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Insomnia and the risk of incident heart failure: a population study

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Aims Insomnia is highly prevalent among heart failure patients, but only a few small studies have investigated insomnia symptoms and risk of heart failure. We aimed to assess the prospective association between self-reported insomnia symptoms and the risk of incident heart failure in a large Norwegian cohort.

Methods and results Baseline data on insomnia symptoms, including difficulty initiating sleep, difficulty maintaining sleep and having non-restorative sleep, socio-demographic variables, and health status, including established cardiovascular risk factors, were collected from 54 279 men and women 20–89 years of age who participated in the Nord-Trøndelag Health study (HUNT) between 1995 and 1997 and were free from known heart failure at baseline. The cohort was followed for incident heart failure from baseline through 2008. We used Cox proportional hazard models to assess the association of baseline insomnia symptoms with the risk of heart failure. A total of 1412 cases of heart failure occurred during a mean follow-up of 11.3 years (SD = 2.9 years), either identified at hospitals or by the National Cause of Death Registry. There was a dose-dependent association between the number of insomnia symptoms and risk of heart failure. The multi-adjusted hazard ratios were 0.96 (0.57–1.61), 1.35 (0.72–2.50), and 4.53 (1.99–10.31) for people with one, two, and three insomnia symptoms, compared with people with none of the symptoms (*P* for trend 0.021).

Conclusions Insomnia is associated with an increased risk of incident heart failure. If our results are confirmed by others and causation is proved, evaluation of insomnia symptoms might have consequences for cardiovascular prevention.

Keywords Insomnia • Heart failure • Prospective study

Introduction

Insomnia symptoms, including having difficulty initiating sleep, maintaining sleep, or having poor sleep quality, are highly prevalent among heart failure (HF) patients.[1] Recent studies indicate that the prevalence of these symptoms among HF patients ranges from 23to 73%.[2–4] However, it is largely unknown whether insomnia is associated with later risk of HF among individuals who were free from HF at baseline. There is a lack of large prospective studies of insomnia and risk of HF with adjustment for established cardiovascular risk factors, psychological distress, and the presence of chronic somatic disorders. Such an association seems plausible since insomnia is considered to be a disorder of chronic activation of stress responses, with sympathetic arousal and activation of the hypothalamic pituitary adrenal axis (HPA axis) which is accompanied by increased heart rate, elevated blood pressure, and elevated levels of pro-inflammatory cytokines and circulating catecholamines.[5]

In the present study, we prospectively investigated the association between insomnia symptoms and the risk of incident HF in a large population-based cohort, taking into account a large number of established cardiovascular risk factors, previous and/or incident acute myocardial infarction (AMI), anxiety or depression, and several chronic somatic disorders.

Methods

Study population

The Nord-Trøndelag Health study (HUNT study) constitutes a large database of clinical, anthropometric, and socioeconomic information

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collected during a three-phase population-based health survey in Nord-Trøndelag County in Norway. The study was primarily designed to address major public health issues in accordance with current national health priorities.

Nord-Trøndelag is one of the 19 Norwegian counties and is located in the central part of Norway. The county is fairly representative for Norway although the average educational and income levels are somewhat lower than for the country as a whole. The population is stable and ethnically homogenous, with only a small percentage (3%) of people of non-Caucasian origin. The size of the population was stable between the HUNT surveys, with a net emigration out of the county of only 0.3% per year.

The adult population of Nord-Trøndelag County was invited to participate in the second phase of the HUNT study from August 1995 to June 1997. In total, 94 187 individuals were invited, and 65 215 (69%) participated in the study. The invitation letter to the survey was sent by mail together with a three-page questionnaire (questionnaire 1). The self-administered questionnaire was to be completed prior to the clinical examination and returned at the screening site. A five-page self-administered questionnaire (questionnaire 2) was handed out at the screening site and was to be completed by the participant and returned by mail free of charge. Details about the HUNT study have been published elsewhere.[6–8]

The study was approved by the regional committee for ethics in medical research, by the National Directorate of Health, and by the Norwegian Data Inspectorate.

Insomnia

Insomnia is defined as a subjective feeling of having difficulties initiating or maintaining sleep or having a feeling of non-restorative sleep.[9] The HUNT questionnaire included three items related to insomnia. One question was related to difficulty initiating sleep ('Have you had difficulties falling asleep in the last month' with the response options never/occasionally/often/almost every night), one was related to difficulty maintaining sleep ('During the last month, have you woken up too early and not been able to get back to sleep' with the response options never/occasionally/often/almost every night), whereas the third question was related to having a feeling of non-restorative sleep ('How often do you suffer from poor sleep' with the response options never or a few times a year/one to two times per month/about once a week/more than once a week). The last question was restricted to individuals who were 20–69 years of age.

We assessed the influence of each insomnia symptom using the original four response categories.

Insomnia symptoms were also dichotomized and the highest categories, i.e. having difficulty initiating sleep almost every night, difficulty maintaining sleep almost every night, and having non-restorative sleep more than once a week, were compared with the rest of the categories. Those in the highest categories were considered to have the respective insomnia symptom in the analysis of the association between the number of insomnia symptoms and HF risk.

Apart from insomnia symptoms, participants 20–69 years of age were also asked whether symptoms related to sleep influenced their work situation ('During the last year, have you been troubled by insomnia to such a degree that it influenced your work performance' with the response options yes or no).

In total, 54 403 participants (83.4%) answered one or more of the insomnia questions. The response rates for the respective questions were 82.5, 82.7, 82.3, and 81.3%. These response rates largely reflect the overall response of the questionnaire that included the insomnia items (84.9%).

Outcome ascertainment

After participating at baseline, the participants were followed up for a first incident of HF, either identified at hospitals or by the National Cause of Death Registry. A total of 124 participants were excluded because their medical records indicated HF before they participated at baseline. Therefore, 54 279 people were included in the analyses of this study. *Figure 1* summarizes the recruitment of the participants.

Hospitalizations for HF were identified through a linkage with medical records from the two hospitals of Nord-Trøndelag County from baseline until 31 December 2008. Heart failure was defined and diagnosed according to the current European Society of Cardiology guidelines.[10] The criteria for HF included symptoms and signs of HF and objective evidence of cardiac dysfunction at rest. The overall quality of the hospital discharge diagnosis of HF is high in Nordic countries.[11,12] To further increase the specificity of the diagnosis, we considered only primary diagnoses of HF, as recommended.[11] Deaths due to HF were identified by the National Cause of Death Registry. We used ICD 9 code 428 and ICD 10 codes I50.0, I50.1, and I50.9 to identify HF.

