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Effects of Postmenopausal Hormone Therapy on Incident Atrial Fibrillation

The Women's Health Initiative Randomized Controlled Trials

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Background—Atrial fibrillation (AF) is less prevalent in women versus men, but associated with higher risks of stroke and death in women. The role hormone therapy plays in AF is not well understood.

Methods and Results—The Women's Health Initiative randomized postmenopausal women to placebo or conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) if they had a uterus (N=16 608) or to conjugated equine estrogens only if they had prior hysterectomy (N=10 739). Incident AF was identified by ECG and diagnosis codes from Medicare claims or hospitalization records. Hazard ratios for incident AF were estimated using Cox proportional hazards regression. After excluding participants with baseline AF, there were 611 incident AF cases over a mean of 5.6 years among 16 128 estrogen plus progestin participants, and 683 cases over a mean of 7.1 years among 10 251 conjugated equine estrogens alone participants. Incident AF was more frequent in the active groups of both trials, reaching statistical significance in the trial of conjugated equine estrogens alone in women with prior hysterectomy (hazard ratio, 1.17; CI, 1.00–1.36; *P*=0.045) and in the pooled analysis (hazard ratio, 1.12; CI, 1.00–1.24; *P*=0.05), but not in the estrogen plus progestin trial (hazard ratio, 1.07; CI, 0.91–1.25; *P*=0.44). These results were only minimally affected by adjustment for incident stroke, coronary heart disease, and heart failure.

Conclusions—Incident AF was modestly elevated in hysterectomized women randomized to postmenopausal E-alone, and in the pooled group randomized to E-alone or estrogen plus progestin. The trend in women with intact uterus receiving estrogen plus progestin, considered separately, was not statistically significant.

Clinical Trial Registration Information—ClinicalTrials.gov; Identifier: NCT00000611.

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Key Words: atrial fibrillation ■ hormones ■ women ■ incidence ■ randomized controlled trial

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by disorganized electrical activity in the atrium, leading to loss of effective atrial contraction. AF affects an estimated 2.2 million people in the United States[1] and is the most common chronic arrhythmia in women, with a prevalence that steadily increases from 0.1% in women <55 years of age to 9.1% in those 85 years or older.[2] In women, this arrhythmia is independently associated with both a 22% to 25% increased risk of stroke over age 65[3] and a 1.9- to 2.1-fold increased risk of death.[4,5]

Although the risk of developing AF is higher in men,[2,6] women are more likely to develop stroke[3,7,8] and may be at a higher risk of death compared with men with AF.[4,7] Women are diagnosed with AF at an older age than men,[9] and once diagnosed, have a lower quality of life.[7,10] Reasons for these sex differences are poorly understood.

Clinical Perspective on p 1116

The role of sex hormones in the predisposition to AF has not been well studied. In the long-term follow-up of the Italian

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Tamoxifen Study Group, women randomized to tamoxifen had higher rates of AF than those women in the placebo group, with an RR of 1.7.[11] We are unaware, however, of any published reports on the effect of menopausal estrogen, alone or combined with a progestin, on the onset of AF.

The Women's Health Initiative (WHI) randomized, placebo-controlled hormone trials were designed with the primary end point of coronary heart disease (CHD) and included a trial of estrogen plus progestin (E+P) in women with a uterus and a trial of estrogen only (E-alone) in women posthysterectomy. The E+P trial was stopped early because of higher breast cancer, CHD, stroke, and pulmonary emboli rates in women assigned to active versus placebo hormone pills.[12] The E-alone trial was also stopped early because of an excess stroke rate and no CHD benefit in the active group.[13] Among secondary end points examined, inclusion of new onset of AF[14,15] provided an opportunity to evaluate the effects of estrogen with and without progestin on AF. Recent linkage of WHI participants to Medicare claims has enhanced the power to study novel outcomes, including AF, within these randomized trials.

Methods

Study Population and Design

Details of the design of the WHI trials have been reported previously.[12,13,15] Briefly, postmenopausal women between the ages of 50 and 79 were recruited between 1993 and 1998 at 40 US clinical centers. Women who had a predicted survival of <3 years, a history of substance abuse, mental illness, or were determined to be unlikely to adhere to the study protocol were excluded, as were women with a history of breast or other cancers, except nonmelanomatous skin cancer, within the past 10 years. Women with systolic blood pressures >200 mm Hg or diastolic blood pressures >105 mm Hg were temporarily excluded until blood pressure was better controlled. Women who were taking menopausal hormones at initial screening were required to stop their hormone therapy (HT) for at least 3 months before being assigned to WHI study pills.

A total of 16 608 women who had not had a hysterectomy were randomized to 0.625 mg/d of conjugated equine estrogens (CEE) plus 2.5 mg/d of medroxyprogesterone acetate (MPA) or placebo; whereas 10 739 women with prior hysterectomy were randomized to 0.625 mg/d of CEE or placebo. Women were instructed to take medications orally, once a day. For the purposes of this analysis, 480 E+P trial participants and 489 E-alone trial subjects with known AF at baseline, determined by either self-report on the initial WHI questionnaires or ECG obtained by WHI at enrolment, were excluded. There were 930 women excluded at baseline with only self-reported AF, 10 with only ECG-evident AF and 29 with both self-reported and ECG-evident AF.

