Trial Designs

Rationale and Methodology of the Impact of Continuous Positive Airway Pressure on Patients With ACS and Nonsleepy OSA: The ISAACC Trial

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is common in acute coronary syndrome (ACS) and a possible cause of increased morbidity and mortality.

Objectives: The main objective is to determine in patients with ACS and OSA if CPAP treatment reduces the incidence of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, and hospitalization for unstable angina or transient ischemic attack). The secondary objectives are to determine the prevalence of nonsleepy OSA in patients with ACS; assess the effect of CPAP on the incidence of newly diagnosed diabetes mellitus, symptoms, and quality of life; identify biomarkers of risk involved in cardiovascular complications in these patients; and conduct a cost-effectiveness analysis of diagnosis and treatment.

Population and Methodology: Multicenter, prospective, randomized and controlled study. Patients are admitted to the coronary care unit with diagnosis of ACS and without daytime sleepiness (Epworth Sleepiness Scale $\leq$10) at 15 teaching hospitals in Spain. All patients undergo a sleep study by cardiorespiratory polygraphy. Patients with an apnea-hypopnea index $\geq$15/hour will be randomized to treatment with CPAP (group 1, 632 patients) or conservative treatment (group 2, 632 patients). Patients with an apnea-hypopnea index $<$15/hour (group 3, 600 patients) will be followed as a reference group. Patients will be monitored at baseline (T0), 1 month (T1), 3 months (T2), 6 months (T3), 12 months (T4), and every 6 months thereafter (where applicable) during the follow-up period.

Conclusions: The ISAACC trial will contribute to evaluating the effect of CPAP treatment on cardiovascular events in patients with ACS and OSA.

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Background

Obstructive Sleep Apnea and Acute Coronary Syndrome

Obstructive sleep apnea (OSA) is characterized by the presence of total or partial respiratory pauses (apneas or hypopneas, respectively) caused by the collapse of the upper airway during sleep. It is a common process that affects 2%–4% of the general population age 30–70 years and is characterized clinically by the presence of snoring, daytime sleepiness, and impaired quality of life.[1,2] Every apnea episode is accompanied by a decrease in arterial oxygen saturation

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that is rapidly normalized after subsequent ventilation (hypoxia-reoxygenation), sudden changes in intrapleural pressure, and increased sympathetic activity. Treatment for OSA involves the application of nasal pressure via continuous positive airway pressure (CPAP) during sleep. Continuous positive airway pressure is an effective treatment for obstructive respiratory events, as it corrects symptoms and improves the quality of life of patients with OSA.[3,4]

Acute coronary syndrome (ACS) affects 1% of the adult world population and is a major world cause of morbidity and mortality, as one-third of the world population dies from cardiovascular disease (CVD).[5] It is estimated that the prevalence of OSA in patients with ACS is higher than in the general population: 54%–69%.[6,7] However, the evaluation of respiratory disorders during sleep does not feature in guidelines for the diagnosis, treatment, and subsequent management of patients with ACS. It is reasonable to suggest that pathogenic alterations described in patients with OSA may have a deleterious effect on the evolution of a patient who has suffered from ACS. Repeated episodes of hypoxia-reoxygenation, increased sympathetic activity, and abrupt changes in intrathoracic pressure can adversely influence the progress of a patient who has suffered from ACS.[8] These changes can also activate several pathogenic pathways that promote atherogenesis, such as oxidative stress, endothelial dysfunction, hypercoagulability, and insulin resistance.[9] These physiological changes may explain the increased risk of CVD in patients with OSA.[10–13] Long-term observational studies show that OSA significantly increases the risk of cardiovascular (CV) events.[14] It is also accepted that patients with OSA have a higher risk of sudden death during sleep than people without OSA,[10,15,16] and that OSA is associated with poor prognosis of CVD.[17–19] A recent study in patients admitted for ACS showed that, after adjusting for various confounding variables, OSA is an independent predictor of the appearance of new CV events during hospitalization (hospital death, acute myocardial infarction [MI], or angina; odds ratio: 3.4, 95% confidence interval [CI]: 1.3-9.0, $P = 0.015$).[20]

