

Sex-gender and atrial fibrillation treatment in the AntiThrombotic Agents in Atrial Fibrillation (ATA-AF) study

Cecilia Politi,¹ Tiziana Ciarambino,¹ Letizia Riva,² Stefania Frasson,³ Donata Lucci,⁴ Gualberto Gussoni,³ Lucio Gonzini,⁴ Mauro Campanini,⁵ Michele Gulizia,⁶ Giuseppe Di Pasquale,² Giovanni Mathieu,⁷ on behalf of ATA-AF Steering Committee and Investigators

¹Department of Internal Medicine, F. Veneziale Hospital, Isernia; ²Unit of Cardiology, Maggiore Hospital, Bologna; ³Clinical Research Department, FADOI Foundation Research Center, Milan; ⁴ANMCO Research Centre, Florence; ⁵Department of Internal Medicine, Maggiore della Carità Hospital, Novara; ⁶Unit of Cardiology, Garibaldi-Nesima Hospital, Catania; ⁷Department of Internal Medicine, E. Agnelli Hospital, Pinerolo (TO), Italy

ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia. This analysis aimed to determine the sex-gender differences in patients with AF enrolled in the observational AntiThrombotic Agents in Atrial Fibrillation (ATA-AF) study. The study was conducted in 360 centers in Italy. During a 4-week period, all consecutive inpatients and outpatients aged ≥ 18 years, with a documented primary or secondary diagnosis of AF, were included. A total of 7148 patients (47% females) were enrolled. Females were significantly older, they more frequently needed assistance and were affected by severe cognitive impairment. The preferred anti-arrhythmic strategy in both genders was heart rate control (females: 54.7%, males: 48.4%, $P < 0.0001$). Among non-valvular AF patients ($n=4845$, females=2139), females displayed greater prevalence of $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ (96.1% vs 80.7%; $P < 0.0001$) and $\text{CHADS}_2 \geq 2$ (68.2% vs 60.4%; $P < 0.0001$). More females were at high risk of bleeding (31.3% vs 26.1%; $P < 0.0001$). Oral anticoagulants (OAC) were used in 55.5% of non-valvular AF patients, less frequently in females (50.9% vs 59.2%; $P < 0.0001$). High hemorrhagic risk [odds ratio (OR) 5.94, 95% confidence interval (CI) 4.70-7.51], paroxysmal AF (OR 3.88, 95% CI 3.11-4.83), cognitive (OR 2.18, 95% CI 1.57-3.02) and functional impairment (OR 1.31, 95% CI 1.02-1.67) were significantly related with non-prescription of OAC, while age > 75 was not (1.00, 95% CI 0.79-1.26). This study defines sex-gender differences in AF patients, including lower OAC prescription in females despite of higher thrombotic risk. Concomitant higher hemorrhagic risk and other characteristics that were more frequent in females (*i.e.*, severe cognitive and functional impairment) may at least partly explain this trend towards gender-related under-prescription of OAC.

Correspondence: Tiziana Ciarambino and Cecilia Politi, Department of Internal Medicine, F. Veneziale Hospital, via Sant'Ippolito, 86170 Isernia, Italy. Tel.: +39.0865.442306. E-mail: tiziana.ciarambino@gmail.com; cecilia.politi@asrem.org

Key words: Atrial fibrillation; sex-gender; oral anticoagulants; $\text{CHA}_2\text{DS}_2\text{-VASc}$ score.

Acknowledgements: the authors thank all participating centers for patients' enrolment and data collection, Barbara Bartolomei and Andrea Lorimer (Heart Care Foundation - ANMCO Research Center), Antonella Valerio and Davide Ghilardi (FADOI Foundation Research Center) for their activity of study management.

See online Appendix for Members of the AntiThrombotic Agents in Atrial Fibrillation (ATA-AF) Steering Committee and Investigators.

Received for publication: 9 September 2015.
Accepted for publication: 8 October 2015.

This work is licensed under a Creative Commons Attribution NonCommercial 4.0 License (CC BY-NC 4.0).