Study hormone pills were discontinued in women who developed breast cancer, endometrial cancer unresponsive to treatment, other cancers, deep-vein thrombosis, pulmonary embolism, meningioma, triglyceride levels >1000 mg/dL, or initiation of prescription HT. Study pills were also temporarily withheld for women who reported acute myocardial infarction, stroke, fracture, major surgery, or immobilizing illness. The trials were reviewed and approved by the institutional review boards at each clinical center and all participants provided written informed consent.

Definition of Baseline Variables and End Points

Details of study questionnaires, physical measurements, blood collection, and quality assurance have been described elsewhere.[14,15] Baseline AF was determined by a questionnaire which probed for self-reported doctor diagnosis of AF or by presence of AF based on a computerized reading of 12-lead ECGs. Baseline hypertension was defined by elevated systolic (≥140 mm Hg) or diastolic (≥90 mm Hg) blood pressure at the initial clinic visit or self-report of taking medications for hypertension. Most other underlying baseline medical conditions, such as CHD and diabetes mellitus, were also determined by self-report.

Women were followed annually with clinic visits and with either clinic visits or telephone calls in between annual visits. Women had follow-up 12-lead ECG testing every 3 years after baseline. At each contact, women underwent a standardized interview and were asked about menopausal symptoms, adherence to medications, potential outcomes, and hospitalizations. Medical records were obtained in the event of hospitalization and the International Classification of Diseases (ICD)-9 code for AF (427.31) was extracted from these records. WHI data were linked with their Centers for Medicare & Medicaid Services (CMS) data using social security numbers, birth dates, and death dates, with 97% of Medicare-eligible WHI participants successfully linked. Among participants with Medicare coverage, incident AF was identified by first occurrence of ICD-9 code 427.31 in any diagnosis position in the inpatient Medicare Analysis and Review file [MEDPAR]), Outpatient and Carrier files during years 1993–2007 and after WHI enrollment. Medicare time eligible for analysis included those intervals where participants were enrolled in fee-for-service Medicare and not simultaneously enrolled in a Medicare managed care plan. Women with AF on follow-up ECG or any single ICD-9 code of 427.31 from review of Medicare claims or hospital records were classified as having new onset AF. Sensitivity analyses using alternative definitions of AF were performed; these included a stricter definition requiring 1 inpatient or 2 outpatient claims, as well as a broader definition that included atrial flutter (codes 427.3 and 427.32).

Statistical Analysis

Baseline characteristics for treatment and placebo groups were compared using either Student *t* tests for continuous variables or χ^2 tests for categorical variables. The associations of CEE+MPA and CEE with AF were determined using Cox proportional hazard regression analysis and Kaplan-Meier plots for each trial individually. Because the Medicare data were available for some participants but not others at different time periods over WHI follow-up, a time-dependent indicator variable of Medicare coverage was added to the model to adjust for the additional outcome exposure. Secondary analyses using time-dependent adjustment for incident stroke, CHD, and congestive heart failure (CHF) were performed. Additional analyses examined the effects of active hormones versus placebo in 20 subgroups within levels of each of 7 stratification variables including age, race, hypertension, smoking, diabetes mellitus, body mass index, and CHD. Ninety-five percentage of CIs is presented throughout.

Primary analyses of time-to-AF were performed with the intention-to-treat principle. The proportional hazards assumption was verified by testing the interaction of time and treatment assignment and through visual inspection of the log-likelihood plot of developing AF over time. Secondary analysis was performed to account for participant adherence which was determined by self-report of those who had stopped taking study drugs, were using <80% of the study drugs, or who had started nontrial-related HT. In the adherence-adjusted analyses, participants' event histories were censored 6 months after they were found to have reduced adherence. In addition, data for the 2 trials were combined and analyses were performed for active postmenopausal HT (PHT=CEE+MPA or CEE alone) versus placebo groups. A test for interaction between trial and PHT was performed. All models were stratified within the model by age group, assignment in the WHI Dietary Modification trial and, in the combined trial analysis, by hysterectomy status. Analyses were performed using SAS statistical software version 9.1.

Results

Baseline Characteristics

After excluding participants with AF at baseline, 8255 women had been randomized to CEE+MPA and 7873 to placebo in the E+P trial and 5064 women had been randomized to CEE

