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Association between smoking and outcomes in older adults with atrial fibrillation

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Abstract

Tobacco smoking is a risk factor for atrial fibrillation (AF), but little is known about the impact of smoking in patients with AF. Of the 4060 patients with recurrent AF in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, 496 (12%) reported having smoked during the past two years. Propensity scores for smoking were estimated for each of the 4060 patients using a multivariable logistic regression model and were used to assemble a matched cohort of 487 pairs of smokers and nonsmokers, who were balanced on 46 baseline characteristics. Cox and logistic regression models were used to estimate the associations of smoking with all-cause mortality and all-cause hospitalization, respectively, during over 5 years of follow-up. Matched participants had a mean age of 70 ± 9 years (± S.D.), 39% were women, and 11% were non-white. All-cause mortality occurred in 21% and 16% of matched smokers and nonsmokers, respectively (when smokers were compared with nonsmokers, hazard ratio = HR = 1.35; 95% confidence interval = 95% CI = 1.01–1.81; p = 0.046). Unadjusted, multivariable-adjusted and propensity-adjusted HR (95% CI) for all-cause mortality associated with smoking in the pre-match cohort were: 1.40 (1.13–1.72; p = 0.002), 1.45 (1.16–1.81; p = 0.001), and 1.39 (1.12–1.74; p = 0.003), respectively. Smoking had no association with all-cause hospitalization (when smokers were compared with nonsmokers, odds ratio = OR = 1.21; 95% CI = 0.94–1.57, p = 0.146). Among patients with AF, a recent history of smoking was associated with an increased risk of all-cause mortality, but had no association with all-cause hospitalization.

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Keywords

Atrial fibrillation; Smoking; Mortality; Propensity score

1. Introduction

Tobacco smoking is a risk factor for cardiovascular disease (CVD) and continuing smoking is associated with poor outcomes in those with CVD (Aronow, 1971, 1978; Aronow et al., 1974; Suskin et al., 2001; Yatsuya et al., 2010). AF is also common and is associated with poor outcomes (Aronow et al., 1989). Smoking has also been described as a risk factor for AF (Goette et al., 2007; Heeringa et al., 2008). However, little is known about the impact of smoking on outcomes in AF. The objective of the current study is to evaluate the association between smoking and outcomes in the patients with AF.

2. Subjects and methods

2.1. Data source and patients

The AFFIRM was a randomized clinical trial to compare two treatment strategies in patients with AF, the details of which have been described before (The AFFIRM Investigators, 2002; Wyse et al., 2002). Briefly, 4060 patients with recurrent AF were enrolled between November 1995 and October 1999 from 213 centers and were randomized to either rate control (n = 2027) or rhythm control (n = 2033) groups. We used a public-use copy of the AFFIRM data obtained from the National Heart, Lung and Blood Institute, which also funded the study. Of the 4060 AFFIRM participants, 496 (12%) self-reported a baseline history of smoking during the past two years. Data on demographic and clinical variables including past medical history, medication use, and symptoms during AF were also collected at baseline.

2.2. Outcomes

The primary outcomes for the current analysis is all-cause mortality during about 6 years of follow-up, also the primary end point of AFFIRM. A secondary outcome was all-cause hospitalization. All events were centrally adjudicated by committees blinded to randomization.

2.3. Propensity score matching

We used propensity score matching to assemble a cohort of smokers and non-smokers who would be balanced on all measured baseline characteristics (Rosenbaum and Rubin, 1983; Rubin, 2001). We estimated propensity scores for smoking for each of the 4060 patients using a non-parsimonious multivariable logistic regression model (Ahmed et al., 2006a,b, 2007, 2008; Ahmed and Aronow, 2008; Alper et al., 2009; Ekundayo et al., 2009a,b; Wahle et al., 2009, Bowling et al., 2010). In the model, we used baseline smoking as the dependent variable, and 46 other baseline characteristics displayed in Figure 1 were entered as covariates. Using a 1 to 1 greedy matching algorithm, we were able to match 487 (98% of the 496) smokers with 487 non-smokers who had similar propensity scores. Pre- and post-match absolute standardized differences are presented as Love plots (Figure 1) (Ahmed et al., 2006a,b, 2007, 2008; Ahmed and Aronow, 2008; Alper et al., 2009; Ekundayo et al., 2009; Wahle et al., 2009; Bowling et al., 2010). An absolute standardized difference of 0% on a covariate indicates no residual bias for that covariate, and values < 10% suggest inconsequential bias (Normand, 2001; Austin, 2008).

