

# Sex-related predictors for thromboembolic events after catheter ablation of atrial fibrillation: The Leipzig Heart Center AF Ablation Registry

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## Abstract

**Background** Females with atrial fibrillation (AF) are at increased risk for ischemic stroke but have been under-represented in AF ablation cohorts. Whether the incidence of TE in women after catheter ablation is higher is unknown. We aimed to analyze the predictive value of thromboembolic scores and other clinical variants for thromboembolism (TE) after AF catheter ablation, separately in women and men.

**Methods** TE was combined endpoint of early (within first month) and late (during long-term follow-up) stroke, transient ischemic attack, or systemic embolism. Oral anticoagulation was prescribed for 6 months after catheter ablation and discontinued if CHADS<sub>2</sub> was <2 and no AF recurrences were documented.

**Results** The study population ( $n = 2,069$ , 66 % male,  $60 \pm 10$  years; 62 % paroxysmal AF) was followed for a median of 18 months (IQR 12–29). Overall 31 TE (1.5 %) occurred with 16 events within 30 days of ablation and 15 TE during the follow-up. Fourteen females (2.0 %) and 17 males (1.2 %) suffered TE ( $p = 0.128$ ). On multivariate analysis, higher CHADS<sub>2</sub> (HR 1.65, 95 % CI 1.10–2.47,  $p = 0.015$ ), CHA<sub>2</sub>DS<sub>2</sub>-VASc (HR 1.42, 95 % CI 1.03–1.96,  $p = 0.034$ ), R<sub>2</sub>CHADS<sub>2</sub> (HR 1.76, 95 % CI

1.32–2.35,  $p < 0.001$ ) scores, and eGFR <60 ml/min/1.73 m<sup>2</sup> (HR 3.95, 95 % CI 1.23–12.7,  $p = 0.021$ ) were significantly associated with TE in men. In females, LV-EF (HR 0.95, 95 % CI 0.91–0.99,  $p = 0.021$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc score (HR 1.52, 95 % CI 1.01–2.28,  $p = 0.044$ ) remained significant predictors for TE.

**Conclusion** TE rates after AF catheter ablation are low in both genders. In females, LV-EF and CHA<sub>2</sub>DS<sub>2</sub>-VASc score and in males all three scores and renal dysfunction were associated with TE.

**Keywords** Atrial fibrillation · Catheter ablation · Thromboembolic · Females · Renal dysfunction

## Abbreviations

AF	Atrial fibrillation
eGFR	Estimated glomerular filtration rate
LA	Left atrial
TE	Thromboembolic events

## Introduction

Catheter ablation of atrial fibrillation (AF) is an effective therapy for the reduction of AF burden, improvement of symptoms, and quality of life [1, 2]. Observational and registry studies have demonstrated low annual rates of thromboembolism (stroke and systemic embolism, TE) in selected populations after AF catheter ablation, ranging between 0.5 [3] and 1.7 % [4], thus reaching event rates that are comparable to patients without AF [4, 5].

Without anticoagulation, women are at higher risk than men for AF-related TE [6–8], but results are not consistent

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[9]. Vascular complication rates of AF ablation had been recently shown to be also higher in females [10]. Since females are under-represented in AF ablation cohorts, it is unclear whether there are any sex-related differences in TE occurrence in such a specific patient population.

Recently, we demonstrated that all three stroke risk stratification scores—i.e., CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, and R<sub>2</sub>CHADS<sub>2</sub>—were associated with late TE risk in anticoagulated AF patients after catheter ablation [11]. Furthermore, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was also predictive for early (i.e., peri-interventional) TE [12].

In current study, we analyzed the predictive value of CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, and R<sub>2</sub>CHADS<sub>2</sub> scores and other clinical variants for TE after AF catheter ablation separately in women and men.

Our objective was to assess sex differences in thromboembolic risk post-ablation and the predictive risk factors (and risk scores) for thromboembolism in females and males.

