Brief Report

Hormone Replacement Therapy and Adverse Outcomes in Women With Atrial Fibrillation
An Analysis From the Atrial Fibrillation Follow-Up Investigation of Rhythm Management Trial

Stavros Apostolakis, MD, PhD; Renee M. Sullivan, MD; Brian Olshansky, MD; Gregory Y.H. Lip, MD

Background and Purpose—Hormone replacement therapy (HRT) use has been related to thromboembolism, but whether HRT increases adverse outcomes in females with atrial fibrillation is uncertain.

Methods—We used the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial data set that included 1594 women (39.3% of the population, mean age 71±8), of whom 376 (23.6%) were taking HRT at baseline. The primary end point, a composite of all-cause death, stroke, systemic/pulmonary embolism, and myocardial infarction, and secondary outcomes (ie, each individual end point) and major bleeding, were considered.

Results—HRT was not independently associated with the primary end point (hazard ratio=0.894; 95% confidence interval, 0.658–1.214; P=0.473) or any secondary outcome. Age (P<0.001), diabetes mellitus (P=0.001), previous stroke (P=0.011), and heart failure (P=0.001) predicted the primary end point. Lack of association between HRT and the primary end point was confirmed in a propensity score–matched control group (hazard ratio=0.966; 95% confidence interval, 0.663–1.409; P=0.858).

Conclusions—HRT does not independently predict mortality, thromboembolism, or bleeding in a large cohort of women with atrial fibrillation.

Key Words: atrial fibrillation • hormone replacement therapy

Compared with men, women with atrial fibrillation (AF) over age 65 are at greater risk of stroke and thromboembolism.1 We hypothesized that women with AF taking hormone replacement therapy (HRT) were at greater risk of all-cause death, ischemic stroke, systemic/pulmonary embolism, myocardial infarction (MI), and major bleeding and explored this hypothesis using the large Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial data set.2

Methods

For this analysis, the primary outcome was a combined end point of all-cause death, stroke, systemic/pulmonary embolism, and MI. Secondary outcomes were each individual end point and major bleeding. The association of HRT and quality of oral anticoagulation or thromboembolic risk profile was investigated. We considered a composite end point of all vascular events based on a net clinical benefit outcome definition,1 which included stroke, MI, cardiovascular death, pulmonary/systemic embolism, or major bleeding. For detailed methods, see online-only Data Supplement.

Adjusted Cox proportional hazards models were used to assess the impact of HRT on outcomes. To reduce bias introduced by lack of randomization, we assembled a more homogeneous subcohort using a matching algorithm based on the estimated propensity score. Survival curves were calculated using the mean of covariates method, in which average values of covariates are entered into a proportional hazards regression equation, adjusted for prognostic variables similar to the total cohort.

Results

AFFIRM recruited 4060 patients, of whom 1594 (39.3%) were women (mean age, 71±8 years) and 376 (23.6%) were prescribed HRT at baseline (Table I in the online-only Data Supplement). Compared with non-HRT-treated females, HRT users were younger and had a lower thromboembolic risk as reflected by CHADS2 (cardiac failure, hypertension, age >75, diabetes, stroke [doubled]) and CHA 2 DS 2 VA Sc (cardiac failure or dysfunction, hypertension, age ≥75 [doubled], diabetes, stroke [doubled]–vascular disease, age 65–74 and sex category [female]) scores (Figures I and II in the online-only Data Supplement). Women prescribed HRT were more likely to be active professionally and have a higher education level (Table II in the online-only Data Supplement, full data not shown). There was no significant difference in warfarin anticoagulation between HRT and non-HRT users, but HRT users had a higher percent time in the therapeutic range (0.61±0.24 versus 0.57±0.27, P=0.02).

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From the University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom (S.A., G.Y.H.L.); University of Missouri Health Care, Columbia (R.M.S.); and University of Iowa Hospitals and Clinics, Iowa City (B.O.).

