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Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Non-Sleepy Obstructive Sleep Apnea: The RICCADSA Randomized Controlled Trial

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Authors' contributions: YP, HG, and JH designed the study in 2005. CE and KW amended the statistical analysis plan after interim analysis in 2010. YP, HG, and ET performed the patient recruitment and clinical follow-ups. YP, CE, and KW performed the statistical analysis. All authors interpreted the data, prepared the manuscript, and drafted the article. YP obtained study funding, and takes full responsibility for the work as a whole, including the

study design, access to data, and the decision to submit and publish the manuscript. All authors approved this manuscript in its final form.

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At a Glance Commentary:

Scientific Knowledge on the Subject: Obstructive sleep apnea is common in patients with coronary artery disease, many of whom do not report daytime sleepiness. Continuous positive airway pressure is first-line treatment for symptomatic obstructive sleep apnea, but its value in patients without daytime sleepiness is uncertain.

What This Study Adds to the Field: This is the first randomized controlled study to address impact of continuous positive airway pressure on adverse cardiovascular outcomes in

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revascularized coronary artery disease patients with obstructive sleep apnea but no daytime sleepiness. Routine prescription of the device did not reduce the adverse outcomes in this high-risk population in intention-to-treat analysis. There was a significant reduction after adjustment for baseline comorbidities and compliance with treatment.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: Obstructive sleep apnea is common in patients with coronary artery disease, many of whom do not report daytime sleepiness. First-line treatment for symptomatic obstructive sleep apnea is continuous positive airway pressure, but its value in patients without daytime sleepiness is uncertain.

Objective: To determine the effects of continuous positive airway pressure on long-term adverse cardiovascular outcome risk in coronary artery disease patients with nonsleepy obstructive sleep apnea.

Methods: This single-center, prospective, randomized, controlled, open-label, blinded evaluation trial was conducted between December 2005 and November 2010. Consecutive patients with newly revascularized coronary artery disease and obstructive sleep apnea (apnea-hypopnea index ≥15/h) without daytime sleepiness (Epworth Sleepiness Scale score <10) were randomized to auto-titrating continuous positive airway pressure (n=122) or no positive airway pressure (n=122).

Measurements: The primary endpoint was the first event of repeat revascularization, myocardial infarction, stroke or cardiovascular mortality.

Main Results: Median follow-up was 57 months. The incidence of the primary endpoint did not differ significantly in patients who did versus did not receive continuous positive airway pressure (18.1% vs. 22.1%; hazard ratio 0.80; 95% confidence interval 0.46–1.41; *P*=0.449). Adjusted on-treatment analysis showed a significant cardiovascular risk reduction in those who used continuous positive airway pressure for ≥4 vs <4 h/night or did not receive treatment (hazard ratio 0.29; 95% confidence interval 0.10–0.86; *P*=0.026).

Conclusions: Routine prescription of continuous positive airway pressure to coronary artery disease patients with nonsleepy obstructive sleep apnea did not significantly reduce long-term

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adverse cardiovascular outcomes in the intention-to-treat population. There was a significant reduction after adjustment for baseline comorbidities and compliance with the treatment.

Keywords: obstructive sleep apnea; coronary artery disease; cardiovascular outcomes

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Introduction

Coronary artery disease (CAD) is one of the most common health problems in Western countries, having a poor prognosis and a high risk of mortality (1). Moreover, an increasing number of patients with CAD undergo percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) with a considerable risk of relapse of CAD in the years following the intervention, despite advances in medical treatment and revascularization techniques (2, 3).

Many of the traditional risk factors contributing to adverse outcomes in these patients are managed. However, obstructive sleep apnea (OSA), a common condition in CAD patients (4), has largely been neglected. The paucity of data on the contribution of OSA to adverse outcomes in cardiac patients has been highlighted by the American Heart Association / American College of Cardiology (5), and probably contributes to a lack of recognition of OSA in the CAD setting.

Elimination of obstructive apneas and hypopneas with nasal continuous positive airway pressure (CPAP) is first-line treatment for OSA, reducing daytime sleepiness and improving quality of life (6). However, the majority of CAD patients with OSA do not experience daytime sleepiness (i.e. asymptomatic), and there is currently no clearly established rationale for treatment of such patients, notwithstanding clinical practice guidelines from the American Academy of Sleep Medicine that generally recommend CPAP treatment for OSA (7). Observational studies have demonstrated that CPAP is beneficial in patients with CAD and OSA who are adherent to treatment (8-10). There are many published short-term randomized controlled trials (RCTs) with CPAP, especially in OSA patients with systemic hypertension, and CPAP has been shown to effectively lower blood pressure (BP) in these patients (11, 12). However, other trials suggest no benefit of CPAP in those without daytime sleepiness (13, 14), except one, suggesting a significant BP reduction in patients with newly diagnosed

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hypertension (15). Overall, there is good evidence to suggest that symptomatic OSA patients should be treated with CPAP to reduce daytime sleepiness (6) and the risk of traffic accidents (16), and also perhaps to lower BP in hypertensive OSA patients (11, 12, 15). Nevertheless, evidence from long-term prospective RCTs to determine whether cardiac patients with nonsleepy OSA should be offered CPAP treatment to reduce cardiovascular morbidity and mortality is lacking.

The Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA (RICCADSA) trial investigated the effects of CPAP on the risk of cardiovascular events in patients with CAD and concomitant OSA without daytime sleepiness. Some of the results have been previously reported in the form of an abstract (17).

Methods

Study Design and Patients

Methodological details have been published previously (18, 19), and are fully detailed in the online supplement. The target population comprised adult patients with angiography-verified CAD who had undergone PCI or CABG in Skaraborg County, West Sweden, in the previous 6 months, and had an apnea-hypopnea index (AHI) of <5/h or ≥15/h during a sleep study (see online supplement). Patients with existing OSA, an AHI of 5.0–14.9/h, and predominantly central apneas with Cheyne-Stokes respiration were excluded (Figure 1). Patients were recruited between December 2005 and November 2010, and follow-up was completed in May 2013. The study was a single-center (two sites), prospective, open, randomized, parallel, interventional, superiority trial of CPAP in CAD patients with nonsleepy OSA (AHI ≥15/h, Epworth Sleepiness Scale [ESS] score <10) (Figure 1). Patients with CAD and sleepy OSA phenotype (AHI ≥15/h, ESS score ≥10) receiving CPAP and CAD patients without OSA were

followed as additional controls in observational arm for further post-hoc comparisons (to be reported separately).

Study Oversight

The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg (approval nr 207-05; 09.13.2005; amendment T744-10; 11.26.2010; amendment T512-11; 06.16.2011), and all patients provided written informed consent. A blinded interim analysis was conducted in February 2010, and the protocol was amended with a new power calculation for the primary endpoints (see below). An Independent Clinical Event Committee (ICEC) reviewed all data obtained from hospital records and death certificates by the end of May 2013, unaware of patient identities and group allocation. A Data Monitoring Board reviewed the protocol and monitored a random 10% selection of the database for baseline clinical data and follow-up procedures, including CPAP adherence and primary endpoints. All authors prepared the manuscript for publication, and made the decision to submit the manuscript without input from or review by ResMed Foundation and ResMed Ltd, who partly funded the trial by institutional grants. All authors guarantee the accuracy and completeness of the data. The trial was registered with the national researchweb.org (FoU i Sverige – Research and development in Sweden; nr VGSKAS-4731; 04.29.2005) and with ClinicalTrials.gov (NCT 00519597).

Sleep Studies, Group Assignment and Randomization

Details of home sleep recordings (cardiorespiratory polygraphy [PG]) and in-hospital polysomnography (PSG) and randomization procedures are provided in the online supplement. The 1:1 random assignment of patients with CAD and nonsleepy OSA was

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scheduled with a block size of eight patients (four CPAP, four controls) stratified by gender and revascularization type (PCI/CABG).

