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Gender Differences in the Risk of Ischemic Stroke and Peripheral Embolism in Atrial Fibrillation:

The AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) Study

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Abstract

Background—Previous studies provide conflicting results about whether women are at higher risk than men for thromboembolism in the setting of atrial fibrillation (AF). We examined data from a large contemporary cohort of AF patients to address this question.

Methods and Results—We prospectively studied 13 559 adults with AF and recorded data on patients' clinical characteristics and the occurrence of incident hospitalizations for ischemic stroke, peripheral embolism, and major hemorrhagic events through searching validated computerized databases and medical record review. We compared event rates by patient sex using multivariable log-linear regression, adjusting for clinical risk factors for stroke, and stratifying by warfarin use. We identified 394 ischemic stroke and peripheral embolic events during 15 494 person-years of follow-up off warfarin. After multivariable analysis, women had higher annual rates of thromboembolism off warfarin than did men (3.5% versus 1.8%; adjusted rate ratio [RR], 1.6; 95% CI, 1.3 to 1.9). There was no significant difference by sex in 30-day mortality after thromboembolism (23% for both). Warfarin use was associated with significantly lower adjusted thromboembolism rates for both women and men (RR, 0.4; 95% CI, 0.3 to 0.5; and RR, 0.6; 95% CI, 0.5 to 0.8, respectively), with similar annual rates of major hemorrhage (1.0% and 1.1%, respectively).

Conclusions—Women are at higher risk than men for AF-related thromboembolism off warfarin. Warfarin therapy appears to be as effective in women, if not more so, than in men, with similar rates of major hemorrhage. Female sex is an independent risk factor for thromboembolism and should influence the decision to use anticoagulant therapy in persons with AF.

Keywords

anticoagulants; atrial fibrillation; risk factors; stroke; women

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Disclosure

Dr Hylek is currently a principal investigator on 2 industry-sponsored research grants limited to analyses of completed databases. Bristol-Myers Squibb, the source of one of these grants, makes the brand-name warfarin (Coumadin). AstraZeneca, the source of the other grant, manufactures the brand-name ximelagatran Exanta. Dr Hylek also served as a panel participant at a symposium sponsored by AstraZeneca.

Atrial fibrillation is the most common clinically significant cardiac arrhythmia and a major risk factor for ischemic stroke and peripheral embolism.¹ Warfarin therapy substantially reduces the risk of atrial fibrillation–related thromboembolism but also increases the risk for hemorrhage.² Optimal administration of warfarin requires appropriate risk stratification.

Several prominent schemes are available to facilitate identification of patients at high-enough risk of thromboembolism to merit anticoagulant therapy.^{2–5} These schemes, however, provide conflicting recommendations as to whether women with atrial fibrillation are at higher risk for stroke independently of other known risk factors. The Stroke Prevention in Atrial Fibrillation (SPAF)³ and Framingham risk scores⁵ consider women to be at higher risk for ischemic stroke, whereas other studies do not (eg, Atrial Fibrillation Investigators [AFI]² and CHADS₂⁴ risk indexes). Notably, the SPAF investigators found only the subset of women >75 years to be at higher risk for stroke.

Variations in the risk assessment for stroke can lead to significant differences in the use of warfarin therapy for atrial fibrillation.⁶ To test the hypothesis of whether women are at higher risk for atrial fibrillation–related thromboembolism, we analyzed data from the large AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study cohort, comparing rates of ischemic stroke and peripheral embolism between male and female patients not taking anticoagulants while controlling for other known risk factors for thromboembolism.

Methods

ATRIA is a cohort study of 13 559 adults with diagnosed nonvalvular atrial fibrillation who received care within Kaiser Permanente of Northern California, a large integrated healthcare delivery system. Details of the cohort assembly and validation have been described previously.⁷ Cohort members were assembled between July 1, 1996, and December 31, 1997, by searching automated inpatient, outpatient, and ECG databases for physician-assigned *International Classification of Diseases, Ninth Revisions, Clinical Modification* (ICD-9) diagnosis of atrial fibrillation (427.31). Patients with diagnosed mitral stenosis, valvular repair or replacement, transient postoperative atrial fibrillation, or concurrent hyperthyroidism were excluded. The cohort was followed up through August 31, 1999, providing a median follow-up of 2.4 years. Follow-up was censored at the time of an outcome event, death, or disenrollment from the health plan.