Need for a Randomized Controlled Trial

Treatment with CPAP reverses obstructive apneas, avoids episodes of hypoxia-reoxygenation, prevents recurrent episodes of negative intrathoracic pressure, and reduces sympathetic activity and blood pressure.[21,22] Clinically, treatment with CPAP reverses excessive daytime sleepiness and improves patients' quality of life,[23] but the data on the impact of CPAP on vascular morbidity and mortality are largely based on observational studies.[24,25] Various studies have assessed the impact of CPAP on the incidence of hypertension and CV events in patients with OSA. A study by the Marin group showed that in men, OSA significantly increases the risk of CV events and death from this cause. This study also showed that CPAP reduces this risk, compared with patients not treated with CPAP (odds ratio: 0.35, $P = 0.008$).[14] Büchner et al reinforce these results and showed, in patients with moderate OSA, that CPAP treatment is an independent protective factor for CV events (hazard ratio: 0.36, 95% CI: 0.21-0.62, $P < 0.001$).[26] Along these lines, Barbé and colleagues recently published another study that included 725 patients without sleepiness (Epworth Sleepiness Scale [ESS] score $\leq$10) and found a lower incidence rate of hypertension and/or CV events in the group of OSA patients complying with CPAP (incidence density ratio: 0.69, 95% CI: 0.50–0.94, $P < 0.05$), compared with untreated OSA patients.[27]

There are currently insufficient data to support the use of CPAP treatment in the primary or secondary prevention of CVD.[28] The overall objective of our study is to evaluate the impact of sleep apnea and its treatment on the clinical course of patients with ACS. We hypothesize that ACS patients with sleep-disordered breathing have a worse prognosis than those without OSA, and that CPAP treatment improves the prognosis. Acceptance of this approach in clinical practice would require changes in coronary units, and the evaluation of night ventilation would become part of the routine explorations of ACS patients. In this article we describe the rationale and methodology of the study according to international guidelines.[29,30]

Main Objectives

The main objective of the study is to determine whether treatment with CPAP reduces the rate of new CV events (CV death, nonfatal MI, nonfatal stroke, hospitalization for heart failure, and hospitalization for unstable angina, transient ischemic attack [TIA], or revascularization procedures) in patients with ACS and OSA. The secondary objectives are to determine the prevalence of OSA (in nonsleepy patients) who have suffered an ACS episode; assess the effect of CPAP on the incidence of newly diagnosed diabetes mellitus (according to the usual standards), symptoms of OSA (ESS and the EuroQol EQ-5D Quality of Life test [EQ-5D]); identify biomarkers of risk related to CV complications in these patients; establish the relationship between CPAP compliance and the incidence of CV events; and conduct a cost-effectiveness analysis of diagnosis and treatment.

Methodology

This is a multicenter, open-label, parallel, prospective, randomized, controlled trial, which started in June 2011. The study will include patients consecutively admitted to each participating center's coronary care unit or cardiology hospitalization room with ACS during the period of the study. Acute coronary syndrome is defined as the acute presentation of coronary disease, with or without ST-elevation infarction (patients with a normal electrocardiogram [ECG] and ischemic symptoms but only a minor rise and fall in any biomarker will be included), unstable angina, or MI type 1.[31] The diagnosis of OSA will be based on the results of the sleep test, in accordance with the guidelines of the national consensus on the apnea-hypopnea syndrome.[32] Patients must meet the criteria for inclusion/exclusion (Table 1).

The estimated duration of the study is 3 years. It involves a total of 15 teaching hospitals in Spain, all with a sleep disorders unit and coronary care unit: Hospital Arnau de Vilanova (Lleida), Hospital Son Espases (Palma de Mallorca), Hospital Clínic (Barcelona), Hospital Germans Tries i Pujol (Barcelona), Hospital de Sant Pau (Barcelona), Txagorritxu Hospital (Vitoria), Hospital de Cruces (Bilbao),

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Table 1. Inclusion/Exclusion Criteria

