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Comparison of Mortality and Non-Fatal Cardiovascular Events in Adults with Atrial Fibrillation with – vs – without Levothyroxine Treatment

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Abstract

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 2001–2007, 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, i.e., myocardial infarction (MI), ischemic stroke (IS) and congestive heart failure (CHF) 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

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Author contribution

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.

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(32.5%) and 266 women (29.4%) were treated with levothyroxine. In fully adjusted Cox regression models (age, co-morbidity, socio-economic factors and warfarin treatment) a significant association between levothyroxine treatment and lower mortality was found among women, hazard ratio (HR) 0.78 (95% CI 0.68–0.91), but not among men, HR 0.87 (95% CI 0.69–1.10). In the secondary analysis, levothyroxine treatment was not associated with the risk of MI, IS or CHF ($p>0.05$). 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.

Keywords

Atrial fibrillation; congestive heart failure; gender; drug treatment; levothyroxine; mortality

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 individuals above 20 years.[1,2] Men develop AF on average five years earlier than women,[3] while 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. Individuals attending any of the participating PHCCs between 2001 and 2008 were included in the study. We used *Extractor* software (http://www.slso.sll.se/SLPOtemplates/SLPOPage1____10400.aspx; accessed September 19, 2010) to extract individual 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 socioeconomic status 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 ICD-10 code (10th version of the WHO's International Classification of Diseases) for atrial fibrillation (I48) in electronic patient records (EPR) 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 socioeconomic status, were included in the study (Supplementary Table 1!). For the secondary analyses regarding hospital-registered events of myocardial infarction (MI; n=11,699; 5,398 women and 6,301 men), ischemic stroke (IS; n=11,517; 5,248 women and 6,269 men) or congestive heart failure (CHF; n=9,424; 4,213 women and 5,211 men) patients with an earlier recorded diagnosis of the specific disorder were excluded. Prescription of levothyroxine (H03AA01) in the EPR in at least one occasion was recorded.

For the primary outcome, time to death after first AF diagnosis was registered (until December 31, 2010). For secondary outcomes, time to first hospital-registered event of MI, IS or CHF after first AF diagnosis was registered. Individuals were divided into the following pre-specified *age groups* 45–54, 55–64, 65–74, 75–84 and ≥ 85 years. Individuals <45 years of age were excluded. *Educational level* was categorized according to pre-specification as ≤9 years (partial or complete compulsory schooling), 10–12 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 three groups according the neighborhood index: > one standard deviation (SD) below the mean (high SES or low deprivation level), > one SD above the mean (low SES or high deprivation level), and within one SD of the mean (middle SES or deprivation level).

The following related cardiovascular-related disorders, identified from diagnoses according to ICD-10 classification in electronic patient records from primary health care (and for some diagnoses also from registered episodes of hospital care) were used as covariates: hypertension (I10–15); coronary heart disease (CHD; I20–25), also including registered hospitalizations for MI; cerebrovascular diseases (CVD; I60–69), including registered hospitalizations for ischemic or haemorrhagic stroke; congestive heart failure (CHF; I50 or I110), also including hospitalizations for CHF; diabetes mellitus (E10–14) ; non-rheumatic valvular diseases (I34–38); cardiomyopathy (I42); hypothyroidism (E03); depression (F32–F34, F38–F39); or anxiety disorders (F40–41). No diagnosis of rheumatic valvular diseases (I05–08) 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 three or more categories by ANCOVA.

Follow-up analyses were performed, firstly by using Cox regression with hazard ratios (HRs) and 95% confidence interval (95% CI), using time to death as the outcome. Model specification was tested, and interaction terms included when relevant. We found no interaction between sex and levothyroxine treatment. Secondly, Laplace regression was used to calculate the difference in years until death for the first 50 % of the participants, i.e. the median, in those prescribed levothyroxine vs. 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 sex, 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 co-morbidity (hypertension, CHD, CHF, diabetes, CVD, valvular heart disease and depression), the third also for socioeconomic factors (educational level, marital status and socio-economic (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 above. 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 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 the models 1–3 for men and women combined as described in the mortality analysis, however, excluding CHD, CVS or CHF as co-morbidities in the respective models.

