Universitat de Girona

Vascular Markers in Patients Diagnosed with Mild to Moderate Obstructive Sleep Apnea: a Cohort Study

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"*We spend a third of our life asleep yet medicine knows so little about it*" – Antón Obrador

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1. Abreviations

ABI: Ankle-brachial index

AHI: Apnea/hypopnea index

BMI: Body mass index

BP: Blood pressure

cfPWV: Carotid-femoral pulse wave velocity

cIMT: Carotid intima-media thickness

CPAP: Continuous positive airway pressure

CV: Cardiovascular

ECG: Electrocardiogram

ESS: Epworth sleepiness scale

GFR: Glomerular filtration rate

HbA1c: Glycated hemoglobin

HDL: High density lipoprotein

IH: Intermittent Hypoxia

IMT: Intima-media thickness

LDL: Low density lipoprotein

MRA: Mandibular repositioning appliances

OSA: Obstructive sleep apnea

PAP: Positive airway pressure

PSG: Polysomnography

QOL: Quality of life

REM: Rapid eye movement

SPSS: Statistical Package for Social Sciences

2. Abstract

Background

Obstructive sleep apnea (OSA) is a widespread and prevalent disorder that affects from 24 to 28% of the population. It is associated to decreased quality of life, increased road traffic accidents and increased cardiovascular (CV) risk. Currently OSA is diagnosed with an overnight polysomnography (PSG) and its 1st line treatment is a continuous positive airway pressure device (CPAP). Current guidelines only recommend CPAP treatment to reduce the CV risk of the severe patients (Apnea/Hypopnea Index≥30) and not the mild to moderate patients (Apnea/Hypopnea Index 5-29.9) even though some of these patients may have an increased CV risk. To identify these patients with an increased CV risk, we propose the use of 3 vascular markers: Ankle-Brachial Index (ABI), Carotid ultrasound and Carotid-Femoral Pulse Wave Velocity.

Objectives

To evaluate the utility of ABI and other vascular markers at identifying high CV risk in patients with mild to moderate minimally symptomatic OSA and no CV disease

Design

The study is a multicentre prospective cohort study performed in the Joan Trueta Hospital of Girona and the Sant Pau Hospital of Barcelona from 2018 to 2030.

Population

The study population will be mild to moderate minimally symptomatic OSA patients, diagnosed with an overnight PSG, with no CV disease diagnosed at baseline. A consecutive non-probabilistic method will be used to recruit the 1080 patients needed. These patients will be divided into 2 groups, patients with an ABI≤0.9 will be considered as “exposed” and patients with an ABI>0.9 will be considered as “not exposed”.

Methods

Patients included into the study will be studied to control for confounding factors and to assure they fulfil all inclusion criteria and no exclusion criteria. After this they will receive a yearly follow-up for 10 years to observe incident CV disease or death.

Keywords:

Obstructive sleep apnea, Vascular markers, Ankle-brachial index, Carotid ultrasound, Carotid-femoral pulse wave velocity, Cohort, Cardiovascular disease

3. Background

3.1 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a potentially serious sleep disorder caused by the repeated complete or partial obstruction of the upper airway during sleep that causes prolonged apneas and/or hypopneas that give rise to transient hypoxia (1–3).

3.1.1 Epidemiology

It's a widespread disorder that although its prevalence may vary across different populations and age groups recent data from Europe and the United States suggests that it affects from 24 to 26% of men and 17 to 28% of women between 30 and 70 years of age (4–6).

OSA has been proven to have genetic and epidemiologic risk factors such as obesity, male sex and age. Obesity is recognized as one of the strongest risk factors for OSA, given the increasing rates of obesity in western society, the prevalence of OSA is likely to increase further. It has a significant economic impact on healthcare systems and society. OSA-related healthcare costs include the direct costs of OSA diagnosis and treatment and the indirect costs of associated conditions (obesity, diabetes, CV disease, depression).

OSA is associated with decreased quality of life (QOL), significant neurocognitive impairment, and increased risk of road traffic accidents. However, the relationship of OSA with medical comorbidity, and in particular cardiovascular (CV) comorbidity, is perhaps the area of most interest from a medical perspective and shall be the main focus of this study (4).

3.1.2 Diagnosis

OSA is currently characterized by patients with excessive daytime sleepiness, cognitive deficits and metabolic and cardiovascular disorders; all secondary to repeated episodes of upper airway collapse.

The current gold-standard diagnostic method is an overnight polysomnography (PSG). The use of PSG for evaluating OSA requires recording the following physiological signals: electroencephalogram, electrooculogram, chin electromyogram, airflow, oxygen saturation, respiratory effort and electrocardiogram (ECG). Additional recommended parameters include body position and leg electromyogram derivation (7).

OSA is defined as A or B:
-A) **5 or more apneas** (no breath flow for 10s or more) or **hypopnea** (reduced breath flow of 30% and no more than 90% for 10 or more seconds) per hour (the so called **apnea/hypopnea index: AHI**) in an overnight PSG study accompanied by the following **symptoms**: loud snoring, apneas, nocturia, headache, excessive daytime sleepiness and deficits in memory and attention with subsequent risk of accident by day (1–3,7).
-B) An **AHI of 15 or more** using an overnight PSG, irrespectively if accompanied by symptoms or not (1–3,7).

It is classified by severity based on the AHI as: 5-14.9/h, **mild**; 15-29.9/h**, moderate**; 30/h or more, **severe** (1–3).

Due to the fact that an overnight PSG is an expensive test alternative tests have appeared that are cheaper, however they tend to underestimate the AHI. Portable monitors, such as respiratory polygraphs, that at least record airflow, respiratory effort and blood oxygenation are often used to reduce costs (7). According to current experience at the Joan Trueta Hospital of Girona, half the patients are diagnosed using overnight PSG and half using portable monitors.

Currently day time sleepiness is characterized by the **Epworth Sleepiness Scale (ESS)**. This questionnaire classifies patients as: 0-9, normal daytime sleepiness or 10-24, mild excessive daytime sleepiness (see Annex 1) (8).

3.1.3 Physiopathology

The physiopathology of OSA isn't fully known and it is believed to have a multifactorial origin where anatomical and functional factors interact. The collapse of the upper airway is

produced principally by an imbalance of factors that keep it open and others that tend to close it. Such factors are lack of muscle tone in the collapsible part of the airway during sleep, enlargement of soft tissues structures within and surrounding the airway (mainly in obese patients) and retrognathia (1,3,9,10).

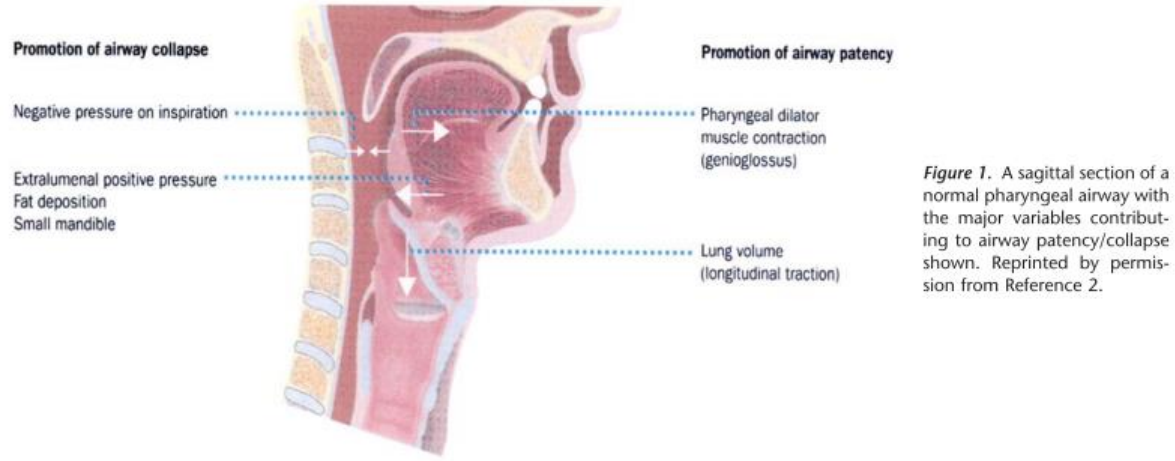

Figure 1. A sagittal section of a normal pharyngeal airway with the major variables contributing to airway patency/collapse shown. Reprinted by permission from Reference 2.

Figure 1:Pathogenesis of Obstructive and Central Sleep Apnea (10)

As figure 1 shows, negative pressure on inspiration and extraluminal positive pressure promote airway collapse. Pharyngeal dilator contraction and lung volume promote airway patency.

Intraluminal negative pressure in a collapsible tube will inherently reduce the airway area. Thus, during each inspiration, the negative pressure produced by the diaphragm diminishes airway size depending on the compliance of the airway walls and opposing dilating forces.

Extraluminal positive pressure is increased in obese patients due to excess extraluminal tissue pressure, in patients with retrognathia and in patients who sleep in a supine position due to the effect of gravity on the airway. This promotes upper airway collapse.

Pharyngeal dilator muscle activation is the primary process that counteracts the collapsing forces mentioned above. First negative pressure detected in the airway activates local mechanoreceptors, leading to a superior laryngeal nerve afferent activity and ultimately increased hypoglossal stimulation of the genioglossus muscle. Second, the respiratory pattern generating neurons in the medulla also influences genioglossal activation. This is most clearly demonstrated by the activation on the genioglossus muscle about 50 to 100ms

before diaphragmatic activation, to prevent airway collapse before the development of negative pressure in the airway.

With the onset of sleep, the control of these muscles changes importantly. The negative-pressure reflex is substantially reduced during non-REM (Rapid eye movement) sleep and further during REM sleep. It is not lost and the muscles can still respond to negative pressure, but not as effectively or as quick as when a person is awake. This promotes upper airway collapse during sleep.

Changes in lung volume can also importantly influence pharyngeal patency. Lung inflation applies a caudal traction on the trachea and larynx, thereby inducing a longitudinal tension on the pharyngeal airway. This caudal force tends to stiffen the airway and reduces collapsibility (10).

3.1.4 Treatment

OSA should be approached as a chronic disease that requires a long-term, multidisciplinary management. Current treatment objectives for OSA can be summarized into 2, reducing symptoms (mainly daytime sleepiness) and minimalizing risk for CV disease and accidents. All patients diagnosed with OSA are given general recommendations and patient education (see Annex 2) (1,7).