2.4. Statistical analysis

The baseline characteristics of patients with and without a recent history of smoking were compared using Pearson's Chi-square and Wilcoxon rank-sum tests for the pre-match cohort and McNemar's test and paired sample t-tests for the post-match cohort as appropriate. The association of smoking with mortality was estimated using Kaplan–Meier survival analysis and Cox regression analysis. We repeated our analysis in the full pre-match cohort of 4060 participants using three different approaches: unadjusted, propensity score adjusted and multivariable adjusted. The multivariable model was adjusted for all covariates used in the propensity score model. Finally, we conducted subgroup analyses and tested interactions to determine any heterogeneity in the association between smoking and all-cause mortality. A formal sensitivity analysis was conducted to quantify the degree of a hidden bias that could invalidate our main conclusions (Rosenbaum, 2002). Due to lack of detailed time to event data for all-cause hospitalization, we used logistic regression to estimate the association of smoking with all-cause hospitalization. The mean follow-up time for smokers and nonsmokers was similar (3.4 years each). All tests were two-tailed, and a $p =< 0.05$ was considered to be statistically significant. SPSS for Windows (Version 18) was used for data analysis.

3. Results

3.1. Patient characteristics

Matched participants had a mean age of 70 ± 9 years, 39% were women, and 11% were non-white. Before matching, compared with nonsmokers, smokers were younger, more likely to be female, and were also more likely to have peripheral arterial disease and pulmonary disease (Table 1). These and other baseline imbalances were balanced after matching (Table 1 and Figure 1).

3.2. Association of age and mortality

All-cause mortality occurred in 21% and 16% of matched smokers and nonsmokers, respectively (when smokers were compared with nonsmokers, hazard ratio = HR = 1.35; 95% confidence interval (CI) = 1.01–1.81; $p = 0.046$; Table 2 and Figure 2). In the absence of a hidden confounder, a sign-score test for matched data with censoring provides strong evidence ($p < 0.0001$) that non-smokers clearly outlived smokers. A hidden covariate that would be a near- perfect predictor of mortality could potentially explain away this association if it also increases the odds ratio = (OR) of smoking by 28.5%. The association between smoking and mortality was homogeneous across various subgroups of patients (Figure 3). Unadjusted, multivariable-adjusted and propensity-adjusted HR (95% CI) for all-cause mortality associated with smoking in the pre-match cohort were: 1.40 (1.13–1.72; $p = 0.002$), 1.45 (1.16–1.81; $p = 0.001$), and 1.39 (1.12–1.74; $p = 0.003$), respectively (Table 2). Smoking had no association with all-cause hospitalization (when smokers were compared with nonsmokers, OR = 1.21; 95% CI = 0.94– 1.57; $p = 0.146$).

4. Discussion

4.1. Key findings

Findings from the current study demonstrate that among patients with recurrent AF, a history of recent smoking was associated with increased all-cause mortality but had no association with all-cause hospitalization. The increased risk of death without an associated increased risk of hospitalization suggests that smoking-associated mortality may have been sudden in nature. Findings from our study suggest that in patients with AF, smoking continues to have an adverse effect on mortality. These findings are important as AF is common among older adults and is one of the few CVD with increasing prevalence.