A *p*-value for two-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 Professor Bottai.[11]

Results

Characteristics of the study population (n=12,283 individuals) are shown separately for men (n=6,646) and women (n=5,637) and also divided into individuals with a prescription of levothyroxine or not (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, while women with levothyroxine treatment had a lower mortality rate vs. women without treatment. The mean follow-up time was 5.8 years (standard deviation (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 patient-years were 6.07 (95% CI 5.81–6.35) for women, and 5.06 (95% CI 4.85–5.29) for men.

Table 2 shows Cox and Laplace regression models for subjects with levothyroxine treatment vs. subjects without this treatment, for men and women combined as well as divided by sex. No significant interaction by sex was found. We found the associations to be statistically significant with decreased risk in Cox regression models, and increased survival in Laplace regression models, for women with levothyroxine treatment vs. women without levothyroxine treatment but not for men. We also performed calculations using propensity score (the model specification was not as good as when using the separate variables), estimating HRs for men and women combined HR = 0.83 (95% CI 0.72–0.96), for men HR = 1.00 (95% CI 0.76–1.31) and for women HR = 0.77 (95% CI 0.65–0.92).

Table 3 shows the sensitivity analysis with mortality as an outcome for subjects with a diagnosis of hypothyroidism vs. subjects without this diagnosis in Cox and Laplace regression models, for men and women combined as well as divided by sex. Results were statistically significant with decreased risks in Cox models and longer survival in Laplace models adjusted for age (and sex), as well as for co-morbidity.

Table 4 shows Cox regression estimates for incident MI, IS and CHF in subjects with or without levothyroxine treatment. No statistically significant associations were found.

Discussion

The main finding of this study was that levothyroxine treatment is associated with lower mortality among women, but not among men, when adjusting for age, comorbidities, socioeconomic factors and warfarin treatment as confounding factors. The association between levothyroxine and cardiovascular events was not significant.

Compared to the earlier findings from this cohort, with a borderline significantly lower mortality among levothyroxine-treated women with AF,[10] we now found a statistically significant association between levothyroxine prescription and mortality among women. In the sensitivity analysis when assessing the risk associated with a hypothyroidism diagnosis we found similar results, although with lower HR estimates in Cox regression models, and also a statistically significant increased survival until an estimated 50% of the patients died.

In previous literature, thyroid dysfunction is described to be a risk factor for cardiovascular diseases, both as regards to hyper- and hypothyroidism, and even in subclinical disorders, e.g. with an increased risk of CHF,[12] as well as of CHD mortality.[13] Hyperthyroidism in itself is associated with increased risk of arrhythmias,[14] and an increased risk of mortality.[15,16] Hypothyroidism is associated with a decreased cardiac function, e.g. CHF in subclinical hypothyroidism.[17] Levothyroxine in itself has been reported to be cardiotoxic.[6,8] However, in the present study we found no significantly increased cardiovascular risk for levothyroxine treatment. In contrast, triiodothyronine administration after coronary artery bypass operation has been found to improve cardiac function.[18] Furthermore, hypothyroidism is also associated with dyslipidemia,[19] which is considerably improved by levothyroxine.[20]

In an earlier, small study from the 1990s, an increased mortality among AF patients with levothyroxine treatment was found,[9] where treatment with beta blockers was hypothesized to be protective. In the early 1990s the rate of beta blocker treatment of AF-patients in Swedish primary care was 30%,[21] vs. 70% in the present study. In the present study we found no statistically significant association between mortality and beta blocker treatment among levothyroxine treated patients (data not shown).

Around 35% of patients treated with levothyroxine were not registered with a diagnosis of hypothyroidism. The most probable explanation is that doctors prescribe levothyroxine without registering the diagnosis in the EPR. The estimates when using a diagnosis of hypothyroidism instead of levothyroxine treatment were lower, and actually statistically significant in the fully adjusted Laplace regression model. The notification of a diagnosis of

hypothyroidism could be a sign of a specific episode of care, with probably also a more careful examination, allowing detection of possible but unmet healthcare needs. The same may also be one explanation to the decreased mortality associated with levothyroxine treatment.

