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JIM Original Article

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Excessive daytime sleepiness, morning tiredness and major adverse cardiovascular events in patients with chronic coronary syndrome

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Abstract. Olszowka M, Held C, Hadziosmanovic N, Denchev S, Manolis A, Wallentin L, White HD, Stewart RAH, Hagström E, the STABILITY Investigators (Uppsala University, Uppsala, Sweden; Medical Institute of Ministry of Interior, Sofia, Bulgaria; Asklepeion Hospital, Athens, Greece; Auckland City Hospital and University of Auckland, Auckland, New Zealand). Excessive daytime sleepiness, morning tiredness and major adverse cardiovascular events in patients with chronic coronary syndrome. *J Intern Med* 2021; **290**: 392–403. https://doi.org/10.1111/joim.13294

Background. Sleep-related breathing disorders (SRBDs), particularly obstructive sleep apnoea, are associated with increased cardiovascular (CV) risk. However, it is not known whether individual questions used for SRBD screening are associated with major adverse CV events (MACE) and death specifically in patients with chronic coronary syndrome (CCS).

Methods. Symptoms associated with SRBD were assessed by a baseline questionnaire in 15,640 patients with CCS on optimal secondary preventive therapy in the STABILITY trial. The patients reported the frequency (never/rarely, sometimes, often and always) of: 1) loud snoring; 2) more than one awakening/night; 3) morning tiredness (MT); 4) excessive daytime sleepiness (EDS); or 5) gasping, choking or apnoea when asleep. In adjusted Cox regression models, associations between the frequency of SRBD symptoms and CV outcomes were assessed with never/rarely as reference.

Results. During a median follow-up time of 3.7 years, 1,588 MACE events (541 CV deaths, 749 nonfatal myocardial infarctions [MI] and 298 nonfatal strokes) occurred. EDS was associated (hazard ratio [HR], 95% confidence interval [CI]) with increased risk of MACE (sometimes 1.14 [1.01–1.29], often 1.19 [1.01–1.40] and always 1.43 [1.15–1.78]), MI (always 1.61 [1.17–2.20]) and all-cause death (often 1.26 [1.05–1.52] and always 1.71 [1.35–2.15]). MT was associated with higher risk of MACE (often 1.23 [1.04–1.45] and always 1.46 [1.18–1.81]), MI (always 1.61 [1.22–2.14]) and all-cause death (always 1.54 [1.20–1.98]). The other SRBD-related questions were not consistently associated with worse outcomes.

Conclusions. In patients with CCS, gradually higher levels of EDS and MT were independently associated with increased risk of MACE, including mortality.

Keywords: cardiovascular risk factors, coronary heart disease, mortality, myocardial infarction, sleep disorders.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, with ischaemic heart disease and stroke accounting for a combined 26.8% (approx. 15.2 million) of all deaths reported in 2018 [1]. Most of the CVD risk can be explained by lifestyle-related and modifiable risk factors [2] such as smoking, hyperlipidaemia, hypertension, abdominal obesity and diabetes, to name a few. International prevention strategies for reduction of premature deaths from noncommunicable diseases have been approved [3]. Yet, forecasts predict a continuous worldwide rise in CVD

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prevalence with a substantial increase in healthcare costs [4,5].

Beyond the established modifiable risk factors, obstructive sleep apnoea (OSA) has, in both the general population and patient cohorts, been associated with increased cardiovascular (CV) risk [6–8]. OSA is a part of sleep-related breathing disorders (SRBDs), and the diagnosis is verified by polysomnography [9]. In the clinical setting, patients at greater risk of OSA may be identified by using self-reported questionnaires, such as the Berlin, or STOP-BANG questionnaires [10–12]. Patients with established CVD and diagnosed with OSA have a higher risk of adverse events such as myocardial infarction (MI), CV death and non-CV death [6–8]. In addition, many of the modifiable risk factors for CVD also play a part in SRBD and the pathophysiological mechanisms behind these factors often intertwine and, in some cases, reinforce each other [13].

Whether individual questions used for SRBD screening are associated with CV events and death in patients with chronic coronary syndrome (CCS) is not established. Therefore, we evaluated the association between SRBD-related questions and their associations with CV prognosis in high-risk patients with CCS on optimal secondary prevention therapies [14].

Methods

This was a substudy of the STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) trial (ClinicalTrials.gov ID NCT00799903), which was a global multicentre randomized clinical trial, evaluating the clinical efficacy and safety of darapladib, a reversible oral inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2), in 15,828 patients with CCS. Study design, rationale and results have been published previously [15,16].

Out of the patients included in the STABILITY trial, 15,640 patients (98.8%) completed a self-reported questionnaire with SRBD-related questions at baseline and were included in this substudy. All included patients provided written informed consent, and the study was approved by the required institutional review boards and performed in accordance with the Declaration of Helsinki.

Study population

The STABILITY trial inclusion and exclusion criteria, with definitions, are listed in the Data S1.

Included patients had to be diagnosed with CCS defined as prior MI (>1 month prior to randomization) or prior coronary revascularization (previous percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or multivessel coronary heart disease (CHD) without revascularization, deemed stable in their symptomatology and were required to be on a statin. The majority of patients had undergone coronary angiography at some point prior to inclusion. Revascularization had been performed in 11,863 (74.9%) of the included patients, and those with planned revascularization were actively excluded from the study.

The study population is characterized by a high CV risk, with at least one additional high-risk enrichment criteria required at inclusion: age ≥60 years, diabetes mellitus requiring pharmacotherapy, high-density lipoprotein cholesterol <1.03 mmol/L, current smoker, significant renal dysfunction or polyvascular disease.

