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Estimates of 10-year risk of cardiovascular death and adherence to cardiovascular risk factor management in Danish patients investigated for obstructive sleep apnea

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) increases the risk of cardiovascular disease (CVD) in both morbidity and mortality. We used the risk chart of Systemic Coronary Risk Evaluation (SCORE) from European Society of Cardiology (ESC) to determine the 10-year risk of cardiovascular death, and adherence to cardiovascular risk factor management in Danish patients investigated for obstructive sleep apnea.

Research design and methods: In a prospective cohort study, 303 patients with mild, moderate and severe OSA were investigated for cardiovascular risk factors before initiating CPAP therapy. Primary outcome was estimates of 10-year risk of cardiovascular death assessed from the ESC risk chart SCORE based on sex, age, smoking status, systolic blood pressure and s-total cholesterol. Furthermore we analyzed treatment indication with statins in patients with mild (apnea-hypopnea index, AHI <15), moderate (AHI 15–29.9) and severe OSA (AHI ≥30).

Results: Patients with mild OSA predominately had low or moderate 10-year risk of CVD (low risk 55.4%, moderate risk 30.8%) while patients with moderate and severe OSA were more likely to have high or very high risk of 10-year CVD ($p = 0.001$). The large majority of included OSA patients had dyslipidemia, 235 (77.6%) and of those, only 27.4% were treated with cholesterol lowering drugs while additional 27.7% were eligible for oral statin supplement as risk-estimated by the ESC SCORE. In multiple regression analysis among statin naive patients, AHI was positively associated with statin eligibility when adjusted for age and sex.

Conclusion: Patients with moderate and severe OSA had an elevated 10-year risk of fatal CVD and were undertreated with CVD risk lowering agents such as statins.

1. Introduction

Obstructive sleep apnea (OSA) is a growing health concern and increasingly common among adult patients. OSA is characterized by repeated pharyngeal collapses during sleep resulting in intermittent hypoxaemia and sleep fragmentation [1]. Prevalence of OSA has increased world-wide and is often linked to obesity. Obesity is an established risk factor for OSA and the risk of OSA correlates with body-mass-index (BMI) [2]. OSA is diagnosed in 3–5% of middle-to older age woman and 10–17% of men in similar age-groups [3,4]. OSA is associated with numerous cardiovascular risk factors including atrial fibrillation (AF), hypertension, diabetes, stroke, heart failure, metabolic syndrome and coronary artery disease [5]. Metabolic syndrome is a general term covering a cluster of risk factors of (abdomal) obesity, dyslipidaemia, hypertension and insulin resistance. The link of metabolic syndrome and OSA is well established and occurrence of elements included in metabolic syndrome increases along with severity of OSA [6].

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Abbreviations:

AHI	Apnea-hypopnea index
AMI	Acute myocardial infarction
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
CABG	Coronary artery bypass grafting
CVD	Cardiovascular disease
ELR	External loop recorder
IHD	Ischemic heart disease
MI	Myocardial infarction
OSA	Obstructive sleep apnea
SCORE	Systematic Coronary risk Evaluation
TIA	Transient ischemic attack

Dyslipidaemia and the connection to cardiovascular disease (CVD) and death is well described. In 2019 it was estimated that about 4.40 million (95% CI 3.30–5.65 million) deaths were ascribed to high plasma LDL-cholesterol levels. Most common are hypercholesterolaemia, accountable for the no 8th leading risk factor for death in 2019 [7]. In terms of treating dyslipidaemia, use of statins has increased over the years promoting large reductions in plasma cholesterol and in countries with high income it has reduced deaths from CVD [7]. Disturbances in metabolism such as hypercholesterolaemia, altered levels of triglyceride and high-density lipoprotein reduction are linked to oxidative processes as seen in OSA [8]. A clear causal correlation between dyslipidaemia and OSA has yet to be demonstrated, but recent studies suggest that OSA is able to cause pro-atherogenic dyslipidaemia that increases triglycerides with high levels of lipoproteins in particular [9].

The risk chart from European Society of Cardiology (ESC) Systematic Coronary Risk Evaluation (SCORE) is a recommended tool for risk stratification and is widely used to identify 10 year risk of fatal cardiovascular event using known risk factors. The aim of this study was to evaluate the calculated 10 year risk of death from a cardiovascular event in patients with OSA based on the ESC 2019 SCORE risk chart and hence the indication for preventive lipid-lowering treatment in patients with OSA.