Patient education	General recommendations
-Findings of study (PSG) -Severity of disease -Pathophysiology of OSA -Explanation of the natural course of the disease and associated disorders -Risk factor modification -Consequences of untreated disease -What to expect from treatment -Outline patient's role in treatment -Address patients concerns and set goals	-Sleep 7-9 hours per night -Maintain a regular sleep schedule -Only use the bed for sleeping or sexual activities -Weight loss in overweight patients (BMI> 25) -Avoid central nervous system depressing drugs (such as benzodiazepines) -Avoid alcohol -Avoid tobacco

Figure 2: Patient education and general recommendations in OSA patients (1)(7) *BMI: Body mass index, OSA: Obstructive sleep apnea, PSG: Polysomnography,*

Other treatments for OSA are:

Continuous positive air pressure devices (CPAP)

This is currently the first line treatment in the majority of OSA patients. The CPAP device provides positive pressure in the airway that maintains the upper airway open during sleep impeding its obstruction. It has been proven to improve daytime sleepiness, QOL, snoring, arousals, sleeps architecture and daytime neurocognitive function. It has also been proven to reduce traffic accidents, blood pressure and CV risk (1,2,7,11–13).

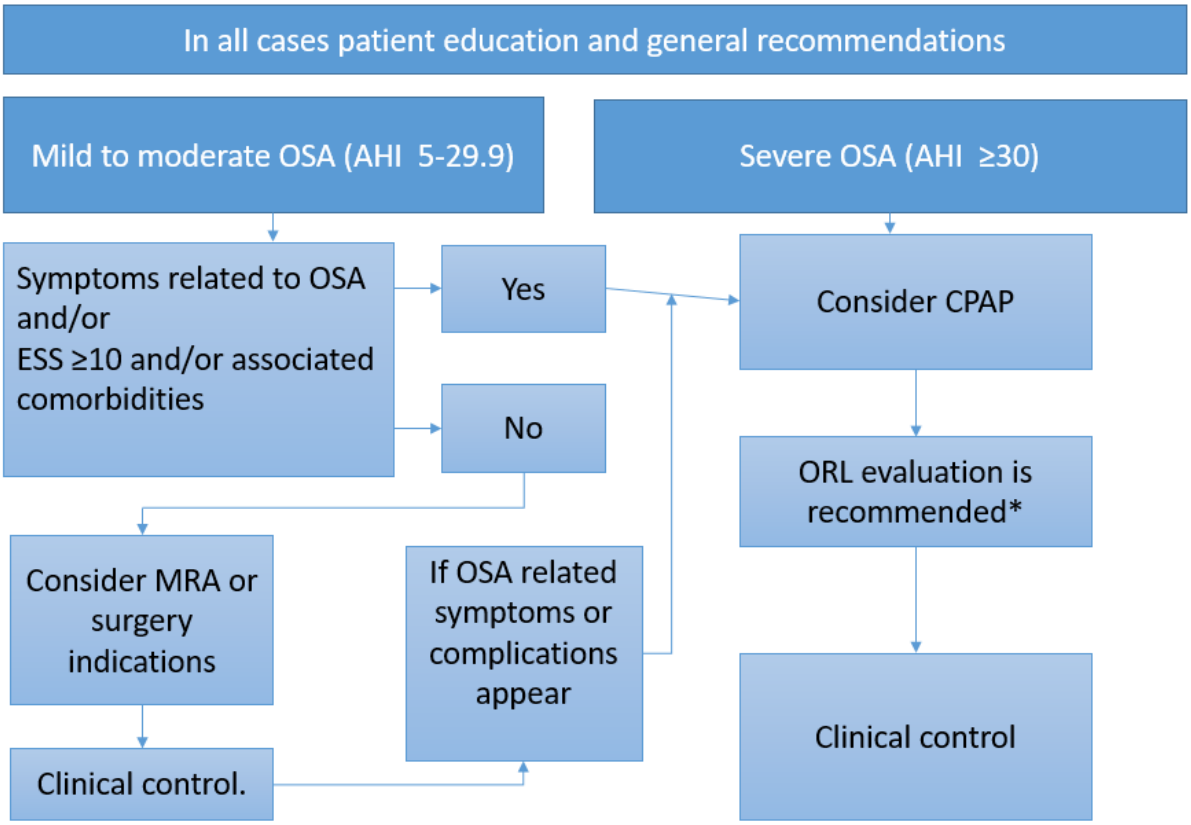

Figure 3: OSA treatment algorithm. Adapted from (1)

CPAP treatment indications are summarized in figure 3. Patients with mild to moderate OSA plus 1 of the next: symptoms related to OSA, ESS≥10 or comorbidities (mainly nocturnal hypertension) (14,15); are candidates for CPAP therapy. All patients with severe OSA (AHI≥30/h), especially if they are under 70 years of age, should receive CPAP therapy to reduce their risk of CV disease. As each patient needs a different positive airway pressure (PAP), before they receive the device, a titration is needed to find this optimal PAP.

The most common side effects of CPAP are nasal congestion, skin rashes, pharyngeal dryness, machine sounds, conjunctivitis, epistaxis, insomnia and aerophagia. The majority appear in the 1st and 2nd week, are temporary and can be resolved with humidifiers, better fitting masks or PAP adjustments. The only absolute contraindication for CPAP treatment are a cerebrospinal fluid fistula and/or severe face pathology that impedes a facial mask (1,7).

To be effective, the CPAP device must be used for a minimum of 4 hours each night (11,12). Standard follow-up is at the 1st month, then every 3 months for the 1st year, then every 6 months for the 2nd year and annually after that. A significant weight loss (10%) or reappearance of symptoms are an indication for a new evaluation (1,7).

Mandibular repositioning appliances (MRA)

MRA cover the upper and lower teeth and hold the mandible in an advanced position with respect to the resting position, this helps prevent upper airway collapse. They are a 2nd line treatment efficient in treating snoring, mild to moderate OSA with a low BMI and non-significant nocturnal desaturations. They are also an option in patients who don't tolerate CPAP or who aren't candidates for surgery. An evaluation by a dentist or ORL is needed before treatment. A PSG is recommended to evaluate its effectiveness (1,7).

Surgery

There are various surgical options to treat OSA but all of them are considered 2nd line treatments. The most frequently used procedures are: Nasal procedures (septoplasty, turbinate reduction, functional rhinoplasty, etc.), Palatopharyngeal surgery, Tongue reduction surgery and Maxillomandibular advancement (1,7).

3.2 Cardiovascular complications

OSA is associated to high CV morbidity and mortality (16,17) such as hypertension (50%),congestive heart failure (25%),acute coronary syndromes (30%) and stroke (60%) (16,18–24).

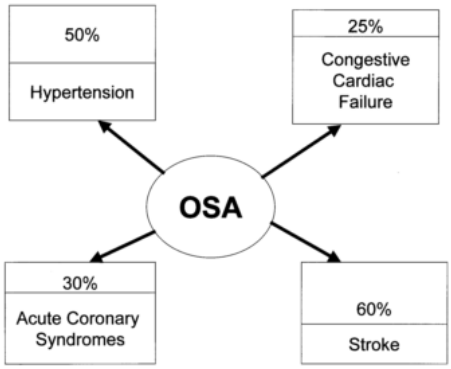

Figure 4: OSA and it'd cardiovascular complications(16) *OSA: Obstructive sleep apnea*

The pathophysiology of CV disease in OSA is complex and multifactorial, as a summary, the main acute physiological consequences of OSA are intermittent hypoxia (IH), intrapleural pressure changes and arousals (24).

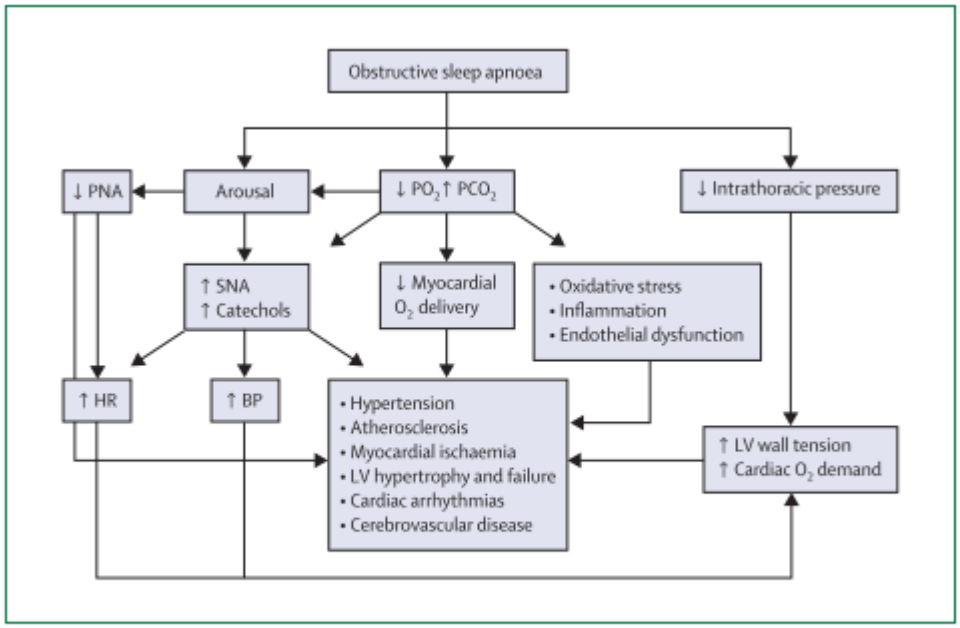

Figure: Pathophysiological effects of obstructive sleep apnoea on the cardiovascular system
PNA=parasympathetic nervous system activity. PO_2=partial pressure of oxygen. PCO_2=partial pressure of carbon dioxide. SNA=sympathetic nervous system activity. HR=heart rate. BP=blood pressure. LV=left ventricular.

Figure 5:OSA and its cardiovascular consequences (24)

Intermittent hypoxia

The apneas and hypopneas that patients with OSA suffer at night are frequently associated with marked blood oxygen desaturations resulting in IH. The repetitive hypoxia and reoxygenation cycle in OSA is thought to be similar to ischemia-reperfusion injury. This IH promotes the production of reactive oxygen species, thereby resulting in increased

oxidative stress. This is proposed to be a pathway that induces systemic inflammation, ultimately leading to decreased bioavailability of endothelial nitric oxide and consequently endothelial dysfunction. It also induces sympathetic activation and reduced myocardial oxygen delivery (24).

Intrapleural pressure changes

The partial or complete collapse of the upper airway during sleep causes a repetitive forced inspiration against the obstructed upper airway that increases intrathoracic pressure swings.