Table 1. Baseline Characteristics of Treatment Arm

	E+P Trial		E-Alone Trial		Combined Trials	
	E+P	Placebo	E-Alone	Placebo	Active HT	Placebo
Characteristics	n=8255	n=7873	n=5064	n=5187	n=13 319	n=13 060
Age, mean (SD)	63.2 (7.1)	63.2 (7.1)	63.5 (7.3)	63.5 (7.4)	63.3 (7.2)	63.4 (7.2)
Body mass index (kg/m^2), mean (SD)	28.5 (5.8)	28.5 (5.9)	30.1 (6.1)	30.1 (6.2)	29.1 (6.0)	29.1 (6.1)
Ethnicity						
White	6929 (83.9)	6607 (83.9)	3833 (75.7)	3896 (75.1)	10 762 (80.8)	10 503 (80.4)
Black	525 (6.4)	561 (7.1)	729 (14.4)	795 (15.3)	1254 (9.4)	1356 (10.4)
Hispanic	461 (5.6)	405 (5.1)	307 (6.1)	320 (6.2)	768 (0.5)	725 (5.6)
Asian/Pacific Islander	193 (2.3)	167 (2.1)	85 (1.7)	75 (1.4)	278 (5.8)	242 (1.9)
American Indian	24 (0.3)	27 (0.3)	39 (0.8)	31 (0.6)	63 (2.1)	58 (0.4)
Unknown	123 (1.5)	106 (1.3)	71 (1.4)	70 (1.3)	194 (1.5)	176 (1.3)
College degree or higher	2831 (34.3)	2773 (35.2)	1166 (23.0)	1289 (24.9)	3997 (30.0)	4062 (31.1)
Hypertension						
No hypertension	4344 (52.6)	4321 (54.9)	2247 (44.4)	2322 (44.8)	6591 (49.5)	6643 (50.9)
Untreated hypertension	1681 (20.4)	1598 (20.3)	1134 (22.4)	1148 (22.1)	2815 (21.1)	2746 (21.0)
Treated hypertension	1580 (19.1)	1566 (19.9)	1372 (27.1)	1350 (26.0)	2952 (22.2)	2916 (22.3)
Diabetes mellitus	361 (4.4)	347 (4.4)	387 (7.6)	379 (7.3)	748 (5.6)	726 (5.6)
Hyperlipidemia	904 (11.0)	928 (11.8)	646 (12.8)	712 (13.7)	1550 (11.6)	1640 (12.6)
Smoker	861 (10.4)	812 (10.3)	523 (10.3)	548 (10.6)	1384 (10.4)	1360 (10.4)
Coronary heart disease	372 (4.5)	386 (4.9)	410 (8.1)	386 (7.4)	782 (5.9)	772 (5.9)
Peripheral artery disease	108 (1.3)	99 (1.3)	109 (2.2)	102 (2.0)	217 (1.6)	201 (1.5)
Statin use at baseline	550 (6.7)	518 (6.6)	363 (7.2)	393 (7.6)	913 (6.9)	911 (7.0)
Aspirin use at baseline	1581 (19.2)	1572 (20.0)	971 (19.2)	992 (19.1)	2552 (19.2)	2564 (19.6)
Warfarin use at baseline	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Hysterectomy	0 (0.0)	0 (0.0)	5310 (100.0)	5429 (100.0)	5064 (38.0)	5187 (39.7)
Bilateral oophorectomy	27 (0.3)	23 (0.3)	1849 (36.5)	2014 (38.8)	1876 (14.1)	2037 (15.6)
Age at hysterectomy*						
<40			2010 (39.7)	2043 (39.4)	2010 (39.7)	2043 (39.4)
40–49			2165 (42.8)	2187 (42.2)	2165 (42.8)	2187 (42.2)
50–54			478 (9.4)	542 (10.4)	478 (9.4)	542 (10.4)
≥55			384 (7.6)	381 (7.3)	384 (7.6)	381 (7.3)
Reproductive/hormone history						
Years since menopause, mean (SD)	13.3 (8.4)	13.3 (8.3)	19.0 (9.9)	19.1 (9.7)	15.4 (9.4)	15.5 (9.3)
Past HT use: E only	856 (10.4)	829 (10.5)	2315 (45.7)	2422 (46.7)	3171 (23.8)	3251 (24.9)
Past HT use: E+P	1473 (17.8)	1357 (17.2)	201 (4.0)	240 (4.6)	1674 (12.6)	1597 (12.2)
Parity						
0	826 (10.0)	811 (10.3)	474 (9.4)	446 (8.6)	1300 (9.8)	1257 (9.6)
1–2	2532 (30.7)	2301 (29.2)	1371 (27.1)	1498 (28.9)	3903 (29.3)	3799 (29.1)
3–4	3338 (40.4)	3280 (41.7)	2039 (40.3)	2103 (40.5)	5377 (40.4)	5383 (41.2)
≥5	1527 (18.5)	1446 (18.4)	1141 (22.5)	1109 (21.4)	2668 (20.0)	2555 (19.6)

All values represent the total (percentage) unless otherwise indicated. E+P indicates estrogen plus progestin; E-alone, estrogen without progestin; and HT, hormone therapy.
*Percentages out of participants with a hysterectomy.

only and 5187 to placebo in the E-alone trial. Baseline characteristics of the active and placebo groups for each trial and the combined trials are presented in Table 1. Baseline demographics and risk factor characteristics were not significantly different between active and placebo groups, except for a small (clinically insignificant) difference in hypertension and hyperlipidemia within the E+P trial. The average age was ≈63 years in all groups. In the E+P trial, 83.9% of the women were white, 4.4% had diabetes mellitus, 4.7% had CHD, and 8444 participants were enrolled in fee-for-service Medicare for an average of 3.85 years. Corresponding data for the E-alone trial was 75.4%, 7.6%, and 7.7%, with 6,045 participants enrolled in fee-for-service Medicare for an average of 4.74 years. There were no significant differences in rates of fee-for-service Medicare enrollment between the HT and placebo arms in either trial.

