Effect of Left Atrial Enlargement on Success Rates of Catheter Ablation for Atrial Fibrillation in Women

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ABSTRACT: **Background:** Catheter ablation (CA) is a well-established therapeutic option for patients with recurrent symptomatic atrial fibrillation (AF). Data on gender-related differences are limited with regard to baseline characteristics and long-term success rates of catheter ablation for AF.

Methods: We analyzed a cohort of 251 consecutive patients who underwent a first catheter ablation for AF in our institute during the period 2008 through 2015. All patients were followed by regular annual clinic visits, electrocardiograms, periodic 24–48 hour Holter monitoring, and loop recorders. The primary endpoint was first recurrence of AF during 1 year of follow-up.

Results: The cohort comprised 26% women (n=65), who were older (62.1 ± 9.6 vs. 54.4 ± 11.3 years, $P < 0.01$) and had a higher proportion of diabetes mellitus (23.1 vs. 5.4%, $P < 0.001$) than male patients. No other significant differences were evident. At 1 year follow-up, the cumulative survival free of AF was significantly higher in women compared with men (83% vs. 66%, respectively, log rank P value = 0.021). Subgroup analysis showed an interaction between female and small indexed left atrial diameter (LADi < 23 mm/m^2).

Conclusions: Our findings suggest that women experience a significantly lower rate of AF recurrence post-CA compared with men. This gender-related advantage appears to be restricted to women without significant left atrial enlargement. It further implies that left atrial enlargement has a stronger negative impact on post-CA AF recurrence in females than in males. Due to the relatively small sample number of females further research is warranted to validate our conclusions.

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Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with a significant burden of morbidity and mortality [1]. Epidemiological studies have demonstrated gender-related differences in the clinical manifestations, management and prognosis of AF patients [2]. While the incidence of AF is higher in men (estimated number of new cases per year 2.7 million for men and 2.0 million in women) [1], the risk of stroke and mortality rates are higher in women with AF [3] and related strokes tend to be more severe and debilitating [4].

Catheter ablation (CA) is a well-established therapeutic approach to symptomatic patients with recurrences of AF. It was endorsed after failure of or intolerance to anti-arrhythmic drug therapy and increasingly favored as first-line treatment in selected cases. However, several studies have shown that women are treated more conservatively and are less likely to be referred to CA compared to men [2]. Moreover, women are referred to CA at a later stage [5]. These findings are particularly surprising in light of the higher incidence of side effects experienced by women treated with anti-arrhythmic drugs [6]. Moreover, delayed intervention may have a detrimental effect on atrial remodeling and the likelihood of maintaining sinus rhythm [7].

Studies regarding gender-related differences in long-term success rates of CA and procedure-related complications are limited and show inconsistent results. While some reported similar outcomes, others found a higher incidence of complications and recurrence of the arrhythmia in women [5,8]. It is possible that prior conflicting data may be related to baseline differences in clinical and echocardiographic parameters between men and women prior to the index CA. Specifically, differences in baseline left atrial (LA) sizes may contribute to variances in AF recurrences in both groups. Therefore, we sought to evaluate differences between men and women referred to their first CA for the treatment of AF as well as the long-term success rates of these procedures in a contemporary cohort of unselected patients. Furthermore, we sought

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to relate those possible gender differences in outcomes to baseline clinical and echocardiographic parameters.

PATIENTS AND METHODS

The study cohort comprised 251 consecutive patients who underwent a first CA procedure for the treatment of symptomatic AF, despite anti-arrhythmic drug therapy, at the Sheba Medical Center during the period 2008 through 2015 and were included in a prospective registry. All patients with a follow-up of more than 90 days (i.e., after the blanking period) were included. Subjects were recruited and followed prospectively according to a standard protocol. Pre-specified standard forms were used to record demographics, clinical data, history and characteristics of AF, as well as history of prior treatments. The study was approved by the local institutional review board. No individual consent was required.