©Copyright C. Politi et al., 2016
Licensee PAGEPress, Italy
Italian Journal of Medicine 2016; 10:207-212
doi:10.4081/ijm.2016.649

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 3 million people in the United States.¹ The lifetime risk for developing AF for men and women aged more than 40 years is 1:4, respectively.² A rising number of papers analyze sex-gender differences in treatment and mortality among patients with AF.³⁻⁵ Women with AF seem to have an increased risk for cardiovascular events, including stroke⁶⁻⁹ and underutilization of oral anticoagulant (OAC) treatment among women has been suggested to be a contributing factor.¹⁰

The present study aimed to evaluate the sex-gender differences in Italian patients with AF enrolled in the large observational AntiThrombotic Agents in Atrial Fibrillation (ATA-AF) study.

Materials and Methods

The observational ATA-AF study was conducted by 360 hospital centers [164 Cardiology (C) and 196 Internal Medicine (M) wards] from May to July 2010. During a period of 4 weeks for each center, all inpa-

tients and patients visited during outpatient clinic activity aged ≥ 18 years, with a documented primary or secondary diagnosis of AF, were included in the study. The diagnosis of AF required confirmation by electrocardiogram. The only exclusion criterion was AF after acute coronary syndrome or cardiothoracic surgery. The therapeutic strategies (antithrombotic, antiarrhythmic) were selected by the participating physicians. All patients gave written informed consent, and the Institutional Review Boards of all participating centers were notified according to the Italian rules for observational research. Details of the study, the subjects' characteristics and the main analyses have been reported in previous papers.^{11,12} In this *post hoc* evaluation, the objective was to determine the sex-gender differences in the treatment of Italian patients with AF enrolled in this study.

Statistical analysis

Descriptive analyses were reported for categorical and continuous variables. In non-valvular atrial fibrillation (NVAF) patients, the association between the non-prescription of oral anticoagulants and potential predictors, including age (>75 vs ≤ 75 type of atrial fibrillation (paroxysmal vs no paroxysmal), need for assistance, cognitive impairment (cognitive deficit/dementia), and modified HASBLED score (without labile international normalized ratio, score ≥ 3 vs < 3) was assessed by multivariable logistic regression analysis.

Results

Clinical characteristics and comorbidity profile

Overall, 7148 patients with AF (47% female and 53% male) were enrolled in the ATA-AF study. Sex-gender related differences in the clinical characteristics of enrolled patients are reported in Table 1. The median age of these patients was 79.0 years for female and 74.0 years for male ($P < 0.0001$). Compared with male patients, females were more frequently living alone and needed all-day-long assistance.

Statistically significant differences were observed between genders for the majority of clinical characteristics of the study population. In details, female patients displayed greater prevalence for arterial hypertension, hypertensive heart disease, angina pectoris, previous pulmonary embolism, anemia, cognitive decline/dementia, hyper- or hypothyroidism, and history of falls. With respect to AF, paroxysmal AF and valvulopathy were more frequent among female patients.

Therapeutic strategies

The preferred anti-arrhythmic strategy in ATA-AF study was heart rate control (51.4%) vs rhythm control (27.3%) in both male and female subjects. Heart rate

control was chosen in 54.7% of female, compared to 48.4% of male subjects (Table 2, $P < 0.0001$), while the rhythm control was preferred in 29.5% of male compared to 25.1% of female subjects ($P < 0.0001$). Compared with males, female patients less frequently underwent electrical cardioversion, as well as ablation and implantation or revision of pacemaker (PMK)/implantable cardioverter defibrillator (ICD); on the other hand, pharmacological cardioversion was more frequently performed in females.

At discharge, amiodarone and angiotensin-converting-enzyme inhibitor (ACE-I) were preferred in male subjects, while angiotensin receptor blockers (ARB) and diuretics were more frequently prescribed in female subjects.