Inclusion Criteria
Men and women age >18 years
Patients admitted for documented symptoms of ACS with or without T segment elevation and have an hospital stay between 48 h and 72 h in the moment to perfom polygraphy
Patients with an ESS score ≤10 (patients without excessive daytime sleepiness)
Signature of informed consent
Exclusion Criteria
Previous treatment with CPAP
Psychophysical inability to complete the questionnaires
Presence of any previously diagnosed sleep disorders: narcolepsy, insomnia, chronic sleep deprivation, regular use of hypnotics or sedative drugs, and restless legs syndrome
Patients with >50% of central apneas or the presence of Cheyne-Stokes respiration
Patients with chronic diseases: neoplasms, renal insufficiency (GFR <15 mL/min/1.73 m²), severe COPD (FEV1 <50%), chronic depression, and other limiting chronic diseases
A medical history that could interfere with the objectives of the study or could, in the opinion of the investigator, jeopardize the findings
Any medical, social, or geographical factor that could jeopardize patient compliance; for example, alcohol consumption (>80 g/d for men and >60 g/d in women), disorientation, or a history of noncompliance
Any process, whether cardiovascular or otherwise, that reduces life expectancy to <1 year
Patients in cardiogenic shock (unlikely to yield results in the short term)

Abbreviations: ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRP, cardiorespiratory polygraphy; ESS, Epworth Sleepiness Scale; FEV1, forced expiratory volume in 1 second; GFR, glomerular filtration rate; OSA, obstructive sleep apnea.

Hospital San Pedro de Alcántara (Cáceres), Hospital Parc Taulí (Barcelona), Hospital de Guadalajara (Guadalajara), Yague Hospital (Burgos), Hospital San Juan (Alicante), Hospital Central de Asturias (Oviedo), Hospital Joan XXIII (Tarragona), and Hospital of Albacete, all members of the Spanish Sleep Network. The trial is led by the coordinator center (Hospital Arnau de Vilanova, Lleida), which has overall responsibility for the design and the study follow-up.

During the patient's hospital stay, the degree of daytime sleepiness (ESS score) will be assessed in patients treated in the coronary care unit with a diagnosis of ACS. Patients without daytime sleepiness (ESS ≤10) who meet the other selection criteria (Table 1) will undergo a cardiorespiratory polygraphy[27,33] after staying between 24 and 72 hours in the hospital. The definitions and diagnosis of the subjects' other disorders will also be carried out according to standard guidelines. All the participating hospitals will use

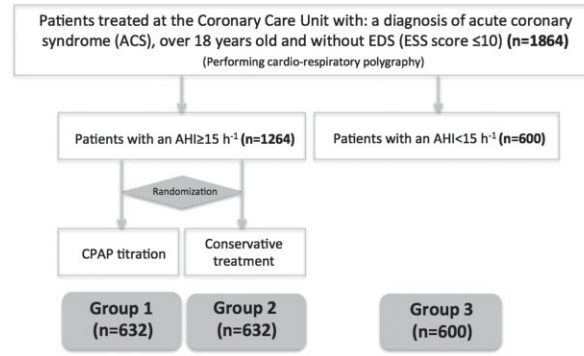

Figure 1. Study flow diagram.

the same model of polygraph (Embletta; ResMed, Spain). Oronasal flow, thoracoabdominal movements, ECG, and pulse oximetry will all be recorded. Apnea is defined by an absence of airflow lasting ≥10 seconds. Hypopnea is defined as a reduction in airflow lasting ≥10 seconds and is associated with oxygen desaturation. Oxygen desaturation is considered as a decrease in SaO_2 >4%. Apnea-hypopnea index (AHI) is defined as the number of apneas and hypopneas per hour of sleep. Excessive daytime sleepiness, as reported by the subject, will be defined as an ESS score >10, and no daytime sleepiness will be defined as an ESS score of ≤10. This distinction is important because, from an ethical viewpoint, a patient with OSA with an ESS score >10 should be treated with CPAP. The degree of self-reported sleepiness/drowsiness will be analyzed by the Spanish version of the ESS test.[34]

The study will consider 3 groups, with a total of 1864 patients, distributed as follows: patients with an AHI ≥15/hour will be randomized to treatment with CPAP (group 1, n = 632) or conservative treatment (group 2, n = 632); patients with an AHI <15/hour will be followed up according to the CV protocols and evaluated as a reference group (group 3, n = 600) (Figure 1). Patients with an ESS >10 will be excluded from the study and referred to the sleep unit of each participating center for evaluation. All participants will receive sleep-hygiene advice and dietary counseling for weight loss from the staff of the sleep units at each scheduled visit.