Incident AF

E+P trial participants were followed for an average of 5.6 years, during which time 323 women developed AF in the active group and 288 developed AF in the placebo group (Table 2). Of the 611 subjects diagnosed with AF, 17 were identified only by ECG reading, 99 only with hospitalized ICD-9 coding, 302 only with Medicare claims coding, and 193 with multiple methods. Development of AF did not differ between active CEE+MPA and placebo groups (Cox hazard ratio [HR], 1.07; 95% CI, 0.91–1.25; *P*=0.44). A Kaplan-Meier plot comparing the cumulative hazard of AF in the 2 treatment arms shows no significant separation of the curves (Log-rank *P*=0.562) (Figure 1A).

E-alone trial participants were followed for an average of 7.1 years, during which time 360 women developed AF in the active group and 323 developed AF in the placebo group (Table 2). Of the 683 subjects diagnosed with AF, 12 were identified only by ECG, 130 only with hospitalized ICD-9 coding, 279 only by Medicare claims coding, and 263 with multiple methods. There was a modest, but statistically significant increased risk of developing AF in active CEE versus placebo groups (Cox HR, 1.17; 95% CI, 1.00–1.36; *P*=0.045). A Kaplan-Meier plot comparing the cumulative hazard of AF in the 2 treatment arms shows a marginal separation of the curves (Log-rank *P*=0.056) (Figure 1B**).**

There was no significant interaction between trial and PHT (*P*=0.41). When the 2 HT trials were combined, women assigned to active versus placebo pills had higher AF incidence (Cox HR, 1.12; CI, 1.00–1.24; *P*=0.05). The Kaplan-Meier Curve showed a marginal separation of the curves (Log-rank *P*=0.095) (Figure 1C).

Time-Dependent Adjustments for Incident Cardiovascular Disease

Additional Cox proportional hazard regression analyses were performed with time-dependent adjustment for incident stroke, CHD, and CHF (Table 2). Time-dependent adjustment for incident stroke did not significantly alter the HR in either trial; however, adjustment for time-dependent incident CHD or CHF mildly attenuated the HR in the E-alone trial (HR, 1.14; CI, 0.98–1.33; *P*=0.072). In the analysis of combined trials, there was slight attenuation of the effect of PHT on incident AF (HR, 1.11; CI, 1.00–1.24; *P*=0.06) after adjustment for incident stroke, CHD, and CHF.

Sensitivity Analyses

Alternative definitions of incident AF were used in sensitivity analyses of the primary Cox proportional hazard regression model assessing for effects of CEE, with and without MPA, on incident AF (Table 3). When a stricter definition of incident AF was based on 1 inpatient diagnosis or 2 outpatient claims, the total number of incident AF cases decreased from 1294 to 1031 but the effect of CEE on incident AF remained significant (HR, 1.19; 95% CI, 1.01–1.41; *P*=0.041). Adding incident atrial flutter to the definition increased the number of incident AF cases to 1341 and attenuated the effect of CEE on incident AF in the E-alone trial (HR, 1.15; CI, 0.99–1.33; *P*=0.073). When AF was ascertained using only Medicare

Table 2. Incidence of Atrial Fibrillation by Intervention

Model	Active Events (Ann%)	Placebo Events (Ann%)	HR	95% CI	*P* Value
E+P trial					
Primary model	323 (0.70)	288 (0.67)	1.07	(0.91–1.25)	0.439
Adherent participants	177 (0.61)	187 (0.64)	1.06	(0.86–1.31)	0.568
Adjusted for time-dependent stroke			1.07	(0.91–1.25)	0.432
Adjusted for time-dependent CHD			1.07	(0.91–1.26)	0.391
Adjusted for time-dependent CHF			1.07	(0.91–1.26)	0.401
Adjusted for time-dependent stroke, CHD, and CHF			1.08	(0.92–1.27)	0.338
E-alone trial					
Primary model	360 (1.03%)	323 (0.90%)	1.17	(1.00–1.36)	0.045
Adherent participants	174 (0.83%)	167 (0.77%)	1.14	(0.93–1.42)	0.215
Adjusted for time-dependent stroke			1.17	(1.00–1.36)	0.044
Adjusted for time-dependent CHD			1.15	(0.99–1.33)	0.072
Adjusted for time-dependent CHF			1.15	(0.99–1.33)	0.072
Adjusted for time-dependent stroke, CHD, and CHF			1.14	(0.98–1.33)	0.087
Combined HT trials					
Primary model	683 (0.85%)	611 (0.77%)	1.12	(1.00–1.24)	0.050
Adherent participants	351 (0.70%)	354 (0.69%)	1.10	(0.95–1.28)	0.208
Adjusted for time-dependent stroke			1.12	(1.00–1.25)	0.049
Adjusted for time-dependent CHD			1.11	(1.00–1.24)	0.057
Adjusted for time-dependent CHF			1.11	(0.99–1.24)	0.067
Adjusted for time-dependent stroke, CHD, and CHF			1.11	(1.00–1.24)	0.060

Ann % indicates annualized percentage; HR, hazard ratio; CHD, coronary heart disease; CHF, congestive heart failure; and HT, hormone therapy.

