Sex Differences in Risk Factors for Incident Atrial Fibrillation (from the Reasons for Geographic and Racial Differences in Stroke [REGARDS] Study)

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We examined whether the sex differences in atrial fibrillation (AF) is related to difference in risk factors leading to AF or due to a differential impact of the same risk factors in 11,806 participants (55.2 % women) from the REGARDS study. Incident AF was ascertained by electrocardiograms and medical history at a follow-up examination. Backwards elimination logistic regression was used to identify AF risk factors in men and women, separately. Over a median follow-up of 9.0 years, 588 (11.1%) men and 428 (6.6%) women (p value <0.001) developed AF. Men had a higher risk of AF than women (age and race adjusted odds ratio [OR] [95% confidence interval (CI)]: 1.61 [1.26, 1.75]). Age, white race, height, weight, use of blood pressure lowering medications and history of cardiovascular disease were identified by backward elimination as AF risk factors shared by both sexes. On the other hand, diabetes was an AF risk factor in women but not in men. Among the shared risk factors between men and women, only age showed a stronger association in women than in men [Interaction p-value = 0.003]. Adjustment for the shared risk factors eliminated the sex difference in AF risk (OR [95% CI]: 0.90 [0.74, 1.09]), which was more noticeable in those younger than the median age (62 years) compared to those who were older (interaction p value 0.003). In conclusion, women and men share several AF risk factors, and these shared risk factors explain the sex differences. However, age association with AF differs by sex, and age modifies the associations between sex and other AF risk factors. **(Am J Cardiol 2019;123:1453−1457)**

The incidence of atrial fibrillation (AF) has been estimated to be 1.5 to 2.0-fold higher in men than in women.[1] The Framingham Heart Study and the Olmstead County, Minnesota study have shown that AF incidence in men is 2.4-fold and 1.7-fold, respectively, the incidence in women.[2,3] Similar to the pattern of sex differences in AF incidence, men showed 1.4 to 1.6-fold higher prevalence of AF than women.[1,4,5] Several AF risk factors already have been identified including older age, obesity, higher blood pressure (BP) and use of BP lowering medications, diabetes, valvular heart disease, heart failure, and coronary heart disease (CHD).[2,6] It is unclear, however, whether sex differences in the distribution of these risk factors or a differential impact of the same risk factors between sexes explain the increased risk of AF in men compared to women. We addressed these questions using data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods

The methodology and design for REGARDS study have been previously published.[7] The REGARDS study was designed to investigate the mechanisms behind black-white and regional differences in stroke mortality. Study participants (n = 30,239) were enrolled between January 2003 to October 2007 with oversampling of blacks from the stroke belt (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) using commercially available postal and telephone records. Verbal consent was obtained, followed by an initial assessment by computer-assisted telephone interview (CATI) along with an in-home physical examination. During the telephone interview, demographics, and medical history were

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obtained. Blood and urine sample collection, electrocardiogram, medication information, height and weight measurements, and blood pressure recording were performed during the in-home examination. Informed written consent was obtained from all participants and the study was approved by the Institutional Review Boards of all participating universities.

Approximately 10 years after the baseline assessment, 15,517 REGARDS participants completed a follow-up examination similar to the baseline visit. Of those, we excluded individuals with baseline AF, missing AF at follow-up visit or missing any baseline covariate data leaving a sample of 11,806 which was included in the analysis.

Incident AF was identified by the study electrocardiogram and also from a self-reported medical history of a physician diagnosis during the CATI surveys, as previously described and validated.[8] The electrocardiograms were read and coded at a central reading center (Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston-Salem, NC) by analysts who were blinded to other REGARDS data. Self-reported AF was defined as an affirmative response to the following question: "Has a physician or a health professional ever told you that you had atrial fibrillation?"

Age, race, sex, education, region of residence, smoking status, physical activity, and previous medical history of diabetes, dyslipidemia and cardiovascular disease (heart failure, coronary heart disease and stroke) as well as use of blood pressure and lipid lowering medications were self-reported. After the participant rested for 5 minutes in a seated position, blood pressure was measured using a sphygmomanometer. Two values were obtained following a standardized protocol and averaged. Electrocardiographic left ventricular hypertrophy (LVH) was defined by the Sokolow-Lyon Criteria.

Potential baseline AF risk factors and participant characteristics mentioned above were compared between men and women using *t* test for continuous variables and chi-square test for categorical variables.