Randomization

The randomization in the ISAACC study will be carried out via an automated system available 24 hours a day, with totally secure access to the study Web site protected by password. The randomization will be stratified by center. Once a patient is included in the study, he or she will be registered and assigned to a randomly selected group (if he or she belongs to the group of patients with an AHI ≥15/hour).

As the frequency of patients with AHI <15/hour is higher than that of patients with AHI ≥15/hour and the rate of inclusion into the reference group must match that of the randomized patients, a probabilistic mechanism integrated into the Web site will select patients once the sleep-test results are known. Only patients selected by the Web site will be included in the study.

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Titration of Continuous Positive Airway Pressure

This will be conducted by means of automated equipment. It will follow the methodology described by our group.[35] After titration, patients will continue with fixed CPAP. This study group will also be instructed in the dietary-hygienic measures recommended for all patients.

Duration of Treatment

All the patients randomized to CPAP treatment will begin as soon as possible after randomization, and their treatment will continue on a daily basis for at least 1 year until the end of the study. Patients who interrupt the treatment will continue with their scheduled clinical visits so that their CV events during the follow-up period can be recorded.

Follow-up

All patients will be evaluated at baseline (T0), 1 month (T1), 3 months (T2), 6 months (T3), 12 months (T4), and every 6 months thereafter (where applicable) during the follow-up period (Table 2). The study will continue until all the patients have participated in it for at least 1 year. No relevant concomitant care or interventions will be prohibited during the trial.

Compliance

The aim of the visits at T1 and T2 is to facilitate adaptation and adherence to CPAP (group 1) and insist on dietary-hygienic modifications. All the collaborating centers have great experience in the management of CPAP treatment. All the patients will be given a phone number allowing them to contact the research team at any time. Telephone follow-up will be undertaken within 15 days of the start of treatment, and, if necessary, additional visits will be scheduled to try to immediately resolve any problems related to the adaptation to CPAP.

Study Variables

Sociodemographic and anthropometric variables will be recorded, along with those associated with the quality of

Table 2. Diagram of the Methodology at Each Visit

	Patient Inclusion (To)	1 Month (T1)	3 Months (T2)	6 Months (T3)	12 Months (T4)	From 18 to 36 Months (Each 6 Months)
Providing written consent to participate in the study	All groups					
Providing written consent for the storage of samples in the biobank	All groups					
CRP	All groups					
Assessment of sleepiness (ESS)	All groups	All groups	All groups	All groups	All groups	All groups
Randomization to treatment with CPAP or conservative	Groups 1 and 2					
Anthropometric and sociodemographic data collection	All groups				All groups	
BP measurement	All groups				All groups	
Performing specific questionnaires (EuroQol, HADS)	All groups				All groups	
Clinical follow-up		All groups	All groups	All groups	All groups	All groups
Monitoring and follow-up	All groups	All groups	All groups	All groups	All groups	All groups
Extraction, processing, and storage of blood samples	All groups				All groups	
Checking for compliance with CPAP treatment		Groups 1 and 2	Groups 1 and 2	Groups 1 and 2	Groups 1 and 2	Groups 1 and 2
Hemogram	All groups				All groups	
Coagulation fibrinolysis	All groups				All groups	
Basic biochemical profile	All groups				All groups	
Evaluation of markers of myocardial damage	All groups				All groups	
Evaluation of other specific biomarkers	All groups				All groups	

Abbreviations: BP, blood pressure; CPAP, continuous positive airway pressure; CRP, cardiorespiratory polygraphy; ESS, Epworth Sleepiness Scale; EuroQol, EuroQol EQ-5D Quality of Life Scale; HADS, Hospital Anxiety and Depression Scale.

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life (EuroQol EQ-5D) and degree of daytime sleepiness. The time of the day of the onset of ACS/MI symptoms will be recorded. The EQ-5D is a standardized instrument used to measure the quality of life, applicable to a wide range of health conditions and treatments; it provides a simple descriptive profile and a single index value for health status.