During 11.3 years of follow-up, 190 participants who left the county, and 7658 participants who died from causes other than HF, were censored at the time of event (emigration or death) in the statistical analysis.

Clinical information

At baseline, a clinical examination was conducted by trained nurses and included standardized assessment of blood pressure, weight, height, and waist and hip circumference. Systolic and diastolic blood pressure were measured using a Dinamap 845XT (Critikon) sphygmomanometer based on oscillometry, and the average of the second and the third out of three measurements was used in the analysis. Height and weight were recorded with participants wearing light clothes without shoes; height was measured to the nearest 1 cm and weight to the nearest 0.5 kg. Waist circumference was measured to the nearest centimetre at the level of the umbilicus. The body mass index (BMI) was computed as weight (in kilograms) divided by the squared value of height (in meters).

Information on health, lifestyle factors and medication was collected by a self-administered questionnaire. The participants extensively assessed and reported their medical history regarding common chronic somatic disorders.

The participants were asked about their usual intake of wine, beer, and spirits, indicated by their usual number of drinks over a 2-week period. We categorized participants according to their alcohol consumption as abstainers, light drinkers (0–1 drinks per day), moderate drinkers (>1 but <2 drinks per day), or heavy drinkers (>2 drinks per day).

The participants were also asked about their level of physical activity. Light physical activity was defined as activity that does not involve sweating or feeling of breathlessness. The participants were classified as (i) inactive if they reported <1 h of hard and <3 h of light physical activity per week, (ii) moderately active if they reported 1–3 h of hard or >3 h of light activity per week, and (iii) physically active if they reported >3 h of hard physical activity per week.

Responses to questions related to smoking were categorized as current, previous, or never smoking.

Education was categorized as low (≤9 years), medium (10–12 years), or high (>12 years). The marital status was dichotomized to living alone or not.

The participants were asked about their use of sleep medication/sedatives ('How often have you taken tranquilizers/sedatives or sleep

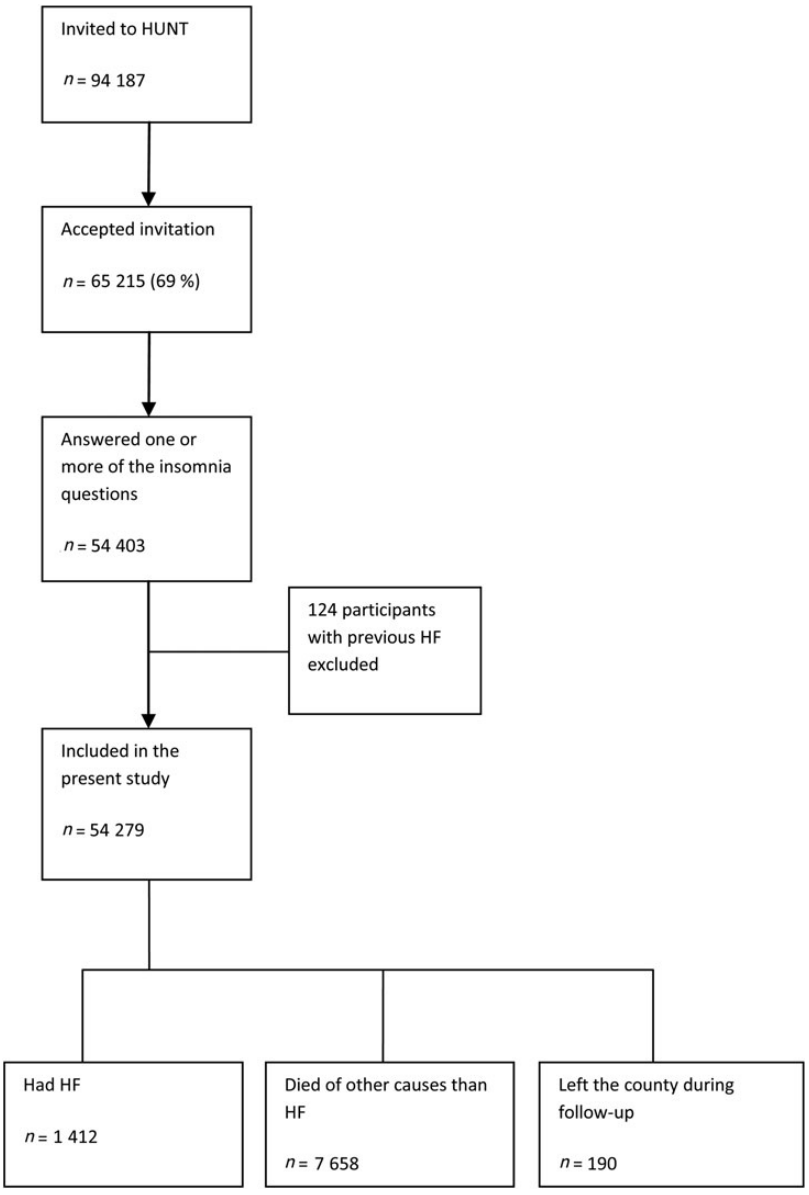

Figure 1 Flow chart for the participants.

medication in the last month?') with the following response options: daily/every week but not every day/less than once a week/never.

Depression and anxiety

The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression. The questionnaire consisted of 14 four-point Likert-scaled items, seven for anxiety, and seven for depression. Scores on both the anxiety and depression subscales ranged from 0 to 21, and increasing score indicated increased symptom load. No somatic items or items regarding sleeping difficulties were included. HADS has been found to have good testing properties in the assessment of symptom severity of anxiety and depression both in primary health care and in hospital settings.[13] The psychometric properties of the scale have previously been validated as part of the HUNT study.[14]

Laboratory measurements

A non-fasting serum sample was drawn from each participant and analysed at the Central Laboratory, Levanger Hospital, using a Hitachi 911 Autoanalyzer (Hitachi, Mito, Japan). Serum was separated from the blood by centrifugation within 2 h at the screening site and placed in a refrigerator (4°C). Time between the last meal and the venopuncture was recorded and the samples were sent to the laboratory on the same day (some samples drawn on a Friday were sent the following Monday).