THE ABLATION PROCEDURE

Patients underwent pulmonary vein isolation using either radiofrequency energy delivered by a catheter with an open irrigated tip or Arctic Front Advance™ Cardiac CryoAblation Catheter (Medtronic, MN, USA). No additional ablation beyond pulmonary vein isolation was performed. When appropriate a three-dimensional mapping system (EnSite Velocity, St. Jude Medical, MN, USA; CARTO 3, Biosense Webster, CA, USA) was used for navigation. Anti-arrhythmic medications were permitted during the first 90 days following ablation (during the post-ablation blanking period), thereafter their use was discouraged but retained at the physician's discretion. Anticoagulation was continued following ablation for a minimum of 90 days. After 90 days, anticoagulation treatment was administered at the discretion of the treating clinician.

FOLLOW-UP AND OUTCOME MEASURES

All patients were evaluated at pre-determined 3 and 12 monthly clinic visits, and annually thereafter. Each visit included a review of the medical history, a 12-lead electrocardiogram and a 24-hour Holter monitor recording. Echocardiography results were also reviewed. Specifically, left atrial diameter (LAD), representing the LA anteroposterior length, measured in the parasternal long axis view using M-mode of 2D was recorded for each patient. Both the absolute values and index-to-body surface area values were recorded. Normal values for LAD, and the definition of LA enlargement, were based on the American Society of Echocardiography (≥ 4.1 cm for males and ≥ 3.9 cm for females), as was the normal value for LADi (1.5–2.3 cm/m^2) [9]. In addition, during the first 6 months following the ablation procedure, patients were supplied with an external loop recorder and were encouraged to use a telemetry service daily as well as during palpitation episodes or any other symptoms. Thereafter, in patients complaining of palpitations, external loop recorders were used as well as other standard measuring devices. The primary endpoint of the study was first event of AF or atrial flutter > 30 seconds after the blanking period and during 1 year of follow-up.

STATISTICAL ANALYSIS

A descriptive analysis was performed by presenting data as mean ± standard deviation (SD), median and interquartile range or frequency and percentage, when appropriate. All data were compared by gender, using Chi-square analysis for categorical variables, Student's *t*-test or Wilcoxon rank sum for continuous variables, as appropriate. The cumulative probabilities of AF recurrence over 2 years of follow-up by gender were graphically displayed according to the Kaplan-Meier method, with comparison of cumulative events by the log-rank test. The association between the primary endpoint and all relevant variables was evaluated by a univariate Cox proportional hazard regression analysis. Multivariate analysis aimed at identifying independent predictors of the primary endpoint was performed using Cox proportional hazards regression modeling. This included a pre-specified model controlling for gender, age above 65, non-paroxysmal AF, large left atrial diameter [upper quartile of indexed left atrial diameter (LADi)], and hypertension introduced both via single iteration and in a stepwise manner. A secondary multivariate analysis was based on the univariate analysis and included all covariates that showed a trend ($P < 0.15$) associated with AF recurrence. Lastly, we performed an interaction-term analysis to evaluate the efficacy of CA in women compared to men in pre-specified subgroups. All analyses were performed using SPSS 21.0 software (SPSS Inc., Chicago, IL). A two-sided P value < 0.05 was used for determining statistical significance.

RESULTS

Our study cohort comprised 251 patients aged 56 ± 11 years, of whom 65 (26%) were women. Most patients presented with paroxysmal AF (85%) and had a preserved left ventricular ejection fraction (LVEF) (55 ± 11%). A comparison of baseline characteristics between men and women is presented in Table 1. Aside from a few notable exceptions, the groups were generally well balanced: (a) women, compared to men, were generally older (62 ± 10 vs. 54 ± 11 years, $P < 0.01$) and had a higher proportion of diabetes mellitus (23 vs. 5%, $P < 0.001$); (b) at the time of the index procedure, fewer women were treated with anti-arrhythmic drugs (48 vs. 37%, $P = 0.017$); (c) no significant differences between the groups were found in terms of body mass index, past history of myocardial infarction and concomitant morbidities such as hypertension, cerebrovascular accident or hypothyroidism; (d) men and women were similar with regard to AF type, LA diameter, LVEF, and systolic pulmonary atrial pressure (SPAP).

