Atrial fibrillation and female sex

Atrial Fibrillation and Female gender

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Abstract

Atrial Fibrillation (AF) is the most common supraventricular arrhythmia. Its prevalence increases with age and preferentially affects male patients. Over 75 years of age, however, being female patients more prevalent, the absolute number of patients affected is similar between genders. Despite this few data are available in literature concerning gender related differences in AF patients. The present systematic review therefore considers comorbidities, referring symptoms, quality of life, pharmacological approaches and transcatheter ablation in female rather than male AF patients in search of parameters that may impact on treatment outcome. In brief, female AF patients more commonly present comorbidities leading to an higher prevalence of persistent AF, moreover they refer to hospital care later and with a longer disease history. AF symptoms relate to low quality of life in female patients, in fact AF paroxysm usually present higher heart rate leading to preferentially adopt a rate rather than a rhythm control strategy. Female AF patients present an increased risk of stroke, worsened by the lower OAT prescription rate related to the concomitant higher haemorrhagic risk profile. Transcatheter ablation is under used in female patients and, on the other side, they are more commonly affected by antiarrhythmic drug side effects.

List of abbreviation

A&P, ablate and pace; AF, Atrial Fibrillation; AAD, antiarrhythmic drugs; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; EF, ejection fraction; HF, heart failure; NOAC, new oral anticoagulant; OR, odd ratio; PVI, pulmonary vein isolation; RA, right atrium; SCI, silent cerebral ischemia; TC, transcatheter; TE, thromboembolic.

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia and, given the progressive ageing of the population, its prevalence is expected to increase. That AF represents a relevant topic is proved by the high number of publications produced every year, however few female patients are included in the available clinical randomized trials and guidelines [1], [2], [3] do not specifically address this subgroups of patients [4], [5] . We therefore performed the present systematic literature review on AF gender related differences to highlight characteristics, AF related risk, therapeutic strategies and outcomes in female suffering AF.

Epidemiology

Atrial Fibrillation prevalence increases with ageing [6],with 50% of AF patients having more than 75 years[7]. Atrial fibrillation can represent an epiphenomena of an underling structural cardiomyopathy but can also occur in patients without any structural heart disease (known as Lone AF). The Framingham Heart Study [8], a population based prospective study on 8725 pts monitored, between 1968 and 1999, the life time risk of AF onset. At 40 years of age the AF onset risk for both genders was 1 in 4. Considering patients without history of heart failure (HF) or ischemic cardiomyopathy (CAD), AF onset risk decreased to 1 in 6. In the Copenhagen City Heart Study [9], instead, considering patients aged 50-89 years, during a period from 1976 to 1994, male sex related to a more than 2 fold AF prevalence increase.

Gender related differences in patients referring for AF.

Comordibities. Several studies have reported gender related differences, concerning clinical characteristics, in patients referring for AF, but overall female prevalence in each study is low (mean female gender prevalence around 33%). In the AFFIRM study [10] (Atrial Fibrillation Follow-up Investigation of Rhythm Management), a prospective study based on 2033 patients, female patients were significantly older (71.8 yrs vs 68.4 yrs, p value < 0.001) with a greater prevalence of valvular cardiomyopathy (p value < 0.001). On the other side male gender was preferentially associated with CAD and HF (both p value < 0.001). In the CARAF study [11] (Canadian Registry of Atrial Fibrillation), a prospective study based on 899 patients aiming to evaluate long-term AF progression rate, arterial hypertension and disthyroidism were preferentially observed in female patients. In the RACE study [12] (Rate Control versus Electrical Cardioversion), a prospective randomized study based on a sample size of 522 patients, female patients were preferentially older (71 yrs vs 67 yrs, p value < 0.001) with a greater prevalence of hypertension and diabetes (both p value < 0.001) and similar results were disclosed in other retrospective studies [13], [14], [15]. Considering the Euro Heart Survey on Atrial Fibrillation [16], a multicentric study based on 5333 AF patients, female patients were older (70 yrs vs 64 yrs, p value < 0.001) with a greater prevalence of diabetes, hypertension, disthyroidism and valvular cardiomyopathy (p value < 0.001). Eventually a recent survey involving 3119 AF patients [17] (40% female), confirmed female gender patients were older, with an higher hypertension prevalence (p value < 0,001) and with an higher prevalence of valvular cardiomyopathies.

