International Journal of Cardiology 215 (2016) 217–222

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Insomnia predicts long-term all-cause mortality after acute myocardial infarction: A prospective cohort study

Emelie Condén [a,b,*,1], Andreas Rosenblad [a,1]

[a] Center for Clinical Research Västerås, Uppsala University, Västerås, Sweden
[b] Department of Medicine, Västmanland County Hospital Västerås, Västerås, Sweden

ARTICLE INFO

Article history:
Received 7 March 2016
Accepted 11 April 2016
Available online 15 April 2016

Keywords:
Acute myocardial infarction
All-cause mortality
Cardiovascular epidemiology
Insomnia
Long-term follow-up
Survival analysis

ABSTRACT

Background: Sleep impairment such as insomnia is an established risk factor for the development of cardiovascular disease and acute myocardial infarction (AMI). The aim of the current study was to examine the association between insomnia and all-cause mortality among AMI patients.
Methods: This prospective cohort study used data on n = 732 patients recruited from September 2006 to May 2011 as part of the Västmanland Myocardial Infarction Study (VaMIS), a prospective cohort study of AMI patients living in Västmanland County, Sweden. Participants were followed up for all-cause mortality until December 9, 2015. The outcome of interest was time-to-death (TTD), with the presence of insomnia being the risk factor of main interest. Data were analyzed using a piecewise Cox regression model with change point for insomnia at two years of follow-up, adjusted for socioeconomic, lifestyle and clinical risk factors.
Results: In total, n = 175 (23.9%) of the participants suffered from insomnia. During a mean (SD) follow-up time of 6.0 (2.5) years (4392 person–years), a total of n = 231 (31.6%) participants died, n = 77 (44.0%) in the insomnia group and n = 154 (27.6%) in the non-insomnia group (log-rank test $p < 0.001$). In a multiple adjusted piecewise Cox regression model, insomnia did not imply a higher risk of death during the first two years after AMI (HR 0.849; 95% CI 0.508–1.421; p = 0.534). During the period after the first two years, however, insomnia implied a 1.6 times higher risk of death (HR 1.597; 95% CI 1.090–2.341; p = 0.016).
Conclusions: Insomnia implies a higher risk of death among AMI patients in the long term.

1. Introduction

Sleep presents a daily process of physiological restitution and recovery. Impaired sleep may be disadvantageous to the effects on endocrinology, immunology and metabolism [1]. Sleep impairment such as insomnia is a well-documented and increasing problem in modern society [2]. Impaired sleep is an established risk factor for the development of cardiovascular disease and myocardial infarction [3,4], but may also adversely affect the prognosis of patients with coronary artery disease (CAD), even after adjustment for coronary risk factors [5,6]. Previous studies have, however, focused on sleep disorders such as heavy snoring and breathing disorders. Studies examining the association between insomnia and mortality have presented inconsistent findings and inconclusive results, and seldom in populations with cardiovascular diseases [5,7,8]. The present study seeks to rectify some of these shortcomings by using a large sample of 732 well-studied patients with acute myocardial infarction (AMI), where relevant socioeconomic, lifestyle, and clinical risk factors are adjusted for in the statistical analyses.

1.1. Aim and hypothesis

The aim of the current study was to examine the association between insomnia and all-cause mortality among AMI patients. It was hypothesized that AMI patients with insomnia had higher all-cause mortality, even after adjusting for relevant confounders.

2. Methods

The present study was based on data from the Västmanland Myocardial Infarction Study (VaMIS; ClinicalTrials.gov Identifier: NCT 01452178), a prospective cohort study of AMI patients living in Västmanland County, Sweden. Each patient gave their informed consent to participate in the study. The study was approved by the Uppsala Regional Ethical Review Board (Dnr: 2005:169) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.1. Design and setting

During the period from November 2005 to May 2011, patients aged ≥18 years old admitted to the coronary care unit of the Central Hospital in Västerås, Västmanland County, with a diagnosis of AMI were considered for inclusion in the study. Patients living in Västerås or neighboring

* Corresponding author at: Center for Clinical Research Västerås, Västmanland County Hospital Västerås, S-721 89 Västerås, Sweden.
E-mail address: emelie.conden@ltv.se (E. Condén).
[1] These authors contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.ijcard.2016.04.080
0167-5273/

municipalities with troponin I ≥ 0.4 μg/L at admission, with a subsequent decline, in combination with either a) ischemic symptoms; b) development of Q waves on ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); or d) coronary artery intervention [9], were included. The participants were followed up for all-cause mortality until December 9, 2015.

2.2. Participants

At the start of the study, the goal was to include 1000 AMI patients. A total of 1459 patients were screened for inclusion, of which 401 patients were excluded due to e.g. logistical problems or language difficulties (Fig. 1). A further 50 patients declined participation, resulting in a total of 1008 patients being included in the VaMIS cohort. For the present study, the risk factor of main interest was insomnia, which was measured in the study from September 2006. Thus, the first 247 included patients did not have any measures of insomnia. Furthermore, of the 761 patients included from September 2006, a total of 29 (3.8%) patients had missing values for insomnia. The study population for the present study thus consisted of the 732 patients with valid values for insomnia. A detailed overview of the recruitment process is given in Fig. 1.