The investigators were mandated to treat included patients according to contemporary international guideline-recommended secondary prevention for CCS. Standard of care was continuously monitored and was optimized during the whole study [15,16].

Follow-up and study end-points

The patients were followed during a median follow-up time of 3.7 years. Outcomes were centrally adjudicated by an independent clinical events committee. Patients who suffered a primary end-point were thereafter censored but could still subsequently meet secondary end-points [15,16].

The primary end-point considered in the study was major adverse cardiovascular events (MACE), defined as a composite of CV death, nonfatal MI or nonfatal stroke. Secondary end-points were CV death, non-CV death, all-cause death, MI, stroke and hospitalization for heart failure.

Questionnaire with sleep-related breathing disorder-related questions

The SRBD-related questions were derived from the Berlin questionnaire [10,11] (Table S1) and

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compiled into a self-reported questionnaire, which patients completed at baseline. Filling out the questionnaire, patients were urged to describe their sleep pattern over the last year.

The questionnaire included the following questions:

- Question 1 – When sleeping, have you been told you snore loudly?
- Question 2 – Do you wake up more than once a night?
- Question 3 – Are you tired first thing in the morning?
- Question 4 – Are you sleepy during the day?
- Question 5 – Have you been told you gasp, choke or stop breathing when asleep?

Each of the questions was answered by grading the frequency of experienced symptoms according to the following 4-level scale: never/rarely, sometimes, often or always.

Questions regarding perceived depression ('Have you felt sad, low in your spirits or depressed?') and stress ('Have you felt stress at home?') were answered in the same way.

Statistical analyses

Descriptive statistics were used to analyse baseline characteristics and demographics. Discrete variables are presented as counts and percentages and continuous variables as mean and standard deviation. Differences between the 4 subgroups of symptom frequency, hereinafter referred to as 'subgroups', for each of the SRBD-related questions were assessed with the chi-square test (categorical variables) and with the Mann–Whitney nonparametric tests (continuous variables).

Event rates of the primary end-point and their development during follow-up were evaluated for each of the questions and every subgroup separately, and are presented as cumulative Kaplan–Meier survival curves. Associations between combinations of or individual subgroups and patient outcomes were assessed using the Cox proportional hazards regression models (hazard ratios [HRs] per 1 category increase, 95% confidence intervals [CI]). When analysing individual subgroups, the never/rarely subgroup served as reference. The results are presented in forest plots and three-dimensional bar charts. The adjustment for covariates was pre-specified in the statistical analysis plan. Two Cox proportional hazards models were used: 'unadjusted', adjusted for randomized treatment only; and 'adjusted', adjusted for randomized treatment, age at randomization, sex, geographic region, smoking status, body mass index (BMI), diabetes mellitus, polyvascular disease, significant renal dysfunction, congestive heart failure (CHF), hypertension, prior MI, prior coronary revascularization (PCI/CABG) and prior multivessel CHD. Further, a model including alcohol usage and physical activity in addition to the adjusted model was applied.

Pairwise comparison using combinations (never/rarely/sometimes or often/always) of EDS and MT subgroups was assessed to evaluate differences in MACE and all-cause mortality between these SRBD-related questions.

Interaction tests and secondary analyses using unadjusted Cox regression models were performed to assess possible influences of other SRBD-related questions and excessive daytime sleepiness (dichotomized into 1 = often/always and 0 = never/rarely/sometimes) on outcomes.

A sensitivity analysis using the 'adjusted' Cox regression model was performed to assess whether the observed associations between the SRBD-related questions and CV outcomes were confounded by symptomatic patients with CHF. The relationship between the study end-points and the combined often/always subgroup was assessed in the whole cohort and after excluding patients with the diagnosis of CHF at baseline. The combination of the never/rarely/sometimes subgroups was used as reference.

p-values <0.05 from two-sided tests were considered statistically significant and were not adjusted for multiple comparisons, due to the exploratory nature of the study. All analyses were performed at the Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, using R Core Team (2019). R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria.

Results

Demographics and baseline characteristics

In total, 15,640 patients with CCS were included and demographics and baseline characteristics, stratified by EDS and MT, are summarized in Table 1 (and in more detail in Table S2). The mean

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Table 1 *Demographics and baseline characteristics – excessive daytime sleepiness and morning tiredness*

