure control was assessed according to age-specific optimal targets defined by the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines[5]. Specifically, uncontrolled hypertension was defined as systolic blood pressure ≥130 mmHg for individuals younger than 65 years, and ≥140 mmHg for those aged 65 years or older.

3.2.4 STUDY VI

Adult patients with suspected OSA were consecutively recruited into the ESADA database from 28 European sleep centers between March 2007 and December 2021. Patient history, comorbidities, and concomitant medications were documented using a standardized protocol. For this longitudinal analysis, we included all adult patients (n = 1,935) with a diagnosis of hypertension and OSA who were receiving either monotherapy or dual combination antihypertensive treatment alongside PAP therapy for OSA. Eligible patients had follow-up data available from at least 2 months up to 3 years after the initial visit. The most recent visit within the 3-year window was used for analysis in cases with multiple follow-up visits. Patients were split into two groups: those receiving monotherapy (n= 1,283)

and those on dual combination therapy (n= 652). Individuals treated with three or more antihypertensive medications (n= 354) were excluded due to the heterogeneity and small sample sizes across various triple-drug combinations. Hypertension was defined by a documented medical history in combination with ongoing antihypertensive treatment. Changes in blood pressure and the degree of blood pressure control following PAP therapy were investigated. Patients with less than 2 months of follow-up were excluded. Blood pressure control was evaluated at both baseline and follow-up using systolic and diastolic thresholds defined by the 2018 ESC/ESH guidelines[5], with control rates calculated as the proportion of patients meeting these criteria.

3.3 ETHICAL CONCIDERATIONS

Ethical approvement was obtained for all studies prior to study start. For study I, III and IV, written and oral informed consent was obtained from each participant prior to study participation. For a listing of ethical approvals please see appendix.

In study II, patients were included into the national quality registries without specific consent procedures according to Swedish Law. All patients can opt out from a registry at any time. All patients went through standard care, and no interventions outside standard care were applied.

3.4 MEASURESMENTS AND ASSESSMENTS

Study I: The medical history and physical status of each participant was evaluated by the sleep physician. Comprehensive information regarding both current and previous medical history was gathered directly from the subjects and medical records. Anthropometric measurements, including body weight and height, as well as data on tobacco exposure and average weekly alcohol consumption, were systematically recorded. Office BP was measured in the seated position in accordance with contemporary guidelines issued by the European Society of Hypertension (ESH)[115].

Fasting blood samples were collected to determine lipid profiles. Information on comorbidities, including CV and metabolic conditions, as well as current pharmacological treatments, was meticulously gathered from patient interviews and supplementary sources such as hospital records and referral documentation. Hypertension status (classified as present or absent) was determined by the responsible physician, based on historical clinical data, current medication use, and blood pressure readings obtained during the clinical visit.

Study II: All data were obtained from both the OSA standard care registries (Swedevox and SESAR) and national mandatory healthcare registries in Sweden as listed in 3.1.2 and 3.2.2.

Data on all AHTs were collected before PAP start, last year before MACE/death or study end. Patients picking up a drug at least twice during the last year are considered on that drug for a visit. At least 2 drug dispensions per year for at least ¾ of the study time with active prescription

of each individual AHT group or statin required for high adherence categorization.

All diagnoses were evaluated before PAP start (or study inclusion for controls) and end of study. MACE or new AF event were recorded at any time. Causes of death collected when applicable.

ICD codes of interest (from patient registries and/or swedevox):

Diabetes (E10-E14), Hyperlipidemia E78, COPD J44, Kidney failure (N17-N19), Depression F32 and 33, Hypertension (I10-I15), OSA G47.3, ischemic heart disease (I20-25), AF I48, Cardiac failure I50, Stroke I61-66. Malignant cancer C00-C97.

MACE (I20-25, I50 or I61-66) and all-cause-death, CV death and traffic accident death were collected during study. ICD codes: I20-I25, I46, I48, I50, I61-I66, were used for CV death.

Study III-VI: Anthropometric and sleep data were captured from standard care in the ESADA[171]. Office BP in study III and VI, was measured according to contemporary recommendations[5] by auscultatory or oscillometric techniques after at least 5 min of rest.

Diagnostic Sleep studies:

Several sleep study methodologies were applied in the four studies of this thesis. In *study I*, a sleep diagnostic system (SomnoCheckII/R&K, SomnoCheckII, SomnoLab or SomnoCheckMicro, Weinmann, Hamburg, Germany), and the overnight recording was applied in the patients' home or in the hospital between approximately 22 and 06 o'clock according to local routines.

Study II, Discovery uses Swedish standard care, i.e. almost exclusively cardiorespiratory polygraphy. In s*tudy III and IV,* ESADA centers follows European standard care for each country, with mixed polygraphy (49.3%) and polysomnography (50.2%) data.

The American Academy of Sleep Medicine 2007 scoring criteria[43] for sleep stage scoring (in case of PSG) and classification of respiratory events were used, including a 4% oxygen desaturation criteria for hypopnea classification.

3.5 STATISTICAL ANALYSES

In this thesis several statistical methods for cross-sectional and longitudinal analyses were applied, including simple comparisons with Chi-square for simple comparisons to advanced mixed effect models. Imputations, COX proportional hazard models and log-rank tests were performed by a professional statistician.

3.5.1 THE P-VALUE AND CONSIDERATIONS REGARDING ALFA AND BETA ERROR

In the context of medical statistics and hypothesis testing, Type I (α) and Type II (β) errors represent two fundamental forms of inferential uncertainty. A Type I error occurs when the null hypothesis (H_0) is incorrectly rejected despite being true, resulting in a false positive. Conversely, a Type II error arises when the null hypothesis is not rejected even though it is false, leading to a false negative outcome. These errors are critical considerations in the design and interpretation of clinical studies. To minimize the risk of Type I error, a significance level (p-value) of less than 0.05 was applied, corresponding to a 5% probability of falsely rejecting the null hypothesis and getting a false positive result. A Type II error rate of 20% ($\beta = 0.20$) was accepted, implying a statistical power of 80%. In these studies, greater emphasis was thus placed on minimizing false positive findings (Type I errors) over false negatives (Type II errors), aligning with standard practice in clinical research where the consequences of incorrect rejection of the null hypothesis are considered more severe.

3.5.2 STUDY ANALYSES

S**tudy I** was a cross-sectional analysis of PPT during sleep for participants with hypertension and/or OSA and as a predictor for hypertension. Descriptive statistics of the study cohort were presented as mean±SD. Group differences were tested by *Student's t test* or *chi-square test*. The association between PPT and potential confounding factors was studied by *Pearson correlation analysis*. *Generalized linear regression models* were used to study the predictors of PPT and hypertension status. Recognized confounders for vascular stiffness including age, sex, body weight, height, smoking history, cardiometabolic comorbidities, and sleep apnea were allowed as potential confounders in the analyses. PPT differences between sleep stages were analysed with *ANOVA* (analysis of variance*)*.

S**tudy II**, is a long-term prospective registry cohort study with survival and incident MACE comparison between 4 groups. Means and standard deviations (SDs) or median and interquartile range (IQR) for not normally distributed variables, are reported as well as p-values for group difference. *ANOVA* was used for normally distributed variables and *Kruskal–Wallis* for non-normally distributed variable group comparisons. Percentage values are reported for category variables. *COX proportional regression models* were used to determine hazard ratios of the groups compared to healthy controls adjusting for multiple confounders (see section 3.1.2) and similar models were used comparing hypertensive OSA patients against OSA patients without comorbid hypertension to assess the modifying effect of PAP treatment adherence.

S**tudy III** is a cross-sectional registry cohort analysis. AHT drug classes in terms of monotherapy and combination therapy groups were compared adjusting for anthropometric data and confounders. *Multivariate linear regression models* were performed after consideration of data distribution and variable type, for monotherapy (SBP and DBP, n=3594) and combination (SBP and DBP, n=2224) therapy to evaluate if the observed pressure differences were independent of confounders. Missing data in the adjusted models was 6.1% (n=219) for the monotherapy group and 7.2% (n=161) for those on a combination therapy. We performed *imputation* (see section 5.3) of missing data (body mass index, SBP, DBP, AHI, as well as hyperlipidemia and diabetes diagnosis), which were stochastically imputed with *Full Conditional Specification* procedure considering site effects (using Proc MI by SAS[176]). For the final adjusted analysis, a *multivariate mixed linear regression model* was applied handling site as a random effect.

In **study VI**, a longitudinal registry cohort study, we used *multiple mixed linear models* to assess BP control during PAP treatment depending on AHT drug or combination, adjusting for major confounders including gender, age, BMI at follow-up, co-morbidities (cardiac failure, ischemic heart disease, and diabetes mellitus), follow-up duration, and BP at baseline. To adjust for potential local differences in patient populations, variation in BP assessments, and local AHT prescription traditions the study site was included as a *random factor* in the final model. Changes in SBP and DBP constituted the dependent variable. Differences in the percentage of in BP control between AHT classes were compared using *McNemar's test.*

Table 9. ***Study Design and Statistical Methods.***

	Study I	Study II	Study III	Study IV
Study type	Cross-sectional cohort study; association analysis and descriptive parts, whole cohort and subgroup analyses.	Longitudinal cohort study; Survival/ incidence analyses, comparing 4 groups.	Cross-sectional cohort study; Comparison of multiple AHTs in mono- or dual therapy	Longitudinal cohort study comparing multiple AHTs in mono- or dual therapy and PAP therapy effects on BP control.
Descriptive section Normally distributed data	Mean, SD, Pearson correlation Student's t-test, Chi square-test, ANOVA	Mean, SD, Chi-square test, Student's t-test, ANOVA	Mean, SD ANOVA	Mean, SD ANOVA
Descriptive non-normal distributed data		Median, IQR, Wilcoxon rank-sum test	Kruskal–Wallis test	
Main models	Generalized linear models (GLM)	Cox proportional hazards models	Multivariate linear regression models	Multiple mixed linear models
Other		Kaplan–Meier, Log-rank test	McNemar's test	McNemar's test

P-value less than 0.05 was considered statistical significance in all studies.

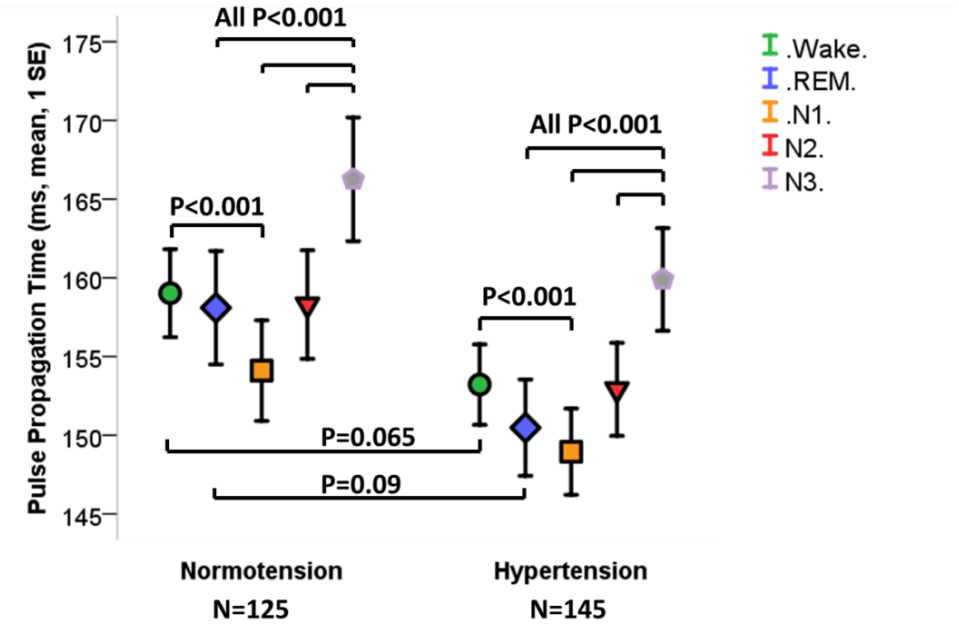
4 RESULTS

4.1 STUDY I

Vascular stiffness determined from a nocturnal digital pulse wave signal: association with sleep, sleep-disordered breathing, and hypertension.

We could confirm that PPT was a marker of overnight vascular stiffness and associated with traditional risk factors for hypertension and CV disease also when controlling for blood pressure. PPT varied significantly across sleep stages with the highest vascular stiffness during sleep stage 1 and lowest during deep sleep (N3) (Figure 20).

Figure 20. ***Pulse propagation time and normotensive and hypertensive OSA patients sleep stages.*** *Shorter PPT corresponds to higher arterial stiffness and longer PPT to lower stiffness. N3 sleep is the sleep stage with maximum relaxation of the cardiovascular system. Hypertensive participant had similar PPT patterns during sleep but shorter PPT in all estimations signalling higher vascular stiffness.*



N1 and 2= light sleep, N3= deep sleep, REM= REM-sleep. Used with permission, courtesy Journal of Hypertension, Sven Svedmyr et al.

The longest PPT was observed during NREM stage N3 sleep, significantly exceeding values recorded during wakefulness and all other sleep stages (NREM N3: 163 ± 41 ms vs. Wake: 156 ± 31 ms; NREM N1: 151 ± 34 ms; NREM N2: 155 ± 37 ms; REM: 154 ± 38 ms; all comparisons $P < 0.001$). These differences were consistent across both normotensive and hypertensive individuals, although hypertensive patients tended to exhibit lower PPT values (p=<0.001) as a measure of increased arterial stiffness.

Factors predicting PPT

In univariate analysis (Table 10), mean overnight PPT were significantly associated with anthropometric data like age, height, body weight. Comorbidities like hyperlipidemia and diabetes were linked to lower PPT (p=0.024 and p=0.031 respectively). In addition, a linear decline in overnight PPT was observed across increasing SBP and DBP categories (ANOVA; $P = 0.005$ and $P < 0.001$, respectively). Finally, OSA severity expressed as apnea-hypopnea index showed a negative correlation with overnight PPT ($r = –0.13$, $P = 0.008$). Severe sleep apnea (AHI>30) significantly reduced PPT in normotensive individuals, with a less pronounced effect in hypertensive patients. Factors independently associated with overnight PPT in the multivariate generalized linear regression analysis were age, height, weight, DBP, smoking status, and AHI.

Table 10. ***Pearson correlation analysis of overnight vascular stiffness (mean pulse propagation time) and conventional confounding factors*** *(full cohort, n = 440).*

	Correlation coefficient	*P* value
Age	−0.53	<0.001
Height	0.32	<0.001
Weight	0.27	<0.001
Waist	0.08	n.s.
SBP	−0.16	0.001
DBP	−0.18	<0.001
Pulse	0.04	n.s.
AHI (n/h)	−0.13	0.008

AHI, apnea– hypopnea index; n.s., not significant. Used with permission, courtesy Journal of Hypertension, Sven Svedmyr et al.

Vascular stiffness during sleep and daytime hypertension

PPT was significantly lower in hypertensive patients compared to normotensive individuals (160 ± 33 ms vs. 177 ± 47 ms, $P < 0.001$). In a multivariate generalized logistic regression model, mean overnight PPT emerged as an independent predictor of hypertension diagnosis, even after

adjusting for age, body mass index, diabetes status, smoking history, heart failure, coronary artery disease, and history of transient ischemic attack or stroke.

4.2 STUDY II

The synergistic effect of obstructive sleep apnea and hypertension on mortality can be reduced by positive airway pressure treatment.

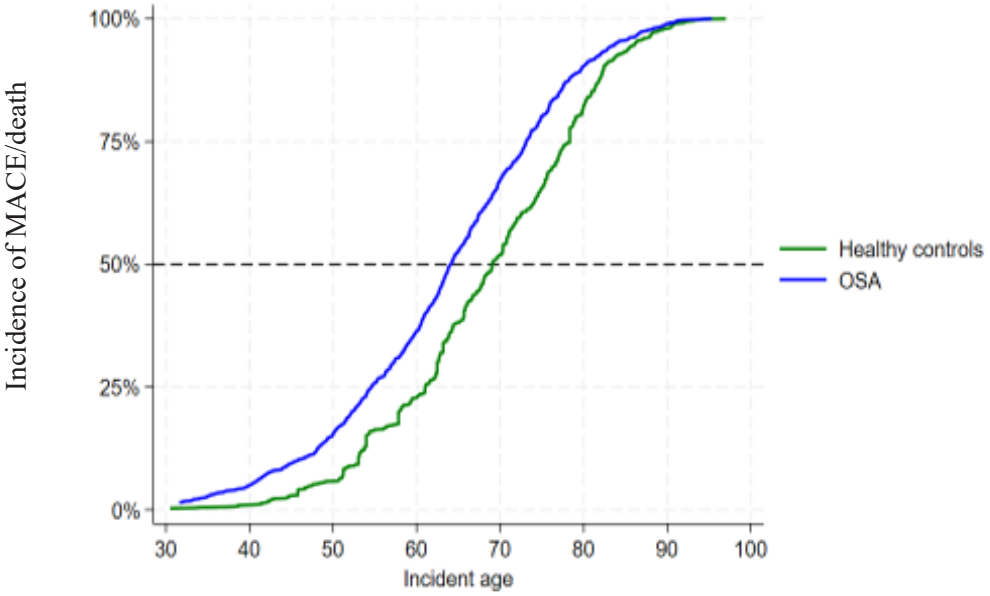
Study Population and Baseline Characteristics

The study included four groups: individuals with OSA (OSA; n =25,586), and those with both OSA and hypertension (OSA+HT; n =57,986), controls (n = 25,586), and hypertensive controls (n =57,986). OSA groups without/with hypertension were matched against corresponding controls for Age, sex, and BMI. Compared to hypertensive groups, the groups without hypertension were 10 years younger. Hypertensive OSA patients were marginally less sleepy than OSA alone. OSA subjects more often had depression. Diabetes and hyperlipidemia were more common in hypertensive groups. Patients in the hypertensive OSA group have more comorbidities (see Table 8 on section 3.1 Study cohorts). The number of prescribed antihypertensive treatments was similar between the hypertensive groups, and the severity of sleep apnea was comparable across the OSA groups.