There are several limitations of this study which must be kept in mind when interpreting the results. The number of men with AF and levothyroxine treatment was low, limiting possible conclusions in men. However, the number of female patients was considerably larger. Besides, we included AF patients registered in primary care, and another study showed that 36% of all registered AF patients in Stockholm County were not registered with a diagnosis in primary health care.[1] Clinical data were mostly taken from EPRs in primary care. Patients with diagnoses of hypertension and diabetes are mainly cared for in primary care in Sweden,[22] while many patients with CHF are not registered with diagnoses in primary care.[23] Thus, it is a strength that we in this study we were able to add diagnoses of CHF, MI and stroke from hospitals. The large rate of co-morbidity, especially of CHF, supports this. Another limitation is the study design, i.e. an observational study. Like in every observational cohort study there may have been residual confounding present. The findings may have been subject to survival treatment selection bias.[24] We did not have access to whether levothyroxine treatment was used on a long-term basis although in most cases such treatment is lifelong. Severity of CHF and CHD were not classified in the patient records. Besides, data on criteria for diagnosis of CHF were not available, but has been shown to have a high validity in the National Patient Register.[25] Moreover, AF could not be classified as paroxysmal, persistent or permanent and heart rhythm could not be classified as sinus rhythm or fibrillation rhythm. Additionally, we had not access to renal function.

A major strength of this study was that we were able to link clinical data from individual EPRs to data from national demographic and socioeconomic registers with < 1% of information missing. As already mentioned, we also supplied diagnoses from primary health care EPRs with hospital diagnoses of CHF, CHD and CVD. Moreover, randomized controlled trials often exclude individuals with co-morbidities, such as AF patients with concomitant diabetes and CHF. In the current study, we had the possibility to include these patients in the analyses, which means that the findings are more representative of the variety of patients encountered in clinical practice today.

In conclusion, we found a decreased mortality among women with AF and levothyroxine treatment in Swedish primary care. From a clinical point of view it is important to note that levothyroxine treatment seem to be safe also among individuals with AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Data for patients aged ≥45 years with diagnoses of atrial fibrillation and with or without levothyroxine treatment (*n*=12,283) in primary care attending 75 primary health care centers between January 1st 2001 and December 31st 2007

	All	Men		Difference		Women		Difference	
Number of patients	**N=12,283**	**No levothyroxine N=6,363 (95.7%)**	**Levothyroxine N=283 (4.3%)**	**Crude p**	**Age-adjusted**	**No levothyroxine N=4,731 (83.9%)**	**Levothyroxine N=906 (16.1%)**	**Crude p**	**Age-adjusted**
Number of deaths	3,954 (32.1%)	1,891 (29.7%)	92 (32.5%)	0.32	0.89	1,705 (36.0%)	266 (29.4%)	0.001	<0.001
Age (years), mean (SD)	74.4 (10.1)	72.1 (10.1)	73.6 (10.1)	0.011	–	77.1 (9.4)	77.0 (8.7)	0.79	–
Age groups (years),				0.001	–			0.20	–
45–54	475 (3.9%)	353 (5.6%)	17 (6.0%)			94 (2.0%)	11 (1.2%)		
55–64	1,743 (14.2%)	1,182 (18.6%)	40 (14.1%)			443 (9.4%)	78 (8.6%)		
65–74	3,308 (26.9%)	1,976 (31.1%)	66 (23.3%)			1,043 (22.1%)	223 (24.6%)		
75–79	2,247 (19.8%)	1,190 (18.7%)	67 (23.7%)			973 (20.6%)	197 (21.7%)		
80–84	2,447 (19.9%)	1,018 (16.0%)	65 (23.0%)			1,145 (24.2%)	219 (24.2%)		
≥85	1,883 (15.3%)	644 (10.1%)	28 (9.9%)			1,033 (21.8%)	178 (19.7%)		
Educational level				0.71	0.79			0.34	0.59
Compulsory schooling	5,085 (45.2%)	2,381 (39.5%)	105 (39.8%)			2,189 (52.9%)	410 (50.4%)		
Secondary schooling	3,995 (35.5%)	2,273 (37.7%)	94 (35.6%)			1,355 (32.8%)	273 (33.6%)		
College and/or university studies	2,161 (19.2%)	1,372 (22.8%)	65 (24.6%)			594 (14.4%)	130 (15.6%)		
Marital status				0.74	0.47			0.27	0.86
Married	5,613 (45.9%)	3,790 (59.8%)	160 (56.9%)			1,398 (29.7%)	265 (29.4%)		
Unmarried	1,029 (8.4%)	604 (9.5%)	26 (9.3%)			339 (7.2%)	60 (6.6%)		
Divorced	1,813 (14.8%)	974 (15.4%)	47 (16.7%)			646 (13.7%)	146 (16.2%)		
Widowed	3,777 (30.9%)	972 (15.3%)	48 (17.1%)			2,325 (49.4%)	432 (47.8%)		
Neighborhood socio-economic status				0.87	0.49			0.084	0.18
High	4,604 (37.5%)	2,541 (39.9%)	115 (40.6%)			1,607 (34.0%)	341 (37.6%)		
Middle	5,897 (47.3%)	2,905 (45.7%)	125 (44.2%)			2,358 (49.8%)	419 (46.3%)		
Low	1,872 (15.2%)	917 (14.4%)	43 (15.2%)			766 (16.2%)	146 (16.1%)		
Diagnosis									
Hypertension	5,586 (45.5%)	2,668 (41.9%)	131 (46.3%)	0.15	0.15	2,347 (49.6%)	440 (48.6%)	0.57	0.57
Coronary heart disease	3,234 (26.3%)	1,642 (25.8%)	80 (28.3%)	0.36	0.60	1,257 (26.6%)	255 (28.2%)	0.33	0.31

