250422 Gothenburg, Sweden

Analysis plan: Twin threat of OSA and hypertension on mortality and protective effect by positive airway pressure treatment.

ClinicalTrials.gov Identifier: NCT06930989

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Analysis plan: Twin threat of OSA and hypertension on mortality/CV-risk and protective effect by positive airway pressure treatment.

HYPOTHESIS

1. Patients with hypertension and obstructive sleep apnea (OSA) have increased risk of MACE (major cardiovascular events and death from these events; stroke, cardiovascular death, acute myocardial infarction, incident heart ischemia or heart failure) or premature death of any cause compared to HT alone or OSA alone and compared to healthy controls.
2. OSA patients compliant with PAP have reduced OSA related risk.

STUDY DESIGN

Discovery[1] ("Course of DISease in patients reported to the Swedish CPAP Oxygen and VEntilator RegistrY") 2.0 is a large clinical cohort on patients with home mechanical ventilation, long-term oxygen treatment and/or CPAP treatment with data from the Swedish national register for patients on Long Term Oxygen Therapy and Home Mechanical Ventilation (Swedevox) and the Swedish Sleep Apnea Registry (SESAR). Data are cross referenced using Swedish personal IDs with data from multiple Swedish national registries including the National Patients diagnosis registry, National prescription registry, National Cause of Death Register, and SCBs registries on socioeconomic information. Data quality in the SWEDEVOX and SESAR registries have been validated for accuracy[2].

The following *inclusion criteria* will be applied:

- All adult patients that started PAP treatment during 2010-2021 in Swedevox with diagnosis of OSA with or without comorbid hypertension diagnosis within 5 years prior

initiation of CPAP therapy.

- Randomly selected individuals from the general population without a known OSA diagnosis but with and without arterial hypertension are selected for control groups.

Exclusion criteria for study participation are:

- Patients with manifest cardiovascular disease (stroke, ischemic heart disease, cardiac failure or atrial fibrillation at baseline).
- Patients with kidney failure at baseline.
- Patients with malignant cancer at baseline.
- Subjects with missing data on any of the main variables in the fitted models.

January 2010 is the start date for the non OSA groups. Follow-up time for the study will be until end of October 2022.

Hazard ratios from Cox proportional survival analyses for all-cause death and first MACE event (including CV death events) will be calculated controlling for anthropomorphic data (age, Body Mass Index (BMI), sex), comorbidities (hyperlipidemia, diabetes, depression and obstructive lung disease) medication (AHTs, statins and compliance of these drugs), and number of AHTs at baseline and socioeconomic factors (education level and income) and differences in age at first event between groups will be evaluated. Secondary analyses will investigate hazard ratios for all cause death and first MACE in OSA and HT+OSA groups, stratified by hourly usage per day of PAP to evaluate potential protective effect of PAP treatment on outcomes.

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Hypertension at baseline is defined as having both hypertension diagnosis AND being prescribed at least one AHT drug. AHT drug is defined as intake of betablockers, diuretics, calcium channel blockers, Renin-Angiotensin-System blockers or centrally acting antihypertensives. Drug dispension data will be used for assessment of patient compliance with drug treatment. Compliance with prescribed AHT and statins will be categorized as follows: At least 2 drug dispensions per year for ¾ of the study time with active prescription of that drug for each individual AHT group or statin required for high compliance. Total AHT compliance will require high compliance of all prescribed AHTs for more than ¾ of the individual study time, while patients only taking some of the prescribed AHTs will count as low combined compliance. The ¾ of study time criteria is used in order to avoid misclassifying change of AHT as poor compliance.

Ethical considerations

The study protocol was approved by the Ethics Committee at the Medical Faculty at Lund University and the Swedish Ethical Review Authority, Dnr. 2018/51, 2019/01420, 2020/02721, 2021/04984, 2022-00745-02, 2022-02012-02, 2022-05523-02, 2024-05277-02, and 2025-00712-02. According to Swedish law, patients entering a national quality registry like Swedevox are informed, can withdraw from registration at any time, but do not sign an informed consent.