4.2. Explanation of study findings

The observed association between smoking and mortality may be explained by residual or unmeasured confounding or it may imply a true association. The magnitude of the unadjusted association between smoking and mortality was rather similar to that observed after multivariable risk adjustment and propensity matching suggesting that despite many imbalances in measured baseline covariates between smokers and nonsmokers, they played minimal confounding roles. This is probably due to fact that the confounders were equally shared by smokers and non-smokers. For example, compared to smokers, nonsmokers were older and compared to nonsmokers, smokers were more likely to be male and have heart failure. It is also possible that the observed association between smoking and mortality may be due to an unmeasured confounder. However, findings from our sensitivity analysis suggest that this association was rather insensitive to an unmeasured confounder. The consistent finding of a strong, significant and rather insensitive association suggests that smoking may have an intrinsic association with mortality in patients with AF.

4.3. Literature comparison

Smoking is known to be associated with poor prognosis in patients with established CVD (Aronow, 1971; Aronow et al., 1998; Suskin et al., 2001). Smoking has been shown to inflict damage on the cardiovascular system through diverse mechanisms that include platelet dysfunction, hypercoagulative effect, lipid peroxidation, increased myocardial oxygen demand and vasomotor dysfunction (Ambrose and Barua, 2004). Smoking has also been shown to be associated with myocardial ischemia, ventricular arrhythmias, and sudden cardiac death (Davis et al., 1984; Hayano et al., 1990; Kinoshita et al., 2009).

4.4. Clinical and public health implications

Although we had no data on cause-specific mortality or hospitalization, the lack of an association between smoking and hospitalization despite a strong association with all-cause mortality suggests that smoking-related deaths may have been sudden in nature thus precluding hospitalization. Although the prevalence of coronary artery disease (CAD) was balanced in the post-match cohort, it is possible that smokers had more severe CAD or for longer duration. Interestingly, findings from our subgroup analysis suggest that the effect of smoking was rather homogeneous regardless of a history of CAD. Findings from our subgroup analyses also suggest that smoking had no association with mortality in the patients with AF who were receiving beta-blockers or were randomized to rate control strategy. Nearly 70% of the patients in the rate control group received beta-blockers at any time (vs. 50% for those in the rhythm control group) (Wyse et al., 2002). Although there was no significant interaction, these findings may have clinical implications as smoking-associated hemodynamic changes have been shown to be mediated through adrenergic mechanisms, which has been shown to be prevented by adrenergic blockade (Cryer et al., 1976; Hung et al., 1995).

4.5. Limitations

There are a few limitations to our study, which should be acknowledged. We had no data on the number of pack-years of smoking or passive smoking exposure. It is also possible that some of smokers may have quit during follow-up while some non-smokers became smokers. However, this regression dilution may have underestimated the true associations observed in our study (Clarke et al., 1999).

5. Conclusion

In the patients with AF, a recent history of smoking was associated with increased mortality but had no association with hospitalization. Patients with AF should be informed of these risks, encouraging smokers to quit and nonsmokers to maintain abstinence.

