Atrial Fibrillation and Stroke in Women

Marialuisa Zedde, MD, FESO
Neurology Unit, Stroke Unit,
Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia
Italy

Disclosures

1. Nothing to disclose

2. Involvement in the topic

   co-chair of ESO-WISE (Women Initiative for Stroke in Europe)

   member of the Task Force on Gender and Diversity - EAN

PREMISE

- Atrial fibrillation (AF) is the most common arrhythmia worldwide

- The estimated prevalence is lower in women (373 per 100,000) than in men (596 per 100,000)

- Elevated BMI, arterial hypertension, diabetes mellitus, coronary heart disease, valvular heart disease, and heart failure constitute major risk factors for AF

- AF has been demonstrated to be partially heritable and some studies have suggested differences in AF genetics between women and men

- There are sex-specific differences in the epidemiology, pathophysiology, presentation, prognosis, and treatment of AF: women with AF experience worse symptoms, poorer quality of life, and have higher risk of stroke and death than men

The true prevalence is likely to be substantially higher given that many individuals remain undiagnosed

Nat Rev Cardiol. 2017 February ; 14(2): 113–124; Nature Reviews Cardiology 2016; 13: 321–332

OUTLINE

Atrial Fibrillation in Women vs Men

- Epidemiology
- Pathophysiology
- Presentation and Stroke
- Treatment and Prognosis
- Take home messages

OUTLINE

Atrial Fibrillation in Women vs Men

- Epidemiology
- Pathophysiology
- Presentation and Stroke
- Treatment and Prognosis
- Take home messages

- In North American and European populations, the **age-adjusted incidence of AF has been estimated to be 1.5–2.0-fold higher in men than in women.** USA studies have reported the AF incidence in women to be 1.6 and 2.7 (per 1,000 person-years), respectively, compared with 3.8 and 4.7 in men.
- **AF incidence increases disproportionately with increasing age in both women and men**, reaching as high as 30.4 per 1,000 person-years in women and 32.9 per 1,000 person-years in men by age 85–89 years.
- **Age-adjusted prevalence of AF is lower in women than in men** in North America and Europe.

Because women typically live longer than men, the absolute number of women with AF exceeds the number of men with AF in Medicare data.

Nature Reviews Cardiology 2016; 13: 321–332

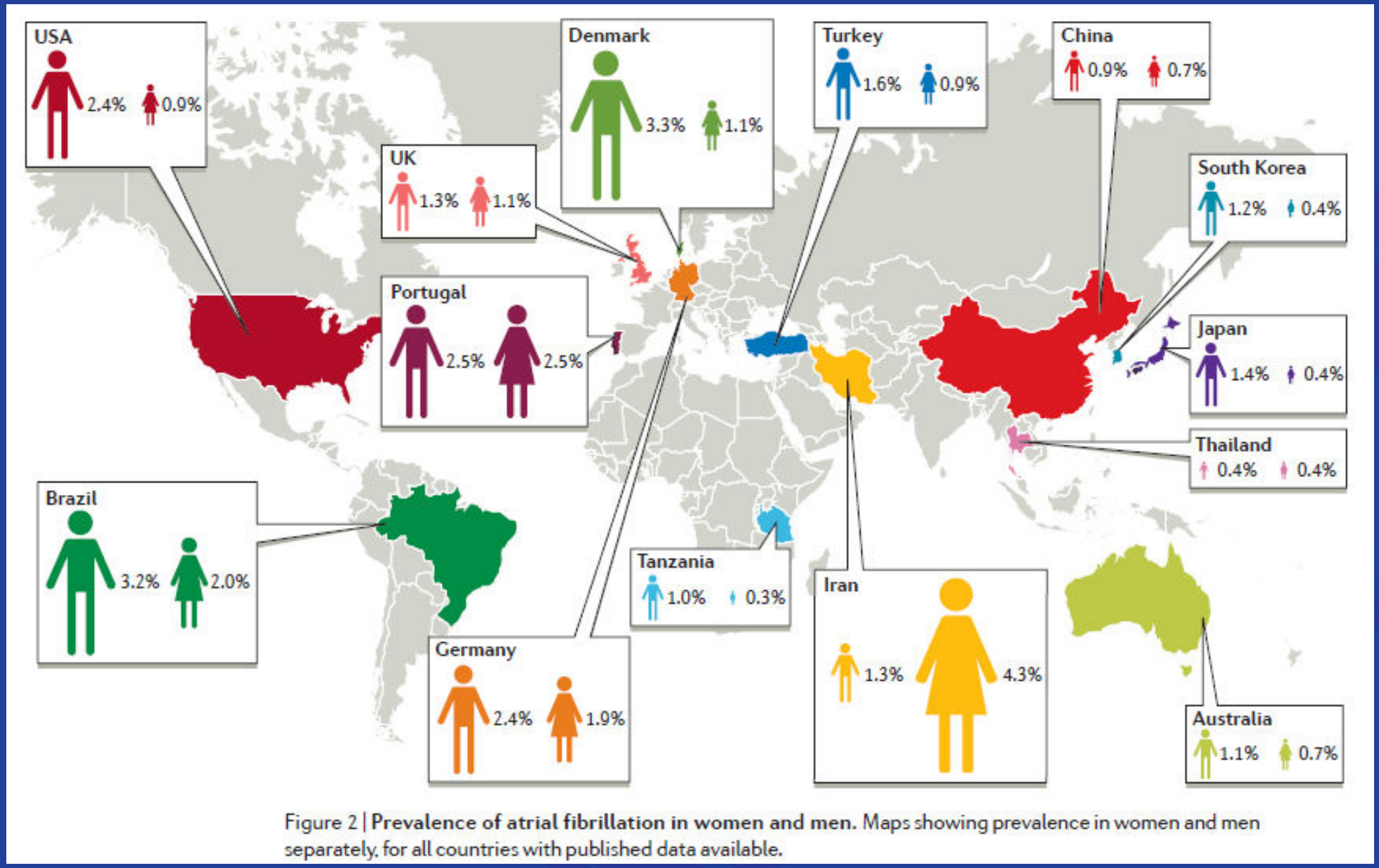


Figure 2 | **Prevalence of atrial fibrillation in women and men.** Maps showing prevalence in women and men separately, for all countries with published data available.