Table 1. Baseline characteristics by gender and predictors of atrial fibrillation recurrence

Characteristic	Men (n=186)	Women (n=65)	*P* value
Age (years)	54.4 ± 11.3	62.1 ± 9.6	‹ 0.01
Age › 55 years	60.3	80.1	0.001
Basal metabolic index (kg/m2)	28.6 ± 4.2	28.2 ± 5.2	0.746
Obesity	31.8	33.3	0.903
Past myocardial infarction	2.2	0	0.233
Hypertension	40.3	35.4	0.482
Diabetes mellitus	5.4	23.1	‹ 0.001
Hyperlipidemia	14.5	3.1	0.013
Cerebrovascular disease	3.2	3.1	0.953
Hypothyroidism	4.8	0	0.071
Severe COPD	4.3	4.6	0.915
Heart failure	20	21.3	0.871
CHADS2, median (IQR)	1 (0–2)	1 (0–1)	0.613
CHADS2, mean ± SD	0.72 ± 0.75	0.85 ± 0.75	0.261
Anti-arrhythmic therapy			0.017
Amiodarone	14.5	20.2	
Sotalol	13.4	12.3	
Propafenone	15.1	6.2	
Flecainide	7.5	13.8	
Other	12.4	0	
None	36.6	47.7	
AF type			0.483
Paroxysmal AF	84.7	87.5	
Persistent AF	13.1	12.5	
Permanent AF	2.2	0	
Echocardiography			
LVEF (%)	55.8 ± 12.6	52.7 ± 17	0.199
LVEDD (cm)	4.8 ± 5.1	4.98 ± 5.4	0.027
LVESD (cm)	2.96 ± 0.5	3.25 ± 0.7	0.02
LA diameter (cm)	4.1 ± 0.5	4.3 ± 0.5	0.193
LA diameter enlargement*	65.4	79.7	0.038
LVEDD indexed (cm/m2)	2.48 ± 0.27	2.46 ± 0.25	0.617
LVESD indexed (cm/m2)	1.52 ± 0.27	1.59 ± 0.31	0.137
LA diameter indexed (cm/m2)	2.1 ± 0.29	2.1 ± 0.29	0.556
LA diameter indexed upper quartile (≥ 2.3 cm/m2, %)	31.5	19.3	0.079
SPAP (mmHg)	32.8	32.8	0.994

Predictors of AF recurrence by univariate Cox regression analysis			
	Hazard ratio	95%CI	*P* value
Men	1.6	1.5–2.53	0.03
Age (per year)	0.95	0.98–1.01	0.266
Age ≥ 65	0.72	0.47–1.1	0.126
Diabetes mellitus	1	0.56–1.78	0.993
Past stroke or TIA	0.89	0.33–2.41	0.890
Hyperthyroidism	1.95	0.72–5.32	0.187
Hyperlipidemia	1.85	1.13–3.02	0.014
Hypertension	0.99	0.69–1.42	0.979
Paroxysmal AF	0.9	0.54–1.48	0.671
LVEF	1.03	0.99–1.06	0.103
LVEF ≤ 45%	0.79	0.44–1.44	0.795
Diabetes mellitus	1	0.56–1.78	0.993
LA area indexed	2.13	1.13–4.03	0.02
Upper quartile of LA area indexed	1.39	0.93–2.1	0.109
SPAP	1.02	0.99–1.05	0.135
Upper quartile of SPAP	1.543	0.95–2.51	0.081
Obesity	1.13	0.58–2.2	0.708
Anti-arrhythmic medication at 12 months	0.85	0.54–1.24	0.477
Duration between AF diagnosis and CA (per month)	1.02	0.95-1.04	0.131

*LA enlargement defined as ≥ 4.1cm for males and ≥ 3.9 cm for females

Continuous variables are expressed as mean ± SD, categorical variables are expressed as (%)

AF = atrial fibrillation, BMI = basal metabolic index, COPD = chronic obstructive pulmonary disease, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, LA = left atrium, SPAP = systolic pulmonary pressure, TIA = transient ischemic attack, 95%CI = 95% confidence interval

POST-ABLATION MANAGEMENT AND FOLLOW-UP

The rates of treatments with anti-arrhythmic drugs progressively declined over the follow-up in both men and women (*P* for trend < 0.001). Notably, there was no statistically significant difference in the proportion of patients treated with anti-arrhythmic drugs between the two groups [Figure 1]. Similarly, the intensity and quality of follow-up was similar in both groups, with similar rates of attendance at each follow-up visit and monitoring test (Holter and loop recorder $P > 0.05$ for all, data not shown).