Interventions and Follow-up

Nonsleepy OSA patients who were randomized to treatment were fitted with an automatic CPAP device (S8® or S9®; ResMed) by trained staff. Additional follow-up details, including adherence to CPAP treatment, are provided in the online supplement.

Outcomes

The primary endpoint was a composite of repeat revascularization, MI, stroke and cardiovascular mortality. Information was obtained from patients' medical records and, when necessary, from the Swedish Hospital Discharge Register as well as the Swedish National Cause of Death Registry. Each event was evaluated separately and as part of the combined endpoint. For patients who experienced more than one event during the follow-up period, only the first event was included in the combined endpoint. All-cause mortality and acute hospital admission for cardiovascular reasons were among the secondary endpoints. Criteria for the cardiovascular diagnosis defined by the ICEC are available in the online supplement.

Statistical Analysis

Descriptive statistics are given as mean ± standard deviation (SD) and as numbers (percentages). For baseline differences between the groups, the chi-squared test, and Fisher's exact test were applied. Total sleep time, time spent on supine position and AHI values on the repeated sleep recordings (PG vs PSG) at the individual level were compared with paired *t*-test. Pearson correlation analysis was performed to test the linear relationship between the AHI values on PG vs PSG. All statistical tests were two-sided, and a *P*-value <.05 was

considered significant. Statistical analysis was performed using SPSS® 22.0 for Windows® (SPSS Inc., Chicago, Illinois, USA) and Stata version 14 (StataCorp LP, College Station, Texas, USA).

Kaplan-Meier analyses and Cox Proportional hazards models were performed in the intention-to-treat (ITT) population to estimate the impact of CPAP on the primary endpoint. For the on-treatment (OT) analysis, a time-dependent Cox model (20, 21)) was used to estimate the impact of CPAP usage on the primary endpoint. This approach accounts for the time-varying character of the intervention because subject follow-up is split into multiple intervals according to the visit dates of the CPAP usage evaluation. Originally, visits were planned after 1, 3, 6 and 12 months and then annually until the end of the study. Incomplete usage data due to missed visits were replaced as follows: one missing episode was replaced by the last observation, if the missing episode was followed by a visit. Two or more subsequent missing visits were replaced by 0. If the data from the first visit after one month were missing, they were replaced by the usage data of the 3-month visit. Multivariate adjustment was made for CPAP nights/period and baseline left ventricular ejection fraction (LVEF), age, gender, AHI, body mass index (BMI), current smoking, revascularization type, former revascularization, acute MI, hypertension, diabetes mellitus and lung disease.

Sample Size Estimation

At the time of the study start in 2005, available literature suggested that the incidence rate for a combination of cardiovascular mortality, acute myocardial infarction and the need for a new revascularization within a year of PCI was 27% (22). Moreover, in a systemic review of the comparative effectiveness of PCI and CABG, the 5-year repeat revascularization rate was reported to be 40.1% in PCI with stents and 9.8% in CABG patients (23). There were no studies in revascularized patients with CAD and concomitant OSA prior to 2005 to accurately inform estimates of study power for the primary outcome assessments; therefore, a composite

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endpoint rate of 25% in nonsleepy patients with untreated OSA over a 3-year follow-up period was hypothesized. The RCT arm was designed to initially comprise a consecutive sample of 200 patients with (100 nonsleepy OSA randomized to CPAP, 100 to no-CPAP). It was assumed that approximately 25% of the OSA subjects would be noncompliant with CPAP during the follow-up period. The trial was expected to have an 80% power to detect a risk reduction in the rate of the composite endpoint from 25% to 10% on an ITT basis ($p<0.05$ level, two-sided test). An interim analysis blinded to randomization group performed in February 2010 revealed an incident rate of 21%, and a CPAP adherence rate of 60% at 1 year, resulting in a protocol amendment. As a result, using an enlarged sample size of 242 patients (121 in each of the randomization arm) and an extended follow-up period of ≥2 years and ≤7 years, a significant risk reduction for the primary endpoint from 25% to 12% was hypothesized.

Results

Study Participants

A total of 1259 patients met the inclusion criteria for screening, of whom 662 (52.7%) agreed to participate in the sleep study (Figure 1). Diagnostic PG was performed at home after an average of 63 days following mechanical revascularization (median 59 days; interquartile range [IQR] 42-78), and patients fulfilling the inclusion criteria for the RCT or the observational arm underwent baseline investigations on average 35 days (median 30; IQR 20-45) after home sleep recordings.

Baseline Characteristics

A total of 244 patients with CAD and OSA fulfilled the inclusion criteria for the randomized controlled (RCT) arm. Nonsleepy OSA patients allocated to CPAP did not differ significantly

from nonsleepy OSA patients allocated to no-CPAP with regard to demographic and clinical characteristics (Table 1).

Numbers Analyzed

Median follow-up time until mortality, loss to follow-up, or the end of the study was 56.9 months (range 6.5–90.2). All patients were included in the ITT analysis for primary outcomes; 16 patients died, and 1 was lost to follow-up (Figure 1). Of 244 patients with AHI ≥15/h on PG, 4 had AHI <5/h on in-hospital PSG the day before the RCT started, 19-54 days after initial at-home PG. Follow-up data for these 4 patients are provided in eTable 1 in the online data supplement), and correlations between AHI values on PG *vs* PSG for the OSA group are shown in eFigure 1 in the online data supplement. Of OSA patients allocated to CPAP at baseline, 49 returned the device within 2 years. Of the nonsleepy OSA patients randomized to no-CPAP, 3 wanted to start CPAP at baseline, and 22 during the amended follow-up period due to reaching the nonfatal endpoints and/or completing the initial 3-year follow-up, or developing daytime sleepiness. CPAP compliance data from CPAP devices are shown in eTable 2 in the online data supplement.

Outcomes

Intention-to-treat

Overall, 49 patients reached the combined endpoint during follow-up, and 22 (18.1%) in the CPAP group, and 27 (22.1%) in the no-CPAP group (not significant). The incidence of the composite endpoint was 4.65 (95% confidence interval [CI] 4.56–4.73) per 100 person-years; 4.18 (95% CI 2.75-6.35) per 100 person-years in CPAP group *vs* 5.21 (95% CI 3.57-7.60) per 100 person-years in no-CPAP group, respectively (P=0.449). Cumulative incidences of the primary endpoint are illustrated in Figure 2. There were no significant differences in the

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individual incidences of the endpoints in the PCI and CABG subgroups (see eTable 3 in the online data supplement). Univariate predictors of adverse outcomes were diabetes mellitus and former revascularization, while CABG at baseline was protective (Table 2). On multivariate analysis, diabetes mellitus (hazard ratio [HR] 2.05; 95% CI 1.06–3.98; P=0.034) and former revascularization (HR 3.29; 95% CI 1.77–6.10; P<0.001) were significantly associated with increased risk for the composite endpoint whereas CABG at baseline (HR 0.30; 95% CI 0.12–0.75; P<0.001) was associated with reduced risk (Table 2).

On-treatment

There was no significant difference in incidence rates between the groups when applying a cut-off level of 3 hours of CPAP usage per night, but there was a significant between-group difference based on CPAP usage for ≥4 hours/night (6 events) vs <4 hours/night or no-CPAP (43 events) with an HR 0.29 and 95% CI 0.10–0.86 with covariable adjustments (Table 3). The incidence of the composite endpoint was 2.31 (95% CI 0.96-5.54) per 100 person-years for CPAP usage for ≥4 hours/night, and 5.32 (95% CI 3.96-7.15) per 100 person-years for CPAP usage <4 hours/night or no CPAP.

Adverse Events

One patient (age 81 years) with CAD and mechanical aortic valve prosthesis, who was on combination therapy with warfarin and clopidogrel after PCI, could not use the CPAP device due to frequent nasal bleeding on treatment. This patient restarted CPAP therapy without any nasal bleeding when clopidogrel was discontinued 3 years after PCI. Other patient-reported side effects during CPAP fitted with the known tolerability profile of CPAP, and included dry mouth, nasal symptoms, claustrophobia, insomnia, noise problems, and mask fit.