World Stroke Organization

WSO Administrative Office
c/o Kenes International
7, rue François-Versonnex C.P. 6053, 1211 Geneva 6, Switzerland
Tel:+ 41 22 908 0488 I Fax:+ 41 22 906 9129
E-mail: admin@world-stroke.org

Nature Reviews Cardiology 2016; 13: 321–332

- Most studies have reported a higher incidence of AF in men than in women. However, **after adjusting for height and other AF risk factors, a multivariable risk score for incident AF in a three-cohort study showed male sex was no longer significantly associated with AF** (part of the increased risk of AF in men was related to body size).
- Over the past 50 years, the prevalence of major risk factors has changed in both women and men with AF. In particular, **BMI has increased significantly**. In the Women's Health Study, the population attributable risk of AF with increased BMI during the 12 years of follow-up was 18.3%.
- **BMI combined with systolic blood pressure or hypertension conferred the highest risk of AF in both sexes.**
- Women with AF have a higher prevalence of hypertension and valvular heart disease and a lower prevalence of coronary heart disease than men with AF

Nature Reviews Cardiology 2016; 13: 321–332

OUTLINE

Atrial Fibrillation in Women vs Men

- Epidemiology
- Pathophysiology
- Presentation and Stroke
- Treatment and Prognosis
- Take home messages

- **The number of studies investigating sex-related differences in the pathophysiology underlying AF are limited**, and the mechanisms remain inadequately understood
- **Women generally have reduced ventricular wall thickness and smaller left atria and ventricles compared with men**.
- In one study of patients undergoing catheter ablation for AF, **women required more-extensive ablation of nonpulmonary vein foci than men**, suggesting that patterns of electrical heterogeneity vary by sex.
- **Whether oestrogen has a direct role in the reduced incidence of AF in women compared with men remains uncertain**, because most women develop AF at an older age, often after menopause.
- **Hormone replacement therapy in postmenopausal women does not seem to be associated with the risk of incident AF**.
- **Female sex is also a risk factor for non-ST-segment elevation MI** in individuals with AF and for HF with preserved ejection fraction.

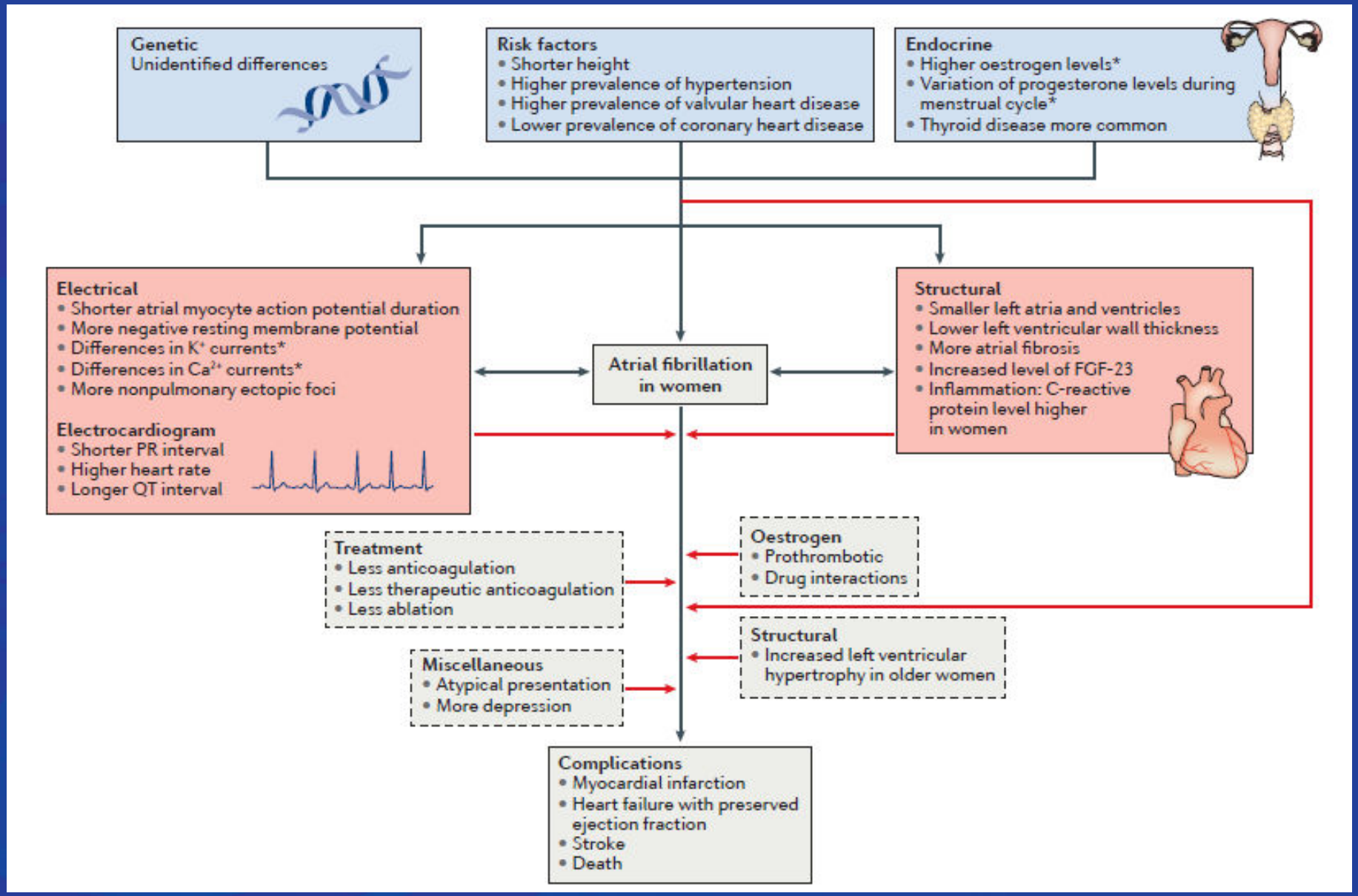
Nature Reviews Cardiology 2016; 13: 321–332

Table 1 Sex differences in prevailing mechanisms/diseases predisposing to atrial fibrillation

	Men	Women
Prevailing risk factors/diseases predisposing to AF	Coronary heart disease and cardiovascular risk factors	Heart failure, particularly diastolic heart failure (HFpEF)
	Excessive sports (vagal AF)	Hypertension and left ventricular hypertrophy Valvular heart disease
	High BMI/metabolic disease (increased epicardial fat)	High BMI/metabolic disease/epicardial fat
	Potential pro-arrhythmic mechanisms increasing AF prevalence in men	**Potential anti-arrhythmic mechanisms reducing AF prevalence in premenopausal women**
Hormonal effects impacting on AF prevalence	Detrimental testosterone effects on atherosclerosis/CAD	Beneficial oestrogen-effects on cardiovascular risk factors
	Pro-arrhythmic testosterone effects on atrial electrical features (shorter APD facilitating re-entry)	Anti-arrhythmic oestrogen-effects on atrial electrical features (longer atrial APD)
	More pronounced fibrotic remodelling in male animals (testosterone-effect?)	Beneficial oestrogen-effects on structural remodelling (attenuation of fibrosis)
		Beneficial oestrogen-effects on diastolic function
		Reduction of epicardial fat (by oestrogen? indirect evidence: more epicardial fat in post-menopausal women)

AF, atrial fibrillation; APD, action potential duration; BMI, body mass index; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction.