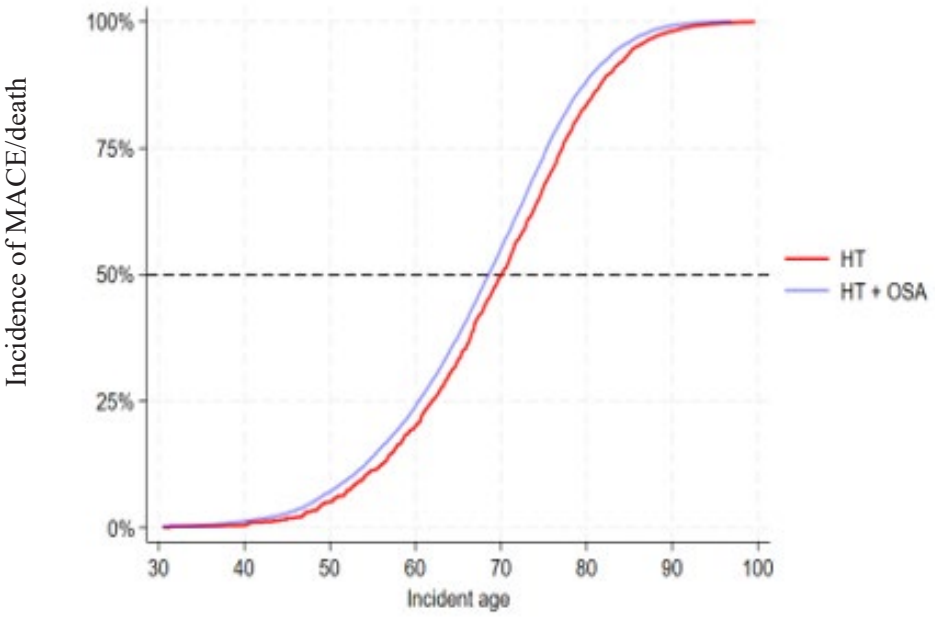
Observation Time and Clinical Outcomes

The median observation period was 6.8 years (interquartile range [IQR]: 4.7-10.1), corresponding to a total of 1,059,644 person-years at risk. The longest time at risk was observed in healthy controls and hypertensive controls (7.7 and 8.7 years [IQR: 5.7-10.7 and 6.0-11.7, respectively]), while individuals with OSA alone (5.0 [[3.2-7.5]) and those with combined OSA and hypertension (5.9 [3.6-8.8]) had shorter observation periods, primarily due to the initiation of positive airway pressure therapy occurring after the study start date. Adherence to antihypertensive treatment was comparable between the hypertensive groups, and PAP adherence was similar across both OSA groups. The incidence of major adverse CV events or death was higher in both hypertensive groups. Notably, the mean age at first MACE or death was 5 years lower in the OSA-alone group compared to healthy controls, and 1.6 years lower in the OSA+hypertension group compared to hypertensive controls without OSA. Differences in age at incident events are illustrated in Figure 21.

Figure 21. ***All MACE/death events plotted against age at first event.***



Healthy controls: 69.1 (61.1-78.3) n=967, OSA 64.1(54.6-73.1) n=806.



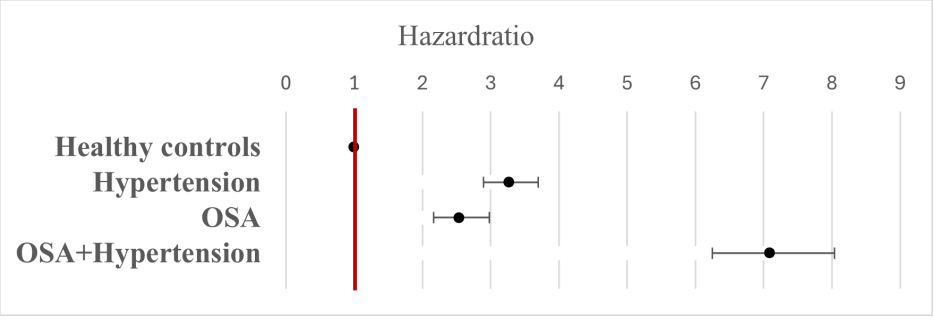
Hypertension: 70.1 (61.9-77.2) n=13,839), Hypertension+OSA: 68.5 (60.4-75.3) n=10,411.

MACE=Major Adverse Cardiovascular Event, OSA=Obstructive Sleep Apnea.

Primary Outcomes: Risk of All-Cause Mortality and Major Adverse Cardiovascular Events

Cox regression survival analyses after adjustment for age, BMI, sex, comorbidities, socioeconomic status, medication use, and treatment adherence, revealed HRs for all-cause mortality of 2.2 (2.0-2.4) for hypertension-only, 1.6 (1.4-1.8) for OSA-only, and 3.1 (2.8-3.5) for OSA+hypertension. Adjusted HRs for MACE were 3.2 (2.9-3.7), 2.6 (2.2-3.0), and 7.0 (6.2-87.9), respectively (Figure 22).

Figure 22. ***Risk of MACE, COX multivariate incidence analysis**** *(n=155,830).*

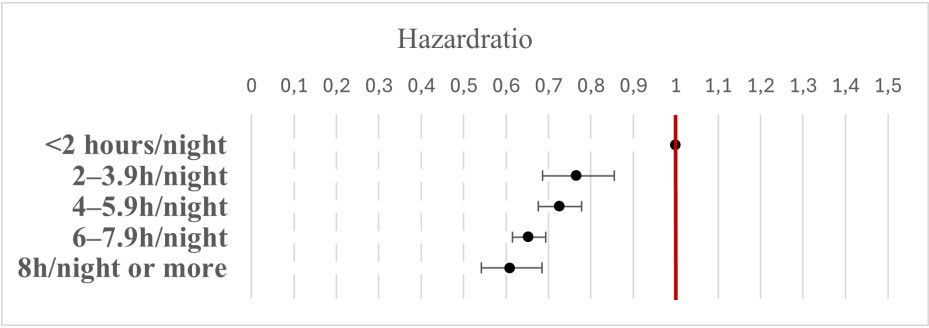


**Adjusted for age, sex, BMI, diabetes, hyperlipidemia, depression, obstructive lung disease, education and income, number of AHTs at baseline, PAP-, AHT- and statin adherence.*

Secondary Outcome: Protective Effects of PAP Therapy and Adherence

In OSA patients initiated on positive airway pressure therapy (n =76,523), multivariate Cox regression analyses revealed a significantly increased risk of all-cause mortality and MACE in the OSA+hypertension group compared with normotensive OSA patients (HR = 2.9 [2.6–3.2] for mortality; HR = 3.8 [3.3–4.4] for MACE). PAP therapy demonstrated a clear dose–response relationship between daily usage and reduction in all-cause mortality. Compared to patients using PAP for less than 2 hours per night, those with 4–5 hours of daily use had a reduced hazard ratio of 0.64 (0.58-0.72), which further declined to 0.58 (0.53-0.64) with 6–<8 hours of use and 0.63 (0.53-0.74) with ≥8 hours of nightly use. For MACE, hazard ratios were 0.74 (0.69-0.79) for 4–5 hours of use and further reduced a HR of 0.61 (0.55-0.69) for ≥8 hours use/night (Figure 23). Even limited adherence (2–<4 hours/night) was associated with meaningful risk reductions: 26% for all-cause mortality (HR =0.74 [0.63-0.87]) and 22% for MACE (HR =0.78 [0.69-0.87]).

Figure 23. ***Risk of MACE and protective effect of PAP, OSA groups only**** *(n=76,523).*



**Adjusted for age, sex, BMI, diabetes, hyperlipidemia, depression, obstructive lung disease, education and income, number of AHTs at baseline, PAP-, AHT- and statin adherence.*

Sensitivity analyses

Several preplanned sensitivity analyses were conducted to address key scientific questions in the field:

A. Hypoxic load

The hypoxic load marker ODI was used to describe OSA severity instead of AHI. The results were comparable, and ODI did not show a stronger predictive effect of MACE or All-cause death.

B. PAP adherence

Restricting the secondary analysis on the potential protective effects of PAP against MACE and death to patients with complete PAP follow-up data (n =31,988) yielded results comparable to the primary analysis. This supports our main findings and validates the assumption that patients lacking follow-up data can reasonably be classified as having low or no PAP adherence.

C. The age effect

The analysis was dichotomized by age 65 years and older compared with below 65 years of age. PAP use was associated with reduced risk of all-cause death and MACE in both younger (<65 years) and older (≥65 years) patients. Notably, the protective effect of PAP in the elderly subgroup was stronger for all-cause mortality than for MACE. The previously noted protective effect of low PAP adherence was not found for MACE in the elderly.

D. Influence of sleepiness

We identified slightly lower outcome risk in the study after adjustment for PAP compliance with a 7/16% risk reduction for MACE/death between sleepy (ESS≥11) and non-sleepy (ESS<11) OSA patients, respectively.

4.3 STUDY III

Superior hypertension control with betablockade in the European Sleep Apnea Database.

This study investigated hypertensive OSA patients on mono- or dual-AHT, in the baseline ESADA cohort assembled during 2007-2017. Patients were not treated for OSA at time of investigation.

Patterns of Antihypertensive Medication Use in Patients with Obstructive Sleep Apnea in Europe

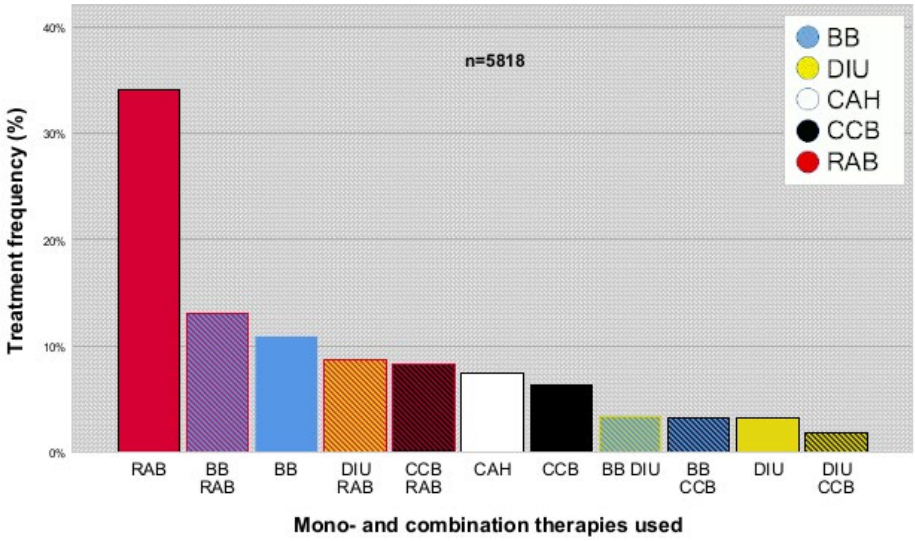
Most patients had monotherapy rather than combination therapy. Among patients diagnosed with OSA, renin-angiotensin blockers (RABs; n = 1986, 55%) and beta-blockers (BBs; n = 632, 18%) were the most frequently prescribed agents as monotherapy (Figure 24). Diuretics (DIUs) were used as monotherapy in only a small subgroup of patients (n = 184, 5%). The most common combination therapies included:

- BB in combination with RAB (n = 758, 34%)
- DIU in combination with RAB (n = 505, 23%)
- Calcium channel blockers (CCBs) in combination with RAB (n = 482, 22%)

Hemodynamic Parameters in Patients Receiving Monotherapy

The BB monotherapy group had significantly lower SBP compared to other monotherapy groups (ANOVA: p=0.016), while diastolic blood pressure did not differ significantly (p=0.32). In fully adjusted models, SBP was lower by 2.2 mmHg (95% CI: 1.4–3.0), 3.0 mmHg (1.7–4.7), and 3.0 mmHg (1.9–4.1) in patients treated with BBs compared to those receiving RAB, central acting antihypertensives (CAH), or CCBs, respectively (Figure 25A, p =0.007, 0.017, and 0.008). Additionally, heart rate, pulse pressure, and rate-pressure product were all significantly lower in the BB group compared to patients treated with RABs, DIUs, CCBs, and CAHs. DBP control was generally higher but no major differences between monotherapies were found.

Figure 24. ***Prescription patterns for anti-hypertensive medication in European hypertensive sleep apnea patients.*** *Data are shown for distribution of mono- and dual combination therapy.*



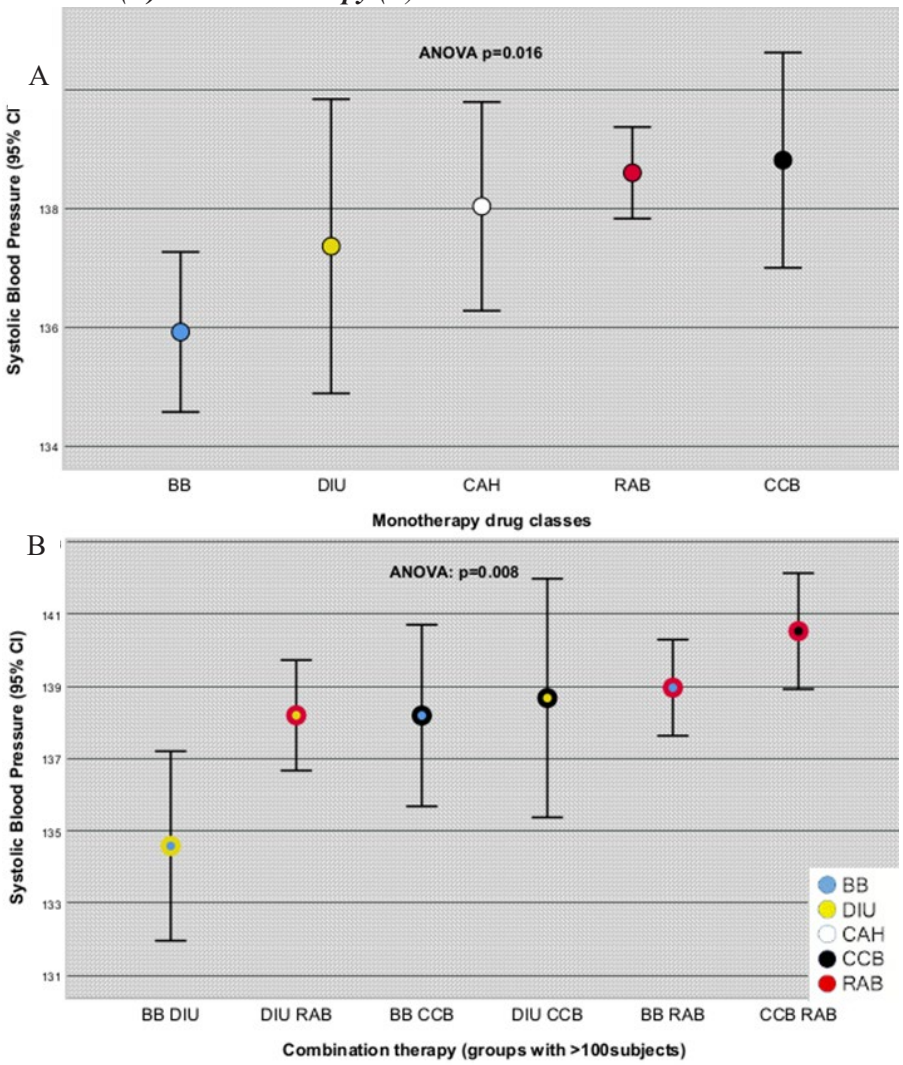
BB=betablocker, CAH=central acting AHT, CCB=calcium channel blocker, DIU=diuretic, RAB=Renin angiotensin blocker; angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Used with permission, courtesy Journal of Hypertension, Sven Svedmyr et al.

Hemodynamic Parameters During Combination Therapy

Patients receiving a combination of beta-blockers and diuretics exhibited significantly lower systolic and diastolic blood pressure compared to those on other combination regimes (ANOVA: $p = 0.008$ and $p < 0.0001$, respectively).

In fully adjusted models, patients receiving a combination of beta-blockers and diuretics had significantly lower SBP compared to those on other combination therapies. Specifically, SBP was 5.5 mmHg lower than in patients treated with CCB/RAB, 5.1 mmHg lower than BB/RAB, 4.3 mmHg lower than BB/CCB, and 3.1 mmHg lower than DIU/RAB combinations (Figure 25B, p=0.0003, 0.0004, 0.018, and 0.036, respectively). DBP was also significantly lower in the BB/DIU group, with differences of 3.3 ± 2.4 mmHg, 2.3 ± 1.4 mmHg, and 2.2 ± 1.3 mmHg compared to CCB/RAB, BB/RAB, and DIU/RAB combinations, respectively ($p = 0.0006$, 0.001, and 0.019). Combination therapies that included a BB component were also associated with lower heart rate and rate-pressure product, indicating a more favourable hemodynamic profile.

Figure 25. ***Mean systolic blood pressure by anti-hypertensive treatments in mono- (A) and dual therapy (B).***



BB=betablocker, CAH=central acting AHT, CCB=calcium channel blocker, DIU=diuretic, RAB=Renin angiotensin blocker; angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Used with permission, courtesy Journal of Hypertension, Sven Svedmyr et al.

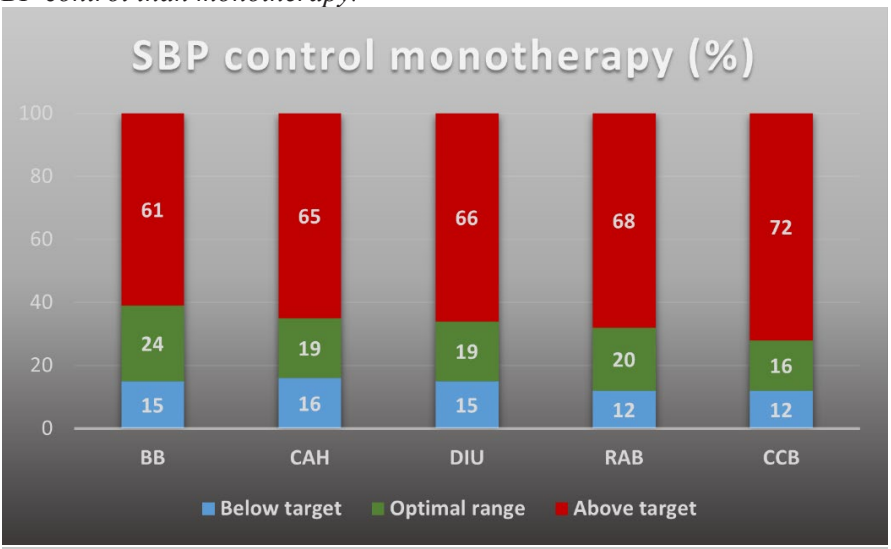
Blood Pressure Control in untreated OSA patients.