These intrathoracic pressure swings are thought to produce extensive shear and wall stresses on intrathoracic blood vessels, including the aorta, resulting in aortic dilatation. These increased differences between intracardiac and extracardiac pressure in addition, increase left ventricular transmural pressure (afterload, a potent stimulus for left ventricular hypertrophy) (25). Negative intrathoracic pressure also draws blood into the thorax, increasing right ventricular preload. IH causes pulmonary vasoconstriction that also increases right ventricular afterload. These 2 forces (increased right ventricular preload and afterload) distend the right ventricle, causing a leftward shift of the interventricular septum during diastole that impedes left ventricular filling and decreases stroke volume (24).

Arousals

As a result of interrupted ventilation, carbon dioxide levels rise, oxygen levels fall and the ventilator effort increases until the patient arouses from sleep, whereupon muscle tone returns to the upper airway as explained before and ventilation is restored. These arousals are associated to state-related increases in sympathetic activity and decreases in parasympathetic activity (24,26).

The exact causal pathways between OSA and CV disease aren't clear but IH, intrapleural pressure changes and arousals are hypothesis with a lot of evidence behind them, especially IH; future research is needed to learn more about these pathways but isn't the focus of this study

Marin et al (27) showed in a long term cohort study that after adjusting for confounding factors the odds ratio for CV death and non-fatal CV events was statistically significant in severe untreated OSA patients but not in mild to moderate untreated OSA patients

		Fully adjusted odds ratio (95%CI)	**p**
Cardiovascular death	Mild to moderate untreated OSA	1.15 (0.34-2.69)	p=0.71
	Severe untreated OSA	2.87 (1.17-7.51)	0.025
Non-fatal cardiovascular events	Mild to moderate untreated OSA	1.57 (0.62-3.16)	0.22
	Severe untreated OSA	3.17 (1.12-7.52)	0.001

Figure 6:Long-term cardiovascular outcomes in men with mild to moderate or severe OSA(27) *CI: Confidence interval*

Yaggi et al (21) showed in a long term cohort study that after adjusting for confounding factors that the hazard ratio for stroke and death was statistically significant in OSA patients with an AHI >36 but not in OSA patients with an AHI of 4-36.

Table 3. Trend Analysis for the Relationship between Increased Severity of the Obstructive Sleep Apnea Syndrome and the Composite Outcome of Stroke or Death from Any Cause (N=1022).*

Severity of Syndrome	Stroke or Death		Mean Follow-up Period	Hazard Ratio (95% CI)
	No. of Events	No. of Patients		
			yr	
AHI ≤3 (reference score)	13	271	3.08	1.00
AHI 4–12	21	258	3.06	1.75 (0.88–3.49)
AHI 13–36	20	243	3.09	1.74 (0.87–3.51)
AHI >36	34	250	2.78	3.30 (1.74–6.26)

* P=0.005 by the chi-square test for linear trend. AHI denotes apnea–hypopnea index, and CI confidence interval.

Figure7:Long-term risk of stroke and death in OSA (21)

As seen above OSA is associated to high CV morbidity and mortality if all patients are included, however if we look at the sub groups classified by AHI as mild, moderate or severe; only the severe group has a CV risk high enough to merit CPAP treatment without

symptoms (1,21,27). Within the mild to moderate group some of the individuals may have a higher CV risk meriting CPAP treatment but we aren't identifying them at the moment (28).

3.3 Cardiovascular markers

Studies have shown that CV consequences may appear early in this disease, for example, occurrence of atherosclerosis without significant associated classical CV risks during OSA (29).

As seen before, among the intermediary mechanisms that could explain the link between OSA and CV morbidity, atherosclerosis has been proposed (30).

Identification of OSA patients at a significant risk for developing atherosclerosis is mandatory to prevent or at least delay the occurrence of this vessel disease. It is known that similar degree of OSA severity may induce a wide spectrum of atherosclerotic changes in different patients. It can be explained by interindividual differences in response to IH, which may mirror congenital or acquired disposition to disease or protective and regenerative potential (28).

In order to anticipate if protective or deleterious mechanisms possibly predominate, several determinants have been proposed to serve as predictive markers of the disease (28).

The National Institutes of Health defines a marker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacologic responses to a therapeutic intervention"(31). Summarized, and in the setting of prevention, vascualr markers reflect early functional or morphological changes, well before overt disease manifests. This identification of subclinical disease opens a window to prevent the occurrence of clinical CV disease by timely treatment (32).

3 vascular markers that indicate changes in vessel structure and increased CV risk are pathological ankle-brachial index (ABI), increased arterial stiffness (measured by carotid-femoral pulse wave velocity (cfPWV)) and increased carotid intima/media thickness or atherosclerotic plaque volume (measured with carotid ultrasonography). These changes are

already detectable in only minimal symptomatic OSA patients and are considered to be early markers of atherosclerosis (28,32–35).

Ankle-brachial index (ABI)

In healthy individuals, systolic blood pressure (BP) are physiologically higher in the lower extremities in comparison with the upper extremities; this is a combined effect of pulse wave reflections and amplification, as well as changes in vessel wall thickness attributed to hydrostatic pressure. The relationship can be quantified with the ABI by comparing systolic BP taken at the brachial artery with systolic BP taken at the ankle. A decreased ratio indicates a late stage of atherosclerosis with hemodynamic compromise attributed to obstructive lesions. Originally described as a non-invasive method to diagnose lower extremity peripheral artery disease, ABI has been later shown to be a marker of cardiovascular disease prognosis. An ABI≤0.9 indicates an increased risk of CV disease (32,36). At higher levels (≥1.40) ABI identifies medial calcinosis (calcification of the tunica media without affecting the arterial lumen), a condition different than atherosclerosis (32).

The standard mode of measurement requires a handheld continuous wave Doppler device and a manual BP cuff. As seen this is a cheap and widely available method of assessing cardiovascular risk that could be used in primary care. We believe that's its simplicity and cheapness make it an ideal vascular marker.

The majority of current guidelines consider it useful for primary and secondary CV disease prevention (32).

Carotid-femoral pulse wave velocity (cfPWV)

Arterial stiffness has been found to be higher in patients with OSA (29,37,38). Due to the fact that waves travel faster in rigid tubes, loss of compliance (as seen in increased arterial stiffness), results in increased velocity of pulse waves. OSA, like other CV risk factors, alters the composition and mechanical properties of arterial walls making them eventually less compliant. Elastic-type arteries, like the aorta, are primarily affected.

There are various invasive and non-invasive methods used to measure arterial stiffness but in this study we shall concentrate on cfPWV as it is a non-invasive method that is considered gold standard (32).

cfPWV is the velocity of the pulse as it travels from the heart to the carotid and the femoral artery. cfPWV is usually measured using the "foot-to-foot" velocity method from a number of waveforms. These are obtained by using surface tonometry probes at the right common carotid artery and the right femoral artery and the time delay is measured between the "foot" of the 2 waveforms (32).

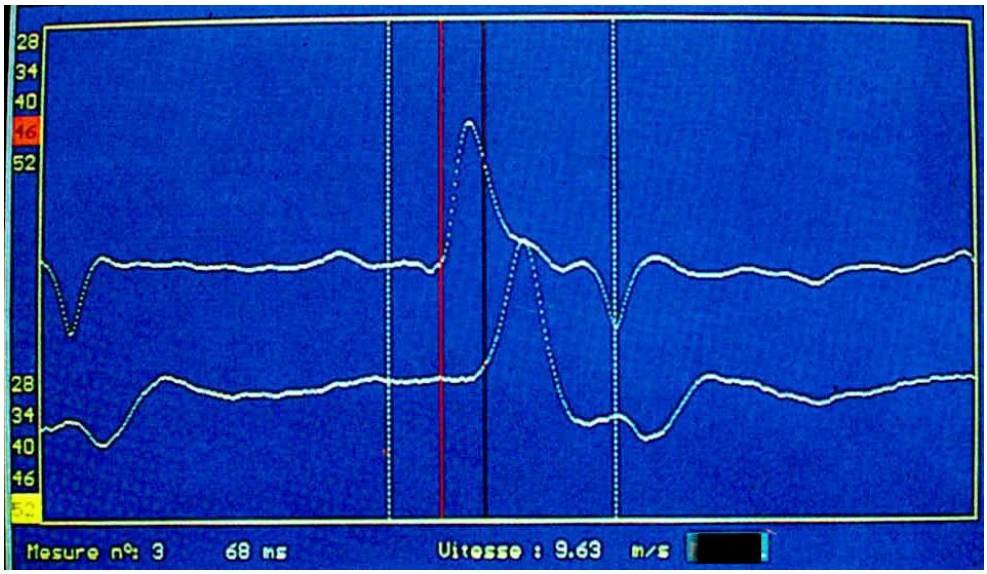

Figure 8: Carotid and femoral pulse waves. The red line represents the carotid "foot" and the black line represents the femoral "foot" (39)

cfPWV is calculated as 0.8 x D/Dt (m/s). D (distance, cm) is the length measured in cm as the difference between the distance from the right femoral site and the sternal notch and the right carotid site and the sternal notch. Dt (time delay, s) is measured between the "foot" of the 2 pressure waves (time delay from the right carotid artery to the right femoral artery). Multiplying by 0.8 is used to correct the overestimation of the superficial measurement of the real travel distance (of the arteries themselves). It has been proven that patients with a cfPWV higher than 10m/s have an increased CV risk (32).

Its non-invasive nature, fast learning curve, the wide choice of available devices, relatively low cost, extensive validation in large population studies and established reference values

are among its advantages. On the other hand, exposure of the inguinal region for measurements and a calibration of the measured travelled distance are needed.

The majority of current guidelines consider it useful for primary and secondary CV disease prevention (32).

Carotid ultrasonography

Infiltration of the subintimal layer of arteries by lipids and inflammatory cells constitutes an early process in the atherosclerosis. Carotid ultrasonography can assist in early detection and quantification of structural changes in the arterial wall that are associated with atheroma, fibrosis and the aging process. A thick intima-media complex and carotid plaque, as a more extreme manifestation, serve as early indicators of generalized atherosclerosis. Though often regarded as 2 distinct phenotypes and markers with different usefulness for risk prediction, both carotid intima-media thickness (cIMT) and plaque presence are assessed during carotid ultrasound providing complementary prognostic information (32).

The cut-off point for increased CV risk is considered as cIMT>0.9 mm and/or presence of carotid plaques (32,40).

Plaques are considered as focal structures in any part of the carotid tree that fulfil any one or more of the following criteria:

- Encroaching into the arterial lumen of 0.5mm or more

- >50% of the surrounding IMT (Intima-media thickness) value

- IMT of the focal structure of 1.5mm or more

Some of the limitations of carotid ultrasonography are the initial cost of the ultrasound device, probe and software, as well as the training of sonographers.

The majority of current guidelines consider it useful for primary and secondary CV disease prevention (32).