RECURRENCE OF ATRIAL FIBRILLATION

The median follow-up was 12.8 months (interquartile range 6.8–31.9 months). During the first year of follow-up, the primary endpoint, recurrence of AF or atrial flutter > 30 seconds was reached by a total of 97 patients (38.6%). When AF recurrence was compared by gender, women were shown to have higher event-free survival compared with men (83% vs. 66% at 1 year, respectively, log rank $P = 0.021$ for the overall comparison during follow-up) [Figure 2]. Notably, this difference was maintained at 2 years follow-up as well (72% vs. 51%). In a univariate analysis, male gender [hazard ratio (HR) = 1.6, $P = 0.03$], indexed LA diameter (HR = 2.1, $P = 0.03$) and hyperlipidemia were associated with recurrence of AF after the first CA [Table 1]. Notably, time from first AF diagnosis or treatment with anti-arrhythmic drugs at 12 months was not significantly associated with its recurrence [Table 1].

Figure 1. Proportion of treatment with anti-arrhythmic drug during follow-up, by gender

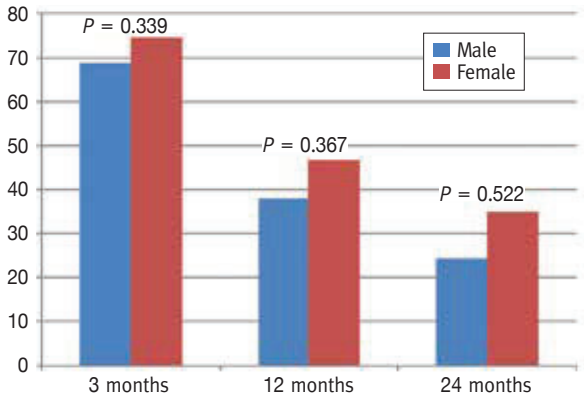
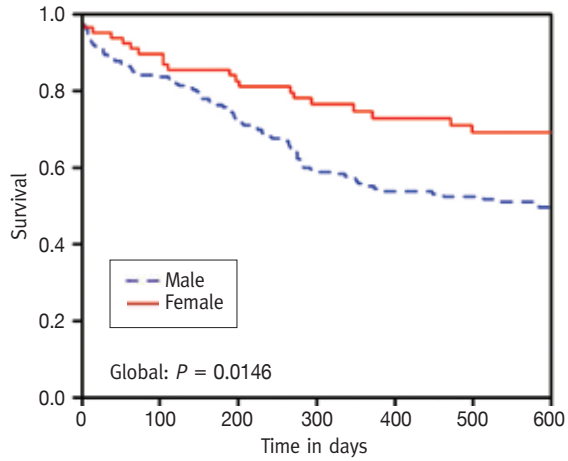


Figure 2. Cumulative survival free of atrial fibrillation, by gender



Under risk						
Male	176	148	101	81	77	66
Female	65	56	48	39	36	35

Figure 3 shows the results of a pre-specified multivariate Cox model that included the interaction between gender and baseline covariates including age > 65 years, and non-paroxysmal AF, large LADi (indexed left atrial diameter in upper quartile). The analysis showed a significant association between patient gender and AF recurrence following CA and LADi ($P = 0.018$ for gender-by-LADi interaction). The advantage observed in women persisted only in patients with a smaller atrial size at the time of the CA procedure and was annulled in the presence of LA enlargement. Hence, among patients with a LADi below the 75th percentile (< 2.3 cm/m^2) the risk for AF recurrence was significantly lower in women compared to men [HR = 0.5 (0.26–0.87)]. However, among patients with a higher indexed LA diameter this association did not reach statistical significance [HR = 1.55 (0.71–3.41)].