Serum concentrations of total cholesterol, HDL cholesterol, and triglycerides were analysed applying reagents from Boehringer Mannheim (Mannheim, Germany). The day-to-day coefficients of variation were 1.3–1.9, 2.4, and 0.7–1.3%, respectively. Total and HDL cholesterol were measured by an enzymatic colorimetric cholesterol esterase method. Measurement of HDL cholesterol was performed after

precipitation with phosphotungsten and magnesium ions. Triglycerides were measured with an enzymatic colorimetric method.

Statistical analysis

We used Cox proportional hazard models to examine the prospective association between insomnia symptoms and subsequent risk of incident HF. We calculated the number of events, person years at risk and hazard ratios (HR) with 95% confidence intervals. Each category of reported insomnia symptoms was compared with the reporting of no insomnia complaints. For tests of trend, we assigned a numeric value of 0–3 to the insomnia categories, with 0 having no insomnia complaints, and the categories were treated as a continuous variable.

In a separate analysis, we calculated the risk associated with an increasing number of dichotomized insomnia symptoms, compared with the risk of participants without any insomnia symptoms. Participants with missing data on any of the insomnia symptoms were excluded from this analysis. Also, the assessment of having a feeling of non-restorative sleep was restricted to participants 20–69 years of age, and the analysis related to the cumulative number of insomnia symptoms was therefore restricted to this age group.

The Kaplan–Meier method was used to evaluate risk for incident HF and overall mortality according to the number of insomnia symptoms.

We included age, sex, education, shift work, and marital status as potentially confounding factors in our models. Established cardiovascular risk factors, such as a history of previous myocardial infarction, high blood pressure, low physical activity, high BMI, smoking, abstinence of alcohol and heavy drinking, dyslipidaemia, and diabetes may act as both confounding and mediating factors in relation to sleep disorders and risk of incident HF. We therefore analysed the data both with and without these factors included in the analysis. Also, it is not clear whether psychological distress is a cause or a consequence of sleep disorders. In separate analyses, we therefore also adjusted for depression and anxiety.

We conducted several stratified analyses to assess whether the association of insomnia symptoms with HF could be modified by other factors. Thus, we investigated the potential effect modification by sex, age (dichotomized at age 65 years), BMI (dichotomized at 35 kg/m^2), cholesterol (dichotomized at 6.5 mmol/L), education (dichotomized at 12 years), shift work (yes/no), blood pressure (high blood pressure was defined as having systolic blood pressure >140 and/or having diastolic blood pressure >90 mmHg), and smoking status (current smoking/no current smoking). We also formally tested the homogeneity of stratum-specific relative risks. For these tests of interaction, we used the insomnia trend variables as defined above.

We performed several sensitivity analyses to assess the robustness of our findings. To address the possibility of reverse causation as an explanation for the observed associations, we excluded the first 5 years of follow-up and repeated the analyses. We also restricted the analyses to HF cases that were confirmed at the hospital; thus, we excluded cases whose diagnosis was based on death certificates alone. In another sensitivity analysis, we adjusted for known chronic disorders, such as stroke, asthma, angina pectoris, diabetes mellitus, goitre, hypo and hyperthyroidism, fibromyalgia, arthritis, rheumatism, ankylosing spondylitis, cancer, epilepsy, diabetes mellitus, or osteoporosis. We also adjusted for the use of sleep medication/sedatives. Since blood sampling was non-fasting, blood lipid values, especially those for triglycerides, could be influenced by time since last meal. In a sensitivity analysis, we therefore adjusted for time between the last meal and the venopuncture. Finally, we tested whether AMI during the follow-up influenced our estimates, and included AMI during the follow-up as a time-dependent variable.

We tested the proportionality of hazards using log–log curves and formal tests of interaction with time or log-time. There was no evidence against the proportionality assumption (all P values >0.10).

The statistical analyses were conducted using Stata 10.1 for Windows (Stata Corp., College Station, TX, USA).

Results

The prevalence of having difficulties initiating sleep almost every night, having difficulties maintaining sleep almost every night, and having non-restorative sleep more than once a week were 3.4%, 2.5%, and 8.1%, respectively.

Table 1 displays the characteristics of the study population according to the cumulative number of insomnia symptoms. The individual insomnia symptoms, i.e. difficulty initiating sleep, difficulty maintaining sleep, and that of non-restorative sleep, showed largely similar associations with these characteristics (data not shown). Older participants were more likely to have insomnia symptoms and symptoms were more frequent in women than men. In general, insomnia symptoms were associated with cardiovascular risk factors in a dose-dependent manner. There was also a strong association between insomnia symptoms and depression, anxiety, and the use of sleep medication/sedatives.

Characteristics of the study population at baseline, by the HF status at follow-up, are shown in *Table 2*. Heart failure was more frequent among older participants and in men, and at baseline, participants who developed HF during the follow-up were physically less active, consumed less alcohol, and were less educated than other participants. They also had more often diabetes, an unfavourable lipid profile, high blood pressure, and higher BMI.

Among the 54 279 participants, a total of 1412 were diagnosed with HF during a mean follow-up of 11.3 years (SD = 2.9 years). A total of 1004 cases were diagnosed at hospital admission, and 408 cases were identified based on information from the National Cause of Death Register.

Table 3 presents the age- and sex-adjusted HRs and several multi-variable adjusted HRs for incident HF in relation to the individual insomnia symptoms. Having difficulty initiating sleep almost every night, difficulty maintaining sleep almost every night, and having the feeling of non-restorative sleep more than once a week were associated with an increased risk of incident HF compared with those who reported never or almost never to have these symptoms. After adjustment for established cardiovascular risk factors and previous AMI, the strength of the associations was attenuated. The estimates of effect were further attenuated after adjustment for depression and anxiety.

The HRs for HF when insomnia with influence on work was compared with insomnia that did not have such an influence were 1.53 (95% CI: 1.10–2.12) and 1.31 (95% CI: 0.86–1.98) in Models 1 and 3, respectively. The associations were not substantially different in the other models.