Europace (2019) 21, 366–376



Potential sex-specific differences in AF pathophysiological mechanisms

Nature Reviews Cardiology 2016; 13: 321–332

OUTLINE

Atrial Fibrillation in Women vs Men

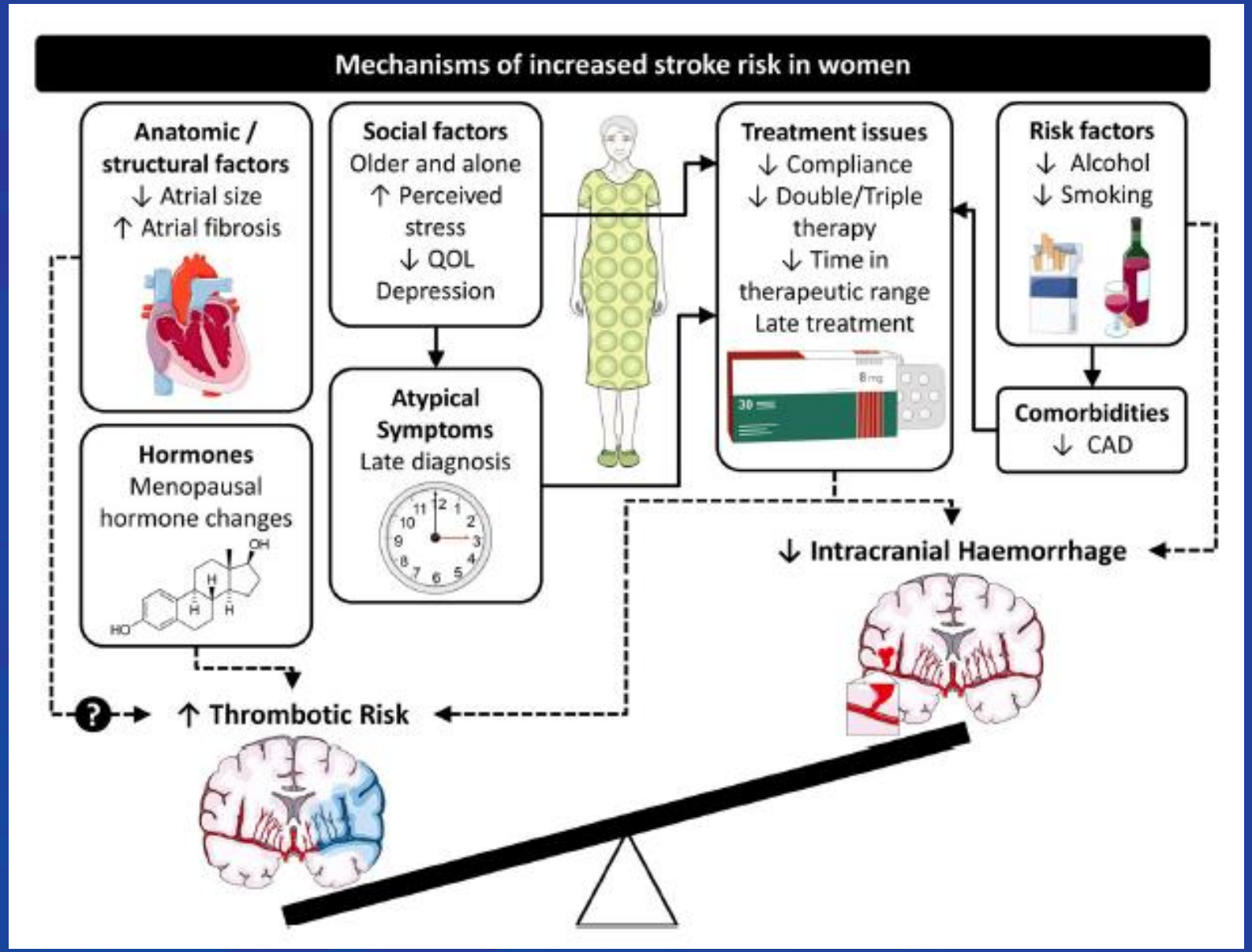
- Epidemiology
- Pathophysiology
- Presentation and Stroke
- Treatment and Prognosis
- Take home messages

- **Asymptomatic AF was less common among women than among men** (relative risk [RR] 0.57, 95% CI 0.52–0.64). In a study of patients visiting the emergency department, women were more likely to have **longer duration of symptoms** and to present with **atypical symptoms**, such as weakness and fatigue.
- **The presence of atypical symptoms might contribute to the worse outcomes seen in women, because they might delay diagnosis and care.**
- The **first presentation** of individuals with **AF** can be with **stroke or cardiomyopathy**.
- **Female sex is a well-recognized, independent risk factor for AF-related stroke and systemic thromboembolism.** According to the **CHA2DS2-VASc** schema, each of the following factors are assigned one point: HF, hypertension, age 65–74 years, diabetes, vascular disease (previous MI, peripheral artery disease, or aortic plaque), and female sex; previous stroke, transient ischaemic attack, or thromboembolism and age ≥75 years qualify for two points each.

Nature Reviews Cardiology 2016; 13: 321–332

- A number of observational studies have demonstrated the **association between female sex and risk of AF-related stroke and thromboembolism**.
- Framingham Heart Study (**HR 1.92**, 95% CI 1.2–3.07), Danish (HR 1.11, 95% CI 1.05–1.18) and Swedish (**HR 1.18**, 95% CI 1.05–1.15) registries, ATRIA study (RR 1.6, 95% CI 1.3–1.9)
- **Female sex was associated with multivariable-adjusted increased risk of stroke in patients with AF who were not receiving oral anticoagulation therapy**.
- **The relationship between female sex and stroke might vary between populations and age groups. Whether female sex confers an additional risk in women aged <65 years without any other risk factors is unclear**.
- The annual risk of stroke is estimated to be very low in women aged <65 years with 'lone' AF. Some studies suggest that female sex might be a substantial risk factor for AF only for those aged >75 years.