Discussion

This study showed that routine prescription of CPAP to patients with CAD and nonsleepy OSA did not significantly reduce the long-term cardiovascular event rate. A significant beneficial effect of CPAP was seen first after adjusting for baseline comorbidities and CPAP adherence.

To our knowledge, this is the first RCT investigating the effect of CPAP on long-term cardiovascular outcomes in patients with CAD and concomitant OSA without daytime sleepiness. Two RCTs are currently underway investigating the impact of CPAP on long-term outcomes in larger cohorts with established cardiovascular disease (24, 25). Many previous studies that showed beneficial effects of CPAP in patients with CAD and OSA had an observational design. A review of 371 patients with OSA and CAD who underwent PCI reported a significantly lower 5-year cardiac death rate (3%) among 175 patients treated with CPAP compared with 196 untreated patients (10%) (10). Data from a sleep clinic cohort, demonstrated that CPAP treatment significantly reduced cardiovascular risk in men with severe OSA (26). Similarly, adequate CPAP treatment has been shown to reduce the risk of a composite endpoint of incident CAD or stroke in women with OSA (27). Moreover, after adjustment for confounding factors, post-MI patients with OSA who were compliant with CPAP had a lower risk of recurrent MI and repeat revascularization than untreated patients, and similar to patients without OSA (28).

In this RCT, CPAP treatment of CAD and nonsleepy OSA patients did not significantly reduce the rate of adverse cardiovascular outcomes. These results may reflect the fact that getting nonsleepy patients to comply with CPAP is challenging. Between-group differences at baseline may also have influenced the findings. Randomization was not stratified by comorbidities, and there was a higher proportion of patients with acute MI, diabetes mellitus and hypertension in the CPAP arm. OT analysis showed that CPAP was effective in

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nonsleepy patients who used the device for ≥4 hours per night, with an adjusted HR that was of similar magnitude to that reported in a previous observational study.[27]

Many CAD patients with OSA do not experience daytime sleepiness, and it has been suggested that nonsleepy OSA patients might have poor CPAP adherence because they don't experience subjective benefits from therapy (29). This may be the case, although overall adherence in the current CAD population did not differ markedly from long-term adherence rates in sleep clinic cohorts (30). Indeed, an observational study of a sleep clinic cohort with CAD suggested comparable adherence to CPAP in sleepy and nonsleepy patients (31), and a larger RCT addressing the impact of CPAP treatment on incident hypertension or cardiovascular events in nonsleepy OSA patients from sleep clinics reported that 64% of patients were using CPAP for ≥4 hours/night after a median 4-year follow-up (32).

The results of the current study suggest that CPAP treatment is feasible in CAD populations with nonsleepy OSA, given the additional assumption that such high-risk patients might expect greater cardiovascular benefits, and may be more motivated to comply with treatment despite the lack of daytime sleepiness. However, initial data from the SAVE trial suggest a lower CPAP compliance rate than in this study, despite an initial 1-week run-in phase with sham-CPAP to exclude noncompliant patients before randomization (15% of all eligible patients were excluded) (33). Thus, adherence remains a challenging issue when evaluating the cardiovascular benefits of CPAP treatment in patients with CAD and concomitant OSA without daytime sleepiness. Also, the finding that CPAP use for ≥4 hours/night is required to achieve cardiovascular benefits in nonsleepy OSA patients is similar to the results of a previous post-hoc analysis (32).

CPAP is not the only treatment option for OSA. In a recent RCT, adherence to a weight loss regimen and CPAP resulted in incremental BP reductions compared with either intervention alone (34). There is also accumulating evidence for a beneficial impact of mandibular

advancement devices on BP in OSA patients (35, 36). Moreover, given the emergence of new mechanical and pharmacological interventions in sleep medicine (37), improved "personalization" of OSA therapy may be possible through better characterization of individual patient pathophysiology.

Despite the lack of conclusive evidence for a beneficial effect of CPAP in the current trial, the high prevalence of OSA in the entire study population (19) indicates that OSA should be considered when assessing the impact of different treatments (e.g. lipid-lowering agents, bare-metal versus drug-eluting stents) in revascularized CAD cohorts. Effective treatment of OSA with CPAP, or other approaches, is challenging in CAD patients with nonsleepy OSA, but needs to be evaluated in secondary prevention models.

The strengths of this study include its randomized controlled design for patients with CAD and nonsleepy OSA with only 1 lost to follow-up. Although the inclusion rate for eligible patients for sleep screening was only 53%, the inclusion design was consecutive, and there were no significant differences in baseline characteristics of patients undergoing versus not undergoing sleep study (19).

This study also had a number of limitations. Firstly, it was a single-center trial with two sites, which limits generalizability of results across geographic regions. Secondly, "nonsleepy" OSA relied on an ESS threshold, which may not reflect an objective sleepiness. However, this is a generally accepted tool for subjective daytime sleepiness, and other methods such as Multiple Sleep Latency Test (38), which is used as an objective tool, is time consuming and not feasible to run for the large-scale cardiac populations. Thirdly, the study was underpowered for the ITT arm for several reasons: CPAP adherence in patients with CAD and nonsleepy OSA was lower than initially expected, which possibly resulted in an inadequately powered sample size estimation. While CPAP adherence rates were slightly higher than those reported in the SAVE trial (33), those data had not been published when the current study

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started or when the interim analysis was performed. Further, revascularized CAD patients were a heterogeneous group, including both PCI and CABG, and both acute/subacute and elective PCI,.and the apparent treatment effect was far smaller than anticipated due to an optimistic first assumption. Fourthlythe trial was open-label, and had no placebo control arm. As previously discussed (39), there is no true sham CPAP or other appropriate placebo for CPAP in a long-term trial in cardiovascular disease patients. It is also possible that sham CPAP consisting of a mask attached to tubing, but without pressure application, would worsen sleep disturbance and act as a "negative placebo" (40). Finally, results of the OT analysis must be interpreted with care because device usage is patient-driven and self-selection bias cannot be excluded.

In conclusion, routine CPAP prescription of CPAP to CAD patients with nonsleepy OSA did not significantly reduce long-term adverse outcomes. However, the study may have had limited power to detect a significant difference in the ITT population. The risk reduction was observed first after adjustment for baseline comorbidities and CPAP adherence. These findings need to be further explored in larger clinical cohorts with more homogenous CAD populations.

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References

1. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, Naghavi M, Mensah GA, Murray CJ. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med* 2015;372:1333-1341.
2. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW, SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-972.
3. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Ståhle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 2011;32:2125-2134.
4. Hedner J, Franklin K, Peker Y. Coronary artery disease and sleep apnea. In: Kryger, Roth, Dement (editors). *Principals and practice of sleep medicine*. 5th edition. 2011. Elsevier Inc, Philadelphia, PA. 1393-1399.
5. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T; American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology; American Heart Association Stroke Council; American Heart Association Council on Cardiovascular Nursing; American College of Cardiology Foundation. Sleep apnea and cardiovascular disease. An American Heart Association/ American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing Council. *Circulation* 2008;118:1080-1111.

6. Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, Douglas NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax* 1998;53:341-345.
7. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults *J Clin Sleep Med* 2009;5:263-276.
8. Milleron O, Pilliére R, Foucher A, de Roquefeuil F, Aegerter P, Jondeau G, Raffestin BG, Dubourg O. Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. *Eur Heart J* 2004;25:728-734.
9. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. *Chest* 2005;127:2076-2084.
10. Cassar A, Morgenthaler TI, Lennon RJ, Rihal CS, Lerman A. Treatment of obstructive sleep apnea is associated with decreased cardiac death after percutaneous coronary intervention. *J Am Coll Cardiol* 2007;50:1310-1314.
11. Pepperell, JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002;359:204-210.
12. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003;107:68-73.