Statistical analyses

Continuous data following a normal distribution will be reported as mean ± standard deviation (SD), while data with a skewed distribution will be presented as median along with the interquartile range (IQR). Categorical data will be represented as frequencies and percentages. Categorical variables will be

analyzed with the chi-squared test, normally and non-normally distributed continuous variables will be analyzed with Student's t-test and the Wilcoxon rank-sum test respectively. ANOVA is used to compared variables between groups.

Medians and 95% CI are reported for follow-up time for the groups and total.

Mortality and MACE incidence will be visualized using Kaplan-Meier cumulative mortality/incidence estimate curves. Survival differences between groups will be analyzed using log-rank tests. Crude and adjusted Cox proportional survival analyses will be made. Covariates are selected using current litterature, clinical experience and directed acyclic graphs. Hazard Ratio, Relative Risk, and CI are reported for COX analyses. Separate Cox proportional survival analyses will be made to investigate difference between the two OSA groups and to assess PAP protective effect and adherence in a similar manner.

Both all-cause death and MACE/CV related deaths will be reported separately for primary and secondary outcomes.

All estimates will be presented with 95% confidence intervals (CIs). Statistical significance is defined as a two-sided p-value < 0.05.

DATA MANAGEMENT

Definition of primary outcome

Hazard ratios for all groups MACE/death event risk. Mean age at MACE/death event for all groups.

Definition of secondary outcome

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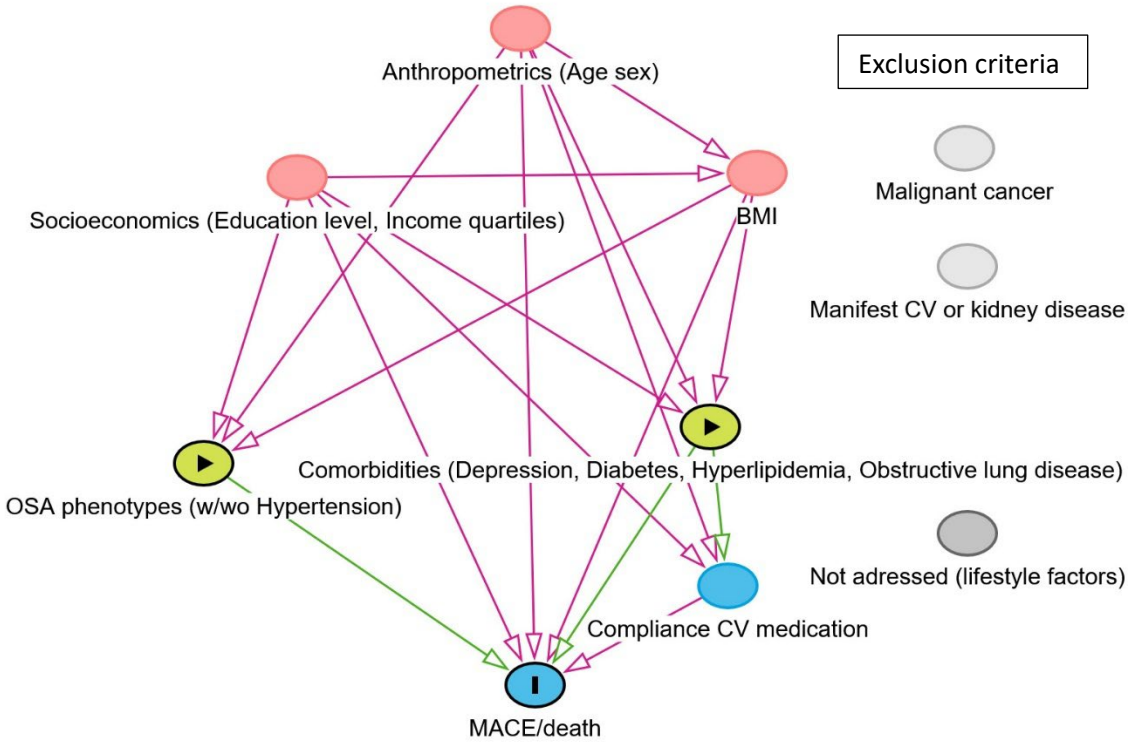
Modifying effect of PAP treatment analysis stratified by compliance/daily usage time per night on primary outcomes.

Definition of exposure

Hypertension diagnosis and or OSA for primary outcomes.