Antithrombotic therapy

Globally speaking, OAC (vitamin K antagonists) were used in 58.8% of the overall study population, with a decreasing trend from North to South of Italy (63.0% Northern, 57.2% Central, and 54.1% Southern Italy; $P < 0.0001$). By considering the subgroup of NVAF patients ($n = 4845$, females = 2139), OAC were used in 55.5% of cases. In non-valvular AF patients, oral anticoagulants were less frequently prescribed in females than in males (50.9% vs 59.2%; $P < 0.0001$). On the other side, significantly more female than male patients received antiplatelet drugs (40.0% vs 32.4%; $P < 0.0001$) (Table 3). In the subgroup of NVAF patients, the CHADS₂ and CHA₂DS₂-VASc scores were used as risk stratification tool to assess indication for antithrombotic therapy. Compared with males, prevalence of CHA₂DS₂-VASc ≥ 2 (96.1% vs 80.7%; $P < 0.0001$) and CHADS₂ ≥ 2 (68.2% vs 60.4%; $P < 0.0001$) was higher in female patients. On the other hand, more females than males in the ATA-AF population were considered at high risk of bleeding according to the study specific modified HASBLED score, being 31.3% and 26.1% the frequencies of patients with score ≥ 3 among females and males, respectively ($P < 0.0001$).

Potential predictors for non-prescription of OAC in the group of NVAF female patients have been evaluated by multivariable analysis, the results of which are reported in Figure 1. High hemorrhagic risk [odds ratio (OR) 5.94, 95% confidence interval (CI) 4.70-7.51], paroxysmal AF (OR 3.88, 95% CI 3.11-4.83), cognitive dysfunction (OR 2.18, 95% CI 1.57-3.02) and need for assistance (OR 1.31, 95% CI 1.02-1.67) were independently and significantly related with non-prescription of OAC, while age > 75 years was not (1.00, 95% CI 0.79-1.26).

One-year follow-up

A subgroup of 1360 patients (females 45.2%) was observed for one year following enrolment. There

Table 1. Clinical characteristics and comorbidity profile. Values are expressed as percentages, unless otherwise stated.

Clinical characteristics	Male (n=3788)	Female (n=3360)	P value
Age (median)	74.0	79.0	<0.0001
Living alone	12.0	18.8	<0.0001
Need all-day-long assistance	7.7	12.7	<0.0001
BMI ≥ 30	18.5	20.4	<0.0001
Active smokers	11.0	3.5	<0.0001
Abuse of alcohol	4.8	0.5	<0.0001
Comorbidities and medical history			
Arterial hypertension	73.0	77.6	<0.0001
Hypercholesterolemia	30.1	27.4	0.01
Hypertensive heart disease	42.0	47.4	<0.0001
Ischemic cardiopathy	24.1	15.2	<0.0001
Heart failure	29.6	25.6	0.0002
Dilated cardiomyopathy	16.7	8.8	<0.0001
Pulmonary embolism	1.3	2.2	0.002
Cerebrovascular disease	13.7	15.7	0.02
COPD	25.6	15.4	<0.0001
Chronic kidney disease	20.2	16.5	<0.0001
Anemia	13.9	17.8	<0.0001
Hyperthyroidism	4.2	6.1	0.0003
Hypothyroidism	4.7	10.9	<0.0001
Sleep apnea	2.2	0.9	<0.0001
Cognitive decline/dementia	8.0	13.1	<0.0001
Previous frequent falls	1.9	3.7	<0.0001
Clinical profile relevant to AF			
AF at admission to hospital	50.7	49.0	<0.05
Lone AF	2.3	1.2	0.0003
Paroxysmal AF	22.5	25.6	<0.0001
Valvulopathy	29.4	37.2	<0.0001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation.

Table 2. Therapeutic strategies.