## Methods

### Patients and risk scores

The study population comprised 2,069 consecutive patients with symptomatic AF who underwent catheter ablation at the Heart Center Leipzig between January 2007 and December 2011. Stroke risk was assessed using the CHADS<sub>2</sub> [congestive heart failure, hypertension, age >75 years, diabetes mellitus, and history of stroke/transient ischemic attack (2 points)] [9] and CHA<sub>2</sub>DS<sub>2</sub>-VASc [congestive heart failure, hypertension, age >75 years (2 points), diabetes mellitus, and history of stroke/transient ischemic attack (2 points)—vascular disease (history of myocardial infarction, peripheral artery disease, or vascular plaques), age 65–74 years, and sex category (female)] scores [13, 14]. The R<sub>2</sub>CHADS<sub>2</sub> score incorporated the components of the CHADS<sub>2</sub> score and also gave 2 points for renal dysfunction defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>2</sup> [15]. eGFR was calculated using the Cockcroft–Gault equation:  $(140 - \text{age}) \times \text{weight (kg)} \times (0.85 \text{ if female}) / 72 \times \text{serum creatinine (mg/dl)}$ .

The study was performed according to the Declaration of Helsinki and Institutional Guidelines. Patients provided written informed consent.

### Catheter ablation and follow-up

Left atrial catheter ablation was performed using a previously described approach [16]. Patients presenting with AF at the beginning of the procedure were electrically cardioverted, and ablation was performed during sinus rhythm (i.e., AF termination with ablation was not attempted). In all

patients, circumferential left atrial ablation lines were placed around the antrum of the ipsilateral pulmonary veins (irrigated tip catheter, pre-selected tip temperature of 48 °C, and maximum power of 30–50 W). In patients with persistent AF, additional linear lesions were added at the left atrial roof, the basal posterior wall, and the left atrial isthmus and according to low voltage areas. Ablation of complex fractionated electrograms was not performed. After circumferential line placement, voltage and pace mapping along the ablation line were used to identify and close gaps. The isolation of all pulmonary veins with bidirectional block was verified with a multipolar circular mapping catheter and was defined as the procedural endpoint. After ablation, class I and III antiarrhythmic drugs were not reinitiated, and proton pump inhibitors were added for 4 weeks.

According to the previous guidelines, oral anticoagulation was prescribed for 3–6 months after ablation and depending on the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores thereafter [17]. Because of patient preferences, lack of symptoms, and ECG recordings of sinus rhythm, it was replaced by aspirin in some patients [11].

All patients were followed in the outpatient clinic for at least 12 months after the catheter ablation. During follow-up, serial 7-day Holter ECG recordings were performed immediately and at 3, 6, and 12 months after the procedure. Additional ECGs and Holter ECG recordings were obtained when patients' symptoms were suggestive of AF.

### Outcomes

The primary endpoint of this study was the composite of ischemic stroke, transient ischemic attack (TIA), and/or systemic embolism. Ischemic stroke was a clinical diagnosis that was made on the basis of typical symptoms lasting at least 24 h. Brain imaging, which was available in all patients with peri-interventional stroke and in the vast majority of patients with later TE, was not required but was recommended for the general diagnosis of stroke. A TIA was defined as sudden-onset focal neurological deficit with duration of <24 h. Systemic embolism was defined as TE events that occurred in peripheral organs (e.g., spleen, eye) or extremities.

### Statistical analysis

Data are presented as means and standard deviation for normally distributed continuous variables and as proportions for categorical variables. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. The differences between continuous values were assessed using an unpaired two-tailed *t* test for normally distributed continuous variables, a Mann–Whitney test for skewed variables, and a Chi-square test for nominal variables.

Cox regression analyses were used to identify factors associated with TE events. Multivariable analysis, which included variables with a *p* value <0.1 found on univariable analysis, was performed to identify independent predictors of TE. In addition, we performed multivariable analyses separately for every stroke risk stratification score with adjustment for renal dysfunction (for the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores) or peripheral artery disease (for the CHADS<sub>2</sub> and R<sub>2</sub>CHADS<sub>2</sub> scores) in males. Because impaired left ventricular ejection fraction (LV-EF) could be considered as a part of all scores (as chronic heart failure), we also used separate MV analyses for clinical variables including all scores.

A *p* value of <0.05 was considered statistically significant. All analyses were performed with SPSS statistical software version 17.

**Results**

**Patient characteristics and thromboembolic events**

The clinical characteristics of 696 women (34 %) and 1,373 men (66 %) included into The Leipzig Heart Center

AF Ablation Registry are summarized in Table 1. Females were significantly older and had more often paroxysmal AF, hypertension, renal dysfunction, and previous stroke, while males had more coronary artery disease, chronic heart failure, larger LA and LV diameters as well as worse EF. Consequently, all stroke risk stratification scores were higher in women. Patients were followed for median (IQR) 18 months (12–29) (3,078 patient-years).

