REVIEW

Anticoagulant drugs and gender: what is in the elderly? A minireview

T. Ciarambino¹, G. Corbi², A. Filippelli³, M. La Regina⁴, O. Para⁵, F. Tangianu⁶, P. Gnerre⁷, N. Ferrara⁸, M. Giordano¹, C. Politi⁹

¹ Department of Medical, Surgical, Neurological, Metabolic and Geriatrics Sciences, Hospital of Marcianise, ASL Caserta, University of Campania "L. Vanvitelli", Naples, Italy; ² Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy; ³ Department of Medicine and Surgery, University of Salerno, Salerno, Italy; ⁴ Department of Internal Medicine, La Spezia, Italy; ⁵ Department of Internal Medicine, Hospital Careggi, Florence, Italy; ⁶ Department of Internal Medicine, Hospital San Martino, Oristano, Italy; ⁷ Department of Internal Medicine, Hospital of La Spezia, Italy; ⁸ Department of Internal Medicine, Hospital of La Spezia, Italy; ⁸ Department of Internal Medicine, Hospital of La Spezia, Italy; ⁸ Department of Internal Medicine, Hospital of La Spezia, Italy; ⁸ Department of Internal Medicine, Hospital of La Spezia, Italy; ⁸ Department of Internal Medicine, Hospital of Naples, Italy; ⁹ Department of Internal Medicine, Hospital of La Spezia, Italy; ⁸ Department of Internal Medicine, Hospital of Naples, Italy; ⁹ Department of Internal Medicine, Hospital of Naples, Italy; ⁹ Department of Internal Medicine, Hospital of F. Veneziale, Isernia, Italy

Atrial fibrillation (AF) is the most common chronic arrhythmia affecting approximately 9% of population. Gender-specific clinical predictors of maintenance of sinus rhythm or adequate rate control are sparsely investigated. Some data suggest gender differences in treatment and response to interventions. Findings from Framingham Heart Study showed sex-specific AF risk-factor-adjusted-odds for death is slightly higher in females than males. Sex differences are possible in the effectiveness of DOACs. Elderly female tended to bleed more with DOACs compared with warfarin, although the risk of bleeding in male was similar for DOACs and warfarin. To this regard, Rengo et al recommend that warfarin could be preferred in patients with high thromboembolic risk. Rivaroxaban may be more effective for stroke prevention compared with dabigatran and warfarin in men, but all 3 drugs seem to provide similar stroke prevention in female. Further studies are needed to understand whether lower rates of OAC use in the elderly female are associated with differences in clinical outcomes, and if so, action is needed to eliminate unnecessary differences in OAC use by sex.

Key words: Elderly, DOACs, Atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) is the most common chronic arrhythmia affecting approximately 9% of population ¹. However, Cacciatore F et al. reported that in the elderly, AF is an important risk factor for dementia ². However, in the elderly, it has been reported the relationships between blood pressure levels, mortality and cognitive impairment ³. Gender-specific clinical predictors of maintenance of sinus rhythm or adequate rate control are sparsely investigated. Some data suggest gender differences in treatment and response to interventions ⁴. Findings from Framingham Heart Study showed sex-specific AF risk-factor-adjusted-odds for death is slightly higher in females than males ⁵.

Di Pasquale et al., have been reported that hypertension was the most prevalent associated comorbidity in patients with AF, followed by hypercholesterolemia (28.9%), heart failure (27.7%) and diabetes (24.3%). Hovewer, the authors reported that patients admitted in Internal Medicine were older, more frequently females and more often with comorbidities than patients admitted to Cardiology Department ⁶. However, as reported by Politi et al., after a first event cerebrovascular, women are hospitalized more frequently than men (7.9 vs 3.9%) ⁷. Limited data exist on the impact

Received: October 19, 2018 - Accepted: December 12, 2018



Correspondence: Tiziana Ciarambino, Department of Internal Medicine, Hospital of Marcianise, via Orto dell'Abate, 81025 Marcianise (CE), Italy. E-mail: tiziana.ciarambino@gmail.com

of gender on cardioversion and prescription or continuation of anticoagulants oral (DOACs), in particular in the elderly patients. Guidelines recommend that physicians should offer effective diagnostic tools and therapeutic management to elderly female and male equally ⁸. In this article, we aimed to review the existing literature about gender-related differences on efficacy, administration and side effects of the most common drugs used for the treatment of ischemic stroke.

THERAPY: DIFFERENCES BY GENDER

In atrial fibrillation, cardioversion to normal sinus rhythms is equally successful in male and female; however, female were less likely to undergo electric cardioversion than male ⁹. It is important to recognize the significant differences in management and outcomes between the sexes. Greater age, higher BMI, comorbidities, and major bleeding events were the most significant risk factors for elderly female. Higher rates of smoking, alcohol use, and CHADS₂ scores were some of the significant risk factors in male with AF ¹⁰. A higher proportion of female were not considered for cardioversion due to rate control compared to male (73.8 vs 63.2%). It is striking that female received more conservative treatment despite having greater comorbidities. In fact, female received warfarin therapy (36.8 vs 25.1%) compared to male ¹¹. Oral anticoagulants

It is important to assess sex-specific effectiveness of treatment strategies that show promise with reducing myocardial ischemic acute (MI), heart failure (HF), and all-cause mortality in patients with AF. Despite a higher risk of stroke, elderly female with non-valvular atrial fibrillation (AF) receive less DOACs than male ¹². Possible explanations for decreased DOACs use in female include under-recognition of their higher thromboembolic risk or concern for on warfarin in female patients ¹³. Female with AF have nearly 2 times higher risk for these cardiovascular events when compared with their male counterparts ¹⁴.