Nature Reviews Cardiology 2016; 13: 321–332



Mechanisms of increased stroke risk in women

Clinical Cardiology. 2020;43:14–23

Do Women With Atrial Fibrillation Experience More Severe Strokes? Results from the Austrian Stroke Unit registry

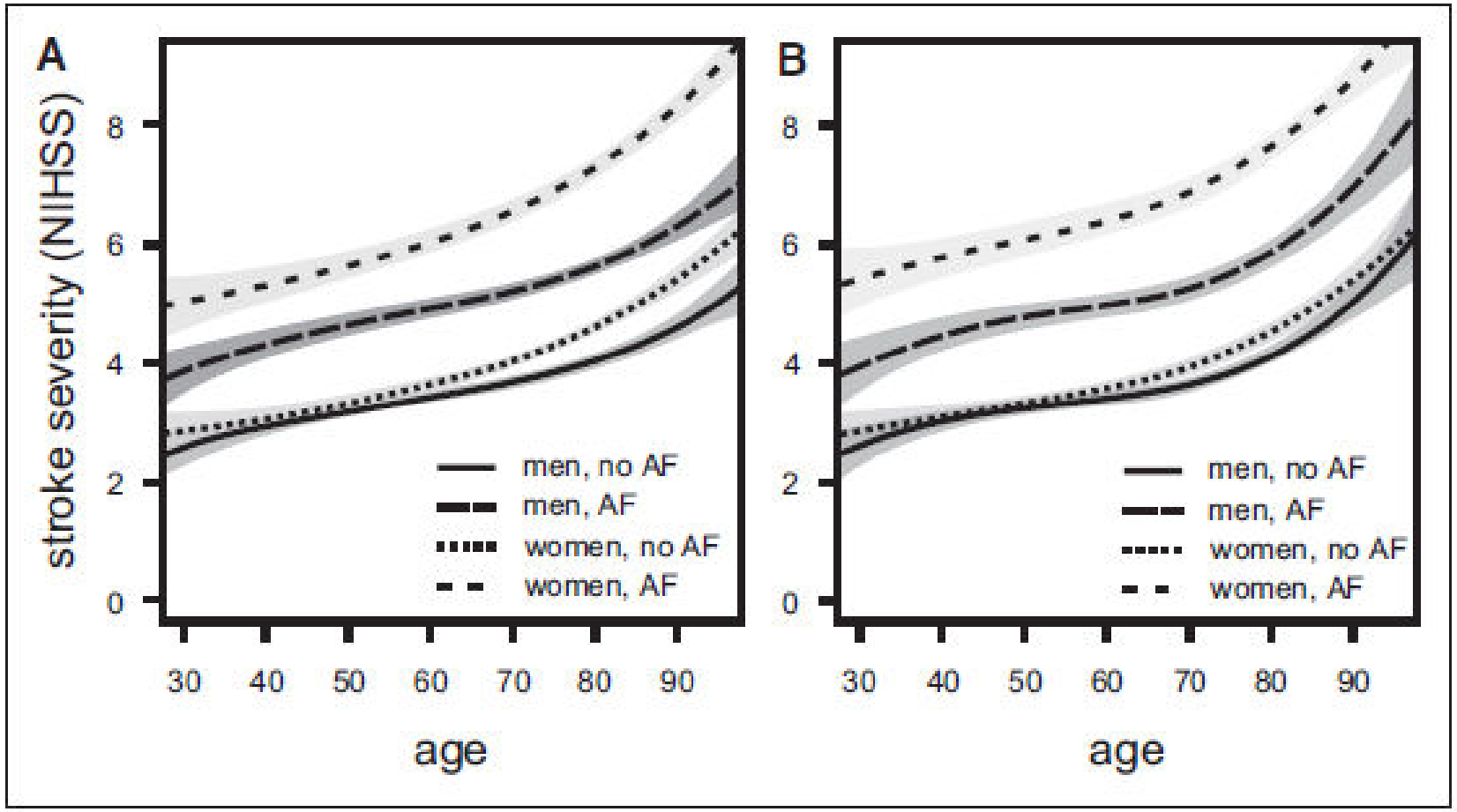


Figure. Association of initial stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS) with age in men and women with or without atrial fibrillation (AF) in the whole population (**A**; n=63 563) and those without previous stroke or disability (**B**; n=35 704).

Women with AF do not only have an increased risk of stroke when compared with men but also experience more severe strokes.

Stroke. 2017;48:778-780

Gender-Specific Differences for Risk of Disability and Death in Atrial Fibrillation-related Stroke

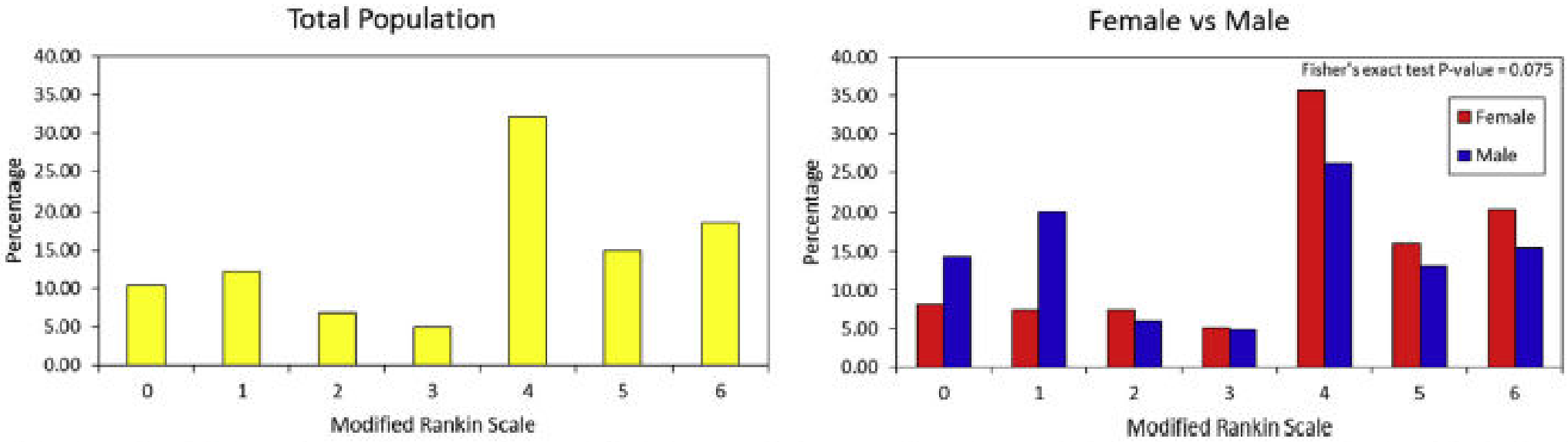


Figure 1. Distribution of mRS in study population. In the overall cohort population *(A)*, 41 patients (18.5%) died (mRS of 6) during their index admission for stroke, and 104 (47%) had severe disabling strokes (mRS of 4 or 5). When broken down by gender *(B)*, a larger percentage of women suffered disabling and fatal strokes. Differences in the distribution of the mRS between men and women were assessed by the Fisher's exact test ($p = 0.075$). This difference became significant when controlled for confounding factors (see text).