The explanation of why female AF patients present more comorbidities is not clear most likely is the results of multiple factors. An attitude to seek for medical advice later compared to males, finally presenting with longer arrhythmia history, may play a role. On the other side the higher prevalence of cardiomyopathies reported in female patients is surely related to the

older age of this subgroups of patients anyhow evidently more affected from degenerative valvulopathies (e.g. rheumatic) than males. Eventually the hormonal asset plays an important role [18], [19]. While estrogen receptors in the cardiac tissue have shown to slow right atrium (RA) conduction and prolong RA refractoriness [20], Progesterone seems to oppose these effects [21]. In fact, higher arrhythmia occurrence has been reported in the luteal phase of the menstrual cycle [22], [23] and several balances may be expected to change in menopause. Table 1 summarizes main gender related differences in AF patients. The evident greater comorbidities background present in female AF patients, in fact, leads to an increased arrhythmia burden determining a greater proportion of persistent/permanent AFcompared to the male counterpart [14,15] .

Symptoms and quality of life. Paquette et al[13] reported that, at referral, female gender was related to a lower quality of life due to higher severity of AF symptoms. Similar results are reported in the study by Lip et al [17]. By consequence the rhythm control strategy proposed, determined a significant improvement, measured by the Physical Health (SF36) questionnaire, especially within female patients. One main reason of the impact of symptoms in females is the higher atrio-ventricular penetrance of the arrhythmia, leading to the faster ventricular heart rate during paroxysms, compared to males [11],[24]. The Canadian Trial of Atrial Fibrillation[25] reported that on a sample size of 234 patients (41% female), female gender was associated with worst functional capacity (DASI score, p value < 0.01), physical performance (SF36, p value < 0.01) and symptoms burden (frequency, p value < 0.01; severity, p value $= 0.04$).Also in this study rhythm control strategy, achieving a reduction of AF paroxysms, brought to quality of life improvement already after three months of treatment.

Within the factors influencing quality of life perception of AF female patients, surely anxiety/depression need to be taken into account [26]. Based on available studies it cannot be excluded that gender related differences concerning QoL perception may relate to higher

sensitivity toward the disease and/or to a different perception of the illness. In fact, female patients do have higher tendency to somatization [27], suggesting that, at least part of the gender related differences, may be of psychosomatic nature.

Thromboembolic and hemorrhagic risk profile. Female gender is associated to a greater AF related thromboembolic (TE) risk. In fact, since the study by Wolf et al [28] demonstrated that TE events were significantly higher in female than in male AF patients (25% vs. 10%) female gender has been included in the Framingham stroke risk scheme [29] and in another contemporary prognostic score [30]. A greater TE event rate in female patients was reported, in addition, in The Euro Heart Survey on Atrial Fibrillation [16] (odds ratio 1.83, p value = 0.019). In The ATRIA study [31], a prospective multicenter study on 17974 pts, after removing other TE risk factors (age, previous stroke, hypertension, HF, CAD, diabetes and estrogens replacement therapy), without assuming oral anticoagulants (OAT), female gender related to a greater TE event rate (3.5% vs. 1.8%; relative risk= 1.6; Figure 1).

Based on these evidences Lip et al [32] proposed the Birmingham 2009 scheme (acronym CHA_2DS_2 –VASc) in which female gender was considered, for the first time, an independent stroke risk factor for AF patients. Many recent studies [33] and meta-analysis [34] have confirmed this theory and have added that the risk is enhanced in older female patients [35] and despite similar levels of anticoagulation [36]. Unfortunately the increased TE risk is also associated with an higher mortality [37]. To date, the only limit is that these conclusions are based on clinical trials involving preferentially patients from western countries. Experiences in eastern countries did not lead to similar results. Inoue H et al [38], followed for 2 years 7406 Japanese patients (29% female gender) appropriately treated with OAT without reporting an increased TE risk within females. Symptomatic TE events may however not best represent the risk. Vermeer et al [39] reported that, based on a sample size of 1077 patients undergoing cerebral

MR, female gender was an independent risk factor also for silent cerebral ischemia (SCI; OR 1.4) known to be related with cognitive decline [40]. In the Rotterdam study [41], in fact, based on a large sample size of 6584 patients aged between 55 and 106 years, AF was significantly related both to dementia (OR 2.3) and cognitive impairment (OR 1.7).