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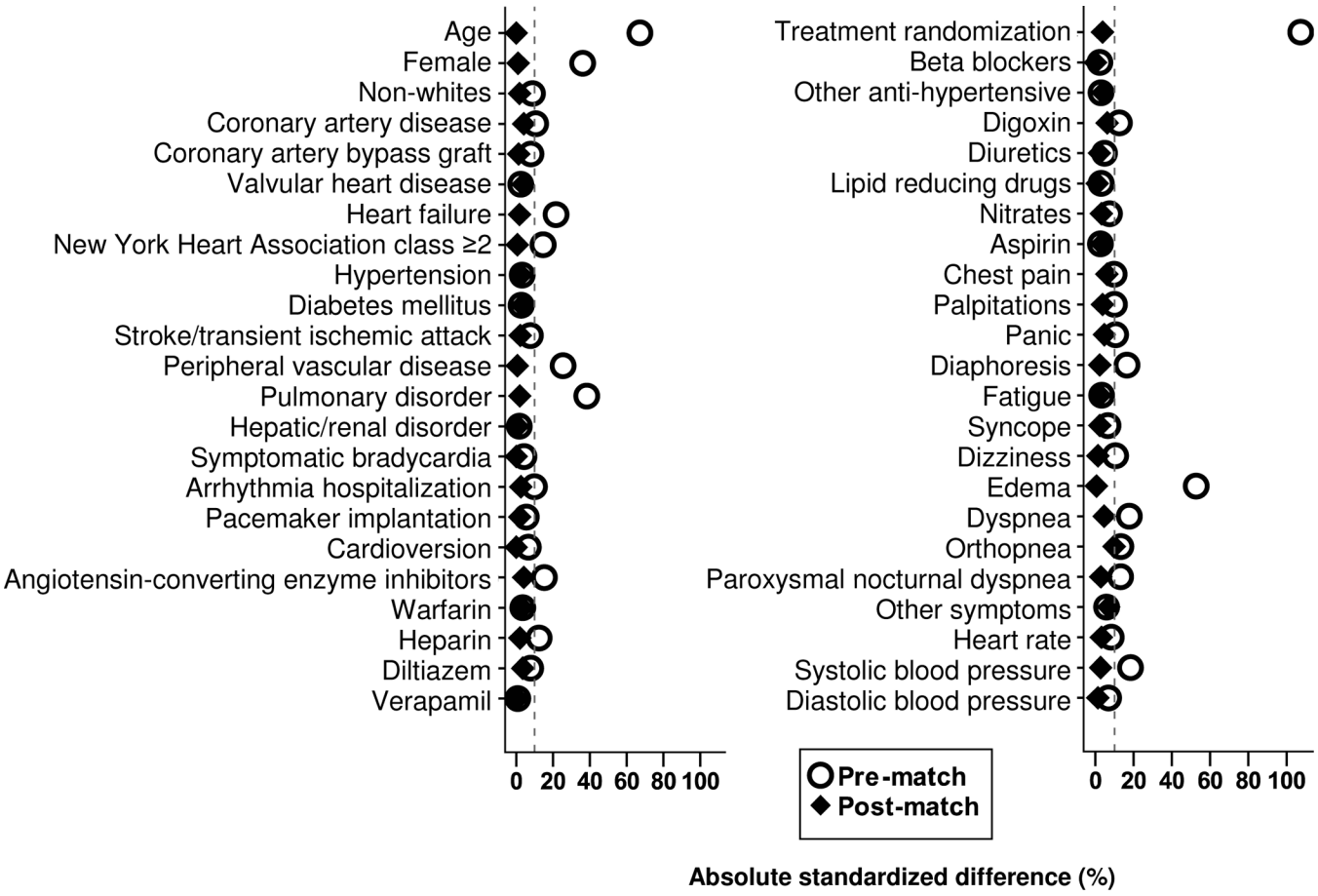
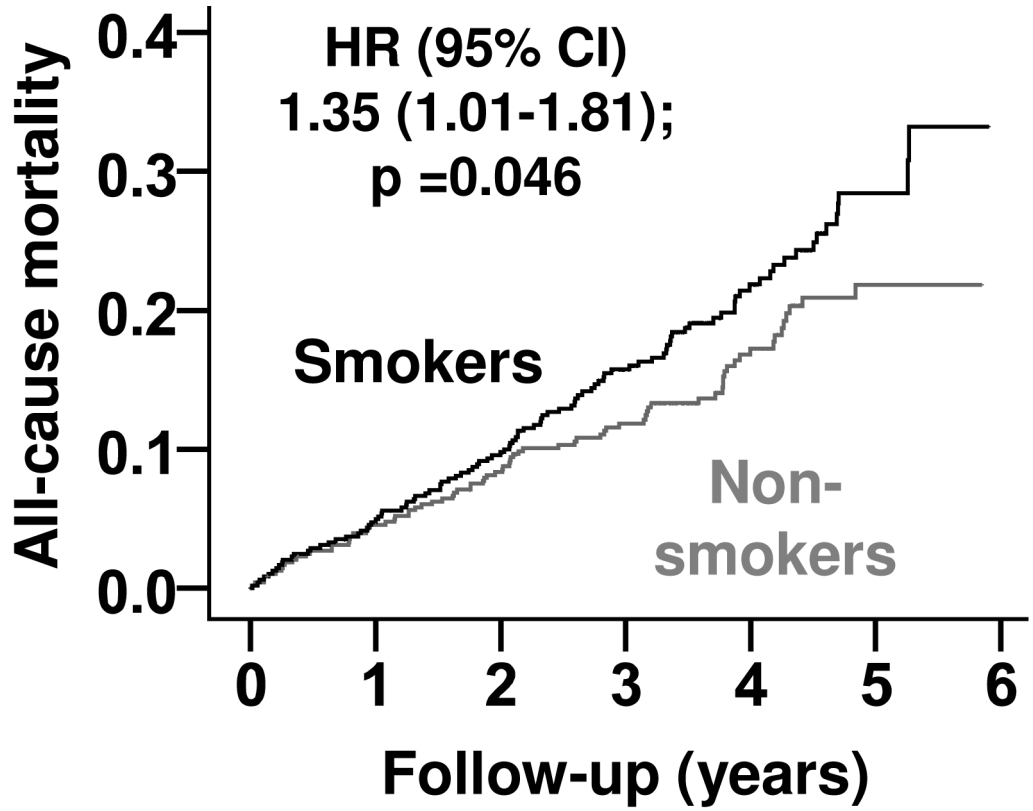


