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Excessive daytime sleepiness, morning tiredness, and prognostic biomarkers in patients with chronic coronary syndrome☆

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ABSTRACT

Background: Sleep-related breathing disorders (SRBD) are related to cardiovascular outcomes in patients with chronic coronary syndrome (CCS). Whether SRBD-related symptoms are associated with prognostic biomarkers in patients with CCS is not established.

Methods: Associations between frequency (never/rarely, sometimes, often, always) of self-reported SRBD-related symptoms (excessive daytime sleepiness [EDS]; morning tiredness [MT]; loud snoring; multiple awakenings/night; gasping, choking, or apnea when asleep) and levels of biomarkers related to cardiovascular prognosis (high-sensitivity C-reactive protein [hs-CRP], interleukin 6 [IL-6], high-sensitivity cardiac troponin T [hs-cTnT], N-terminal pro B-type natriuretic peptide [NT-proBNP], cystatin C, growth differentiation factor 15 [GDF-15] and lipoprotein-associated phospholipase A_2 activity) were assessed at baseline in 15,640 patients with CCS on optimal secondary preventive therapy in the STABILITY trial. Cross-sectional associations were assessed by adjusted linear regression models testing for trends with the never/rarely category serving as reference.

Results: EDS was associated (geometric mean ratio, 95% confidence interval) with increased levels of IL-6 (often 1.07 [1.03–1.10], always 1.15 [1.10–1.21]), GDF-15 (often 1.03 [1.01–1.06], always 1.07 [1.03–1.11]), NT-proBNP (always 1.22 [1.12–1.33]), and hs-cTnT (always 1.07 [1.01–1.12]). MT was associated with increased levels of IL-6 (often 1.05 [1.01–1.09], always 1.09 [1.04–1.15]), and GDF-15 (always 1.06 [1.03–1.10]). All symptoms were to some degree associated with higher levels of hs-CRP and loud snoring was also associated with decreased levels of NT-proBNP and hs-cTnT.

Conclusions: In patients with CCS, stepwise increased frequency of SRBD-related symptoms, such as EDS and MT, were associated with gradually higher levels of IL-6 and GDF-15, each reflecting distinct pathophysiological pathways.

1. Introduction

Cardiovascular (CV) disease still represents the main cause of death globally [1,2] and the reported CV mortality decrease observed over the past half century has slowed substantially [2]. Beyond the increasing exposure to some established risk factors [3] such as abdominal obesity, alcohol usage, diabetes mellitus (DM), hypertension and physical inactivity [2], data have been accumulating during the last decade on the importance of sleep disturbances and the association with increased CV risk. [4–7]

Sleep-related breathing disorders (SRBD), particularly obstructive sleep apnea (OSA), are associated with CV morbidity and mortality.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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[8–11] SRBD are characterized by associated symptoms, such as excessive daytime sleepiness (EDS), morning tiredness (MT), and loud snoring. These symptoms are used in screening for OSA in the population, and are individually associated with an incremental risk for CV death and myocardial infarction (MI) in patients with chronic coronary syndrome (CCS) independently of established risk factors, and regardless of optimal secondary prevention measures. [12–14] In addition, OSA is associated with a wide range of CV diseases and CV risk factors, such as hypertension, heart failure, coronary artery disease, type 2 DM, all with the potential of negative feedback i.e., worsens these co-morbidities which in turn may worsen OSA. [4]

Furthermore, differences in the associations between individual SRBD-related symptoms and CV disease suggest the coexistence of several underlying pathophysiological mechanisms and phenotypes causing adverse prognosis in individuals with concomitant frequent SRBD-related symptoms and established CCS. [12] Associations between SRBD-related symptoms and prognostic biomarkers in patients with CCS have not been evaluated and could further elucidate the complex heterogeneity driving CV prognosis in CCS patients.

Therefore, we aimed to evaluate associations between individual SRBD-related symptoms and levels of biomarkers reflecting distinct disease pathways in patients with CCS as a sub-study of the STABILITY trial.

2. Methods

2.1. Main study design

The STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) trial (ClinicalTrials.gov ID NCT00799903) was an international multi-center randomized clinical trial, evaluating the clinical efficacy and safety of a reversible oral inhibitor of lipoprotein-associated phospholipase A_2, in 15,828 patients with CCS on optimal secondary prevention therapy. Darapladib did not have an effect on the primary outcome. [14,15]

CCS was defined as prior myocardial infarction (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. The majority had undergone coronary angiography prior to inclusion, revascularization had been performed in 11,863 (74.9%; PCI in 50.3% and CABG in 30.1%), and patients with planned PCI/CABG procedures were actively excluded. Included patients were required to be stable in their angina pectoris, with ongoing statin therapy, and presenting at least one additional high-risk enrichment criteria: age ≥ 60 years, DM requiring pharmacotherapy, high-density lipoprotein cholesterol <1.03 mmol/L, current or previous smoker, significant renal dysfunction (defined as estimated glomerular filtration rate [eGFR] ≥30 and ≤ 59 mL/min per 1.73 m2 or urine albumin creatinine ratio [ACR] ≥30 mg albumin/g creatinine), or polyvascular disease. Details on inclusion and exclusion criteria are presented in the Supporting Information.

