



Somatic symptoms of anxiety and nonadherence to statin therapy



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ABSTRACT

Background: The association between anxiety and nonadherence to preventive therapies remains unclear. We investigated whether somatic symptoms of anxiety predict statin nonadherence.

Methods: This is a prospective cohort study of 1924 individuals who responded to a questionnaire survey on health status and initiated statin therapy after the survey during 2008–2010. We followed the cohort for nonadherence, defined as the proportion of days covered <80%, during the 365 days since the first dispensation after the survey. We used log-binomial regression to estimate the predictors of nonadherence.

Results: 18% of participants reported no experience of the eight somatic symptoms of anxiety (palpitation without exercise, irregular heartbeat, chest pain upon anger or emotion, sweating without exercise, flushing, tremor of hands or voice, muscle twitching) before the statin initiation, and 16% had experienced at least one symptom on average weekly to daily. 49% of respondents were nonadherent. Weekly to daily occurrence of these symptoms predicted a 33% increase in the risk of nonadherence (risk ratio [RR] 1.33, 95% confidence interval, CI, 1.13–1.57) compared to no symptoms when adjusted for sociodemographics, lifestyle risks, cardiovascular comorbidities, and depression. Particularly, chest pain upon anger or emotion (RR 1.21, 95% CI 1.01–1.46) and muscle twitching (RR 1.24, 95% CI 1.08–1.42) predicted an increased risk of nonadherence to statin therapy. Psychological symptoms of anxiety were not associated with nonadherence when adjusted for somatic symptoms.

Conclusions: Somatic anxiety-related symptoms predicted nonadherence to statin therapy. Information on pre-existing somatic symptoms may help identifying patients at increased risk of statin nonadherence.

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1. Introduction

Hypercholesterolemia is one of the most common chronic conditions affecting approximately 40% of the adult population globally [1]. Large randomized controlled trials and meta-analyses provide convincing evidence for the benefits of lowering low-density lipoprotein cholesterol by statins in the primary and secondary prevention of cardiovascular events [2,3]. The effectiveness and cost-effectiveness of statin therapy, however, depend on the extent to which patients adhere to their statin therapy [4–6]. The average prevalence of nonadherence to statin therapy, often defined as the proportion of days covered (PDC) by the dispensed statin tablets less than 80%, is almost 50% [4,7].

Despite extensive research, reliable indicators for nonadherence to statin therapy have not been found [7,8]. Large healthcare utilization database studies suggest that statin nonadherence is more common in patients free of established cardiovascular disease (CVD), hypertension

or diabetes, among those from low income groups or with high out-of-pocket costs, and when there is a lack of lipid monitoring [7,9]. Also mood disorders, such as depression and anxiety, may influence patients' preferences and capacity to adhere to medication as these disorders affect patients' motivation, cognitive function, and energy [10]. For example, a meta-analysis of US studies on medication adherence among patients with chronic conditions found that depressed patients have almost twice the odds of being nonadherent to their antihypertensive or lipid-lowering medication compared to their nondepressed counterparts [11], although database studies employing objective adherence measures based on pharmacy records, such as PDC, have reported somewhat weaker associations between depression and nonadherence to statin therapy [8,12–14].

Anxiety is a heterogeneous disorder ranging from panic to obsessive-compulsive disorder and generalized anxiety about health; it may also be associated with nonadherence to preventive cardiovascular medication although this association is not necessarily straightforward [10]. Being anxious about one's health and fear of complications of the condition being treated can promote adherence while concerns about potential adverse effects of the medication can lead to nonadherence

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[15]. One cross-sectional study found that hypertensive patients with high anxiety sensitivity, that is, fear of the negative social, physical or cognitive consequences of anxiety-related sensations, had almost double the likelihood of being nonadherent to their antihypertensive medication compared to those with low anxiety sensitivity [16]. Every second patient with high anxiety sensitivity reported having experienced adverse drug effects while less than one in four patients with low anxiety sensitivity reported them. Among patients who have discontinued their statin therapy, perceived harmful effects from statins or fear of them are the most commonly reported reasons for discontinuing the therapy [17–19].

Anxiety is a multidimensional concept with cognitive, emotional and biological domains [20,21], but it appears that the tendency to experience neurovegetative symptoms associated with anxiety, such as palpitation, sweating, trembling, chest pain and hot flushes or cold chills [21], may be particularly relevant in terms of nonadherence. However, we are not aware of any studies that have investigated the association between these somatic anxiety-related symptoms and nonadherence to statin therapy. The aim of the current study is therefore to investigate whether somatic symptoms of anxiety predict future nonadherence to statins.