Overall, SBP control was markedly impaired across both monotherapy and combination therapy groups, with 52 to 72% of hypertensive patients with OSA exceeding the upper threshold for optimal SBP control (Figure 26). Among the treatment regimens, patients receiving

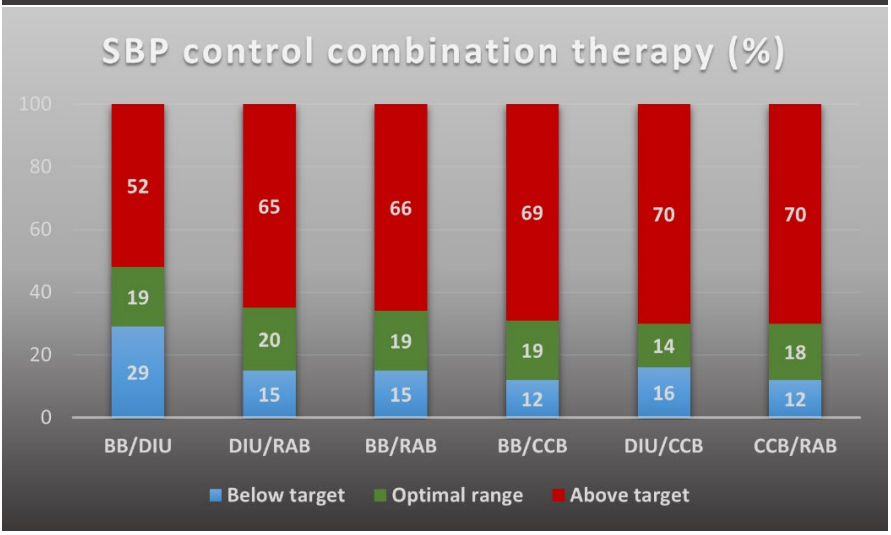
beta-blockers as monotherapy and those treated with a combination of BB and diuretics exhibited a significantly lower proportion of uncontrolled SBP compared to other therapeutic approaches (Figure 26, monotherapy: p=0.009; combination therapy: p<0.001).

Figure 26. ***Systolic blood pressure control for mono (A) and dual (B) anti-hypertensive treatments.*** *Combination therapy had slightly better BP control than monotherapy.*

A



B



BB=betablocker, CAH=central acting AHT, CCB=calcium channel blocker, DIU=diuretic, RAB=Renin angiotensin blocker; angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Used with permission, courtesy Journal of Hypertension, Sven Svedmyr et al.

4.4 STUDY IV

Blood pressure control in hypertensive sleep apnea patients of the ESADA cohort-effects of PAP and antihypertensive medication.

This study followed hypertensive OSA patients treated with PAP, and simultaneously with one or two AHTs. We compared baseline BP control with BP control at follow-up (at least 2 months, max 3 years), stratified by the different AHTs used.

Baseline clinical data

A total of 1,935 hypertensive OSA patients were included in the analysis, 1,283 receiving monotherapy and 652 receiving dual therapy. Patients on dual therapy exhibited a higher prevalence of CV comorbidities and were more frequently diagnosed with diabetes mellitus compared to those on monotherapy. In contrast, anthropometric measures, OSA severity at screening, and the prevalence of hyperlipidemia and smoking were comparable between the two treatment groups.

Independent predictors of BP change following positive airway pressure.

Adherence to PAP therapy was generally high across the cohort (daily usage, 5.6 ± 1.6/5.7 ± 1.9 h/day for mono/combination respectively). In controlled mixed models, baseline blood pressure emerged as a significant predictor of the magnitude of blood pressure reduction following PAP treatment. Additionally, treatment duration was a significant predictor of blood pressure improvement in patients receiving monotherapy ($p<0.0001$), but not in those on dual therapy.

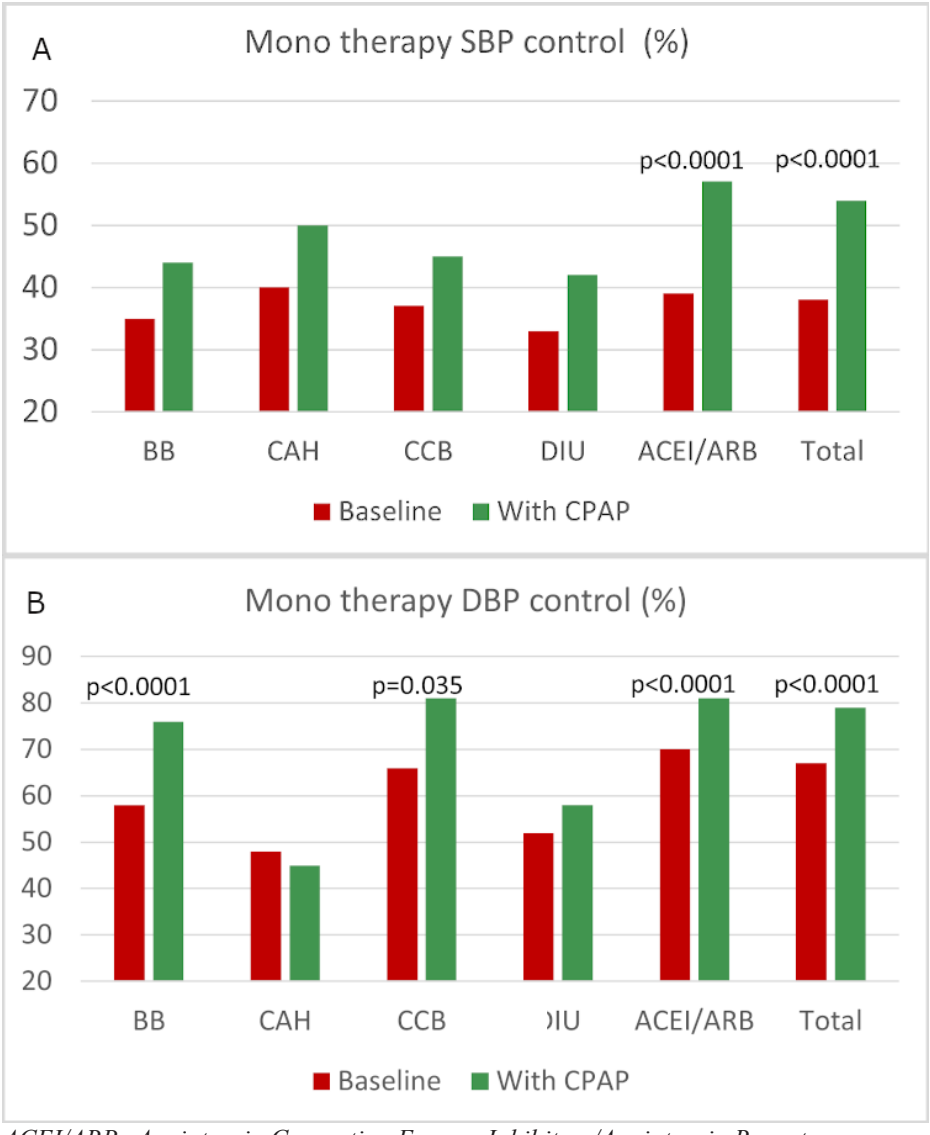
Regarding antihypertensive drug classes, combination therapies that included ACE inhibitors or angiotensin receptor blockers (ACEI/ARBs) were associated with significantly greater reductions in systolic blood pressure. Specifically, SBP in PAP treated OSA patients were more reduced in patients taking combinations such as betablocker (BB) + ACEI/ARB, calcium channel blockers (CCB) + ACEI/ARB, and diuretic (DIU) + ACEI/ARB were associated with SBP reductions of −4.76 ± 1.82 mmHg, −4.94 ± 2.13 mmHg, and −6.90 ± 2.29 mmHg, respectively compared to non-ACEI/ARB combinations. In contrast, the observed changes in diastolic blood pressure following PAP treatment (−3.0 ± 9.8 mmHg, p=<0.0001) were not independently associated with any specific antihypertensive drug combination.

Control of hypertension before and after PAP treatment

In patients receiving monotherapy (Figure 27), systolic blood pressure control improved significantly with positive airway pressure treatment, increasing from 38% to 54% ($p<0.0001$). This improvement was particularly evident among those treated with ACE inhibitors or angiotensin receptor blockers. However, even within this group, only 57% achieved adequate SBP control following PAP therapy. In contrast, DBP control was generally better across all monotherapy groups, with approximately 80% of patients achieving target DBP levels compared to approximately 65% before PAP, especially those treated with ACEI/ARBs, CCB, or BB.

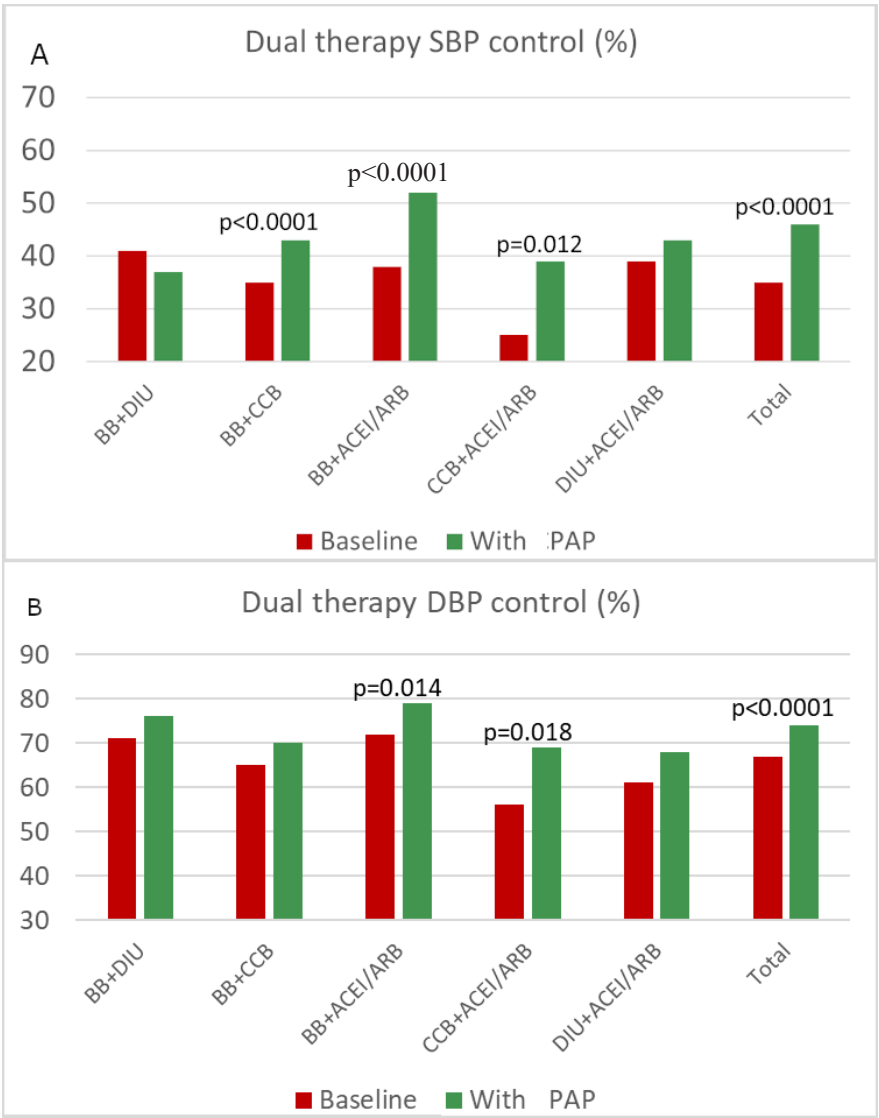
Among OSA patients on dual AHT, SBP control improved with PAP treatment in all drug combinations except for BB+DIU (Figure 28). Nevertheless, the overall proportion of patients achieving well controlled SBP remained low, with only the BB+ACEI/ARB combination exceeding 50% of patients. DBP control, on the other hand, improved across all dual therapy combinations and was consistently stronger than SBP control (Figure 28).

Figure 27A and B. ***Monotherapy, SBP (A) and DBP (B) control percentage before and after PAP treatment.***



ACEI/ARB=Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers, BB=beta blocker, BP=Blood Pressure, CAH=Central acting antihypertensives, CCB=Calcium Channel blockers, DBP=Diastolic BP, DIU=Diuretics, SBP=Systolic BP. PAP=Positive airway pressure. Used with permission, courtesy Oxford University press, European Heart Journal Open, Sven Svedmyr et al.

Figures 28A and B. ***Dual therapy, SBP (A) and DBP (B) control before and after PAP treatment.***



ACEI/ARB=Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers, BB=beta blocker, BP=Blood Pressure, CAH=Central acting antihypertensives, CCB=Calcium Channel blockers, DBP=Diastolic BP, DIU=Diuretics, SBP=Systolic BP. PAP=Positive airway pressure. Used with permission, courtesy Oxford University press, European Heart Journal Open, Sven Svedmyr et al.

5 DISCUSSION

5.1 GENERAL DISCUSSION

As previously described, OSA and hypertension are highly prevalent disorders worldwide[5,6]. This thesis examines multiple factors contributing to the overlap between these conditions and how they may amplify and accelerate each other's impact on CV risk. The prevalence of OSA is increasing, partly due to lifestyle changes and rising obesity rates globally, but also because of greater awareness and improved diagnostic availability. In addition, as Western populations age and life expectancy continues to rise[177], both hypertension and OSA are expected to become even more prevalent, as they increase in prevalence and severity with increasing age. Advances in healthcare have significantly improved CV disease prognosis and prevented many first MACEs. Consequently, patients with OSA are likely to live longer but experience a greater lifetime disease burden than before. The growing population with chronic OSA, hypertension, and CV complications will pose a major challenge for future healthcare systems. Effective management of multiple modifiable risk factors, such as OSA, hypertension, diabetes, and hyperlipidemia, throughout as much of this lifetime burden as possible will have a substantial impact on quality of life, age at first MACE, and prognosis for survivors. Longer life expectancy will also increase the overlap of multiple risk-enhancing conditions, underscoring the need for more research on patients with multimorbidity to optimize and individualize treatment strategies.

With the rising prevalence of both OSA and hypertension, and given the constraints on healthcare resources, it is increasingly critical to identify which patients are at the highest CV risk and determine which treatments yield the greatest benefit in these high-risk groups. This thesis studied several aspects of long-term CV risk in patients with OSA with or without comorbid hypertension. In OSA patients treated with PAP, CV risk was increased, and OSA patients suffered from the first serious CV event earlier in life compared to controls without OSA. The CV risk is further amplified in OSA patients with comorbid hypertension. PAP treatment mitigates the OSA related CV risk increase, but a residual risk increase remains. Both OSA and hypertensive control is limited in hypertensive OSA patients contributing to residual CV risk increase. Information on best AHT use in OSA was sorely lacking. In this thesis, we demonstrate that the type of AHT influences BP control, and that consideration of the degree of OSA control is essential for optimal individualization of AHT treatment decisions.

5.2 METHOLOGICAL CHALLENGES: EPIDEMIOLOGICAL STUDIES VS RCTS -PROS AND CONS

Randomized controlled trials (RCTs) are considered the gold standard for evaluating causal relationships and causality in clinical research. Their design allows for the minimization of confounding variables and ensures comparability between study groups for known and unknown confounders, thereby enabling precise control over study conditions[178]. However, RCTs require substantial investments of time and financial resources, and recruiting large sample sizes can be challenging. Consequently, sample sizes are typically determined through statistical power calculations conducted prior to study initiation. Well-constructed RCTs are the best way to establish causality, and history has shown that associations seen in cross-sectional or longitudinal cohort studies, are not always verified when strict RCTs are performed. While RCTs often involve homogeneous and highly selected patient populations to enhance internal validity, this can limit the generalizability of findings to broader, more diverse clinical populations[179,180]. For instance, women have historically been underrepresented in RCTs, resulting in a lack of gender-specific insights across various medical conditions. Similarly, data on treatment-efficacy and safety in pediatric and geriatric populations are frequently insufficient due to their limited inclusion.

Cohort studies offer a powerful and practical approach to clinical and epidemiological research. One of their key strengths is the ability to reflect real-world clinical practice by including diverse patient populations and capturing the full spectrum of clinical variability[181,182]. This also allows researchers to study underrepresented groups, such as elderly with sleep apnea and high comorbidity burden, and to gain insights that are often missed in more controlled settings. While cohort studies do face challenges, particularly in accounting for group differences and controlling for many confounding variables (Table 11), significant progress has been made. Modern statistical techniques, including advanced matching procedures and robust adjustment models, have greatly improved our ability to manage these complexities. When applied appropriately and with careful consideration of inherent limitations, these analytical tools enable researchers to draw meaningful and reliable conclusions from observational data[183,184].

Table 11. ***Sources of Bias in non-randomized Longitudinal Cohort Studies Evaluating Treatment Effects on MACE and Mortality.*** *Used mitigation strategies in this thesis in italics. Adapted from ENCePP guide on Methodological Standards in Pharmacoepidemiology*[185].