	Male	Female	P value
Anti-arrhythmic strategies			
Heart rate control (%)	48.4	54.7	<0.0001
Rhythm control (%)	29.5	25.1	<0.0001
Previous electrical cardioversion (%)	32.5	29.9	0.03
Pharmacological cardioversion	44	61	<0.0001
Previous ablation (%)	4.6	3.0	0.001
Implantation or revision PMK/ICD (%)	3.9	2.9	0.01
Amiodarone (%)	13.4	10.0	<0.0001
Cardiovascular therapies			
ACE-I (%)	38.9	33.4	<0.0001
ARBs (%)	25.8	29.3	0.001
Diuretics (%)	56.0	61.4	<0.0001

PMK/ICD, pacemaker/implantable cardioverter defibrillator; ACE-I, angiotensin-converting-enzyme inhibitor; ARBs, angiotensin receptor blockers.

were no statistically significant gender differences concerning the rate of ischemic stroke (0.8% in females vs 1.9% in males, P=0.09) or hemorrhagic events (0.6% vs 0.1%, P=0.12), nor for all-cause (12.0% vs 8.9%, P=0.07) or cardiovascular death (5.3% vs 4.5%, P=0.56).

The discontinuation rate of warfarin was slightly but significantly higher in male than in female subjects (16.7% vs 12.5%; P<0.001).

Discussion

The ATA-AF study represents one of the largest real-life studies concerning clinical profile and man-

agement of patients with atrial fibrillation. In this *post hoc* analysis we have shown some differences due to sex-gender. Female patients were older than males, with higher level of comorbidity and frailer (more frequently affected by cognitive decline/dementia, requiring all-day long assistance and living alone). Thrombotic risk, stratified by CHADS₂ and CHA₂DS₂-VASc scores, was higher in female than in male patients, as well as the hemorrhagic risk as assessed by a study specific modified HASBLED score. Fewer female patients were treated with oral anticoagulants, independently of age, but in relation to other characteristics that were more frequently associated with female patients in our study population (*i.e.*, severe

Table 3. Thrombotic and hemorrhagic risk profile, and antithrombotic therapy, in non-valvular patients.

Scores	Male (n=2706)	Female (n=2139)	P value
CHA ₂ DS ₂ -VASc ≥2 (%)	80.7	96.1	<0.0001
CHADS ₂ ≥2 (%)	60.4	68.2	<0.0001
Modified HASBLED (%)	26.1	31.3	<0.0001
Antithrombotic therapy			
OAC (%)	59.2	50.9	<0.0001
Antiplatelet drugs (%)	32.4	40.0	<0.0001

OAC, oral anticoagulants.