2.3. Risk factors

Insomnia was the risk factor of main interest in the current study. This was measured with a single question in a study specific questionnaire, "Do you have difficulty falling asleep?" (yes/no), that was answered by the participants at the time of inclusion. Those answering "yes" were classified as having insomnia, while those answering "no" were classified as not having insomnia. The study specific questionnaire also included information regarding taking a nap (yes/no), sleep time (hours), male sex (yes/no), living alone (yes/no), highest education level (elementary school or no formal education/secondary school/college or university), alcohol consumer (yes/no), current smoker (yes/no), physical activity during leisure time (low/mild/moderate or strenuous), known claudication (yes/no), known diabetes (yes/no), known heart failure (yes/no), known hypertension (yes/no), known angina pectoris (yes/no), prior myocardial infarction (yes/no), prior stroke (yes/no), hospitalization during the last year (yes/no), and negative affectivity (score 0–28). Negative affectivity (NA), considered one of the personality traits most relevant to psychopathology, in particular depression and anxiety [10,11], was measured using the NA part of the DS-14 instrument [12].

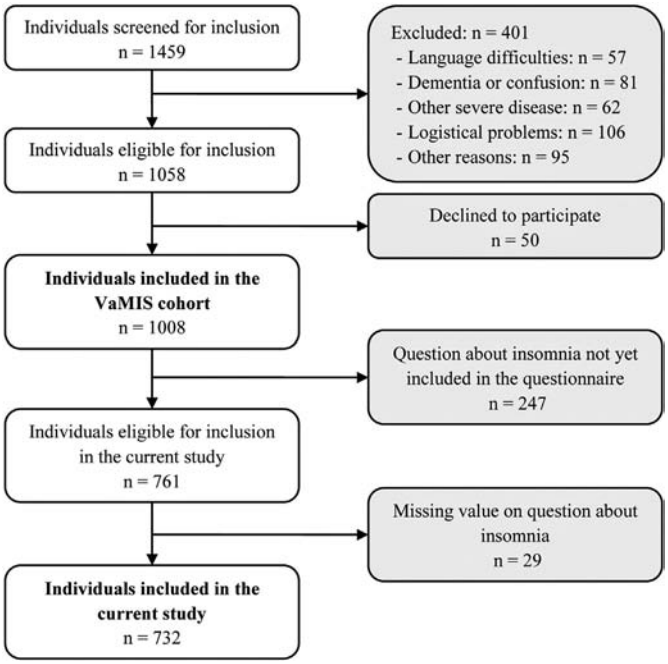

Fig. 1. Flow chart of the inclusion process for the present study.

At the time of inclusion, the patients underwent a clinical examination by a research nurse, measuring peak expiratory flow (L/min), hand grip strength (lbf), body mass index (BMI; kg/m^2), waist–hip-ratio, systolic and diastolic blood pressure (mm Hg), pulse pressure (mm Hg), and heart rate (bpm). Hemoglobin (g/L), creatinine (μmol/L), CRP (mg/L), and troponin I (μg/L) were extracted from blood samples taken during the acute phase of the AMI, while NT-proBNP (ng/L) was taken at inclusion, during the convalescent stage. Using echocardiographic examinations, left ventricular systolic dysfunction (yes/no) was defined as a left ventricular ejection fraction <45%. Coronary angiography was performed on 619 (84.6%) of the patients, resulting in a classification as severe angiography results (yes/no), with yes defined as having a left main stem stenosis > 50% and/or a 3-vessel disease (stenoses > 50%). Additionally, a list of medications at discharge was compiled, including the use of angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs; yes/no), beta blockers (yes/no), statins (yes/no), and sleep medications (yes/no). Finally, information about percutaneous coronary intervention (PCI; yes/no) and coronary artery bypass grafting (CABG; yes/no) during index hospitalization was obtained from the National Patient Register (NPR) maintained by the Swedish National Board of Health and Welfare. Being an immigrant (yes/no) was obtained from the Population Register maintained by the Swedish National Tax Board, while age (years) was measured by taking the difference between date of inclusion and date of birth, where the latter was obtained from the participant's personal identification number.

2.4. Outcome

Time-to-death (TTD), the outcome of interest in the current study, was calculated as the time in days from date of inclusion to date of death or censoring. Date of emigration and end of follow-up were used as censoring dates. Data on date of death and emigration were obtained from the Population Register.

2.5. Statistical analyses

For descriptive statistics, categorical data are reported as frequencies and percentages, n (%), while continuous data are reported as means and standard deviations (SD). Tests of differences between the insomnia and non-insomnia groups were performed using Pearson's χ^2-test for categorical data and Student's *t*-test for continuous data. Kaplan–Meier curves and log-rank tests were used to test for differences in TTD between the two groups, while Cox regression was used to estimate the magnitude of the impact of the explanatory variables on TTD. The results of the Cox regression analyses are presented as hazard ratios (HRs), with accompanying 95% confidence intervals (CI). Since the Kaplan–Meier curves for the presence and absence of insomnia showed a distinct break at about two years of follow-up, a piecewise Cox regression model was applied for this variable, with a change point for insomnia at two years (731 days) of follow-up. Thus, for all models including insomnia as a risk factor, separate HRs for insomnia were obtained for the two time periods ≤2 years (731 days) of follow-up and >2 years (731 days) of follow-up.

Three different Cox regression models were used: (i.) an unadjusted model, including insomnia as the only explanatory variable; (ii.) a full model, including insomnia and all variables with p-values < 0.20 from the tests of differences between the insomnia and non-insomnia groups; and (iii.) a reduced model, constructed by applying a backward elimination procedure to the full model, in which the variable with the highest p-value was removed from the regression model and the model re-estimated, until only variables with p-values < 0.20 remained in the