As further discussed in the next session (see Oral Anticoagulant therapy) the increased stroke risk observed in female patients is worsened by the lower OAT prescription rate, most likely due to the concomitant higher haemorrhagic risk profile. In the CARAF study [11], based on 899 patients (37.7 % female) the mean INR observed at the time of an haemorrhagic event was above the normal range in both genders: 4.02 in female pts, 4.37 in male pts (p value 0.787). However female gender was associated with an increased hemorrhagic risk related to OAT (9.2% vs 2.8%; RR 5.49) with female patients treated with OAT having a more than 3 fold increased risk of a major hemorrhagic event compared to males (Figure 1). Similar results are reported in the SPORTIF trial [42].

AF management

Oral anticoagulant therapy. Despite female gender represents an independent stroke risk factor, female patients are not properly prescribed OAT. Majeed et al [43] based on 1.4 million UK patients reported a lower OAT prescription rate in female (25% vs 34%) than male patients. Similar conclusions are reported in a prospective study based on a sample size of 228 AF patients [44]. In this study OAT eligibility, considering the SPAF 3 score, was confirmed in 41% of the patients, but between these only 23% were properly treated by OAT. Moreover OAT was preferentially prescribed in male patients aged between 65 and 74 years (41%), on the other side female patients aged more than 75 years old were less prescribed OAT (12%). In the CARAF study [11] female patients aged more than 75 years old were preferentially

prescribed Acetylsalicylic acid rather than OAT; in fact considering elderly AF patients with ≥ 1 stroke risk factor OAT was more commonly prescribed in male than in female patients (44.9% vs. 24.5%, p value = 0.034). More recently, in The Euro Heart Survey study [16], at least at discharge, OAT was equally proposed to male rather than female patients (65% vs 65%, p value NS) and the situation was similar within 7406 Japanese patients [38]. Eventually, however, a large sample size study reported a lower OAT prescription rate in female patients rather than the male counterpart (76.2 and 95.3% respectively, $P < 0.001$)[17].

Concerning new oral anticoagulant (NOAC) [45], [46], [47], [48] instead, while with dabigatran the annual absolute risk reduction was similar between male and female, with apixaban there was a trend to lower risk of major bleeding among females (p=0.08).

Pharmacological therapy and transcatheter ablation. Unfortunately few studies report if AF management is influenced by gender. Exhaustive data are reported solely in The Euro Heart Survey study [16] in which, female patients presented greater AF burden and higher heart rate during AF paroxysms. In this Survey, in case of referral for typical symptoms (for instance syncope or irregular heartbeat) no gender related differences in AF management emerged. In case of atypical symptom presentation, or in asymptomatic patients, instead, female patients were treated less aggressively and most often by rate control strategy (Figure 2).Similar results are reported in a recent study by Salam et al [49] in which, based one large series of patients (n 3849, females 36.8%) from Middle East, female AF patients were preferentially treated, at discharge, with digoxin and calcium channel blockers for rate control strategy.

In case rhythm control strategy by antiarrhythmic drugs (AAD) fails and AF remains symptomatic a further option is transcatheter (TC) AF ablation [50]. Also in this respect, few