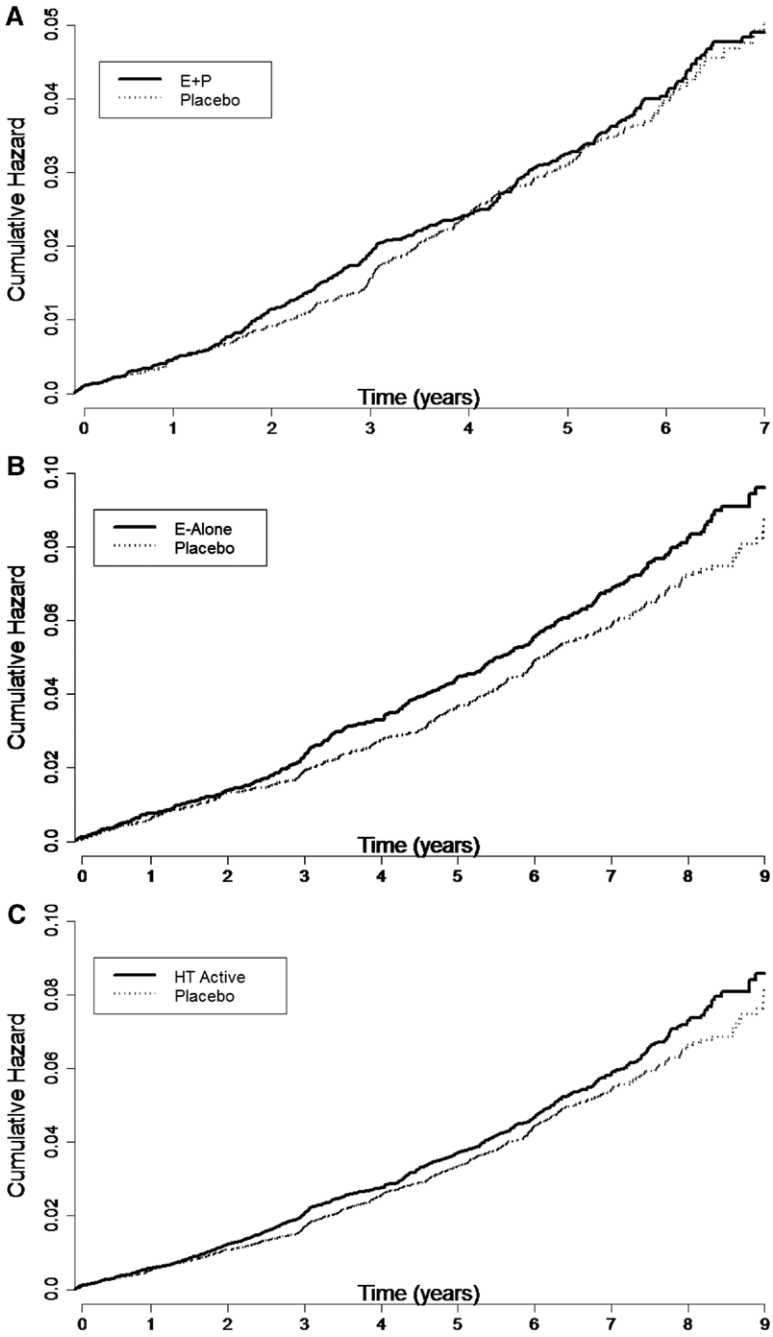

Figure 1. Kaplan-Meier estimates of cumulative incidences (**A**) in the estrogen plus progestin (E+P) trial, (**B**) in the estrogen only (E-alone) trial, and (**C**) in the combined hormone therapy trials.

codes in women enrolled in CMS at baseline, the association was more pronounced in the combined trial analysis (HR, 1.16; CI, 1.02–1.31; *P*=0.025), whereas using only WHI data ascertained fewer cases, albeit with a similar, though no longer statistically significant effect size (HR, 1.11; CI, 0.96–1.28; *P*=0.174).

Subgroup Analyses

There were no significant interactions of treatment effects on AF with age, race, hypertension, smoking status, diabetes mellitus, or history of CHD in either the E+P trial (Figure 2A), the E-alone trial (Figure 2B), or the combined HT trials (Figure 2C). There was a marginally statistically significant interaction of treatment effects on AF with body mass index in the E-alone trial (*P*=0.035), however this interaction was not statistically significant in the E+P trial or the combined therapy trials. Within the E-alone trial, women who reported having diabetes mellitus at baseline were at elevated risk of developing AF if assigned to active CEE versus placebo (HR, 1.73; CI, 1.08–2.78; *P*=0.022). In the analysis of combined hormone trials, active HT increased incident AF among women reporting diabetes mellitus at baseline (HR, 1.49; CI, 1.02–2.13; *P*=0.038) (Figure 2C), women aged 70 to 79 (HR, 1.25; CI, 1.06–1.46; *P*=0.007) and women with body mass index≥30 kg/m^2 (HR, 1.25; CI, 1.06–1.48; *P*=0.008). These associations, however, did not remain statistically significant after adjusting for the multiple hypotheses tested.