Figure 1.

Absolute standardized differences between baseline characteristics of smoker versus non-smoker older atrial fibrillation patients, before and after propensity score matching



Number of patients at risk

Non-smokers	487	429	189
Smokers	487	425	180

Figure 2.
Kaplan-Meier plot for all-cause mortality (HR=hazard ratio; CI=confidence interval)

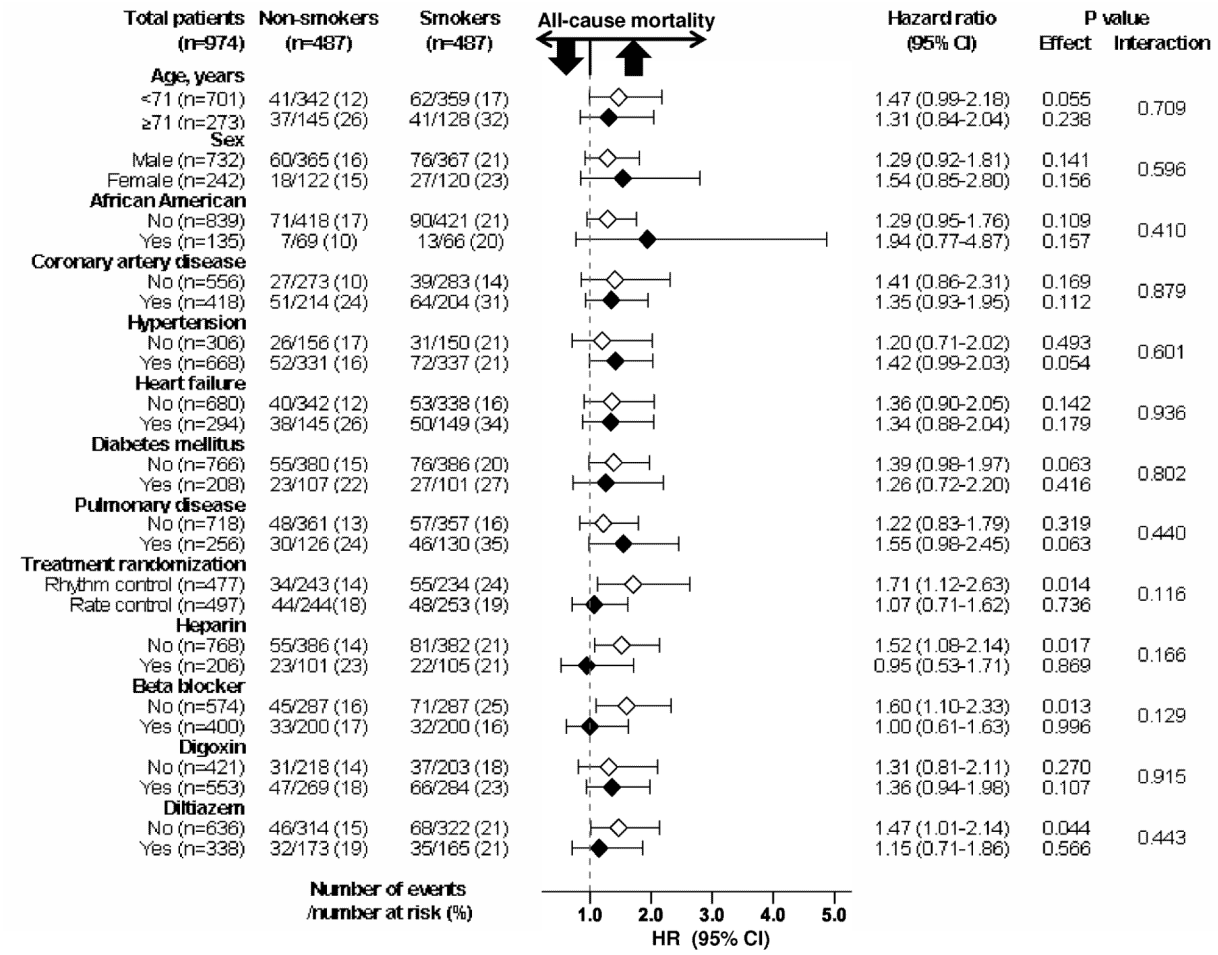


Figure 3.

Association of recent smoking history with all-cause mortality in subgroups of propensity score-matched participants in the AFFIRM (HR = hazard ratio; CI = confidence interval)

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Table 1

Baseline patient characteristics by history of smoking before and after propensity matching, mean ± S.D., n (%)

Variable	Before propensity matching			After propensity matching		
	Nonsmokers (n = 3564)	Smokers (n = 496)	p	Nonsmokers (n = 487)	Smoker (n = 487)	p
Age, years	70 ± 8	65 ± 8	<0.001	65 ± 9	65 ± 8	1.000
Female	1472 (41)	122 (25)	<0.001	122 (25)	120 (25)	0.935
Non-whites	392 (11)	69 (14)	0.055	69 (14)	66 (14)	0.852
NYHA[a] Class II or higher	306 (9)	65 (13)	0.001	63 (13)	64 (13)	1.000
Randomization to rate control	1778 (50)	255 (51)	0.525	244 (50)	253 (52)	0.614
Past medical history						
Hypertension	2531 (71)	345 (70)	0.503	331 (68)	337 (69)	0.735