	Excessive daytime sleepiness					Morning tiredness				
	Never/rarely	Sometimes	Often	Always	Total	Never/rarely	Sometimes	Often	Always	Total
	N = 4779	*N* = 7689	*N* = 2272	*N* = 774	*N* = 15514	*N* = 7457	*N* = 5677	*N* = 1600	*N* = 750	*N* = 15484
Age	64.1 (9.2)	64.6 (9.3)	64.3 (9.5)	64.0 (10.2)	64.4 (9.3)	65.3 (9.1)	63.8 (9.4)	62.5 (9.7)	62.8 (9.7)	64.4 (9.3)
Sex (male)	3949 (82.6%)	6248 (81.3%)	1825 (80.3%)	602 (77.8%)	12624 (81.4%)	6315 (84.7%)	4543 (80.0%)	1222 (76.4%)	516 (68.8%)	12596 (81.3%)
Body mass index	28.3 (4.6)	29.1 (5.0)	29.6 (5.4)	29.3 (5.9)	28.9 (5.0)	28.3 (4.6)	29.3 (5.2)	29.8 (5.4)	30.6 (5.8)	28.9 (5.0)
Current smoker	852 (17.8%)	1356 (17.6%)	444 (19.5%)	143 (18.5%)	2795 (18.0%)	1158 (15.5%)	1083 (19.1%)	367 (22.9%)	186 (24.8%)	2794 (18.0%)
Standard drinks/week	4.2 (7.0)	3.9 (6.6)	3.6 (6.4)	2.7 (5.6)	3.9 (6.6)	4.0 (6.7)	4.0 (6.7)	3.6 (6.3)	3.2 (6.5)	3.9 (6.6)
Asian/Pacific	886 (18.5%)	1154 (15.0%)	330 (14.5%)	173 (22.4%)	2543 (16.4%)	1492 (20.0%)	771 (13.6%)	205 (12.8%)	76 (10.1%)	2544 (16.4%)
Asthma or COPD	341 (7.1%)	763 (9.9%)	305 (13.4%)	123 (15.9%)	1532 (9.9%)	588 (7.9%)	598 (10.5%)	210 (13.1%)	131 (17.5%)	1527 (9.9%)
Congestive heart failure	990 (20.7%)	1608 (20.9%)	541 (23.8%)	189 (24.4%)	3328 (21.5%)	1482 (19.9%)	1308 (23.0%)	390 (24.4%)	140 (18.7%)	3320 (21.4%)
NYHA no class/class 1	3706 (77.5%)	5923 (77.0%)	1672 (73.6%)	557 (72.0%)	11858 (76.4%)	5830 (78.2%)	4249 (74.8%)	1173 (73.3%)	587 (78.3%)	11839 (76.5%)
Diabetes mellitus	1653 (34.6%)	2988 (38.9%)	999 (44.0%)	364 (47.0%)	6004 (38.7%)	2787 (37.4%)	2173 (38.3%)	687 (42.9%)	344 (45.9%)	5991 (38.7%)
Hypertension	3315 (69.4%)	5552 (72.2%)	1662 (73.2%)	559 (72.2%)	11088 (71.5%)	5228 (70.1%)	4140 (72.9%)	1150 (71.9%)	558 (74.4%)	11076 (71.5%)
Multivessel CHD	683 (14.3%)	1152 (15.0%)	357 (15.7%)	145 (18.7%)	2337 (15.1%)	1086 (14.6%)	845 (14.9%)	275 (17.2%)	129 (17.2%)	2335 (15.1%)
Polyvascular disease	600 (12.6%)	1190 (15.5%)	392 (17.3%)	144 (18.6%)	2326 (15.0%)	970 (13.0%)	923 (16.3%)	276 (17.3%)	155 (20.7%)	2324 (15.0%)
Prior myocardial infarction	2850 (59.6%)	4510 (58.7%)	1332 (58.6%)	450 (58.1%)	9142 (58.9%)	4392 (58.9%)	3387 (59.7%)	920 (57.5%)	415 (55.3%)	9114 (58.9%)
Prior PCI or CABG	3545 (74.2%)	5805 (75.5%)	1680 (73.9%)	590 (76.2%)	11620 (74.9%)	5565 (74,6%)	4275 (75.3%)	1191 (74.4%)	569 (75.9%)	11600 (74.9%)
Significant renal dysfunction	1325 (27.7%)	2330 (30.3%)	739 (32.5%)	283 (36.6%)	4677 (30.1%)	2308 (31.0%)	1615 (28.4%)	497 (31.1%)	247 (32.9%)	4667 (30.1%)
Sleep apnoea	216 (4.5%)	528 (6.9%)	210 (9.2%)	91 (11.8%)	1045 (6.7%)	338 (4.5%)	438 (7.7%)	156 (9.8%)	112 (14.9%)	1044 (6.7%)

Age, body mass index and standard drinks/week are presented as mean and standard deviation (SD). The rest are presented as nominal values with percentages.

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; NYHA, New York Heart Association Classification; PCI, percutaneous coronary intervention.

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age was 64.4 years, 81.4% were males, BMI was 28.9 kg/m^2, and previously diagnosed OSA was reported in 6.7% (1,045) of the patients.

Patients reporting frequent EDS were more likely to be females, be current smokers, have chronic obstructive pulmonary disease (COPD)/asthma, CHF, diabetes mellitus, multivessel CHD and polyvascular disease and have higher BMI, compared with patients reporting less frequent EDS.

Patients reporting more frequent MT symptoms were younger, more likely to be females, current smokers, living alone, and more likely to have COPD/asthma, diabetes mellitus, multivessel CHD, peripheral artery disease, polyvascular disease, significant renal dysfunction and higher BMI. These patients were also less likely to have CHF but more likely to report being stressed and having symptoms of depressed mood.

Although loud snoring was not consistently associated with outcomes, the demographics and baseline characteristics are summarized in Table S3.

Clinical outcomes

The analyses revealed consistent associations between EDS, MT, and CV outcomes and death. Hereinafter, mainly results regarding EDS and MT are presented. The results from the remaining SRBD-related questions are available in the Supporting Information.

The primary end-point of MACE occurred in 1,588 patients – 541 CV deaths, 749 nonfatal MIs and 298 nonfatal strokes. Unadjusted rates of MACE, MI, CV death, all-cause death, non-CV death and hospitalization for heart failure were highest in the patients reporting higher frequency of EDS and MT (Table S4), with large differences across the subgroups. During the 46-month follow-up, there was a graded increase in the rate of MACE with higher frequency of EDS (Fig. 1a) and MT (Fig. 1b). Event curves for patients 'always' experiencing EDS or MT separated early and showed the highest rate of MACE throughout the 46-month follow-up.