Classical CV risk scores such as SCORE and REGICOR aren't validated in OSA patients; it could be an interesting future area of study. Even though they aren't validated, all of their items (age, sex, smoking habit, diabetes, total cholesterol, high density lipoprotein (HDL) cholesterol and blood pressure) are collected after diagnosis of OSA by the attending physician (1,7).

Summarizing, the risk stratification for the development of atherosclerosis in OSA by means of different markers would enable better monitoring of disease dynamics and, if required, early treatment initialization.

OSA patients at elevated risk for CV diseases benefit mostly from early diagnosis and appropriate treatment. However, the recognition of such patients is not easy as there are no standardized criteria for CV risk stratification in OSA. The markers described above have been proposed to be a useful tool for anticipation of a vessel disease and are increased in OSA patients (28,30,41–43).

4. Justification

Obstructive sleep apnea (OSA) is a potentially serious sleep disorder caused by the repeated complete or partial obstruction of the upper airway during sleep that causes prolonged apneas and/or hypopneas that give rise to transient hypoxia (1–3).

It's a widespread disorder that affects from 24 to 26% of men and 17 to 28% of women, this prevalence is believed to increase over the next years due to the increasing rates of obesity, one of OSA main risk factors (4–6).

OSA is associated with decreased QOL, decreased daytime cognitive function and increased road traffic accidents. The most important association from a medical point of view is its relationship with CV comorbidity. We know that OSA is associated to high CV morbidity and mortality (16)(17) such as hypertension (50%),congestive heart failure (25%),acute coronary syndromes (30%) and stroke (60%) (16,18–24).

However, after being stratified into severity groups, only the severe OSA group has been shown to have a high enough CV risk to merit CPAP with the objective to reduce this risk (21,27).

CPAP treatment is currently the 1st line treatment in OSA and has been proven to improve daytime sleepiness, QOL, snoring, arousals, sleeps architecture and daytime cognitive function. It has also been proven to reduce traffic accidents, blood pressure and CV risk (1,2,7,11–13).

If mild to moderate OSA patients are taken as a whole, studies don't show that they have a CV risk high enough to merit CPAP treatment, however, some patients in this group may have a significant CV risk that currently we aren't identifying and therefor aren't receiving treatment (21,27,28).

To identify these patients and to be able to treat them earlier when their disease is still subclinical, we propose the use of vascular markers that have already been validated in other populations. These markers are ABI, cfPWV and carotid ultrasonography. All 3 are recommended for primary and secondary CV disease prevention and has been proven to be increased in OSA patients (29,32,34,37,41–44).

This study is intended to discover if vascular markers, especially ABI, can identify mild to moderate OSA patients with minimal symptoms (ESS<10) and no comorbidities that have a high risk of CV disease. These are patients, according to the most recent guidelines, wouldn't receive CPAP treatment but could possibly benefit from it (1–3,28). Proving that ABI can be used as a marker to identify these patients is especially interesting, due to its simplicity, cheapness and the ability to apply it in primary care.

5. Hypothesis

5.1 Main hypothesis

Patients with mild to moderate (AHI 5-29.9/h) OSA and an ESS<10 with subclinical signs of atherosclerosis (ABI≤0.9) have a higher rate of CV disease than patients with mild to moderate OSA and an ESS<10 without subclinical signs of atherosclerosis.

6. Objectives

6.1 Main objective

Compare the long term CV complications in patients with mild to moderate (AHI 5-29.9/h) OSA and an ESS<10 with and without subclinical signs of atherosclerosis (ABI≤0.9).

6.2 Secondary objectives

Compare mortality from all causes in patients with mild to moderate (AHI 5-29.9/h) OSA and an ESS<10 with and without subclinical signs of atherosclerosis (ABI≤0.9).

All hypothesis and objectives will also be applied to:

- Patients with mild to moderate (AHI 5-29.9/h) OSA and an ESS<10 with and without subclinical signs of atherosclerosis (cIMT higher than 0.9 and/or presence of a carotid plaque)
- Patients with mild to moderate (AHI 5-29.9/h) OSA and an ESS<10 with and without arterial stiffness (cfPWV higher than 10m/s)

7. Methodology

7.1 Study design

The study design is a multicentre prospective cohort study with a 10 year follow-up period.

7.2 Population definition

The target population is composed patients with mild to moderate (AHI 5-29.9/h) OSA* and an ESS<10 without CV disease, diagnosed by an overnight PSG in the Joan Trueta Hospital of Girona and the Sant Pau Hospital of Barcelona. They will be later classified into 2 cohorts according to their ABI: a) patients with an ABI≤0.9 b) patients with an ABI higher than 0.9.

*OSA diagnosis and severity classification will be done with an overnight PSG according to the American Academy of Sleep Medicine. Patients diagnosed with a respiratory polygraph will have a PSG programmed for them and the PSG results will be used to classify them.

Inclusion criteria

- Patients aged 18-70 years old
- Patients diagnosed with mild to moderate OSA (AHI: 5-29.9/h) with an overnight PSG
- Patient with an ESS<10
- Patients who agree with and sign the informed consent

Exclusion criteria

- Incapacity to follow the study (due to unsolvable language barriers, inability to attend the follow up visits or tests and other causes decided by the attending physician)
- Chronic respiratory failure (SaO2 <90% and/or pO2 <60mmHg while resting) of any cause
- Neuromuscular diseases with respiratory repercussions
- Active smoking in the last 6 months
- High-risk alcohol consumption (weekly alcohol consumption higher than 14 standard drink units in females or 21 in males will be considered high-risk consumption)
- Active drug addictions (DSM-V criteria)

- Pregnancy
- Patients diagnosed with other sleep diseases (narcolepsy, hypoventilation obesity syndrome, restless legs syndrome)
- Patients treated with CPAP or mechanical ventilation
- Patients with severe chronic diseases: Chronic renal failure in treatment with dialysis, active oncological disease or severe psychiatric disease.
- Patient diagnosed with type 1 or type 2 diabetes (American Diabetes Association 2017 criteria)
- Obesity (BMI ≥ 30)
- Patients with a cardiovascular risk at ten years higher than 10% using the REGICOR CV risk calculator
- Nocturnal hypertension
- Patients with a cardiovascular disease:
  Coronary artery disease (ICD-10 code: I20-I25), stroke (ICD-10 code: I61-I66), transitory ischemic accident (ICD-10 code: G45.9), symptomatic peripheral arterial disease (ICD-10 code: I70.2, I73.9), heart failure (ICD-10 code: I11.0, I13.0, I13.2, I50.1, I50.9), atrial fibrillation (ICD-10 code: I49.0).
- Patients with an ABI equal or higher than 1,4

7.3 Sample selection and sample size

Sample selection

A consecutive non-probabilistic method will be performed to recruit the patients into the study. Patients with a new diagnosis of mild to moderate OSA who fulfil the inclusion criteria and none of the exclusion criteria will be offered to enter the study by the physician attending them.

All patients will be informed about the purpose of the study and will be invited to read and sign the informed consent. (see Annex 3)

The patients will be recruited in the Joan Trueta Hospital of Girona and the Sant Pau Hospital of Barcelona.

Sample size

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **108 "**exposed" subjects and **972** "non-exposed" subjects are necessary to recognize as statistically significant a relative risk greater than 2.3. A proportion in the non-exposed group has been estimated to be 0.089. A drop-out rate of 10% has been anticipated according to the current patient loss at follow-up at the Joan Trueta Hospital of Girona (21,27,32,41,43).

With a total sample size of **1080 patients** we expect to recruit them in a 2 year period at the 2 centres

7.4 Variables definition

7.4.1 Independent variables

ABI: measured with a handheld continuous wave Doppler device and a manual BP cuff. It will be calculated by taking the highest pressure between the systolic BPs of the posterior tibial and dorsalis pedis artery divided by the highest systolic BP between both arms, the lower of the 2 lower limbs ABI (right and left) will be used to assess cardiovascular risk of the subject. Patients with an ABI ≤0.9 will be considered as "exposed" and patients with an ABI of 0.91 to 1.39 will be considered as "not exposed". Patients with an ABI of 1.4 or higher will be excluded from the study (32).

Carotid ultrasonography: measured with a transcutaneous ultrasound in B-mode to obtain images of the carotid tree. Mean cIMT will be measured in the distal common carotid artery based on the Mannheim consensus (40). Presence of plaques will be measured in the entire carotid tree. Patients with a cIMT higher than 0.9mm and/or presence of carotid plaques will be considered as "exposed" and patients with a cIMT of 0.9mm or lower and no carotid plaques will be considered as "not exposed" (32).

cfPWV: measured with a surface tonometry probe at the right common carotid artery and the right femoral artery. cfPWV is calculated as 0.8 x D/Dt (m/s). D (distance, cm) is the length measured in cm as the difference between the distance from the right femoral site and the sternal notch and the right carotid site and the sternal notch. Dt (time delay, s) is measured between the "foot" of the 2 pressure waves (time delay from right carotid artery

to right femoral artery). Multiplying by 0.8 is used to correct overestimation of the superficial measurement of the real travel distance. Patients with a cfPWV higher than 10 m/s will be considered as “exposed” and patients with a cfPWV of 10 m/s or lower will be considered as “not exposed” (32).

7.4.2 Dependent variables

Global mortality: death from any causes (R96, R98, R99).

Cardiovascular morbidity: coronary artery disease (ICD-10 code: I20-I25), stroke (ICD-10 code: I61-I66), transitory ischemic accident (ICD-10 code: G45.9), symptomatic peripheral arterial disease (ICD-10 code: I70.2, I73.9), heart failure (ICD-10 code: I11.0, I13.0, I13.2, I50.1, I50.9), atrial fibrillation (ICD-10 code: I49.0).

7.4.3 Covariables

Age: in years

Sex: female or male

BMI: dividing the weight by the square of the height (Kg/m^2). The patient will be weighed and measured

HDL-cholesterol, low density lipoprotein (LDL)-cholesterol and triglycerides: measured in mg/dl according to the European society of hypertension

Basal glucose: measured in mg/dl according to the World health organization

Renal function alteration: Glomerular filtration rate (GFR) calculated using CKD-EPI (45) and expressed as glomerular filtrate <60mL/min/1,73m^2

OSA related symptoms:

- Excessive daytime sleepiness: measured with ESS (0-9: Normal daytime sleepiness, 10-24: Mild excessive daytime sleepiness)

- Average hours of sleep: Measured in hours

- Daytime nap: yes or no, and if yes length will also be collected

- Snoring: Yes or no

- Nocturia: Yes or no, and if yes how many times a night

- Sleep Apnea: Yes or no, witnessed by another person

- Mouth dryness: Yes or no

Blood pressure: measured in mmHg with a blood pressure monitor

Mallampati score: measured in I, II, III, IV (see Annex 4) (46).