AJRCCM Articles in Press. Published on 25-February-2016 as 10.1164/rccm.201601-0088OC

13. Barbé F, Mayoralas LR, Duran J, Masa JF, Maimó A, Montserrat JM, Monasterio C, Bosch M, Ladaria A, Rubio M, Rubio R, Medinas M, Hernandez L, Vidal S, Douglas NJ, Agustí AG. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. *Ann Intern Med* 2001;134:1015-1023.

14. Robinson GV, Smith DM, Langford BA, Davies RJ, Stradling JR. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. *Eur Respir J* 2006;27:1229-1235.

15. Duran-Cantolla J, Aizpuru F, Montserrat JM, Ballester E, Terán-Santos J, Aguirregomoscorta JI, Gonzalez M, Lloberes P, Masa JF, De La Peña M, Carrizo S, Mayos M, Barbé F, Spanish Sleep and Breathing Group. Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: Randomised controlled trial. *BMJ* 2010;341:c5991.

16. Mazza S, Pépin JL, Naëgelé B, Rauch E, Deschaux C, Ficheux P, Lévy P. Driving ability in sleep apnoea patients before and after CPAP treatment: evaluation on a road safety platform. *Eur Respir J* 2006;28:1020-1028.

17. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Impact of Continuous Positive Airway Pressure Treatment on Cardiovascular Outcomes in Coronary Artery Disease and Obstructive Sleep Apnea: The RICCADSA Trial. *Am J Respir Crit Care Med* 2015;191:A6317.

18. Peker Y, Glantz H, Thunstrom E, Kallryd A, Herlitz J, Ejdebäck J. Rationale and design of the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea—RICCADSA trial. *Scand Cardiovasc J* 2009;43:24-31.

19. Glantz H, Thunström E, Herlitz J, Cederin B, Nasic S, Ejdebäck J, Peker Y. Occurrence and predictors of obstructive sleep apnea in a revascularized coronary artery disease

cohort. *Ann Am Thorac Soc* 2013;4:350-356.

20. Cox DR. Regression models and life tables (with discussion). *J Royal Stat Soc Series B* 1972;34:187-220.
21. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. *Annu Rev Public Health* 1999;20:145-157.
22. Odell A, Gudnason T, Andersson T, Jidbratt H, Grip L. One-year outcome after percutaneous coronary intervention for stable and unstable angina pectoris with or without application of general usage of stents in unselected European patient groups. *Am J Cardiol* 2002;90:112-118.
23. Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, Kapoor JR, Ardehali R, Owens DK, Hlatky MA. Systematic review: The comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med* 2007;147(20):703-716.
24. McEvoy RD, Anderson CS, Antic NA, Chen B, He Q, Heeley E, Huang S, Huang Y, Wang J, Zhong N. The sleep apnea cardiovascular endpoints (SAVE) trial: Rationale and start-up phase. *J Thorac Dis* 2010;2:138-143.
25. Esquinas C, Sanchez-de-la Torre M, Aldoma A, Florés M, Martínez M, Barceló A, Barbé F, Spanish Sleep Network. Rationale and methodology of the impact of continuous positive airway pressure on patients with ACS and nonsleepy OSA: the ISAACC Trial. *Clin Cardiol* 2013;36:495-501.
26. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcome in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046-1053.
27. Campos-Rodriguez F, Martinez-Garcia MA, Reyes-Nunez N, Caballero-Martinez I,

AJRCCM Articles in Press. Published on 25-February-2016 as 10.1164/rccm.201601-0088OC

Catalan-Serra P, Almeida-Gonzalez CV. Role of sleep apnea and continuous positive airway pressure therapy in the incidence of stroke or coronary heart disease in women. *Am J Respir Crit Care Med 2014*;189:1544-1550.

28. Garcia-Rio F, Alonso-Fernandez A, Armada E, Mediano O, Lores V, Rojo B, Fernández-Lahera J, Fernández-Navarro I, Carpio C, Ramírez T. CPAP effect on recurrent episodes in patients with sleep apnea and myocardial infarction. *Int J Cardiol* 2013;168:1328-1335.

29. Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. *Progress Cardiovasc Dis* 2009;5:434-451.

30. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173-178.

31. Sampol G, Rodés G, Romero O, Jurado MJ, Lloberes P. Adherence to nCPAP in patients with coronary disease and sleep apnea without sleepiness. *Respir Med* 2007;101:461-466.

32. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, Martínez-Alonso M, Carmona C, Barceló A, Chiner E, Masa JF, Gonzalez M, Marín JM, Garcia-Rio F, Diaz de Atauri J, Terán J, Mayos M, de la Peña M, Monasterio C, del Campo F, Montserrat JM; Spanish Sleep And Breathing Network. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012;307:2161-2668.

33. Chai-Coetzer CL, Luo YM, Antic NA, Zhang XL, Chen BY, He QY, Heeley E, Huang SG, Anderson C, Zhong NS, McEvoy RD. Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. *Sleep* 2013;36:1929-1937.

34. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, Foster GD, Maislin G, Saif H, Broderick P, Chittams J, Hanlon AL, Pack AI. CPAP, weight loss, or both for obstructive sleep apnea? *N Engl J Med* 2014;370:2265-2275.

35. Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. *Sleep* 2004;27:934-941.

36. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2013;187:879-887.

37. Peker Y, Redline S. Update in sleep medicine 2013. *Am J Respir Crit Care Med* 2014;1345-1350.

38. Wise Ms. Objective measures of sleepiness and wakefulness: application to the real world? *J Clin Neurophysiol* 2006;23:39-49.

39. Bradley TD, Logan AG, Floras JS, CANPAP Investigators. Rationale and design of the Canadian Continuous Positive Airway Pressure Trial for Congestive Heart Failure patients with Central Sleep Apnea – CANPAP. *Can J Cardiol* 2001;17:677-684.

40. Leung RS, Tkacova R, Bradley TD. Obstructive sleep apnoea. *Lancet* 1999;354:1212-1213.

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Figure legends

Figure 1. Flow of patients through the study.

Definition of abbreviations: AHI, apnea-hypopnea index; CAD; coronary artery disease; CPAP, continuous positive airway pressure; CSA-CSR, central sleep apnea-Cheyne Stokes respiration; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; RICCADSA, Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea.

Figure 2. Cumulative incidences of the composite endpoint in the intention-to-treat population.

Definition of abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio; OSA, obstructive sleep apnea.

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Table 1. Demographic and clinical characteristics of study patients at baseline.

	CPAP (n=122)	**no-CPAP (n=122)**	***P* Value**
Age, y	65.5 (8.5)	66.5 (8.2)	0.382
AHI, events/h	28.3 (12.7)	29.3 (14.0)	0.545
ODI, events/h	16.7 (11.4)	16.3 (11.8)	0.804
ESS score	5.5 (2.4)	5.5 (2.2)	0.991
BMI, kg/m^2	28.4 (3.8)	28.5 (3.5)	0.840
LVEF, %	56.9 (9.0)	56.1 (9.9)	0.479
Obesity, %	27.9	27.9	1
Female, %	18.0	13.9	0.382
Current smoker, %	18.0	13.9	0.382
Pulmonary disease, %	3.3	9.8	0.067
Hypertension, %	68.9	59.0	0.110
Acute MI at baseline, %	53.3	45.9	0.249
CABG at baseline, %	27.0	27.0	1
Previous PCI or CABG, %	22.1	18.9	0.526
Diabetes mellitus, %	27.9	20.5	0.178
β-blocker use, %	91.5	86.7	0.230

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Diuretic use, %	20.3	22.7	0.660
CCB use, %	22.9	16.7	0.229
ACE inhibitor use, %	47.5	47.5	0.995
ARB use, %	12.7	16.7	0.389
Anticoagulant† use, %	100	97.5	0.083
Lipid-lowering agent use, %	96.6	93.3	0.248

Values are mean (standard deviation) or percent patients.