In adjusted Cox regression analyses, patients reporting a higher frequency of EDS had an increased hazard rate of MACE (sometimes HR 1.14 [95% CI, 1.01–1.29], often HR 1.19 [95% CI, 1.01–1.40] and always HR 1.43 [95% CI, 1.15–1.78]; $p = 0.0063$), MI, CV death, all-cause death, hospitalization for heart failure and non-CV death (Fig. 2a). Similarly, patients reporting more frequent MT had an increased risk of MACE (often HR 1.23 [95% CI, 1.04–1.45] and always HR 1.46 [95% CI, 1.18–1.81]; $p = 0.0015$), MI, CV death and all-cause death (Fig. 2b). Loud snoring was inversely but inconsistently related to MACE (sometimes HR 0.85 [95% CI, 0.75–0.96] and often HR 0.84 [95% CI, 0.72–0.98]; $p = 0.0357$), CV death and all-cause death (Figure S1a). Gasping, choking or apnoea when asleep and more than one awakening per night were not consistently associated with outcomes (Figure S1b,c). The results were essentially the same when also adjusting for alcohol usage and physical activity (Table S5).

Three-dimensional bar charts plotted with hazard ratios for MACE (Figure S2a) and all-cause mortality (Figure S2b) stratified by the subgroups of EDS and MT show an overall trend towards an increased risk for MACE and all-cause mortality for higher frequency of EDS without a certain relation with the frequency of MT. The highest risk of MACE and all-cause mortality for MT is observed in the always subgroup, and the risk seems inversely associated with the frequency of EDS.

Pairwise comparisons for MACE (Table S6A) revealed significant differences between the often/always MT subgroup and the never/rarely/sometimes EDS subgroup (1.35 HR; $p = 0.012$), and between the often/always MT subgroup and the often/always EDS subgroup (1.22 HR; $p = 0.03$). Only two comparisons for all-cause mortality (Table S6B) showed no significant difference.

Interaction tests

There were interactions (Table S7) between EDS and MT for MACE ($p = 0.0189$) and hospitalization for heart failure, and between EDS and loud snoring for CV death and hospitalization for heart failure.

Secondary analyses

In secondary analyses (Table S8), patients always experiencing MT had an increased risk of MACE (HR 2.05 [95% CI, 1.50–2.80]; $p \leq 0.0001$) (Figure S3a) and hospitalization for heart failure (Figure S3b), when excluding the often/always EDS subgroup. Patients sometimes, often or always experiencing loud snoring had a decreased risk of CV death (Figure S4a), and the often loud snoring

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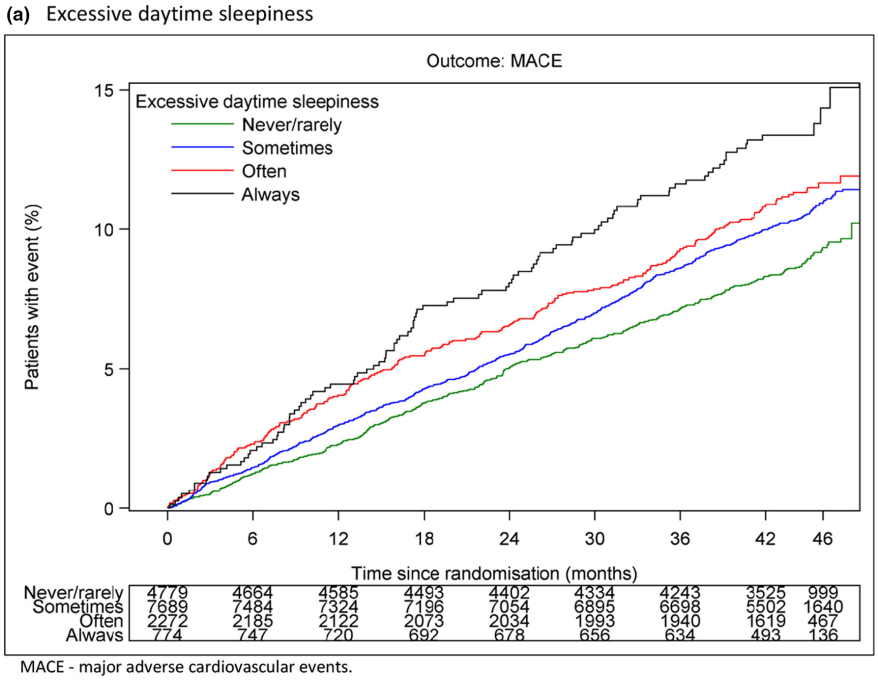

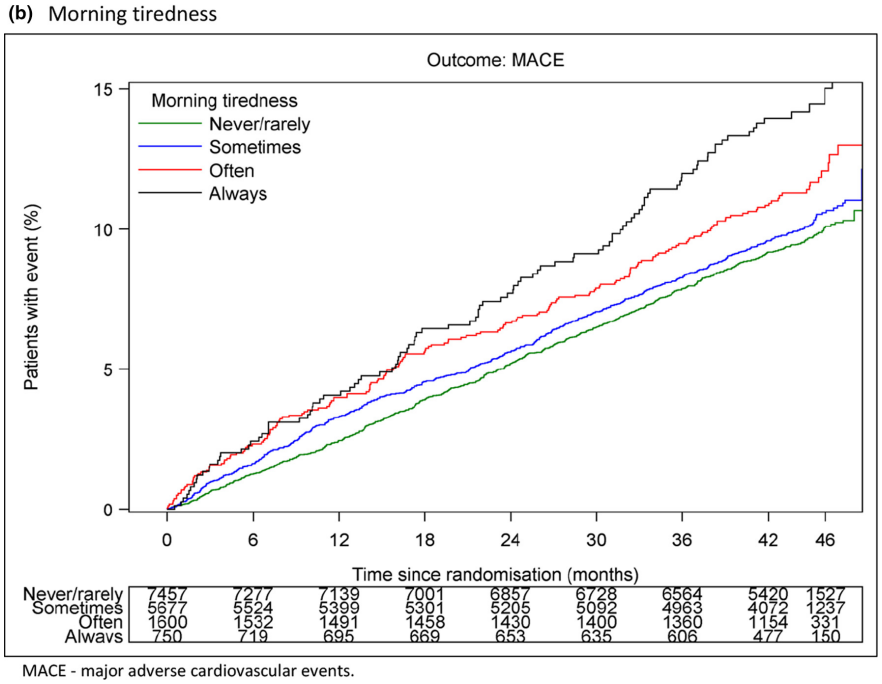

Fig. 1 *Kaplan –Meier survival curves of excessive daytime sleepiness, morning tiredness and major adverse cardiovascular events. Event rates during follow-up for each of the symptom frequency subgroups.*