Patients were treated according to contemporary international guideline-recommended secondary prevention therapies and standard of care was continuously scrutinized and optimized during the follow-up time (median of 3.7 years).

The study was performed in accordance with the Declaration of Helsinki after acquiring approvals from required institutional review boards and written informed consent from all included patients.

2.2. Self-reported questionnaire with sleep-related breathing disorder-related questions

At baseline, 15,640 (98.8%) of the patients included in the STABILITY trial completed a lifestyle questionnaire, including SRBD-related questions.

The SRBD-related questions were derived from the Berlin questionnaire [16] (Supporting Table S1) and answered by grading the frequency of experienced symptoms on a 4-level scale: never/rarely, sometimes, often, or always. The patients were to grade their sleep pattern during the last year accordingly to one of these categories.

The questionnaire included five SRBD-related 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 (MT)?
- Question 4 – Are you sleepy during the day (EDS)?
- Question 5 – Have you been told you gasp, choke, or stop breathing when asleep?

2.3. Prognostic biomarkers

The following seven biomarkers, all having been shown to hold prognostic information, each reflecting different CV disease pathways and related to adverse CV risk in patients with established CCS, were analyzed: cystatin C (CystC), growth differentiation factor 15 (GDF-15), high-sensitivity C-reactive protein (hs-CRP), high-sensitivity cardiac troponin T (hs-cTnT), interleukin 6 (IL-6), lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity, and N-terminal pro B-type natriuretic peptide (NT-proBNP).

2.4. Laboratory analyses

Plasma samples were drawn at baseline after an overnight fast. Routine laboratory analyses were performed with standardized methods. Analyses of plasma concentrations of hs-CRP were analyzed using a particle-enhanced immunonephelometry assay (CardioPhase© hsCRP, Siemens Healthcare) and of IL-6 with an enzyme-linked immunoSorbent assay (ELISA) technique (R&D Systems Inc., Minneapolis, Minnesota, USA). Lp-PLA_2 activity was measured in an automated enzyme assay system (PLAC® Test for Lp-PLA_2 Activity, diaDexus, San Francisco, California, USA) at Quest Diagnostics Clinical Laboratories, Inc. (Valencia, California, USA). Levels of CystC, GDF-15 (precommercial assay), hs-cTnT, and NT-proBNP were determined by specific electrochemiluminescence immunoassays (Cobas Analytics e601, Roche Diagnostics, Penzberg, Germany) at the UCR laboratory (Uppsala University, Uppsala, Sweden).

2.5. Statistical analyses

All analyses were stratified by the four individual symptom frequency categories (never/rarely, sometimes, often, or always) of each of the five SRBD-related questions. Baseline characteristics and demographics are presented in tables as counts or percentages (discrete variables), means, and standard deviations (continuous variables). Baseline biomarker levels are presented in tables and boxplots as means, medians, maximum/minimum values, first and third quartiles, and with outliers plotted. Differences between sub-groups were assessed with the χ^2 test (categorical variables) and with the Kruskal-Wallis test (continuous variables).

Cross-sectional associations between baseline biomarker levels, on log-transformed scale, and individual symptom frequency sub-groups were assessed using linear regression models (geometric mean ratio [GMR] per sub-group increase, 95% confidence intervals [CI]) testing for trends, with the never/rarely category serving as reference. The results are presented in Forest plots and tables.

Symptom frequency categories were treated as ordinal variables. We performed an overall test between the outcome and symptom frequency categories and the overall *p*-value for (linear) trend is presented. Pairwise differences between the reference group and the other groups are also presented.

Two models were used: unadjusted and adjusted, with adjustments

Table 1
Demographics, baseline characteristics and biomarkers[a] – excessive daytime sleepiness and morning tiredness.