Logistics regression analysis was used to compute odds ratios (OR) and 95% confidence intervals (95% CI) for the association between AF risk factors and participant characteristics with incident AF in men and women, separately. Backwards elimination was used to identify risk factors associated with AF in each sex separately, eliminating variables with a p-value >0.05. Significant similar risk factors remained in the model after backwards elimination in men and women were identified and referred to as "shared risk factors." To examine if these shared risk factors have differential impact on AF risk by sex, multiplicative interaction terms between each of these risk factor and sex were tested. We also examined whether these shared risk factors explain the increased risk of AF in men compared to women by examining the magnitude of attenuation of the association between sex and AF after adjusting for shared risk factors.

Sex-specific population attributable fractions (PAF) and 95% CI of AF risk factors were computed. The PAF represents the fraction of the event rate or risk in a given period that is attributable to the exposure of interest, and we hypothesized that the magnitude of the PAF for each risk factor will vary by sex. Statistical significance for all comparisons including interactions was defined as $p < 0.05$. SAS Version 9.4 (Cary, North Carolina) was used for all analyses.

Results

A total of 11,806 participants (mean age 63.0 ± 8.4 years; 55.2 % women; 36.1 % black) were included in this analysis. The baseline characteristics of the study participants, overall and stratified by sex, are shown in Table 1. Compared to women, men were more likely to be older, white, with a college degree or higher, taller, and obese (manifested as higher values in weight and waist circumference), although they appeared to exercise more frequently than women. Higher prevalence of previous cardiovascular disease and use of blood pressure lowering medications, lipid lowering medications and aspirin were observed in men compared to women (Table 1).

During an average of 9.3 years (median 9.0 years), 1016 (8.6%) participants developed AF. A higher proportion of men developed AF than women (588 [11.1%] vs 428 [6.6%], respectively, p value <0.001).

Using backwards elimination logistic regression models in men and women separately, the following risk factors remained in the models in both sexes: age, race, height, weight, use of blood pressure lowering medications and history of cardiovascular disease. On the other hand, diabetes remained in the model as a significant AF risk factor in women but not in men. Among the shared risk factors between men and women, only age showed a stronger association in women than in men (Interaction p value = 0.003) (Table 2).

Adjustment for the shared risk factors eliminated the higher AF risk in men versus women (OR [95%CI] for men vs women 0.90 [0.74, 1.09]) compared to a model adjusted for age and race only (OR [95%CI] 1.61 [1.26, 1.75]). However, this was more pronounced in those older than the median age (62 years) compared to those who were younger (interaction p-value 0.003) (Table 3).

Age- and race-adjusted PAFs for height, weight and use of blood pressure medication tended to be higher in men than women, whereas PAFs of the previous cardiovascular disease seemed to be comparable in both sexes. On the other hand, PAFs of diabetes, which was not a significant risk factor in men using backwards elimination logistic regression, were higher in women than men (Table 4).

Discussion

In this analysis from the REGARDS study we examined whether the increased risk of AF in men is related to the sex difference in distribution of risk factors or the differential impact of these risk factors. We showed that women and men share several AF risk factors, and that these shared risk factors explain the sex differences. We also showed that age association with AF differs by sex, and age modifies the associations between sex and other AF risk factors.

The AF risk factors identified in our analysis of men and women are in agreement with the established risk factors reported by several epidemiological studies.[2,6,9] Although adjusting for these risk factors in our models attenuated the