2. Methods

2.1. Study population

303 patients investigated for sleep disordered breathing were included as a part of an observatory prospective study and underwent one night sleep examination with a type 3 portable monitoring device (Nox T3™ device (ResMed, CA, USA). Based on outcome of the sleep examination, patients were allocated in groups of mild, moderate and severe OSA according to the Apnea-hypopnea Index (AHI). Hearth rhythm analysis was additionally performed with external loop recorder at home.

Patients were included at two sites; the outpatient sleep clinic at the department of Otorhinolaryngology and Maxillofacial Surgery at Zealand University Hospital in Denmark and at a Private Ear, Nose and Throat (ENT) clinic. Enrolment period was from Oct 1st, 2018–May 29th, 2020. As the overall study additionally was designed to determinate silent, unknown atrial fibrillation, patients already receiving anticoagulation treatment or with known atrial fibrillation were excluded as well as patients with incomplete monitoring or lack of blood samples or ECG performed. 143 eligible patients did not wish to participate, resulting in a total of 192 patients were excluded in the study (Fig. 1). Results on silent atrial fibrillation and OSA have recently been published [10].

Baseline information of risk factors and patient characteristics, previous hospitalisations and medical records or ICD-10 codes was assessed at first-visit interview. When enrolled, patients were questioned of their smoking habits, medications and general medical history including existent cardiovascular risk factors such as type 2 diabetes, hypertension and hypercholesterolaemia.

Waist-hip circumference and blood pressure were measured and ECG together with blood samples including full lipid profile and blood glucose were obtained. Diagnostic criteria for hypertension were measurements of 3 consecutive blood pressures at resting state of a minimum of 140 mmHg systolic or 90 mmHg diastolic pressure at time of enrolment or current antihypertensive treatment. Metabolic syndrome was defined as central obesity (waist circumference >94 cm for men and >80 cm for women) and two of the following; triglycerides >1.7 mmol/L, or treatment; HDL >1.0 for men and >1.3 for women; resting fasting blood glucose >5.6 or previously diagnosed with type 2 diabetes; blood pressure >130/85 or treatment for hypertension [11]. Dyslipidaemia was defined as elevated plasma concentrations (p-concentration) of LDL-cholesterol (>4.9 mmol/L) or total-cholesterol (>5 mmol/L) or triglycerides >2.6 mmol/L or low *p*-HDL or a combination or treatment with oral cholesterol lowering drugs [7,12]. Statin eligibility was calculated from SCORE risk calculations and defined as patients naive patients at inclusion but qualified for dyslipidaemia from the *2019 ESC/EAS guideline for management of dyslipidaemia*[13].

2.2. AHI-index and heart rhythm monitoring

Apnea Hypopnea Index (AHI) was used to determine the severity of sleep apnea. It was characterized by the number of apneas, hypopneas, mixed and central apneas per hour of sleep. AHI below 5 is considered normal, 5–14.9 was defined as mild OSA, an AHI of 15–29.9 were moderate, and an AHI of 30 or above was defined as severe OSA [14]. Sleep examination was performed with the Nox T3™ device *(ResMed, CA, USA*).

Home monitoring of hearth rhythm and outcomes from this *study have already been submitted for publishing*. Patients were investigated at home with an event-triggered, external loop recorder (ELR) device for a period of 7 days. In this study the device used was the R.Test Evolution 4® *(NorDiaTech, Paris, France).*

2.3. Outcome measures

Primary outcome was estimates of 10-year risk of cardiovascular death assessed from the 2019 ESC/EAS risk chart Systematic Coronary Risk Estimation (SCORE) [13] in a population of patients investigated for sleep disordered breathing. Cardiovascular risk was defined as the likelihood of a person developing an arteriosclerotic cardiovascular event over a specific period of time. The 10-year risk of fatal cardiovascular death was based on several risk factors including age, gender, smoking, systolic blood pressure and total cholesterol [13]. In this study, we have used the low-risk chart for the Danish population, as risk estimations differs between countries. Patients with OSA were stratified in groups according to the cardiovascular risk categories of low, moderate, high and very high risk defined by the 2019 ESC risk chart SCORE [13]:

Low-risk (calculated SCORE <1% for 10-year risk of fatal CVD). *Moderate-risk* (young patients with type 1 diabetes mellitus <50 years with a diabetes duration <10 years and without other risk factors, or a calculated SCORE >1% and <5% for 10-year risk of fatal CVD). *High-risk* (individuals with elevated single risk factors; etc. Total cholesterol >8 mmol/L, LDL >4.9 mmol/L or blood pressure