Coronary artery disease	1339 (38)	212 (43)	0.026	214 (44)	204 (42)	0.566
Heart failure	783 (22)	156 (32)	<0.001	145 (30)	149 (31)	0.822
Diabetes mellitus	709 (20)	104 (21)	0.575	107 (22)	101 (21)	0.698
Cerebrovascular events	464 (13)	78 (16)	0.097	80 (16)	76 (16)	0.789
Pulmonary disease	453 (13)	138 (28)	<0.001	126 (26)	130 (27)	0.813
Valvular heart disease	439 (12)	65 (13)	0.618	68 (14)	62 (13)	0.651
Symptomatic bradycardia	253 (7)	30 (6)	0.389	30 (6)	30 (6)	1.000
Peripheral arterial disease	215 (6)	67 (14)	<0.001	63 (13)	62 (13)	1.000
Hepatic/renal disease	201 (6)	30 (6)	0.713	28 (6)	29 (6)	1.000
Cardioversion	1464 (41)	220 (44)	0.165	214 (44)	214 (44)	1.000
Coronary bypass surgery	457 (13)	51 (10)	0.109	53 (11)	51 (11)	0.914
Pacemaker implantation	225 (6)	25 (5)	0.269	23 (5)	25 (5)	0.885
Hospitalization for arrhythmia	1642 (46)	253 (51)	0.039	253 (52)	247 (51)	0.752
Symptoms during atrial fibrillation[b]						
Fatigue	1982 (56)	284 (57)	0.489	274 (56)	280 (58)	0.745
Dyspnea	1896 (53)	307 (62)	<0.001	288 (59)	299 (61)	0.499
Palpitation	1741 (49)	267 (54)	0.038	250 (51)	259 (53)	0.615
Dizziness	1200 (34)	192 (39)	0.027	192 (39)	189 (39)	0.897
Chest pain	833 (23)	137 (28)	0.038	142 (29)	129 (27)	0.397
Diaphoresis	702 (20)	132 (27)	<0.001	133 (27)	128 (26)	0.778

