

Comparison of Mortality and Nonfatal Cardiovascular Events in Adults With Atrial Fibrillation With Versus Without Levothyroxine Treatment



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Levothyroxine has been suggested to be cardiotoxic, but previous studies on the risk of cardiovascular events associated with levothyroxine treatment have been inconclusive. We aimed to study the association between levothyroxine treatment and all-cause mortality as well as cardiovascular events. Study population included all adults ($n = 12,283$) ≥ 45 years diagnosed with atrial fibrillation (AF) at 75 primary care centers in Sweden in 2001 to 2007, with ($n = 1,189$; 283 men and 906 women) or without ($n = 11,094$) levothyroxine treatment. Outcome was defined as all-cause mortality and cardiovascular events, that is, myocardial infarction, ischemic stroke, and congestive heart failure until December 31, 2010. During a mean 5.8 years (standard deviation 2.4 years) of follow-up, a total of 3,954 patients died (32.2%), among whom 92 men (32.5%) and 266 women (29.4%) were treated with levothyroxine. In fully adjusted Cox regression models (age, co-morbidity, socioeconomic factors, and warfarin treatment), a significant association between levothyroxine treatment and lower mortality was found among women (hazard ratio 0.78, 95% confidence interval 0.68 to 0.91), but not among men (hazard ratio 0.87, 95% confidence interval 0.69 to 1.10). In the secondary analysis, levothyroxine treatment was not associated with the risk of myocardial infarction, ischemic stroke, or congestive heart failure ($p > 0.05$). In conclusion, in a large representative cohort, we found that levothyroxine treatment decreased the mortality risk in women with AF, which suggests that such treatment could be of benefit in this setting. © 2017 Elsevier Inc. All rights reserved. (*Am J Cardiol* 2017;120:1974–1979)

Atrial fibrillation (AF) is the most common arrhythmia in the general population, and the prevalence of a registered diagnosis of AF is estimated at almost 3% in subjects above 20 years.^{1,2} Men develop AF an average of 5 years earlier than women,³ whereas women with AF exert both a higher relative risk of stroke and of mortality than men with AF do.⁴ Furthermore, women have a higher prevalence of hypothyroidism and levothyroxine treatment,⁵ and this treatment could possibly be cardiotoxic in patients with heart disease.⁶ Earlier studies have shown conflicting results, with no increased morbidity or mortality,⁷ increased cardiovascular morbidity,⁸ a higher mortality among women with levothyroxine treatment,⁹ or signs of a decreased mortality among women.¹⁰ The primary aim was to study the association between levothyroxine treatment and all-cause mortality among patients with AF in Swedish primary care. Our hypothesis was that levothyroxine is associated with a lower mortality. As a secondary aim, we aimed to study the association between levothyroxine treatment and the risk of specific adverse cardiovascular events.

Methods

The study was based on individual-level patient data from 75 primary health-care centers (PHCCs), 48 of which were located in Stockholm County. Subjects attending any of the participating PHCCs between 2001 and 2008 were included in the study. We used the Extractor software (http://www.slsso.sll.se/SLPOtemplates/SLPOPage1____10400.aspx; accessed September 19, 2010) to extract individual

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PW, ACC, JS, and KS designed the study, PW and ACC analyzed data, and all authors participated in the interpretation of data; PW and ACC drafted the manuscript, and all other authors revised it critically for important intellectual content.

See page 1978 for disclosure information.

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electronic patient records (EPRs). National identification numbers were replaced with new unique serial numbers to ensure anonymity. The files were linked to a database constructed using the Swedish Total Population Register, the Inpatient Register, and the Swedish Cause-of-Death Register, which contains individual-level data on age, gender, education, hospital admissions, mortality, and cause of death for all residents registered in Sweden. Thus, a new research database containing clinical data and information on SES on the individuals ($n = 1,098,420$) registered at the 75 PHCCs was created. Ethical approvals were obtained from regional boards at Karolinska Institutet and the University of Lund.

The study included all patients with diagnosed AF, identified by the presence of the 10th version of the World Health Organization's International Classification of Diseases for AF (I48) in EPRs in primary health care. In total, 12,283 individuals (6,646 men and 5,637 women) aged ≥ 45 years at the time of AF diagnosis and who visited any of the 75 participating PHCCs from January 1, 2001, until December 31, 2007, and with data on neighborhood SES were included in the study (Supplementary Table 1). For the secondary analyses regarding new hospital-registered events of myocardial infarction (MI; $n = 1,000$; 472 women and 528 men), ischemic stroke (IS; $n = 1,465$; 768 women and 697 men), or congestive heart failure (CHF; $n = 2,259$; 1,124 women and 1,135 men), patients with an earlier recorded diagnosis of the specific disorder were excluded. Prescription of levothyroxine (H03AA01) in the EPR in at least 1 occasion was recorded.