Bias Type	Definition	Example	Mitigation Strategies
Confounding Bias	Differences in baseline characteristics between treatment groups influence outcomes.	Patients receiving the intervention may be younger or have fewer comorbidities.	Propensity score *matching*, inverse probability weighting, stratification, *multivariable adjustment. Sensitivity analysis.*
Selection Bias	Systematic differences in who enters the cohort or receives the intervention.	Healthier patients are more likely to receive treatment; sicker patients excluded.	Careful inclusion/exclusion criteria, *sensitivity analyses.* *The entire population during set study period used.*
Immortal Time Bias	Period during which outcome cannot occur because treatment has not yet started.	Survival time before treatment incorrectly attributed to treatment group.	*Time-dependent exposure modeling* (e.g., Cox models with time-varying covariates).
Informative Censoring	Loss to follow-up or censoring related to prognosis or treatment.	Patients discontinuing treatment due to adverse effects may have higher MACE risk.	Inverse probability of censoring weights, *sensitivity analyses. Censored time at risk used. We had outcome data on all patients in study II.*
Measurement Bias	Misclassification of exposure or outcome.	Inaccurate coding of MACE events or incomplete mortality data.	Validation of outcome definitions, *linkage to mandatory registries.*
Residual Confounding	Unmeasured or poorly measured confounders remain after adjustment.	Lifestyle factors (diet, exercise) often missing in administrative data.	Instrumental variable analysis, negative control outcomes. *Indirect adjustment through related confounders/mediators*

Treatment Crossover & Adherence Bias	Patients switch treatments or have poor adherence, diluting effect estimates.	Non-adherence to statins in CV prevention study.	Per-protocol and as-treated analyses, marginal structural models. *Reliable adherence registry data on all treatments*
Competing Risk Bias	Death from non-CV causes prevents observation of MACE.	Cancer-related mortality in elderly patients.	Competing risk models (Fine-Gray sub distribution hazard). *Both were main outcomes. Exclusion criteria limit competing risks.*
Calendar Time & Secular Trend Bias	Changes in standard care or diagnostic criteria over time affect outcomes.	Introduction of new therapies during follow-up.	Adjustment for calendar time, stratified analyses. *No major changes in PAP or AHT treatment during the study.*

Leveraging existing databases further enhances the value of cohort studies. This approach not only reduces selection bias but also saves considerable time and resources by bypassing extensive data collection processes. Moreover, it allows for longer follow-up periods without the need to wait years for prospective data, making cohort studies especially well-suited for investigating long-term outcomes. Although some uncertainty remains, particularly when compared to RCTs, this can be mitigated through large sample sizes and thoughtful study design. Overall, cohort studies provide a flexible, cost-effective, and highly informative framework for exploring complex health trajectories and real-world treatment effects[183,184,186].

Recently, embedding prospective RCTs within registry studies has been suggested, to combine advantages of RCTs and registry studies. Integrating prospective RCTs into registry-based research combines the methodological rigor of randomization with the efficiency and real-world relevance of observational data. This approach allows for large-scale enrolment at lower cost, leverages existing infrastructure for follow-up, and enhances external validity by reflecting routine clinical practice. Furthermore, registry-based RCTs facilitate rapid implementation, long-term outcome tracking, and subgroup analyses without the extensive resource demands of traditional standalone trials[187,188]. However, these methods were not implemented when this thesis was planned.

A compelling example of the strengths and limitations of different study designs can indeed be seen in research on long-term CV risk in OSA, particularly in relation to PAP treatment[189]. While randomized controlled trials have contributed valuable insights, they have also faced notable constraints. Most RCTs in this area have focused on patients with established CV disease, often with limited follow-up durations and restrictive inclusion criteria (mostly secondary prevention). Ethical considerations—such as the exclusion of patients with excessive daytime sleepiness, for whom withholding PAP would be inappropriate, both due to symptom burden and accident risks—have further narrowed the study populations. Additionally, suboptimal adherence to PAP therapy in the non-sleepy study population, has complicated interpretation of outcomes[189,190]. These limitations have contributed to largely negative findings regarding the protective effects of PAP, except in PAP adherent subgroups[191-194]in several post-hoc analyses in these RCTs. In contrast, large-scale cohort studies have consistently demonstrated an elevated long-term CV risk in individuals with untreated OSA[15,195-197], and importantly, a substantial reduction in this risk among those who adhere to PAP therapy[159,189,198]. Several methodological biases were identified, the healthy behaviour bias where patients with good PAP adherence also had other healthy lifestyle factors (good AHT adherence, diet, exercise etc) and the immortality bias where failure to identify proper time at risk led to an event free time between study start and treatment initiation. These findings underscore the value of cohort studies in capturing real-world treatment patterns and long-term outcomes while addressing relevant confounders.

5.3 METHOLOGICAL CHALLENGES: MISSING DATA AND IMPUTATION

Large registry databases will contain missing values on one or more variables for patients. Indeed, the chance of having complete patients' data decreases considerably with increasing number of recorded variables. Thus, if we exclude all patients with any missing data, we risk losing considerable study power. This may lead to unnecessary and sometimes unethical discarding of valuable study information and increased risk of incorrect conclusions being drawn[199,200]. In most registries there are many variables, and they are not completely unrelated to each other. For example, a patient's systolic BP is affected by multiple other variables, especially other BP values (diastolic, mean etc.) but also BMI, smoking status, OSA degree

and more. Imputation uses these associations to predict the most likely number for each variable with missing value[201]. Multiple simulations to account for data distribution and accuracy, are often used to also get an accurate prediction of the accuracy of the predicted value so distribution and spread of the variable can also be reported[202]. These imputation methods have been shown to be accurate and superior to previously suggested imputation of mean variable values for missing variables. Optimal imputation method varies depending on if missing values are random or related to outcomes, study type and size[201]. By using imputation all the existing data for patients with some missing values can be saved and study power increased without the imputed data wrongly impacting the study results. We used imputation in study III as described in chapter 3.5.

5.4 PRIMARY PREVENTION

Primary prevention efforts are often hindered by the human tendency to prioritize immediate comfort and short-term benefits over long-term health gains. This is particularly evident in studies of adherence to AHT[134,135,203,204], and even more so in the case of positive airway pressure treatment[21,205,206], which is inherently more burdensome than simply taking a couple of pills daily.

Several key factors influence treatment adherence:

- Patient motivation and understanding of the condition and its treatment.
- User-friendly treatment options, characterized by fewer side effects, lower time demands, and reduced costs.
- Regular follow-up to optimize and adjust treatment as needed.
- Individual personality traits that affect health behaviours.
- Social support, including encouragement from family and friends, and financial support for patients with limited economic resources or challenging living conditions.
- Technological aids, such as mobile apps and reminder systems.

This thesis aims to contribute with more distinct information on disease prognosis, treatment outcomes and particularly vulnerable patient groups.

Thereby, patient participation can be increased through informed decision making and improved patient motivation. Furthermore, the emerging evidence on the protective effects of even low-adherence PAP use may prompt a re-evaluation of current minimum daily usage recommendation. As the number of patients diagnosed with OSA continues to rise, the healthcare system will face increasing challenges in providing adequate follow-up. However, these challenges can be mitigated through technological solutions, such as remote monitoring of PAP usage and mask leak[207-209] and feedback-loop of information to the patients via mobile apps[210,211]. While regular follow-up has the potential to enhance adherence, resource constraints in sleep clinics may necessitate prioritizing such efforts for patients at the highest predicted CV risk.

5.5 OUR FINDINGS AND CURRENT KNOWLEDGE IN THE FIELD

While studies with a focus on patients with OSA and comorbid hypertension are sparse, most of our findings have support on previous knowledge in the field. The pathophysiological mechanisms underlying both disorders have been extensively investigated, as outlined in the introduction of this thesis. Our hypotheses are built on general knowledge on previous clinical studies and current guidelines for hypertension, OSA and CV prevention. Research on arterial stiffness and pulse-wave analysis has progressed since our initial study, further confirming and expanding our 2016 insights[212]. Pulse-wave velocity measurements as examined in Study I are now incorporated into contemporary hypertension and CV prevention guidelines[22,27]. Moreover, machine learning and AI-driven CV risk prediction tools utilizing diverse pulse-wave signals[156,213,214] are now commercially available (For example, Arteriograph®, Complior®, Sphygmocor®, pOpmètre®) and more advanced wearables. Similarly, in Study II, which demonstrates a more-than-additive CV risk in patients with combined hypertension and OSA, align with previous reports focusing on either OSA[49] or hypertension alone[27,215]. Our finding of a protective effect of PAP even with low adherence is consistent with results from a major pooled-data meta-analysis[189]. While the role of OSA in accelerating vascular aging and atherosclerosis has been previously suggested[216], the differences in age at first MACE has not previously been explored to our knowledge. Despite the limited number and size of studies investigating antihypertensive drug classes specifically in hypertensive OSA patients,

mechanistic studies have highlighted the central role for sympathetic activation[152,217] and renin-angiotensin system activation[119,218] in OSA. These findings are consistent with the results in Studies III and IV, which indicate improved BP control with betablockers and RAAS targeting AHTs. Importantly, our results strongly indicate that the type of AHT does matter for treatment of hypertension in OSA patients. These findings should inspire more studies in this area of research.

5.6 DIAGNOSIS OF CV RISK IN OSA: PPT AS AN INDICATOR OF ARTERIAL STIFFNESS

5.6.1 DIAGNOSTIC CHALLENGES IN OSA

The main reason for delayed diagnosis in OSA and hypertension is that the disorders are often asymptomatic and may be present for a long time before being diagnosed. Even with healthcare devices getting smarter and easier to use, further increased awareness and screening will likely need to be used to reach the asymptomatic patients earlier. Technological advances do make sleep investigations more accessible and give more information to guide individualized care. The advancement of wearable devices that are increasingly used in the general population, will likely aid finding asymptomatic patients earlier and take an important part in early investigations/screening. In this thesis, study I focused on getting more information out of regular sleep studies with PPT mirroring arterial stiffness to contribute towards CV risk estimations based on the finger pulse wave.

5.6.2 PULSE WAVE ANALYSIS

The findings in study I, suggest that PPT is a useful parameter when assessing vascular function in overnight recordings.

A few limitations of the study should be addressed. A key consideration is whether PPT and central arterial stiffness assess the same physiological properties. Central arterial stiffness primarily reflects the elasticity and reduced compliance of the large arteries, which act to reduce the dampening of the pulse wave. It is typically measured over a short duration during wake rest to minimize variability caused by stress and physical activity. While similar information can be derived from peripheral vessels, such as those in

the finger vascular bed, these vessels also exhibit more dynamic behaviour and functional variability. PPT measures the time it takes for the pulse wave to travel through the large arteries, thus capturing comparable data[174,175]. However, it likely includes contributions from more peripheral vessels, which may reduce repeatability in snapshot assessments.

Patients with suspected sleep apnea demonstrated a higher cardiometabolic risk profile when compared to the general population. Male patients aged 50–65 years were disproportionately represented; however, risk prediction is particularly relevant within this age group. A gold-standard assessment of vascular stiffness was not performed in this study. Nevertheless, photoplethysmographic PPT has previously been validated against radial pulse wave tonometry and shown to correlate with established measures of arterial stiffness[212,219]. Night to night repeatability of the results were not studied. However, a recent PhD study reported reasonable agreement between two PPT values obtained at day and night[212]. A direct comparison with ambulatory overnight blood pressure was not conducted. It has recently been studied and found good agreement between methods[220]. Finally, the cross-sectional design of this study precludes any inference regarding causality between overnight PPT and its predictors.

The findings clearly demonstrate significant vascular relaxation during deep sleep. Measurements taken during this relaxed sleep stage may best reflect central arterial stiffness and intrinsic vascular stiffness while minimizing the influence of transient stress responses such as white coat syndrome. This further supported by nighttime BP being lowest and sympathetic activity being lowest during deep sleep[221]. Deep sleep has been shown to play a critical role in central nervous system recovery, particularly through activation of the glymphatic system[36], which facilitates the clearance of “metabolic waste” during sleep. In addition to its neuroprotective functions and vigilance recovery, deep sleep is also essential for cellular repair and systemic recovery processes[222,223]. The finding of increased PPT during deep sleep suggests that the observed vascular relaxation during deep sleep could reflect a period of enhanced CV recovery, potentially influencing long-term vascular health and resilience. Conversely, REM sleep has PPT, BP and sympathetic activation close to wake levels. More studies are needed to determine if deep sleep provides an optimal window for arterial stiffness investigation. Importantly, the dynamic nature of peripheral vessels also provides a unique opportunity to investigate influences from autonomic regulation, stress, hypoxia, and sleep

fragmentation, factors that may contribute to long-term stiffening of central arteries.

Longitudinal data collected during sleep provides a robust dataset, whereas multiple daytime assessments would be both time-consuming and costly. The shortened PPT in hypertension and OSA seen during all sleep stages and the wake state is likely a strong indicator of the increased CV risk in these patients as shown in study II.

5.7 EPIDEMIOLOGICAL INSIGHTS INTO CV RISK IN OSA AND COMORBID HYPERTENSION

Study II is the first long-term survival study on patients with OSA and hypertension. It is large enough to study multiple subgroups and to address secondary outcomes with adjustment for a high number of relevant confounders. However, some limitations need to be considered. First, we did not have access to actual BP measurements during the study, which limited our ability to assess the degree of hypertension control in our hypertensive groups. Leading cardiology societies in both the United States and in Europe (American Heart Association, European Society of Cardiology) have emphasized the importance of several modifiable factors for improving CV health, including dietary habits, smoking status, physical activity, and sleep duration, quality, and regularity[25,224]. Unfortunately, we did not comprehensively evaluate these lifestyle factors in the study. To partially account for these variables, we included several proxy confounders in our final analysis, such as BMI, socioeconomic status, treatment adherence, and the presence of obstructive lung disease. As demonstrated in previous research[225], our study is susceptible to the healthy user bias, wherein adherence to PAP therapy may reflect broader health-conscious behaviours, including compliance with CV medications. To mitigate this bias, we incorporated data on the actual use of statins and AHT medications, obtained from a highly reliable Swedish prescribed drug registry (Läkemedelsregistret), alongside PAP usage in our final model. Consistent with prior findings[205,226], we observed a correlation between low adherence to PAP therapy and poor adherence to prescribed medications. Although the resolution of PAP follow-up data was limited, outcome data were available for all participants. Our study did not systematically evaluate OSA patients receiving non-PAP therapies, which warrants investigation in

future research. Lastly, the low baseline risk for MACE in the "healthy" population-based non-OSA, non-hypertension control group may have amplified the hazard ratios in our results, a factor that should be considered when interpreting the findings.

We identified that PAP treatment for as little as 2-4hrs/night already has significant CV protective effects. This protective effect in low PAP usage has previously only been shown in meta-analyses with pooled data[189,227,228]. It is interesting to consider why using the PAP for only parts of the night may already have detectable protective effects. Our study I, results suggest that deep sleep CV recovery may provide an important explanation of the phenomenon. Patients with low adherence in the clinical setting usually show similar patterns of use. They put on their PAP mask when they go to bed in the evening but fail to keep it on later during the night. Thus, it is likely low adherence patients mainly use their PAP during the first part of the night. If we consider sleep physiology, deep sleep is mainly produced during the first sleep cycles, while REM is increasing during the later sleep cycles. It may therefore be the timing of the PAP use that explains the positive results even with low usage time/night. The limited PAP use may be sufficient to maintain deep sleep, a period of relative CV system off-loading. The results in study II reaffirm OSA as a strong accelerator of the development of CV disease and emphasize the importance of recognizing OSA patients with hypertension as having a very high CV risk. Multiple previous cohort studies have demonstrated an increased CV risk in patients with OSA[15,195,196]. Although these studies may lack certain confounders that vary across cohorts, the overall consistency of their findings is striking, which reduces the likelihood of data misinterpretation and strengthens the combined level of evidence. Our finding of an even higher CV risk in hypertensive OSA patients has the clear implication that evaluating BP in OSA patients in routine care is important as well as diagnosing comorbid OSA in hypertensive patients. Patients with both disorders may warrant more regular follow-ups to increase adherence to treatments, optimize them and assess other modifiable CV risk factors like obesity, hyperlipidemia and metabolic dysfunction. This is in line with previous findings of increased OSA prevalence in hypertensive patients and especially in those with resistant hypertension[61,136]. Lastly, we must consider the residual CV risk increase even in PAP treated OSA. It suggests that PAP treatment cannot fully reverse previous OSA damage of the CV system even with optimal adherence. This is most likely due to early asymptomatic OSA and diagnosis and treatment delay. Most patients have suffered from OSA for

many years before PAP treatment is started. This delay may have allowed for initial dynamic CV changes to reach an irreversible state with manifest vessel remodelling and atherosclerosis development[198,228]. Another possible pathway may be that the OSA has already activated other downstream effects that PAP cannot modify although they may still be reversed by CV protective medication. In fact, our model clearly shows that intake of AHTs and statins have a strong risk reducing effect in our OSA patients with comorbid OSA. Further studies are warranted on the interaction of these CV risk increasing conditions and their treatments.

5.8 MANAGING HYPERTENSION IN OSA PATIENTS

Information evaluating AHT in hypertensive OSA was previously very sparse. Interestingly, our results demonstrate that different classes of AHT varied in effectiveness before and after PAP treatment of OSA. Betablockers with or without diuretics experienced the best BP control before OSA treatment but there was no advantage in high adherence PAP treated OSA patients. In this group the renin-angiotensin blockers provided the best BP control. Whether these results are affected by the degree of PAP adherence will need to be investigated further. For patients with poor to medium adherence each night, a combination of a betablocker and RAB may be advantageous.

Study III highlights the need for a more nuanced approach to managing hypertension in patients with comorbid OSA. Current guidelines do not recommend specific AHT classes for OSA patients with hypertension due to lack of data. The findings in study III and IV suggest that treatment with beta-blockers, alone or in combination with diuretics, may be particularly effective with respect to BP control in patients with untreated OSA or in treated OSA with poor adherence to device therapy. An alarming finding is the poor hypertension control among patients with OSA which has since been confirmed in other studies[39,229,230]. Again, patients treated with BBs, alone or in combination with DIUs, exhibited significantly higher rates of controlled office BP, independent of key confounding factors, but the overall proportion is close to only 50%. Although renin-angiotensin blockers were the most prescribed antihypertensive agents, they appeared to be less effective in the untreated OSA population and rates of controlled hypertension were even worse. Considering increased sympathetic drive is along with hypoxia, the main OSA pathways to hypertension[49], our results

are not unexpected. Betablockers are seldom the first choice AHT in accordance with current general hypertension guidelines[22] except in patients with comorbid conditions treated with BB (tachycardia, chronic ischemic heart disease, cardiac failure atrial fibrillation, migraine etc.). Non-selective BB have been linked to an increased risk of new-onset diabetes in predisposed individuals, particularly those with metabolic syndrome[231]. In addition, BBs generally exhibit a less favourable side-effect profile compared to RAB, with higher rates of treatment discontinuation observed under real-world conditions[232].

In Study IV, AHTs, BP and BP control was reassessed after initiation of PAP therapy. The results indicate that ACEi or ARB, either as monotherapy or in combination with other drug classes, are particularly effective in lowering BP and improving BP control when used alongside PAP therapy in OSA patients. Prospective, long-term studies are warranted to validate these observations and to guide future strategies for personalized antihypertensive treatment in both treated and untreated OSA populations.