	Excessive daytime sleepiness					Morning tiredness				
	Never/rarely	Sometimes	Often	Always	*p*-value	Never/rarely	Sometimes	Often	Always	*p*-value
	N = 4779	*N* = 7689	*N* = 2272	*N* = 774		*N* = 7457	*N* = 5677	*N* = 1600	*N* = 750	
Age	64.1 (9.2)	64.6 (9.3)	64.3 (9.5)	64.0 (10.2)	0.0309	65.3 (9.1)	63.8 (9.4)	62.5 (9.7)	62.8 (9.7)	<0.0001
Sex (male)	3949 (82.6%)	6248 (81.3%)	1825 (80.3%)	602 (77.8%)	0.0040	6315 (84.7%)	4543 (80.0%)	1222 (76.4%)	516 (68.8%)	<0.0001
Body mass index	28.3 (4.6)	29.1 (5.0)	29.6 (5.4)	29.3 (5.9)	<0.0001	28.3 (4.6)	29.3 (5.2)	29.8 (5.4)	30.6 (5.8)	<0.0001
Current smoker	852 (17.8%)	1356 (17.6%)	444 (19.5%)	143 (18.5%)	0.0128	1158 (15.5%)	1083 (19.1%)	367 (22.9%)	186 (24.8%)	<0.0001
Standard drinks/week	4.2 (7.0)	3.9 (6.6)	3.6 (6.4)	2.7 (5.6)	<0.0001	4.0 (6.7)	4.0 (6.7)	3.6 (6.3)	3.2 (6.5)	<0.0001
MET hours/week	53.8 (49.0)	54.3 (48.8)	48.0 (46.6)	41.8 (45.6)	<0.0001	52.4 (47.9)	53.9 (48.8)	50.8 (49.3)	46.7 (49.6)	<0.0001
Asian/Pacific	886 (18.5%)	1154 (15.0%)	330 (14.5%)	173 (22.4%)	<0.0001	1492 (20.0%)	771 (13.6%)	205 (12.8%)	76 (10.1%)	<0.0001
Asthma or COPD	341 (7.1%)	763 (9,9%)	305 (13.4%)	123 (15.9%)	<0.0001	588 (7.9%)	598 (10.5%)	210 (13.1%)	131 (17.5%)	<0.0001
Congestive heart failure	990 (20.7%)	1608 (20.9%)	541 (23.8%)	189 (24.4%)	0.0024	1482 (19.9%)	1308 (23.0%)	390 (24.4%)	140 (18.7%)	<0.0001
NYHA no class/class 1	3706 (77.5%)	5923 (77.0%)	1672 (73.6%)	557 (72.0%)	<0.0001	5830 (78.2%)	4249 (74.8%)	1173 (73.3%)	587 (78.3%)	<0.0001
Diabetes mellitus	1653 (34.6%)	2988 (38.9%)	999 (44.0%)	364 (47.0%)	<0.0001	2787 (37.4%)	2173 (38.3%)	687 (42.9%)	344 (45.9%)	<0.0001
Hypertension	3315 (69.4%)	5552 (72.2%)	1662 (73.2%)	559 (72.2%)	<0.0001	5228 (70.1%)	4140 (72.9%)	1150 (71.9%)	558 (74.4%)	0.0012
Multivessel CHD	683 (14.3%)	1152 (15.0%)	357 (15.7%)	145 (18.7%)	0.0109	1086 (14.6%)	845 (14.9%)	275 (17.2%)	129 (17.2%)	0.0194
Polyvascular disease	600 (12.6%)	1190 (15.5%)	392 (17.3%)	144 (18.6%)	<0.0001	970 (13.0%)	923 (16.3%)	276 (17.3%)	155 (20.7%)	<0.0001
Prior MI	2850 (59.6%)	4510 (58.7%)	1332 (58.6%)	450 (58.1%)	0.6800	4392 (58.9%)	3387 (59.7%)	920 (57.5%)	415 (55.3%)	0.0863
Prior PCI or CABG	3545 (74.2%)	5805 (75.5%)	1680 (73.9%)	590 (76.2%)	0.2024	5565 (74,6%)	4275 (75.3%)	1191 (74.4%)	569 (75.9%)	0.7198
Renal dysfunction	1325 (27.7%)	2330 (30.3%)	739 (32.5%)	283 (36.6%)	<0.0001	2308 (31.0%)	1615 (28.4%)	497 (31.1%)	247 (32.9%)	0.0037
Sleep apnea	216 (4.5%)	528 (6.9%)	210 (9.2%)	91 (11.8%)	<0.0001	338 (4.5%)	438 (7.7%)	156 (9.8%)	112 (14.9%)	<0.0001
hs-CRP	2.83 (6.68)	2.95 (6.51)	3.10 (5.49)	4.24 (9.05)	<0.0001	2.80 (6.61)	3.02 (6.11)	3.47 (7.98)	3.78 (6.25)	<0.0001
IL-6	2.73 (3.04)	2.80 (2.78)	3.04 (2.84)	3.37 (3.65)	<0.0001	2.81 (2.87)	2.80 (2.97)	2.98 (3.12)	3.17 (2.75)	<0.0001
hs-cTnT	11.9 (19.5)	12.5 (16.3)	13.0 (16.6)	13.6 (12.1)	<0.0001	12.4 (15.8)	12.5 (19.7)	12.3 (15.1)	12.5 (14.7)	0.0007
NT-proBNP	360.3 (828.6)	354.1 (672.7)	397.8 (999.5)	458.3 (754.4)	<0.0001	378.3 (851.0)	354.3 (648.1)	365.2 (953.0)	357.4 (578.9)	0.0171
CystC	1.03 (0.27)	1.05 (0.29)	1.08 (0.32)	1.10 (0.33)	<0.0001	1.06 (0.29)	1.04 (0.29)	1.05 (0.30)	1.05 (0.32)	<0.0001
GDF-15	1476.0 (1031.9)	1563.7 (1102.6)	1685.9 (1458.4)	1833.6 (1449.4)	<0.0001	1560.0 (1083.7)	1548.0 (1175.5)	1600.7 (1339.1)	1727.8 (1393.3)	0.0005
Lp-PLA_2	174.6 (47.3)	176.1 (48.0)	176.1 (48.5)	176.8 (48.8)	0.5733	174.6 (47.8)	176.2 (47.7)	176.7 (48.2)	179.3 (50.0)	0.1764