Table 1
Baseline participant characteristic

Characteristic*	Total (n = 11,806)	Men (n = 5,290)	Women (n = 6,516)	p Value
Age (years)	63.0 ± 8.4	63.42 ± 8.14	62.65 ± 8.51	<.001
Black (%)	4266 (36.1%)	1562 (29.5%)	2704 (41.5%)	<.001
Region				<.001
Stroke belt	3954 (33.5%)	1745 (33.0%)	2209 (33.9%)	
Stroke buckle	2596 (22.0%)	1046 (19.8%)	1550 (23.8%)	
Non-belt	5256 (44.5%)	2499 (47.2%)	2757 (42.3%)	
Education				<.001
Less than high school	854 (7.2%)	320 (6.1%)	534 (8.2%)	
High school graduate	2729 (23.1%)	1095 (20.7%)	1634 (25.1%)	
Some college	3132 (26.5%)	1295 (24.48)	1837 (28.19)	
College graduate and above	5091 (43.1%)	2580 (48.8%)	2511 (38.5%)	
Exercise (times/week)				<.001
1 to 3	4623 (39.2%)	2095 (39.6%)	2528 (38.8%)	
4	3735 (31.6%)	2001 (37.8%)	1734 (26.61)	
0	3448 (29.2%)	1194 (22.6%)	2254 (34.6%)	
Systolic blood pressure (mm Hg)	125.5 ± 15.5	126.9 ± 14.9	124.5 ± 15.9	<.001
Dyslipidemia	6070 (51.4%)	2760 (52.2%)	3310 (50.8%)	0.14
Waist circumference (cm)	95.1 ± 15.2	99.7 ± 13.3	91.3 ± 15.6	<.001
Height (inch)	66.9 ± 3.9	70.0 ± 2.8	64.3 ± 2.7	<.001
Weight (kg)	84.4 ± 18.8	90.8 ± 17.2	79.2 ± 18.5	<.001
Current smoking	1300 (11.0%)	585 (11.1%)	715 (11.0%)	0.88
Diabetes mellitus	2035 (17.2%)	943 (17.8%)	1092 (16.8%)	0.13
Use of blood pressure medications	5790 (49.0%)	2442 (46.2%)	3348 (51.4%)	<.001
Lipid-lowering therapies	3762 (31.9%)	1877 (35.5%)	1885 (28.9%)	<.001
Regular use of aspirin	4893 (41.5%)	2603 (49.2%)	2290 (35.1%)	<.001
Left ventricular hypertrophy	962 (8.2%)	414 (7.8%)	548 (8.4%)	0.25
Prior cardiovascular disease	2886 (24.5%)	1431 (27.1%)	1455 (22.3%)	<.001
Incident atrial fibrillation	1016 (8.6%)	588 (11.1%)	428 (6.6%)	<.001

* Values expressed as *mean* ± *standard deviation* or *n (%)*.
Dyslipidemia = total cholesterol >240 mg/dl or low-density lipoprotein (LDL) >160 mg/dl or high-density lipoprotein (HDL) <40 mg/dl or current use of cholesterol-lowering medication; Diabetes = fasting plasma glucose >126 mg/dl, nonfasting plasma glucose >200 mg/dl or current use of antidiabetic medications.

association between sex and AF, the exact etiology for the sex differences in the AF risk and AF risk factors remains unclear, and possibly involves a combination of underlying genetic, structural, and hormonal differences.[2,6,9–16]

Previous studies have shown that the age-adjusted incidence and prevalence of AF is higher in men compared to women.[2,4,5,17] Advancing age is considered the most significant risk factor for AF with data to suggest a two fold increase in AF incidence with every 10-year increase.[6] However, it has been noted that women with AF are usually older than men.[2,9,18] The reasons for this finding are unclear but since women have more longevity than men, the absolute number of women with AF exceeds men.[5] This may explain the stronger association of age with AF in women compared to men in our study.

In a sub-study from the CHARGE-AF consortium, after adjusting for height and other risk factors, the incidence of

Table 2
Atrial fibrillation risk factors identified by backwards elimination logistic regression in men and women

	Odds ratio (95% confidence interval)		
Risk factor*	Men	Women	p Value for interaction †
Age (per decade)	1.78 (1.58, 2.00)	2.27 (2.00, 2.58)	0.003
Race (White vs. Black)	2.29 (1.82, 2.89)	2.44 (1.93, 3.09)	0.57
Height (per10 inches)	1.87 (1.32, 2.65)	1.91 (1.30, 2.81)	0.50
Weight (per 1 kg)	1.02 (1.01, 1.02)	1.01 (1.01, 1.02)	0.19
Use of blood pressure lowering meds	1.46 (1.22, 1.76)	1.25 (1.00, 1.56)	0.55
History of cardiovascular disease	1.59 (1.32, 1.92)	1.68 (1.34, 2.09)	0.69
Diabetes††	N/A	1.34 (1.04, 1.75)	N/A

* Backwards elimination approach was used to identify AF risk factors in each sex separately from the list of variables in Table 1 eliminating variables with a p value ≥0.05. The shaded areas denote variables unshared by both sexes.
† p value for interaction between each of the shared risk factors with sex in the association with atrial fibrillation in a model adjusted for other shared factors.
†† Odds ratio (95% confidence interval) of diabetes in men is 1.13 (0.91, 1.42), adjusting for age, race, height, weight, use of blood pressure lowering medications, and cardiovascular disease. p value for interaction between diabetes and sex is 0.55, adjusting for age, race, height, weight, and use of blood pressure lowering medications.