Table 3. Sensitivity Analyses of Atrial Fibrillation Ascertainment

Model	Active Events (Ann%)	Placebo Events (Ann%)	HR	95% CI	*P* Value
E+P trial					
Primary model (427.31)	323 (0.70)	288 (0.67)	1.07	(0.91–1.25)	0.439
Stricter AF*	247 (0.54)	230 (0.53)	1.01	(0.85–1.21)	0.884
Any AF†	323 (0.70)	288 (0.67)	1.07	(0.91–1.25)	0.439
AF or atrial flutter‡	331 (0.72)	304 (0.71)	1.03	(0.89–1.21)	0.672
CMS enrollment at baseline	254 (1.36)	223 (1.23)	1.10	(0.92–1.32)	0.295
WHI data alone§	162 (0.35)	147 (0.34)	1.04	(0.83–1.30)	0.753
E-alone trial					
Primary model (427.31)	360 (1.03)	323 (0.90)	1.17	(1.00–1.36)	0.045
Stricter AF*	295 (0.84)	259 (0.72)	1.19	(1.01–1.41)	0.041
Any AF†	361 (1.04)	324 (0.90)	1.17	(1.00–1.36)	0.045
AF or atrial flutter‡	369 (1.06)	337 (0.94)	1.15	(0.99–1.33)	0.073
CMS enrollment at baseline	268 (1.77)	235 (1.47)	1.21	(1.01–1.44)	0.035
WHI data alone§	215 (0.61)	190 (0.52)	1.17	(0.97–1.43)	0.107
Combined HT trials					
Primary model (427.31)	683 (0.85)	611 (0.77)	1.12	(1.00–1.24)	0.050
Stricter AF*	542 (0.67)	489 (0.62)	1.10	(0.98–1.25)	0.119
Any AF†	684 (0.85)	612 (0.77)	1.12	(1.00–1.24)	0.051
AF or atrial flutter‡	700 (0.87)	641 (0.81)	1.09	(0.98–1.21)	0.117
CMS enrollment at baseline	522 (1.54)	458 (1.35)	1.16	(1.02–1.31)	0.025
WHI data alone§	377 (0.46)	337 (0.42)	1.11	(0.96–1.28)	0.174

E+P indicates estrogen plus progestin; HR, hazard ratio; AF, atrial fibrillation; CMS, Centers for Medicare & Medicaid Services; and WHI, Women's Health Initiative.

*Atrial fibrillation (427.31) defined in CMS records as either 1 inpatient record or a combination of 2 outpatient claim records within a year.

†Atrial fibrillation using codes 427.3 or 427.31 3.

‡Atrial fibrillation or atrial flutter using codes 427.3, 427.31, or 427.32.

§Atrial fibrillation ascertained using WHI hospitalization and ECG data, without CMS linkage.

Adherence Analyses

When subjects were censored because of reduced adherence to the randomized treatments, incident AF events were significantly decreased to 364 in the E+P trial and 341 in the E-alone trial. Although the trends remained similar in this analysis, the HR for incident AF were no longer statistically significant in either the E+P (HR, 1.06; CI, 0.86–1.31; *P*=0.568) or the E-alone (HR, 1.14; CI, 0.93–1.42; *P*=0.215) trials.

Discussion

The WHI randomized controlled trials are the largest placebo-controlled trials conducted to date to examine the effects of PHT on AF and other cardiovascular outcomes. Previous observational data suggested that women's increased cardiovascular disease risk with age could be blunted by PHT.[16] However, the WHI trials demonstrated no CHD benefit and an increased risk of stroke with PHT; in fact, CHD was increased in the first year of combined estrogen plus progestin in the E+P trial.[12,13,17] We report a modest, but statistically significant increase in the risk of developing AF in women assigned to active PHT, driven primarily by effects of CEE in women with prior hysterectomy. The elevated incidence of AF by PHT was attenuated by adjustment for incident CHD or CHF, suggesting that the PHT effect on incident AF may be at least in part, mediated through an increase in incident cardiovascular disease caused by PHT use.

It is unclear how endogenous estrogens relate to differences in arrhythmia incidence between men and women, noting that premenopausal women have higher values of estradiol compared with men, whereas postmenopausal women have much lower values of estradiol compared with men.[18] Premenopausal women generally have higher resting heart rates, longer QT intervals, and lower atrial effective refractory periods compared with men.[19–22]

There remains anxiety about the use of hormone replacement therapy in postmenopausal women with hypertension, which is a major determinant of left ventricular hypertrophy and is associated with myocardial fibrosis and higher rates of AF. PHT use has been associated with increased levels of inflammatory markers such as C-reactive protein,[23] a prothrombotic state,[12] and improved endothelial function[24] which disappears after a few months for as yet unclear reasons. Hypertension-related left ventricular hypertrophy, endothelial dysfunction, and inflammation may be contributing to arrhythmogenesis in postmenopausal women treated with PHT, independent of progression of coronary disease. This may be why the effects of PHT use on AF are only partially mediated by the increase in incident cardiovascular disease.