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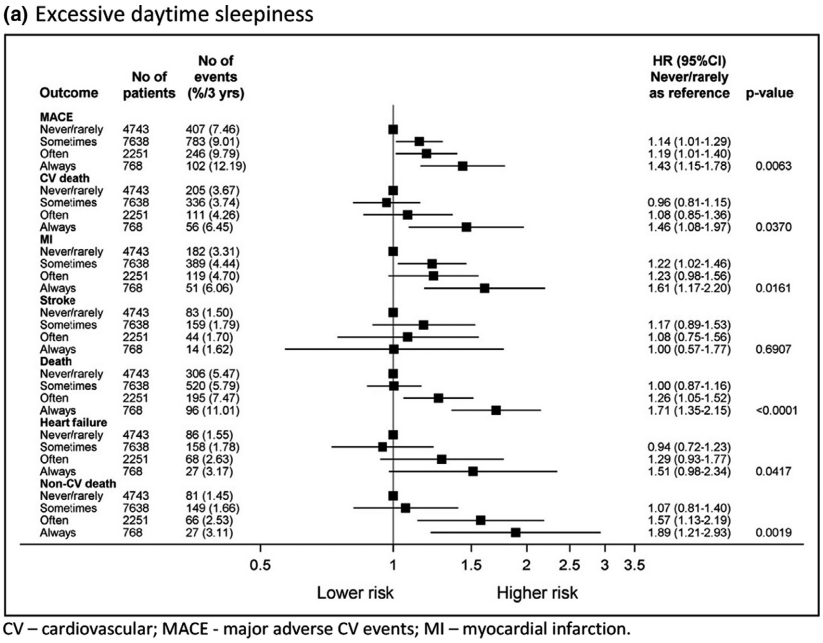
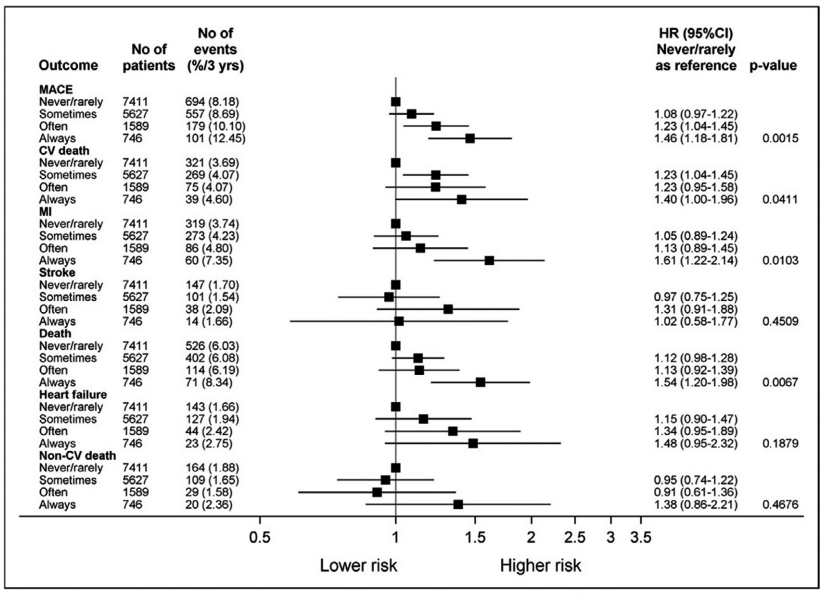


CV – cardiovascular; MACE - major adverse CV events; MI – myocardial infarction.



CV – cardiovascular; MACE - major adverse CV events; MI – myocardial infarction.

Fig. 2 *Adjusted Cox regression analysis of associations between excessive daytime sleepiness, morning tiredness and outcomes. Hazard ratios for all studied end-points from the 'adjusted' model (randomized treatment, age at randomization, sex, geographic region, smoking status, body mass index, diabetes mellitus, polyvascular disease, significant renal dysfunction, congestive heart failure, hypertension, prior myocardial infarction, prior coronary revascularization and prior multivessel coronary heart disease) stratified by symptom frequency subgroups with the never/rarely subgroup serving as reference.*

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subgroup also decreased risk of hospitalization for heart failure (Figure S4b), when excluding the often/always EDS subgroup.

Sensitivity analysis

Results were similar in the whole cohort (Table S9A) and the cohort excluding patients diagnosed with CHF (n = 3,336; 21.5%) at baseline (Table S9B).

Discussion

In this large study of high-risk patients with chronic coronary syndrome[14] followed for almost 4 years, excessive daytime sleepiness and morning tiredness were independently associated with an up to twofold increased risk of major ischaemic outcomes, hospitalization for heart failure and death. These data indicate that perceived tiredness may capture prognostic information beyond routine clinical markers of risk.