Definition of abbreviations: ACE, angiotensin converting enzyme; AHI, apnea hypopnea index; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; MI, myocardial infarction; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; SD, standard deviation. †Anticoagulant use refers to aspirin and/or clopidogrel and/or warfarin use.

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Table 2. Cox regression analysis of baseline covariables associated with risk for adverse cardiovascular outcomes in revascularized patients with coronary artery disease and obstructive sleep apnea without daytime sleepiness in the intention-to-treat analysis (n=244; 49 patients reached the composite endpoint).

	Univariate			Multivariate		
	Hazard Ratio	**95% CI**	***P* Value**	**Hazard Ratio**	**95% CI**	***P* Value**
CPAP assignment vs. no-CPAP	0.80	0.46–1.41	0.449	0.62	0.34–1.13	0.120
Age	1.02	0.98–1.05	0.372	1.01	0.98–1.05	0.474
Females vs. males	0.48	0.17–1.33	0.155	0.43	0.15–1.23	0.114
Apnea-hypopnea index	1.00	0.98–1.02	0.783	0.99	0.97–1.01	0.363
Body mass index	1.01	0.94–1.09	0.753	0.99	0.91–1.08	0.802
CABG vs. PCI	0.38	0.17–0.84	0.017	0.30	0.12–0.75	0.010
Current smoking	1.29	0.63–2.67	0.485	1.78	0.80–3.96	0.156
Hypertension	1.09	0.60–1.96	0.776	1.59	0.81–3.12	0.176
Diabetes mellitus	1.92	1.06–3.47	0.030	2.05	1.06–3.98	0.034
Acute myocardial infarction	1.02	0.58–1.79	0.947	1.03	0.54–1.94	0.937
Previous PCI or CABG	3.36	1.91–5.93	<0.001	3.29	1.77–6.10	<0.001
Pulmonary disease	1.39	0.50–3.85	0.532	0.95	0.33–2.74	0.925
Left ventricular ejection fraction	0.99	0.96–1.02	0.594	0.99	0.96–1.02	0.513

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Definition of abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; CPAP, continuous positive airway pressure; PCI, percutaneous coronary intervention.

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Table 3. Cox regression analysis of the association between time-dependent CPAP usage (hours/night) and adverse cardiovascular outcomes in 244 revascularized patients with coronary artery disease and obstructive sleep apnea without daytime sleepiness (49 patients reached the composite endpoint).

	Univariate			Multivariate		
	Hazard Ratio	**95% CI**	***P* Value**	**Hazard Ratio**	**95% CI**	***P* Value**
CPAP usage ≥3 hours/night	0.64	0.31–1.33	0.234	0.91	0.16–5.13	0.911
CPAP usage ≥4 hours/night	0.43	0.18–1.02	0.057	0.29	0.10–0.86	0.026
CPAP usage ≥5 hours/night	0.43	0.17–1.09	0.075	0.34	0.10–1.12	0.075

Definition of abbreviations: CPAP, continuous positive airway pressure, CI, confidence interval.

*Adjusted for age, gender, body mass index, apnea hypopnea index, current smoking, pulmonary disease, hypertension, diabetes mellitus, acute myocardial infarction, revascularization type at baseline, former revascularization, and left ventricular ejection fraction at baseline.

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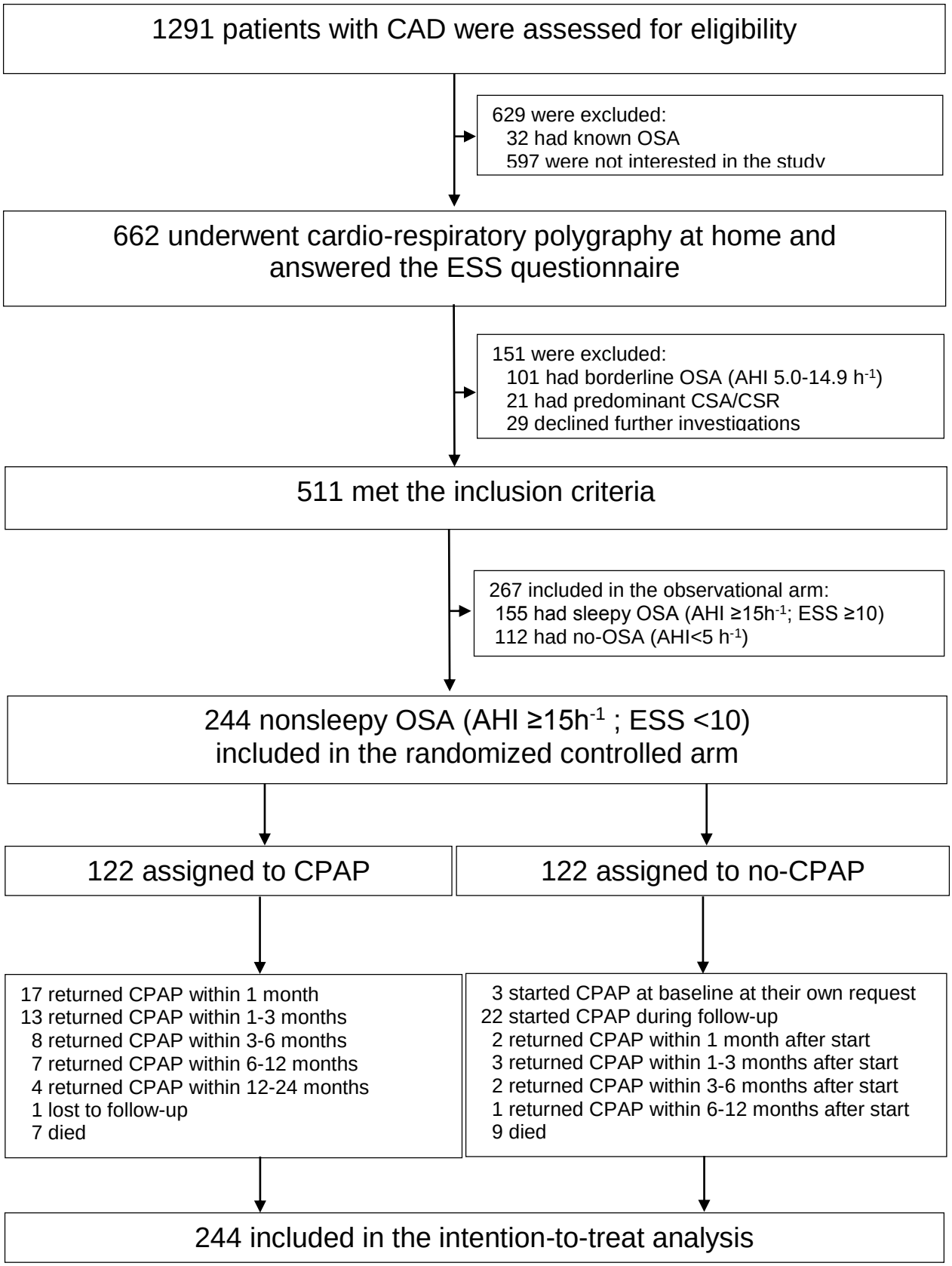