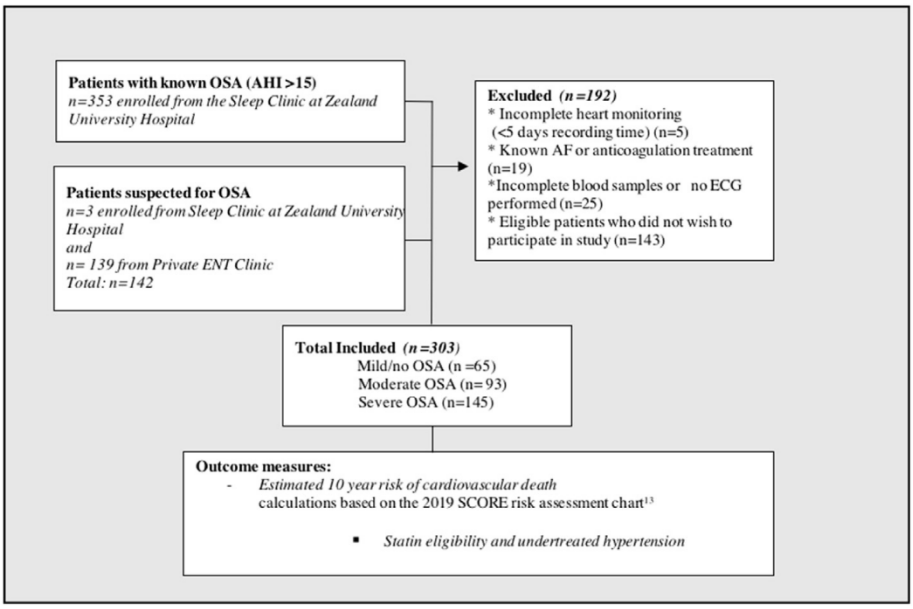

Fig. 1. Patient flow diagram.
AHI: apnea-hypopnea-index. OSA: obstructive sleep apnea. SCORE: systematic coronary risk evaluation.

>180/110 mmHg or familial hypercholesterolaemia without other major risk factors or a calculated SCORE of ≥5% and <10% for 10-year risk of fatal CVD) [13].

Very-high-risk (individuals with any of the following: verified arteriosclerotic cardiovascular disease; including previously acute coronary syndrome (unstable angina or myocardial infarction), stable angina, coronary revascularization (PCI, CABG) stroke and TIA or a calculated score of ≥10% for fatal CVD).

2.4. Statistics

Categorical data are in absolute numbers (percentages) and continuous data are presented as mean value (± standard deviation (SD). In comparisons of categorical data we used chi-square test and unpaired - test for continuous variables. One-way analysis of variance, ANOVA, was used for analysis of independent groups. All test were two-sided, and a value of <0.05 was considered statistically significant. Multiple regression analysis with stepwise backwards elimination listed as odds ratios (OR) with confidence intervals (95% CI) was performed and used to identify risk factors independently associated with AHI, dysregulated hypertension and statin eligibility. For analysing data we used R studio v.1.1.463 and SPSS v.28 for MAC/OS X.

2.5. Ethics

Permissions were obtained from the Danish Regional Ethics Committee and The Danish Data Protection Agency *(protocol number: SJ-714)* and *(case number: reg-033-2018)*. Informed and written consent was obtained from all patients in the study.

3. Results

In this prospective observational study, the total cohort consisted of 303 patients with varying degrees of OSA; 65 (21.5%) patients had mild OSA while 93 (30.7%) and 145 (47.9%) patients presented with moderate and severe OSA. Table 1 shows the baseline characteristics of patients, classified according to mild, moderate and severe OSA.

Dyslipidemia was found in more than 3 of 4 patients (n = 235, 77.6%) of which almost half was unknown (49.8%). Lipid status from blood samples including *p*-LDL, p-triglyceride and total p-cholesterol varied among groups of OSA severity in univariate analysis (Table 1). Furthermore, the lowest values of *p*-HDL were found in patients with the highest degree of sleep apnea. A higher BMI, a higher waist/hip ratio and prevalence of metabolic syndrome were more frequent in patients with moderate and severe OSA. Elevated heart rate and both higher systolic, diastolic blood pressure were more prevalent with increasing OSA severity (Table 1). Similarly, we found a positive dose-response association of severity of OSA and prevalence of higher p-Hb1Ac, prediabetes and type 2 diabetes (Table 1).