studies have focused on gender related differences. The study by Forleo et al [14] underlines how female patients referring for TC AF ablation, not only present more comorbidities, but also have a longer AF history (60 vs. 47 months, p value = 0.04), significantly larger left atriums (AP diameter 44 mm vs. 40 mm, p value = 0.003) and lower prevalence of Paroxysmal AF (56.3 vs. 61.3, p value NS). In a study by Patel et al [15] female patients referred for AF TC ablation were significantly older (59 ± 13 vs. 56 ±19 years; p value <0.01), with a lower prevalence of Paroxysmal AF (46% vs. 55%; p value <0.001), with a greater number of previous ineffective AAD (4 ± 1 vs. 2 ± 3; p value = 0.04) and a longer AF history (6.51 ± 7 vs. 4.85 ± 6.5 years; p value = 0.02) than males. In addition female patients underwent also a greater number of failed AF ablation procedures (31.5% vs. 22.5%; p value < 0 .001).Recently Zhang et al [51], considering a sample size of 200 patients (33% female) undergoing AF TC ablation reported how Lone AF was less frequently observed in female patients (27.4% vs 47.6%; p value = 0.004).

Outcome

In the RACE study 8522 patients have been enrolled and prospectively randomized to rate or rhythm control to evaluate long-term outcome and safety gender related differences. Female patients enrolled in the rhythm control strategy reported a higher incidence of HF, TE events and AAD related adverse events (p value = 0.002) in comparison to female patients enrolled in the rate control strategy.

More specifically concerning rhythm control strategies Essebag et al [52] have enrolled 1005 patients with new onset AF to evaluate safety and efficacy of long-term therapy with Amiodarone. In this study bradycardia induced by Amiodarone was more pronounced in

female patients (HR, 4.69; vs. HR, 1.05; p value = 0.02) even excluding confounding factors such as body weight, BMI, Amiodarone daily dosage and assumption of other drugs (both for rhythm or rate control strategies). In fact, gender related differences on efficacy of AAD are also reported in the CARAF study [11] in which arrhythmia recurrence rate was higher in female patients (p value < 0.05 for ecg documented recurrences, p value < 0.001 for non documented recurrences). However, despite a higher arrhythmic burden in female patients the progression rate to permanent AF was identical between genders (18.9%), so as the mean time of progression (1092 days vs 1138 days, p value = 0.35).

Concerning AF TC ablation, instead, Forleo et al [14] failed to report any safety and efficacy gender related difference. Periprocedural complication rate was 5.0%, similar between genders. In this study aim of radiofrequency ablation was complete pulmonary vein isolation (PVI); cavo-tricuspid isthmus block was also pursued in each procedure, but left atria linear lesion were performed according to the operator discretion. After a median follow up of 22.5 ± 11.8 months the proportion of patients arrhythmia free was similar (83.1 vs. 82.7% female vs. male patients), and similar results were reported also for quality of life were only a slightly superior improvement occurred in female patients (p value < 0.05 in comparison to baseline in both genders). Differently Patel et al [15] reported that female gender was associated with periprocedural hemorrhagic complications, in particular, greater hematoma (2.1% vs. 0.9%; p value = 0.026) and pseudoaneurism incidence (0.6% vs. 0.1%; p value = 0.031) in comparison with male patients. In this study PVI for paroxysmal and PVI + atrial linear lesions + complex fractioned atrial electrograms (CFAE) for persistent AF patients were performed. After a median follow up of 24 ± 16 months, female patients were affected by an higher recurrence rate with a lower percentage of arrhythmia free survival (68.5% vs. 77.5% p value < 0.001). Female gender was associated with an higher rate of periprocedural complications, in