At baseline and after 1-year follow-up, blood samples will be obtained in fasting. These samples will be processed and sent to the Hospital Son Espases for the analysis of biomarkers related to CV function: markers of endothelial dysfunction, platelet activation, fibrinolytic system markers, markers of hemodynamic dysfunction, oxidative stress markers (isoprostanes), markers of inflammation (C-reactive protein, interleukin-6, interleukin-8, adiponectin), and markers of bone metabolism (vitamin D, intact parathyroid hormone) and antioxidant vitamins (A, E, and C). Aliquots of serum and plasma from patient blood samples will be immediately processed and stored at $-80\,^{\circ}C$ prior to dispatch to the Hospital Son Espases. Additional biochemical biomarkers will be analyzed individually in each participant center.

Patients treated with CPAP will be monitored for compliance. The degree of compliance will be determined by dividing the number of hours of use (obtained from the internal clock of the CPAP device) by the number of days of treatment. Compliance is defined as CPAP use $\geq$4 hours/day.

Main dependent variables: Each follow-up visit will also include assessments of CV events, such as CV death, nonfatal MI, nonfatal stroke, and hospitalization for heart failure (with reduced or preserved ejection fraction) or unstable angina, TIA, or revascularization procedures. Hospitalization for heart failure is defined as hospital or emergency admission for the administration of intravenous diuretics and/or use of inotropes, for an acute illness with dyspnea and/or evidence of heart enlargement and/or pulmonary interstitial changes compatible with pulmonary edema.

All these events must be reported and documented via records provided by the patient or derived from the center's own records. Secondary dependent variables are biological risk markers implicated in CV complications, symptoms and quality of life, and the cost-effectiveness of the diagnosis and treatment with CPAP.

Criteria for Discontinuation

The follow-up for the main outcome will be terminated whenever a patient experiences a new CV event, withdraws informed consent, is unable to complete the follow-up, or moves from the conservative group to CPAP treatment. Exposure time was defined as the time between randomization and the first CV event, date of death, date of the last study visit, date of withdrawal, or loss to follow-up.

Data Collection and Analysis

The coordinating center (Hospital Arnau de Vilanova, Lleida) will prepare guidelines to standardize procedures in the protocol for all questionnaires and data collection and explain how to implement them. The center will provide instructions for entering data onto a database on a specific Web domain, taking into account the legal requirements for data protection. Informed consent will be obtained by the collaborating investigators. All the forms and questionnaires collected from patients will be processed in accordance with properly validated methods. The project will be completed by a cost study designed to quantify the costs of each process in each patient group according to the different results. The costs will be calculated on the basis of the direct cost of the data extracted from the medical records of each participating center. A cost-effectiveness study will also be developed, including an estimate of the quality-adjusted life-years gained. An external data safety monitoring committee will review the quality of the recorded data in each center. A blinded clinical events committee (CEC), comprising 3 external staff from the Hospital Arnau de Vilanova in Lleida, the Hospital Clínic in Barcelona, and the Hospital Son Espases in Palma de Mallorca, will assess the study's outcomes (CV events). All the reported primary and secondary outcomes will be centrally reviewed by the CEC, which will obtain data on the ECG and enzymatic changes and confirm any episode that meets all the diagnostic criteria for such an event. In case of doubt, the CEC will review the additional supporting documentation, such as computed tomography and magnetic resonance imaging, as well as neurological reports, enzyme readings, chest X-rays and blood tests, if available. Training sessions will be organized for the participating center to provide them with backup information and documentation to enhance the evaluation and diagnosis of CV events. Any event or serious adverse effect is defined by the World Health Organization criteria for International Drug Monitoring (1994).