3.1. Calculated 10-year risk of fatal CVD

The calculated SCORE for 10-year risk of death from a cardiovascular event varied between groups of patients with mild, moderate and severe OSA ($p < 0.001$) with a mean ranging from 1.1 to 3.1% (SD 2.2–3.4) risk in ANOVA analysis (Table 2). The risk variables of patients with OSA and their corresponding SCORE risk categories *low, moderate, high* and *very high* are illustrated in Table 3. Most patients with mild OSA had *low* (55.4%) or *moderate (30.8%)* 10-year risk of fatal CVD.

In patients with moderate OSA, most patients (41.9%) had moderate 10-year risk of fatal CVD, however, >20% of patients had *high* 10-year risk of fatal CVD and 12.9% had *very high* 10-year risk of fatal CVD (Table 3). In patients with severe OSA, 28.3% had *high* 10-year risk of fatal CVD and 16.6% had *very high* risk (Table 3). Fig. 2 visualizes how the prevalence of low risk of 10-year risk of fatal CVD decreases with increasing severity of OSA and in contrast, the prevalence of moderate to very high risk of 10-year risk of fatal CVD increases significantly with severity of OSA ($p = 0.001$, Table 3, Fig. 2).

In the total cohort of 303 patients, 235 (77.6%) patients had dyslipidemia and out of these 235 patients with dyslipidemia, 83 (27%) were already receiving cholesterol lowering drugs, while

Table 1
Characteristics of patients with mild, moderate and severe OSA, mean (SD) Data shown as mean value, SD unless indicated otherwise. For continuous data comparisons, one-way ANOVA was used for analysing, while chi-square test was used for nominal data. % in parenthesis.

	All Patients n = 303	Patients with AHI <15 n = 65	Patients with AHI 15–30 *n = 93*	Patients with AHI >30 *n = 145*	*p-value*
Male, n (%)	208 (68.6)	*37 (56.9)*	61 (65.6)	110 (75.9)	*0.018*
Age, years, mean (SD)	56.4 (12.4)	50.2 (13.1)	57.6 (11.5)	57.6 (11.9)	*<0.001*
Hypertension, n %	200 (66.0)	28 (43.1)	60 (64.5)	112 (77.2)	*<0.001*
Dysregulated hypertension[a]	83 (27.4)	9 (13.8)	23 (24.7)	51 (35.2)	*0.005*
Hypertension, unknown n, %	78 (25.7)	12 (18.5)	25 (26.9)	41 (28.3)	*0.31*
Undertreated hypertension n, %	161 (53.1)	21(32.3)	48 (51.6)	92 (63.5)	*<0.001*
Dyslipidaemia, n %	235 (77.6)	44 (67.7)	73 (78.5)	118 (81.4)	*0.08*
Dyslipidaemia, unknown n, %	151 (49.8)	31(47.7)	48 (51.6)	72 (49.7)	*0.89*
Treatment with oral cholesterol lowering drugs	83 (27.4)	13 (20)	25 (26.9)	45 (31)	*0.25*
BMI, kg/m2, mean (SD)	31.6 (6.6)	29.6 (5.6)	31.0 (6.6)	32.9 (6.8)	*0.002*
Type 2 diabetes, n %	48 (15.8)	4 (6.2)	13 (14.0)	31 (21.4)	*0.017*
Type 2 diabetes unknown, n	9 (2.9)	1 (1.5)	2 (2.2)	6 (4.1)	*0.51*
Prediabetes, n % (HbA1c 42–47 mmol/L)	36 (11.8)	2 (3.1)	13 (14.0))	21 (14.5)	*0.046*
HbA1c, mmol/L, mean (SD)	40 (10.2)	36.9 (11.5)	38.7 (7.5)	42.3 (10.6)	*<0.001*
Pack-years, cigarettes, mean, (SD)	13.9 (17.5)	7.9 (9.7)	15.3 (18.1)	15.9 (19.2)	*0.004*
Triglyceride, mmol/L, mean (SD)	2.2 (1.5)	1.8 (1.4)	2.1 (1.2)	2.4 (1.7)	*0.019*
HDL cholesterol mmol/L, mean (SD)	1.3 (0.4)	1.4 (0.5)	1.4 (0.4)	1.2 (0.4)	*0.043*
LDL cholesterol mmol/L, mean (SD)[b]	2.9 (0.9)	3.1 (1.0)	2.9 (0.9)	2.8 (1.0	*0.07*
Waist/hip ratio, mean, (SD)	1.0 (0.1)	0.9 (1.2)	1.0 (0.1)	1.0 (0.1)	*<0.001*
Systolic blood pressure, mmHg, mean (SD)	143.7 (19.9)	134.9 (17.6)	144.5 (18.3)	147.3(20.9)	*<0.001*
Diastolic blood pressure, mmHg, mean (SD)	88.2 (11.8)	87.3 (10.3)	85.6 (10.4)	90.3 (12.9)	*0.009*
Heart-rate, mean (SD)	72.4 (12.8)	70.8 (14.2)	68.8 (11.3)	75.6 (12.5)	*<0.001*
Metabolic syndrome	212 (70.0)	28 (43.0)	70 (75.3)	114 (78.6)	*<0.001*
Central apneas (SD)	10.3 (26.3)	2.1 (3.3)	6.0 (8.1)	16.8 (36.4)	*<0.001*