[a] Age, body mass index, standard drinks/week, and prognostic biomarkers are presented as mean and standard deviation (SD). The remaining are presented as nominal values with percentages. CABG – Coronary artery bypass grafting; COPD – Chronic obstructive pulmonary disease; CHD – coronary heart disease; MET – Metabolic equivalent of task; NYHA – New York Heart Association classification; PCI – Percutaneous coronary intervention; CysC – Cystatin C, GDF-15 – Growth differentiation factor 15, hs-CRP – high-sensitivity C-reactive protein, IL-6 – Interleukin 6, hs-cTnT – high-sensitivity cardiac Troponin T, NT-proBNP – N-terminal pro B-type natriuretic peptide, Lp-PLA_2 – Lipoprotein associated phospholipase A_2 activity

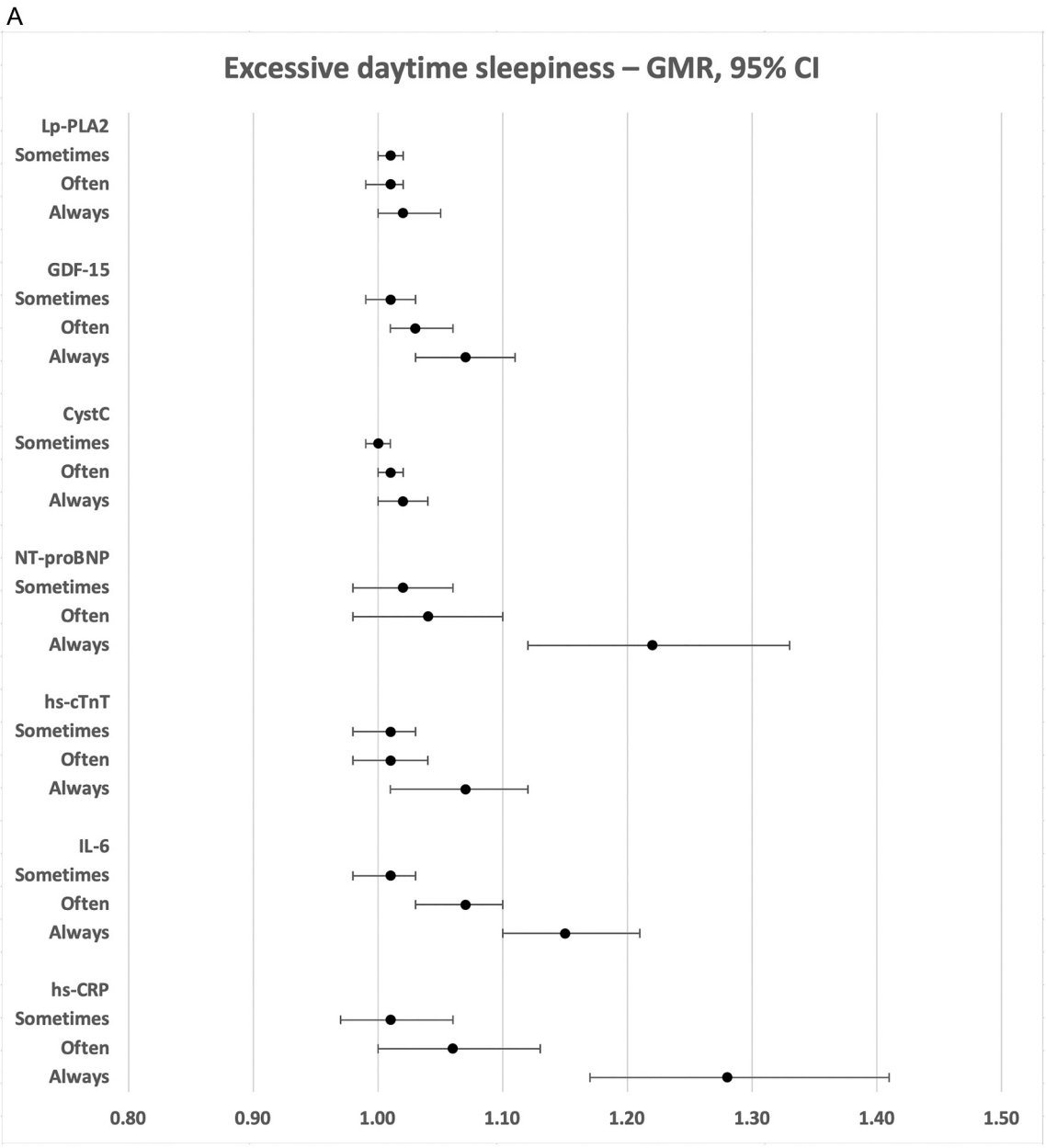

Fig. 1. Adjusted analysis[11] of associations between sleep-related breathing disorder-related questions and geometric mean ratios of prognostic biomarkers.

for, age at randomization, sex, geographic region, alcohol usage, smoking status, physical activity, body mass index (BMI), DM, polyvascular disease, significant renal dysfunction, congestive heart failure (CHF), hypertension, prior MI, prior coronary revascularization (PCI/CABG), and prior multivessel CHD. All covariates utilized were prespecified in the statistical analysis plan.