PAP treatment (Swedevox 2010-2023) for secondary outcomes.

DAG:



Lifestyle factors include smoking, food habits and physical activity, where we lack data. Will be indirectly controlled for thru inclusion of socioeconomic factors, anthropometrics, compliance of treatments and obstructive lung disease.

Analysis plan: The synergistic effect of OSA and hypertension on mortality can be attenuated by positive airway pressure treatment.

Variables and timing of variables to be obtained from database(s):

Below are the variables to be considered in the analysis listed.

All non-outcome variables for baseline inclusion as well as latest available at study end. For sleep data first available data will be considered baseline information.

Sleep data

AHI, ODI, ESS (Epworth sleepiness scale), mean saturation. Date of OSA diagnosis and PAP start. *Baseline or if missing; above mentioned data are possibly available from the CPAP start.* For sleep data first available data will be considered baseline information.

Sleep follow-up data during treatment follow-up

PAP compliance (hrs/day) closest before MACE/death or end of study. Continuous and stratified compliance and considered to have the same compliance for rest of study duration.
ESS.

Medication

All **AHT** *before PAP start, last* year *before MACE/death or study end*. Patients picking up a drug at least twice during the last year are considered on that drug for a visit. *Dosing needed separately for each drug.*

Statins at *baseline and end of study*.

Number of medication pickup dates for each calendar year will be calculated and used for compliance estimations.

Diagnosis

All diagnoses before PAP start and end of study. MACE or new AF *at any time*. Reasons for death when applicable.

ICD codes of interest (both patient registries and/or swedevox):
Diabetes (E10-E14), Hyperlipidemia E78, COPD J44, Kidney failure (N17-N19), Depression F32 and 33, Hypertension (I10-I15), OSA G47.3, ischemic heart disease (I20-25), AF I48, Cardiac failure I50, Stroke I61-66. Malignant cancer C00-C97. Ischemic heart disease or infarction, Atrial fibrillation, Cardiac failure or Stroke *Baseline and first new diagnosis for MACE*.

All else *baseline and study end*.

Socioeconomic data

Baseline and study end. European socioeconomic classification (ESeC/YSEG in SCB), Education level, Income quartiles.

Smoking

Indirectly assessed through “Obstructive lung disease” (diagnosis captured from medication use), socioeconomic variables, BMI and compliance with primary preventive treatments.

Anthropometrics

Baseline Age, BMI, gender. *PAP start and study end*.

Control group

One healthy group and one group with hypertension only. Same data (except to OSA/PAP data) and timepoints.

Death registry

All deaths, CV death and Traffic accident death *during study*. ICD codes: I20-I25, I46, I48, I50, I61-I66, for CV death.

Main Analysis

COX proportional regression model (every group compared to healthy control) for all-cause

death and MACE including CV death. Comparison between survival curves will be made by Log Rank test

Included variables in main analyses:

- Age, sex and BMI
- Comorbidities: Depression, Diabetes, Hyperlipidemia and Obstructive lung disease (see above).
- Number of AHTs at baseline
- Compliance AHTs
- Statin Y/N and compliance
- Socioeconomic: Education level and Income quartiles
- OSA severity
- EDS
- Observation time (time at risk) part of COX
- AHI or ODI (use the one with strongest association with outcomes). Collinearity will be a problem if both are used.
- PAP compliance

Variables with no effect on outcomes that are not deemed essential can be excluded from the reported analysis.

Outcomes (patients censored after first event):

- First MACE or death.
- Age at MACE/death

Secondary analyses

COX proportional regression models comparing OSA+HT group against OSA-only group.

Same as above but with stratified PAP usage to assess if any PAP protective effect is increasing with higher compliance.

Analysis plan: The synergistic effect of OSA and hypertension on mortality can be attenuated by positive airway pressure treatment.

FUTURE AMENDMENTS

Version 1: 240905

Version 2: 250321

Final version: 250407

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REFERENCES

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2. Ekström M, Albrecht D, Andersson S, Grote L, Kärrsten Rundström B, Palm A, et al. Validation of the Swedevox registry of continuous positive airway pressure, long-term mechanical ventilator and long-term oxygen therapy. ERJ Open Res 2021; 7.