Sample-Size Calculation

According to the data in the literature, the prevalence of OSA in people with CVD is 54%–69%.[6,7] An estimated 12%–20% of patients with ACS have a new CV event in the first year.[10,14] This percentage is higher in the population with concomitant OSA.[22] It is estimated that the number of patients required to detect a decrease of $\geq$25% in the likelihood of further CV events after starting treatment with CPAP in this group of patients is 632 subjects in each intervention group (groups 1 and 2). For comparisons between groups, it has been determined that a total of 600 subjects would be required in group 3, thus requiring the inclusion of 1864 subjects. This calculation assumes an α error of 0.05 and a statistical power of 80%. It has also been estimated that 10% of the patients will be lost in the follow-up. The sleep study should be performed in approximately 4214 patients with ACS. It is expected that, of the 4214 patients evaluated, approximately 1264 (40%) will have an AHI >15/hour.

Ethical Issues

The study will be conducted according to the guidelines and principles of the Declaration of Helsinki and standard ethical conduct for research involving humans. The study will also guarantee compliance at all times with Law 15/1999 on Protection of Personal Data (Spanish Government). The identity of all the participants and all the data pertaining to them will be held in complete confidentiality. The Ethics Committees for Clinical Research of all the participating centers approved this study. All the study subjects will provide written informed consent before participating. They

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must also give informed consent for the storage of biological samples in the biobanks of the participating centers. This study is registered with ClinicalTrials.gov (NCT01335087).

Statistical Analysis

All the study variables will be tabulated on a database accessible only to the study investigators. In the case of the qualitative variables, their frequency and valid percentage will be determined. Missing values will be taken into account for the results. The quantitative variables will include measures of central tendency and measures of dispersion and position.

Analysis of evolution variables (dependent variables): The statistical analysis will be based on the principle of intention to treat. In a first analysis, the time until a first CV event will be compared between treatment groups (groups 1 and 2) using a Cox proportional hazards model. Similarly, the Kaplan-Meier test will be used to prepare survival tables and the log-rank statistical function will be used to compare the event-free time between all groups. Secondly, a multivariate study will be undertaken, using a Poisson regression model; this will include interaction and/or confusion variables that identified in the descriptive analysis between groups (such as the level of compliance with treatment, comorbidities, age, and body mass index). A secondary per-protocol analysis will be performed, considering patients with CPAP compliance (use CPAP $\geq$4 hours/day). Multiple imputation will be used in all the models to include participants who were lost to the follow-up.

Secondary objectives: We will determine the prevalence of OSA in the population with ACS admitted to the coronary care units. We will study the differences between the study groups by analysis of variance for the different variables of interest. There will be a collinearity study between variables, using Spearmen correlations. The qualitative variables will be evaluated using the χ^2 test (or the Fisher exact test if any frequency is expected to be <5).

Cost-effectiveness analysis: There will be a study of the cost-effectiveness of treatment with CPAP in patients with OSA and new ACS, using the Bayesian model. This will include the results obtained after 12 months of follow-up in patients with OSA and new ACS without excessive daytime sleepiness. One group of patients will be treated for OSA with CPAP, and in another group the disease will be allowed to follow its natural course without treatment (conservative treatment). We shall calculate the effectiveness and cost of both alternatives and compare them by means of the cost-effectiveness ratio.

All the tests will be conducted at a significance level $\alpha = 0.05$ and the CIs will be calculated at the CI $(1\text{-}\alpha) = 0.95$. The SPSS version 19 software (IBM Corp., Armonk, NY) will be used for all analyses.

Progress During the Start-up Phase

Planning for the ISAACC study began in 2010. Fifteen centers are collaborating in the trial. The Hospital Arnau de Vilanova (Lleida) is the coordinating center. Recruitment began in June 2011, with the coordinating center as the first center; the last center was incorporated in December 2012. As of April 25, 2013, 437 patients with AHI $\geq$15/hour have been randomized into the trial and 220 patients have been included in the reference group. The impediments to recruitment have varied, but the most important point is that the prevalence of AHI $\geq$15/hour in patients with ACS is lower than expected.

Relevance of the Study

The results of this project will determine the impact of the sleep apnea syndrome and its treatment with CPAP on the evolution and prognosis of patients suffering from ACS. Acceptance of its relevance in clinical practice would require changes in coronary units, and the evaluation of night ventilation would become part of the routine explorations of ACS patients. The study also sought to identify clinical markers and/or the related biological clinical course of patients with ACS and OSA, making it possible to identify those individuals most susceptible to complications.

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