	All	Men		Difference		Women		Difference	
Number of patients	**N=12,283**	**No levothyroxine N=6,363 (95.7%)**	**Levothyroxine N=283 (4.3%)**	**Crude p**	**Age-adjusted**	**No levothyroxine N=4,731 (83.9%)**	**Levothyroxine N=906 (16.1%)**	**Crude p**	**Age-adjusted**
Congestive heart failure	5,684 (46.3%)	2,723 (42.8%)	133 (47.0%)	0.16	0.42	2,352 (49.7%)	476 (52.5%)	0.12	0.098
Diabetes mellitus	2,405 (19.6%)	1,242 (19.5%)	70 (24.7%)	0.031	0.026	901 (19.0%)	192 (21.2%)	0.13	0.14
Valvular disease	571 (4.7%)	283 (4.5%)	11 (3.9%)	0.65	0.57	230 (4.9%)	47 (5.1%)	0.68	0.68
Cardiomyopathy	90 (0.7%)	58 (0.9%)	2 (0.7%)	1.00	0.89	23 (0.5%)	7 (0.8%)	0.28	0.29
Cerebrovascular disease	2,566 (20.9%)	1,224 (19.2%)	53 (18.7%)	0.83	0.57	1,100 (23.3%)	189 (20.9%)	0.12	0.12
Hypothyroidism	822 (6.7%)	8 (0.1%)	185 (65.4%)	<0.001	<0.001	35 (0.7%)	594 (65.6%)	<0.001	<0.001
Depression	1,039 (8.5%)	392 (6.2%)	20 (7.1%)	0.54	0.53	504 (10.7%)	123 (13.6%)	0.010	0.011
Anxiety disorders	496 (4.0%)	174 (2.7%)	9 (3.2%)	0.65	0.66	265 (5.6%)	48 (5.3%)	0.72	0.71

Information on educational level and marital status is missing for some individuals.

Am J Cardiol. Author manuscript; available in PMC 2018 December 01.