particular vascular complications. A similar finding was, in fact, reported also in a single centre retrospective study on 1295 patients by Baman et al [53]. In addition recently Zhang et al[51], on a small cohort of 220 patients (33.2% females), reported an higher periprocedural vascular complication rate in female patients (6.8% vs 0.7%, p value 0.027). In this study ablation procedure was performed with the aim to complete PVI and linear lesions plus CFAE were pursued and ablated in case of persistent AF. Female gender resulted an independent risk factor for AF recurrences following AF ablation (mean follow up time 19 ± 5 months, 35.6% vs 57.1%; p value = 0.003, HR 1.663, CI 1.114 – 2.485; p value = 0.013). Eventually, as for Forleo et al [14], Takigawa et al [54], considering a large sample size study (n 1124 patients, 23.1% female), reported that female gender was not associated with an higher periprocedural complication rate (p value = 0.73) and neither with a lower efficacy following the first AF ablation procedure (mean follow up time 31.7 ± 24.4 months, 56.4% vs. 59.3% at 5 years, p value = 0.24). A lower efficacy rate was reported, instead, in female patients undergoing a redo procedure (mean follow up time 39.0 ± 21.8 months, 76.5% vs. 81.3% at 5 years, p value = 0.007). Despite an ablation protocol aiming to PVI in all patients and atrial linear ablations if required (spontaneous AF from undetermined origins or atrial tachycardia). Eventually obesity has shown to increase periprocedural complication rate especially in female gender patients [55]. Indeed to afore described studies are heterogeneous and the outcome reported is surely influenced by differences in baseline characteristics. When female patients presented more comorbidities (e.g. Patel et al [15]) AF TC ablation's outcome was worst while when baseline characteristics were comparable to those of enrolled males (e.g. Takigawa et al[54]) outcome did not differ. Therefore, differently from AAD, there are to date no reasons to support an inter-gender outcome difference following AF ablation given similar baseline comorbidities and stage of the disease [56], [57]. In fact, a recent investigation has shown no systematic between gender differences in PV or atrial substrate when stratified by

cardiovascular comorbidities known to be associated with atrial remodelling [58]. In our opinion, therefore, the most important discriminating factor remains the timing of the therapeutic intervention aiming towards rhythm control.

Eventually concerning device therapy, ablate and pace (A&P) followed by a cardiac resynchronization therapy (CRT) should be adopted in all patient with uncontrolled heart rate with reduced ejection fraction (EF) and any QRS duration (Class IIa, Level B) [59]; however no specific gender related differences have been reported on this approach.

In general, however, a multicenter registry focusing on AF management in females is warranted.

Conclusion.

Atrial fibrillation is the most common sustained supraventricular arrhythmia. Its onset is age and sex related, in fact, elderly people and males are preferentially involved. Despite this, considering that beyond 75 years of age females are more prevalent, the absolute number of patients affected in this age frame are similar between genders. Despite this few data are available in literature concerning gender related differences in AF patients.

Based on the present systematic review the following observations deserve, in our opinion, attention from the medical community (Figure 3).

- Female patients represents about one third of patients enrolled in available studies and generally present more comorbidities.

- Female AF patients present a lower quality of life and referral to hospital care occurs later and with a longer disease history. This commonly leads to preferentially adopt a rate rather than a rhythm control strategy, while the latter, by reducing the arrhythmic burden, has proved to more significantly improve quality of life in female vs. male patients.

- Female AF patients present an increased risk of stroke, worsened by the lower OAT prescription rate related to the concomitant higher haemorrhagic risk profile.

- Rhythm control strategy pursued by pharmacological therapy is associated with an higher risk of adverse events, and, may be affected by lower efficacy on thelong-term follow up. On the other side AF TC ablation is under prescribedin female patients and, in particular, females are referred later, with greater comorbidities and longer AF history.

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Figure Legends

Figure 1 Thromboembolic and haemorrhagic events stratified by gender in two large cohorts.[12, 52]

Figure 2 Atrial Fibrillation management stratified by gender and symtpoms at referral in the Euro Heart Survey [25]

Figure 3 Main gender related AF differences

Table 1

First author, year	Sample size (females, %)	Significant gender related differences	p value
Kaufman ES et al 2004	2033 (37.9 %)	Age (Older)	< 0.001
		Valvular cardiomyopathy	< 0.001
Humphries K et al 2001	899 (37.7%)	Age (Older)	< 0.001
		Hypertension	< 0.001
		Disthyroidism	< 0.03
Paquette et al 2000	170 (36.5%)	Age (Older)	< 0.05
		Hypertension	< 0.05
Rienstra M et al 2005	522 (36.8%)	Age (Older)	< 0.001
		Hypertension	< 0.001
		Diabetes	< 0.001
Forleo et al 2007	221 (32.1%)	Age (Older)	= 0.002
		Hypertension	= 0.04
Patel D. et al 2010	3265 (15.8%)	Age (Older)	< 0.01
		Diabetes	0.016
		Hypertension	< 0.001
		Previous stroke	< 0.001
Dagres N et al 2007	5333 (42%)	Age (Older)	< 0.001
		Hypertension	< 0.001
		Diabetes	< 0.001
		Valvular cardiomyopathy	< 0.001
		Disthyroidism	< 0.001

Table 1 Main Gender related differences of patients referring for Atrial Fibrillation.