Thromboembolic and Hemorrhagic Events

We searched hospitalization and billing claims databases for primary discharge diagnoses of thromboembolic events (ischemic stroke and peripheral embolism) using validated algorithms.⁸ All potential events were individually validated through medical records review by 2 members of a 3-physician outcomes committee, with discordances resolved by consensus of the 3-member committee, including outside consultant review in selected circumstances. A validated ischemic stroke was defined as the sudden onset of a neurological deficit persisting >24 hours and not explained by other origins. A validated peripheral embolism required confirmation by radiographic imaging, intraoperative examination, or pathological findings and the absence of underlying atherosclerotic disease in the affected artery. We excluded patients who developed events during inpatient hospitalization or from periprocedural complications. Mortality at 30 days after outcome events was based on review of medical records, health plan databases, and California State death files.⁹

Using previously described and validated methods,⁸ we identified hemorrhagic events by searching for primary and secondary diagnoses of intracranial hemorrhage and primary diagnoses of extracranial hemorrhage. We excluded intracranial hemorrhages from major

trauma. We defined major hemorrhage as fatal, requiring transfusion of 2 U packed blood cells, or hemorrhage into a critical anatomic site.

Clinical Characteristics

Data on patient age and sex were obtained from administrative databases. Medical diagnoses related to stroke and hemorrhage risk were obtained by searching hospital discharge and ambulatory visit databases for specific ICD-9 – coded diagnoses using previously described and validated methods.⁷ Warfarin exposure was determined using a combination of pharmacy, laboratory, and ambulatory visit databases.⁸ Anticoagulation intensity was measured using outpatient assessments of the international normalized ratio (INR) obtained from health plan laboratory databases. For patients receiving warfarin, we calculated the proportion of person-time at different INR intervals using an adapted linear interpolation method.¹⁰ If a person was on warfarin by pharmacy records but the interval between INR measurements was >8 weeks, we did not interpolate INR values for this extended period and categorized these INR periods as “not available”; 18% of total person-time fell into this category. Finally, we assessed for longitudinal exposure to oral estrogens (either alone or in combination therapy with progesterone) on the basis of filled prescriptions found in health plan pharmacy databases and a previously validated algorithm.¹¹

Statistical Analyses

We compared clinical characteristics of men and women during periods off warfarin using χ^2 tests and compared thromboembolism rates using log-linear models with generalized estimating equations. Multivariable log-linear regression was then used to adjust for previously identified stroke risk factors: age (as a continuous variable by decades), prior ischemic stroke, hypertension, congestive heart failure, coronary artery disease, diabetes mellitus, and estrogen replacement therapy,^{12,13} with time-dependent covariates as appropriate. We also tested whether an interaction existed between patient sex and age in the rate of thromboembolism off warfarin, first testing whether an interaction existed when age was dichotomized at 75 years (as reported in SPAF)³ and then with age as a continuous variable. To assess whether the effectiveness of warfarin varied by sex, we tested the interaction term of warfarin and patient sex in models of thromboembolism that included patients both on and off warfarin therapy. We also compared rates of major hemorrhage by sex, adjusting for risk factors for extracranial and intracranial hemorrhage (age, prior gastrointestinal hemorrhage, hematuria, or other prior hemorrhage, cirrhosis, dementia, mechanical fall during a prior hospitalization, prior stroke, hypertension, and anticoagulation intensity)¹⁴ and tested the interaction term for warfarin and patient sex in models predicting hemorrhagic events.

Results

The cohort included 5795 women and 7764 men. Women were generally older and more likely to have a history of stroke or hypertension but were less likely to have diagnosed coronary disease or diabetes mellitus than men (Table 1). Most men and women had CHADS₂ risk scores between 0 and 2; only a small proportion of the cohort was categorized in the highest-risk group (Table 1). Among women not taking warfarin, the proportion of person-time on oral estrogen therapy was 21.4% compared with 22.5% among women taking warfarin.