The cumulative number of insomnia symptoms was associated with an increased risk of HF in a dose-dependent manner in all models (*Table 4*). The age- and sex-adjusted HRs (with 95% CI) between insomnia and overall mortality were 1.24 (1.08–1.43), 1.65 (1.37–2.00), and 2.39 (1.75–3.26) for one, two, and three insomnia symptoms, respectively, compared with participants who

Table 1 Baseline characteristics of the participants according to cumulative number of insomnia symptoms

Number of insomnia symptoms	*n*	0	1	2	3
Variable		**% (*n*)**	**% (*n*)**	**% (*n*)**	**% (*n*)**
Total	44 047	91.1 (40 134)	6.2 (2711)	2.2 (978)	0.5 (224)
Sex (male)	20 205	47.0 (18 870)	34.2 (926)	34.8 (340)	29.9 (67)
Diabetes mellitus	770	1.7 (666)	2.4 (66)	3.1 (30)	3.6 (8)
Smoking	43 909				
Never	19 626	45.7 (18 269)	36.3 (980)	30.2 (294)	37.4 (83)
Former	10 860	24.7 (9885)	25.4 (685)	24.6 (239)	23.0 (51)
Current	13 423	29.6 (11 858)	38.4 (1037)	45.2 (440)	39.6 (88)
Alcohol	41 825				
Abstainer	14 203	33.0 (12 609)	42.7 (1082)	43.3 (401)	53.6 (111)
Light drinker	21 420	52.0 (19 827)	44.9 (1136)	40.8 (378)	38.2 (79)
Moderate drinker	4856	11.8 (4498)	9.5 (240)	11.3 (105)	6.3 (13)
Heavy drinker	1346	3.2 (1226)	2.9 (74)	4.5 (42)	1.9 (4)
Physical activity	41 762				
Inactive	15 140	35.2 (13 456)	46.6 (1145)	49.3 (436)	52.6 (103)
Moderately active	22 275	54.1 (20 695)	45.8 (1125)	42.7 (378)	39.3 (77)
Physically active	4347	10.7 (4075)	7.5 (185)	8.0 (71)	8.2 (16)
Shift work[a]	7685	22.3 (7108)	22.9 (420)	20.9 (129)	21.7 (28)
Living alone	16 496	37.7 (15 108)	34.8 (941)	36.8 (359)	39.3 (88)
Education	43 112				
≤9 years	12 703	27.7 (10 905)	47.1 (1230)	48.2 (455)	52,8 (113)
10–12 years	20 395	48.2 (18 951)	38.4 (1004)	38.5 (363)	36.0 (77)
>12 years	10 014	24.1 (9484)	14.5 (380)	13.4 (126)	11.2 (24)
Use of sleep medicine/sedatives daily	1235	1.8 (663)	10.8 (269)	24.4 (221)	39.0 (80)
Previous myocardial infarction	709	1.5 (609)	2.2 (60)	3.3 (32)	3.6 (8)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	44 047	44.1 (13.2)	49.5 (12.5)	50.1 (13.2)	53.0 (12.0)
BMI (kg/m^2)	43 916	26.1 (4.0)	26.7 (4.6)	26.8 (4.6)	26.5 (4.6)
Systolic BP (mmHg)	43 922	133.5 (18.7)	135.9 (19.7)	134.2 (19.7)	136.9 (20.7)
Diastolic BP (mmHg)	43 922	79.1 (11.6)	80.9 (11.6)	79.9 (11.7)	81.9 (11.3)
Total cholesterol (mmol/L)	43 966	5.7 (1.2)	6.1 (1.3)	6.1 (1.3)	6.3 (1.4)
HDL cholesterol (mmol/L)	43 954	1.38 (0.38)	1.41 (0.40)	1.39 (0.42)	1.42 (0.43)
Triglycerides (mmol/L)	43 966	1.7 (1.1)	1.8 (1.2)	1.9 (1.3)	2.0 (1.2)
Depressive symptom score	43 513	3.1 (2.8)	5.1 (3.7)	6.1 (3.9)	7.0 (4.3)
Anxiety symptom score	43 286	4.1 (3.1)	6.6 (4.0)	7.7 (4.3)	9.0 (4.8)

[a]Those who answered yes to the question: 'Do you have shift work, night work or standing by duties?'.

reported no symptoms. The corresponding multi-adjusted estimates (according to Model 3 in *Table 4*) were 1.20 (1.02–1.41), 1.38 (1.10–1.73), and 2.03 (1.39–2.95).

Figures 2 and *3* show Kaplan–Meier curves for incident HF and overall mortality according to number of insomnia symptoms. The figures show that the number of insomnia symptoms was positively associated with both risk of HF and overall mortality.

Compared with men (*Table 5*), women appeared to have a higher relative risk of HF associated with non-restorative sleep and with the cumulative symptoms of insomnia. For other stratified variables, we found no statistical evidence for any effect modification, including age, BMI, cholesterol, education, shift work, blood pressure, and smoking status.

Sensitivity analyses

A total of 1073 HF cases occurred after the fifth year of follow-up, and even after the exclusion of the first 5 years the estimated associations remained unchanged. For example, in Model 3, the HR for having three insomnia symptoms was 4.57 (95% CI: 1.85–11.25).

We obtained similar results by restricting follow-up to hospital confirmed cases of HF ($n = 1004$, data not shown).

Adjustment for chronic diseases ($n = 33\,819$) only slightly attenuated the association of insomnia with HF risk compared with the results of the main analyses. For example, in Model 3, the HR for having three insomnia symptoms was 4.21 (95% CI: 1.84–9.61).

The association between insomnia and HF risk did not substantially change after adjustment for the use of sleep medications/

Table 2 Baseline characteristics of the participants according to heart failure during the follow-up

Variable	*n*	No HF during follow-up % (*n*)	HF during follow-up % (*n*)
Sex (male)	54 279	45.2 (23 900)	50.7 (716)
Diabetes mellitus	54 180	2.8 (1462)	12.4 (174)
Smoking	54 011		
Never	24 899	46.1 (24 271)	44.9 (628)
Former	13 964	25.6 (13 476)	34.9 (488)
Current	15 148	28.3 (14 866)	20.2 (282)
Alcohol	51 046		
Abstainer	20 995	40.3 (20 079)	72.1 (916)
Light drinker	23 442	46.5 (23 148)	23.2 (294)
Moderate drinker	5163	10.3 (5119)	3.5 (44)
Heavy drinker	1446	2.9 (1430)	1.3 (16)
Physical activity	48 879		
Inactive	18 974	38.4 (18 371)	59.4 (603)
Moderately active	25 234	51.9 (24 862)	36.6 (372)
Physically active	4671	9.7 (4630)	4.0 (40)
Shift work[a]	37 142	21.1 (7750)	5.2 (22)
Living alone	54 160	38.6 (20 359)	43.8 (619)
Education	51 724		
≤9 years	18 820	35.6 (17 965)	71.4 (855)
10–12 years	22 297	43.6 (22 029)	22.2 (2,681)
>12 years	10 607	20.9 (10 533)	6.2 (74)
Use of sleep medicine/ sedatives daily	2215	4.3 (2051)	13.4 (164)
Previous myocardial infarction	1715	2.7 (1416)	21.3 (29.9)
	n	Mean (SD)	Mean (SD)
Age (years)	54 279	49.6 (16.9)	74.0 (9.2)
BMI (kg/m^2)	53 942	26.3 (4.1)	27.9 (4.6)
Systolic BP (mmHg)	54 111	137.5 (21.5)	156.8 (25.5)
Diastolic BP (mmHg)	54 111	80.2 (12.1)	85.5 (14.8)
Total cholesterol (mmol/L)	54 174	5.9 (1.3)	6.4 (1.3)
HDL cholesterol (mmol/L)	54 158	1.39 (0.39)	1.30 (0.40)
Triglycerides (mmol/L)	54 174	1.7 (1.1)	2.1 (1.3)
Depressive symptom score	52 610	3.4 (3.1)	4.5 (3.4)
Anxiety symptom score	51 751	4.2 (3.3)	3.8 (3.3)