A sensitivity analysis using the adjusted linear regression model was performed to assess if the observed associations between the SRBD-related symptoms and biomarkers in the whole cohort were confounded by symptomatic patients with CHF. Accordingly, the relationship between the individual symptom frequency categories and the log-transformed biomarker levels was assessed after excluding all patients with the diagnosis of CHF at baseline.

Previously published interaction tests [12] have suggested the coexistence of multiple pathophysiological mechanisms and phenotypes promoting adverse CV risk in the STABILITY trial cohort. Consequently, we also performed interaction tests to evaluate the possibility of interactions between SRBD-related questions having an influence on mutual associated biomarkers.

The statistical analyses were performed at the Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, using SAS 9.4 (SAS Institute, Cary, North Carolina, USA). All p-values <0.05 were considered significant.

3. Results

Demographics, baseline characteristics, and biomarkers, stratified by EDS and MT are summarized in Table 1. Absolute biomarker levels for the reference categories are presented in the Supporting Information (Supporting Table S2).

Clinical characteristics between EDS and MT differed in a higher proportion of atrial fibrillation/flutter in patients experiencing higher frequencies of EDS and a higher proportion of living alone when experiencing higher frequencies of MT (Table 1 and Supporting Table S3).

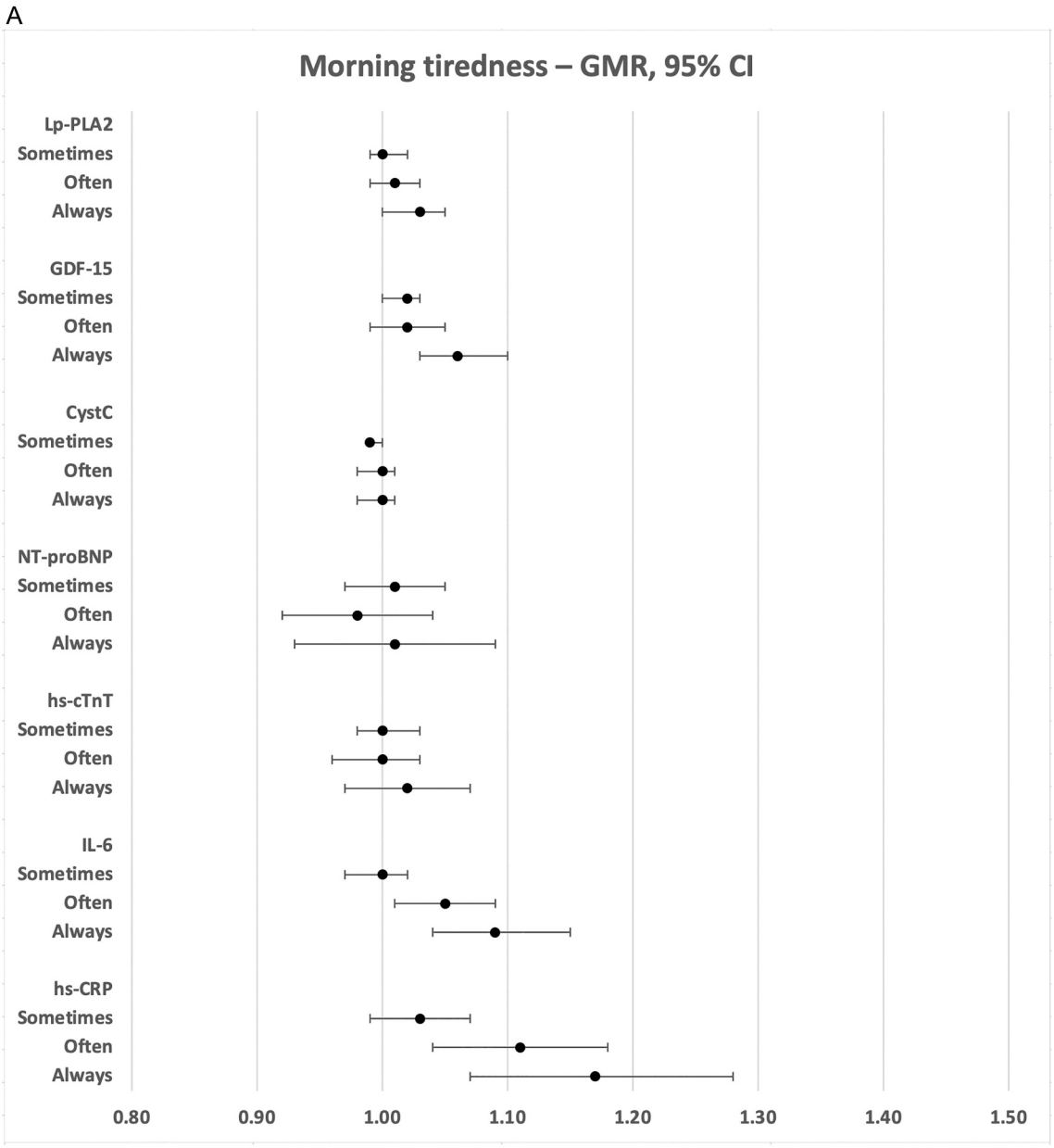

Fig. 1. (*continued*).