Interestingly, we did not detect an association between loud snoring or gasping and choking or apnoea, and a worsened CV prognosis. Somewhat surprisingly, patients with higher frequency of loud snoring had a better CV prognosis regardless of their reported frequency of EDS, despite also adjusting for alcohol usage and physical activity. Snoring is arguably the most commonly known and used SRBD-related question, and higher intensity and frequency of snoring is correlated with a higher prevalence of OSA, but is not pathognomonic for OSA [17]. Possible explanations for this result could be that patients were extensively screened for OSA before inclusion and that the treatment of symptomatic (sleepy) OSA in the cohort was effective or that the majority of snoring patients did not have OSA.

Three-dimensional bar charts for major adverse cardiovascular events and all-cause mortality showed an inverse association between the higher frequency of MT and EDS. In the secondary analyses, patients always being tired in the morning but seldom experiencing EDS had an approximately twofold increased risk of MACE and hospitalization for heart failure. This may reflect the coexistence of multiple phenotypes and/or pathophysiological mechanisms driving outcome.

The main results could in part be driven by patients reporting frequent EDS and MT, not due to OSA, but due to symptomatic CHF. However, in sensitivity analysis excluding patients with CHF, the overall results persisted albeit with some, expected, attenuation. Most of the attenuation in the sensitivity analysis was deemed as a loss of power, and similar trends were observed in the overall population.

Previous knowledge on SRBD and outcomes is mainly derived from population-based settings and patient cohorts describing associations between OSA and CV mortality and morbidity [6–8]. The associations between adverse CV outcomes and death with commonly used SRBD-related questions have previously not been investigated in a large global high-risk patient cohort with CCS [14].

The SRBD-related questions explored in this substudy have previously mainly been used as a screening tool for OSA. A small study has implied that SRBD-related questions not necessarily screen for OSA in patients with CVD [18] and the specificity of commonly used screening questionnaires in this patient group is at the most modest [11,12,18]. The role of OSA as a modifiable risk factor in the setting of CCS is still debated, partly because patients with established CVD and OSA seldom present with SRBD-related symptoms (non-sleepy OSA) [19]. Also, the gold standard treatment for OSA, continuous positive airway pressure (CPAP), has yet to show a beneficial effect on cardiovascular morbidity and mortality in non-sleepy OSA when evaluated in a prospective manner [20–22].

In this cohort, 6.7% of the patients had clinically diagnosed OSA at baseline and the proportion was higher with increasing frequency of EDS and MT. A recent study of 3874 patients did not show a relationship between EDS and moderate–severe OSA and association with the risk of developing CVD [23]. Further, a study of 104 patients suggested that EDS was an independent prognostic factor of adverse outcome after myocardial infarction with moderate–severe OSA having an additive effect on worse CV prognosis [24]. Thus, the prognostic impact of EDS seems, at least to some extent, to be independent of the simultaneous intra-individual occurrence of CCS and moderate–severe OSA. Approximately, three quarters of all patients in the STABILITY trial were included 1 year after the qualifying event [14].

EDS is the cardinal symptom of obstructive sleep apnoea (sleepy OSA) [25], which subsequently has

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an impact on CV prognosis [6–8]. In some cases, patients with OSA experience residual sleepiness, despite proven effective treatment with CPAP. This could be the result of coinciding possibly treatable conditions, such as insufficient sleep, depression, anxiety, restless legs syndrome and obesity. There have also been reports suggesting that the residual sleepiness may be the result of long-term exposure to OSA-related adverse consequences and studies of wake-promoting medications have shown promising results [25].

Previously, MT has mainly been described as a symptom reflecting depression and anxiety, which in turn are well-described risk factors and amplifiers of other CVD risk factors [26]. A previous study on general health [27] in the STABILITY cohort described an association between perceived poor/average general health and MACE. Also, depressive symptoms and low physical activity were strongly associated factors. Another study of the same patient cohort revealed an association between psychosocial stress and MACE [28], and data from the SWEDEHEART registry [29] show that approximately a third of patients have symptoms of emotional distress at 12-month follow-up post-MI. Further, previous depression and/or anxiety, female gender, younger age and smoking were strongly related factors. Although, women with OSA tend to be underdiagnosed and undertreated [30], and more often report fatigue than sleepiness when suffering from OSA [31].

In the current study, the CV risk factor burden was similar for EDS and MT and increased with higher frequency of symptoms. Patients with more frequent MT and EDS were more likely females, having a higher CV risk with more current smokers, having comorbidities such as diabetes mellitus, multivessel CHD, polyvascular disease and greater BMI, and feeling stressed and depressed. The use of secondary prevention treatments for CHD in the trial was extensive and monitored regularly. Efforts were made to continuously optimize the treatment regimen during follow-up, which resulted in a well-managed cohort [14]. The implication of this is that many risk factors for CVD were treated effectively and to a high standard of care, but regardless, there was still a significant residual risk for adverse CV outcomes [16].

Since the conclusion of the STABILITY trial, there has been progress made in the treatment of residual CV risk in patients with CCS. As an example, low-grade inflammation has successfully been treated with anti-inflammatory agents in a couple randomized trials with improved CV outcomes as a consequence [32,33]. Several of the preventive treatment strategies, that is lowering low-density lipoprotein (LDL), increased physical activity, adjusted diet, weight loss, may reduce the inflammatory burden and the progression of atherosclerosis. OSA is also considered a chronic low state inflammatory process but with substantial heterogeneity governed by genetic, environmental factors and lifestyle [34]. Approximately a quarter of the included patients in the STABILITY trial had an elevated high-sensitivity C-reactive protein (hs-CRP) above 3 mg/L, and elevated plasma levels of interleukin 6 (IL-6) in this cohort have been associated with poor CV outcomes [16,35]. Hence, the inflammatory milieu partly driving the atherosclerotic process played a role in the increased risk of CV outcomes in the original cohort. However, whether inflammation relates to the SRBD-related questions in this substudy remains to be investigated.