Figure 1

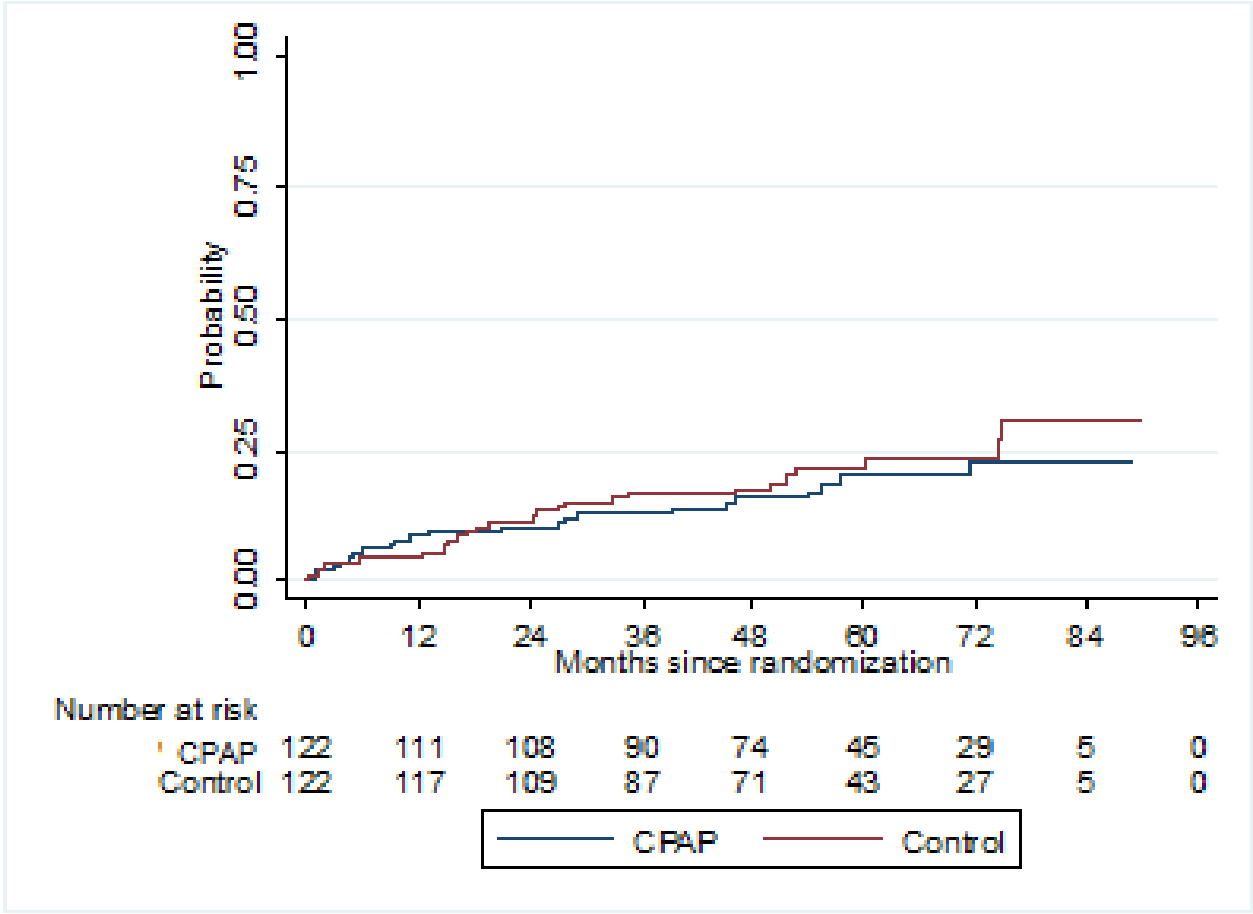

Figure 2

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Online Data Supplement

Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Non-Sleepy Obstructive Sleep Apnea: The RICCADSA Randomized Controlled Trial

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Methods

Study design and patients

Patients were recruited from two hospitals with training and research facilities serving a population of approximately 250,000 living in the Skaraborg County of West Götaland, Sweden. Percutaneous coronary intervention (PCI) was performed either as an elective or acute/subacute procedure at the hospital in Skövde or at the Sahlgrenska University Hospital in Gothenburg, which is the regional hospital. Coronary artery bypass grafting (CABG) was performed in Gothenburg, and all patients were moved to the study hospitals in Skövde or Lidköping when clinically stable after revascularization. Eligible patients who gave informed consent to participate in the study were referred to the Sleep Medicine Unit for sleep studies.

Sleep recordings

Cardiorespiratory polygraphy at home

The portable, limited polygraphy (PG) sleep study performed with the Embletta® PDS (Portable Digital System) device (Embla, Broomfield, CO, USA), consisted of the following: 1) nasal pressure detector using nasal cannulae/pressure transducer system, recording the square root of pressure as an index of flow; 2) thoraco-abdominal movement detection through two XactTrace™ inductive belts with respiratory inductance plethysmography (RIP) technology; 3) finger pulse oximeter detecting heart rate and oxyhemoglobin saturation (SpO_2); and 4) body position and movement detection. The patient's sleep time was estimated on the basis of self-reporting as well as the pattern of body movement during the sleep study. Patients with an estimated sleep time of <4 hours were offered a new home-based sleep study. Apneas were defined as an almost complete (≥90%) cessation of airflow. Hypopneas were defined as a ≥50%

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reduction in thoracoabdominal movement and/or a ≥50% decrease in the nasal pressure amplitude for ≥10 seconds (E1, E2). In addition, the total number of significant oxyhemoglobin desaturations (decrease of ≥4% from the immediately preceding baseline) were scored, and the oxygen desaturation index (ODI) was calculated as the number of significant desaturations per hour of estimated sleep. Events with a ≥30% reduction in thoracoabdominal movement and/or a ≥50% decrease in the nasal pressure amplitude for ≥10 seconds were also scored as hypopneas if there was a significant desaturation (≥4%). Patients with an apnea-hypopnea index (AHI) ≥15 per hour of estimated sleep time, independent of symptom occurrence, were defined as having OSA. All baseline screening recordings were scored by the same observer (YP).

Overnight polysomnography in hospital

All patients with CAD and a diagnosis of OSA based on the first PG screening investigation underwent unattended overnight polysomnography (PSG) in hospital using a computerized recording system (Embla A10®, Embla, Broomfield, CO, USA) for the comparison between sleepy versus non-sleepy OSA phenotypes as one of the secondary analyses (E3). The PSG system included sleep monitoring through three-channel electroencephalography (EEG [C4/A1, C3/A2, CZ/A1]), two-channel electrooculography (EOG), one-channel submental electromyography (EMG), bilateral tibial EMG and two-lead electrocardiogram (ECG) in addition to the cardiorespiratory channels as described for the Embletta system above. PSG recordings were scored based on 30-second epochs according to the Rechtschaffen and Kales criteria (E4) by an observer blinded to clinical data and baseline screening results from the previous PG recordings. Obstructive events on the PSGs were scored according to the same AASM criteria applied for the PGs (E1). CAD patients without OSA on PG did not undergo overnight PSG in hospital because AHI values of <5/h on the PG system used have been shown

to reliably exclude OSA (E5).

Epworth Sleepiness Scale

Excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) questionnaire (E6). The ESS contains eight questions to evaluate the chance of dozing off under eight scenarios in the past month. Each item is scored from 0 to 3 (0 for would never doze, 1 for slight chance of dozing, 2 for moderate chance of dozing, and 3 for high chance of dozing). The ESS score ranges from 0 to 24. Excessive daytime sleepiness was defined as an ESS score of ≥10.

Baseline assessments

Venous blood samples were drawn between 07.00 and 08.00 hours in the morning following overnight PSG, after a fast of ≥10 hours, for determination of secondary endpoints as described previously (E3). Other assessments included quality of life questionnaires and echocardiographic investigations at baseline before the start of the randomized controlled trial (RCT) period (E3).