Overall, TE occurred in 31 patients (1.4 %). Sixteen patients (0.8 %) suffered TE within first 30 days after catheter ablation (peri-interventional TE) and 15 (0.7 %) during follow-up. There were nine ischemic strokes and seven TIAs in patients with peri-interventional TE and five ischemic strokes, eight TIAs, and two systemic embolisms during follow-up. Patients with TE had more often renal dysfunction, previous TE, and consequently higher stroke risk stratification scores than patients without TE (Table 2). There were no significant differences between patients with early and late TE (Table 2).

**Sex-related predictors of thromboembolic events**

Using three separate multivariate Cox regression (Table 3) analyses, the CHADS<sub>2</sub>, R<sub>2</sub>CHADS<sub>2</sub>, and CHA<sub>2</sub>DS<sub>2</sub>-VASc

**Table 1** Baseline characteristics of the study population

	Total <i>n</i> = 2,069	Sex		<i>p</i> value
		Women ( <i>n</i> = 696)	Men ( <i>n</i> = 1,373)	
Age, years	61 (54–68)	66 (58–70)	59 (52–67)	<0.001
AF type (paroxysmal)	1,292 (62.4)	471 (67.7)	821 (59.8)	0.001
Previous ablation	380 (18)	129 (19)	251 (18)	0.900
BMI, kg/m <sup>2</sup>	28 (25–31)	28 (25–31)	28 (26–31)	0.275
Co-morbidities				
Hypertension	1,467 (70.9)	527 (75.7)	940 (68.5)	0.001
Diabetes mellitus	314 (15.2)	115 (16.5)	199 (14.5)	0.224
Coronary artery disease	297 (14.4)	65 (9.3)	232 (16.9)	<0.001
Chronic heart failure	148 (7.2)	34 (4.9)	114 (8.3)	0.004
Peripheral artery disease	162 (7.8)	53 (7.6)	109 (7.9)	0.796
Previous TE	181 (8.7)	80 (11.5)	101 (7.4)	0.002
Renal dysfunction	144 (7.0)	66 (9.5)	78 (5.7)	<0.001
eGFR, ml/min/1.73 m <sup>2</sup>	96 (77–120)	82 (67–100)	103 (85–126)	<0.001
CHADS <sub>2</sub>	1 (1–2)	1 (1–2)	1 (0–2)	<0.001
R <sub>2</sub> CHADS <sub>2</sub>	1 (1–2)	1 (1–2)	1 (0–2)	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc	2 (1–3)	3 (2–4)	1 (1–2)	<0.001
Echocardiographic parameters				
LAD, mm	42 (39–46)	41 (37–45)	43 (39–47)	<0.001
EF, %	60 (55–65)	61 (57–65)	60 (54–65)	<0.001
LVEDd, mm	49 (45–53)	46 (43–50)	51 (47–55)	<0.001
Thromboembolic events				
Peri-interventional strokes	14 (0.7)	7 (1.0)	8 (0.6)	0.284
TE during longer follow-up	17 (0.8)	7 (1.0)	9 (0.7)	0.390
Follow-up, months	18 (12–28)	19 (12–29)	18 (12–28)	0.155

Data are presented as number (%), continuous as median (IQR)

BMI body mass index, TE thromboembolic events, eGFR estimated glomerular filtration rate, LAD left atrial diameter, EF ejection fraction, LVEDd left ventricular end-diastolic diameter