Limitations

Despite multiple adjustments in the statistical analyses, we cannot exclude residual confounding. For instance, the use of hypnotics and sedatives was not adjusted for due to lack of data.

Included patients did not undergo polysomnography studies to confirm which patients suffered from SRBD, and the exact prevalence of sleepy OSA in this patient cohort is unknown. It would have been helpful to differentiate between these groups, but the usefulness is questionable because of the mostly asymptomatic (non-sleepy) nature of OSA in patients with CCS and the debatable treatment effect in these patients [20–22]. In addition, we do not have information on CPAP treatment adherence in the patient group already diagnosed with OSA, and failure to comply with such treatments could negatively impact CV risks, as shown in other studies [20,22,36]. Further, we cannot disentangle a general feeling of being unwell, a predictor of poor prognosis and symptoms of sleepy OSA.

The self-reported questionnaire is similar but not identical to the Berlin questionnaire [10] and has not been validated; therefore, the results are not interchangeable.

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Conclusion

In this large prospective study of patients with CCS, increasing prevalence of excessive daytime sleepiness and morning tiredness, two symptoms frequent in patients with OSA, were independently associated with CV outcomes and death. Further, EDS and MT probably describe two distinctive entities despite both being associated with the same CV risk factors. Interestingly, we did not detect an association between loud snoring, gasping, choking, or apnoeas and adverse prognosis. These results indicate that simple questions regarding perceived tiredness capture information beyond established markers of disease and risk.

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Conflict of interest

MO has received institutional research grants from GlaxoSmithKline. CH has received honoraria from Pfizer; and consultant and advisory board fees from AstraZeneca, Bayer and Boehringer Ingelheim. NH has received institutional research grant from GlaxoSmithKline. SD and AM have no conflict of interest. LW has received institutional research grants from AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Merck & Co, Roche Diagnostics and Boehringer Ingelheim; has received consulting fees from Abbott; and holds two patents involving GDF-15, both licensed to Roche Diagnostics. HDW has received research grants from GlaxoSmithKline; grants and steering committee fees from Eli Lilly and Company, Omthera Pharmaceuticals, Eisai Inc., Dalcor Pharma UK and American Regent; grants and steering committee and advisory board fees from CSL Behring LLC; grants, steering committee and personal fees from Sanofi-Aventis Australia Pty Ltd, Esperion Therapeutics Inc. and Sanofi-Aventis; advisory board fees from Genentech, Inc.; and personal fees from AstraZeneca. RAHS has received research grants from GlaxoSmithKline. EH has received research grants and speaker fees from Amgen and Sanofi; and expert committee fees from Novo Nordisk.

References

1 World Health Organization. *Global health estimates 2016: Deaths by cause, age, sex, by country and by region, 2000-2016*. Geneva: World Health Organization; 2018.

2 Yusuf PS, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet*. 2004;**364(9438):**937–52.

3 Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2016;**37(29):**2315–81.

4 Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the future of cardiovascular disease in the United States: A policy statement from the American Heart Association. *Circulation*. 2011;**123(8):**933–44.

5 Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, et al. European Society of Cardiology: Cardiovascular disease statistics 2017. *Eur Heart J*. 2018;**39(7):**508–79.

6 Park JG, Ramar K, Olson EJ. Updates on definition, consequences, and management of obstructive sleep apnea concise review for clinicians. *Mayo Clin Proc*. 2011;**86(6):**549–55.

7 Loke YK, Brown JWL, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: A systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2012;**5(5):**720–8.

8 Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep Apnea: Types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol*. 2017;**69(7):**841–58.

9 Sateia MJ. International classification of sleep disorders-third edition. *Chest*. 2014;**146(5):**1387–94.

10 Senaratna CV, Perret JL, Matheson MC, Lodge CJ, Lowe AJ, Cassim R, et al. Validity of the Berlin questionnaire in detecting obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Med Rev*. 2017;**36:**116–24.

11 Chiu HY, Chen PY, Chuang LP, Chen N-H, Tu Y-K, Hsieh Y-J, et al. Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth sleepiness scale in detecting obstructive sleep apnea: A bivariate meta-analysis. *Sleep Med Rev*. 2017;**36:**57–70.

12 Maurer JT. Early diagnosis of sleep related breathing disorders. *GMS Curr Top Otorhinolaryngol Head Neck Surg*. 2008.**7:** Doc03

13 Gonzaga C, Bertolami A, Bertolami M, Amodeo C, Calhoun D. Obstructive sleep apnea, hypertension and cardiovascular diseases. *J Hum Hypertens*. 2015;**29:**705–12.

14 Vedin O, Hagström E, Stewart R, Brown R, Krug-Gourley S, Davies R, et al. Secondary prevention and risk factor target achievement in a global, high-risk population with established coronary heart disease: Baseline results from the STABILITY study. *Eur J Prev Cardiol*. 2013;**20(4):**678–85.

15 White H, Held C, Stewart R, Watson D, Harrington R, Budaj A, et al. Study design and rationale for the clinical outcomes of the STABILITY Trial (STabilization of Atherosclerotic plaque by Initiation of darapLadIb TherapY) comparing darapladib versus placebo in patients with coronary heart disease. *Am Heart J*. 2010;**160(4):**655–61.e2.

16 White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, et al. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med*. 2014;**370(18):**1702–11.