Several limitations in studies III and IV need to be discussed. First, follow-up data were only available for a subset of patients, raising concerns about potential selection bias. It is likely that patients with follow-up data differ systematically from those without, particularly in terms of higher treatment overall acceptance and adherence. Recent studies showed that patients on high PAP use are also more often adherent with AHT medication use – the so-called healthy behaviour bias[226]. However, for the purpose of our study this bias may likely apply equally to all AHT´s and would not affect individual AHT comparison. Individuals who continue PAP therapy over several years are typically those who tolerate it well and maintain good adherence. However, there is also a significant number of patients with low or withdrawn PAP treatment at follow-up. It is important to emphasize that our findings regarding hypertension management and the effects of PAP therapy on blood pressure control apply primarily to patients who are adherent to treatment. Additionally, given the variability in clinical routines and patient populations across participating centers, we controlled for study site (reporting sleep center) in our analyses. As a result, our findings are most representative for the average European patient and may not be generalizable among other populations with more outlier characteristics (higher mean BMI, more smokers, regional CV risk etc.). We also assumed that anti-hypertensive medication regimens remained stable during the study period. This assumption was supported by our data: changes in AHT therapy were infrequent, with only 3% of patients on monotherapy and 4%

on dual therapy increasing the number of medications, and 3% of dual therapy patients decreasing their regimen. Sensitivity analyses excluding patients with changes medication did not change our results.

Altogether, study III and IV demonstrate very poor BP control in hypertensive OSA patients in Europe. Poor BP control emphasizes the high CV risk these populations already have as shown in study II. As we can show differences in BP control with AHT drug types in study III and IV, AHT in OSA patients with comorbid hypertension needs further exploration in order for us to understand how to improve BP control and to reduce CV risk in these very high-risk populations.

5.9 DEBATED QUESTIONS IN THE FIELD

5.9.1 HYPOXIC BURDEN

Historically, the AHI has been the primary metric for assessing OSA severity and estimating risk. However, recent studies have shifted focus toward hypoxic load, the total burden of nocturnal hypoxemia, as a potentially more relevant predictor of CV outcomes. Various methods have been employed to quantify hypoxic burden, including the ODI (not a great predictor for MACE)[233], time spent below 90% saturation[234], lowest oxygen saturation[235], and more advanced measures such as the area under the curve for hypoxia[236]. There is strong rationale stating that the magnitude of hypoxia may be of a particular clinical interest compared to the frequency of respiratory events. Several studies have demonstrated a stronger association between these hypoxia-based markers and the CV risk compared with the AHI alone. Conversely, less hypoxic but highly disruptive respiratory events can still lead to substantial sleep fragmentation and sympathetic activation, triggering other pathogenic pathways beyond hypoxia. While consensus exists that AHI alone is insufficient to fully characterize OSA severity, an optimal biomarker integrating hypoxia, sleep disruption, and event frequency remains elusive[237]. For Study II, we therefore selected the strongest available OSA marker in our cohort in a preplanned manner. The registry included both AHI and ODI; however, due to strong collinearity, both could not be included in the main models. When ODI did not emerge as a stronger predictor of CV events in our population, we opted for the more traditional AHI to maintain consistency with previous major registry-based cohort studies. Sensitivity analyses

substituting AHI with ODI yielded very similar results in models stratified by OSA severity.

5.9.2 THE PAP PROTECTIVE EFFECT IN PRIMARY/SECONDARY PREVENTION AND IN THE ELDERLY

While secondary prevention with PAP in patients with OSA and established CV disease has yielded negative or inconclusive results[238], observational real-world data from cohort studies consistently demonstrate both a high CV risk in OSA[15,195] and a protective effect of PAP therapy[159] (see Sections 1.3 and 5.2). The comparison will also be highly affected by investigated patients' age. There is currently no consensus on whether PAP therapy provides CV protection in elderly patients with limited life expectancy and for them treatment is mainly to improve symptoms and quality of life. Whether PAP offers greater benefit in primary prevention compared to secondary prevention remains debated, largely due to the absence of RCTs in primary prevention settings.

Several arguments support the hypothesis that primary prevention may be more effective. From a pathophysiological perspective, early-stage hypertension is more dynamic and potentially reversible, whereas established hypertension is often accompanied by atherosclerosis and arterial stiffness, likely limiting reversibility. Scientific evidence also indicates that patients with prior CV events and advanced atherosclerotic disease have a markedly higher risk of recurrent events[239,240]. Furthermore, previous studies have shown greater PAP benefits in younger patients[189], and Study II confirms this finding, demonstrating similar effects in hypertensive OSA patients. Importantly, even among older patients (age quartile 4) without manifest CV disease, PAP appears to confer a protective effect, at least in cases with good tolerance and adherence. The best preventive effect was actually recorded in the first age quartile.

Nevertheless, our results also highlight that even optimally treated OSA patients retain some residual increased CV risk, underscoring the need for comprehensive risk factor management beyond PAP alone.

5.9.3 PAP ADHERENCE

The optimal duration of nightly PAP use required to achieve treatment benefits has long been debated. Ideally, patients should use PAP throughout

their entire sleep period, which varies considerably between individuals. However, many patients fail to maintain full-night use, often due to involuntary mask removal during sleep or not reapplying the mask after awakenings, such as bathroom visits. Early studies[241,242] introduced a threshold of ≥4 hours per night as "adequate use", This criterion has remained the minimum requirement for continued treatment in most countries. More recent research provides a more nuanced understanding, indicating that different treatment goals require different adherence levels[243]. For CV prevention, minimum of 4–6 hours per night is generally recommended, whereas symptom relief and reductions in hospitalizations or emergency visits may be achieved with as little as ≥2 hours per night[244]. In Study II, we demonstrate that even low adherence of 2–4 hours per night confers significant CV protection, with over 20% risk reduction, and that protective effects increase with greater adherence. Previously, such benefits of low adherence have only been reported in pooled-data meta-analyses[189]. In high-risk patients, such as those with hypertensive OSA, even partial PAP adherence may therefore have clinical merit, suggesting that strict enforcement of the 4-hour minimum requirement for continued treatment might be reconsidered.

5.9.4 CV RISK IN SYMPTOMATIC/ASYMPTOMATIC OSA

After the negative/inconclusive secondary prevention RCTs in OSA that focused on non-sleepy patients, there has been a lot of discussion on if patients with excessive daytime sleepiness (EDS) might have higher CV risk and better effect of PAP in OSA[245]. There is data suggesting similar CV risk in sleepy patients[197] but better PAP response in the form of reduced arterial stiffness[246] and MACE risk[196]. In study II, EDS did not have major impact on CV risk. We saw a 7-16% risk reduction for sleepy patients in our EDS stratification sensitivity analysis of the main primary COX regression analysis for sleepy patients after adjustment for PAP adherence.

5.9.5 SEX DIFFERENCES

There are less data and knowledge of OSA outcomes in females as the disorder is more common in men especially before women reach menopause. OSA prevalence and severity in women increase after menopause and with increasing age, but OSA in women may have different clinical presentations and prognosis than in men. Though not the main focus in this thesis some important information is provided by our studies. Women have decreased risk of MACE and all-cause death, independent of

OSA and hypertension of 61% and 47% in our cohort. PAP treated OSA women with or without hypertension have lower risk of MACE 37% and all-cause death 46% risk reduction and suffer from their first event almost 4 years later than men (data not shown).

5.9.6 ANTI-HYPERTENSIVE TREATMENT IN OSA

Real-world data on AHT in patients with OSA are scarce (Tables 6 and 7), and the few available RCTs have been small, with only one comparing multiple AHT classes[247]. Cohort studies have sporadically addressed this topic along with small placebo controlled trials, suggesting potential benefits of RAB[248] or MRA[249,250], but without accounting for the degree of OSA control. Due to the lack of conclusive evidence indicating major differences between AHT classes, current hypertension management in OSA follows general population guidelines, and the topic has received limited attention despite the well-documented challenge of achieving optimal blood pressure control in OSA patients. Our results in the field are groundbreaking as they demonstrate significant differences in effect between specific AHTs and AHT combinations. Importantly, these effects were strongly influenced by the degree of OSA control. We also confirmed that blood pressure control is poorer in OSA patients compared to non-OSA populations, combined with a markedly elevated CV risk in those with both OSA and hypertension. These results highlight an urgent need to revisit treatment strategies and conduct further research to improve outcomes, quality of life, and life expectancy in this high-risk population.

6 CONCLUSIONS

This thesis added new and comprehensive evidence from clinical cohort studies in the following domains:

1. **Epidemiology**
   It is known in the field that OSA induces additional load to the CV system, both during daytime and sleep. OSA is also known to markedly increase the risk for hypertension development, especially when occurring early in life. Thereby, OSA is an accelerator for CV ageing and CV disease development. Patients with comorbid hypertension are at very high CV risk. An alarming finding is that BP control in OSA is very poor even in a group of hypertensive patients with a potentially healthy behaviour bias.
2. **Diagnosis**
   Identifying patients with increased CV risk will be increasingly important as increasing numbers of OSA patients will burden clinics already under time and economical constraints. A pulse wave assessment using the oximeter signal recorded during a routine sleep study may be a useful technique to better identify patients with early deterioration of vascular function during sleep.
3. **Treatment**
   Encouraging findings include the 10-15% improvement of blood pressure control when OSA is treated with PAP treatment.
   When OSA and comorbid hypertension are manifest in patients, they need optimized CV primary prevention including adequate OSA and hypertension control. In the real-world data of our studies, the most effective antihypertensive drugs in OSA varies depending on OSA control. Betablockers are associated with the highest rates of blood pressure control in the untreated OSA condition, while RAAS blockade was associated with better BP control in well controlled OSA patients.

The data warrant A; confirmation in other large real-world datasets and B; restart of attempts for larger controlled clinical trials to identify the optimal AHT regime in this patient group with very high CV risk.
The findings of this thesis may help to answer several important clinical questions and provide valuable information for the diagnosis, treatment, assessment of prognosis and treatments in patients with combined OSA and hypertension.
These results point to a need for a holistic approach to CV risk factor treatments to reduce risk and to improve outcome in these high-risk patients.

7 FUTURE PERSPECTIVES

The future of OSA and hypertension care will be challenging as the numbers of patients with OSA, and comorbid hypertension keep increasing. However, multiple new steps towards improved treatments are currently being developed.

There is a need to investigate the different long-term effects of the different AHTs on CV risk and age at first event. Although BP control may appear to favour certain AHTs, it is essential to demonstrate comparable effects on MACE before recommending an optimal treatment strategy for patients with hypertensive OSA. AHTs may have other pharmacologic properties that could exert negative long-term effects through mechanisms independent of BP control. In fact, these studies are already planned for my post doc period by starting the AHPAP study[251]. Investigating PPT in patients with hypertensive OSA might give additional information on AHTs used. Improved technological advancements will also contribute to better remote care and more information from regular sleep investigations aiding us in optimizing treatments.

Additional OSA treatment options, both mechanical and pharmacological, will soon be more commonly available and OSA treatment will likely be more personalized and optimized for each patient depending on different phenotypes as well as tolerance for treatment options. Combination therapy with pharmacological addons to treatment devices will be more common. For instance, the introduction of better tools for pharmacological weight reduction such as the GLP-1 agonists may offer CV protective effects on top of weight loss and decreased OSA severity.

For better primary CV prevention increased cooperation between caregivers both in primary and specialized care with different focuses will be needed.

This thesis has hopefully contributed information on important mechanisms that may promote future studies on and optimize hypertension treatment in OSA patients.

8 ACKNOWLEDGEMENT

First, I would like to express my gratitude to my family.

My wife Johanna has encouraged me to get this finished, pushed when needed and always supported me through this thesis and my health issues. I would not be here without you!

My sons Isak and Kasper are always my inspiration and love.

My parents, with my mother Karin, who always encouraged me and my late father Nils, who clearly showed me and many others that science is not only possible but rewarding.

Nathalie, my nephew, who helped provide the cover art for the thesis and the rest of you for general encouragement and support.

Next, I would like to thank my supervisors for all the support and wise advice through all these years.

Ludger Grote has guided me and provided ideas and valuable feedback while giving me the freedom to evolve and take successively more initiatives. You have provided structural boundaries and pushed me into action when needed. I thank you for your personal, intellectual and financial support, but most of all your friendship, inspiration and care.

Ding Zou you have ever been available for moral support, statistical and even nutritional aid and especially for reminding me that I was doing fine, even when the years flew by with busy clinic work or health issues. Quality indeed can be more important than speed. I value our many discussions and your unlimited knowledge of all literature and references.

Jan Hedner, you have ever been both an inspirational and fatherly supervisor. You always take your time when needed for both clinical and scientific questions and your anecdotes raised our spirits on many occasions. Thank you for being patient with my stubbornness. I know my father was and would have been even prouder if he had seen all your many achievements. I especially thank you for starting our sleep unit where so many of us have thrived and that have aided countless patients.

Thank you all for your patience and friendship! We had lots of fun along the way as well.

I would like to thank my fellow PhD students and colleagues, especially with Erik and Daniel having to share our poorly ventilated room in the lab, Christian for your technical knowledge and support, Benedict, Dimitri, Martin, and Mio for the many “fikas”, lunches and stories shared.

Joel, my current sleep unit “partner” and friend, without who I might well have given up by now! Your positive energy and never-ending improvement ideas are inspiring to see.

Catarina Dellborg and Karin Rahm for giving me the opportunity to pursue my thesis goal along my clinical work, and for finding ways to adapt and support me thru all challenges.

Ann-Christin, Anna, Jeanette, Lena and Per at the Sleep and Vigilance disorder lab, for great teamwork and friendship.

Heart lung foundation and VGR for financing large parts of this thesis work.

”Kliniska forskarskolan” for a solid foundation and giving me the knowledge I needed to handle even registry-based epidemiology.

Johan-Emil Bager for great discussions and advice.

Registry keepers for their efforts and making registry studies possible.

My co-authors, the ESADA network and Discovery group for many great discussions and support.

My opponent Karin Rådholm and Elmir Omerovic, Sören Berg and Annika Rosengren the examining committee for taking the time and effort to address this thesis and Jesper for taking care of us all during the dissertation.

Finally, I would like to express my gratitude to all our patients without whom none of this would be possible.

APPENDIX

Other publications *relevant for the thesis* but not part of it:

-Hypertension treatment in patients with sleep apnea from the European Sleep Apnea Database (ESADA) cohort – towards precision medicine, J Sleep Res 2022 [252]

All figures and tables, adapted or not, have been used with permission from respective publishers.

Springer Nature

Licensee: Goteborgs Universitet

Order Date: Nov 14, 2025

Order Number: 6147581261900

Publication: Nature

Structure: The anatomy of sleep

American Heart Association

Licensee: Goteborgs Universitet

Order Date: Nov 20, 2025

Order Number: #21643-SSVEDMYR

Publication: Circulation

Structure: Circulation.2022;146:e18-e43

Journal of Physiology

Order Date: Nov 14, 2025

Order Number: 6147630712555

Oxford University Press

License Number 6101980431774

License date Sep 04, 2025

Wolters Kluwer Health, Inc. and Copyright Clearance Center.

License Number 5812510902164

License date Jun 19, 2024

License Number 6107610461717

License date Sep 14, 2025

License Number 6107610503408

License date Sep 14, 2025

Biorender was used for Figure 4 and 5 with permission.

Agreement number: FN28WVYF0I

Date 251024

AI declaration

AI support *Copilot* has been used to reformulate the English wording, checking spelling and English sentence structure only. *Gamma.app* was used in making tables and a figure.

Ethical approval diary numbers

Study I, Ethics Committee at the Medical Faculty at Göteborg, Dnr 521-09.

Study II, Discovery, Ethics Committee at the Medical Faculty at Lund University and the Swedish Ethical Review Authority, Dnr. 2018/51, 2019/01420, 2020/02721, 2021/04984, 2022-00745-02, 2022-02012-02, 2022-05523-02, 2024-05277-02, and 2025-00712-02.

Study III and IV, ESADA, Ethics Committee at the Medical Faculty at Göteborg, Dnr 386-09.