For the primary outcome, time to death after the first AF diagnosis was registered (until December 31, 2010). For secondary outcomes, time to the first hospital-registered event of MI, IS, or CHF after the first AF diagnosis was registered. Individuals were divided into the following prespecified age groups: 45 to 54, 55 to 64, 65 to 74, 75 to 84, and ≥ 85 years. Individuals < 45 years of age were excluded. Educational level was categorized according to prespecification as ≤ 9 years (partial or complete compulsory schooling), 10 to 12 years (partial or complete secondary schooling), and > 12 years (college and/or university studies). Marital status was classified as married, unmarried, divorced, or widowed. The neighborhood socioeconomic status (SES) areas were categorized into 3 groups according to the neighborhood index: > 1 SD below the mean (high SES or low deprivation level), > 1 SD above the mean (low SES or high deprivation level), and within 1 SD of the mean (middle SES or deprivation level).

The following related cardiovascular-related disorders, identified from diagnoses according to the 10th version of the World Health Organization's International Classification of Diseases in EPRs from primary health care (and for some diagnoses also from registered episodes of hospital care), were used as covariates: hypertension (I10 to I15); coronary heart disease (CHD; I20 to I25), also including registered hospitalizations for MI; cerebrovascular disease (CVD; I60 to I69), including registered hospitalizations for ischemic or hemorrhagic stroke; CHF (I50 or I110), also including hospitalizations for CHF; diabetes mellitus (E10 to E14); nonrheumatic valvular diseases (I34 to I38); cardiomyopathy (I42); hypothyroidism (E03); depression (F32 to F34, F38 to F39); or anxiety disorders (F40 to F41). No diagnosis of rheumatic valvular diseases (I05 to I08) was recorded.

Differences in means and distributions between men and women were compared by Student's *t*-test, chi-square analysis, and Fisher's exact test. Age adjustment for background variables was performed by logistic regression or in case of 3 or more categories by analysis of covariance.

Follow-up analyses were performed, first by using Cox regression with hazard ratios (HRs) and 95% confidence intervals (CIs), using time to death as the outcome. Model specification was tested, and interaction terms were included when relevant. We found no interaction between gender and levothyroxine treatment. Second, Laplace regression was used to calculate the difference in years until death for the first 50% of the participants, that is, the median, in those prescribed levothyroxine versus those without levothyroxine.¹¹ Different distributions and mathematical calculations were used to obtain results in Cox and Laplace regression. Thus, we considered the results to be more robust when findings were statistically significant with both methods. Four regression models were used for both Cox and Laplace regression. The first model was adjusted for age (and for gender, when applicable), where age groups showed better specification than age as a continuous variable, although estimates were very similar. The second model was additionally adjusted for comorbidity (hypertension, CHD, CHF, diabetes, CVD, valvular heart disease, and depression), the third also for socioeconomic factors (educational level, marital status, and SES neighborhood status and change of SES neighborhood), and the fourth also for warfarin treatment (B01AA03). Besides, we also tested matching by propensity score for all factors previously mentioned. As a sensitivity analysis, we also performed the same analyses as for levothyroxine in patients with a registered diagnosis of hypothyroidism.

We also performed Cox regression analyses by using time to hospital diagnosis of the first MI, IS, or CHF (excluding cases with a first hospitalization for MI, IS, or CHF before the first recorded diagnosis of AF). We used models 1 to 3 for men and women combined as described in the mortality analysis, however excluding CHD, CVD, or CHF as comorbidities in the respective models.

A *p* value for 2-sided tests of < 0.01 was considered statistically significant due to the multiple comparisons between men and women. A two-sided *p* value of < 0.05 was considered statistically significant for variables in the Cox regression and Laplace regression analyses. All analyses were performed in STATA 14.1, with an amendment for Laplace regression provided by Bottai and Zhang.¹¹

Results

Characteristics of the study population ($n = 12,283$ subjects) are shown separately for men ($n = 6,646$) and women ($n = 5,637$) and also divided into subjects with and without a prescription of levothyroxine (Table 1). Overall, there were few differences between men and women with or without levothyroxine treatment; men with levothyroxine treatment showed a different age profile, whereas women with levothyroxine treatment had a lower mortality rate versus women without treatment. The mean follow-up time was 5.8 years (SD 2.4), and HRs were calculated based on 71,602 person-years at risk (39,154 person-years among men and 32,448 among women). Incidence rates for mortality per 100

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