DISCUSSION

Our study, based on analysis of 251 unselected subjects with AF who underwent a first CA and were followed for a median of 12.8 months (interquartile range 6.8–31.9), yielded three major findings. First, women appear to be under-represented in this contemporary AF CA cohort, comprising only 26% of the study population. Compared with men, the proportion of women in our cohort was significantly low. Furthermore, this proportion is much lower than the reported rates of women with AF in the general population, indicating underutilization of CA ablation in women with AF. Second, during 1 year of follow-up, women in our cohort had significantly lower rates of AF recurrence after a first CA. Notably, this advantage was maintained at 2 years as well. Third, the reduced risk of AF recurrence following CA among women compared with men in the present study appeared to be confined only to those with a smaller atrial size, suggesting that the protective effect of female gender disappeared once the atria were markedly enlarged.

FEMALE UNDER-REPRESENTATION

A recent study, based on the largest health services organization in Israel, Clalit, which includes most of the adult population in Israel, portrays an intriguing picture of AF patients in Israel: women comprised 50% of incident non-valvular AF cases in 2004–2012, with a similar prevalence of AF in both genders [10]. These data provide a robust estimate of the proportion of women among AF patients in Israel. The fact that our cohort included only 26% female patients strongly implies differences in the management of AF in Israel. Of note, several other previous studies have reported disproportionately lower rates of women among subjects undergoing CA for the treatment of AF [8].

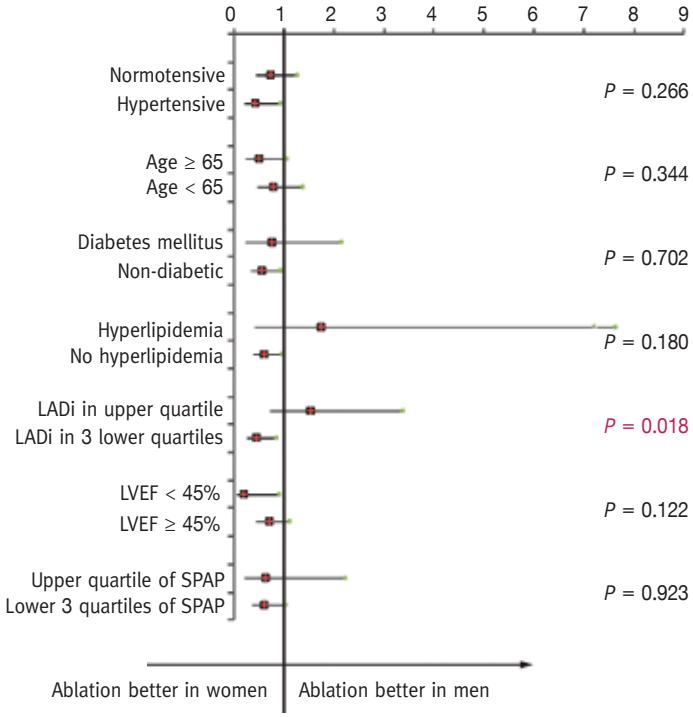
One explanation may be a tendency to treat women more conservatively and less aggressively than male patients. This trend has been noted in several other cardiovascular interventions [11]. In fact, this was also seen in various aspects of AF treatment, including poorer hypertension control [12], undertreatment with oral anticoagulants in post-stroke patients [13], and lower tendency to undergo an electrical cardioversion [14]. Another plausible explanation is that AF symptoms are more likely to be attributed to stress, panic or anxiety in women, and thus they are not treated adequately [15]. Furthermore it is possible that women are less likely to be referred to a specialist (an electrophysiologist), similar to female patients with heart failure [16], a phenomenon that may further contribute to a more conservative management.

As for other therapeutic options, one might argue that women respond to medical treatment, obviating the need for CA. The literature on this matter, however, ranges between reports of similar response to anti-arrhythmic drugs in both genders [17] and studies reporting higher rates of adverse

reactions and, therefore, lower rates of adherence to treatment in female patients [18].

Lastly, since most of the current data on CA practice have been derived from studies enrolling predominantly male patients, the ability to extrapolate success and safety rates to women is unclear. It has been argued that CA is less advisable for women, due to a lower success rate and a higher risk of procedural complications [19]. Previous studies have shown inconsistent results, with some reporting worse outcomes in women. These findings were attributed to anatomical differences and smaller heart chambers in women, making the procedure more difficult and prone to failure [8].