Am J Cardiol 2017;119:256e261

OUTLINE

Atrial Fibrillation in Women vs Men

- Epidemiology
- Pathophysiology
- Presentation and Stroke
- Treatment and Prognosis
- Take home messages

- **Sex-specific differences in health-care utilization in cardiovascular treatments are well-documented**
- **Women are less likely to undergo rhythm-control treatment than men; among individuals undergoing rhythm-control treatment, women are less likely to receive electrical cardioversion and catheter ablation than men**
- No significant differences exist in the use of oral anticoagulants between women and men; however, **among individuals receiving dabigatran, women are more likely to receive the lower dose than men**
- **Warfarin and non-vitamin K antagonist oral anticoagulants (NOACs) have similar efficacy and bleeding risk in women and men; however, among individuals receiving warfarin, women might have higher residual risk of stroke or systemic embolism**

Nature Reviews Cardiology 2016; 13: 321–332

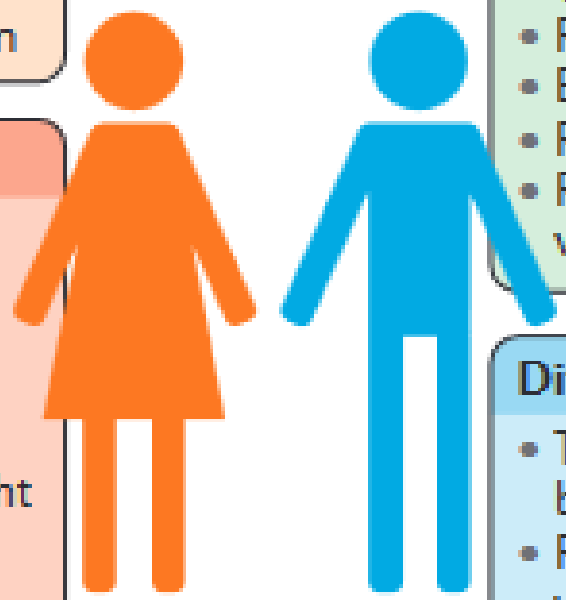
Rate/rhythm control

Similarities

Utilization and outcomes of pharmacological cardioversion

Differences

- Rate control more common in women
- Rhythm control might be associated with higher rates of adverse events in women
- Electrical cardioversion might be less common and less successful in women
- Catheter ablation might be less common in women and might be associated with greater risk of complication



Stroke prevention

Similarities

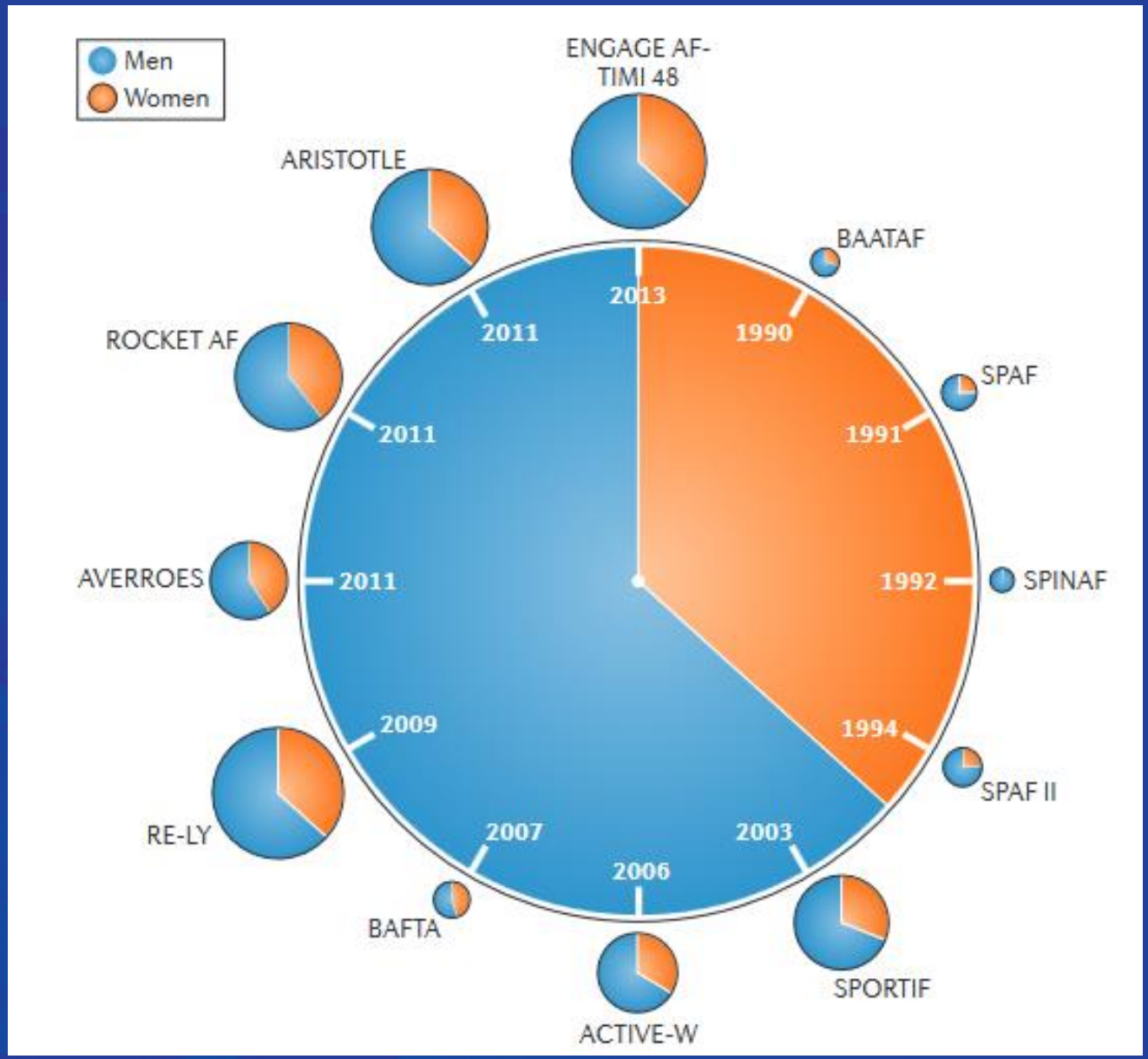
- Warfarin and NOAC prescription
- Risk of bleeding with warfarin
- Efficacy of NOAC versus warfarin
- Residual risk of stroke with NOAC
- Risk of bleeding with NOAC versus warfarin

Differences

- Time in therapeutic range might be lower in women
- Residual risk of stroke with warfarin higher in women
- Dabigatran 110 mg prescribed more in women
- Lower risk of bleeding with oral anticoagulant in women

Figure 1 | **Overview of treatment of atrial fibrillation in women compared with in men.** A summary of the major findings for each aspect covered in this Review. NOAC, non-vitamin K antagonist oral anticoagulant.