The primary analyses (trend testing using the adjusted linear regression model) yielded the following results: EDS (Fig. 1A, Supporting Table S5A) was associated with higher levels of IL-6 (often GMR 1.07; 95% CI, 1.03–1.10, always 1.15; 1.10–1.21), GDF-15 (often 1.03; 1.01–1.06, always 1.07; 1.03–1.11), hs-CRP (always 1.28; 1.17–1.41), NT-proBNP (always 1.22, 1.12–1.33), and hs-cTnT (always 1.07; 1.01–1.12) as compared with the reference group (*p*-value for all <0.0001). Similarly, MT (Fig. 1B, Supporting Table S5B) was associated with elevated levels of hs-CRP (often 1.11; 1.04–1.18, always 1.17; 1.07–1.28; *p*-value <0.0001), IL-6 (often 1.05; 1.01–1.09; always 1.09; 1.04–1.15; *p*-value <0.0001), and GDF-15 (always 1.06; 1.03–1.10; *p*-value 0.0005).

When compared to EDS, loud snoring (to a lesser extent associated with CV prognosis in previously published data) was associated with a higher proportion of males, higher amount of standard drinks/week, less atrial fibrillation/flutter, less congestive heart failure/lower NYHA-class, less polyvascular disease, and higher absolute levels of Lp-PLA_2 activity (Supporting Table S4). Loud snoring (Supporting Table S5C) was also associated with lower levels of NT-proBNP (sometimes 0.94; 0.90–0.98, often 0.92; 0.87–0.97, always 0.87; 0.81–0.92), and hs-cTnT (always 0.94; 0.91–0.98) but also with higher levels of hs-CRP (always 1.11; 1.04–1.19) compared with the reference group (*p*-value for all <0.0001).

[1] Adjusted – adjusted for age at randomization, sex, geographic region, alcohol usage, smoking status, physical activity, 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; GMR – Geometric mean ratio, CI – Confidence interval; CysC – Cystatin C, GDF-15 – Growth differentiation factor 15, hs-CRP – high-sensitivity C-reactive protein, IL-6 – Interleukin 6, hs-cTnT – high-sensitivity cardiac Troponin T, NT-proBNP – N-terminal pro B-type natriuretic peptide, Lp-PLA_2 – Lipoprotein associated phospholipase A2 activity