Risk of Thromboembolism Off Warfarin Therapy

During periods off warfarin therapy, we identified 394 valid thromboembolic events (369 ischemic strokes) over 15 494 person-years of follow-up. Women had higher annual incidence rates of thromboembolism off warfarin than did men (3.5% versus 1.8%), with an

unadjusted rate ratio (RR) of 1.9 (95% CI, 1.6 to 2.4). These higher rates of thromboembolism among women were observed across various stroke risk factors and categories of the CHADS₂ Index⁴ (Table 2). In a multivariable model controlling for stroke risk factors (age, prior stroke, diagnosed hypertension, congestive heart failure, coronary artery disease, diabetes mellitus, and estrogen replacement therapy), women had a greater independent risk of thromboembolism than men, with an adjusted RR of 1.6 (95% CI, 1.3 to 1.9). Results were similar when analyses were restricted to only ischemic strokes (adjusted RR, 1.5; 95% CI, 1.2 to 1.8). Of note, exposure to oral estrogen replacement therapy in multivariable analyses was not associated with a significantly increased risk of thromboembolism in women (adjusted RR, 1.0; 95% CI, 0.7 to 1.4). Thirty-day mortality after ischemic stroke did not differ significantly by patient sex (23.4% for men and 23.7% for women; $P=0.94$).

Women were at higher risk for incident thromboembolism than men at both younger and older ages (the Figure). The adjusted RR for women versus men was 1.6 (95% CI, 1.0 to 2.3) for those ≤ 75 years of age and 1.8 (95% CI, 1.4 to 2.3) for those >75 years of age. The difference between these 2 rate ratios was not statistically different ($P=0.38$ for the interaction of sex and age, dichotomized as >75 versus ≤ 75 years). The interaction between sex and age was also not statistically significant when age was coded as a continuous variable ($P=0.11$).

Effect of Warfarin Therapy in Women Compared With Men

The distribution of INR intensities was similar between men and women. In men taking warfarin, 26.8% of the person-time was spent at INR levels <2.0 and 62.7% between 2.0 and 3.0; in women, the proportions were 27.9% and 61.3% (These proportions were calculated excluding the 18% of total person-time for which INR was not available).

Among warfarin users, there were 204 thromboembolic and 167 major hemorrhagic events over $\approx 15\,000$ person-years of follow-up. Rates of thromboembolism on warfarin were lower than rates observed in patients off warfarin: annual unadjusted rates of thromboembolism on warfarin were 1.5% in women and 1.2% in men. After multivariable adjustment for other risk factors for stroke, warfarin therapy continued to be associated with a significant reduction in the rate of thromboembolism, with an adjusted RR of 0.4 (95% CI, 0.3 to 0.5) in women and 0.6 (95% CI, 0.5 to 0.8) in men. In multivariable models including patients both on and off warfarin therapy, the reduction in rates of thromboembolism with warfarin was larger in women than in men ($P=0.01$ for the interaction of sex and warfarin).

Rates of Major Hemorrhage on Warfarin Therapy

On warfarin, women had similar rates of all major hemorrhage compared with men (1.0% versus 1.1%; adjusted RR, 0.8; 95% CI, 0.6 to 1.1). Women were less likely than men to develop intracranial hemorrhage while on warfarin (0.36% versus 0.55%; adjusted RR, 0.5; 95% CI, 0.3 to 0.9). In multivariable models assessing predictors of intracranial hemorrhage that included patients both on and off warfarin therapy, warfarin therapy was associated with an increased risk for intracranial hemorrhage (adjusted RR, 1.6; 95% CI, 1.1 to 2.4), but women were not at greater risk for developing intracranial hemorrhage with warfarin therapy than were men ($P=0.10$ for the interaction term between sex and warfarin use).

Discussion

In this large cohort of patients with atrial fibrillation, women had higher rates of ischemic stroke and peripheral embolism while not taking warfarin than did men, even after adjustment for established clinical risk factors for stroke. Higher rates of thromboembolism

among women were observed at both younger and older ages and across all stroke risk factor categories. The 30-day mortality rate following an ischemic stroke did not differ by sex, indicating that the increased risk of stroke faced by women was not due to the occurrence of less severe strokes.¹⁵

Warfarin appears to be at least as effective for women in reducing the risk of thromboembolism, if not more so, than in men. This observation in our cohort was also reported in the pooled analyses of 5 randomized trials of warfarin for atrial fibrillation.² Warfarin therapy did not pose a greater risk of major hemorrhagic complications in women. This was particularly true for the most important hemorrhagic complication, namely intracranial hemorrhage.