[a]Those who answered yes to the question: 'Do you have shift work, night work or standing by duties?'.

sedatives. For example, in Model 3, the HR for having three insomnia symptoms was 4.33 (1.80–10.41).

Adjustment for time since last meal did not influence the estimates (data not shown).

In the present study, a total of 1715 participants had a previous AMI at baseline and 2928 had an AMI during the follow-up. Among HF patients, 299 participants had a previous AMI at baseline and 431 had an AMI during the follow-up. No appreciable change in our estimates occurred after adjustment for incident AMI as a time-dependent covariate during the follow-up (data not shown).

Discussion

In this large prospective study of people free from known HF at baseline, we found that having difficulty initiating sleep, maintaining sleep almost every night, and that of having non-restorative sleep more than once a week were associated with an increased risk of incident HF. After adjustment for cardiovascular risk factors and previous AMI, the strengths of the associations were slightly weakened. The cumulative number of insomnia symptoms was related to an increased risk of incident HF in a dose-dependent manner: those who reported suffering from all insomnia symptoms simultaneously were at considerably higher risk than those who had no symptoms or only a few symptoms. These results were confirmed in several additional sensitivity analyses, suggesting that the findings are robust.

To our knowledge, this is the largest study to date of the association of insomnia with the risk of incident HF. The association has previously been investigated in a two small studies.[15,16] In a recent prospective study by Ingelsson *et al.*,[15] 282 out of 2314 middle-aged men were hospitalized with HF over 30 years of follow-up. Similar to our findings, they reported that difficulty initiating sleep increased the risk of incident HF with 22% (HR: 1.22, 95% CI: 1.03–1.43) while difficulty maintaining sleep increased the risk by 14% (HR: 1.14, 95% CI: 0.96–1.36). The authors adjusted for several established risk factors for HF, including interim myocardial infarction, but they did not adjust for other somatic disorders or depression. Newman[16] found that daytime sleepiness at baseline predicted incident HF and cardiovascular mortality in 5888 participants >65 years of age over a 5-year follow-up. However, the authors did not adjust for several important established risk factors for HF in the latter study.

In contrast to these two previous studies, which assessed the association between some selected insomnia symptoms and risk of HF, we investigated all aspects of sleep problems that are typically used to identify insomnia.[9] Therefore, we could also investigate the joint effect of these symptoms. Similar to the previous studies, we found a moderate risk increase related to the individual insomnia symptoms. However, the risk among those with all the three insomnia symptoms simultaneously was particularly high even after adjustment for established cardiovascular risk factors and psychological distress. This finding may be interpreted as suggesting that compromising some aspects of sleep may be somehow compensated for, and the net effect on cardiovascular disease may be limited. For example, having difficulty falling asleep might be compensated for by a satisfactory depth and a good continuity of sleep. However, if the initiation of sleep is poor and combined with repeated awakenings and superficial sleep, there may not be any compensatory mechanisms.

Several previous studies have investigated insomnia symptoms and risk of coronary heart disease (CHD). In these studies,

Table 3 Hazard ratios and 95% confidence intervals[a] for heart failure according to insomnia symptoms

Variable	Events/person time	Model 1 95% CI	Model 2 95% CI	Model 3 95% CI	Model 4 95% CI	Model 5 95% CI
Difficulty initiating sleep						
Never	626/334 660	Ref.	Ref.	Ref.	Ref.	Ref.
Occasionally	517/218 627	1.05 (0.93–1.18)	1.05 (0.93–1.19)	0.98 (0.85–1.15)	0.96 (0.82–1.12)	0.98 (0.83–1.15)
Often	76/32 500	1.10 (0.86–1.40)	1.13 (0.88–1.47)	1.08 (0.80–1.47)	0.99 (0.72–1.37)	0.98 (0.70–1.37)
Almost every night	134/18 322	1.66 (1.38–2.01)	1.67 (1.35–2.05)	1.32 (1.01–1.72)	1.26 (0.95–1.66)	1.27 (0.95–1.71)
P for trend		<0.001	<0.001	0.111	0.293	0.289
Difficulty maintaining sleep						
Never	351/289 978	Ref.	Ref.	Ref.	Ref.	Ref.
Occasionally	777/259 228	1.04 (0.91–1.18)	1.02 (0.89–1.17)	0.94 (0.80–1.10)	0.90 (0.76–1.06)	0.89 (0.75–1.06)
Often	153/42 176	1.14 (0.94–1.38)	1.11 (0.90–1.36)	0.97 (0.76–1.24)	0.92 (0.71–1.19)	0.92 (0.70–1.20)
Almost every night	86/14 071	1.30 (1.03–1.66)	1.36 (1.05–1.75)	1.26 (0.93–1.72)	1.18 (0.86–1.63)	1.13 (0.81–1.58)
P for trend		0.028	0.035	0.424	0.778	0.979
Feeling of non-restorative sleep						
Never, few times a year	211/357 749	Ref.	Ref.	Ref.	Ref.	Ref.
1–2 times per month	48/86 079	0.81 (0.59–1.11)	0.84 (0.61–1.17)	0.63 (0.42–0.95)	0.59 (0.39–0.89)	0.64 (0.42–0.96)
Once a week	23/36 503	0.77 (0.51–1.22)	0.85 (0.54–1.33)	0.75 (0.45–1.24)	0.69 (0.41–1.15)	0.79 (0.47–1.32)
More than once a week	54/41 209	1.50 (1.10–2.04)	1.46 (1.02–2.07)	1.08 (0.72–1.61)	0.91 (0.59–1.39)	1.02 (0.66–1.59)
P for trend		0.114	0.138	0.647	0.236	0.601

Model 1, adjusted for age and sex.
Model 2, Model 1 + marital status, education, and shift work.
Model 3, Model 2 + systolic blood pressure, total cholesterol, diabetes mellitus, BMI, physical activity, smoking, alcohol, and previous AMI.
Model 4, Model 3 + depression.
Model 5, Model 3 + anxiety.