Variable
Effect

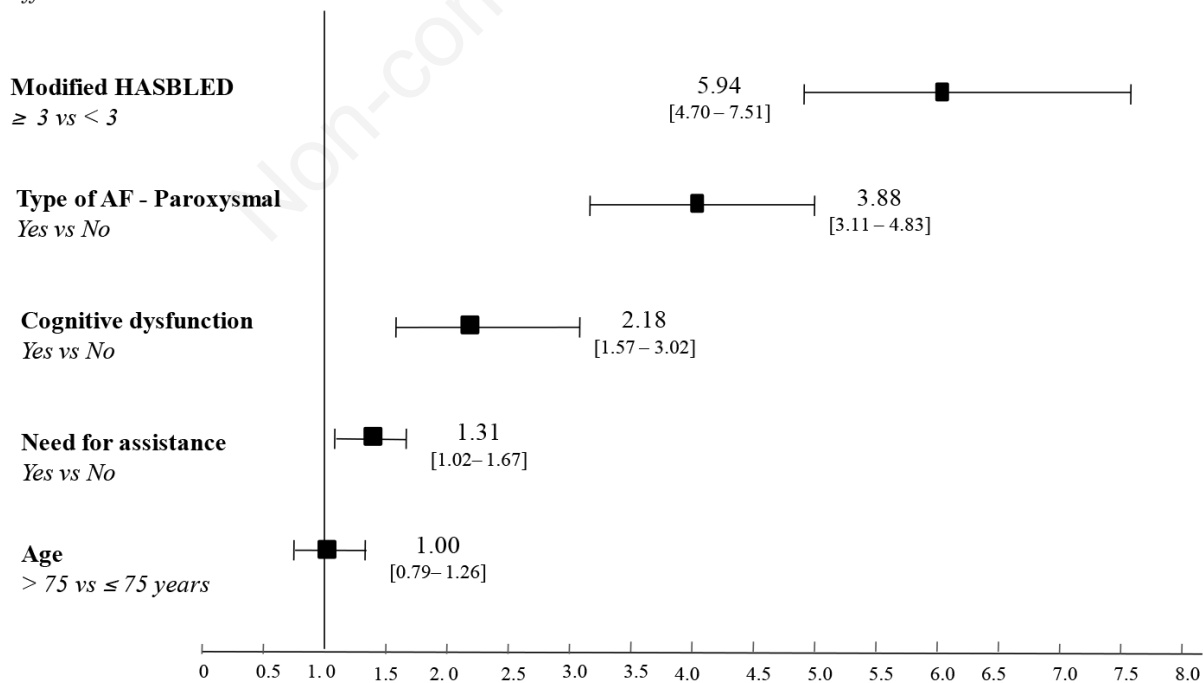


Figure 1. Predictors of non-prescription of oral anticoagulants in female non-valvular atrial fibrillation (AF) patients. Results of multivariable logistic regression analysis.

cognitive and functional impairment). Heart rate control was significantly more performed in females than males, while the contrary occurred for rhythm control. Finally, female patients less frequently underwent invasive therapeutic strategies (electrical cardioversion, ablation, implantation or revision PMK/ICD).

The demographic and clinical profile of female and male patients in the ATA-AF study show a markedly different being. As previously reported, female subjects were older, had worse functional and cognitive conditions, and high rate of comorbidities.³⁻¹³

It has been already reported that female patients have an increased risk of ischemic cardiovascular events, associated with AF.⁶⁻⁹ Shroff *et al.* raised concern about a *gender gap* in prescription of warfarin among women, despite a paradoxically higher hazard of ischemic stroke.¹⁴ In agreement with other studies^{5,15,16} and in contrast with recent reports,¹⁷ our female subjects were less frequently treated with OAC therapy. To this regard, aging in social isolation and cognitive decline have been reported as potential reasons,¹⁸⁻²⁰ but in our study advanced age was not independently related to non-prescription of OAC. Despite the risk of stroke is similar for paroxysmal versus persistent/permanent AF,^{21,22} our data show that AF type determined OAC treatment decision, since paroxysmal AF was a strong negative predictor of OAC prescription in female patients. As pointed out by Volgman *et al.*, the reluctance of physicians and patients to use warfarin anticoagulation in women may be due to an increased risk of bleeding;²³ this was also the case in our study population, being high HAS-BLED score the strongest predictor of non-prescription of vitamin K antagonists. An unresolved question is the minor OAC prescription in Southern than in Northern Italy, since no differences were detected in the characteristics of patients in relation to their geographical residence. A possible explanation for this finding is related to a more efficient monitoring system for patients of Northern Italy, allowing an easier and more accurate management of patients receiving vitamin K antagonists.

Gender disparities and underutilization of therapies have been previously reported for diagnostic and therapeutic procedures in women with cardiovascular diseases.²⁴ Lip *et al.* have reported that, among patients with typical AF symptoms, there was no gender-related difference in the choice of rate or rhythm control.¹⁷ In ATA-AF patients, heart rate control was the preferred anti-arrhythmic strategy, with higher prevalence in females. Furthermore, female patients of our study population had received less previous electrical cardioversion, previous ablation, implantation or revision of PMK/ICD than male patients. Gevaert *et al.* have not observed sex disparities in the application of evidence-based AF therapies before and

during admission and at discharge, with the exception of aldosterone receptor antagonists at discharge, which were more prescribed to women.²⁵ In our analysis we reported that ARBs and diuretics were prescribed more to female subjects, while ACE-I and amiodarone were more frequently used in males.

Conclusions

Female patients with atrial fibrillation are older, with more frequent cognitive and functional impairment, and higher rate of comorbidity than males. Prevention of thromboembolic complications in AF patients is an imperative clinical need. Data from literature raise concern about a *gender gap* in prescription of oral anticoagulants among women, despite a paradoxically higher hazard of thromboembolic complications. These findings seem confirmed by the result of our study. However, concomitant higher hemorrhagic risk and other characteristics that were more frequent in female patients of our study population (*i.e.*, severe cognitive and functional impairment) may at least partly explain this trend towards gender-related under-prescription of oral anticoagulants.