Some studies have shown that women, especially older women, are less likely to receive warfarin for atrial fibrillation.^{7,16,17} Our findings indicate that women with atrial fibrillation face a higher absolute risk for thromboembolism independently of other risk factors and should gain more from anticoagulant therapy.

Available risk stratification schemes differ on whether female sex is a risk factor for atrial fibrillation-related thromboembolism (Table 3). We found that women had consistently higher rates of thromboembolism across all stroke risk factor strata and after multivariable adjustment. Our cohort analysis offers several advantages over prior studies. We had substantially greater numbers of person-years of follow-up and outcome events, providing a more powerful assessment. Our cohort is also more contemporary and based in a usual clinical practice setting, potentially yielding more generalizability. In comparison, the AFI and SPAF risk schemes were based on participants in randomized trials completed 10 to 15 years ago.^{2,3} In contrast to the SPAF analysis, we did not find a significant interaction between patient sex and age >75 years. Another advantage of the large size of the cohort is that it allowed us to assess whether women faced an increased risk of warfarin-associated hemorrhage, particularly intracranial hemorrhage. Prior studies did not observe sufficient numbers of intracranial hemorrhages to assess warfarin-sex interactions. This is especially important because the health consequences of intracranial hemorrhage are worse than those resulting from the ischemic strokes we seek to prevent through anticoagulation.^{18,19} In our ATRIA cohort, warfarin was not more dangerous in women than in men.

The mechanism behind the observed difference in atrial fibrillation-related thromboembolism risk between men and women is unclear. Atrial fibrillation is associated with higher levels of prothrombotic factors, endothelial dysfunction, and markers of platelet activation,^{20–23} but sex-related differences in these factors have not been well characterized. Interestingly, women with atrial fibrillation may have higher levels of pro-thrombin fragment F1.2,²⁴ von Willebrand factor,²² and tissue plasminogen activator antigen,²⁵ but studies have not clearly linked these factors to an increased risk of stroke in atrial fibrillation. It also remains to be seen whether differences in left atrial structure and function^{26,27} contribute to differential thromboembolism risk by sex. Although estrogen replacement therapy has been reported to increase risk of ischemic stroke among postmenopausal women,¹³ it was not a significant risk factor in our study.

Our study has several limitations. We lacked data on potential differences in left ventricular systolic function and blood pressure control between men and women, factors shown to affect stroke risk.^{5,28} Although we controlled for the diagnosis of hypertension, we could not adjust for individual patients' blood pressure levels. It is noteworthy, however, that these factors were also not used in the AFI and CHADS₂ risk schemes. We did not have comprehensive information on the use of aspirin in our pharmacy database because many patients used nonprescription forms of aspirin. We addressed this shortcoming in a previous

review of the medical charts of 232 randomly sampled patients in our cohort who were not taking warfarin.⁸ In these nonusers of warfarin, 38% of women and 56% of men were recorded as taking aspirin. Assuming that aspirin reduces thromboembolic event rates by 21%,²⁹ differential use of aspirin between men and women would not materially change our original estimate. Thus, it is unlikely that variation in aspirin use between men and women explains their differing rates of thromboembolism. Finally, we note that stroke rates in our cohort were generally lower than those reported in other earlier studies. The reason for these lower rates is not clear but may reflect a somewhat healthier, insured population of patients. Because we lacked information on individual patients' blood pressure measurements, we were unable to determine whether control of hypertension was better in our cohort than in other populations. In addition, we required that each stroke event be validated by chart review. It is possible that our search strategy missed some stroke events because searching for cerebrovascular diseases using ICD-9 codes may not be highly sensitive.^{30,31}

In conclusion, women have a higher risk than men for atrial fibrillation–related thromboembolism at both younger and older ages that is independent of the presence of other risk factors for stroke. Furthermore, warfarin therapy appears to be at least as effective in women as in men in preventing thromboembolism. Finally, women do not have a higher risk than men for intracranial or other major bleeding events associated with warfarin. On balance, the overall net benefit of warfarin therapy for atrial fibrillation appears to be greater in women compared with men. Our findings indicate that female sex is an important factor supporting the use of anticoagulant therapy in patients with atrial fibrillation.