Table 4 Hazard ratios and 95% confidence intervals for heart failure according to cumulative number of insomnia symptoms

Number of symptoms	Events/person time	Model 1		Model 2		Model 3		Model 4		Model 5	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
0	270/471 292	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	28/31 515	1.17	0.79–1.73	1.20	0.80–1.80	0.96	0.57–1.61	0.91	0.59–1.52	0.95	0.55–1.62
2	18/11 037	1.92	1.19–3.11	1.88	1.13–3.13	1.35	0.72–2.50	1.20	0.64–2.26	1.43	0.76–2.69
3	7/2490	2.95	1.39–6.27	2.69	1.19–6.08	4.53	1.99–10.31	3.83	1.66–8.85	5.25	2.25–12.22
HR for each symptom increase		1.37	1.15–1.62	1.35	1.12–1.62	1.29	1.04–1.61	1.23	0.98–1.54	1.34	1.06–1.68
P for trend			<0.001		0.001		0.021		0.077		0.013

For models, see *Table 2*.

including our own,[7] the researchers generally found that insomnia was associated with an increased risk of CHD.[17–28] Although CHD is an important risk factor for HF, most HF cases are not preceded by a coronary event.[29] In our analyses, we adjusted for both baseline AMI and incident AMI. These adjustments did not change the association between insomnia and incident HF. Moreover; the association of insomnia with incident HF was much stronger than for incident AMI. For example, having all the three insomnia symptoms compared with none increased the risk of incident HF by 317% (HR: 4.17) while the risk of AMI increased by 85% (HR: 1.85) after adjustment for cardiovascular risk factors (Model 3). Thus, it seems unlikely that the association between insomnia and HF observed in this study is due to the previously established association between insomnia and AMI.

Differences by sex

The distribution of causes and risk factors of HF differs between men and women. Men more often suffer from pre-existing CHD

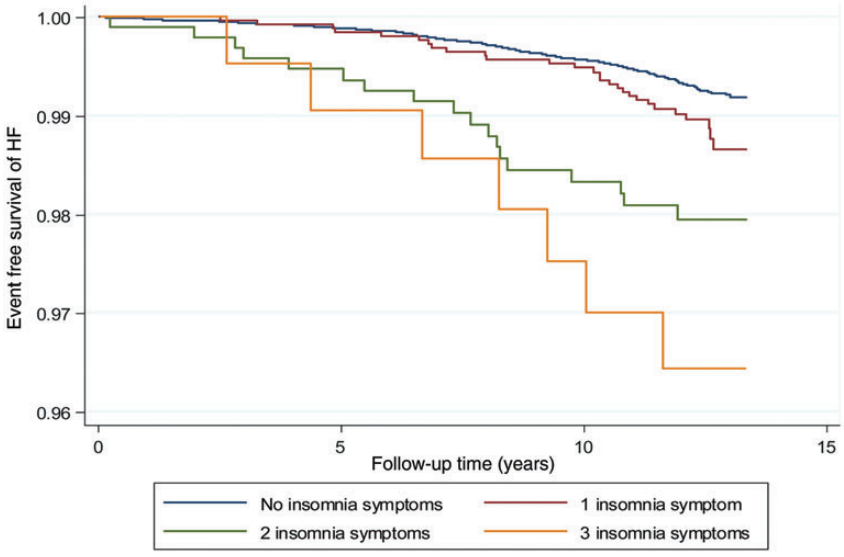

Figure 2 The Kaplan–Meier curve of incident heart failure during the follow-up according to number of insomnia symptoms.

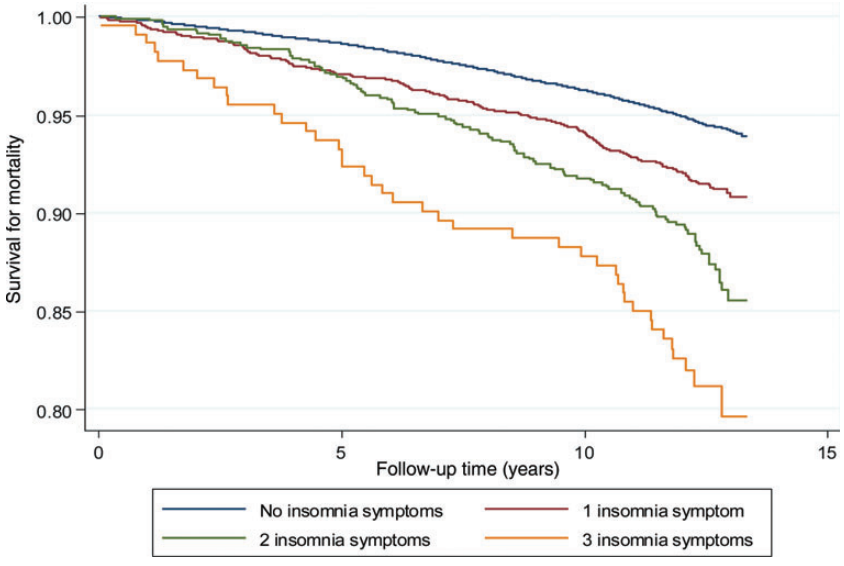

Figure 3 The Kaplan–Meier curve of overall mortality during the follow-up according to number of insomnia symptoms.

and present with dilated cardiomyopathy and impaired left ventricular function, whereas women more often suffer from hypertension and diabetes mellitus and tend to present with sustained left ventricular function.[30–32] The results of many studies have also suggested that women are more prone to insomnia than men.[33] Therefore, a sex difference in the association between insomnia and HF risk appears to be plausible, but sex differences were not evaluated in other studies.[15,34] In the present study, the relative risks of HF related to having a feeling of non-restorative sleep and cumulative insomnia symptoms in women were higher than in men. However, this finding should be interpreted with caution, because it does not necessarily suggest that insomnia is more dangerous for women in relation to HF. Instead, it is possible that the differences in relative risk by sex may be attributable to the lower baseline HF risk among women.