REFERENCES

1. Broadbent WH. ON CHEYNE-STOKES' RESPIRATION IN CEREBRAL HÆMORRHAGE. *The Lancet* 1877;**109**:307-309. doi: https://doi.org/10.1016/S0140-6736(02)21857-7
2. Guilleminault C, Dement WC. 235 cases of excessive daytime sleepiness: Diagnosis and tentative classification. *Journal of the Neurological Sciences* 1977;**31**:13-27. doi: https://doi.org/10.1016/0022-510X(77)90003-X
3. Motta J, Guilleminault C, Schroeder JS, Dement WC. Tracheostomy and hemodynamic changes in sleep-inducing apnea. *Ann Intern Med* 1978;**89**:454-458. doi: 10.7326/0003-4819-89-4-454
4. Lugaresi E, Cirignotta F, Coccagna G, Piana C. Some epidemiological data on snoring and cardiocirculatory disturbances. *Sleep* 1980;**3**:221-224. doi: 10.1093/sleep/3.3-4.221
5. Williams LB, Mancia EG, Spiering YHW*, et al.* 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. *Journal of Hypertension* 2018;**36**:1953-2041. doi: 10.1097/HJH.0000000000001940
6. Benjafield AV, Ayas NT, Eastwood PR*, et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *The Lancet Respiratory Medicine* 2019;**7**:687-698. doi: 10.1016/S2213-2600(19)30198-5
7. Javaheri S, Peker Y, Yaggi HK, Bassetti CLA. Obstructive sleep apnea and stroke: The mechanisms, the randomized trials, and the road ahead. *Sleep medicine reviews* 2022;**61**:101568-101568. doi: 10.1016/j.smrv.2021.101568
8. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med* 2005;**352**:1206-1214. doi: 10.1056/NEJMoa041832
9. Gottlieb DJ, Yenokyan G, Newman AB*, et al.* Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;**122**:352-360. doi: 10.1161/circulationaha.109.901801
10. Javaheri S, Brown LK, Abraham WT, Khayat R. Apneas of Heart Failure and Phenotype-Guided Treatments: Part One: OSA *Chest* 2020;**157**:394-402. doi: 10.1016/j.chest.2019.02.407
11. Parati G, Lombardi C, Castagna F*, et al.* Heart failure and sleep disorders. *Nature Reviews Cardiology* 2016;**13**:389-403. doi: 10.1038/nrcardio.2016.71

12. Shahar E, Whitney CW, Redline S*, et al.* Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *American journal of respiratory and critical care medicine* 2001;**163**:19. doi: 10.1164/ajrccm.163.1.2001008
13. Javaheri S, Barbe F, Campos-Rodriguez F*, et al.* Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. *Journal of the American College of Cardiology* 2017;**69**:841-858. doi: https://doi.org/10.1016/j.jacc.2016.11.069
14. Punjabi NM, Caffo BS, Goodwin JL*, et al.* Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;**6**:e1000132. doi: 10.1371/journal.pmed.1000132
15. Young T, Finn L, Peppard PE*, et al.* Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 2008;**31**:1071. doi: 10.5665/sleep/31.8.1071
16. Gami AS, Hodge DO, Herges RM*, et al.* Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;**49**:565-571. doi: 10.1016/j.jacc.2006.08.060
17. Grote L, Ploch T, Heitmann J*, et al.* Sleep-related breathing disorder is an independent risk factor for systemic hypertension. *American journal of respiratory and critical care medicine* 1999;**160**:1875. doi: 10.1164/ajrccm.160.6.9811054
18. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;**342**:1378-1384. doi: 10.1056/nejm200005113421901
19. Javaheri S, Javaheri S, Somers VK*, et al.* Interactions of Obstructive Sleep Apnea With the Pathophysiology of Cardiovascular Disease, Part 1: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2024;**84**:1208-1223. doi: 10.1016/j.jacc.2024.02.059
20. Grote HL, Hedner HJ, Peter HJ. Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension. *Journal of Hypertension* 2000;**18**:679-685. doi: 10.1097/00004872-200018060-00004
21. Zampogna E, Spanevello A, Lucioni AM*, et al.* Adherence to Continuous Positive Airway Pressure in patients with Obstructive Sleep Apnoea. A ten year real life study. *Respir Med* 2019;**150**:95-100. doi: 10.1016/j.rmed.2019.02.017
22. Mancia G, Kreutz R, Brunström M*, et al.* 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* 2023;**41**:1874-2071. doi: 10.1097/hjh.0000000000003480

23. Lisik D, Zou D. Treatable Traits-Based Pharmacologic Treatment of Sleep Apnea. *Sleep Med Clin* 2025;**20**:103-114. doi: 10.1016/j.jsmc.2024.10.002
24. WHO. Cardiovascular diseases (CVDs). https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
25. Lloyd-Jones DM, Allen NB, Anderson CAM*, et al.* Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. *Circulation* 2022;**146**:e18-e43. doi: 10.1161/CIR.0000000000001078
26. Hamad R, Glymour MM, Calmasini C*, et al.* Explaining the Variance in Cardiovascular Disease Risk Factors: A Comparison of Demographic, Socioeconomic, and Genetic Predictors. *Epidemiology* 2022;**33**:25-33. doi: 10.1097/ede.0000000000001425
27. Visseren FLJ, Mach F, Smulders YM*, et al.* 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). *European Heart Journal, 2021, Vol. 42, Iss. 34, pp. 3227-.3337* 2021;**42**:3227-3337. doi: doi:10.1093/eurheartj/ehab484
28. Lakhiani R, Shanavas S, Melnattur K. Comparative biology of sleep in diverse animals. *Journal of Experimental Biology* 2023;**226**. doi: 10.1242/jeb.245677
29. Ramar K, Malhotra RK, Carden KA*, et al.* Sleep is essential to health: an American Academy of Sleep Medicine position statement. *Journal of Clinical Sleep Medicine* 2021;**17**:2115-2119. doi: doi:10.5664/jcsm.9476
30. Sharon O, Ben Simon E, Shah VD, Desel T, Walker MP. The new science of sleep: From cells to large-scale societies. *PLOS Biology* 2024;**22**:e3002684. doi: 10.1371/journal.pbio.3002684
31. Zschocke J, Bartsch RP, Glos M*, et al.* Long- and short-term fluctuations compared for several organ systems across sleep stages. *Frontiers in Network Physiology* 2022;**Volume 2 - 2022**. doi: 10.3389/fnetp.2022.937130
32. Albrecht U. Orchestration of gene expression and physiology by the circadian clock. *J Physiol Paris* 2006;**100**:243-251. doi: 10.1016/j.jphysparis.2007.05.004
33. Peplow M. Structure: The anatomy of sleep. *Nature* 2013;**497**:S2-S3. doi: 10.1038/497S2a

34. Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *J Biol Rhythms* 2006;**21**:482-493. doi: 10.1177/0748730406294627
35. Albrecht U. Molecular orchestration of the hepatic circadian symphony. *Genome Biol* 2006;**7**:234. doi: 10.1186/gb-2006-7-9-234
36. Hablitz LM, Nedergaard M. The Glymphatic System: A Novel Component of Fundamental Neurobiology. *J Neurosci* 2021;**41**:7698-7711. doi: 10.1523/jneurosci.0619-21.2021
37. Grote L HJ. Handbook of practical sleep medicine: Affecta.
38. Patel AK, Reddy V, Shumway KR, Araujo JF. Physiology, Sleep Stages. In. StatPearls. Treasure Island (FL) ineligible companies. : StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.; 2025.
39. Torres G, Sánchez-de-la-Torre M, Gracia-Lavedan E*, et al.* Long-term effect of obstructive sleep apnoea management on blood pressure in patients with resistant hypertension: the SARAH study. *Eur Respir J* 2024;**64**. doi: 10.1183/13993003.00269-2024
40. Shahrbabaki SS, Linz D, Hartmann S, Redline S, Baumert M. Sleep arousal burden is associated with long-term all-cause and cardiovascular mortality in 8001 community-dwelling older men and women. *Eur Heart J* 2021;**42**:2088-2099. doi: 10.1093/eurheartj/ehab151
41. Full KM, Huang T, Shah NA*, et al.* Sleep Irregularity and Subclinical Markers of Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc* 2023;**12**:e027361. doi: 10.1161/jaha.122.027361
42. Grandner MA, Patel NP, Gehrman PR, Perlis ML, Pack AI. Problems associated with short sleep: Bridging the gap between laboratory and epidemiological studies. *Sleep Medicine Reviews* 2010;**14**:239-247. doi: https://doi.org/10.1016/j.smrv.2009.08.001
43. C Iber SA-I, A Chesson, S Quan. The AASM Manual for the Scoring Of Sleep And Associated Events: Rules, Terminology And Technical Specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
44. Redline S, Azarbarzin A, Peker Y. Obstructive sleep apnoea heterogeneity and cardiovascular disease. *Nat Rev Cardiol* 2023;**20**:560-573. doi: 10.1038/s41569-023-00846-6
45. Douglas NJ, White DP, Weil JV*, et al.* Hypoxic ventilatory response decreases during sleep in normal men. *Am Rev Respir Dis* 1982;**125**:286-289. doi: 10.1164/arrd.1982.125.3.286
46. Schäfer T, Schläfke ME. Variability of CO2-sensitivity during sleep. *Adv Exp Med Biol* 2001;**499**:459-463. doi: 10.1007/978-1-4615-1375-9_74

47. McNicholas WT, Pevernagie D. Obstructive sleep apnea: transition from pathophysiology to an integrative disease model. *J Sleep Res* 2022;**31**:e13616. doi: 10.1111/jsr.13616
48. White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med* 2005;**172**:1363-1370. doi: 10.1164/rccm.200412-1631SO
49. Lévy P, Kohler M, McNicholas WT*, et al.* Obstructive sleep apnoea syndrome. *Nature Reviews Disease Primers* 2015;**1**:15024. doi: 10.1038/nrdp.2015.24
50. Lévy P, Kohler M, McNicholas WT*, et al.* Obstructive sleep apnoea syndrome. *Nature Reviews Disease Primers* 2015;**1**:15015. doi: 10.1038/nrdp.2015.15
51. Perger E, Arzt M. Central sleep apnea: treating the epiphenomenon and neglecting the disease? *Sleep* 2023;**46**. doi: 10.1093/sleep/zsad189
52. Liu D, Armitstead J, Benjafield A*, et al.* Trajectories of Emergent Central Sleep Apnea During CPAP Therapy. *CHEST* 2017;**152**:751-760. doi: 10.1016/j.chest.2017.06.010
53. Javaheri S, Badr MS. Central sleep apnea: pathophysiologic classification. *Sleep* 2023;**46**. doi: 10.1093/sleep/zsac113
54. Osman A, Carter S, Carberry J, Eckert D. Obstructive sleep apnea: current perspectives. *Nature and Science of Sleep* 2018;**10**:21-34. doi: 10.2147/NSS.S124657
55. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea: Identification of novel therapeutic targets. *American journal of respiratory and critical care medicine* 2013;**188**:996-1004. doi: 10.1164/rccm.201303-0448OC
56. Deacon-Diaz N, Malhotra A. Inherent vs. Induced Loop Gain Abnormalities in Obstructive Sleep Apnea. *Front Neurol* 2018;**9**:896. doi: 10.3389/fneur.2018.00896
57. Heffron TM, Gurubhagavatula I, Trotti LM*, et al.* Clinical significance of sleepiness: an American Academy of Sleep Medicine position statement. *J Clin Sleep Med* 2025;**21**:1103-1107. doi: 10.5664/jcsm.11658
58. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. *Jama* 2020;**323**:1389-1400. doi: 10.1001/jama.2020.3514
59. Zinchuk A, Yaggi HK. Phenotypic Subtypes of OSA. *Chest* 2020;**157**:403-420. doi: 10.1016/j.chest.2019.09.002
60. Javaheri S, Martinez-Garcia MA, Campos-Rodriguez F. CPAP Treatment and Cardiovascular Prevention: We Need to Change the Design and Implementation of Our Trials. *Chest* 2019;**156**:431-437. doi: 10.1016/j.chest.2019.04.092

61. Shiina K. Obstructive sleep apnea -related hypertension: a review of the literature and clinical management strategy. *Hypertension Research* 2024. doi: 10.1038/s41440-024-01852-y
62. Lombardi C, Pengo M, Parati G. Systemic hypertension in obstructive sleep apnea. *Journal Of Thoracic Disease* 2018;**10**:S4231-S4243. doi: 10.21037/jtd.2018.12.57
63. Kent BD, McNicholas WT, Ryan S. Insulin resistance, glucose intolerance and diabetes mellitus in obstructive sleep apnoea. *J Thorac Dis* 2015;**7**:1343-1357. doi: 10.3978/j.issn.2072-1439.2015.08.11
64. Gündüz C, Basoglu OK, Hedner J*, et al.* Obstructive sleep apnoea independently predicts lipid levels: Data from the European Sleep Apnea Database. *Respirology (Carlton, Vic.)* 2018. doi: 10.1111/resp.13372
65. Asgari A, Soltaninejad F, Farajzadegan Z, Amra B. Effect of CPAP therapy on serum lipids and blood pressure in patients with obstructive sleep apnea syndrome. *Tanaffos* 2019;**18**:126-132. doi:
66. Logan GA, Perlikowski MS, Mente STA*, et al.* High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *Journal of Hypertension* 2001;**19**:2271-2277. doi: 10.1097/00004872-200112000-00022
67. Møller DS, Lind P, Strunge B, Pedersen EB. Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea. *Am J Hypertens* 2003;**16**:274-280. doi: 10.1016/s0895-7061(02)03267-3
68. Lavalle S, Masiello E, Iannella G*, et al.* Unraveling the Complexities of Oxidative Stress and Inflammation Biomarkers in Obstructive Sleep Apnea Syndrome: A Comprehensive Review. *Life* 2024;**14**:425. doi:
69. Schwarz EI, Puhan MA, Schlatzer C, Stradling JR, Kohler M. Effect of CPAP therapy on endothelial function in obstructive sleep apnoea: A systematic review and meta-analysis. *Respirology* 2015;**20**:889-895. doi: 10.1111/resp.12573
70. Steiropoulos P, Papanas N. Increased Carotid Intima-Media Thickness in Obstructive Sleep Apnea: An Additional Issue to Consider. *Angiology* 2017;**68**:569-570. doi: 10.1177/0003319717705270
71. Hui DS, Shang Q, Ko FW*, et al.* A prospective cohort study of the long-term effects of CPAP on carotid artery intima-media thickness in Obstructive sleep apnea syndrome. *Respiratory Research* 2012;**13**:22. doi: 10.1186/1465-9921-13-22
72. Bonsignore MR, Randerath W, Schiza S*, et al.* European Respiratory Society statement on sleep apnoea, sleepiness and driving risk. *European Respiratory Journal* 2021;**57**:2001272. doi: 10.1183/13993003.01272-2020

73. Garbarino S, Guglielmi O, Sanna A, Mancardi GL, Magnavita N. Risk of Occupational Accidents in Workers with Obstructive Sleep Apnea: Systematic Review and Meta-analysis. *Sleep* 2016;**39**:1211-1218. doi: 10.5665/sleep.5834
74. Karimi M, Hedner J, Häbel H, Nerman O, Grote L. Sleep Apnea Related Risk of Motor Vehicle Accidents is Reduced by Continuous Positive Airway Pressure: Swedish Traffic Accident Registry Data. *Sleep* 2015;**38**:341-349. doi: 10.5665/sleep.4486
75. Grote L, Svedmyr S, Hedner J. Certification of fitness to drive in sleep apnea patients: Are we doing the right thing? *J Sleep Res* 2018:e12719. doi: 10.1111/jsr.12719
76. Tan BKJ, Teo YH, Tan NKW*, et al.* Association of obstructive sleep apnea and nocturnal hypoxemia with all-cancer incidence and mortality: a systematic review and meta-analysis. *J Clin Sleep Med* 2022;**18**:1427-1440. doi: 10.5664/jcsm.9772
77. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981;**1**:862-865. doi: 10.1016/s0140-6736(81)92140-1
78. Richter M, Schroeder M, Domanski U, Schwaibold M, Nilius G. Reliability of respiratory event detection with continuous positive airway pressure in moderate to severe obstructive sleep apnea - comparison of polysomnography with a device-based analysis. *Sleep Breath* 2023;**27**:1639-1650. doi: 10.1007/s11325-022-02740-w
79. Messineo L, White DP, Hete B*, et al.* Auto-adjusting positive airway pressure: the fine line between engineering and medicine. *Sleep Breath* 2025;**29**:253. doi: 10.1007/s11325-025-03409-w
80. Pépin JL, Tamisier R, Baguet JP*, et al.* Fixed-pressure CPAP versus auto-adjusting CPAP: comparison of efficacy on blood pressure in obstructive sleep apnoea, a randomised clinical trial. *Thorax* 2016;**71**:726-733. doi: 10.1136/thoraxjnl-2015-207700
81. Pépin J-L, Bailly S, Rinder P*, et al.* CPAP Therapy Termination Rates by OSA Phenotype: A French Nationwide Database Analysis. *Journal of Clinical Medicine* 2021;**10**:936. doi:
82. Trzepizur W, Cistulli PA, Glos M*, et al.* Health outcomes of continuous positive airway pressure versus mandibular advancement device for the treatment of severe obstructive sleep apnea: an individual participant data meta-analysis. *Sleep* 2021;**44**. doi: 10.1093/sleep/zsab015
83. Johal A, Hamoda MM, Almeida FR, Marklund M, Tallamraju H. The role of oral appliance therapy in obstructive sleep apnoea. *Eur Respir Rev* 2023;**32**. doi: 10.1183/16000617.0257-2022
84. Hamoda MM, Huynh N, Ayas NT*, et al.* Continuous positive airway pressure and mandibular advancement splints: the CHOICE

multicentre, open-label randomised clinical trial. *Eur Respir J* 2025;**65**. doi: 10.1183/13993003.01100-2024
85. Figard C, Ben Messaoud R, Baillieul S*, et al.* Effect of sleep apnoea interventions on multiple health outcomes: an umbrella review of meta-analyses of randomised controlled trials. *EClinicalMedicine* 2025;**89**:103529. doi: 10.1016/j.eclinm.2025.103529
86. Malhotra A, Heilmann CR, Banerjee KK*, et al.* Weight reduction and the impact on apnea-hypopnea index: A systematic meta-analysis. *Sleep Med* 2024;**121**:26-31. doi: 10.1016/j.sleep.2024.06.014
87. Malhotra A, Curtis A, Dunn J, Bunck MC, Bednarik J. 0572 Weight reduction and the impact on apnea-hypopnea index: a meta-analysis. *Sleep* 2023;**46**:A251-A252. doi: 10.1093/sleep/zsad077.0572
88. Al Oweidat K, Toubasi AA, Tawileh RBA, Tawileh HBA, Hasuneh MM. Bariatric surgery and obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Breath* 2023;**27**:2283-2294. doi: 10.1007/s11325-023-02840-1
89. Messineo L, Bakker JP, Cronin J, Yee J, White DP. Obstructive sleep apnea and obesity: A review of epidemiology, pathophysiology and the effect of weight-loss treatments. *Sleep Med Rev* 2024;**78**:101996. doi: 10.1016/j.smrv.2024.101996
90. Malhotra A, Grunstein RR, Fietze I*, et al.* Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. *N Engl J Med* 2024;**391**:1193-1205. doi: 10.1056/NEJMoa2404881
91. Hamza M, Papamargaritis D, Davies MJ. Tirzepatide for overweight and obesity management. *Expert Opin Pharmacother* 2025;**26**:31-49. doi: 10.1080/14656566.2024.2436595
92. Lisik D, Zou D. Breaking Ground: From CPAP Treatment to the First Medicine for OSA Patients with Obesity. *Current Pulmonology Reports* 2025;**14**:3. doi: 10.1007/s13665-024-00365-w
93. Tan SN, Yang HC, Lim SC. Anatomy and Pathophysiology of Upper Airway Obstructive Sleep Apnoea: Review of the Current Literature. *Sleep Med Res* 2021;**12**:1-8. doi: 10.17241/smr.2020.00829
94. Halawani M, Alsharif A, Alanazi OI*, et al.* Efficacy and Safety of Adenotonsillectomy for Pediatric Obstructive Sleep Apnea Across Various Age Groups: A Systematic Review. *Pediatr Rep* 2025;**17**. doi: 10.3390/pediatric17040071
95. Sundman J, Nerfeldt P, Fehrm J*, et al.* Effectiveness of Tonsillectomy vs Modified Uvulopalatopharyngoplasty in Patients With Tonsillar Hypertrophy and Obstructive Sleep Apnea: The TEAMUP Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg* 2022;**148**:1173-1181. doi: 10.1001/jamaoto.2022.3432
96. Sundman J, Browaldh N, Fehrm J, Friberg D. Eight-Year Follow-up of Modified Uvulopalatopharyngoplasty in Patients With