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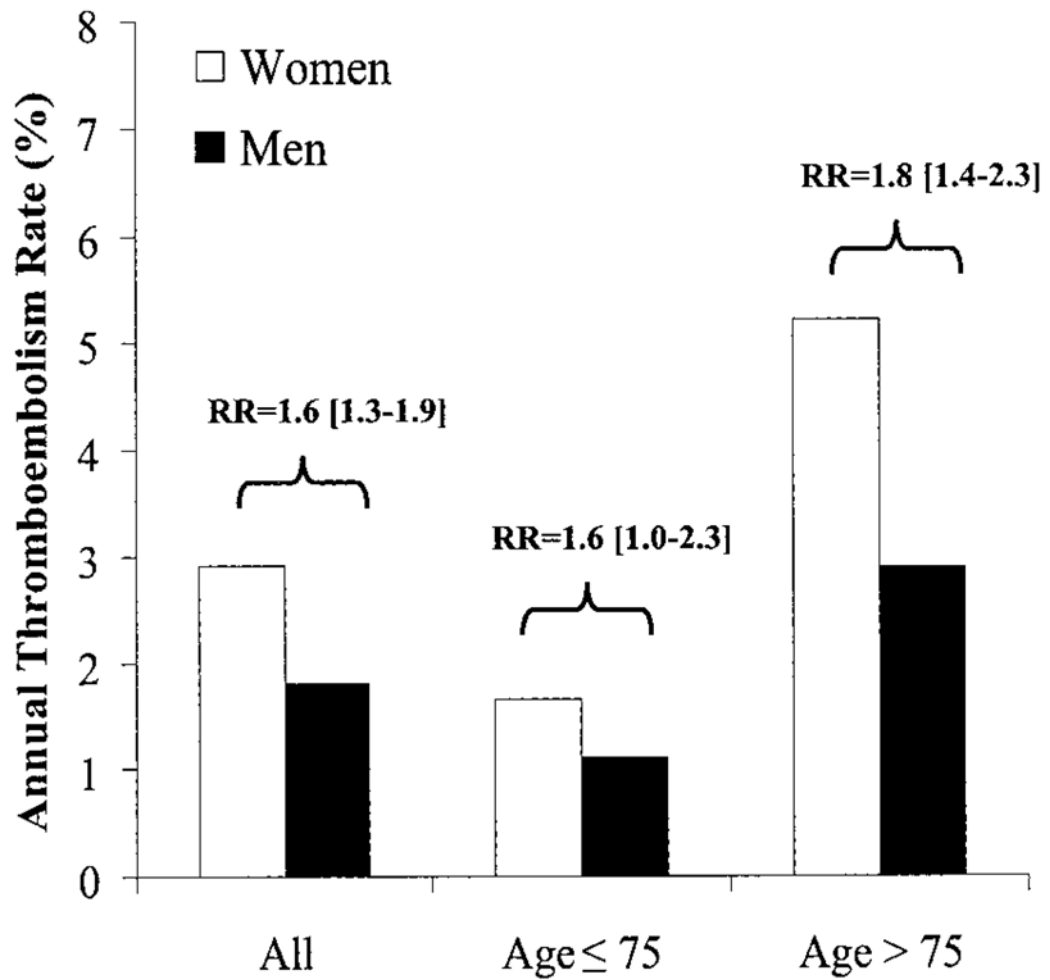


Figure 1.

Annualized adjusted rate of thromboembolism (ischemic stroke and peripheral embolism) during off-warfarin periods among women and men with atrial fibrillation with age, prior stroke, hypertension, congestive heart failure, coronary artery disease, diabetes mellitus, and estrogen use controlled for. Age cutoffs of ≤ 75 and >75 years used as in the SPAF analysis.³ RR indicates adjusted RR and 95% CI.