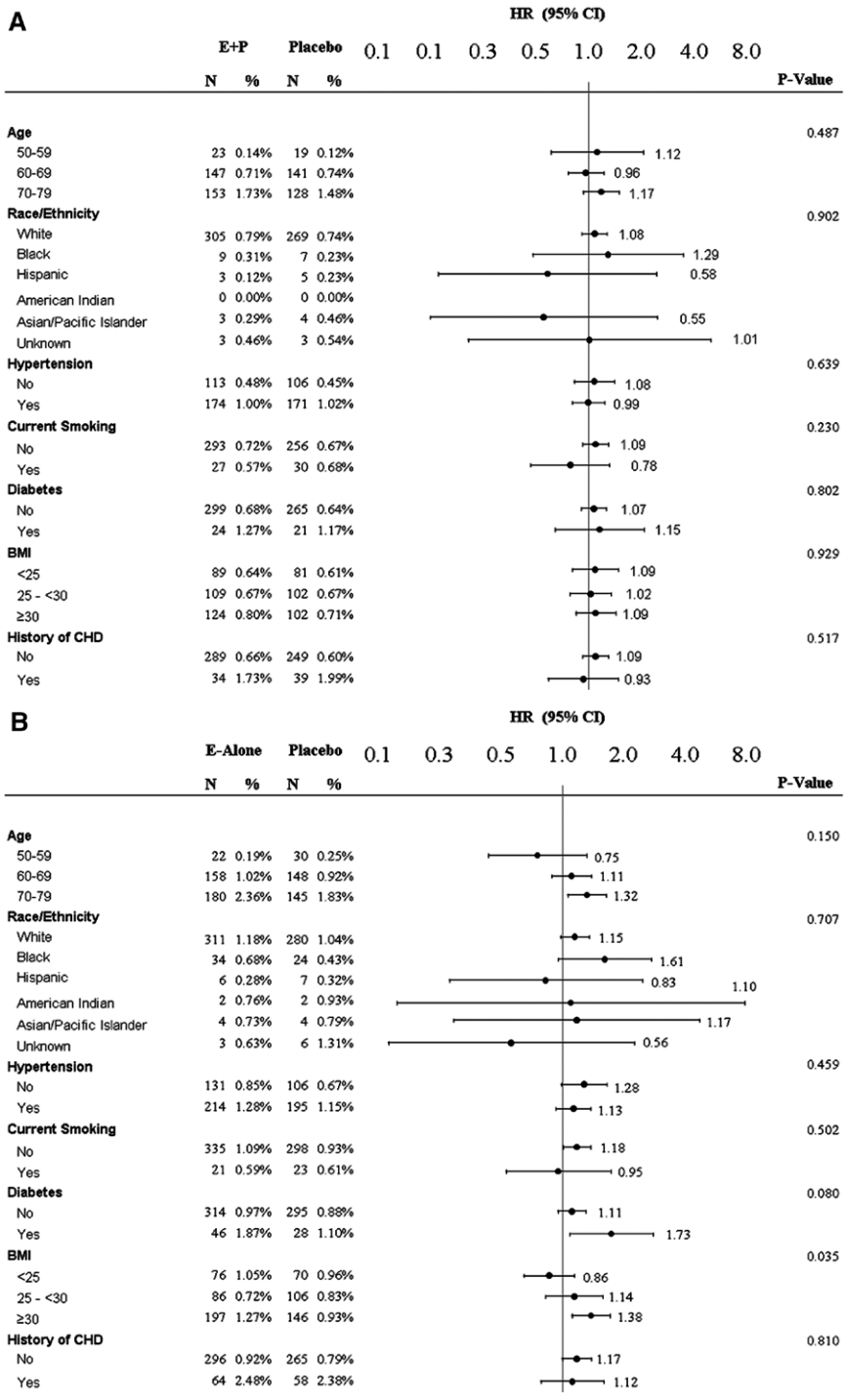

Figure 2 Hazard ratios of incident atrial fibrillation (AF) by subgroup (**A**) in the estrogen plus progestin (E+P) trial, (**B**) in the E+P trial, and

The absence of an increased risk of AF in women randomized to E+P may be attributable to differences in the E+P (women with a uterus) and E-alone (women with prior hysterectomy) trial cohorts, including the previously reported higher cardiovascular risk profile in the E-alone trial participants, compared with those in the E+P trial[25]; however, it is also possible that the progestin component mitigates estrogen effects on arrhythmogenesis, or that differences were attributable to random chance.