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Correspondence to Gregory Y.H. Lip, MD, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, B18 7QH Birmingham, United Kingdom. E-mail g.y.h.lip@bham.ac.uk

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.114.006668
Overall, 326 primary end point events occurred over a 3.5-year median follow-up corresponding to an annualized incidence of 5.8 events/100 patient-years. During follow-up, 116 major bleeding events occurred (2.1 events/100 patient-years).

The primary composite end point was more common among non-HRT-treated women versus HRT-treated women (6.3 events/100 patient-years versus 4.2 events/100 patient-years; univariate analysis; P=0.002). All-cause death and the composite net clinical benefit occurred more often in non-HRT women (P=0.007 and P=0.001, respectively); no statistically significant differences were observed in the other individual outcomes (Tables 1 and 2). In a univariate analysis of the propensity-matched cohort, event rate comparisons did not reach the cut-off point of statistical significance (Tables 1 and 2).

In a multivariable Cox regression analysis adjusted for age, prior stroke, hypertension, diabetes mellitus, heart failure, prior MI, peripheral arterial disease, warfarin treatment on recruitment, and treatment arm, HRT use was not independently associated with the primary end point (hazard ratio, 0.894; 95% confidence interval, 0.658–1.214; P=0.473; Tables 1 and 2 and Figure [A]). A Cox regression analysis in the total cohort found that age (P=0.00000002), diabetes mellitus (P=0.001), previous stroke (P=0.0003), heart failure (P=0.00000001), and time in therapeutic range (P=0.000001) were strongly correlated with the primary outcome (hazard ratio, 0.966; 95% confidence interval, 0.663–1.409; Table III in the online-only Data Supplement; Figure [B]).

### Table 1. Impact of HRT on Mortality, Thromboembolism, and Bleeding

<table>
<thead>
<tr>
<th>Absolute Number of Events and Event Rates per 100 Patient-Years in the Study Cohorts</th>
<th>Total Cohort</th>
<th>Propensity Score-Matched Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT</td>
<td>No HRT</td>
</tr>
<tr>
<td>Primary end point</td>
<td>56 (4.3)</td>
<td>270 (6.3)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>41 (3.1)</td>
<td>202 (4.7)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>13 (1.0)</td>
<td>67 (1.6)</td>
</tr>
<tr>
<td>Composite of MI, PE, SE</td>
<td>9 (0.7)</td>
<td>46 (1.1)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>24 (1.8)</td>
<td>92 (2.2)</td>
</tr>
<tr>
<td>Net clinical benefit</td>
<td>68 (5.2)</td>
<td>321 (7.5)</td>
</tr>
</tbody>
</table>

Primary end point is the composite of all-cause death, ischemic stroke, systemic embolism, pulmonary embolism, and myocardial infarction. Net clinical benefit is defined as the composite of the primary end point and major bleeding (Hohnloser et al). HRT indicates hormone replacement therapy; MI, myocardial infarction; PE, pulmonary embolism; and SE, systemic embolism.

### Table 2. Hazard Ratios for the Risk of Adverse Outcomes With HRT in Women With AF (Full Cohort)

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>0.894</td>
<td>0.658–1.214</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.949</td>
<td>0.661–1.363</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.778</td>
<td>0.424–1.430</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.007</td>
<td>0.629–1.612</td>
</tr>
<tr>
<td>Composite of MI, PE, SE</td>
<td>0.796</td>
<td>0.381–1.664</td>
</tr>
<tr>
<td>Net clinical benefit</td>
<td>0.893</td>
<td>0.677–1.176</td>
</tr>
</tbody>
</table>

The model included clinical factors associated with adverse outcomes in patients with atrial fibrillation: CHADS, variables (cardiac failure, hypertension, age >75, diabetes, stroke [doubled]), warfarin (on recruitment), rate/rhythm control management, and hormone therapy. AF indicates atrial fibrillation; HRT, hormone replacement therapy; MI, myocardial infarction; PE, pulmonary embolism; and SE, systemic embolism.