Neck diameter: Measured in cm with a tape measure. Enlarged neck circumference will be entered in men >43cm and women >37cm.

OSA gravity: Measured using the AHI. Mild: AHI 5-14.9 and Moderate: AHI 15-29.9

7.5 Measurements and instruments

ABI: measured with a handheld continuous wave Doppler device and a manual BP cuff. The measurements will be taken from the posterial tibial, dorsalis pedis and braquial arteries.

All measurements were performed after 3 hour fasting and an abstinence of caffeine. Subjects were studied under supine resting conditions in a quiet, temperature-controlled room (22-24°C)

Members of the study responsible for data collection will receive a special course to reduce inter- and intrapersonal variability of measurements

Carotid ultrasonography: measured with a transcutaneous ultrasound in B-mode to obtain images of the carotid tree according to the Mannheim consensus (40).

cIMT is a double-line pattern visualized by echography on both walls of the distal common carotid artery in a longitudinal image. 2 parallel lines form it: the lumen-intima and media-

adventitia interfaces. cIMT will be measured semi-automatically using the ultrasound machine software. Mean cIMT will be used to classify patients

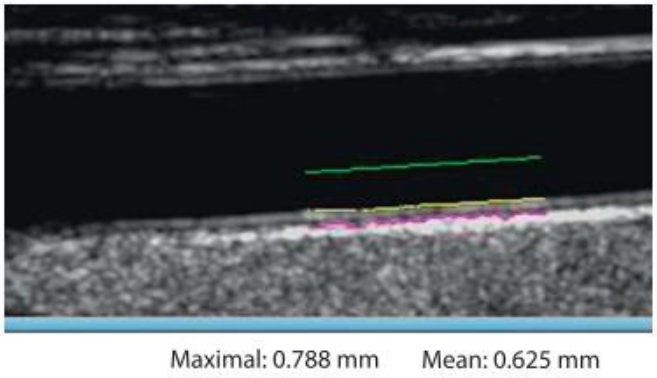

Figure 9: Carotid ultrasound. The yellow line represents the lumen-intima interface and the pink line represents the media-adventitia interface. (40)

Plaques will be considered as focal structures in any part of the carotid tree that fulfil any one or more of the following:

- Encroaching into the arterial lumen of 0.5mm or more

- >50% of the surrounding IMT (Intima-media thickness) value

- IMT of the focal structure of 1.5mm or more

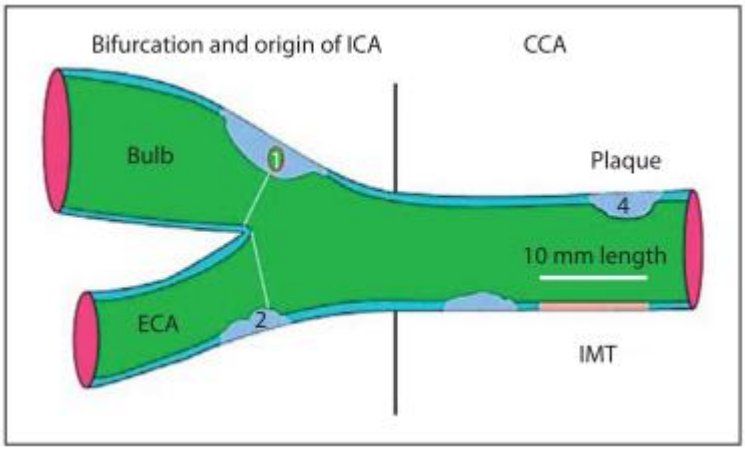

Figure 10: Drawn representation of carotid tree, with plaque and IMT measurement according to Mannheim consensus: 1: thickness >1.5mm; 2: lumen encroaching > 0.5mm; 4: >50% of the surrounding IMT value. CCA: Common carotid artery; ECA: External carotid artery, ICA: Internal carotid artery; IMT: Intima-media thickness (40)

All measurements were performed after 3 hour fasting and an abstinence of caffeine. Subjects were studied under supine resting conditions in a quiet, temperature-controlled room (22-24°C).

Members of the study responsible for data collection will receive a special course to reduce inter- and intrapersonal variability of measurements.

cfPWV: measured with a surface tonometry probe that will capture pressure waves at the right common carotid artery and the right femoral artery. Each wave has a form and the "foot" of the wave is defined as the end of the diastole, when the steep rise of the wavefront begins. The time it takes the pulse wave to move from the carotid artery to the femoral artery is known as the delay time (Dt) as it is also the time delay from the "foot" of the wave at the carotid artery and the "foot" of the wave at the femoral artery.

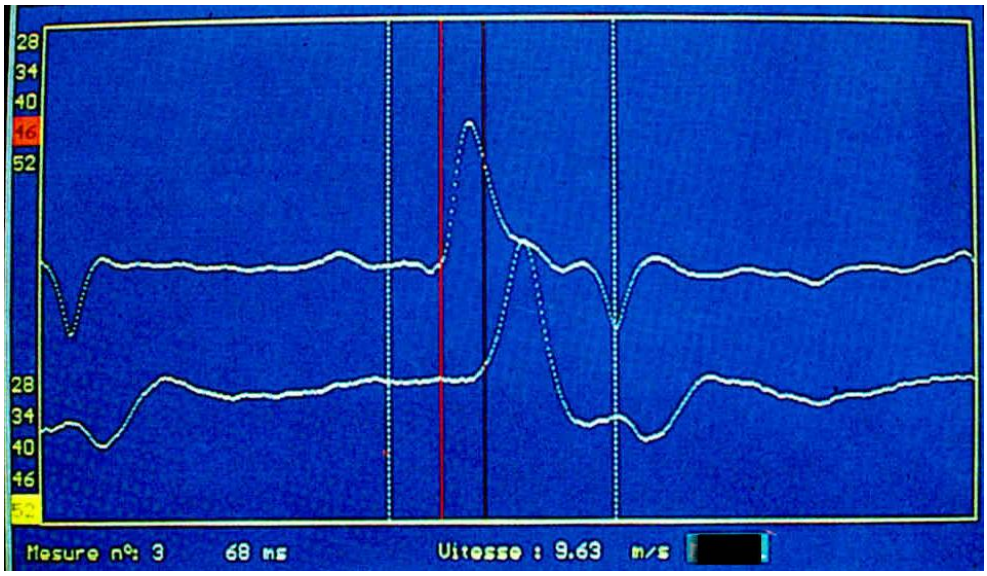

Figure 8: Carotid and femoral pulse waves. The red line represents the carotid "foot" and the black line represents the femoral "foot" (39)

cfPWV will be measured under *Compilor* system specifications that are already validated (47). The distance is measured in cm as the difference between the distance from the right femoral site and the sternal notch and the right carotid site and the sternal notch. At least 3 measurements will be made and will be repeated until the difference between cfPWV is less than 1m/s (47).

All measurements were performed after 3 hour fasting and an abstinence of caffeine. Subjects were studied under supine resting conditions in a quiet, temperature-controlled room (22-24°C)

Members of the study responsible for data collection will receive a special course to reduce inter- and intrapersonal variability of measurements.

ECG: 12 standard derivations

Pulse oximetry: (SaO2 <90% while resting will be considered chronic respiratory failure)

Blood and urine sample: Josep Trueta's laboratories and Sant Pau's laboratories will be responsible for analysing blood and urine samples using standard and validated methods.

-Complete blood count (Red blood cells, white blood cells and platelets)

-Total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides

- Glycaemia and glycated hemoglobin (HbA1c)

-Creatinine, Urea, GFR and microalbuminuria

-Ionogram (iodine, sodium, potassium, magnesium, calcium, chloride, iron and ferritin)

-Coagulation (Partial thromboplastin time, prothrombin time and fibrinogen)

- Human chorionic gonadotropin: To evaluate pregnancy

Blood pressure: OMRON 705 CP and OMRON 705 IT monitors will be used as blood pressure monitors.

24 hour ambulatory blood pressure monitoring: SPACELABS 90207 devices will be used and a night time systolic BP≥120 and/or a night time diastolic BP≥70 will be considered nocturnal hypertension according to the European Society of Hypertension and the European Society of Cardiology (48,49).

7.6 Study procedure

All patients diagnosed with mild to moderate OSA (AHI: 5-29.9) will be invited to join the study if they fulfil the inclusion criteria and none of the exclusion criteria. If they agree to join and after signing the informed consent the following tests will be programmed for them: (see Annex 5)

ABI

Carotid ultrasonography

cfPWV

Electrocardiogram (ECG): 12 standard derivations

Pulse oximetry

Blood and urine sample

24 hour ambulatory blood pressure monitoring

After all the tests are completed and analysed, the patients will be seen by a physician for a follow-up where the patient will receive an explanation of the test results. If the results indicate that the patient has CV disease, chronic pulmonary failure, nocturnal hypertension, a CV risk at ten years higher than 10% (using the REGICOR CV risk calculator), an ABI≥1.40 or is pregnant, they will be excluded from the study and referred to the corresponding physician.

After that the patient will receive a yearly follow-up for 10 years. The physician that is responsible for the follow-up will not know the ABI, cfPWV or carotid ultrasonography results.