Table 1: Baseline characteristics before initiating CPAP treatment. AHI: apnea-hypopnea-index, Dysregulated hypertension: patients treated pharmacological for hypertension with blood pressure at consult >140 systolic and/or 90 diastolic mmHg measured 3 times at resting state. Dyslipidemia: Treatment with oral cholesterol-lowering drugs or total cholesterol >5 mmol/L or triglycerides >2.6 mmol/L. Metabolic syndrome: central obesity (waist circumference >94 cm for men and >80 cm for women) and two of the following; triglycerides >1.7 mmol/L, or treatment; HDL >1.0 for men and >1.3 for women; resting fasting blood glucose >5.6 or previously diagnosed with type 2 diabetes; blood pressure >130/85 or treatment for hypertension. OSA: obstructive sleep apnea. SD: standard deviation. Undertreated hypertension: dysregulated hypertension in patients with known hypertension and unknown hypertension.
[a] Patients in treatment with oral supplements for hypertension.
[b] Missing blood samples from 20 patients due to very high triglycerides, the formula of Friedewald is not used on these patients.

Table 2
Calculated SCORE for 10-year risk of fatal CVD in patients with varying amount of OSA, mean (SD) Data shown as mean value, SD unless indicated otherwise. One-way ANOVA was used for analysing continuous data.

	All patients *(n = 303)*	Mild OSA AHI <15 *(n = 65)*	Moderate OSA AHI 15–30 *(n = 93)*	Severe OSA AHI >30 *(n = 145)*	*p-value*
Calculated SCORE, mean (SD)	2.6 (3.2)	1.1 (2.2)	2.9 (3.3)	3.1 (3.4)	*<0.001*
Statin eligibility based on SCORE risk n, (%)[a]	54 (17.8)	6 (13)	17 (33.3)	31 (45)	*0.030*

Table 2: Calculated SCORE for 10 year risk of fatal CVD in patients with mild, moderate and severe OSA.
AHI: apnea hypopnea index. ANOVA: analysis of variance. CVD: cardio vascular disease. OSA: obstructive sleep apnea. SCORE: Systematic Coronary risk Evaluation SD: standard deviation.
[a] Statin eligibility based on SCORE risk calculations was defined as patients not already receiving statin treatment at inclusion but meet the criteria for statin treatment according to the *2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk*. Calculations of statin eligibility was based on data from the 220 patients not already in treatment with oral cholesterol lowering drugs.

additional 54 (17.8%) patients were eligible for pharmacological intervention with statin treatment. More patients with moderate and severe OSA were eligible for statin treatment in univariate analysis (p = 0.003) compared to patients with mild OSA.

In multiple regression analysis, AHI was significantly associated with statin eligibility when adjusted for age and sex (Table 4). In the total cohort of 303 OSA patients, 200 (66%) had hypertension and in 78 (25.7%) of these hypertension cases, the diagnosis was unknown. Of patients taking medication for hypertension, 27.4% were still dysregulated in their hypertension. Overall, undertreated hypertension (includes both patients with poorly regulated hypertension in patients with known hypertension in addition to patients with unknown hypertension) was seen in a total of 161 (53%) patients (Table 1). Undertreated hypertension was positively associated with higher age and higher AHI in multiple regression analysis (Table 5).