TABLE 1

Clinical Characteristics and Proportion of Person-Time in CHADS₂ Risk Categories Between Women and Men With Atrial Fibrillation Who Were Not Taking Warfarin

	Person-Years, n (%)		P
	Women	Men	
Total follow-up, person-years	6828	8850	
Age, y			<0.0001
<60	651 (9.5)	1844 (20.8)	
60–69	1134 (16.6)	1819 (20.6)	
70–80	2381 (34.9)	2883 (32.6)	
80	2662 (39.0)	2303 (26.0)	
Prior ischemic stroke	435 (7.1)	528 (6.0)	0.02
Diagnosed hypertension	3938 (57.7)	4235 (47.9)	<0.0001
Diagnosed congestive heart failure	1825 (26.7)	2350 (26.6)	0.85
Diagnosed coronary artery disease	1635 (23.9)	2741 (31.0)	<0.0001
Diabetes mellitus	968 (14.2)	1416 (16.0)	0.01
Prior gastrointestinal bleed	416 (6.1)	635 (7.2)	0.03
Prior hematuria	48 (0.7)	223 (2.5)	<0.0001
Prior other bleed	65 (0.9)	103 (1.2)	0.30
History of cirrhosis	52 (0.8)	154 (1.7)	<0.0001
Diagnosed dementia	465 (6.8)	409 (4.6)	<0.0001
Previous mechanical fall during prior hospitalization	571 (8.4)	374 (4.2)	<0.0001
Oral estrogen replacement therapy	1464 (21.4)
CHADS ₂ score			<0.0001
0	1078 (15.8)	2102 (23.8)	
1	2090 (30.6)	2892 (32.7)	
2	2084 (30.5)	2327 (26.3)	
3	1086 (15.9)	1005 (11.4)	
4	349 (5.1)	351 (4.0)	
5	116 (1.7)	133 (1.5)	
6	24 (0.4)	39 (0.4)	

TABLE 2

Annual Unadjusted Incidence Rates of Thromboembolism Among Men and Women With Atrial Fibrillation Not Taking Warfarin Stratified by Known Risk Factors for Stroke and CHADS₂ Score*

Risk Factor	Annual Thromboembolism Rate (95% CI)	
	Women	Men
Age ≥ 75 y	5.0 (4.3–5.7)	2.8 (2.3–3.4)
Prior ischemic stroke	9.7 (7.0–13.6)	7.3 (5.2–10.3)
Diagnosed hypertension	4.0 (3.4–4.7)	2.4 (2.0–3.0)
Diagnosed congestive heart failure	5.7 (4.7–6.9)	2.5 (1.9–3.2)
Diagnosed coronary artery disease	4.7 (3.8–6.0)	2.4 (1.9–3.1)
Diabetes mellitus	5.0 (3.7–6.6)	3.1 (2.3–4.2)
CHADS ₂ score		
0	0.6 (0.2–1.2)	0.5 (0.3–0.9)
1	1.8 (1.3–2.4)	1.2 (0.9–1.7)
2	4.4 (3.6–5.4)	1.9 (1.4–2.6)
3	6.1 (4.8–7.8)	3.9 (2.8–5.3)
4	9.1 (6.2–13.3)	6.5 (4.2–10.0)
5	7.7 (3.6–16.5)	2.6 (0.8–8.1)
6	11.4 (2.5–51.9)	16.2 (7.4–35.6)

* CHADS₂ score calculated by assigning 2 points to prior stroke or transient ischemic attack and 1 point to any of the following risk factors: congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus.

TABLE 3

Relative Risk of Thromboembolism in Atrial Fibrillation Patients Not Taking Warfarin Comparing Women and Men Across Various Risk Stratification Schemes

	Time Off Warfarin, person-years	Women, %	Events, n	Relative Risk, Women vs Men
ATRIA cohort	15 494	44	369 Ischemic strokes, 25 peripheral emboli	1.6 (1.3–2.0) [*]
AFI ²	3432	34	81 Ischemic strokes, 10 peripheral emboli	1.2 (0.8–1.8) [†]
SPAF ³	3977	28	130 Ischemic strokes	1.6 (<i>P</i> =0.01) [†]
Framingham cohort ⁵	2844	48	83 Strokes (both ischemic and hemorrhagic)	1.9 (1.2–3.1) [†]

^{*} Reported as rate ratio.

[†] Reported as hazard ratio.