Figure 1
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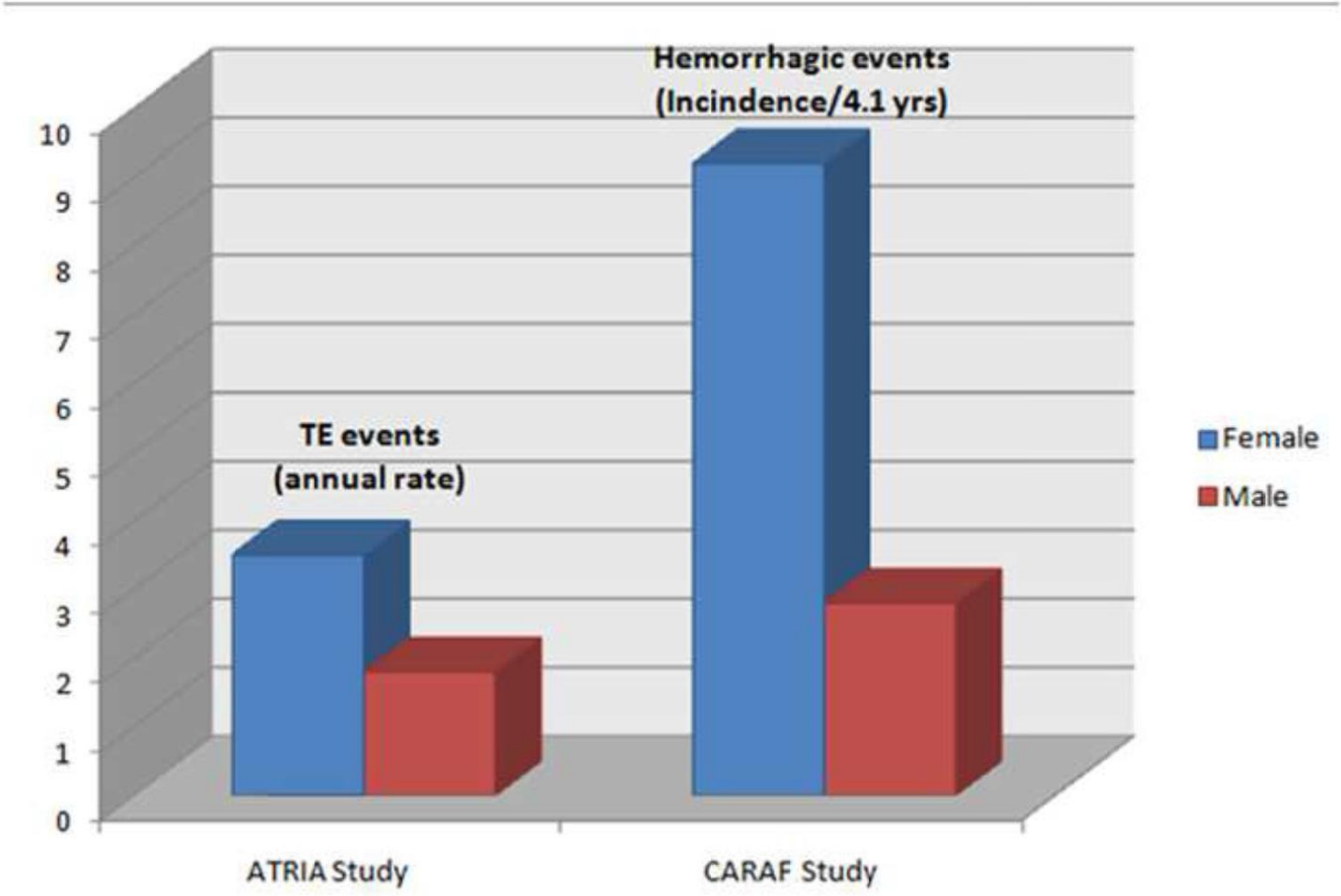