All 238 (78.6%) patients with undertreated hypertension, dyslipidemia or diabetes were contacted and advised further treatment by their general practitioner. Additionally, one patient was admitted directly to the emergency room for treatment due to a systolic blood pressure >215 mmHg and another patient with severe OSA (AHI = 108) was admitted to the emergency room after enrolment period for acute pancreatitis and additional unknown type 2 diabetes due to high triglycerides (p-triglyceride = 15 mmol/L).

4. Discussion

In this cohort of patients with mild to severe OSA, the 10-year risk of fatal CVD increased significantly with severity of OSA. Notably, we demonstrated that a considerable proportion of OSA patients had *high* or *very high* 10-year risk of fatal CVD, which in most cases represented an indication for cholesterol lowering therapy. We used the ESC/EAS guidelines on the use of statins for

Table 3
Calculated SCORE risk variables for 10-year risk of fatal CVD in patients with mild, moderate and severe OSA Data shown as mean value, SD unless indicated otherwise. For continuous data comparisons, unpaired *t*-test was used, while chi-square test was used for nominal data. % in parenthesis.

	Low-risk (Calculated SCORE <1%)	Moderate-risk (Calculated SCORE ≥1% and <5%)	High-risk (Calculated SCORE ≥5% and <10)	Very-high-risk (Calculated SCORE ≥10%)	P value
Mild OSA (AHI <15), N = 65	*36 (55.4)*	*20 (30.8)*	*4 (6.2)*	*5 (7.7)*	
Male gender, n %	19 (52.8)	12 (60)	3 (75)	3 (60)	0.83
Age, mean (SD)	42.7 (8.7)	56.7(9.7)	59.0(13.6)	71 (13.2)	<0.001
Systolic blood pressure, mmHg, mean (SD)	129.5 (25.2)	138.6 (18.2)	147.8 (15.3)	148.8 (21.8)	0.020
Total cholesterol, mean (SD)	5.1 (1.1)	5.6 (1.1)	5.9 (0.9)	4.5 (1.1)	0.13
Current smokers, n %	7 (19.4)	4 (20)	1 (25)	1 (20)	0.995
SCORE risk for 10-year fatal ASCVD, mean (SD)	0.03 (0.2)	1.7 (0.9)	2.8 (2.6)	5.4 (5.6)	<0.001
Moderate OSA (AHI 15-29.9), N = 93	*22 (23.7)*	*39 (41.9)*	*20 (21)*	*12 (12.9)*	
Male gender, n %	13 (59)	24 (61.5)	14 (70)	10 (83.3)	0.47
Age, mean (SD)	44.4 (9.1)	58.0 (6.9)	64.5 (8.5)	68.6 (9.1)	<0.001
Systolic blood pressure, mmHg, mean (SD)	131.6 (16.9)	146.7 (16.8)	150.4 (17.8)	151.1 (17.2)	0.001
Total cholesterol, mean (SD)	4.9 (0.9)	5.4 (1.0)	5.3 (1.2)	4.6 (1.1)	0.089
Current smokers, n %	7 (31.8)	12 (30.8)	3 (15)	3 (25)	0.56
SCORE risk for 10-year fatal ASCVD, mean (SD)	0.0 (0.0)	2.0 (1.5)	4.9 (3.1)	7.5 (4.6)	<0.001
Severe OSA (AHI <30), N = 145	*29 (20)*	*51 (35.2)*	*41(28.3)*	*24 (16.6)*	
Male gender, n %	23 (79.3)	37 (72.6)	31(75.6)	19 (79.2)	0.88
Age, mean (SD)	43 (8.1)	56.3 (8.3)	64.2 (10.2)	66.8 (7.2)	<0.001
Systolic blood pressure, mmHg, mean (SD)	141.4 (21.1)	151 (21.9)	147.5 (18.4)	149.6 (19.3)	0.21
Total cholesterol, mean (SD)	5.2 (0.8)	5.4 (0.8)	5.1 (1.3)	4.5 (1.0)	0.011
Current smokers, n %	7 (24.4)	14 (72.6)	15 (36.6)	7 (29.2)	0.67
SCORE risk for 10-year fatal ASCVD, mean (SD)	0.03 (0.2)	2.0 (1.1)	5.3 (3.5)	5.7 (4.3)	<0.001

Table 3: SCORE risk categories for 10 year risk of fatal CVD in patients with mild, moderate and severe OSA. AHI: apnea-hypopnea-index.
AHI: apnea-hypopnea index. ASCVD: arteriosclerotic cardiovascular disease. CVD: cardiovascular disease. OSA: obstructive sleep apnea. SCORE: Systematic Coronary risk Evaluation. SD: standard deviation.