Obstructive Sleep Apnea. *Laryngoscope* 2021;**131**:E307-e313. doi: 10.1002/lary.28960
97. Kaffenberger TM, Soose RJ, Woodson BT*, et al.* Modified uvulopalatopharyngoplasty in modern obstructive sleep apnea treatment: a narrative review. *J Clin Sleep Med* 2025. doi: 10.5664/jcsm.11810
98. Camacho M, Certal V, Brietzke SE*, et al.* Tracheostomy as treatment for adult obstructive sleep apnea: a systematic review and meta-analysis. *Laryngoscope* 2014;**124**:803-811. doi: 10.1002/lary.24433
99. Aishah A, Loffler KA, Toson B*, et al.* One Month Dosing of Atomoxetine plus Oxybutynin in Obstructive Sleep Apnea: A Randomized, Placebo-controlled Trial. *Ann Am Thorac Soc* 2023;**20**:584-595. doi: 10.1513/AnnalsATS.202206-492OC
100. Randerath W, Grote L, Stenlöf K*, et al.* Sultiame once per day in obstructive sleep apnoea (FLOW): a multicentre, randomised, double-blind, placebo-controlled, dose-finding, phase 2 trial. *Lancet* 2025;**406**:1983-1992. doi: 10.1016/s0140-6736(25)01196-1
101. Taranto-Montemurro L, Messineo L, Wellman A. Targeting Endotypic Traits with Medications for the Pharmacological Treatment of Obstructive Sleep Apnea. A Review of the Current Literature. *Journal of Clinical Medicine* 2019;**8**:1846. doi:
102. Hedner J, Zou D. Turning Over a New Leaf—Pharmacologic Therapy in Obstructive Sleep Apnea. *Sleep Medicine Clinics* 2022;**17**:453-469. doi: https://doi.org/10.1016/j.jsmc.2022.06.010
103. Sands SA, Edwards BA, Terrill PI*, et al.* Phenotyping Pharyngeal Pathophysiology using Polysomnography in Patients with Obstructive Sleep Apnea. *American Journal of Respiratory and Critical Care Medicine* 2018;**197**:1187-1197. doi: 10.1164/rccm.201707-1435OC
104. Serghani M-M, Heiser C, Schwartz AR, Amatoury J. Exploring hypoglossal nerve stimulation therapy for obstructive sleep apnea: A comprehensive review of clinical and physiological upper airway outcomes. *Sleep Medicine Reviews* 2024;**76**:101947. doi: https://doi.org/10.1016/j.smrv.2024.101947
105. Dedhia RC, Bliwise DL, Quyyumi AA*, et al.* Hypoglossal Nerve Stimulation and Cardiovascular Outcomes for Patients With Obstructive Sleep Apnea: A Randomized Clinical Trial. *JAMA Otolaryngology–Head & Neck Surgery* 2024;**150**:39-48. doi: 10.1001/jamaoto.2023.3756
106. Laub RR, Tønnesen P, Jennum PJ. A Sleep Position Trainer for positional sleep apnea: a randomized, controlled trial. *Journal of Sleep Research* 2017;**26**:641-650. doi: https://doi.org/10.1111/jsr.12530
107. Vanderveken OM, Gagnadoux F. Comparative outcomes in obstructive sleep apnea therapy: mean disease alleviation as a more

appropriate measure—it's about time. *Sleep* 2023;**46**. doi: 10.1093/sleep/zsad210
108. Bonsignore MR, Fanfulla F, Ingrao P*, et al.* Management options for excessive daytime sleepiness in patients with obstructive sleep apnea. *Expert Rev Respir Med* 2025;**19**:325-345. doi: 10.1080/17476348.2025.2479614
109. Le VV, Mitiku T, Sungar G, Myers J, Froelicher V. The blood pressure response to dynamic exercise testing: a systematic review. *Prog Cardiovasc Dis* 2008;**51**:135-160. doi: 10.1016/j.pcad.2008.07.001
110. Budoff MJ, Alpert B, Chirinos JA*, et al.* Clinical Applications Measuring Arterial Stiffness: An Expert Consensus for the Application of Cardio-Ankle Vascular Index. *American Journal of Hypertension* 2021;**35**:441-453. doi: 10.1093/ajh/hpab178
111. Lopez-Jimenez F, Deshmukh A, Bisognano J*, et al.* Development and Internal Validation of an AI-Enabled Cuff-less, Non-invasive Continuous Blood Pressure Monitor Across All Classes of Hypertension. *J Cardiovasc Transl Res* 2025;**18**:280-290. doi: 10.1007/s12265-024-10589-5
112. Schutte AE. Wearable cuffless blood pressure tracking: when will they be good enough? *J Hum Hypertens* 2024;**38**:669-672. doi: 10.1038/s41371-024-00932-3
113. Folkow B. Physiological aspects of primary hypertension. *Physiol Rev* 1982;**62**:347-504. doi: 10.1152/physrev.1982.62.2.347
114. Liu J, Wu J. The Pathogenesis and Impact of Arterial Stiffening in Hypertension: The 2023 John H. Laragh Research Award. *American Journal of Hypertension* 2024;**37**:241-247. doi: 10.1093/ajh/hpae006
115. Brien E, Asmar R, Beilin L*, et al.* European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *Journal of Hypertension* 2003;**21**:821-848. doi: 10.1097/00004872-200305000-00001
116. Kelly TN, Sun X, He KY*, et al.* Insights From a Large-Scale Whole-Genome Sequencing Study of Systolic Blood Pressure, Diastolic Blood Pressure, and Hypertension. *Hypertension* 2022;**79**:1656-1667. doi: 10.1161/hypertensionaha.122.19324
117. Grassi G, Drager LF. Sympathetic overactivity, hypertension and cardiovascular disease: state of the art. *Curr Med Res Opin* 2024;**40**:5-13. doi: 10.1080/03007995.2024.2305248
118. Yamaguchi H, Gomez RA, Sequeira-Lopez MLS. Renin Cells, From Vascular Development to Blood Pressure Sensing. *Hypertension* 2023;**80**:1580-1589. doi: 10.1161/hypertensionaha.123.20577

119. Loh HH, Lim QH, Chai CS*, et al.* 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. doi: 10.1111/jsr.13726
120. Fletcher E, Orolinova N, Bader M. Blood pressure response to chronic episodic hypoxia: The renin-angiotensin system. *Journal of Applied Physiology* 2002;**92**:627-633. doi: 10.1152/japplphysiol.00152.2001
121. Rahmouni K, Correia MLG, Haynes WG, Mark AL. Obesity-Associated Hypertension. *Hypertension* 2005;**45**:9-14. doi: 10.1161/01.HYP.0000151325.83008.b4
122. Gallo G, Volpe M, Savoia C. Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. *Frontiers in Medicine* 2022;**Volume 8 - 2021**. doi: 10.3389/fmed.2021.798958
123. Humphrey JD. Mechanisms of Vascular Remodeling in Hypertension. *American Journal of Hypertension* 2020;**34**:432-441. doi: 10.1093/ajh/hpaa195
124. Wojtasińska A, Frąk W, Lisińska W*, et al.* Novel Insights into the Molecular Mechanisms of Atherosclerosis. *International Journal of Molecular Sciences* 2023;**24**:13434. doi:
125. Booth J. A Short History of Blood Pressure Measurement. *Proceedings of the Royal Society of Medicine* 1977;**70**:793-799. doi: 10.1177/003591577707001112
126. Kario K, Thijs L, Staessen JA. Blood Pressure Measurement and Treatment Decisions. *Circ Res* 2019;**124**:990-1008. doi: 10.1161/circresaha.118.313219
127. Staplin N, de la Sierra A, Ruilope LM*, et al.* Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. *Lancet* 2023. doi: 10.1016/s0140-6736(23)00733-x
128. Li Y, Wang JG. Isolated nocturnal hypertension: a disease masked in the dark. *Hypertension* 2013;**61**:278-283. doi: 10.1161/hypertensionaha.111.00217
129. Mancia G, Verdecchia P. Clinical value of ambulatory blood pressure: evidence and limits. *Circ Res* 2015;**116**:1034-1045. doi: 10.1161/circresaha.116.303755
130. Conroy RM, Pyörälä K, Fitzgerald AP*, et al.* Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987-1003. doi: 10.1016/s0195-668x(03)00114-3
131. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J* 2021;**42**:2439-2454. doi: 10.1093/eurheartj/ehab309

132. Stergiou GS, Palatini P, Parati G*, et al.* 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement. *J Hypertens* 2021;**39**:1293-1302. doi: 10.1097/hjh.0000000000002843
133. Tacchini V, Dobretz K, Bevand A, Ehret G. [ESC Hypertension guidelines 2024 : targeting at-risk patients]. *Rev Med Suisse* 2025;**21**:1593-1597. doi: 10.53738/revmed.2025.21.930.47793
134. Choudhry NK, Kronish IM, Vongpatanasin W*, et al.* Medication Adherence and Blood Pressure Control: A Scientific Statement From the American Heart Association. *Hypertension* 2022;**79**:e1-e14. doi: 10.1161/hyp.0000000000000203
135. Borghi C, Tubach F, De Backer G*, et al.* Lack of control of hypertension in primary cardiovascular disease prevention in Europe: Results from the EURIKA study. *International Journal of Cardiology* 2016;**218**:83-88. doi: 10.1016/j.ijcard.2016.05.044
136. Martínez-García FM-A, Navarro-Soriano MC, Torres JG*, et al.* Beyond Resistant Hypertension: Relationship Between Refractory Hypertension and Obstructive Sleep Apnea. *Hypertension* 2018;**72**. doi: 10.1161/HYPERTENSIONAHA.118.11170
137. Navarro-Soriano C, Torres G, Barbé F*, et al.* The HIPARCO-2 study: long-term effect of continuous positive airway pressure on blood pressure in patients with resistant hypertension: a multicenter prospective study. *Journal of hypertension* 2021;**39**:302. doi: 10.1097/HJH.0000000000002664
138. Heinzer R, Vat S, Marques-Vidal P*, et al.* Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *The Lancet Respiratory Medicine* 2015;**3**:310-318. doi: 10.1016/S2213-2600(15)00043-0
139. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *British Medical Journal* 2000;**320**:479-482. doi: 10.1136/bmj.320.7233.479
140. Young T, Peppard P, Palta M*, et al.* Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Archives of Internal Medicine* 1997;**157**:1746-1752. doi: DOI 10.1001/archinte.157.15.1746
141. Nieto FJ, Young TB, Lind BK*, et al.* Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *Jama* 2000;**283**:1829-1836. doi: 10.1001/jama.283.14.1829
142. Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB. Undiagnosed sleep apnea in patients with essential hypertension. *Ann Intern Med* 1985;**103**:190-195. doi: 10.7326/0003-4819-103-2-190

143. Hou H, Zhao Y, Yu W*, et al.* Association of obstructive sleep apnea with hypertension: A systematic review and meta-analysis. *Journal of global health* 2018;**8**:010405-010405. doi: 10.7189/jogh.08.010405
144. Marin JM, Agusti A, Villar I*, et al.* Association between treated and untreated obstructive sleep apnea and risk of hypertension. *Jama* 2012;**307**:2169-2176. doi: 10.1001/jama.2012.3418
145. El Meouchy P, Wahoud M, Allam S*, et al.* Hypertension Related to Obesity: Pathogenesis, Characteristics and Factors for Control. *Int J Mol Sci* 2022;**23**. doi: 10.3390/ijms232012305
146. Mallevays M, Mauries S, Maruani J*, et al.* Effects of nicotine on sleep architecture and ventilatory parameters: Results of the Tab-OSA cross-sectional observational study. *Sleep Medicine* 2026;**137**:106894. doi: https://doi.org/10.1016/j.sleep.2025.106894
147. Pataka A, Kotoulas S, Kalamaras G*, et al.* Does Smoking Affect OSA? What about Smoking Cessation? *J Clin Med* 2022;**11**. doi: 10.3390/jcm11175164
148. Kolla BP, Foroughi M, Saeidifard F*, et al.* The impact of alcohol on breathing parameters during sleep: A systematic review and meta-analysis. *Sleep Med Rev* 2018;**42**:59-67. doi: 10.1016/j.smrv.2018.05.007
149. Bonsignore MR, Saaresranta T, Riha RL. Sex differences in obstructive sleep apnoea. *Eur Respir Rev* 2019;**28**. doi: 10.1183/16000617.0030-2019
150. Martins FO, Conde SV. Gender Differences in the Context of Obstructive Sleep Apnea and Metabolic Diseases. *Frontiers in Physiology* 2021;**Volume 12 - 2021**. doi: 10.3389/fphys.2021.792633
151. Chouchou F, Pichot V, Pépin JL*, et al.* Sympathetic overactivity due to sleep fragmentation is associated with elevated diurnal systolic blood pressure in healthy elderly subjects: the PROOF-SYNAPSE study. *European Heart Journal* 2013;**34**:2122-2131. doi: 10.1093/eurheartj/eht208
152. 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? *Journal of Hypertension* 1988;**6**:S529-531. doi:
153. Tamisier R, Pepin JL, Remy J*, et al.* 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. *Eur Respir J* 2011;**37**:119-128. doi: 10.1183/09031936.00204209
154. Lavie L. Oxidative stress inflammation and endothelial dysfunction in obstructive sleep apnea. *Front Biosci (Elite Ed)* 2012;**4**:1391-1403. doi: 10.2741/469

155. Kaiser Y, Dzobo KE, Ravesloot MJL*, et al.* Reduced baroreflex sensitivity and increased splenic activity in patients with severe obstructive sleep apnea. *Atherosclerosis* 2022;**344**:7-12. doi: 10.1016/j.atherosclerosis.2022.01.004
156. Alastruey J, Charlton PH, Bikia V*, et al.* Arterial pulse wave modeling and analysis for vascular-age studies: a review from VascAgeNet. *Am J Physiol Heart Circ Physiol* 2023;**325**:H1-h29. doi: 10.1152/ajpheart.00705.2022
157. Meliante PG, Zoccali F, Cascone F*, et al.* Molecular Pathology, Oxidative Stress, and Biomarkers in Obstructive Sleep Apnea. *Int J Mol Sci* 2023;**24**. doi: 10.3390/ijms24065478
158. Kritikou I, Basta M, Vgontzas AN*, et al.* Sleep apnoea and the hypothalamic-pituitary-adrenal axis in men and women: effects of continuous positive airway pressure. *Eur Respir J* 2016;**47**:531-540. doi: 10.1183/13993003.00319-2015
159. Bradicich M, Pengo MF, Steier J, Schwarz EI. Cardiovascular effects of obstructive sleep apnoea and effects of continuous positive airway pressure therapy: evidence from different study models. *ERJ Open Research* 2024:00718-02024. doi: 10.1183/23120541.00718-2024
160. Jean-Louis G, Zizi F, Clark LT, Brown CD, McFarlane SI. Obstructive sleep apnea and cardiovascular disease: role of the metabolic syndrome and its components. *J Clin Sleep Med* 2008;**4**:261-272. doi:
161. Igelström E, Craig P, Lewsey J*, et al.* Causal inference and effect estimation using observational data. *Journal of Epidemiology and Community Health* 2022;**76**:960-966. doi: 10.1136/jech-2022-219267
162. Kozlowski D. On the limits of causal theory for studying inequalities in science. *Quantitative Science Studies* 2025;**6**:238-241. doi: 10.1162/qss_c_00347
163. Ip MS, Tse HF, Lam B, Tsang KW, Lam WK. Endothelial function in obstructive sleep apnea and response to treatment. *Am J Respir Crit Care Med* 2004;**169**:348-353. doi: 10.1164/rccm.200306-767OC
164. Nguyen PK, Katikireddy CK, McConnell MV, Kushida C, Yang PC. Nasal continuous positive airway pressure improves myocardial perfusion reserve and endothelial-dependent vasodilation in patients with obstructive sleep apnea. *J Cardiovasc Magn Reson* 2010;**12**:50. doi: 10.1186/1532-429x-12-50
165. Comondore VR, Cheema R, Fox J*, et al.* The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: a pilot feasibility randomized crossover trial. *Lung* 2009;**187**:17-22. doi: 10.1007/s00408-008-9115-5
166. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N*, et al.* Ambulatory blood pressure after therapeutic and subtherapeutic nasal

continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002;**359**:204-210. doi: 10.1016/s0140-6736(02)07445-7
167. Lui MM, Tse HF, Lam DC*, et al.* Continuous positive airway pressure improves blood pressure and serum cardiovascular biomarkers in obstructive sleep apnoea and hypertension. *Eur Respir J* 2021;**58**. doi: 10.1183/13993003.03687-2020
168. Schwarz EI, Schlatzer C, Rossi VA, Stradling JR, Kohler M. Effect of CPAP Withdrawal on BP in OSA: Data from Three Randomized Controlled Trials. *Chest* 2016;**150**:1202-1210. doi: 10.1016/j.chest.2016.07.012
169. Palm A, Ågren K, Grote L*, et al.* Course of DISease In patients reported to the Swedish CPAP Oxygen and VEntilator RegistrY (DISCOVERY) with population-based controls. *BMJ Open* 2020;**10**:e040396. doi: 10.1136/bmjopen-2020-040396
170. SCB. Statistics on Income and Living Conditions (SILC). doi:http://www.scb.se/le0101-en
171. Hedner J, Grote L, Bonsignore M*, et al.* The European Sleep Apnoea Database (ESADA): report from 22 European sleep laboratories. *Eur Respir J* 2011;**38**:635-642. doi: 10.1183/09031936.00046710
172. Bonsignore MR, Group ES. Adaptive responses to chronic intermittent hypoxia: contributions from the European Sleep Apnoea Database (ESADA) Cohort. *The Journal of Physiology* 2023;**n/a**. doi: https://doi.org/10.1113/JP284108
173. Sommermeyer D, Zou D, Eder DN*, et al.* The use of overnight pulse wave analysis for recognition of cardiovascular risk factors and risk: a multicentric evaluation. *J Hypertens* 2014;**32**:276-285. doi: 10.1097/HJH.0000000000000039
174. Sommermeyer D, Zou D, Ficker JH*, et al.* Detection of cardiovascular risk from a photoplethysmographic signal using a matching pursuit algorithm. *Med Biol Eng Comput* 2016;**54**:1111-1121. doi: 10.1007/s11517-015-1410-8
175. Millasseau SC, Ritter JM, Takazawa K, Chowienczyk PJ. Contour analysis of the photoplethysmographic pulse measured at the finger. *J Hypertens* 2006;**24**:1449-1456. doi: 10.1097/01.hjh.0000239277.05068.87
176. Liu Y, De A. Multiple Imputation by Fully Conditional Specification for Dealing with Missing Data in a Large Epidemiologic Study. *International Journal of Statistics in Medical Research* 2015;**4**:287-295. doi: 10.6000/1929-6029.2015.04.03.7
177. OECD. Health at a Glance 2025. In. OECD Publishing, Paris: OECD Indicators, OECD Publishing; 2025.