### Table 3. Factors Associated With the Primary End Point in Multivariable Cox Regression Analysis in the Total Cohort

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.053</td>
<td>1.034–1.073</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.156</td>
<td>0.874–1.529</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.599</td>
<td>1.223–2.091</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.697</td>
<td>1.273–2.264</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.978</td>
<td>0.713–1.341</td>
</tr>
<tr>
<td>Rhythm control</td>
<td>1.259</td>
<td>0.996–1.592</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.078</td>
<td>1.615–2.675</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0.950</td>
<td>0.609–1.484</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.167</td>
<td>0.851–1.600</td>
</tr>
<tr>
<td>Time in therapeutic range</td>
<td>3.018</td>
<td>1.937–4.703</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>0.894</td>
<td>0.658–1.214</td>
</tr>
</tbody>
</table>

Primary end point is the composite of all-cause death, ischemic stroke, systemic embolism, pulmonary embolism, and myocardial infarction. The model included clinical factors associated with adverse outcomes in patients with atrial fibrillation: CHADS, variables (cardiac failure, hypertension, age >75, diabetes, stroke [doubled]), treatment with warfarin (on recruitment), rate/rhythm control management, and hormone therapy.

### Discussion

HRT use among female patients with AF enrolled in AFFIRM use was not independently associated with adverse cardiovascular outcomes, major bleeding, or mortality. Indeed, HRT use did not increase risk of the composite primary end point, nor end points of all-cause death, ischemic stroke, major bleeding, or the composite of MI, pulmonary embolism, and systemic embolism—even in a propensity score–matched cohort. This analysis, investigating the impact of HRT on stroke risk in women with AF, is the largest of its kind.

In these subjects, independent predictors of the primary end point were age, diabetes mellitus, prior stroke, and heart failure. Age, diabetes mellitus, and prior stroke are well-validated risk factors for stroke. Data for heart failure are less consistent, but moderate-to-severe systolic impairment and recent decompensated heart failure increase stroke risk irrespective of ejection fraction.

Notwithstanding the benefits of HRT on osteoporosis and menopausal symptoms, the influence of HRT on cardiovascular disease and stroke has been subject to debate, with some studies reporting that HRT increased stroke risk while others have not. Prior studies have been conducted in general populations not confined to AF per se and the Heart and Estrogen/Progestin Replacement Study (HERS) trial was a
much smaller trial and not powered for stroke as an end point although an excess of venous thromboembolism was seen.\textsuperscript{8}

The present analysis represents the largest cohort investigating a link between HRT use and stroke in female patients with AF. The only available prior data assessing HRT use on the risk of stroke in women with AF were from the Stroke Prevention in Atrial Fibrillation (SPAF) I-III trials and that data included 90 women in the HRT group within a cohort of only 274 women.\textsuperscript{9} Our findings are pertinent given the interest into understanding the excess risk of thromboembolic events associated with females with AF.\textsuperscript{1} Possibly, social factors affect overall health and medication adherence, leading to improved outcomes although general studies of adherence suggest that education beyond high school and current working status may decrease adherence.\textsuperscript{10}

**Limitations**

Residual confounding due to incomplete control for imperfectly measured and unmeasured parameters cannot be excluded. Propensity score matching may reduce bias from lack of randomization but cannot control for unmeasured confounders. Specific hormonal preparations prescribed were not evaluated. Finally, the study may be underpowered to detect harm from HRT.

**Conclusions**

In conclusion, this analysis of female patients with AF in AFFIRM, HRT did not predict the primary composite end point, nor all-cause death, ischemic stroke, or major bleeding.

**Disclosures**

Drs Apostolakis, Olshansky, and Lip have received research funding and honoraria from various pharmaceutical companies in relation to atrial fibrillation for meetings and educational symposia. Dr Sullivan has no conflicts to declare.