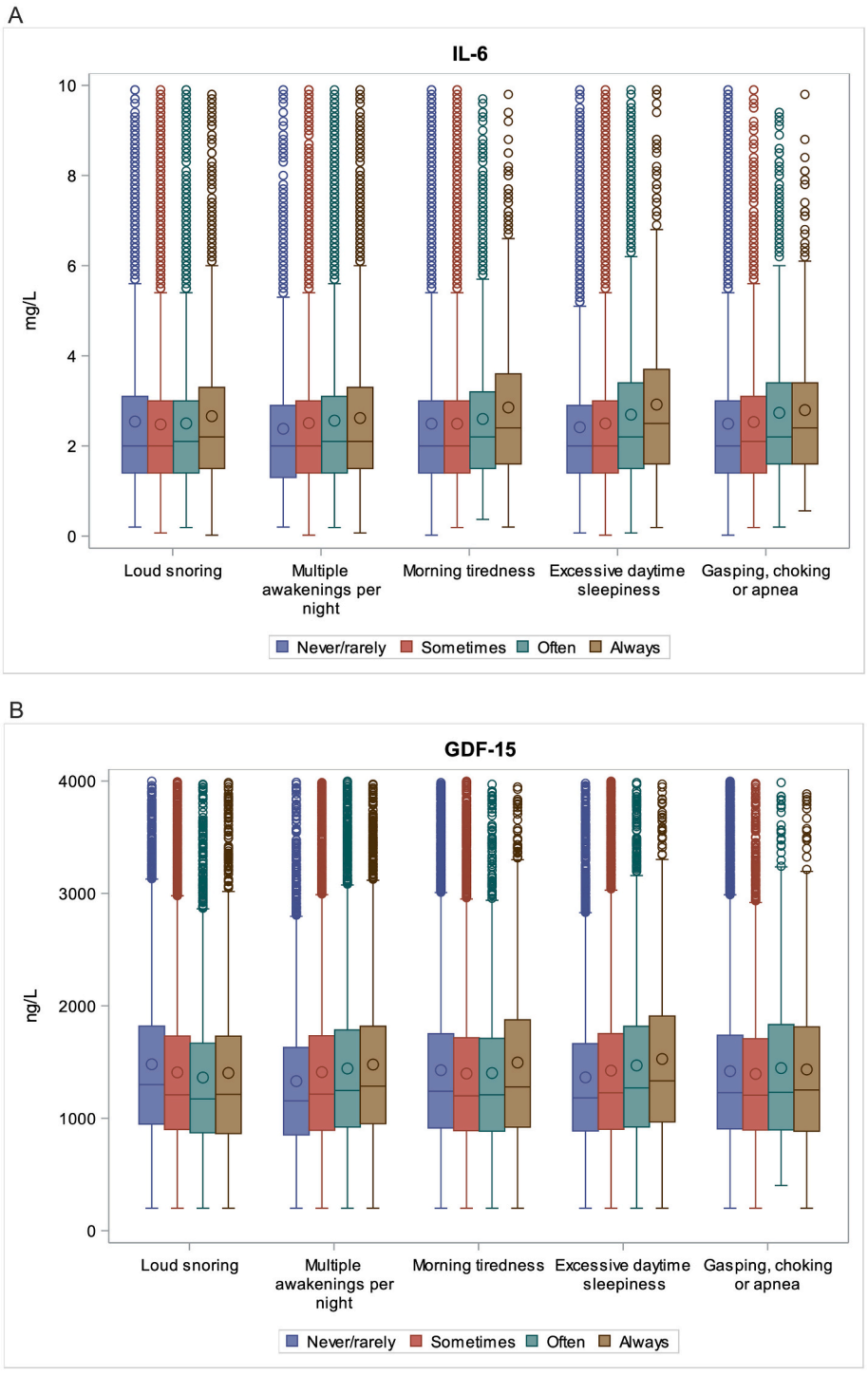

Fig. 2. Boxplots[21] presenting interquartile ranges of the absolute levels of biomarkers stratified by sleep-related breathing disorder-related questions.

All SRBD-related questions were to some extent associated with increased levels of hs-CRP. For SRBD-related symptoms, not related to prognosis, such as multiple awakenings per night (Supporting Table S6A) and gasping, choking or apnea when asleep (Supporting Table S6B) this was the only significant, albeit consistent, association with biomarkers.

Absolute levels of these biomarkers are consistent with the associations described above (Fig. 2A-B, Supporting Fig. S1A—C).

There were no changes in the associations with biomarkers in the adjusted models (Supporting Table S7A—C), after excluding patients with a CHF diagnosis ($n = 3336$; 21.5%) at baseline. Also, there were no interactions (Supporting Table S8) between EDS, MT, and loud snoring affecting the levels of the mutual associated biomarkers: IL-6, GDF-15, hs-cTnT, and NT-proBNP.

4. Discussion

The stratification by SRBD-related symptoms of this cohort of patients with high CV risk CCS on optimal secondary prevention therapies has previously revealed independent associations between higher frequencies of EDS and MT (to a lesser extent loud snoring) and CV prognosis, possibly linked to coexisting multiple pathophysiological

mechanisms and phenotypes. [12]

There are three key findings from this study. First, compared with patients never/rarely reporting EDS symptoms, those with often and always EDS, had 7–15% higher levels of IL-6, and 3–7% higher levels of GDF-15. Second, the always EDS group also had 22% and 7% higher levels of NT-proBNP and hs-cTnT, respectively. Third, patients reporting often and always having MT had 5–9% higher levels of IL-6 and the always MT group also had 6% higher levels of GDF-15.

The clinical relevance of differences in biomarker levels based on frequency of SRBD questions is difficult to assess. We have showed significant associations, but we cannot claim causality. However, we have previously shown that hs-cTnT, NT-proBNP, GDF-15, and IL-6 all are prognostically important for the CV prognosis in these patients.

EDS and MT were most consistently associated with elevated IL-6, an upstream cytokine, induced and amplified by the inflammasome (interleukin 1) [17], and more specific for relative risk prediction in this high CV risk cohort than hs-CRP. IL-6 has a proven causal link with atherosclerosis progression [18] and adverse CV outcomes [19–22]. There was also an association with GDF-15 which in turn is associated with adverse CV outcomes including MI and CV death. [23] The biological role of GDF-15, in the cardiovascular system is not well understood and there are reports of both antiatherogenic and proatherogenic effects. [24] Recently, GDF-15 has been described as a central mediator induced by inflammation, potentially with cardioprotective effects caused by maintaining triglyceride levels via hepatic beta-adrenergic signaling. [25] The exact pathophysiological mechanism remains unknown, but regardless, GDF-15 should be regarded as an important associated biomarker upregulated in the patients with frequent EDS and MT.

Of the prognostic biomarkers in this study, CRP, IL-6, NT-proBNP, and cTnT have previously been studied in relation with SRBD-related questions (EDS defined as daytime sleep >1 h per day) but this was performed in older men recruited from the general population. [26] The referenced study showed that EDS was associated with higher levels of CRP, NT-proBNP, and cTnT, which is in line with our results in patients with CCS. IL-6 was not associated with EDS in this study of the general population, which reiterates its value as a biomarker of relative risk in a high CV risk cohort of patients with CCS on optimal secondary prevention therapies.