Nature Reviews Cardiology 2016; 13: 321–332



Participation of women in anticoagulation trials for stroke prevention in atrial fibrillation

Nature Reviews Cardiology 2016; 13: 321–332

- **In GARFIELD-AF registry the overall rate of anticoagulant use did not differ between women (60.8%) and men (60.9%).** Both undertreatment and over-treatment were common regardless of sex.
- **In the PINNACLE registry, women were more likely than men to receive aspirin instead of OACs after multivariable adjustments** (relative prescription rate of aspirin instead of OAC for men 0.91, 95% CI 0.90–0.92, P <0.001)
- **In a meta-analysis of the warfarin treatment groups** of the ARISTOTLE, BAFTA, RE-LY, ROCKET AF, and SPORTIF III and V trials, **women had a significantly higher residual risk of stroke and systemic thromboembolism than men** (OR 1.28, 95% CI 1.11–1.47, P = 0.001).
- **Major bleeding rates for men and women with AF on AVK reported in 4 randomized trials were similar** (OR, 0.926; 95% CI, 0.81–1.059; P=0.26).
- **DOACs were associated with significantly less major bleeding in women than in men** (OR, 0.844; 95% CI, 0.745–0.955; P=0.007).

Nature Reviews Cardiology 2016; 13: 321–332

Comparing Management and Outcomes in Men and Women with Nonvalvular Atrial Fibrillation
Data From a Population-Based Cohort

TABLE 2 Cumulative Incidence of Ischemic Stroke in Men and Women With NVAF

	Ischemic Stroke			
	Men (n = 42,573)	Women (n = 46,640)	p Value	Adjusted HR for Women vs. Men, Multivariate Analysis* (95% CI; p Value)
All patients	2,475 (5.8)	3,277 (7.0)	<0.001	1.14 (1.08-1.21; p < 0.001)† 0.91 (0.77-1.06; p = 0.22)‡
Stroke rate and adjusted stroke relative risk for female patients with AF subdivided by age groups				
Patient age <65 yrs	737 (5.7)	480 (5.7)	0.966	0.97 (0.83-1.14; p = 0.72)
Patient age 65-74 yrs	1,120 (10.6)	1,159 (10.9)	0.44	1.01 (0.91-1.13; p = 0.30)
Patient age ≥75 yrs	2,235 (11.3)	3,918 (13.8)	<0.001	1.25 (1.16-1.34; p < 0.001)
Cumulative incidence for stroke and adjusted stroke relative risk for female patients				

Men and women with AF had a similar risk of ischemic stroke, except for women 75 years of age or older, who had a higher risk. Our findings support using a similar anticoagulation strategy for prevention of stroke in men and women with a similar number of risk factors.

as in Table 1.

J Am Coll Cardiol EP 2018;4:604–14

Comparison of the Efficacy and Safety Outcomes of Edoxaban in 8040 Women Versys 13065 Men with Atrial Fibrillation in the ENGAGE AF-TIMI 48 Trial

- Female sex is an independent risk factor for stroke and systemic embolic events in patients with atrial fibrillation.
- Women had higher baseline endogenous factor Xa activity in comparison with men placing women at potential increased risk of thrombosis. Treatment with a higher-dose edoxaban regimen caused a greater reduction of anti-Xa activity in women than in men, resulting in similar intensity of achieved anticoagulation.
- The treatment effect of the higher-dose edoxaban regimen (versus warfarin) on the risk of stroke/systemic embolic events and major bleeding was similar in women and men.
- However, the higher-dose edoxaban regimen reduced the risk of several bleeding outcomes including hemorrhagic stroke to a greater extent in women than in men.

Outcome	Women (n=2641) Number of events (rate/y %)	Men (n=4395) Number of events (rate/y %)	Adjusted hazard ratio* (95% CI)	*P* value
Efficacy outcomes				
Stroke/systemic embolic event	141 (2.00)	196 (1.67)	1.21 (0.94–1.56)	0.14
Stroke	131 (1.86)	186 (1.59)	1.17 (0.90–1.51)	0.24
Hemorrhagic stroke	36 (0.50)	54 (0.46)	1.14 (0.70–1.87)	0.59
Ischemic stroke	100 (1.41)	135 (1.15)	1.18 (0.87–1.59)	0.28
Systemic embolic event	12 (0.17)	11 (0.09)	2.16 (0.78–6.01)	0.14
All-cause death	274 (3.77)	565 (4.70)	0.85 (0.71–1.01)	0.063
Cardiovascular death	199 (2.73)	412 (3.43)	0.86 (0.70–1.06)	0.15
Safety outcomes				
Major bleeding	188 (3.35)	336 (3.47)	0.90 (0.72–1.12)	0.34
Any intracranial bleeding	51 (0.89)	81 (0.82)	1.04 (0.68–1.58)	0.86
Life-threatening bleeding	53 (0.93)	69 (0.70)	1.16 (0.76–1.77)	0.49
Gastrointestinal bleeding	61 (1.08)	129 (1.31)	0.91 (0.64–1.31)	0.61
Major and clinically relevant nonmajor bleeding	670 (13.55)	1091 (12.71)	1.12 (1.00–1.26)	0.055
Any overt bleeding	808 (17.14)	1306 (15.97)	1.14 (1.02–1.26)	0.017
Net outcome†	513 (7.54)	949 (8.46)	0.91 (0.80–1.04)	0.18

Circulation. 2021;143:673–684

Sex Difference in Oral Anticoagulation and Outcomes of Stroke and Intracranial Bleeding in Newly Diagnosed Atrial Fibrillation

World Stroke Organization

CLINICAL PERSPECTIVE

What Is New?