Among men, we found an inverse association between having the feeling of non-restorative sleep and risk of incident HF. One may speculate that non-restorative sleep might be a pathway for

Table 5 Hazard ratios and 95% confidence intervals[a] for heart failure according to insomnia symptoms stratified by sex

Variable	Women		Men		P for interaction
	HR	95% CI	HR	95% CI	
Difficulty initiating sleep					
Never	Ref.	Ref.	Ref.	Ref.	
Occasionally	0.99	0.79–1.25	0.96	0.79–1.17	0.604
Often	1.07	0.71–1.62	1.06	0.67–1.70	
Almost every night	1.11	0.78–1.59	1.61	1.07–2.42	
P for trend		0.544		0.151	
Difficulty maintaining sleep					
Never	Ref.	Ref.	Ref.	Ref.	
Occasionally	1.01	0.77–1.32	0.91	0.74–1.11	0.113
Often	1.05	0.73–1.51	0.90	0.64–1.29	
Almost every night	1.42	0.94–2.14	1.09	0.66–1.80	
P for trend		0.149		0.695	
Feeling of non-restorative sleep					
Never, few times a year	Ref.	Ref.	Ref.	Ref.	
1–2 times per month	0.74	0.37–1.46	0.58	0.35–0.97	0.004
Once a week	0.87	0.40–1.89	0.67	0.34–1.33	
More than once a week	1.68	0.97–2.92	0.60	0.29–1.22	
P for trend		0.117		0.033	
Cumulative insomnia symptoms					
0	Ref.	Ref.	Ref.	Ref.	
1	1.53	0.78–3.04	0.64	0.28–1.45	0.016
2	1.75	0.79–3.90	0.81	0.26–2.54	
3	6.81	2.68–17.29	2.04	0.28–14.63	
P for trend		0.001		0.581	

HRs, hazard ratio; CI, confidence interval; HF, heart failure.
[a]Adjustments were performed as in Model 3, *Table 2*. The estimates did not considerably differ after including the depressive symptom score or the anxiety score in the model, respectively.

a possible protective effect of insomnia in some subgroups. However, this was an unexpected and unexplained finding that should be confirmed in other studies.

Possible mechanisms for the observed association

The pathophysiology of insomnia and its links to cardiovascular disease have not yet been fully understood. Insomnia is a disorder of hyperarousal accompanied by chronic activation of stress responses with increased activity in the HPA axis and sympathetic nervous system leading to increased secretion of cortisol and up-regulation of the renin–angiotensin–aldosterone system.[5] This stress response is also accompanied by increased heart rate, decreased heart rate variability and increased blood pressure, and secretion of pro-inflammatory cytokines and catecholamines, which are all strong risk factors for HF.[35] Furthermore, the increased sympathetic activation and hypercortisolaemia in persons with insomnia have been implicated in the pathophysiology of insulin resistance and the metabolic syndrome.[36] Insomnia is associated with an unhealthy lifestyle, including a high prevalence of obesity and physical inactivity.[37] Consequently, persons suffering from insomnia are more likely to have hypertension, unfavourable lipid levels and impaired fasting glucose. This may in turn contribute to endothelial dysfunction, atherosclerosis, renal dysfunction, and progressive left ventricular remodelling. Thus, abnormalities in the autonomic nervous system and neuroendocrine system may represent a biologically plausible causal link between insomnia and HF. In the present study, we adjusted for a large set of potential confounders, and the association between cumulative insomnia symptoms and HF was largely independent of the established cardiovascular risk factors or psychosocial distress which indirectly supports a possible causal role for insomnia in the pathogenesis of HF.

Clinical perspective

Our results suggest that the evaluation of insomnia symptoms may add useful information to clinical cardiovascular risk assessment. If subsequent studies confirm our findings and if causality is better established, the observed prospective association between insomnia and HF risk could have implications for cardiovascular

prevention since insomnia is an easily recognizable and potentially manageable condition.[33]

Strengths and limitations

Our study is the largest prospective population-based study to date, following men and women of all ages over a long time. Insomnia was assessed thoroughly with information collected about all the major symptoms.[9]

There is an overlap between insomnia and psychological distress, especially depressive symptoms.[38] Previous studies of the association between insomnia and cardiovascular disease have not adequately adjusted for potentially confounding factors, such as depression and anxiety. Because the HUNT study consists of information on a large number of variables, we had the ability to adjust for many relevant covariates including cardiovascular risk factors, depression, and anxiety. Furthermore, many common chronic somatic disorders cause insomnia symptoms and are also related to HF risk.[39] Contrary to previous studies, we adjusted for common chronic disorders in our sensitivity analyses.

Because some participants with insomnia at baseline could have had undiagnosed HF, it was important to address the possibility of reverse causation. In a sensitivity analysis, we therefore excluded participants with <5 years of follow-up. This did not change our estimates, which again supports the overall conclusions of the study.

The present work has some important limitations. Similar to other prospective studies, we did not assess sleep objectively, for example, by performing a polysomnography. However, polysomnography is not routinely used for the evaluation of insomnia,[34] because difficulties initiating or maintaining sleep or non-restorative sleep cannot necessarily be measured objectively. In fact, insomnia may be present even if a polysomnographic evaluation shows no sign of an objective sleep disturbance.[34] Furthermore, we did not rely on a formal definition of insomnia, and in the analyses, we assessed the severity of symptoms both separately and in combination in relation to HF. However, our evaluation of insomnia symptoms largely reflected the current diagnostic criteria used in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders.[9]

Because objective measurements of insomnia were not conducted, we had no information on the prevalence of sleep apnoea syndrome. Sleep apnoea is a possible confounder for the association between insomnia and HF, since sleep apnoea syndrome is an established risk factor for cardiovascular diseases.[40] Although daytime sleepiness is the most characteristic symptom for sleep apnoea syndrome, apnoea patients often complain about difficulty initiating or maintaining sleep, and they often suffer from early awakenings.[41] However, according to a large polysomnographic study of nearly 5000 patients referred to sleep-wake disorders clinics in the USA, only 6% of those with insomnia symptoms had sleep apnoea syndrome.[42] Nonetheless, the authors did not evaluate non-restorative sleep, and only initiating and maintaining sleep were used in the definition of insomnia. This finding is in accordance with a European population-based study that suggested that the prevalence of other sleep disorders, including obstructive sleep apnoea, is only ~5% among persons who suffer from insomnia.[33] However, the strength of the association between sleep apnoea and insomnia is not clear, and it has been suggested that the association could be explained, at least in part, by confounding by age or depression.[41,43] In our study, we adjusted for age and depression as well as for blood pressure and BMI, i.e. two very strong correlates of both sleep apnoea syndrome and HF. Although we acknowledge the possibility that confounding by sleep apnoea could possibly be of importance, it appears unlikely that sleep apnoea alone could explain the higher risk of HF among people with insomnia symptoms.