Recent, successful efforts to link WHI participants to their Medicare claims records allowed us to identify 581 additional incident AF cases that had not been identified previously. The majority (74%) of these additional cases were outpatient claims events that had not been identified by the WHI hospitalization record review, which included only 63% of self-reported hospitalizations.[26] In the subgroup of WHI subjects enrolled in fee-for-service Medicare, 98% of incident cases identified by WHI ECG or ICD-9 coding from hospitalization were identified through CMS linkage, suggesting that CMS-linked ICD-9 coding was a highly sensitive method for identifying cases of AF in our population. In addition, of the 262

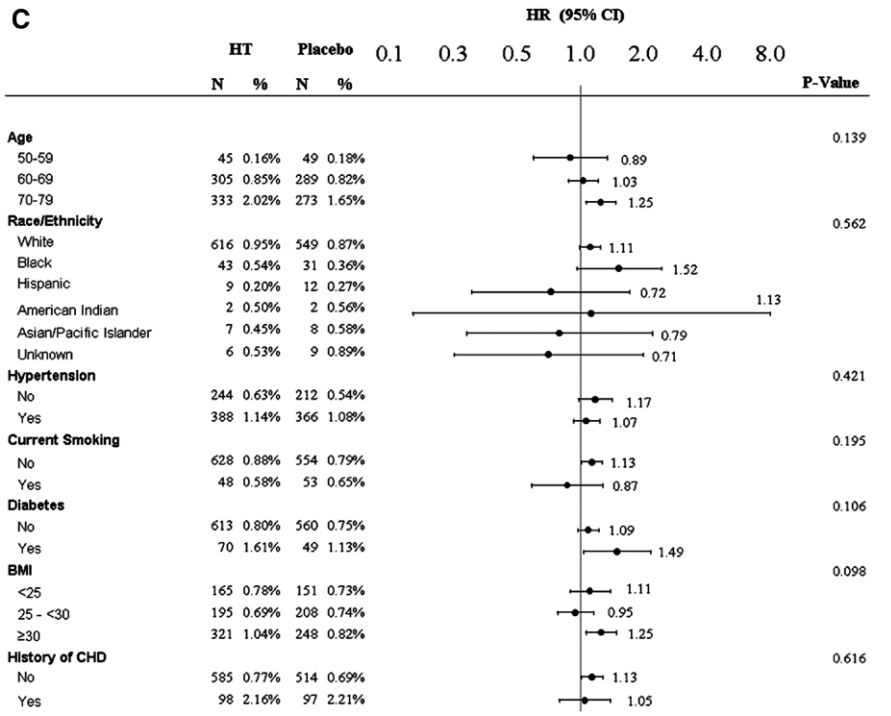

Figure 2 (Continued). (**C**) combined hormone therapy trial.

participants who had AF identified only by WHI hospitalization records, only 1.5% had CMS coverage at the time.

ICD-9 codes for identification of AF have been used by the National Registry of AF[27] and several large population-based cohorts.[2,28,29] The use of ICD-9 coding to correctly identify incident AF has been validated in numerous inpatient cohorts including the Atherosclerosis Risk in Communities Study with a sensitivity of 84% and specificity of 98%.[28] Studies that used review of medical records to validate AF reported positive predictive values of ICD-9 coding ranging from 70% to 96%, with a median positive predictive value of 89% as detailed in a recent systematic review.[30]

Because there is no standardized method of classifying incident AF using CMS codes, we performed a sensitivity analysis using alternative definitions of incident AF, with the finding that stricter definitions did not significantly change our findings. The stricter definition resulted in lower rates of AF, but not by the degree seen in other chronic conditions such as diabetes mellitus, possibly because AF is not often listed as a rule out diagnosis. We kept a liberal definition of AF to capture single episodes of paroxysmal AF that may have been noted on only 1 occasion. Additional sensitivity analyses using CMS data or WHI data separately resulted in effect sizes of similar magnitude and direction, which implied a degree of homogeneity needed to combine these methods of ascertainment in our primary analyses. Although there is a potential for misclassification regardless of the definition used, the biases introduced would generally be nondifferential, likely resulting only in dilution of associations toward the null.

In summary, we report for the first time a modest, but statistically significant increased risk of AF in women assigned to active postmenopausal hormones, particularly in women with prior hysterectomy assigned to estrogen alone in the largest randomized controlled trials of postmenopausal HT to date. Further studies to elucidate the relationship between estrogen use and arrhythmogenesis are necessary.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Although rates of atrial fibrillation (AF) are higher in men compared with women, AF remains the most common arrhythmia in women and rates of death and stroke are higher in women with AF compared with men. The reasons for these differences are not well understood. There are measurable differences in fundamental electrophysiologic parameters between men and women, including differences in QT intervals and atrial effective refractory periods. We aimed in this study to better determine whether hormone exposure plays a role in incident AF. The recent linkage of Medicare records to the Women's Health Initiative participants has allowed us to better study outcomes such as AF in this well-characterized postmenopausal cohort. We analyzed rates of AF in women exposed to postmenopausal hormone therapy compared with placebo in the 2 large randomized hormone therapy trials. We found that there was a small, but statistically significant increase in rates of incident AF in women exposed to estrogen alone compared with placebo, adding to growing evidence that hormone exposure plays a role in arrhythmogenesis. Based primarily on previous results from the Women's Health Initiative randomized controlled trials showing no coronary heart disease benefit and an increased risk of stroke with hormone therapy, clinical practice has already shifted away from the routine use of postmenopausal hormone therapy. Whether certain subgroups, such as diabetics, may benefit from postmenopausal hormone therapy remains controversial. Our findings suggest that women with obesity or diabetes mellitus treated with postmenopausal hormone therapy may incur higher rates of AF, although these subgroup analyses will need to be validated.