Table 2

Cox and Laplace regression models for mortality among patients (n=12,283) aged 45–104 years with atrial fibrillation and levothyroxine prescription compared to those without a prescription (referents) attending 75 primary health care centers between January 1st 2001 and December 31st 2007

		Model 1	Model 2	Model 3	Model 4
Cox		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
	All	0.83 (0.74; 0.92)	0.85 (0.79; 0.90)	0.81 (0.75; 0.88)	0.81 (0.72; 0.92)
	Women	0.78 (0.69; 0.89)	0.76 (0.67; 0.87)	0.78 (0.67; 0.90)	0.78 (0.68; 0.91)
	Men	0.96 (0.78; 1.19)	0.94 (0.77; 1.16)	0.88 (0.70; 1.11)	0.87 (0.69; 1.10)
Laplace 50%		Years (95% CI)	Years (95% CI)	Years (95% CI)	Years (95% CI)
	All	0.60 (0.17; 1.04)	0.59 (0.19; 1.00)	0.57 (0.11; 1.02)	0.54 (0.11; 0.97)
	Women	0.79 (0.42; 1.17)	0.83 (0.39; 1.28)	0.74 (0.30; 1.19)	0.67 (0.19; 1.15)
	Men	0.10 (−0.39; 0.59)	0.05 (−0.54; 0.63)	0.12 (−0.60; 0.84)	0.12 (−0.71; 0.95)

Model 1 is adjusted for age and sex; Model 2 for age, sex and co-morbidity (with interaction terms between age and congestive heart failure, and age and cerebrovascular disease); Model 3 adjusted for age, sex, co-morbidity, individual socio-economic factors (with interaction term between age and marital status, and age and congestive heart failure), and neighborhood socio-economic status; and Model 4 also for warfarin treatment. HRs in Cox models, and years gained to death of first 50% in Laplace models, and 95% CIs are shown.

Table 3

Cox and Laplace regression models for mortality among patients (n=12,283) aged 45–104 years with atrial fibrillation and a diagnosis of hypothyroidism or not (referents) attending 75 primary health care centers between January 1st 2001 and December 31st 2007

		Model 1	Model 2	Model 3	Model 4
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cox	All	0.70 (0.61; 0.80)	0.70 (0.61; 0.80)	0.70 (0.60; 0.81)	0.69 (0.75; 0.88)
	Women	0.71 (0.60; 0.83)	0.71 (0.61; 0.84)	0.73 (0.61; 0.87)	0.73 (0.61; 0.87)
	Men	0.67 (0.50; 0.89)	0.68 (0.51; 0.90)	0.59 (0.43; 0.82)	0.58 (0.42; 0.81)
		Years (95% CI)	Years (95% CI)	Years (95% CI)	Years (95% CI)
Laplace 50%	All	1.07 (0.67; 1.47)	1.13 (0.67; 1.60)	1.13 (0.66; 1.60)	1.23 (0.63; 1.83)
	Women	1.00 (0.60; 1.41)	1.14 (0.66; 1.61)	1.03 (0.46; 1.59)	1.04 (0.34; 1.73)
	Men	1.17 (0.04; 2.30)	1.17 (0.49; 1.85)	1.59 (0.52; 2.66)	1.74 (0.55; 2.93)

Model 1 is adjusted for age and sex; Model 2 for age, sex and co-morbidity (with interaction terms between age and congestive heart failure, and age and cerebrovascular disease); Model 3 for age, sex, co-morbidity, individual socio-economic factors (with interaction term between age and marital status), and neighborhood socio-economic status; and Model 4 also for warfarin treatment.

HRs in Cox models, and years gained to death of first 50% in Laplace models, and 95% CIs are shown.

Table 4

Cox regression models for myocardial infarction, ischemic stroke or congestive heart failure among patients (*n*=12,283) aged 45–104 years with atrial fibrillation and levothyroxine prescription compared to those without a prescription (referents) attending the 75 primary health care centers between January 1st 2001 and December 31st 2007

		Model 1	Model 2	Full Model
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Myocardial infarction	All	1.06 (0.87; 1.30)	1.05 (0.86; 1.29)	1.04 (0.84; 1.30)
Ischemic stroke	All	0.88 (0.74; 1.05)	0.89 (0.75; 1.07)	0.86 (0.71; 1.04)
Congestive heart failure	All	1.12 (0.98; 1.28)	1.10 (0.96; 1.26)	1.08 (0.88; 1.07)

Model 1 is adjusted for age and sex, Model 2 for age, sex and co-morbidity (for congestive heart failure also interaction term between age and diabetes), and Full Model for age, sex, co-morbidity, individual socio-economic factors, and neighborhood socio-economic status. Hazard ratios (HRs) in Cox models, and 95% CIs are shown.