- Compared with men, women with newly diagnosed atrial fibrillation were older, with higher CHA_2DS_2-VASc scores and higher comorbidity burden.
- Despite this, women were less likely to receive oral anticoagulation to reduce the risk of stroke, including direct oral anticoagulants.
- Women, compared with men, had a higher risk of ischemic stroke and hospitalization but lower risk of intracranial bleeding.

What Are the Clinical Implications?

- Oral anticoagulation among women partially mediated the observed risk differences by sex in ischemic stroke and hospitalization, suggesting an important target for improving outcomes in women with new atrial fibrillation.

Table 2. Anticoagulation by Sex and CHA_2DS_2-VASC and HAS-BLED Scores

Medication(s)	All Patients (N=358 649), n (%)	Male (N=205 756), n (%)	Female (N=87 581), n (%)	*P* Value	Anticoagulation-Eligible Patients* (N=226 94)9, n (%)	Male (N=107 439), n (%)	Female (N =119 510), n (%)	*P* Value
No anticoagulation	176 239 (49.1)	96 424 (46.9)	79 815 (52.2)	<0.0001	105 255 (46.4)	46 121 (42.9)	59 134 (49.5)	<0.0001
Any anticoagulation	182 410 (50.9)	109 332 (53.1)	73 078 (47.8)	<0.0001	121 694 (53.6)	61 318 (57.1)	60 376 (50.5)	<0.0001
Warfarin	142 868 (39.8)	84 637 (41.1)	58 231 (38.1)	<0.0001	97 374 (42.9)	49 130 (45.7)	48 244 (40.4)	<0.0001
Direct oral anticoagulants	49 193 (13.7)	30 318 (14.8)	18 875 (12.4)	<0.0001	31 034 (13.9)	15 545 (14.5)	15 489 (13)	<0.0001
Dabigatran	22 057 (6.2)	14 017 (6.8)	8040 (5.3)	<0.0001	13 775 (6.1)	7163 (6.7)	6612 (5.5)	<0.0001
Rivaroxaban	20 587 (5.7)	12 466 (6.1)	8121 (5.3)	<0.0001	12 946 (5.9)	6301 (5.9)	6645 (5.6)	0.0018
Apixaban	6549 (1.8)	3835 (1.9)	2714 (1.8)	0.05	4313 (1.9)	2081 (1.9)	2232 (1.9)	0.23

*Anticoagulation eligible defined as CHA_2DS_2-Vasc Score>2 and HAS-BLED score <3.

Table 3. Primary Outcomes (N=358 649)

Outcomes	Sex	Patients, N	Events, N (%)	Unadjusted Incidence Rate (per 1000 person-years)	Unadjusted Hazard Ratio* (95% CI)	*P* Value	Adjusted Hazard Ratio*† (95% CI)	*P* Value
All-cause hospitalization	Female	152 893	93 068 (60.9)	344.7 (342.5–346.9)	1.14 (1.13–1.15)	<0.001	1.06 (1.05–1.07)	<0.0001
	Male	205 756	115 558 (56.2)	297.9 (296.2–299.6)				
Stroke	Female	152 893	5114 (3.3)	10.9 (10.6–11.2)	1.52 (1.46–1.59)	<0.0001	1.27 (1.21–1.32)	<0.0001
	Male	205 756	4574 (2.2)	7.2 (7.0–7.4)				
ICH	Female	152 893	921 (0.6)	1.9 (1.8–2.1)	1.04 (0.95–1.13)	0.39	0.91 (0.83–0.99)	0.03
	Male	205 756	1189 (0.6)	1.8 (1.7–2.0)				

ICH indicates intracranial hemorrhage.

*Reference group is male.

†Adjusted for age, Charlson Comorbidity Index score, congestive heart failure, hypertension, diabetes mellitus, region, insurance plan, and receipt of concomitant drug therapies (antiplatelet agent, angiotensin-converting enzyme/angiotensin receptor blocker, stain, niacin/fibrate).

J Am Heart Assoc. 2020;9:e015689

Mortality

- In 1998, investigators from the Framingham Heart Study established that **AF was associated with increased mortality**, when they reported a **1.5-fold increase in the risk of death in men and a corresponding 1.9-fold increase in women**, adjusting for clinical risk factors. In the study from Olmsted County, Minnesota, new-onset AF was shown to double the risk of death.

- **Multiple longitudinal studies have evaluated whether an interaction exists between sex and AF-related risk of death, but the results have not been consistent.**

- **A meta-analysis of 19 studies (disease-based samples) showed increased risk of all-cause mortality in women compared with in men (RR 1.12, 95% CI 1.07–1.17)**.

Nature Reviews Cardiology 2016; 13: 321–332

OUTLINE

Atrial Fibrillation in Women vs Men

- Epidemiology
- Pathophysiology
- Presentation and Stroke
- Treatment and Prognosis
- Take home messages

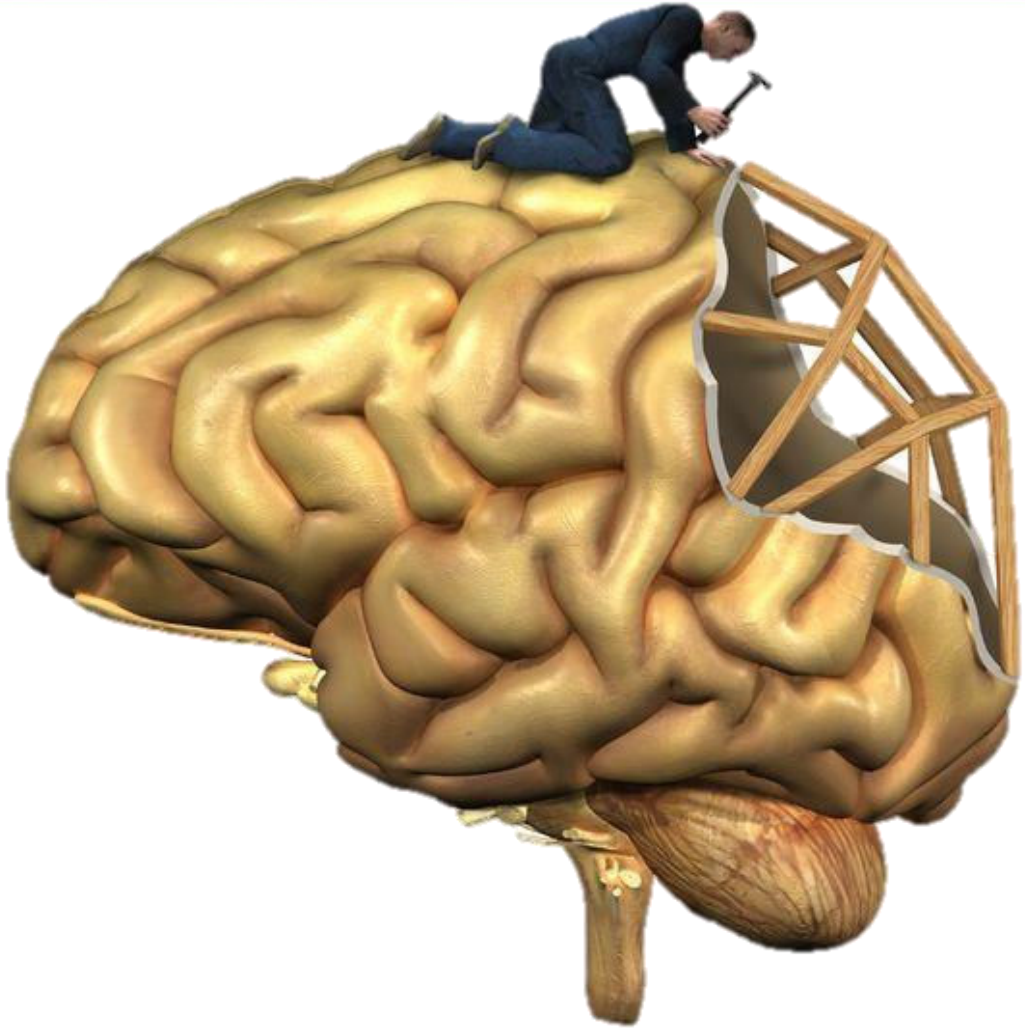
- Women generally have lower age-adjusted incidence and prevalence of AF than men; however, given the greater longevity of women, the absolute number of men and women with AF is similar