References

1. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009;104:1534-9.
2. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042-6.
3. Dagues 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;49:572-7.
4. Avgil Tsadok M, Jackevicius CA, Rahme E, et al. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA* 2012;307:1952-8.
5. Carlsson AC, Wändell P, Sundquist K, et al. Differences and time trends in drug treatment of atrial fibrillation in men and women and doctors' adherence to warfarin therapy recommendations: a Swedish study of prescribed drugs in primary care in 2002 and 2007. *Eur J Clin Pharmacol* 2013;69:245-53.
6. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113:359-64.
7. Friberg J, Scharling H, Gadsbøll N, et al. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol* 2004;94:889-94.
8. Friberg L, Benson L, Rosenqvist M, Lip GY. Assess-

- ment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ* 2012;344:e3522.
9. Cove CL, Albert CM, Andreotti F, et al. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. *Thromb Haemost* 2014;111:385-91.
 10. Gage BF, Boechler M, Doggett AL, et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. *Stroke* 2000;31:822-7.
 11. Di Pasquale G, Mathieu G, Maggioni AP, et al. Current presentation and management of 7148 patients with atrial fibrillation in cardiology and internal medicine hospital centers: The ATA AF study. *Int J Cardiol* 2013;167:2895-903.
 12. Gussoni G, Di Pasquale G, Vescovo G, et al. Decision making for oral anticoagulants in atrial fibrillation: the ATA-AF study. *Eur J Intern Med* 2013;24:324-32.
 13. Fang MC, Singer DE, Chang Y, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the Anticoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005;112:1687-91.
 14. Shroff GR, Solid CA, Herzog CA. Atrial fibrillation, stroke and anticoagulation in Medicare Beneficiaries: trends by age, sex, and race, 1992-2010. *J Am Heart Assoc* 2014;3:e000756.
 15. Sabouret P, Depret-Bixio LD, Cotte FE, et al. Sex differences in stroke prevention in atrial fibrillation in French primary care. Results of the AFIGP (Atrial Fibrillation In General Practice) Database. *Clin Res Cardiol* 2014;103:887-93.
 16. Stock EO, Redberg R. Cardiovascular disease in women. *Curr Probl Cardiol* 2012;37:450-526.
 17. Lip GYH, Laroche C, Boriani G, et al. Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Programme Pilot survey on Atrial Fibrillation. *Europace* 2015;17:24-31.
 18. Sullivan RM, Zhang G, Zamba G, et al. Relation of gender-specific risk of ischaemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). *Am J Cardiol* 2012;110:1799-802.
 19. Goli NM, Thompson T, Sears SF, et al. Educational attainment is associated with atrial fibrillation symptom severity. *Pacing Clin Electrophysiol* 2012;35:1090-6.
 20. Ball J, Carrington MJ, Wood KA, et al. Women versus men with chronic atrial fibrillation: insights from the standard versus atrial fibrillation specific management study (SAFETY). *PLoS One* 2013;8:e65795.
 21. Hart RG, Pearce LA, Rothbart RM, et al. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. *J Am Coll Cardiol* 2000;35:183-7.
 22. Lip GY. Paroxysmal atrial fibrillation, stroke risk and thromboprophylaxis. *Thromb Haemost* 2008;100:11-3.
 23. Volgman AS, Manankil MF, Mookherjee D, Throhman RG. Women with atrial fibrillation: greater risk, less attention. *Gend Med* 2009;6:419-32.
 24. Lansky AJ, Hochman JS, Ward PA, et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. *Circulation* 2005;111:940-53.
 25. Gevaert SA, de Bacquer D, Willems AM, et al. Gender differences in the management and outcome of atrial fibrillation complication acute heart failure. *J Card Fail* 2014;20:431-7.