Group assignment, randomization, interventions, and follow-up

Group assignment was based on the cardiorespiratory PG recordings. In hospital PSG for OSA patients the day before start of the RCT was mainly planned for subsequent studies of further evaluation of sleep architecture in different OSA phenotypes as well as for comparison with the baseline PG recordings (E3). Scoring of the PSGs was done later during the follow-up period and group allocation was not changed on the basis of these results. The 1:1 random assignment of

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patients with CAD and nonsleepy OSA was scheduled by the sealed envelope system with a block size of eight patients (four CPAP, four controls) stratified by gender and revascularization type (PCI/CABG). Thus, 4 groups of sealed envelopes (8 in each group; a. PCI-men; b. PCI-women; c. CABG-men; d. CABG-women) were prepared in advance by the investigator (YP) and the study nurse, and the patients were enrolled in the randomization procedure in the morning after overnight PSG, which was scheduled by the study nurse with no knowledge about the details of the patient characteristics and comorbidity data. The patients allocated to CPAP treatment were informed about the technical procedure in the morning after overnight PSG and provided with an automatic (self-titrating) CPAP device (S8®, or S9®; ResMed, Sydney, Australia) and a nasal or full-face mask and humidifier by trained staff at the study center. All participants assigned to CPAP were instructed to use the device at home every night for ≥4 hours, contacted by telephone after one week and given a check-up in the clinic after 1 month, 3 months, 6 months, 1 year, and then yearly to end of the main study. Nonsleepy OSA patients who were randomized to the control group and who were obese were given advice about weight reduction, and all OSA patients randomized to no-CPAP were informed about the tennis ball technique to avoid the supine position during sleep (E7). All patients were evaluated at 3, 6, and 12 months, and annually thereafter, and were given standard cardiology treatment by their physicians. A new PG sleep recording was performed in all patients at 3 and 12 months, and annually thereafter (with CPAP in treated OSA patients) as part of a planned future post-hoc analysis comparing reports from the PG device regarding residual AHI and pressures applied during CPAP treatment, and for analysis of the natural course of OSA in patients who were randomized to no-CPAP.

Adherence to CPAP

OSA patients receiving CPAP treatment brought their device to the clinic at each scheduled follow-up visit; monitoring settings and hours of CPAP use were obtained from the machines' internal clocks and recorded. In addition, pressure level, mask leak and residual AHI measures were noted. All necessary adjustments of the CPAP device and mask fittings were done according to clinical routines by the sleep medicine unit staff. Patients who were unable to adhere to CPAP treatment were followed as part of the treatment arm as defined in the intention-to-treat (ITT) analysis.

Cardiovascular endpoint criteria

An Independent Clinical Event Committee (ICEC) reviewed all data obtained from hospital records and death certificates by the end of May 2013, blinded to personal identity and group allocation. The ICEC review was based on a previously described definition of the endpoints (E8), which was applied in the HOT study (E9), and other trials. In summary, overall mortality was based on the death certificate. Cardiovascular mortality was defined as death from any of the following: myocardial infarction, stroke (cerebral hemorrhage or cerebral infarction), ruptured aortic aneurysm (thoracic or abdominal), heart failure (as determined by the treating physician), sudden death with no cause other than presumed cardiac (malignant arrhythmias), death during or within 28 days of CABG or PCI, and pulmonary embolism. Myocardial infarction was defined as ≥2 of the following signs/symptoms: sudden chest pain and/or sudden shortness of breath and/or syncope; new left bundle branch block or new ST-elevation or transient ST- or T-wave changes; increase of troponin I levels to >0.10 μg/L in ≥2 samples or increases in myocardial necrosis biomarkers (other causes of troponin elevation should be excluded). Evidence of myocardial

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infarction at autopsy could also be used as a single criterion. Stroke was defined as sudden onset of focal neurological signs lasting >24 hours (other causes such as brain tumor, subdural or epidural hematoma, subarachnoid haemorrhage, psychosomatic, peripheral nerve lesions should be excluded). Stroke was defined as cerebral hemorrhage if computed tomography (CT) or magnetic resonance imaging (MRI) of the brain showed intracerebral blood, and as cerebral infarction if early CT brain was normal and subsequent follow-up was compatible with stroke, or if later CT brain or MRI showed signs of infarction; or, as a single criterion, evidence of cerebral haemorrhage or infarction at autopsy and determined by the pathologist as the cause of death. CABG was defined as an operation with grafts to coronary arteries, and PCI was defined as dilatation of the coronary arteries with or without stents. Pulmonary embolism was defined sudden onset of chest pain and/or shortness of breath and/or syncope together with typical CT findings of the pulmonary arteries or pulmonary scintigraphy. Aortic aneurysm (either thoracic or abdominal) was defined as all 3 of: sudden onset of chest pain or abdominal pain; typical findings on chest or abdominal radiography or ultrasound; need for intervention (blood pressure treatment, or surgery, or percutaneous transluminal intervention with or without stent). Acute hospital admissions for cardiovascular reasons included myocardial infarction, stroke, pulmonary embolism, aortic aneurysm (as defined above) as well as acute hospital admissions for heart failure, transient ischemic attacks, chest pain of presumed cardiac origin (e.g. angina pectoris), peripheral emboli, atrial fibrillation and other cardiac arrhythmias, and intermittent claudication.

Data collection and analysis

The primary outcome variables were documented prospectively and were not subject to observer bias. Baseline comorbidity data, results of sleep recordings, and CPAP compliance data were prospectively recorded in separate files at a specific server of the study hospital by research personnel blinded to study group allocation and/or unaware of the study outcomes.

Results

Comparison between home PG and in-hospital PSG

All OSA patients underwent unattended overnight PSG in hospital after baseline cardiorespiratory PG recordings (median 29 days, range 5-146 days). The mean total sleep time (TST) recorded during PSG was 372±92 minutes compared with 424±63 minutes estimated sleep time during cardiorespiratory PG (P<0.001). Moreover, time spent on supine position was 30.7±25.3% on home PG, and 35.7±27.8% on PSG (P=0.011). Average AHI values were, as expected, higher (40.4±22.9/h) on PSG compared with those on PG (28.9±13.3/h; P<0.001) because home PGs usually underestimate AHI due to recording time exceeding actual sleep time. As illustrated in eFigure 1, there was a linear correlation between AHI values based on PG vs. PSG (r=0.528; P<0.001). On the other hand, among patients who had an AHI ≥15/h on home-based PG, 23 had mild OSA (AHI ≥5 to <15/h), and 4 no OSA (AHI<5/h) according to PSG. However, the repeated PG recordings and data from the CPAP devices in treated patients were supportive of the initial group allocation (eTable 1).

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eTable 1. Results of repeated sleep recordings and follow-up data of 4 OSA patients who demonstrated AHI <5/h on in-hospital PSG

Patients	TST* (min)	Time spent in supine position (%)	Overall AHI (events/h)	Overall ODI (events/h)	CPAP level in 95 percentile (cmH_2O)	Adjusted CPAP usage (h/night) x (nights/period)†
Nr 301, Nonsleepy OSA						
At baseline (PG)	422	61.8	17.9	7.7	-	-
At baseline (PSG)	405	17.5	0.7‡	1.3	-	-
At 3 mo (PG with CPAP)	518	29.9	3.4	3.5	8.8	6.2
At 1 yr (PG with CPAP)	500	20.7	0.2	0.4	7.5	6.3
Nr 128, Nonsleepy OSA						
At baseline (PG)	430	66.1	30.7	7.5	-	-
At baseline (PSG)	323	missing	2.0	0.0	-	-
At 3 mo (PG no-CPAP)	529	47.1	21.4	6.5	No-CPAP	No-CPAP
At 1 yr (PG no-CPAP)	496	50.7	19.1	6.4	No-CPAP	No-CPAP
Nr 242, Nonsleepy OSA						

At baseline (PG)	391	16.6	16.6	5.1	-	-
At baseline (PSG)	495	25.1	2.3	2.8	-	-
At 3 mo (on CPAP)	-	-	1.3†	-	8.2†	5.3
At 1 yr (on CPAP)	-	-	1.5†	-	8.2†	5.4
Nr 322, Nonsleepy OSA						
At baseline (PG)	365	22.3	15.0	7.4	-	-
At baseline (PSG)	353	3.8	3.1	2.4	-	-
At 3 mo (PG with CPAP)	504	48.4	4.5	4.3	12.7	0.5
At 1 yr (on CPAP)	-	-	3.6†	-	11.0†	1.8

Definition of abbreviations: AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; mo, month; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PG, polygraphy; PSG, polysomnography; TST, total sleep time; yr, year.