Bold values indicate significant *p* values

**Table 2** Baseline characteristics of the study population with and without TE

	Thromboembolic events		<i>p</i> value	Thromboembolic events		<i>p</i> value
	No ( <i>n</i> = 2,039)	Yes ( <i>n</i> = 31)		Early ( <i>n</i> = 16)	Late ( <i>n</i> = 15)	
Age, years	61 (54–68)	67 (57–72)	0.067	67 (55–73)	67 (57–72)	0.922
Females	682 (34)	14 (45)	0.171	7 (47)	7 (44)	0.870
Persistent AF	750 (37)	13 (41)	0.577	5 (33)	8 (50)	0.347
BMI, kg/m <sup>2</sup>	30 (25–31)	27 (24–30)	0.404	27 (24–30)	28 (24–31)	0.841
eGFR, ml/min/1.73 m <sup>2</sup>	96 (77–120)	82 (61–98)	<b>0.036</b>	81 (60–98)	82 (70–99)	0.919
eGFR <60 ml/min/1.73 m <sup>2</sup>	138 (7)	6 (19)	<b>0.006</b>	3 (20)	3 (19)	0.930
Previous ablation	374 (18)	6 (19)	0.888	3 (20)	3 (19)	0.930
Hypertension	1,442 (71)	25 (80)	0.229	10 (67)	15 (94)	0.056
Diabetes mellitus	307 (15)	7 (23)	0.247	3 (20)	4 (25)	0.739
Coronary artery disease	291 (14)	6 (19)	0.424	2 (13)	4 (25)	0.411
Chronic heart failure	145 (7)	3 (10)	0.583	1 (7)	2 (13)	0.583
Peripheral artery disease	157 (8)	5 (16)	0.083	2 (13)	3 (19)	0.682
Previous thromboembolic events	173 (9)	8 (26)	<b>0.001</b>	3 (20)	5 (31)	0.474
CHADS <sub>2</sub>	1 (1–2)	2 (1–3)	<b>&lt;0.001</b>	1 (0–2)	2 (1–3)	0.196
R <sub>2</sub> CHADS <sub>2</sub>	1 (1–2)	2 (1–3)	<b>&lt;0.001</b>	1 (0–3)	3 (1–4)	0.370
CHA <sub>2</sub> DS <sub>2</sub> -VAsc	2 (1–3)	3 (2–6)	<b>&lt;0.001</b>	2 (2–4)	3 (2–5)	0.172
LAD, mm	42 (39–46)	43 (39–49)	0.256	43 (38–48)	46 (39–51)	0.446
EF, %	60 (55–65)	60 (49–63)	<b>0.040</b>	56 (47–64)	60 (45–63)	0.770
LVEDd, mm	49 (45–53)	47 (43–52)	0.443	46 (42–52)	50 (44–55)	0.190
Follow-up, months	18 (12–28)	24 (12–35)	0.545	14 (11–24)	27 (20–35)	0.141

Bold values indicate significant *p* values

**Table 3** Clinical predictors for combined thromboembolic events in the entire population (*n* = 2,069)

Cox regression	UV			MV			Model 1	MV			Model 2	MV			Model 3
	HR	95 % CI	<i>p</i> value	HR	95 % CI	<i>p</i> value		HR	95 % CI	<i>p</i> value		HR	95 % CI	<i>p</i> value	
Age	1.04	0.997–1.08	<b>0.070</b>												
Males	0.61	0.30–1.25	0.173												
Persistent AF	1.29	0.63–2.65	0.494												
BMI	0.97	0.90–1.06	0.507												
eGFR <60 ml/min/1.73 m <sup>2</sup>	3.0	1.20–7.57	<b>0.019</b>	2.18	0.83–5.75	0.115						1.86	0.70–4.92	0.213	
PAD	2.56	0.99–6.83	<b>0.052</b>	1.99	0.75–5.29	0.170	1.99	0.75–5.29	0.170						
EF	0.97	0.94–0.99	<b>0.045</b>												
LAD	1.04	0.98–1.11	0.187												
CHADS <sub>2</sub>	1.59	1.20–2.12	<b>0.001</b>	1.50	1.11–2.04	<b>0.009</b>									
R <sub>2</sub> CHADS <sub>2</sub>	1.53	1.21–1.93	<b>&lt;0.001</b>					1.49	1.18–1.89	<b>0.001</b>					
CHA <sub>2</sub> DS <sub>2</sub> -VAsc	1.48	1.20–1.83	<b>&lt;0.001</b>									1.43	1.14–1.80	<b>0.002</b>	

UV univariable analysis, MV multivariable analysis, PAD peripheral artery disease, eGFR estimated glomerular filtration rate, EF ejection fraction, LAD left atrial diameter

Bold values indicate significant *p* values

scores were significant predictors of TE in the entire cohort.

In females (*n* = 696), using the uni- and multivariable Cox regression analyses, LV-EF (HR 0.95, 95 %CI 0.91–0.99, *p* = 0.021) and CHA<sub>2</sub>DS<sub>2</sub>-VAsc scores (HR

1.52, 95 %CI 1.01–2.28, *p* = 0.044) were significant predictors for TE (Table 4). In men, all three stroke risk stratification scores and renal function (MV models 1 and 3 for the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VAsc scores, respectively) were significant predictors for TE (Table 5).