178. Akobeng AK. Understanding randomised controlled trials. *Arch Dis Child* 2005;**90**:840-844. doi: 10.1136/adc.2004.058222
179. Sheldrick RC. Randomized Trials vs Real-world Evidence: How Can Both Inform Decision-making? *JAMA* 2023;**329**:1352-1353. doi: 10.1001/jama.2023.4855
180. Monti S, Grosso V, Todoerti M, Caporali R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. *Rheumatology* 2018;**57**:vii54-vii58. doi: 10.1093/rheumatology/key109
181. Azoulay L. Rationale, Strengths, and Limitations of Real-World Evidence in Oncology: A Canadian Review and Perspective. *The Oncologist* 2022;**27**:e731-e738. doi: 10.1093/oncolo/oyac114
182. Morrow B. An overview of cohort study designs and their advantages and disadvantages. *International Journal of Therapy and Rehabilitation* 2010;**17**:518-523. doi: 10.12968/ijtr.2010.17.10.78810
183. Toews I, Anglemyer A, Nyirenda JLZ*, et al.* Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials: a meta-epidemiological study. *Cochrane Database of Systematic Reviews* 2024. doi: 10.1002/14651858.MR000034.pub3
184. Ricotta EE, Bustos Carrillo FA, Angelli-Nichols S*, et al.* Observational research in epidemic settings: a roadmap to reform. *BMJ Global Health* 2025;**10**:e017981. doi: 10.1136/bmjgh-2024-017981
185. EMA. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 11). In: EMA/95098/2010.; 2010.
186. Schneeweiss S, Patorno E. Conducting Real-world Evidence Studies on the Clinical Outcomes of Diabetes Treatments. *Endocrine Reviews* 2021;**42**:658-690. doi: 10.1210/endrev/bnab007
187. Doherty DA, Tong SYC, Reilly J*, et al.* Registry randomised trials: a methodological perspective. *BMJ Open* 2023;**13**:e068057. doi: 10.1136/bmjopen-2022-068057
188. Nyberg K, Hedman P. Swedish guidelines for registry-based randomized clinical trials. *Upsala Journal of Medical Sciences* 2019;**124**:33–36. doi: 10.1080/03009734.2018.1550453
189. Benjafield AV, Pepin JL, Cistulli PA*, et al.* Positive airway pressure therapy and all-cause and cardiovascular mortality in people with obstructive sleep apnoea: a systematic review and meta-analysis of randomised controlled trials and confounder-adjusted, non-randomised controlled studies. *Lancet Respir Med* 2025;**13**:403-413. doi: 10.1016/S2213-2600(25)00002-5

190. Cohen O, Kundel V, Barbé F*, et al.* The Great Controversy of Obstructive Sleep Apnea Treatment for Cardiovascular Risk Benefit: Advancing the Science Through Expert Consensus. An Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc* 2024;**22**:1-22. doi: 10.1513/AnnalsATS.202409-981ST
191. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M*, et al.* Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *Jama* 2012;**307**:2161-2168. doi: 10.1001/jama.2012.4366
192. McEvoy RD, Antic NA, Heeley E*, et al.* CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *The New England journal of medicine* 2016;**375**:919. doi: 10.1056/NEJMoa1606599
193. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S*, et al.* Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* 2020;**8**:359-367. doi: 10.1016/s2213-2600(19)30271-1
194. Peker Y, Glantz H, Eulenburg C*, et al.* Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. *Am J Respir Crit Care Med* 2016;**194**:613-620. doi: 10.1164/rccm.201601-0088OC
195. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *The Lancet (British edition)* 2005;**365**:1046-1053. doi: 10.1016/S0140-6736(05)71141-7
196. Gervès-Pinquié C, Bailly S, Goupil F*, et al.* Positive Airway Pressure Adherence, Mortality, and Cardiovascular Events in Patients with Sleep Apnea. *American Journal of Respiratory and Critical Care Medicine* 2022;**206**:1393-1404. doi: 10.1164/rccm.202202-0366OC
197. Trzepizur W, Blanchard M, Ganem T*, et al.* Sleep Apnea-Specific Hypoxic Burden, Symptom Subtypes, and Risk of Cardiovascular Events and All-Cause Mortality. *Am J Respir Crit Care Med* 2022;**205**:108-117. doi: 10.1164/rccm.202105-1274OC
198. Divo MJ, Martinez-Garcia MA, Gonzalez M*, et al.* MACE or Death Risk in Obstructive Sleep Apnoea and the Effect of Positive Airway Pressure. *Eur Respir J* 2025. doi: 10.1183/13993003.00519-2025
199. Karahalios A, Baglietto L, Carlin JB, English DR, Simpson JA. A review of the reporting and handling of missing data in cohort studies

with repeated assessment of exposure measures. *BMC Medical Research Methodology* 2012;**12**:96. doi: 10.1186/1471-2288-12-96
200. Ross RK, Breskin A, Westreich D. When Is a Complete-Case Approach to Missing Data Valid? The Importance of Effect-Measure Modification. *American Journal of Epidemiology* 2020;**189**:1583-1589. doi: 10.1093/aje/kwaa124
201. Afkanpour M, Tehrany Dehkordy D, Momeni M, Tabesh H. Conceptual framework as a guide to choose appropriate imputation method for missing values in a clinical structured dataset. *BMC Medical Research Methodology* 2025;**25**:43. doi: 10.1186/s12874-025-02496-3
202. Karuppasamy S, Premkumar PS, Mohan VR. Handling missing outcomes in time-to-event analyses in randomised controlled trials: a scoping review with a focus on multiple imputation. *BMC Med Res Methodol* 2025;**25**:220. doi: 10.1186/s12874-025-02676-1
203. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to Single-Pill Versus Free-Equivalent Combination Therapy in Hypertension: A Systematic Review and Meta-Analysis. *Hypertension* 2021;**77**:692-705. doi: 10.1161/hypertensionaha.120.15781
204. Tomaszewski M, White C, Patel P*, et al.* High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart* 2014;**100**:855-861. doi: 10.1136/heartjnl-2013-305063
205. Tekumalla S, Plawecki A, Kaffenberger T*, et al.* The relationship between positive airway pressure tolerance and adherence: defining a new metric. *J Clin Sleep Med* 2024;**20**:1033-1038. doi: 10.5664/jcsm.11050
206. Javaheri S, Martinez-Garcia MA, Campos-Rodriguez F, Muriel A, Peker Y. Continuous Positive Airway Pressure Adherence for Prevention of Major Adverse Cerebrovascular and Cardiovascular Events in Obstructive Sleep Apnea. *Am J Respir Crit Care Med* 2020;**201**:607-610. doi: 10.1164/rccm.201908-1593LE
207. Kneeland E, Ali N, Maislin DG*, et al.* Achieving adherence to positive airway pressure in commercial drivers using an employer-mandated remote management programme. *ERJ Open Res* 2024;**10**. doi: 10.1183/23120541.00132-2024
208. Verbraecken J, Amodio E, Basoglu OK*, et al.* European Respiratory Society statement on advanced telemedicine for obstructive sleep apnoea (e-Sleep). *Eur Respir J* 2025;**66**. doi: 10.1183/13993003.00557-2025
209. Fridriksson B, Berndtson M, Hamnered H*, et al.* Beneficial Effects of Early Intervention Telemedicine-based Follow-Up in Sleep Apnea: A Randomized Controlled Multicenter Trial. *Ann Am Thorac Soc* 2023;**20**:1499-1507. doi: 10.1513/AnnalsATS.202208-723OC

210. Aalaei S, Tabesh H, Shahraki H*, et al.* Remote monitoring system to support positive airway pressure therapy in patients with obstructive sleep apnea: a multi-center randomized controlled trial. *Sleep Breath* 2024;**28**:2759-2773. doi: 10.1007/s11325-024-03108-y
211. Petrov ME, Epstein DR, Krahn L*, et al.* SleepWell24, a Smartphone Application to Promote Adherence to Positive Airway Pressure Therapy: Feasibility and Acceptability in a Randomized Controlled Trial. *Behav Sleep Med* 2024;**22**:420-432. doi: 10.1080/15402002.2023.2289442
212. Hinz F. Validation of a New Automatic Algorithm "Autonomic State Indicator" (ASI) for Cardiovascular Risk Assessment Using Photoplethysmographic Pulse Wave Analysis. der Ruhr-Universität Bochum, 2021.
213. Weng WH, Baur S, Daswani M*, et al.* Predicting cardiovascular disease risk using photoplethysmography and deep learning. *PLOS Glob Public Health* 2024;**4**:e0003204. doi: 10.1371/journal.pgph.0003204
214. Strassberger C, Zou D, Penzel T*, et al.* Beyond the AHI-pulse wave analysis during sleep for recognition of cardiovascular risk in sleep apnea patients. *J Sleep Res* 2021;**30**:e13364. doi: 10.1111/jsr.13364
215. Flint AC, Conell C, Ren X*, et al.* Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes. *The New England journal of medicine* 2019;**381**:243. doi: 10.1056/NEJMoa1803180
216. Lévy P, Pépin JL, Arnaud C*, et al.* Obstructive sleep apnea and atherosclerosis. *Prog Cardiovasc Dis* 2009;**51**:400-410. doi: 10.1016/j.pcad.2008.03.001
217. Parati G, Lombardi C, Hedner J*, et al.* Recommendations for the management of patients with obstructive sleep apnoea and hypertension. *Eur Respir J* 2013;**41**:523-538. doi: 10.1183/09031936.00226711
218. Barceló A, Piérola J, Esquinas C*, et al.* 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. doi: 10.1371/journal.pone.0084362
219. Seoni S, Segers P, Beeckman S*, et al.* Real-time beat-to-beat pulse wave velocity estimation: a quality-driven approach using laser Doppler vibrometry. *Med Biol Eng Comput* 2025. doi: 10.1007/s11517-025-03417-8
220. Hellqvist H, Rietz H, Grote L*, et al.* Overnight stiffness index from finger photoplethysmography in relation to markers of cardiovascular risk and vascular ageing. *Heart Vessels* 2025;**40**:895-904. doi: 10.1007/s00380-025-02537-3

221. Javaheri S, Redline S. Sleep, Slow-Wave Sleep, and Blood Pressure. *Current Hypertension Reports* 2012;**14**:442-448. doi: 10.1007/s11906-012-0289-0
222. Sassin JF, Parker DC, Mace JW*, et al.* Human growth hormone release: relation to slow-wave sleep and sleep-walking cycles. *Science* 1969;**165**:513-515. doi: 10.1126/science.165.3892.513
223. Ishii T, Taweesedt PT, Chick CF, O'Hara R, Kawai M. From macro to micro: slow-wave sleep and its pivotal health implications. *Frontiers in Sleep* 2024;**Volume 3 - 2024**. doi: 10.3389/frsle.2024.1322995
224. Burlacu A, Kuwabara M, Brinza C, Kanbay M. Key Updates to the 2024 ESC Hypertension Guidelines and Future Perspectives. *Medicina (Kaunas)* 2025;**61**. doi: 10.3390/medicina61020193
225. Patel SR. Unraveling the Healthy Adherer Effect in the Clinical Management of Sleep Apnea With CPAP. *CHEST* 2024;**166**:671-672. doi: 10.1016/j.chest.2024.06.3795
226. Launois C, Bailly S, Sabil A*, et al.* Association Between Healthy Behaviors and Health Care Resource Use With Subsequent Positive Airway Pressure Therapy Adherence in OSA. *Chest* 2024;**166**:845-856. doi: 10.1016/j.chest.2024.05.024
227. Balk EM, Adam GP, Cao W*, et al.* Long-term effects on clinical event, mental health, and related outcomes of CPAP for obstructive sleep apnea: a systematic review. *J Clin Sleep Med* 2024;**20**:895-909. doi: 10.5664/jcsm.11030
228. Pengo MF, Schwarz EI, Barbé F*, et al.* Effect of CPAP therapy on blood pressure in patients with obstructive sleep apnoea: a worldwide individual patient data meta-analysis. *Eur Respir J* 2025;**65**. doi: 10.1183/13993003.00837-2024
229. Delsart P, Takla M, Marboeuf P*, et al.* Evaluation of blood pressure control in an obstructive sleep apnea population followed in cardiology. *High Blood Press Cardiovasc Prev* 2015;**22**:159-164. doi: 10.1007/s40292-015-0088-1
230. Zota IM, Sascau R, Statescu C*, et al.* Hypertension control in patients with moderate-severe obstructive sleep apnea. *Journal of Hypertension Research* 2018:90+. doi:
231. Carella AM, Antonucci G, Conte M*, et al.* Antihypertensive treatment with beta-blockers in the metabolic syndrome: a review. *Curr Diabetes Rev* 2010;**6**:215-221. doi: 10.2174/157339910791658844
232. Corrao G, Zambon A, Parodi A*, et al.* Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens* 2008;**26**:819-824. doi: 10.1097/HJH.0b013e3282f4edd7

233. Sutherland K, Sadr N, Bin YS*, et al.* Comparative associations of oximetry patterns in Obstructive Sleep Apnea with incident cardiovascular disease. *Sleep* 2022;**45**. doi: 10.1093/sleep/zsac179
234. Henríquez-Beltrán M, Dreyse J, Jorquera J*, et al.* Is the time below 90% of SpO2 during sleep (T90%) a metric of good health? A longitudinal analysis of two cohorts. *Sleep and Breathing* 2024;**28**:281-289. doi: 10.1007/s11325-023-02909-x
235. Huang Z, Wu Y, Huang K*, et al.* The Nadir Oxygen-Specific Heart Rate Response in Sleep Apnea Links With the Occurrence of Acute Myocardial Infarction. *Front Cardiovasc Med* 2022;**9**:807436. doi: 10.3389/fcvm.2022.807436
236. Martinez-Garcia MA, Sánchez-de-la-Torre M, White DP, Azarbarzin A. Hypoxic Burden in Obstructive Sleep Apnea: Present and Future. *Arch Bronconeumol* 2023;**59**:36-43. doi: 10.1016/j.arbres.2022.08.005
237. Malhotra A, Ayappa I, Ayas N*, et al.* Metrics of sleep apnea severity: beyond the apnea-hypopnea index. *Sleep* 2021;**44**. doi: 10.1093/sleep/zsab030
238. Sánchez-de-la-Torre M, Gracia-Lavedan E, Benitez ID*, et al.* Adherence to CPAP Treatment and the Risk of Recurrent Cardiovascular Events: A Meta-Analysis. *Jama* 2023;**330**:1255-1265. doi: 10.1001/jama.2023.17465
239. Miao B, Hernandez AV, Alberts MJ*, et al.* Incidence and Predictors of Major Adverse Cardiovascular Events in Patients With Established Atherosclerotic Disease or Multiple Risk Factors. *J Am Heart Assoc* 2020;**9**:e014402. doi: 10.1161/jaha.119.014402
240. Bhatt DL, Eagle KA, Ohman EM*, et al.* Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *Jama* 2010;**304**:1350-1357. doi: 10.1001/jama.2010.1322
241. Kribbs NB, Pack AI, Kline LR*, et al.* Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;**147**:887-895. doi: 10.1164/ajrccm/147.4.887
242. Engleman HM, Douglas NJ. Cognitive effects and daytime sleepiness. *Sleep* 1993;**16**:S79. doi:
243. 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. doi: 10.1016/j.jsmc.2020.10.001
244. Gagnadoux F, Bequignon E, Prigent A*, et al.* The PAP-RES algorithm: Defining who, why and how to use positive airway pressure therapy for OSA. *Sleep Med Rev* 2024;**75**:101932. doi: 10.1016/j.smrv.2024.101932

245. McEvoy RD, Sánchez-de-la-Torre M, Peker Y*, et al.* Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias. *Sleep* 2021;**44**. doi: 10.1093/sleep/zsab019
246. Mineiro MA, Silva PMD, Alves M*, et al.* The role of sleepiness on arterial stiffness improvement after CPAP therapy in males with obstructive sleep apnea: a prospective cohort study. *BMC Pulm Med* 2017;**17**:182. doi: 10.1186/s12890-017-0518-z
247. 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. doi: 10.1164/ajrccm.161.5.9909024
248. Revol B, Jullian-Desayes I, Bailly S*, et al.* What is the best treatment strategy for obstructive sleep apnoea-related hypertension? *Hypertens Res* 2018;**41**:1070-1072. doi: 10.1038/s41440-018-0114-5
249. 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. *Journal of Hypertension* 2014;**32**:673-680. doi: 10.1097/HJH.0000000000000047
250. Yang L, Zhang H, Cai M*, et al.* Effect of spironolactone on patients with resistant hypertension and obstructive sleep apnea. *Clinical and Experimental Hypertension* 2016;**38**:464-468. doi: 10.3109/10641963.2015.1131290
251. S S. Antihypertensive and PAP Treatment in Obstructive Sleep Apnea Patients With Hypertension (AHPAP). https://clinicaltrials.gov/study/NCT05115994?term=AHPAP-MCE%2Fdeath&rank=1
252. Svedmyr S, Hedner J, Bonsignore MR*, et al.* Hypertension treatment in patients with sleep apnea from the European Sleep Apnea Database (ESADA) cohort - towards precision medicine. *J Sleep Res* 2022:e13811. doi: 10.1111/jsr.13811