*Estimated sleep time for PG recordings; - Not applicable; †Obtained from the CPAP device; ‡The scorer noted difficulties in the differentiation between periodic limb movements events and respiratory events on the PSG recording.

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eTable 2. CPAP compliance data over time in 122 revascularized patients with coronary artery disease and obstructive sleep apnea (patients who returned the devices are excluded)

	Number of patients on CPAP	Number of CPAP devices checked	CPAP use (hours/night)	CPAP use (% nights/period)	CPAP level in 95th percentile (cmH_2O)	Residual AHI (events/hour)
At 1 month	105	98	4.4 (2.3)	70.4 (29.8)	9.3 (2.2)	9.5 (2.4)
At 3 months	92	88	5.1 (2.1)	73.4 (25.9)	9.7 (1.6)	6.2 (5.1)
At 6 months	83	79	5.5 (1.9)	71.6 (27.4)	9.9 (2.8)	6.2 (4.9)
At 1 year	76	73	5.8 (1.7)	76.6 (24.1)	9.5 (1.6)	5.9 (4.3)
At 2 years	70	67	6.0 (1.7)	74.0 (24.9)	9.6 (2.9)	5.4 (3.6)
At 3 years	55	53	6.1 (1.8)	74.5 (22.6)	9.2 (1.7)	6.0 (3.4)
At 4 years	35	33	6.2 (1.7)	73.4 (22.6)	8.7 (1.7)	5.4 (2.8)
At 5 years	21	12	6.9 (1.2)	78.0 (16.4)	10.4 (5.1)	4.5 (3.4)
At 6 years	11	9	6.6 (1.3)	69.1 (19.1)	9.5 (2.4)	5.0 (2.4)

Values are mean (standard deviation).

Definition of abbreviations: AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

eTable 3. Number of individual primary and secondary endpoint events in subgroups of the intention-to-treat population (between-group differences were not statistically significant).

	Nonsleepy OSA on CPAP	**Nonsleepy OSA no-CPAP**
Overall	n=122	n=122
Repeat revascularization	17	14
Acute myocardial infarction	11	8
Stroke	3	6
Cardiovascular death	3	7
Noncardiovascular death	4	2
Acute hospital admissions for CVD	30	32
PCI subgroups	n=89	n=89
Repeat revascularization	16	12
Acute myocardial infarction	10	6
Stroke	2	4
Cardiovascular death	2	6
Noncardiovascular death	2	1
Acute hospital admissions for CVD	25	28
CABG subgroups	n=33	n=33
Repeat revascularization	1	2
Acute myocardial infarction	1	2
Stroke	1	2
Cardiovascular death	1	1

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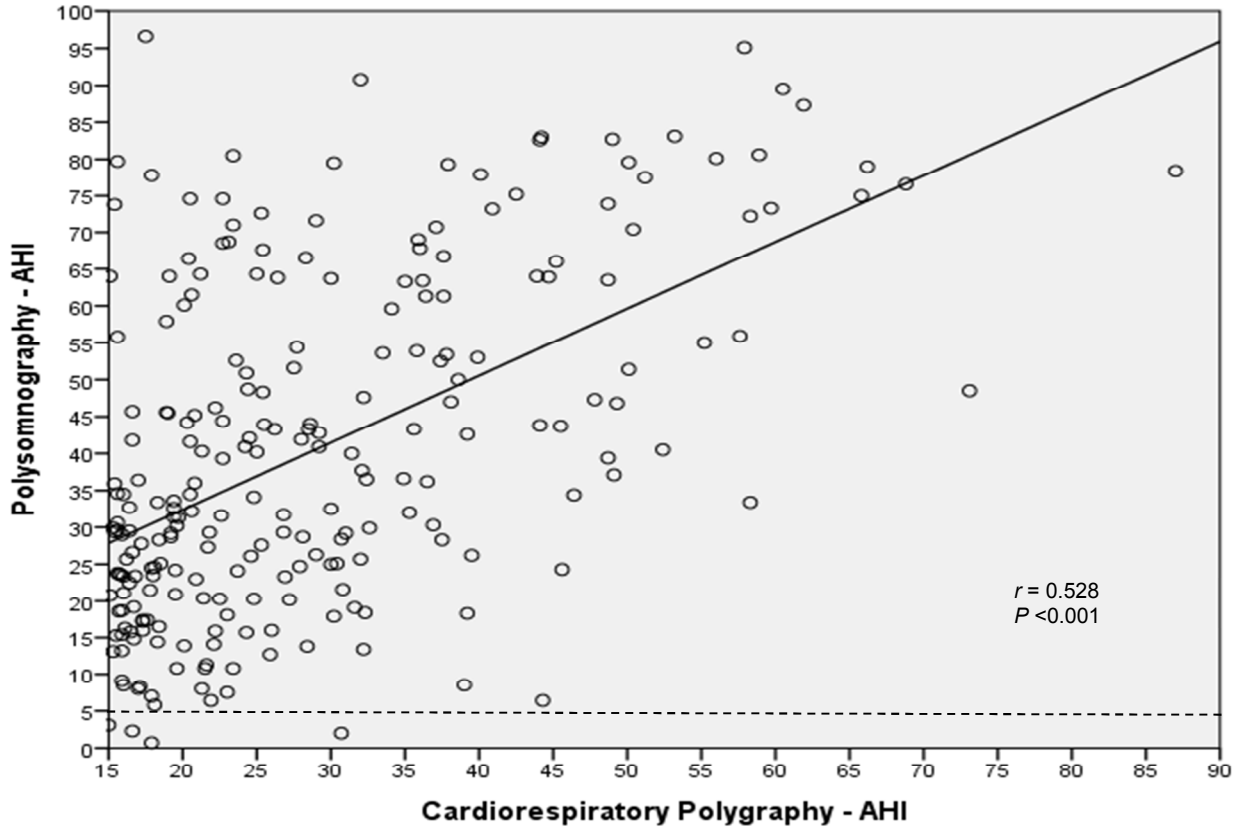
Noncardiovascular death	2	1
Acute hospital admissions for CVD	5	4

Definition of abbreviations: CABG, coronary artery bypass grafting; CVD, cardiovascular disease; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

eFigure 1. Apnea-hypopnea index (AHI) in OSA patients based on polygraphy versus polysomnography



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References

E1. American Academy of Sleep Medicine Task Force Report. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999;22:667-689.

E2. Norman RG, Ahmed MM, Walsleben JA, Rapoport DM. Detection of respiratory events during NPSG: nasal cannula/pressure sensor versus thermistor. *Sleep* 1997; 20:1175-1184.

E3. Peker Y, Glantz H, Thunström E, Kallryd A, Herlitz J, Ejdebäck J. Rationale and design of the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea (RICCADSA) trial. *Scand Cardiovasc J* 2009;43:24-31.

E4. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda, Maryland, U.S. Department of Health, Education, and Welfare Public Health service - National Institutes of Health, 1968.

E5. Dingli K, Coleman EL, Vennelle M, Finch SP, Wraith PK, Mackay TW, Douglas NJ. Evaluation of a portable device for diagnosing the sleep apnoea/hypopnoea syndrome. *Eur Respir J* 2003;21:253-259.

E6. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-545.

E7. Oksenberg A, Silverberg D, Offenbach D, Arons E. Positional therapy for obstructive sleep apnea patients: A 6-month follow-up study. *Laryngoscope* 2006;116:1995-2000.

E8. Hansson L, Hedner T, Dahlöf B. Prospective randomized open-blinded end-point (PROBE) study: a novel design for intervention trials. *Blood Pressure* 1992;1:113-119.

E9. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in

patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998;351:1755-1762.