During the follow-up period the following items will be checked: (see Annex 5)

-CV disease

-Mortality

-Physical exploration

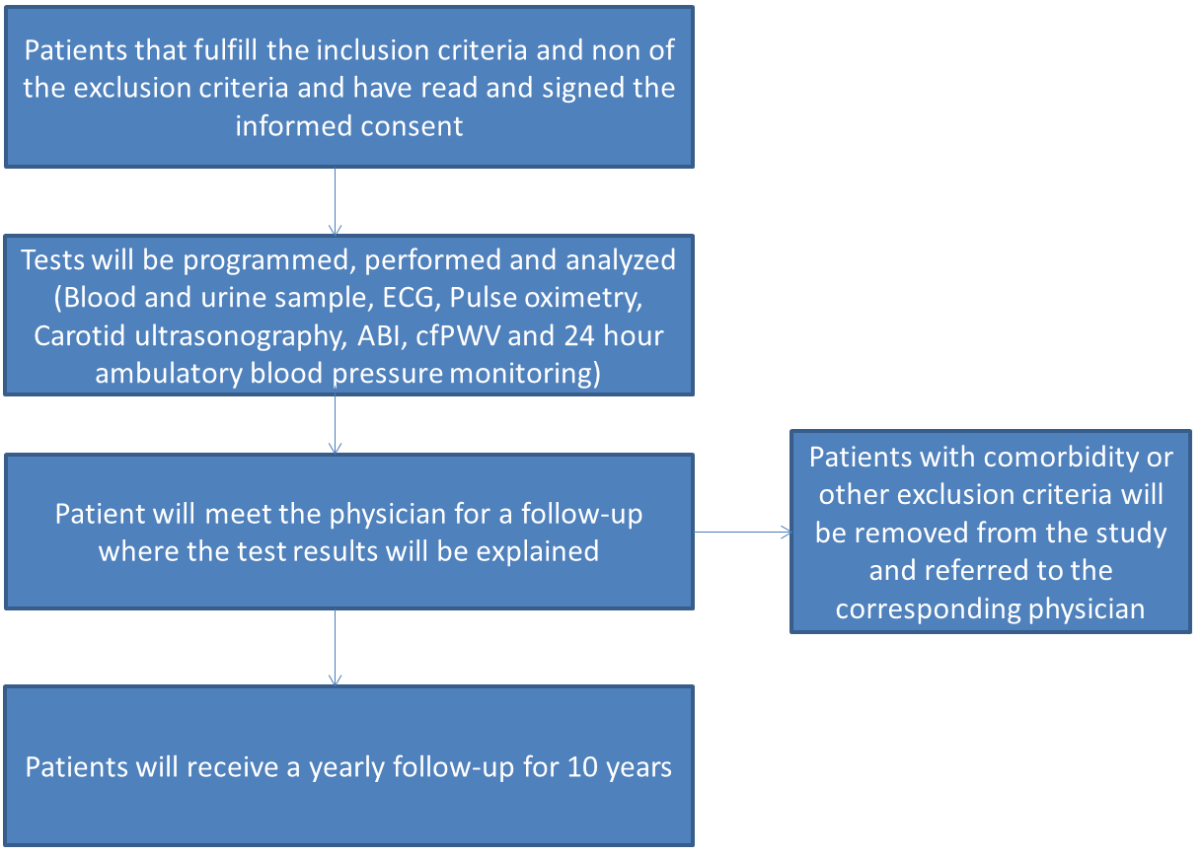

Figure 11: Study procedure summary ABI: Ankle-brachial index, cfPWV: carotid femoral pulse wave velocity, ECG: Electrocardiogram

7.7 Feasibility, schedule and chronogram

This study is expected to last around 13 years. All the staff and material needed to carry out this project are available at the Joan Trueta Hospital of Girona and the Sant Pau Hospital of Barcelona. All the activities carried out during this period of time will be organized into 4 stages that are detailed bellow.

Stage 1: Preparation, coordination and formation (September 2017-April 2018)

This 1st phase of the study will consist in:

- Elaboration of the protocol.

- Coordination and formation of the research team.

- Protocol evaluation and its approval by the Ethics Committee.

The entire team participating will meet between March 2017 and April 2018 in order to specify which will be the tasks of every member of the team. During this period, specific training will be given to ensure a homogenous assessment and treatment of the patients and a standardized data collection.

On April 2018, the protocol will be presented to the Ethical Committee for its evaluation and approval.

Stage 2: Participant inclusion, evaluation and data collection (May 2018-May 2030)

The data collection will be carried out during 12 years, between May 2018 and May 2030.

Patient recruitment and evaluation will be carried out by the co-investigators during 2 years, between May 2018 and May 2020.

Patients who are diagnosed with mild to moderate OSA (AHI:5-29.9) during this period at our centers who fulfill the inclusion criteria and none of the exclusion criteria will be offered to enter the study. They will be included after reading and signing the informed consent (see Annex 3).

During this period patients will be recruited, evaluated and put into the “exposed” or “not exposed” groups.

Patient follow-up will be carried out by the pneumologist expertized in sleep medicine between May 2018 and May 2030.

During this period patients will receive a yearly follow-up with their attending pneumologist expertized in sleep medicine.

Stage 3: Data analysis (May 2022-September 2030)

Intermediate analysis will be performed by the expert statistician during May 2022 until August 2022 and May 2026 until August 2026.

Once all the data is collected and entered into the SPSS software, the expert statistician will analyze it from June 2030 until September 2030.

Stage 4: Interpretation and publication of results (August 2030-April 2031)

The main investigator will interpret the results, communicate them to the rest of the research team and write the conclusions in the corresponding article. After this, the study must be published and disseminated. This is planned to happen between August 2030 and April 2031

As the study is longitudinal and will last about 12 years, the researchers will meet half way through the data collection period (May 2019), at the end of the data collection period (May 2020), half way through the follow-up period (August 2026), at the end of the follow-up period (May 2030), after data analysis (August 2030) and after result interpretation (November 2030). The objective of these meetings is to identify deficiencies in the study and to correct methodological errors.

Members of the team:

Study coordinator: Responsible for overseeing the study (according to the study protocol) and coordination and formation of the research team

Main investigator: Responsible for, elaboration of the protocol, overseeing the study (according to the study protocol), coordination and formation of the research team, results interpretation, writing of the conclusions and results publication and dissemination.

Co-investigators:

- **Pneumologist expertized in sleep medicine (P)**: Responsible for analyzing the PSG, analyzing the ECG, patient inclusion, explanation of the test results and patient follow-up.
- **Nephrologist**: Responsible for performing and analyzing the carotid ultrasound, the cfPWV, the ABI and the 24 hour ambulatory blood pressure monitoring.
- **Nursing staff**: Responsible for performing the PSG, performing the ECG, obtaining blood and urine sample and obtaining patient BP, weight and height.

Expert statistician: Responsible for the statistical analysis of the study.

Tasks	Personnel	2017	2018			2019		2020		2021	2022	2023	2024	2025	2026	2027	2028	2029	2030			2031
		Sep-Dec	Jan-March	March-April	May-Dec	Jan-May	April-Dec	Jan-May	April-Dec	Jan-Dec	Jan-Dec	Jan-Dec	Jan-Dec	Jan-Dec	Jan-Dec	Jan-Dec	Jan-Dec	Jan-Dec	Jan-May	June-Sep	Aug-Dec	Jan-April
1 Preparation, coordination and formation																						
Elaboration of the protocol	Main investigator																					
Coordination and formation of the research team	Main investigator and Study coordinator																					
Protocol evaluation and its approval by the Ethics Committee	Main investigator and Ethics Committee																					
2 Participant inclusion, evaluation and data collection																						
Participant recruitment and evaluation period	Co-investigators																					
Data collecting period	P																					
3 Data analysis																						
Intermediate analysis	Expert statistician										May-Aug				May-Aug							
Final analysis	Expert statistician																					
4 Interpretation and publication of results																						
Interpreta-tion and publication of results	All investigators																					

8. Statistical analyses

Statistical analysis will be performed using Statistical Package for Social Sciences (SPSS) software:

8.1 Univariate analysis

In the univariate analysis, variables will be defined as qualitative (categorical) or quantitative variables:

- For qualitative variables, the results will be expressed in percentages, proportions or frequencies
- For quantitative variables, being either continuous or discrete, we will determine if they follow a normal distribution or not by using a histogram. We will use mean ± standard derivation (when they follow a symmetric distribution) or median and interquartile range (when they follow an asymmetric distribution).

8.2 Bivariate analysis

Comparison of variables between the 2 groups ("exposed": ABI≤0.9 and "not exposed": ABI>0.9) will be carried out using Student-t test (for quantitative variables with a symmetric distribution), Mann-Whitney U (for quantitative variables with an asymmetric distribution) and Chi-square (for categorical variables).

If multiple bivariate tests are done, Bonferroni correction will be used to adjust *p*-value.

Specifically we will contrast if there are differences between "exposed" and "not-exposed" at baseline

To measure the association between the independent variable and the dependent ones a Chi-square will be used as the dependent variables are qualitative.

8.3 Multivariate analysis

A multivariate analysis will be performed to adjust for the covariables, trying to avoid potential confounders that could modify the results and for variables that were different at baseline

To analyze the relationship among the independent variable and the dependent ones and to adjust the effect by potential, a multivariate regression logistic model will be used to estimate odds ratio and 95% confidence intervals.

A *p*-value <0.05 will be considered statistically significant.

A Cox model, with the same covariables as above, will be used to estimate the incidence rate of CV disease and death from all causes.

9. Ethical considerations

All patients in this study will receive treatment and follow-up according to the most recent clinical guidelines of OSA. The extra measurements that the patients will receive are non-invasive and do not mean a risk or discomfort for the patient.

The present study will be conducted according to the requirements expressed in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects* signed by the World Medical Association in 1964 and last revised in October 2013.

A patient will not enter the study until he/she has been properly informed, has been given time to contemplate participation and has freely given his/her consent by reading and signing the informed consent (see Annex 3). This will be done prior to performing any study related procedures. Patient autonomy will be respected, not only before entering the trial, but at all times.

Approval of the protocol before its implication will be done by the Committee for Ethics and Clinical Research at the Catalan Health Institute.

Patient data anonymity will be guaranteed to preserve patient confidentiality. Patient anonymity and rights will be based on the Organic Law 15/1999 of the 13th of December on the Protection of Data, the Basic Law 41/2002 on the autonomy of the patient and rights and obligations with regard to clinical information and documentation and the Royale Decree 1090/2015, of the 24th of July, on Biomedical Research.

The patient's confidentiality will be preserved using codes to identify the patient instead of their names. Only the principal investigator, study coordinator and physicians will know the relation between the inclusion codes and the patient's name.

All investigators of this study will have to declare conflict of interest if they exist

10. Limitations and strengths

10.1 Limitations

-Intrinsic limitations related with the design of the study, although we believe that a prospective cohort is the best choice for our objectives.

-Selection bias due to consecutive sampling method; not all the general population use the public health system as a first choice and not all patients with undiagnosed OSA will be referred to a sleep specialist. However this bias is limited as 90% of the population goes to the doctor once at least every 2 years. As for undiagnosed OSA patients, recently programs have been implemented to increase OSA diagnosis and referrals in primary health care centers, such as the use of the STOP-BANG questionnaire for OSA screening (50).

-Withdrawal and losses during the follow-up can cause a selection bias. They will be registered. To avoid this bias the sample size has been calculated with expectations of future losses and withdrawals.

-The impossibility to randomize the patients of the study. We have tried to minimalize the effects of possible confounding bias by defining the plausible confounding factors described in the literature as covariables, using some of them as exclusion criteria and with the use of multivariate logistic regression analyses.

-Inter- and intraobserver differences in the measurement of independent variables. For this reason the observers will receive a training course, calibration of devices will be checked, semi-automatic measurement will be used when possible (cIMT) and all measurents will be obtained following current guidelines.

-We won't control for diet or exercise in our patients, these could be confounding factors but due to not being able to measure them precisely we decided that we wouldn't collect this information. We have controlled for weight and BMI which are more objective variables of diet and exercise outcome. We also recommend a balanced diet and physical activity to all patients included in the study.