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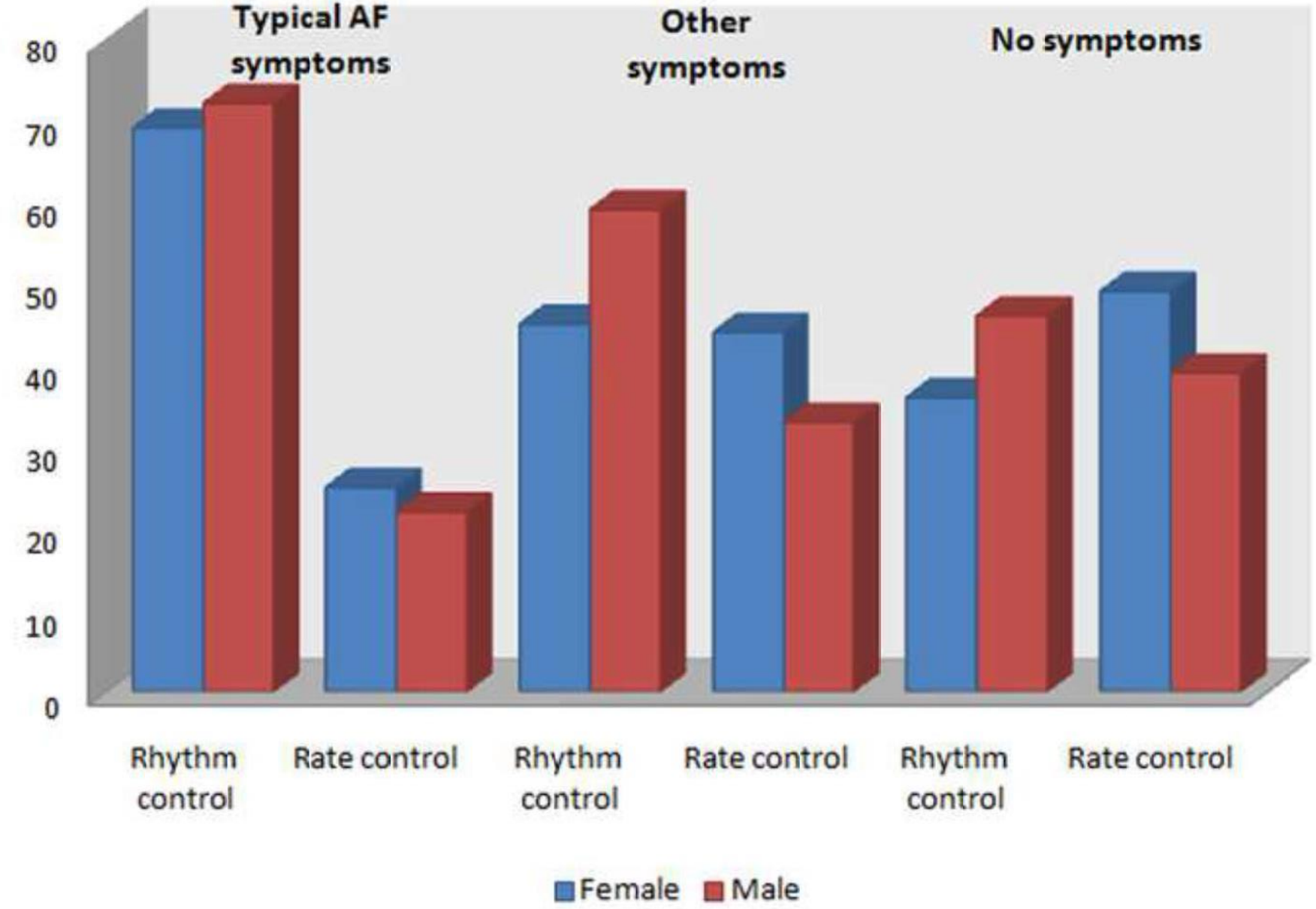

Figure 3
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