The identification and ascertainment of HF could also be prone to misclassification. However, the overall quality and reliability of the hospital discharge registers of HF is high in Nordic countries.[11,12] To further increase the specificity of the diagnosis, we considered only primary diagnosis of HF, as recommended.[11] The reliability of the diagnosis due to deaths of HF from the Cause of Death Registry is somewhat lower than the reliability of hospital discharge diagnosis. However, we obtained essentially similar results by restricting follow-up to hospital confirmed cases of HF; and therefore, it seems unlikely that low reliability of HF deaths could explain the higher risk of HF among people with insomnia symptoms.

Observational studies inherently limit causal inference. Although we adjusted for several potential confounders in our multi-variable analyses, we cannot exclude the possibility of uncontrolled confounding behind the observed associations, i.e. that factors for which we had no information could confound the observed association. Nevertheless, any remaining confounder potentially able to influence our results considerably would need to be strongly associated with both insomnia and risk of HF and generally be unrelated to the factors included in our models.

Our findings from Norway cannot be directly generalized to countries at different latitudes, with different underlying HF risk, or with different sleeping patterns or circadian habits. Moreover, the question related to non-restorative sleep was restricted to people younger than 70 years, and therefore, our results concerning this particular variable, and the cumulative number of insomnia symptoms, cannot readily be generalized to elderly populations. Also, these analyses had less statistical power than the analyses on difficulty initiating and maintaining sleep.

Finally, measured values at baseline may change during a long follow-up. Insomnia was only evaluated once at the beginning of the follow-up; thus, we could not examine the possible effects of time-dependent changes in the severity of insomnia. However, lack of repeated measurements of insomnia cannot possibly explain the observed association between insomnia and the risk of subsequent HF.

Conclusion

In summary, we found that insomnia symptoms are associated with an increased risk of HF. Insomnia is a frequent, easily recognizable, and potentially manageable condition. If our results are confirmed by others and causation is proved, evaluation of insomnia symptoms might have consequences for cardiovascular prevention.

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Conflict of interest: none declared.

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CARDIOVASCULAR FLASHLIGHT

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First three-dimensional optical frequency domain imaging evaluation of a bioabsorbable vascular scaffold implantation in an instent-restenosis 6 years after CYPHER stenting

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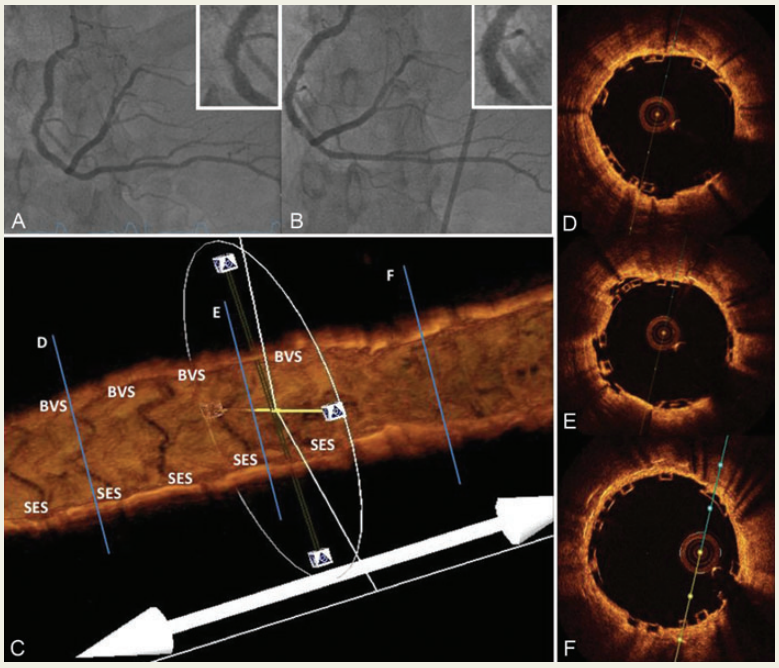

A 60-year-old male patient with a past history of acute ST-segment elevation myocardial infarction in 2007 and primary percutaneous coronary intervention of the right coronary artery (RCA) was referred to the Andreas Gruentzig Catheterization Laboratories for elective evaluation due to angina symptoms and a positive stress perfusion magnetic resonance imaging (MRI) with an inferoseptal ischaemic burden and furthermore a reduced left ventricular ejection fraction of 39% was detected by MRI. An angiogram was performed and as culprit lesion a 70% in-CYPHER-Stent restenosis in the middle portion of the RCA (*Panel A*) was detected. After passing the lesion with a BMW guide wire and a vascular sealing with a 3.0 × 15 mm Maverick balloon and a 3.0 × 12 mm non-compliant Maverick balloon (25 atmosphere), a bioabsorbable vascular scaffold (BVS) 3.5 × 18 mm was implanted in the middle portion of the RCA. Subsequently, after post-dilatation with a 3.5 × 15 mm non-compliant Maverick balloon (25 atmosphere), the final angiogram (*Panel B*) and three-dimensional (3D)-optical frequency domain imaging (OFDI) (*Panel C*) demonstrated an optimal post-procedural result with well-apposed scaffold struts in all cross-sectional images (*Panels D–F*).

Bioabsorbable vascular scaffold has been utilized to cover simple, *de novo* lesions so far. Scarce data exist on the potential use of BVS in off-label indications, such as acute coronary syndromes, in bifurcation lesions, chronic total occlusions and in-stent restenosis. Interventional studies are now underway to answer the safety issues of these indications.

Three-dimensional optical frequency domain imaging as a high-frame rate and high resolution intravascular imaging shows the strut apposition of implanted scaffolds inapparent in coronary angiography. Furthermore, the rapid spiral pullback enables the 3D reconstruction and visualization of the strut rupture and whole scaffold structure. Herein, we present for the first time a 3D-OFDI to demonstrate the performance and feasibility of BVS in a patient with in-stent restenosis.