-Due to the multicenter character, the laboratory determinations may be different. Both laboratories will use standard and validated methods to try to reduce this inter-center variability.

-Patients with early signs of atherosclerosis (ABI and/or carotid ultrasonography) or arterial stiffness (cfPWV) will be informed that current literature indicates that they are at a higher risk of CV disease and death. This could provoke healthy lifestyle changes that could act as an information bias, however, not informing the patient would be unethical.

-This cohort study, as well as the majority of long term cohort studies has a high cost to execute. We believe that this cost is justified by the benefits that this study can bring to scientific knowledge and day to day clinical practice.

10.2 Strengths

-Physicians doing the follow-up don't know the patients ABI, cfPWV or carotid ultrasonography result and therefore can't be influenced by this knowledge.

-Due to the strengths of the cohort design, this study will provide strong evidence on the causal association between vascular biomarker and CV disease in our study population.

-Known confounding factors will be controlled for using exclusion criteria and multivariate analysis.

11. Impact on the health system

This study is intended to discover if vascular markers, especially ABI, can identify patients with mild to moderate OSA, an ESS<10 and no comorbidities that have a high risk of CV disease. These are patients, according to the most recent guidelines, wouldn't receive CPAP treatment but could possibly benefit from it (1–3,28).

OSA has a significant economic impact of the healthcare systems and society. OSA-related healthcare costs include the direct costs of OSA diagnosis and treatment and the indirect cost of associated conditions (obesity, diabetes, CV disease, depression). Studies have proven that mean annual medical costs for OSA patients are significantly greater ($2720) than matched controls without OSA ($1384) (51). OSA is associated with decreased QOL, significant neurocognitive impairment, increased risk of road traffic accidents and CV comorbidity (4).

CPAP treatment is currently the 1st line treatment in OSA and has been proven to improve daytime sleepiness, QOL, snoring, arousals, sleeps architecture and daytime cognitive function. It has also been proven to reduce traffic accidents, blood pressure and CV risk (1,2,7,11–13).

If this study proves that vascular markers, especially ABI, can identify these patients with a high CV risk, they can benefit from a stricter follow-up process and possibly from earlier treatment (a clinical trial would be necessary to prove if CPAP therapy is effective in this population at reducing CV disease incidence).

ABI is a vascular marker that is cheap and easy to implement. It could be performed by the sleep department after diagnosis or even in primary health care centers.

12. Budget

The budget includes all the possible expenses that will be needed to realize the study. Material used in daily clinical practice for OSA patients and follow-up visits carried out in centers attached to the study are not considered additional costs of the study as they are part of normal clinical practice.

The study will require a statistician who will be hired for 250 hours and will be paid 40€/hour with a total cost of 10.000€.

Due to the multicenter nature of the study, the long period of time it will take and the amount of patients that will be included the study will require a study coordinator working part-time for 12 years who will be paid 10.000€/year with a total cost of 120.000€.

Due to the fact that half of the patients diagnosed with OSA will already have a PSG performed only half the sample (545 patients) will need a PSG that wouldn't be part of normal clinical practice.

ABI, carotid ultrasound, cfPWV and 24h ambulatory blood pressure monitoring are all included in the same price as it as inclusive service that the nephrology department offers.

The research team will assume the tasks related to patient recruitment, data collection and interpretation of results as part of their normal activities.

ITEM	PRICE PER UNIT	NUMBER OF UNITS	TOTAL
PERSONNEL COSTS			
Statistician	40€/h	250h	40€/h x 250h = 10.000€
Study coordinator	10.000€/year (part-time)	12 years	10.000€/year x 12 years= 120.000€
Personnel formation			1.000 €
			Subtotal: 131.000 €
MATERIAL COSTS			
ABI Carotid ultrasound cfPWV 24h ambulatory blood pressure monitoring	100 €	1.080	108.000 €
ECG	18 €	1.080	19.440 €
Pregnancy test	7 €	545	3.815 €
PSG	500 €	545	272.500 €
Information sheet and informed consent printing	0,30 €	1.080	324 €
Case Report forms printings	0,10 €	1.080 x 10 =10.800	1.080 €
			Subtotal: 405.159 €
MEETING EXPENSES			
Coordination meetings	400 €	6	400€ x 6 = 2.400€
PUBLICATION AND DISSEMINATION COSTS			
Cost of publication			2.000€
National congress			1.500€
			Subtotal 3.500 €
			TOTAL = 542.059 €

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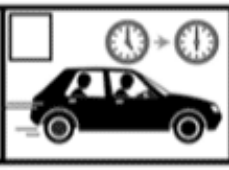
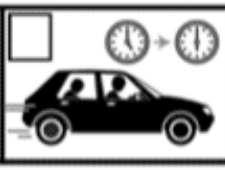
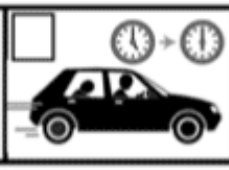
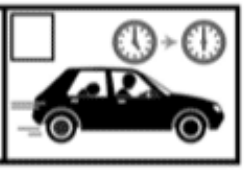
Annexes

Annex 1: Epworth Sleepiness Scale

Name: _____ Date: ___/___/___ Hospital No: _____ Date of Birth: ___/___/___

In contrast to just feeling tired, how likely are you to doze off or fall asleep in the following situations? Even if you have not done some of these things recently, try to work out how they would affect you.

Use the following scale to choose the most appropriate number for each situation.

Situation ☑ *Please tick box*	0 No chance of dozing	1 Slight chance	2 Moderate chance	3 Definitely would doze
Sitting and reading	☐ 	☐ 	☐ 	☐ 
Watching TV	☐ 	☐ 	☐ 	☐ 
Sitting inactive in a public place (e.g. Theatre or a meeting)	☐ 	☐ 	☐ 	☐ 
As a passenger in a car for an hour without a break	☐ 	☐ 	☐ 	☐ 
Lying down to rest in the afternoon when circumstances permit	☐ 	☐ 	☐ 	☐ 
Sitting and talking to someone	☐ 	☐ 	☐ 	☐ 
Sitting quietly after lunch without alcohol	☐ 	☐ 	☐ 	☐ 
In a car, while stopped for a few minutes in traffic	☐ 	☐ 	☐ 	☐ 

Epworth sleepiness scale (8)

Annex 2: Sleep hygiene recommendations

Institut Català de la Salut

CONSELLS HIGIENE DE SON

És molt IMPORTANT que segueixi els consells següents, per CONTROLAR (disminuir o eliminar) la SÍNDROME D'APNEES DEL SON i també per millorar el ronc i la qualitat del seu son.

- DORMIR LES HORES QUE FACIN FALTA. La majoria de persones necessiten de 7 a 9 hores de son, inclòs quan ens fem grans. Dormir poques hores empitjoren les apnees i el ronc.
- HA DE TENIR UN HORARI REGULAR DE DORMIR. No és aconsellable anar a dormir molt aviat o tard, com tampoc aixecar-se aviat o tard del llit.
  Cal mantenir un horari de son regular tots els dies de la setmana, de dilluns a diumenge.
- EL LLIT ÉS PER DORMIR. Si no pot dormir, aixequis i faci altres activitats fins que tingui son. NO es posi al llit si no és per dormir.
- DORMIR AMB POSTURA LATERAL. Dormir de cara enlaire empitjora les apnees i el ronc.
- DISMINUIR EL PES I NO ENGREIXAR-SE. Les apnees del son i el ronc són més freqüents a les persones obeses i amb excés de pes. Si controla bé el seu pes podrà trobar una millora considerable.
- NO PRENDRE HIPNÒTICS I/O TRANQUILITZANTS. Aquesta medicació relaxa els teixits de les vies respiratòries superiors i empitjora les apnees del son i el ronc.
- NO PRENDRE ALCOHOL. Les begudes alcohòliques empitjoren el dormir i augmenten les apnees i el ronc, principalment si es prenen a la tarda-nit.
- EVITAR BEGUDES ESTIMULANTS (cafè, té begudes de cola, xocolata). Aquestes begudes alteren el son principalment a les hores properes d'anar a dormir.
- NO FUMAR. El tabac irrita els teixits de les vies respiratòries superiors i pot afectar la respiració i augmentar la intensitat del ronc. La nicotina també altera la qualitat del son.

Ha de recordar que són moltes les coses que pot fer per aconseguir un bon son... però seguint aquests consells pot aconseguir una millor qualitat de vida i millorar les seves apnees durant el son que us comporta un empitjorament de la salut.

Annex 3: Informed consent

FULL INFORMACIÓ:

Ens dirigim a vostè per informar-lo sobre la realització d'un estudi d'investigació en el que se'l convida a participar. El present estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC), d'acord amb la legislació vigent, *Real Decret 1090/2015, del desembre,* sobre la investigació biomèdica.

La nostre intenció és que vostè rebi la informació de manera correcta i que aquesta sigui suficient per tal que pugui decidir si vol participar o no en aquest estudi. Per aquest motiu, li agrairíem que llegeixi atentament aquest full informatiu i posteriorment nosaltres li aclarirem els dubtes que li puguin sorgir.

Primerament ha de saber que la participació en aquest estudi és de forma completament voluntària. Si decideix participar en l'estudi ha de saber que podrà abandonar-lo en qualsevol moment sense que això suposi una alteració de la relació amb el seu metge/metgessa ni es produeixi cap perjudici en el seu tractament.

-Títol de l'estudi: Marcadors vasculars en pacients diagnosticats amb Síndrome de Apnea Obstructiva del Son (SAOS) lleu a moderat: un estudi de cohorts

-Lloc de realització: Unitats de son del Hospital Universitari Joan Trueta de Girona i Hospital de la Santa Creu i Sant Pau de Barcelona

-Finalitat: Avaluar la capacitat dels marcadors vasculars per identificar pacients diagnosticats amb SAOS lleu a moderat amb un alt risc cardiovascular (CV)

-Beneficis pel pacient: La realització d'aquest estudi comportarà un millor coneixement de la SAOS, cosa que es traduirà en una possible millora en el maneig d'aquests pacients. Durant l'estudi, el pacient serà controlat de manera continua amb els mètodes que estan més ben relacionats amb la mortalitat i el control de la SAOS.

-Riscos associats: El pacient seguirà el protocol de la SEPAR, sense estar exposat a cap risc

-Extensió i duració: El pacient rebrà un seguiment anual durant 5 anys

-Per què fem aquest estudi? Alguns pacients amb SAOS lleu a moderat tenen un risc CV més elevat que podria merèixer tractament però ara mateix no tenim cap forma de identificar a aquests pacients. El nostre objectiu es observar si els marcadors vascular són útils per identificar aquests pacients.