**Table 4** Clinical predictors for combined TE events in women (*n* = 696)

Cox regression variables	UV			MV <sup>a</sup>			Model 1	MV		Model 2
	HR	95 % CI	<i>p</i> value	HR	95 % CI	<i>p</i> value	<i>p</i> value	HR	95 % CI	<i>p</i> value
Age	1.02	0.96–1.09	0.534							
Persistent AF	2.02	0.71–5.77	0.188							
BMI	0.92	0.82–1.03	0.147							
eGFR <60 ml/min/1.73 m <sup>2</sup>	0.79	0.103–6.05	0.820							
PAD	2.14	0.46–9.2	0.343							
EF	0.94	0.90–0.98	<b>0.005</b>	0.95	0.91–0.99	<b>0.021</b>				
LAD	1.09	0.90–1.20	<b>0.082</b>	1.06	0.96–1.17	0.229		1.08	0.98–1.19	0.129
CHADS <sub>2</sub>	1.29	0.81–2.07	0.290							
R <sub>2</sub> CHADS <sub>2</sub>	1.17	0.78–1.75	0.446							
CHA <sub>2</sub> DS <sub>2</sub> -VASc	1.38	0.96–2.0	<b>0.084</b>					1.52	1.01–2.28	<b>0.044</b>

UV univariable analysis, MV multivariable analysis, PAD peripheral artery disease, eGFR estimated glomerular filtration rate, EF ejection fraction, LAD left atrial diameter

<sup>a</sup> Because impaired left ventricular ejection fraction (EF) could be considered as a part of all scores (i.e., chronic heart failure), we used separate MV models for EF and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores

Bold values indicate significant *p* values

**Table 5** Clinical predictors for combined TE events in men (*n* = 1,373)

Cox regression Variables	UV			MV <sup>a</sup>			Model 1	MV			Model 2	MV			Model 3
	HR	95 % CI	<i>p</i> value	HR	95 % CI	<i>p</i> value	<i>p</i> value	HR	95 % CI	<i>p</i> value	<i>p</i> value	HR	95 % CI	<i>p</i> value	<i>p</i> value
Age	1.04	0.99–1.10	0.143												
Persistent AF	0.94	0.34–2.59	0.905												
BMI	1.03	0.95–1.11	0.495												
eGFR <60 ml/min/1.73 m <sup>2</sup>	5.95	1.99–17.8	<b>0.001</b>	3.95	1.23–12.66	<b>0.021</b>						3.62	1.09–12.03	<b>0.036</b>	
PAD	3.18	0.89–11.34	<b>0.075</b>	2.52	0.69–9.14	0.160		2.52	0.69–9.13	0.161					
EF	0.98	0.94–1.03	0.447												
LAD	1.03	0.95–1.11	0.542												
CHADS <sub>2</sub>	1.86	1.26–2.73	<b>0.002</b>	1.65	1.10–2.47	<b>0.015</b>									
R <sub>2</sub> CHADS <sub>2</sub>	1.78	1.34–2.36	<b>&lt;0.001</b>					1.76	1.32–2.35	<b>&lt;0.001</b>					
CHA <sub>2</sub> DS <sub>2</sub> -VASc	1.57	1.17–2.12	<b>0.003</b>									1.42	1.03–1.96	<b>0.034</b>	

UV univariable analysis, MV multivariable analysis, PAD peripheral artery disease, eGFR estimated glomerular filtration rate, EF ejection fraction, LAD left atrial diameter

<sup>a</sup> We performed multivariable analyses separately for every stroke risk stratification score with adjustment for renal dysfunction (for the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores) or peripheral artery disease (for the CHADS<sub>2</sub> and R<sub>2</sub>CHADS<sub>2</sub> scores)

Bold values indicate significant *p* values

**Discussion**

To the best of our knowledge, this is the largest study assessing sex-related incidence and risk factors for thromboembolic complications after AF catheter ablation with a special focus on renal dysfunction and stroke risk stratification scores. The main findings are that both early and late TE after AF catheter ablation are rare. Renal dysfunction and all three stroke risk stratification scores, i.e., CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, R<sub>2</sub>CHADS<sub>2</sub>, were

associated with TE risk in males, while impaired LV-EF and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were significant independent predictors for TE in females.

**Catheter ablation and TE**

The first study analyzing peri-interventional events and TE during follow-up associated with AF catheter ablation was presented by Oral et al. [5]. Pooling patients with early and late TE, they did not find any clinical predictors for TE;

however, this study was the first which indicated a risk reduction of TE during follow-up, despite being associated with the risk for post-interventional events.