Figure 3. Subgroup analysis



LADi = indexed left atrial diameter, LVEF = left ventricular ejection fraction, SPAP = systolic pulmonary arterial pressure

LA ENLARGEMENT AND ITS INTERACTION WITH FEMALE GENDER

LA enlargement is a well-established risk factor for new onset of AF. LA diameter is a well-validated metric of LA enlargement and has been shown to be strongly associated with AF [20]. According to the Framingham Heart Study, every 5 mm increase in LA diameter is translated to a 39% increase in the risk of AF developing in elderly patients [21]. Furthermore, LA enlargement was shown as an independent risk factor for stroke and death in patients with and without AF [22]. The excess risk of cardiovascular mortality observed in subjects with both AF and LA enlargement is further magnified in females [23]. Of note, the upper quartile of LADi found in our study (> 2.3 cm/m^2) is similar to the upper normal limit for LADi endorsed by the American Society of Echocardiography [9]. In addition to its association with the incidence of new-onset AF, LA enlargement also adversely affects the clinical response to the various therapeutic options. Patients with enlarged LA have higher rates of AF recurrences when treated with rate control or rhythm control and following electrical or pharmaceutical cardioversions [24]. Specifically, dilated LA has been associated with failure of CA for the treatment of AF [7].

Men and women in our cohort had similar indexed LA diameters and, in accordance with previous research, an enlarged LA did indeed increase the risk of AF recurrence after CA. Interestingly, enlargement of the LA reverted the observed association between patient gender and AF recurrence. It subjected female patients with enlarged LA to more AF recurrences, nullifying the putative protection displayed in those without LA enlargement. Evidently, the interaction between female gender and large LADi (> 75th percentile) indicates the strong impact that enlargement of the LA has on the failure of CA in female patients. LA size is gender dependent, and it is widely accepted that these differences are accounted for when adjusting for body mass index [9]. Nevertheless, previous studies have shown that while this holds true for the general population, gender differences may still persist despite adjustments in cohorts of patients with cardiovascular disease [25]. Both female gender and advanced age are independently associated with larger LA. Women in our cohort were older than men and therefore were expected to have a larger LA. The LADi was, in fact, similar in both groups, implying that women in our cohort might have been subjected to less atrial remodeling or were more resistant to its effect. Both hypothetical mechanisms could explain the more favorable outcome observed in women in our study. Another possible explanation is that women in our cohort had AF over a shorter time period. Since we have no data regarding AF onset this explanation remains mere speculation.

LIMITATIONS

This was a single-center study, of modest sample size, with only 65 women. This may limit the generalizability of our results to other populations. In addition, our study has some notable limitations mostly resulting from the retrospective nature of the analysis that are inherent to the use of registries. We could only speculate the reasons for under-representation of women in our cohort. Furthermore, we had limited data regarding the time from initial diagnosis of AF. Clearly, a significant difference between the groups may account for differences in outcomes, although most studies report that women are usually referred to ablation at a later stage [5]. Our evaluation of LA size was based on diameter alone, a less accurate method than echocardiographic estimations and calculation of LA volume. As a result, we may only speculate the actual differences in LA sizes

in our cohort. Therefore, further study, based on LA volume, is warranted to validate our results. Nevertheless, left atrial diameter is a well-validated predictor of adverse outcome among AF patients. Patient follow-up in our study relied on Holter monitors and loop recorders; therefore, we may have underestimated the recurrence rate because of asymptomatic undocumented arrhythmia episodes. However, it is likely that these unnoticed episodes would be equally distributed in both groups. Lastly, it is essential to acknowledge the statistical limitations of subgroup analysis. While our results are clinically plausible and supported by current literature, further research is required to confirm their validity. A larger study, based preferably on LA volume rather than LAD, would better test the gender-specific effect of LA size on CA success. Despite these shortcomings, our study is based on a contemporary real-life unselected population followed meticulously over an extended period.

CONCLUSIONS

In a cohort of unselected subjects followed after a first attempt of catheter ablation for the treatment of atrial fibrillation, women had higher rates of arrhythmia-free survival despite being older. Significant LA enlargement nullifies the advantage we observed in women. These results may suggest that women should be referred to CA earlier, preferably before extensive left atrial remodeling has occurred.