-Per què hem pensat en incloure'l en aquest estudi? El seu metge ha detectat que pateix una malaltia anomenada SAOS. Al ser un pacient lleu-moderat poc simptomàtic, vostè seria un candidat idoni ja que compleix tots els criteris de inclusió i cap d'exclusió establerts per l'estudi.

-Que li demanem que faci? La seva participació en l'estudi és totalment voluntària. Li demanem que assisteixi als controls que es faran cada any i que es faci les probes que seran sol·licitades per el teu metge per conèixer millor la teva patologia. Al tenir els resultats de les proves els rebrà explicats per el seu metge.

-Com es protegeix la seva intimitat, autonomia i drets inherents? Aquest estudi segueix les lleis actuals de l'Estat en referència a la Investigació: Llei orgànica 15/1999 de Protecció de Dades, la Llei 41/2002 bàsica reguladora de l'autonomia del pacient i de drets i obligacions en matèria d'informació i documentació clínica, i el Real Decret 1090/2015 d'investigació biomèdica.

Vostè té el dret de revocar el consentiment en qualsevol moment, sense perjudici en el seu tractament mèdic, a decidir el destí de les seves mostres i dades personals en cas de decidir-se retirar-se de l'estudi.

Aquest estudi ha estat aprovat pel CEIC de l'Institut d'Assistència Sanitària. Tan si finalitza l'estudi com si no, les seves dades seran confidencials i se li garanteix que el seu nom no sortirà a cap publicació o informe relatiu a l'estudi. Les seves dades seran anonimitzades, utilitzats codis per identificar-lo en comptes del seu nom. La relació entre la seva identitat només serà coneguda per l'investigador principal i el metge assistencial.

CONSENTIMENT INFORMAT PER ESCRIT:

Per tal de dur a terme aquest projecte i d'acord amb les normatives legals vigent, li demanem la seva autorització. Pot realitzar les preguntes que cregui convenients al personal sanitari responsable. Així com, quedar-se una còpia del present document.

Títol de l'estudi: Marcadors vasculars en pacients diagnosticats amb Síndrome de Apnea Obstructiva del Son (SAOS) lleu a moderat: un estudi de cohorts

Centre:

Dades del participant/pacient:

Persona que proporciona la informació i el full de consentiment:

Jo.....,

(nom i cognom del pacient escrits per ell)

Dono el meu ple consentiment, de manera lliure, per participar en aquest estudi. He llegit el full informatiu sobre el projecte. He rebut suficient informació sobre l'estudi i he entès que aquest treball és una contribució als coneixements mèdics. Sé que puc retirar el meu consentiment en qualsevol fase del procediment.

Estic d'acord en què s'utilitzin les meves dades per l'estudi indicat i els possibles estudis que en deriven d'ell.

Dono el meu permís perquè les dades de la meva història clínica siguin utilitzades per l'equip d'investigació per fins relacionats amb aquest estudi, entenent que després de la seva comprovació s'eliminarà del registre tota la informació que em pogués identificar.

Se m'ha entregat una còpia del Full d'Informació pel Pacient i una còpia d'aquest Consentiment Informat, datat i firmat.

Se m'han explicat les característiques i l'objectiu de l'estudi i els possibles beneficis i riscos del mateix.

Se m'ha donat temps i oportunitat per realitzar preguntes. Totes les preguntes van estar respostes a la meva sencera satisfacció.

Sé que es mantindrà la confidencialitat de les meves dades.

El consentiment l'atorgo de manera voluntària i sé que sóc lliure de retirar-me de l'estudi en qualsevol moment del mateix, per qualsevol raó sense que això tingui cap efecte sobre el meu tractament mèdic futur.

_____	_____	_____
(Data)	(Nom i cognoms del participant)	(Firma del participant)

Confirmo que he explicat al pacient el caràcter i el propòsit de l'estudi.

.....(Firma d'un membre equip del projecte)

REVOCACIÓ DEL CONSENTIMENT INFORMAT:

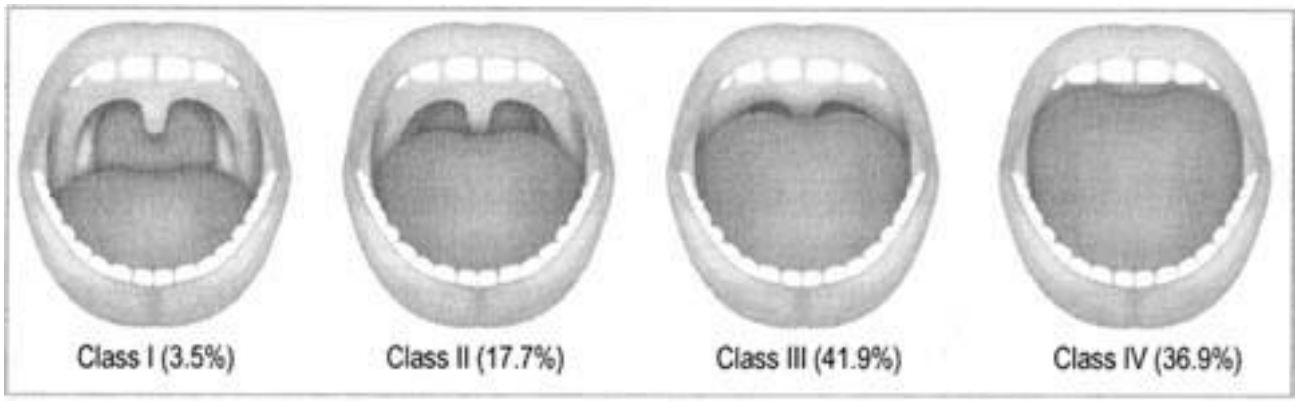
Jo,....., revoco el consentiment informat signat per la participació en l'estudi especificat a dalt.

, _____, , _____,

(Signatura del pacient) (Signatura de l'investigador)

Lloc i data: ..... , ... de ..... del 20.....

Annex 4: Modified Mallampati score



Modified Mallampati classification ranging from class I to class IV, including the percentage of patients in each class (46)

Annex 5: 1st visit and follow-up visit forms

1st visit form

Data d'inclusió a l'estudi: .....

Dades de filiació: .....

Història: .....

Centre/Hospital: .....

Nom: .....

Cognom1: .....

Cognom2: .....

Codi d'estudi: .....

Adreça: .....

Sexe (0=home, 1=dona) .....

Data naixement: .....

Factors de risc cardiovasculars:

- Tabaquisme (0=No, 1=Si) .....
- Dislipèmia (0=No, 1=SI) .....
- Diabetes Mellitus (0=No, 1=Si) .....
- Hàbit Enòlic (0=No, 1=Si; >14 unitat de beguda estàndard en dones i >21 unitat de beguda estàndard en homes) .....

Malaita cardiovascular clínica:

- Cardiopatia isquèmica (0=No, 1=Si) .....
- Insuficiència cardíaca (0=No, 1=Si) .....
- Ictus (0=No, 1=Si) .....
- Accident isquèmic transitori (0=No, 1=Si) .....
- Arteriopatia perifèrica simptomàtica (0=No, 1=Si) .....
- Fibril·lació auricular (0=No, 1=Si) .....
- Altres malalties cardiovasculars (Especificar diagnòstic) .....

Exploració Física

- Talla actual (cm) .....
- Pes actual (Kg) .....
- Índex de massa corporal (Kg/m^2) .....
- Escala de Mallampati (I, II, III o IV) .....
- Diàmetre de coll (cm) .....
- Pressió arterial sistòlica (mmHg) .....
- Pressió arterial diastòlica (mmHg) .....
- Pulsioxímetre (SaO2 en %) .....

Analítica:

- HDL colesterol (mg/dl) .....
- LDL colesterol (mg/dl) .....
- Colesterol total (mg/dl) .....
- Triglicèrids (mg/dl) .....
- Glucosa basal (mg/dl) .....
- HbA1c (%) .....
- Taxa de filtració glomerular (ml/min/1.73 m^2) .....

Símptomes relacionats amb SAOS:

- Excessiva somnolència diürna (Escala d'Epworth) .....
- Horari de son (hora de dormir) .....
- Horari de son (hora de despertar) .....
- Mitjana de hores de son (hores) .....
- Minuts de migdiada (Minuts) .....
- Roncs (0=No, 1=SI) .....
- Nictúria (0=No, 1=Si) .....
- Nictúria si present (mitjana per nit) .....
- Apnees presenciades (0=No, 1=Si) .....
- Sequedat de boca (0=No, 1=Si) .....

Gravetat del SAOS (0=Lleu, IAH: 5-14.9/h; 1=Moderat, IAH:15-29.9/h) .....

Índex turmell-braç (ITB) (0=Normal, 1=Anormal) .....

ITB Normal: 0.91-1.39 ITB Anormal: ≤0,9

Velocitat de l'ona de pols (0=Normal, 1=Anormal) .....

Normal: <10m/s Anormal: ≥10m/s

Ecografia de troncs supraaortics (0=Normal, 1=Anormal) .....

Segons el consens de Mannheim

Monitorització ambulatòria de pressió arterial de 24h (0=Normal, 1=Hipertensió nocturna) .....

Segons la Societat Europea de Hipertensió i la Societat Europea de Cardiologia

Electrocardiograma (0=Normal, 1=Alterat) .....

Follow-up form

Data de la visita de seguiment .....

Mortalitat (0=No, 1=Si) .....

Data de mort .....

Causa de la mort (0=No cardiovascular, 1=Cardiovascular, 2=Mort sobtada) .....

Mort cardiovascular (0=Cardiopatia isquèmica, 1=Insuficiència cardíaca, 2=Accident vascular cerebral, 3=altres) .....

Anamnesi

- Cardiopatia isquèmica (0=No, 1=Si) .....
- Insuficiència cardíaca (0=No, 1=Si) .....
- Ictus (0=No, 1=Si) .....
- Accident isquèmic transitori (0=No, 1=Si) .....
- Arteriopatia perifèrica simptomàtica (0=No, 1=Si) .....
- Fibril·lació auricular (0=No, 1=Si) .....
- Altres malalties cardiovasculars (Especificar diagnòstic) .....

Exploració física

- Talla actual (cm) .....
- Pes actual (Kg) .....
- Índex de massa corporal (Kg/m^2) .....
- Escala de Mallampati (I, II, III o IV) .....
- Diàmetre de coll (cm) .....
- Pressió arterial sistòlica (mmHg) .....
- Pressió arterial diastòlica (mmHg) .....
- Auscultació cardiorespirartòria (0=Normal, 1=Alterada) .....
- Polsos perifèrics (0=Normal, 1=Alterada) .....