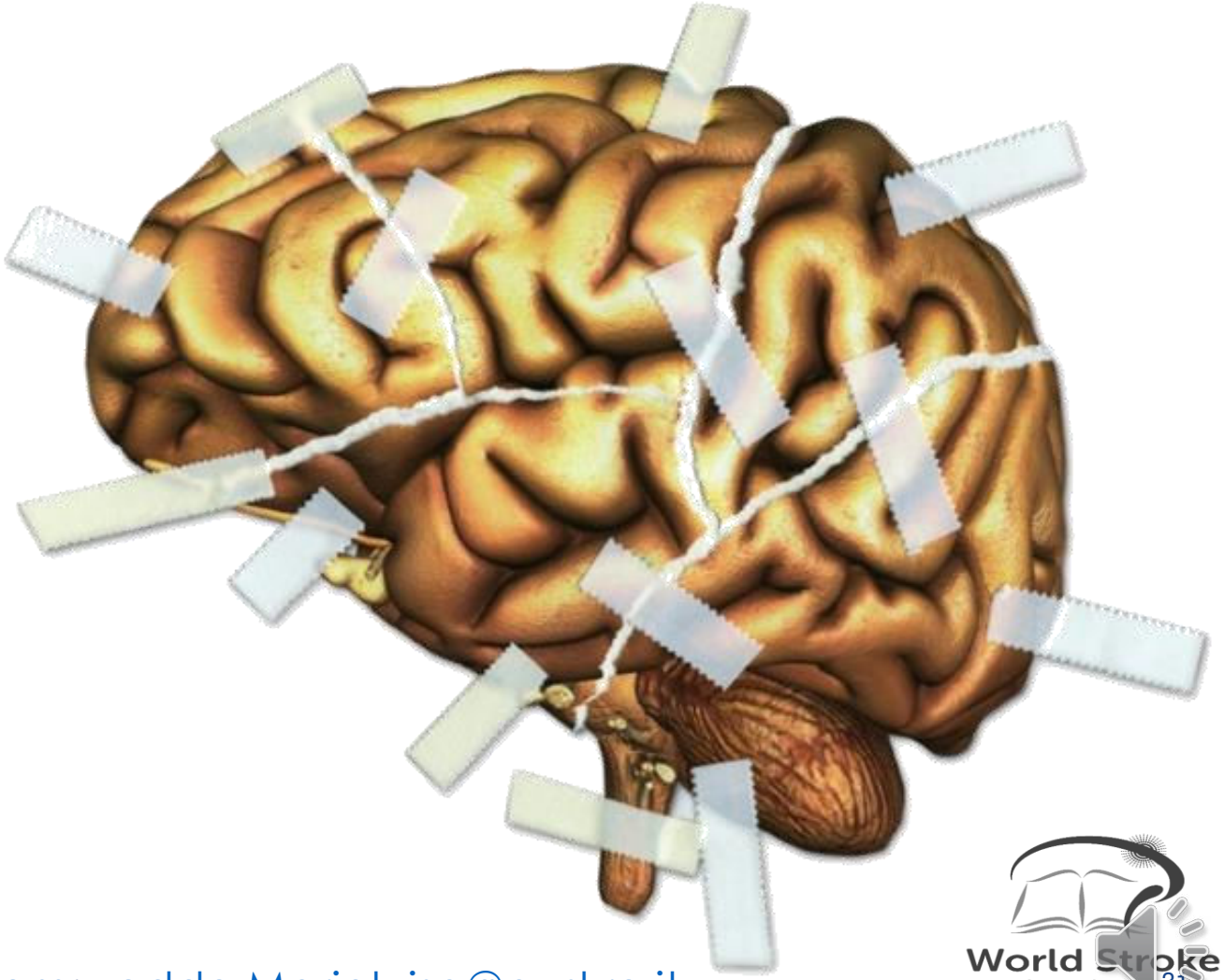
- The prevalence of major risk factors differ by sex; women have higher prevalence of hypertension and valvular heart disease, and lower prevalence of coronary heart disease, than men

- Women are more likely to present with atypical symptoms, such as weakness and fatigue, have longer duration of symptoms, and report worse quality of life and more-frequent depression than men

- Female sex is a risk factor for AF-related stroke or thromboembolism, myocardial infarction, and mortality, but has not been associated with incident heart failure or dementia.
- Increased thrombotic risk in women is multifactorial, involving hormonal changes after menopause, structural, endocrine and lifestyle/social factors and their interactions.
- Women benefit from anticoagulant treatment and that their bleeding risk is similar to men.
- Women should therefore receive equivalent treatment to men, based on the validated criteria for anticoagulation therapy.
- However, women are not represented equally in the large randomized studies and sex-related information in many fields is lacking.

Thank you for your attention





www.world-stroke.org

Marialuisa.Zedde@gmail.com; zedde.Marialuisa@ausl.re.it