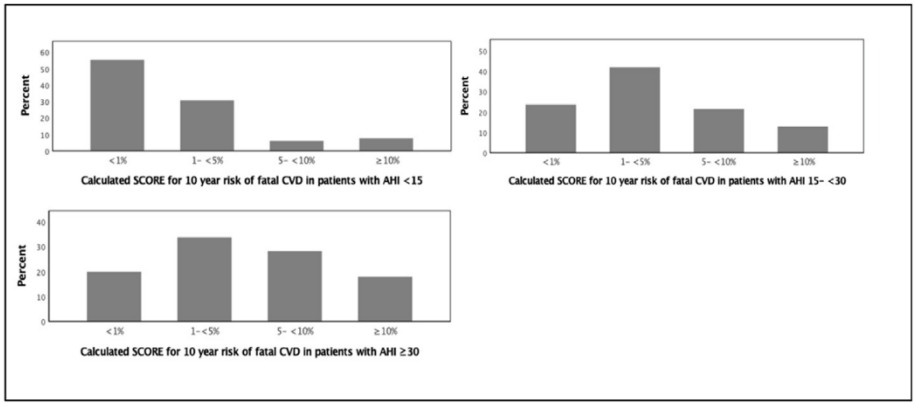

Fig. 2. Patients with varying severity of OSA and their 10-year risk for fatal CVD based on the *ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk*[13].
AHI: apnea-hypopnea-index. OSA: obstructive sleep apnea. SCORE: systematic coronary risk evaluation.

Table 4
Adjusted odds ratio in multiple logistic regression analysis for statin eligibility Multiple regression analysis, backward stepwise elimination (n = 220).

	Odds Ratio	95% CI for exp. Odds Ratio		*p-value*
		Lower	Upper	
Age	1.10	1.1	1.1	<0.001
Male sex	1.56	0.8	3.6	0.21
AHI (increase by 1 in apnea-hypopnea index)	1.02	1.0	1.0	0.019

Table 4: Multiple regression analysis, backward stepwise elimination for AHI and covariates and statin eligibility as the dependent variable. Variables in the model were known risk factors for statin eligibility in addition to baseline variables with a p-value <0.1 from Table 1 were entered in the multiple logistic regression model: age, male sex, AHI, BMI, systolic blood pressure, diabetes, atrial fibrillation, IHD. AHI: apnea-hypopnea-index. AMI: acute myocardial infarction. BMI: body mass index. CI: confidence-interval. IHD: ischemic heart disease.

Table 5
Adjusted odds ratio in multiple logistic regression analysis for undertreated hypertension Multiple regression analysis, backward stepwise elimination (n = 303).

	Odds Ratio	95% CI for exp. Odds Ratio		*p-value*
		Lower	Upper	
Age (increase by 1 year)	1.04	1.0	1.1	<0.001
Male sex	1.08	0.6	1.8	0.78
AHI (increase by 1 in apnea-hypopnea index)	1.02	1.0	1.0	0.001

Table 5: Multiple regression analysis, backward stepwise elimination for AHI and covariates and undertreated hypertension as the dependent variable. Variables in the model were known risk factors for statin eligibility in addition to baseline variables with a p-value <0.1 from Table 1 were entered in the multiple logistic regression model: age, male sex, AHI, BMI, systolic blood pressure, diabetes, atrial fibrillation, IHD. AHI: apnea-hypopnea-index. AMI: acute myocardial infarction. BMI: body mass index. CI: confidence-interval. IHD: ischemic heart disease.

primary prevention of ASCVD (atherosclerotic cardiovascular disease) and found that a large subgroup of at risk, yet statin naïve OSA patients, were eligible for cholesterol lowering therapy. The severity of OSA predicted statin eligibility independently of age and sex. Numerous studies have described the link between OSA and cardiovascular disease [1,5,15,16], but to our knowledge, this is the first published study to investigate the 10-year risk of death from CVD and undertreatment of dyslipidemia in patients with OSA using SCORE risk chart.