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References

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; 129 (8): 837-47.
2. Poli D, Antonucci E. Epidemiology, diagnosis, and management of atrial fibrillation in women. *Int J Women's Health* 2015; 7: 605-14.
3. Gillis AM. Atrial fibrillation and ventricular arrhythmias: sex differences in electrophysiology, epidemiology, clinical presentation, and clinical outcomes. *Circulation* 2017; 135 (6): 593-608.
4. Findler M, Molad J, Bornstein NM, Auriel E. Worse outcome in patients with acute stroke and atrial fibrillation following thrombolysis. *IMAJ* 2017; 19 (5): 293-5.
5. Forleo GB, Tondo C, De Luca L, et al. Gender-related differences in catheter ablation of atrial fibrillation. *Europace* 2007; 9 (8): 613-20.
6. Rienstra M, Van Veldhuisen DJ, Hagens VE, et al. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. *J Am Coll Cardiol* 2005; 46 (7): 1298-306.
7. Zhuang J, Wang Y, Tang K, et al. Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. *Europace* 2012; 14 (5): 638-45.
8. Patel D, Mohanty P, Di Biase L, et al. Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm* 2010; 7 (2): 167-72.
9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28 (1): 1-39 e14.
10. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. *JAMA* 2015; 4 (1): e001486.
11. Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. *Circulation* 2007; 115 (7): 833-9.
12. Gomberg-Maitland M, Wenger NK, Feyzi J, et al. Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. *Eur Heart J* 2006; 27 (16): 1947-53.
13. Glader EL, Stegmayr B, Norrving B, et al. Sex differences in management and outcome after stroke: a Swedish national perspective. *Stroke* 2003; 34 (8): 1970-5.
14. Dagres N, Nieuwlaat R, Vardas PE, et al. 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 (5): 572-7.
15. Paquette M, Roy D, Talajic M, et al. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. *Am J Cardiol* 2000; 86 (7): 764-8.
16. Cook NL, Ayanian JZ, Orav EJ, Hicks LS. Differences in specialist consultations for cardiovascular disease by race, ethnicity, gender, insurance status, and site of primary care. *Circulation* 2009; 119 (18): 2463-70.
17. Cadrin-Tourigny J, Wyse DG, Roy D, et al. Efficacy of amiodarone in patients with atrial fibrillation with and without left ventricular dysfunction: a pooled analysis of AFFIRM and AF-CHF trials. *J Cardiovasc Electrophysiol* 2014; 25 (12): 1306-13.
18. Suttorp MJ, Kingma JH, Koomen EM, van 't Hof A, Tijssen JG, Lie KI. Recurrence of paroxysmal atrial fibrillation or flutter after successful cardioversion in patients with normal left ventricular function. *Am J Cardiol* 1993; 71 (8): 710-13.
19. Michowitz Y, Rahkovich M, Oral H, et al. Effects of sex on the incidence of cardiac tamponade after catheter ablation of atrial fibrillation: results from a worldwide survey in 34 943 atrial fibrillation ablation procedures. *Circ Arrhyth Electrophysiol* 2014; 7 (2): 274-80.
20. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol* 2003; 41 (6): 1036-43.
21. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. *Circulation* 1994; 89 (2): 724-30.
22. Patel DA, Lavie CJ, Milani RV, Shah S, Gilliland Y. Clinical implications of left atrial enlargement: a review. *Ochsner J* 2009; 9 (4): 191-6.
23. Proietti M, Raparelli V, Basili S, Olshansky B, Lip GY. Relation of female sex to left atrial diameter and cardiovascular death in atrial fibrillation: The AFFIRM Trial. *Int J Cardiol* 2016; 207: 258-63.
24. Olshansky B, Heller EN, Mitchell LB, et al. Are transthoracic echocardiographic parameters associated with atrial fibrillation recurrence or stroke? Results from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *J Am Coll Cardiol* 2005; 45 (12): 2026-33.
25. Zemrak F, Ambale-Venkatesh B, Captur G, et al. Left atrial structure in relationship to age, sex, ethnicity, and cardiovascular risk factors: MESA (Multi-Ethnic Study of Atherosclerosis). *Circ Cardiovasc Imaging* 2017; 10 (2).

"Those who dream by day are cognizant of many things that escape those who dream only at night"

Edgar Allan Poe (1809–1849), American writer, poet, editor and literary critic