**References**


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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/09/19/STROKEAHA.114.006668.DC1

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SUPPLEMENTARY MATERIAL
Detailed Methods

*Statistical analysis*

Means and standard deviations were calculated for continuous variables. Frequencies and percentages were calculated for categorical variables. Continuous variables were analyzed using one-way ANOVA or independent sample t-test. Categorical variables were analyzed using chi-square or Fisher’s exact test as appropriate.

Adjusted Cox proportional hazards models were used to assess the impact of HRT on the outcome of women with AF. The multivariable model was adjusted for prognostic variables including CHA₂DS₂VASc score factors (congestive heart failure, hypertension, age, diabetes, previous stroke, previous myocardial infarction, history of peripheral arterial disease), treatment with warfarin (on randomization), treatment arm (rhythm or rate control) and time in therapeutic range (TTR) measuring warfarin control.

To reduce bias introduced by lack of randomization we assembled a more homogeneous sub-cohort using a matching algorithm based on the estimated propensity score. Propensity scores were calculated using a cumulative logistic regression model. Baseline characteristics that differ among the two groups in a univariate analysis at an alpha level <0.2 were introduced as covariates (Supplementary Table 1). The model was adjusted for time in therapeutic range, age, diabetes, congestive heart failure, smoking and treated dyslipidemia. Body mass index was not introduced in the model due to the significant number of missing values (37.2%). The tolerance for the score in matching cases and controls was set to an absolute value of the difference in propensity scores less than or equal to 0.1. The value was selected as the minimum value that would allow a 1:1, case: control ratio. A higher tolerance value would result in less well matched groups while smaller values produced closer matches but increased the number of unmatched cases and reduced the sample size.
Adjusted Cox proportional hazards models were used to assess the impact of HR on the outcome of women with AF in the propensity score matched cohort. Survival curves were calculated using the mean of covariates method, in which average values of covariates are entered into a proportional hazards regression equation. The model was adjusted for prognostic variables similar to the total cohort.

A p value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 19.0 (SPSS, Inc., Chicago, Illinois) and R software www.r-project.org.
Supplementary Table I
Baseline clinical and demographic characteristics of female subjects stratified by HRT use

<table>
<thead>
<tr>
<th></th>
<th>Total cohort</th>
<th>Propensity score-matched cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT (n = 376)</td>
<td>No HRT (n = 1218)</td>
</tr>
<tr>
<td>Age in years¹, (SD)</td>
<td>69 (7.4)</td>
<td>72 (7.4)</td>
</tr>
<tr>
<td>Body mass index, (SD)</td>
<td>27.7 (5.8)</td>
<td>27.6 (5.8)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>276 (73.4)</td>
<td>888 (72.9)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>62 (16.5)</td>
<td>243 (20)</td>
</tr>
<tr>
<td>Dyslipidemia (treated) (%)</td>
<td>80 (21.3)</td>
<td>198 (16.3)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>86 (7.1)</td>
<td>86 (9.6)</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>108 (28.7)</td>
<td>357 (29.3)</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>39 (10.4)</td>
<td>148 (12.2)</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>70 (18.6)</td>
<td>288 (23.6)</td>
</tr>
<tr>
<td>Peripheral arterial disease (%)</td>
<td>26 (6.9)</td>
<td>72 (5.9)</td>
</tr>
<tr>
<td>Valvular heart disease (%)</td>
<td>59 (15.7)</td>
<td>192 (15.8)</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>56 (14.9)</td>
<td>156 (12.8)</td>
</tr>
<tr>
<td>Hepatic or renal failure (%)</td>
<td>18 (4.8)</td>
<td>60 (4.9)</td>
</tr>
<tr>
<td>Pulmonary disease (%)</td>
<td>44 (11.7)</td>
<td>156 (12.8)</td>
</tr>
<tr>
<td>Rhythm control (%)</td>
<td>181 (48.1)</td>
<td>590 (48.4)</td>
</tr>
<tr>
<td>Higher education² (%)</td>
<td>41/86 (47.7)</td>
<td>66/216 (30.6)</td>
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<tr>
<td>Professionally active³ (%)</td>
<td>14/87 (16.1)</td>
<td>17/220 (7.7)</td>
</tr>
<tr>
<td>Warfarin (on recruitment) (%)</td>
<td>319 (84.8)</td>
<td>1007 (82.7)</td>
</tr>
<tr>
<td>% time in therapeutic range (SD)</td>
<td>0.61 (0.24)</td>
<td>0.57 (0.27)</td>
</tr>
<tr>
<td>CHADS² median (IQR)</td>
<td>1.5 (1-2)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>CHA²DS²VASc median (IQR)</td>
<td>3 (3-4)</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td>HAS-BLED median (IQR)</td>
<td>2 (1-2)</td>
<td>2 (1-3)</td>
</tr>
</tbody>
</table>
P value for chi square/Fisher exact test or independent sample t-test as appropriate. HRT, hormone replacement therapy; CHADS₂ score (one point each for the presence of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus; two points for history of stroke or transient ischemic attack, TIA); CHA₂DS₂-VASc score (two points each for age ≥ 75 years and previous stroke/TIA; one point each for systolic heart failure, hypertension, diabetes mellitus, age 65–74 years, vascular disease and female gender); HAS-BLED (one point each for the presence of uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, age ≥ 65 years, and concomitant drugs (e.g. aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol use.