The results of our study implies that patients with moderate and severe OSA have a higher risk of a fatal cardiovascular event compared to patients with mild OSA. Comparably, prior studies found a reduction of multifactorial endpoints e.g. cardiovascular death, acute coronary syndrome, severe heart failure in patients treated with CPAP, weight loss or surgery for OSA. However, no randomized trial study have accomplished to demonstrate a clear impact of therapy with CPAP on hard CVD endpoints in OSA patients [17,18].

The ESC/EAS SCORE risk chart is used in a clinical setting to determine whether or not to recommend treatment for possible risk factors of ASCVD. These risk factors include elevated systolic blood pressure, elevated total cholesterol/high LDL, male sex, smoking status and age. When considering possible ways to reduce risk of 10-year fatal CVD in our cohort of patients with OSA, we investigated the link of dyslipidemia, statin eligibility and OSA severity. In univariate analysis, a dose response relationship with OSA severity and statin eligibility was found and increased AHI remained positively associated in multiple regression analysis when adjusting for age and male sex. A Danish population study from 2020 of >45.000 persons of 40–75 years investigated statin eligibility using both the 2016 and 2019 ECS/EAS guideline [19]. They found that 32.3% of individuals were eligible for statin treatment according to the 2019 ECS/EAS guidelines. In our cohort, 45.2% of OSA patients were either statin eligible (17.8%) or on cholesterol lowering drugs (27.4%). This indicates that OSA patients as a risk group have a higher statin eligibility than the background population.

We also found a dose-response relationship for metabolic syndrome, and for the cluster of risk factors that constitutes the metabolic syndrome, including type 2 diabetes, prediabetes, hypertension, dyslipidaemia, BMI and waist-hip ratio. This finding is consistent with other studies linking increased AHI and prevalence of metabolic syndrome [5,6,20,21]. In the ESC guideline, antihypertensive treatment should be considered in patients with moderate SCORE risk (≥1% and <5%) in combination with grade 1 to 3 hypertension [22]. In our study, 27.7% patients had dysregulated and 25.7% unknown hypertension, and total of 53% had undertreated hypertension.

The screening of cardiovascular risk factors, metabolic syndrome and other comorbidities in patients with OSA in Denmark is not consistent and differs among regions. To the best of our knowledge, there are no national or international ENT guidelines considering systematic screening for comorbidities in patients with OSA. Our findings suggest, that the quality of cardiovascular risk factor management in patients with OSA is inconsistent, and many patients might not be aware of the cardiovascular risk factors that are closely linked to sleep apnea. Indications for Class 1/A recommended statin therapy have doubled the number of individuals eligible for therapy with the ESC/EAS 2019 vs. 2016 guidelines [19] and improves prevention of arteriosclerotic CVD. We believe, that the ESC/EAS 10-year risk chart is an essential tool, easily used in a clinical setting when screening for potential risk factors of OSA. This could help to prevent possible future fatal CVD in patients with OSA.

5. Limitations

This study is a secondary analysis of the main prospective and observatory cohort, which was powered to investigate silent and unknown atrial fibrillation in patients with OSA. This cohort was therefore not sample sized to the present analysis of cardiovascular risk and whether the degree of OSA is independently associated with an indication for lipid lowering therapy. It is therefore likely that there exist unrecognized risk associations of OSA and CVD, which this analysis may have been too underpowered to determine.

The ESC risk SCORE was not designed for patients with coexisting coronary disease. Patients with OSA and known concurrent CVD were rare in this cohort not excluded from the study as the prevalence of CVD did not differ between OSA severity groups.

6. Conclusion

The 10-year risk of fatal CVD increased along with cardiovascular risk factors with the severity of OSA. A considerable proportion had dyslipidaemia and a high or very high 10-year risk of fatal CVD, which in most cases represented an indication for cholesterol lowering therapy. In statin naïve patients with OSA and dyslipidaemia, more than 1 in 4 were eligible for statin therapy. The severity of OSA predicted statin eligibility independently of age and sex. We recommend greater attention to consistent cardiovascular risk factor management to improve prevention of cardiovascular morbidity and mortality in the treatment of OSA.

Author contributions

This study was designed, directed and coordinated by AH, TB, MMS, PT and PH. As the principal investigator AH planned, performed and carried out the study. AH and MMS participated in clinical committees and PH additionally contributed in analysing data. AH performed the statistical analysis with MMS and PH who also helped to draft the manuscript. All authors have read, commented and approved the final manuscript.

Declaration of competing interest

Author AH, MMS, PT, TB and PH declared no conflict of interest.

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