17 Sowho M, Sgambati F, Guzman M, Schneider H, Schwartz A. Snoring: a source of noise pollution and sleep apnea predictor. *Sleep*. 2019;**43(6):**zsz305.

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18 Reuter H, Herkenrath S, Treml M, Halbach M, Steven D, Frank K, et al. Sleep-disordered breathing in patients with cardiovascular diseases cannot be detected by ESS, STOP-BANG, and Berlin questionnaires. *Clin Res Cardiol*. 2018;**107 (11):**1071–8.
19 Garbarino S, Scoditti E, Lanteri P, Conte L, Magnavita N, Toraldo DM. Obstructive sleep apnea with or without excessive daytime sleepiness: Clinical and experimental data-driven phenotyping. *Front Neurol*. 2018;**9:**505.
20 McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;**375(10):**919–31.
21 Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med*. 2016;**194 (5):**613–20.
22 Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet. Respir Med*. 2019;**8(4):**359–67.
23 Ogilvie RP, Lakshminarayan K, Iber C, Patel SR, Lutsey PL. Joint effects of OSA and self-reported sleepiness on incident CHD and stroke. *Sleep Med*. 2018;**44:**32–7.
24 Xie J, Kuniyoshi FHS, Covassin N, Singh P, Gami AS, Chahal CAA, et al. Excessive daytime sleepiness independently predicts increased cardiovascular risk after myocardial infarction. *J Am Heart Assoc*. 2018.**7 2:**e007221.
25 Javaheri S, Javaheri S. Update on persistent excessive daytime sleepiness in OSA. *Chest*. 2020;**158(2):**776–86.
26 Polanka BM, Berntson J, Vrany EA, Stewart JC. Are cardiovascular risk factors stronger predictors of incident cardiovascular disease in U.S. Adults with versus without a history of clinical depression? *Ann Behav Med*. 2018;**52(12):**1036–45.
27 Stewart RAH, Hagström E, Held C, Wang TKM, Armstrong PW, Aylward PE, et al. Self-reported health and outcomes in patients with stable coronary heart disease. *J Am Heart Assoc*. 2017;**6(8):**e006096.
28 Hagström E, Norlund F, Stebbins A, Armstrong PW, Chiswell K, Granger CB, et al. Psychosocial stress and major cardiovascular events in patients with stable coronary heart disease. *J Intern Med*. 2018;**283(1):**83–92.
29 Norlund F, Lissåker C, Wallert J, Held C, Olsson EMG. Factors associated with emotional distress in patients with myocardial infarction: Results from the SWEDEHEART registry. *Eur J Prev Cardiol*. 2018;**25(9):**910–20.
30 Lindberg E, Benediktsdottir B, Franklin KA, Holm M, Johannessen A, Jögi R, et al. Women with symptoms of sleep-disordered breathing are less likely to be diagnosed and treated for sleep apnea than men. *Sleep Med*. 2017;**35:**17–22.
31 Eliasson AH, Kashani MD, Howard RS, Vernalis MN, Modlin RE. Fatigued on Venus, sleepy on Mars—gender and racial differences in symptoms of sleep apnea. *Sleep Breath*. 2015;**19(1):**99–107.
32 Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;**377(12):**1119–31.
33 Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;**381(26):**2497–505.
34 Kheirandish-Gozal L, Gozal D. Obstructive sleep apnea and inflammation: Proof of concept based on two illustrative cytokines. *Int J Mol Sci*. 2019;**20(3):**459.
35 Held C, White HD, Stewart RAH, Budaj A, Cannon CP, Hochman JS, et al. Inflammatory biomarkers interleukin-6 and c-reactive protein and outcomes in stable coronary heart disease: Experiences from the STABILITY (stabilization of atherosclerotic plaque by initiation of darapladib therapy) trial. *J Am Heart Assoc*. 2017;**6(10):**e005077.
36 Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease. A perspective and future directions. *Prog Cardiovasc Dis*. 2009;**51(5):**434–51.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. STABILITY inclusion and exclusion criteria.

Table S1. Berlin questionnaire.

Table S2. Demographics and baseline characteristics – excessive daytime sleepiness and morning tiredness.

Table S3. Demographics and baseline characteristics – loud snoring.

Table S4. Unadjusted analysis of association between sleep related breathing disorder-related questions and outcomes.

Table S5. Adjusted analysis of association between with sleep related breathing disorder-related questions and outcomes

Table S6. Pairwise comparisons between frequency sub-group combinations of excessive daytime sleepiness and morning tiredness and association with outcomes.

Table S7. Interaction tests between excessive daytime sleepiness and other sleep related breathing disorder-related questions by all outcomes.

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Table S8. Secondary analysis of association between excessive daytime sleepiness and other sleep related breathing disorder-related questions and outcomes.

Table S9. (a) Adjusted analysis of association between sleep related breathing disorder-related questions and outcomes. (b) Adjusted analysis of association between sleep related breathing disorder-related questions and outcomes after excluding patients with congestive heart failure at baseline.

Figure S1. Adjusted analysis of association between frequency of loud snoring and gasping, choking, and apnea when asleep, and more than one awakening per night and outcomes.

Figure S2. Three-dimensional bar charts plotted with hazard ratios for major adverse cardiovascular events (Y-axis) from adjusted Cox regression analysis and the frequency sub-groups of excessive daytime sleepiness (Z-axis) and morning tiredness (X-axis)

Figure S3. Secondary analysis of association between excessive daytime sleepiness and morning tiredness and outcomes by excluding the often/always sub-group of excessive daytime sleepiness (red line).

Figure S4. Secondary analysis of association between excessive daytime sleepiness and loud snoring and outcomes by excluding the often/always sub-group of excessive daytime sleepiness (red line).

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