1 Information available in 1002 (62.8) participants of the total cohort.
2 Information available in 302 participants in the Quality of Life (QoL) substudy; defined as college education (with or without degree) or above.
3 Information available for 307 participants in the Quality of Life (QoL) substudy; defined as currently employed (full or part time)
### Supplementary Table II.

**Differences in baseline clinical and demographic characteristics of female subjects stratified by HRT use**

<table>
<thead>
<tr>
<th></th>
<th>Hormone therapy</th>
<th></th>
<th></th>
<th></th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 376)</td>
<td>No (n = 1218)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, (SD)</td>
<td>69 (7.4)</td>
<td>72 (7.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Body mass index¹, (SD)</td>
<td>29.0 (7.3)</td>
<td>27.6 (5.8)</td>
<td>0.003</td>
<td></td>
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<td>Hypertension (%)</td>
<td>276 (73.4)</td>
<td>888 (72.9)</td>
<td>0.894</td>
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<tr>
<td>Diabetes (%)</td>
<td>62 (16.5)</td>
<td>243 (20)</td>
<td>0.154</td>
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<tr>
<td>Dyslipidemia (treated) (%)</td>
<td>80 (21.3)</td>
<td>198 (16.3)</td>
<td>0.029</td>
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<tr>
<td>Smoking (%)</td>
<td>86 (7.1)</td>
<td>86 (9.6)</td>
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<tr>
<td>Coronary artery disease %</td>
<td>108 (28.7)</td>
<td>357 (29.3)</td>
<td>0.846</td>
<td></td>
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<tr>
<td>Previous myocardial infarction (%)</td>
<td>39 (10.4)</td>
<td>148 (12.2)</td>
<td>0.409</td>
<td></td>
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</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>70 (18.6)</td>
<td>288 (23.6)</td>
<td>0.041</td>
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<tr>
<td>Peripheral arterial disease (%)</td>
<td>26 (6.9)</td>
<td>72 (5.9)</td>
<td>0.463</td>
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<tr>
<td>Valvular heart disease (%)</td>
<td>59 (15.7)</td>
<td>192 (15.8)</td>
<td>1.000</td>
<td></td>
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<tr>
<td>Previous stroke (%)</td>
<td>56 (14.9)</td>
<td>156 (12.8)</td>
<td>0.298</td>
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</tr>
<tr>
<td>Hepatic or renal failure (%)</td>
<td>18 (4.8)</td>
<td>60 (4.9)</td>
<td>1.000</td>
<td></td>
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</tr>
<tr>
<td>Pulmonary disease (%)</td>
<td>44 (11.7)</td>
<td>156 (12.8)</td>
<td>0.656</td>
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<tr>
<td>Rhythm control (%)</td>
<td>181 (48.1)</td>
<td>590 (48.4)</td>
<td>0.953</td>
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<td></td>
</tr>
<tr>
<td>Higher education² (%)</td>
<td>41/86 (47.7)</td>
<td>66/216 (30.6)</td>
<td>0.007</td>
<td></td>
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<tr>
<td>Professionally active³ (%)</td>
<td>14/87 (16.1)</td>
<td>17/220 (7.7)</td>
<td>0.036</td>
<td></td>
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<td>Warfarin (on recruitment) (%)</td>
<td>319 (84.8)</td>
<td>1007 (82.7)</td>
<td>0.345</td>
<td></td>
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<tr>
<td>% time in therapeutic range (SD)</td>
<td>0.61 (0.24)</td>
<td>0.57 (0.27)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS₂ (SD)</td>
<td>1.64 (1.10)</td>
<td>1.87 (1.16)</td>
<td>0.016</td>
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<td></td>
</tr>
<tr>
<td>CHA₂DS₂VASc (SD)</td>
<td>3.60 (1.29)</td>
<td>3.92 (1.36)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED (SD)</td>
<td>1.83 (1.02)</td>
<td>1.93 (0.99)</td>
<td>0.085</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p* value for chi square/Fisher exact test or independent sample t-test as appropriate. HRT, hormone replacement therapy; CHADS₂ score (one point each for the presence of
congestive heart failure, hypertension, age ≥75 years, diabetes mellitus; two points for history of stroke or transient ischemic attack, TIA; CHA₂DS₂-VASc score (two points each for age ≥ 75 years and previous stroke/TIA; one point each for systolic heart failure, hypertension, diabetes mellitus, age 65–74 years, vascular disease and female gender); HAS-BLED (one point each for the presence of uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, age ≥ 65 years, and concomitant drugs (e.g. aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol use).