Recently, meta-analyses confirmed the relationship between OSA severity and elevated levels of hs-CRP in adults [27] and increased circulating levels of IL-6 [28] in individuals with OSA. There is also evidence from randomized clinical trials [29] that inflammatory biomarkers are elevated in patients with OSA regardless of concomitant obesity, most likely caused by intermittent hypoxemia. Treatment with Continuous Positive Airway Pressure (CPAP) may lower IL-6 levels in both symptomatic (sleepy) and asymptomatic (non-sleepy) patients with OSA [30], but further studies are mandatory. GDF-15 has not shown a correlation with OSA in the literature. [31] There is a dose-response relationship in women between the severity of sleep apnea and B-type natriuretic peptide [32] and CPAP-treatment has been shown to reduce NT-proBNP levels in patients with OSA [33]. Moreover, inflammation is known to promote elevation of NT-proBNP levels [34], and elevated NT-proBNP levels are not necessarily associated with heart failure with reduced or preserved ejection fraction in patients with septic cardiomyopathy [35]. The association between cTnT and OSA severity, in particular the degree of nocturnal hypoxia, has previously been established, although the exact mechanism causing the subclinical myocardial injury is not known. [36]

Loud snoring was consistently associated with decreased levels (the sometimes, often, and always groups had 6–13% lower levels) of NT-proBNP, a well-known prognostic biomarker in this patient group [42–44] and a biomarker indicating risk of heart failure, where it serves as a cardioprotective hormone released by cardiomyocytes in response to pressure or volume overload. [45] A total of 21.5% of included patients had a diagnosis of CHF at baseline. However, sensitivity analyses excluding these patients showed practically no changes in biomarker levels at all. In patients with a prior MI, NT-proBNP levels show a considerable variation with lower levels after 1 year [46]. Performing PCI on a > 90% coronary artery stenosis in the left anterior descending artery (LAD) in patients with CCS and normal left ventricular ejection fraction significantly lowers NT-proBNP levels. [47]

While EDS was associated with higher levels of NT-proBNP and hs-cTnT, loud snoring was associated with lower levels. Lower levels of prognostic biomarkers with more frequent loud snoring is a novel and unexpected finding, the results are however in accordance with some previous studies underlining the importance of sleepiness for cardiovascular risk in SRBD.

In a community-based study, women with the combination of snoring and EDS had an increased risk of developing heart failure, while snorers without EDS had not. [38] There is also a growing literature on symptom-based sub-types of OSA and risk for cardiovascular endpoints, with several [5,39,40] but not all [41] studies reporting an increased risk in the excessively sleepy sub-type.

Higher frequencies of all SRBD-related symptoms were associated with elevated levels of hs-CRP which is in line with the literature on the effect of OSA and sleep fragmentation on inflammation. The associations were most consistent with multiple awakenings/night and gasping, choking, or apnea when asleep, which had no additional impact on CV risk in our previously published data [12]. Witnessed apneas is the most specific symptom of OSA but limited due to the requirement of other party witnessing the event.

This suggest that in the context of patients with high CV risk CCS and SRBD-related symptoms, hs-CRP is rendered a biomarker without any additional prognostic information regarding CV risk and likely more suitable as a biomarker for monitoring of treatment efficacy and/or as a tool for more general screening for high CV risk in patients with CCS. This statement is reinforced by studies of the poor prognostic ability of hs-CRP in the same cohort [22], pathophysiological role as a downstream acute phase response [37], and a recent phase 2 trial of a fully human monoclonal antibody (ziltivekimab), effectively neutralizing IL-6 and consequently only lowering hs-CRP [17]. Also, the clinical interpretation of hs-CRP is often complicated due to the possibility of multiple causes of elevated levels such as concomitant co-morbidities and/or gene polymorphisms.

The above-mentioned differences in associations with biomarkers levels reinforce the suspicion of multiple pathophysiological mechanisms governing CV risk in patients with CCS, at least when stratifying by SRBD-related questions, although separate pathways may be involved to a greater extent in certain sub-groups.

5. Limitations

The study was performed in patients with CCS and results cannot be extrapolated to other populations, such as healthy individuals. The study exposure is based on self-reported data. Polysomnography evaluations were not performed in the study, so details on prevalence of SRBDs and OSA is not known. At baseline, around 7% of patients were previously diagnosed with OSA. In these patients, there is a lack of data regarding adherence to CPAP treatment and the effects on experienced symptoms. These data are of importance to estimate the residual CV risk linked with undertreated symptomatic (sleepy) OSA.

The self-reported questionnaire used questions derived from the Berlin questionnaire (results are not interchangeable), but it has not been validated. Despite multiple adjustments in the linear regression models, residual confounding cannot be excluded. Also, the cross-

[2] Mean, median, first and third quartile, minimum and maximum values, and outliers; GDF-15 – Growth differentiation factor 15, IL-6 – Interleukin 6

sectional design does not allow for distinguishing between causation and correlation. Thus, we cannot exclude that the elevated levels of the biomarkers are a result of underlying cardiovascular disease, concomitant co-morbidities, or gene polymorphisms.

6. Conclusion

In this cross-sectional study of patients with CCS, stepwise increased frequency of SRBD-related symptoms, such as EDS and MT, were associated with gradually higher levels of IL-6 and GDF-15, each reflecting distinct pathophysiological pathways.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131395.

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