In contrast to Oral et al. [5], we performed our analyses in much larger AF ablation cohort with >2,000 patients with longer follow-up and more thromboembolic events. Despite obvious differences in the likely pathophysiology of early versus late TE (i.e., peri-procedural anticoagulation, procedure characteristics in early TE versus anticoagulation regime in late TE), we found similar incidence of early and late TE without any significant differences among the groups (exception for hypertension). All three stroke stratification scores and renal dysfunction were significant predictors for pooled early and late TE after catheter ablation. Previously, we could not demonstrate that renal dysfunction was a risk factor for late TE occurrence in patients after AF catheter ablation [11]. The current study with selected patient cohort, however, confirms previous suggestions indicating the association between impaired renal function and thromboembolism in AF [18]. Interestingly, the new score  $R_2CHADS_2$ —with renal dysfunction as an additional risk factor—was highly significant as predictor for TE ( $p < 0.001$ ), while the “classic”  $CHADS_2$  and  $CHA_2DS_2-VASc$  scores remained associated with TE after adding renal dysfunction to the multivariable model, too. Of note, renal dysfunction itself was a predictor for TE in the whole population in MV model with  $CHADS_2$  score ( $p = 0.041$ ) but was not significant in the model with  $CHA_2DS_2-VASc$  ( $p = 0.109$ ). This is partly in accordance with recent study analyzing improvement of predictive ability of the both scores by adding renal dysfunction [19]. A possible explanation for this finding would be the association between renal dysfunction with the stroke risk factors listed within both scores.

#### Sex-related predictors for TE

Women are often an under-represented cohort in AF ablation populations. Numerous studies and observational data were performed to investigate the role of female sex as a risk factor for AF and with AF-associated co-morbidities [20] as well as thromboembolic complications [6, 8] there are no data about incidence of TE in women after catheter ablation. With current study, we demonstrate that predictors for pooled TE in men and women are different. Because men constitute the large part of ablation cohorts, it was not a surprise to find an association between renal dysfunction and thromboembolic risk scores as we have already demonstrated previously [11]. Despite more renal dysfunction in females, neither impaired eGFR nor  $R_2-CHADS_2$  score was significant predictors for pooled TE in women.

Heart failure has been associated with higher stroke rates [8, 21]. In clinical routine, impaired left ventricular ejection fraction (LV-EF) is often used as an equivalent for the heart failure. However, recently it had been shown that AF patients with heart failure and normal (preserved) LV-EF also have greater TE risk compared with only AF patients [22]. Our finding that impaired EF is significant predictor for TE in females supports previous studies. However, the novel aspect is the importance of EF for risk assessment in women after catheter ablation.

#### Female sex as a risk factor for TE

Inclusion of female sex has been shown to improve the accuracy of the  $CHADS_2$  schema [23]. Later,  $CHA_2DS_2-VASc$  score demonstrated better predictive value compared to  $CHADS_2$  score among patients enrolled in the Euro Heart Survey for AF (c-statistic = 0.61 versus 0.56, respectively) [14]. The risk for ischemic stroke in women doubles between the ages of 55 and 65, the menopausal period during which estradiol levels decrease by about 60 % [24]. Interestingly, the effect of hormone replacement therapy (HRT) on the risk for ischemic stroke in females is not consistent. While several studies demonstrated increased TE rates in females with HRT [25], no association between HRT and stroke was found among the ATRIA study population [6]. Although HRT has some known protective effects on the cardiovascular system, it also has significant pro-thrombotic effects including an up-regulation of coagulation factors and down-regulation of anti-coagulant proteins [26]. Furthermore, during menopause occurring, decline in endogenous estrogen receptors contributes to an up-regulated production of inflammatory cytokines, with further link to the hypercoagulable state [27]. Interestingly, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels are higher in females compared to men across age and degree of heart failure [28]. Of note, recently NT-pro-BNP and troponin I were shown to be associated with an increased risk of stroke in AF, independent of  $CHA_2DS_2-VASc$  score [29].

#### Limitations

This study is limited by its registry design, although we had careful follow-up data in a large consecutive series. The results of this study need to be confirmed by prospective randomized trials. Taken together, although the low event rate may affect statistical power, our findings are consistent and reveal plausible associations. Finally, TE was assumed to be thromboembolic based on clinical history and brain imaging, but other aetiologies may be possible.



In conclusion, the incidence of thromboembolic events after AF catheter ablation is low in men and women. In females, low LV-EF and CHA<sub>2</sub>DS<sub>2</sub>-VASc score were independent predictors for TE.

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**Conflict of interest** None.

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