Table 3
Association between sex and atrial fibrillation overall and in age stratified analysis

	Odds ratio (95% confidence interval) for AF in men vs. women		
	Model 1*	Model 2†	Interaction p value††
Total sample (n= 11,806)	1.61 (1.41, 1.84)	0.90 (0.74, 1.09)	N/A
Age >62 years (median) (n = 5894)	1.45 (1.23, 1.70)	0.83 (0.65, 1.05)	0.003
Age <=62 years (median) (n = 5912)	1.95 (1.54, 2.46)	1.39 (0.99, 1.96)	

* Model 1: Adjusted for age and race. For the age stratified analysis, model 1 is adjusted for race only.
† Model 2: Adjusted for model 1 variables plus atrial fibrillation risk factors in men and women (race, height, weight, use of blood pressure lowering medication, and history of previous cardiovascular disease and diabetes).
†† p value from model 2.

Table 4
Age- and race-adjusted population attributable fraction of atrial fibrillation risk factors by sex

	Population attributable fraction (95% confidence interval)	
Risk factor	Men	Women
Height	18.0% (11.0%, 25.0%)	11.6% (2.5%, 20.6%)
Weight	25.9% (18.5%, 33.3%)	23.7% (14.7%, 32.7%)
Use of blood pressure lowering meds	22.3% (15.3%, 29.3%)	19.6% (10.4%, 28.8%)
Cardiovascular disease	15.2% (10.1%, 20.3%)	15.0% (9.5%, 20.6%)
Diabetes *	6.86% (2.9%, 10.8%)	9.9% (5.4%, 14.5%)

* Diabetes was not a risk factor in men using backward elimination.

AF among men was no longer significant.[19] These findings suggest that the increased risk of AF in men is likely related to body size. Likewise, in our study population, men had higher age- and race-adjusted PAF's for height and weight, suggesting that increased body mass index (BMI) leads to a higher AF risk. The role of BMI is supported by two recent large population-based studies from Europe. Results from the BiomarCaRE consortium showed that BMI is related to a higher incidence of AF in men[20] whereas the Tromso study revealed that increased BMI led to a higher risk of AF in both men and women.[21] This points towards a role for exercise and risk factor modification in both sexes to reduce the risk of future development of AF.

In women, diabetes remained a significant risk factor in the multivariable model and the PAF for diabetes was higher, as well. These findings are supported by previous studies which show that diabetes in women is associated with higher risk of incident AF.[22–24] Furthermore, women with AF have a higher risk for myocardial infarction,[25] AF-related stroke and thromboembolism[26–29] and some studies suggest increased mortality as well.[30,31] The higher risk of AF-related complications warrants aggressive preventive and treatment strategies in women.

Our results should be interpreted in the context of certain limitations. Self-reported questionnaires were used to obtain some of the baseline characteristics which could subject our study to recall bias. Also, a significant proportion of the participants did not attend the follow up exam which could subject our sample to selection bias. It is possible we missed cases of paroxysmal AF since we utilized resting ECG and self-reported history of AF. Although we adjusted for several risk factors, residual confounding remains a possibility. Finally, we focused on the established risk factors for AF and cardiovascular disease. It is possible that there are other factors contributing and explaining the sex differences which we did not include in our analysis. Our study has several strengths as well such as the large sample size, racial diversity, and well-ascertained variables and outcomes. These strengths enabled us to adequately demonstrate that women and men share several AF risk factors which explain the sex differences, and that age association with AF differs by sex and modifies the associations between sex and other AF risk factors.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

1. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016;13:321–332.
2. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;386:154–162.
3. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119–125.
4. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. *Circulation* 2015;131:2176–2184.
5. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Benjamin EJ, Curtis LH. Incidence and prevalence of atrial

fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circulation Cardiovasc Qual Out* 2012;5:85–93.
6. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840–844.
7. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, Graham A, Moy CS, Howard G. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiol* 2005;25:135–143.
8. Soliman EZ, Howard G, Meschia JF, Cushman M, Muntner P, Pullicino PM, McClure LA, Judd S, Howard VJ. Self-reported atrial fibrillation and risk of stroke in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Stroke* 2011;42:2950–2953.
9. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobbe S, Kremastinos DT, Breithardt G, Cokkinos DV, Crijns HJ. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol* 2007;49:572–577.
10. Potpara TS, Marinkovic JM, Polovina MM, Stankovic GR, Seferovic PM, Ostojic MC, Lip GY. Gender-related differences in presentation, treatment and long-term outcome in patients with first-diagnosed atrial fibrillation and structurally normal heart: the Belgrade atrial fibrillation study. *Int J Cardiol* 2012;161:39–44.
11. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen SP, Wohlfahrt J, Melbye M. Familial aggregation of lone atrial fibrillation in young persons. *J Am Coll Cardiol* 2012;60:917–921.
12. Kishi S, Reis JP, Venkatesh BA, Gidding SS, Armstrong AC, Jacobs DR Jr., Sidney S, Wu CO, Cook NL, Lewis CE, Schreiner PJ, Isogawa A, Liu K, Lima JA. Race-ethnic and sex differences in left ventricular structure and function: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *J Am Heart Assoc* 2015;4:e001264.
13. Rosano GM, Leonardo F, Sarrel PM, Beale CM, De Luca F, Collins P. Cyclical variation in paroxysmal supraventricular tachycardia in women. *Lancet* 1996;347:786–788.
14. Rosenberg MA, Patton KK, Sotoodehnia N, Karas MG, Kizer JR, Zimetbaum PJ, Chang JD, Siscovick D, Gottdiener JS, Kronmal RA, Heckbert SR, Mukamal KJ. The impact of height on the risk of atrial fibrillation: the Cardiovascular Health Study. *Eur Heart J* 2012;33:2709–2717.
15. Hanna IR, Heeke B, Bush H, Brosius L, King-Hageman D, Beshai JF, Langberg JJ. The relationship between stature and the prevalence of atrial fibrillation in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;47:1683–1688.
16. Nystrom PK, Carlsson AC, Leander K, de Faire U, Hellenius ML, Gigante B. Obesity, metabolic syndrome and risk of atrial fibrillation: a Swedish, prospective cohort study. *PloS one* 2015;10:e0127111.
17. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837–847.
18. Ball J, Carrington MJ, Wood KA, Stewart S. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). *PLoS One* 2013;8:e65795.
19. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kääb S, Couper D, Harris TB, Soliman EZ, Stricker BH, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;2:e000102.
20. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njolstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Mathiesen E, Jørgensen T, Söderberg S, Kuulasmaa K, Zeller T, Lacoviello L, Salomaa V, Schnabel RV. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation* 2017;136:1588–1597.
21. Ball J, Lochen ML, Wilsgaard T, Schirmer H, Hopstock LA, Morseth B, Mathiesen EB, Njølstad I, Tiwari S, Sharashova E. Sex differences in the impact of body mass index on the risk of future atrial fibrillation: insights from the longitudinal population-based Tromso study. *J Am Heart Assoc* 2018;7:e008414.
22. Schoen T, Pradhan AD, Albert CM, Conen D. Type 2 diabetes mellitus and risk of incident atrial fibrillation in women. *J Am Coll Cardiol* 2012;60:1421–1428.
23. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. *J Am Coll Cardiol* 2011;108:56–62.
24. Smith JG, Platonov PG, Hedblad B, Engstrom G, Melander O. Atrial fibrillation in the Malmo Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. *Euro J Epidemiol* 2010;25:95–102.
25. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial infarction. *JAMA Int Med* 2014;174:107–114.
26. Frost L, Engholm G, Johnsen S, Moller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch Int Med* 2001;161:272–276.
27. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;290:1049–1056.
28. Bekwelem W, Connolly SJ, Halperin JL, Adabag S, Duval S, Chrolavicius S, Pogue J, Ezekowitz MD, Eikelboom JW, Wallentin LG, Yusuf S, Hirsch AT. Extracranial systemic embolic events in patients with nonvalvular atrial fibrillation: incidence, risk factors, and outcomes. *Circulation* 2015;132:796–803.
29. Madsen TE, Howard VJ, Jimenez M, Rexrode KM, Acelajado MC, Kleindorfer D, Chaturvedi S. Impact of conventional stroke risk factors on stroke in women: an update. *Stroke* 2018;49:536–542.
30. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946–952.
31. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* 2016;532:h7013.