1Information available in 1002 (62.8) participants of the total cohort.
2Information available in 302 participants in the Quality of Life (QoL) substudy; defined as college education (with or without degree) or above.
3Information available for 307 participants in the Quality of Life (QoL) substudy; defined as currently employed (full or part time).
Supplementary Table III.

Factors associated with the primary endpoint in multivariable Cox regression analysis in the propensity score-matched cohort

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Age</td>
<td>0.956</td>
<td>0.931</td>
<td>0.982</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.139</td>
<td>0.745</td>
<td>1.742</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.627</td>
<td>1.063</td>
<td>2.490</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2.339</td>
<td>1.514</td>
<td>3.615</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.872</td>
<td>0.545</td>
<td>1.395</td>
</tr>
<tr>
<td>Rhythm control</td>
<td>1.006</td>
<td>0.695</td>
<td>1.456</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.376</td>
<td>1.580</td>
<td>3.571</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0.769</td>
<td>0.387</td>
<td>1.527</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.820</td>
<td>1.121</td>
<td>2.953</td>
</tr>
<tr>
<td>Time in therapeutic range</td>
<td>4.063</td>
<td>2.005</td>
<td>8.235</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>0.966</td>
<td>0.663</td>
<td>1.409</td>
</tr>
</tbody>
</table>

Primary endpoint is the composite of all cause death, ischemic stroke, systemic embolism, pulmonary embolism and myocardial infarction. The model included clinical factors associated with adverse outcomes in patients with atrial fibrillation: CHADS$_2$ variables, treatment with warfarin (on recruitment), rate/rhythm control management and hormone therapy.
Supplementary Figure I.

Age distribution of the study population.

Women on hormone therapy were significantly younger (mean age 69±7.4 vs. 72±7.4 p<0.001).
Supplementary Figure II.

Distribution of the population in CHADS$_2$ risk categories.

Women on hormone therapy had significantly lower estimated thromboembolic risk as reflected by mean CHADS$_2$ score (1.64±1.10 vs. 1.87±1.16 p=0.016) and CHA$_2$DS$_2$VASc (3.6±1.3 vs. 3.9±1.4, p=0.001) scores.