2. Materials and methods

2.1. Population and design

This study is a part of the Finnish Public Sector (FPS) study, an ongoing cohort study of employees of ten towns and six hospital districts who had a job contract for at least six months during the years 1991–2005 [22]. Subcohorts nested within this register cohort have been targeted by questionnaire surveys in 2/4-year intervals since 2000. The present study included those cohort members who were employed by the ten towns and responded to the 2008/09 survey that for the first time collected information on somatic symptoms of anxiety (42,877 responded; response rate 69%). We linked the participants' responses to the survey to records of filled statin prescriptions using personal identification numbers and then restricted the sample to those participants who began statin therapy after the survey. A new statin user refers to an individual who had not filled any statin prescriptions within 365 days preceding the survey. With these inclusion criteria the analytic cohort of this study includes 1924 new statin users who had full data on statin dispensations for 12 months (365 days) by the end of follow-up (Dec 31, 2011).

According to the Finnish law, there is no requirement for written consent for register-based and survey research, as long as participation is voluntary. The participants of the FPS study were informed about the aims of the study and the possible record linkages. Participants' information was anonymized and de-identified prior to analyses. The Ethics Committee of the Helsinki and Uusimaa Hospital District approved the study.

2.2. Somatic symptoms of anxiety

Autonomic arousal is common among individuals liable to anxiety [21]. For example, in the diagnoses of generalized anxiety disorder the following somatic symptoms are emphasized: symptoms of autonomic arousal (palpitation, sweating, trembling, dry mouth), chest and abdominal symptoms (difficulty breathing, feeling of choking, chest pain, nausea), and general symptoms (hot flushes or cold chills, numbness or tingling, muscle tension, restlessness and inability to relax, difficulty swallowing) [21]. The FPS study assessed somatic anxiety-related symptoms with an 8-item scale focusing on symptoms of sympathetic nervous system activation [23]. The participants were requested to report occurrence of the following eight symptoms during the past month: 1) "Palpitation without exercise," 2) "Irregular heartbeat," 3) "Chest pain upon anger or emotion," 4) "Sweating without exercise,"

5) "Flushing," 6) "Tremor of hands," 7) "Tremor of voice," 8) "Muscle twitching." The answer choices for each item were: daily or almost daily, weekly, less often, never. The answer choices were assigned values from 0 to 3. The mean score of the eight items was calculated and divided into three categories (0 = never, 0 < less often than weekly < 1, > 1 = weekly to daily). When calculating the mean symptom score, missing information on an individual item was coded as 0. The scale has shown adequate psychometric properties (Cronbach $\alpha = 0.77$; 5-year test-retest reliability $r = 0.59$) [23].

2.3. Nonadherence to statin therapy

The outcome of interest was nonadherence to statins (Anatomical Therapeutic Chemical [ATC] code C10AA), measured by PDC during the 365 days since the first dispensation in 2008–2010. Data on filled statin prescriptions came from the Finnish Prescription Register, pharmacy-claims database managed by the Social Insurance Institution of Finland (SII) [24]. The database contains records of all medications that are dispensed and reimbursed under the National Health Insurance Scheme. For each medication, the dispensing date, the ATC classification code [25] and the quantity dispensed are recorded. Information on prescribed dose or duration of therapy is not available in a structured format; therefore, we calculated the days' supply in each dispensation on the assumption of one tablet per day [26]. We defined nonadherence as PDC < 80%. The threshold of 80% is widely used both by adherence research [4] and many quality measures [27], and it corresponds to the level of statin adherence above which patients with coronary artery disease have been shown to benefit from statin therapy [28].

The National Health Insurance Scheme provides prescription drug coverage for all ~5.4 million non-institutionalized residents of Finland. The current reimbursement system has three categories (basic, lower special, and higher special refund) graded according to medical criteria based on the severity of the illness and the necessity of the drug therapy [29]. Statins are available by prescription only, and they are reimbursed under the basic refund category; however, patients with familial hypercholesterolemia or coronary artery disease are eligible for lower special refund. During the study years, the reimbursement was 42% and 72% of the price of the statin in the basic and lower special refund categories, respectively. Statin therapy was typically started with low-cost generic simvastatin (for 97% of new users in 2008 [30]); therefore, statin costs are likely to have only a minor impact on adherence in our study.

2.4. Covariates

We included age, sex, marital status, and education as sociodemographic covariates. Statistics Finland provided information on the level of education (vocational or basic education vs. university or college degree) [31] while information on marital status (married or cohabiting vs. single, divorced, or widowed) came from the survey responses. We classified participants as current smokers if they reported smoking daily or almost daily at the time of the survey. Extreme drinking occasions were identified by asking the participants whether they had passed out due to heavy drinking during the past 12 months. Heavy alcohol use was defined as consuming >210 grams of pure alcohol/week [32] based on the habitual frequency and amount of beer, wine, and spirits intake reported by the participants. Physical activity was measured by the Metabolic Equivalent Task (MET) index and expressed as the summed score of MET hours/day. Reporting < 2 MET hours per day indicated physical inactivity. Self-reported weight and height were used to determine body mass index (BMI) and obesity (BMI > 30 kg/m²). Finally, we used a binary variable (any of the five risk factors vs. none) to indicate the presence of lifestyle risks.

Information on comorbid cardiovascular conditions came from the SII Special Refund Register and the Finnish Care Register. Presence of a comorbid condition was defined as entitlement to special refund for medication costs due to diabetes mellitus, chronic hypertension, heart

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