Variable	Before propensity matching			After propensity matching		
	Nonsmokers (n = 3564)	Smokers (n = 496)	p	Nonsmokers (n = 487)	Smoker (n = 487)	p
Leg swelling	671 (19)	105 (21)	0.214	104 (21)	103 (21)	1.000
Orthopnea	513 (14)	96 (19)	0.004	75 (15)	93 (19)	0.145
Paroxysmal nocturnal dyspnea	254 (7)	54 (11)	0.003	46 (9)	50 (10)	0.744
Panic	360 (10)	67 (14)	0.020	75 (15)	67 (14)	0.519
Syncope	152 (4)	15 (3)	0.192	17 (4)	15 (3)	0.860
Other symptoms	370 (10)	43 (9)	0.237	34 (7)	43 (9)	0.321
Medications						
Warfarin	3020 (85)	414 (84)	0.464	401 (82)	407 (84)	0.656
Digoxin	1863 (52)	290 (59)	0.010	269 (55)	284 (58)	0.342
Beta-blocker	1521 (43)	206 (42)	0.629	200 (41)	200 (41)	1.000
Diuretics	1510 (42)	222 (45)	0.313	221 (45)	216 (44)	0.799
ACE[c] inhibitors	1355 (38)	226 (46)	0.001	209 (43)	219 (45)	0.565
Diltiazem	1083 (30)	169 (34)	0.096	173 (36)	165 (34)	0.642
Verapamil	372 (10)	53 (11)	0.866	54 (11)	53 (11)	1.000
Aspirin	944 (27)	137 (28)	0.592	127 (26)	134 (28)	0.669
Lipid lowering agents	796 (22)	117 (24)	0.531	114 (23)	116 (24)	0.937
Nitrate	656 (18)	106 (21)	0.113	95 (20)	101 (21)	0.693
Heparin	608 (17)	109 (22)	0.007	101 (21)	105 (22)	0.811
Heart rate per minute	73 ± 14	74 ± 15	0.081	74 ± 15	74 ± 15	0.619
Systolic blood pressure, mm Hg	135 ± 19	132 ± 19	<0.001	131 ± 18	132 ± 19	0.672
Diastolic blood pressure, mm Hg	76 ± 10	76 ±10	0.148	76 ±10	76 ± 10	0.842

[a] NYHA—New York Heart Association.

[b] Symptoms associated with clinical diagnosis of atrial fibrillation.

[c] ACE—angiotensin-converting enzyme.

Table 2

Association of history of smoking with all cause mortality

All-cause mortality	Events (%)		Absolute risk difference (%)[a]	Hazard ratio (95%CI)	p
	Nonsmokers	Smokers			
Pre-match	n = 3564	n = 496			
Unadjusted	560 (16%)	106 (21%)	+ 5	1.40 (1.13–1.72)	0.002
Multivariable-adjusted	---	---	--	1.45 (1.16–1.81)	0.001
Propensity-adjusted	---	---	---	1.39 (1.12–1.74)	0.003
Post-match	n = 487	n = 487			
Propensity-matched	78 (16%)	103 (21%)	+ 5	1.35 (1.01–1.81)	0.046

[a]Absolute risk differences were calculated by subtracting the events in non-smokers from those in smokers.