To this regard, Corbi et al have been reported that the use of International Warfarin Pharmacogenetics Consortium algorithm could estimate the right warfarin dose in the female elderly, and to reduce bleeding risk by over dosed ¹⁵.

However, in the literature it has been reported that rivaroxaban [RIVA], dabigatran [DABI], and warfarin are associated with a reduction in all-cause mortality and vascular mortality including those related to HF hospitalizations in patients with AF ¹⁶. Data assessing sex-specific associations of DOACs with the risk of MI, HF, and all-cause mortality are lacking in the literature. In analysis of Medicare claims data for elderly patients with newly diagnosed AF in the United States, it has been reported a significant differences in cardiovascular outcomes and all-cause mortality by anticoagulant type within sex. In male, RIVA use was associated with a lower risk of MI compared with either DABI use or warfarin use, while the risk of MI was similar across all 3 anticoagulants in female. In male and female, RIVA and DABI use were both associated with lower risk of HF admissions and all-cause mortality compared with warfarin use ¹⁷. The authors demonstrated that both RIVA and DABI use were associated with a reduction in HF risk compared with warfarin in male as well as female with AF¹⁸. In this cohort of US patients with AF and indications for OAC, female sex was associated with significantly less OAC use compared to male sex across the spectrum of thromboembolic risk. Over the past decade, OAC use has gradually increased each year for both female and male. Warfarin use has been declining and DOAC use increasing; these changes have been slightly more pronounced in female compared to male. Even with these shifts in therapy type, female remained significantly less likely than male to receive OAC at all time points. These findings suggest that sex differences in OAC use may be primarily due to differences in the use of warfarin. Over the past 5 years, warfarin use has gradually decreased, and DO-AC use has increased by as much as 50% per year in both female and male with a slightly greater rate of increase for female. For example, female may be more likely to decline OAC therapy, particularly warfarin, due to concerns for bleeding, inconvenience, or lack of social support (ie, transportation for international normalized ratio check) ¹⁹. However, prior studies have demonstrated that sex-related differences in the risk of stroke decrease when OAC are used ¹⁹. Also, sex differences were observed at the highest level of estimated thromboembolic risk (CHA2DS2-VASc \geq 6), suggesting that even small absolute differences in OAC use may translate into significant sex differences in clinical outcomes, Lauren E. Thompson et al. have been reported in patients with AF and indications for anticoagulation, that female were 9 to 33% less likely than male to receive OAC at all levels of thromboembolic risk ²⁰. The reduced risk of ischemic stroke in patients taking rivaroxaban, compared with dabigatran and warfarin, seems to be limited to male, whereas the higher risk of bleeding seems to be limited to female. The most striking result was the evidence that the therapeutic approach for stroke is often different according to patients' gender with a clear detrimental prognostic effect for female. A major effort is necessary to overcome this problem in order to ensure equal right to treatment without any sexual discrimination²¹.

In another nationwide retrospective cohort study, male and female 65 years and older have a clinically relevant benefit of anticoagulation treatment with warfarin. Warfarin is beneficial in patients < 65 years of age in male with CHA2DS2-VASc score > 2 and in female > 3points ²². Sex-specific comparative effectiveness of direct oral anticoagulants among patients with non-valvular atrial fibrillation is not known. In a subgroup analysis of the ROCKET-AF²³ trial that compared sex-specific effectiveness of rivaroxaban versus warfarin, the risk of stroke and major bleeding were similar with rivaroxaban compared with warfarin in both male and female ²³. In contrast, it has been reported that rivaroxaban to be more effective than warfarin for stroke prevention in male and to be similarly effective as warfarin in female. Also, risk of major bleeding was higher in female (but not in male) with rivaroxaban use ²⁴. In a sex-specific subgroup analysis of RELY ²⁵ dabigatran 150 mg BID was superior to warfarin for stroke prevention in both male and female, whereas sex-specific bleeding outcomes were not reported. The baseline stroke risk of RELY trail participants (CHADS2 score of 2.1 ± 1.1) were similar to male (2.3 ± 0.97) and female (2.4 ± 1.1) using dabigatran. In spite it has noted similar effectiveness of dabigatran to warfarin with stroke protection in male and female, whereas RELY reported superiority of dabigatran to warfarin for stroke prevention in male and female. Observational data have both supported ²⁶ and contradicted ²⁷. A Canadian study ²⁸, using a propensity-matched analysis involving 31.786 women and 31.324 men with AF, compared sex-specific effectiveness of dabigatran (110 and 150 mg) to warfarin. The study concluded that dabigatran use was associated with similar stroke risk compared with warfarin in both sexes but was protective against major bleeding only in male. The results of this Canadian observational study are in concordance with these findings, in spite of the fact that all study participants used dabigatran 150 mg BID. In this study, dabigatran and warfarin were similarly effective for stroke prevention in both sexes, while dabigatran decreased risk of major bleeding in male but not in female. In the literature it has been suggest the possibility of a higher bleeding risk in female with AF treated with DOACs ²⁷. The meta-analysis by Alotaibi et al. ²⁵ reported a 21% higher relative risk of bleeding in female treated with DOACs for venous thromboembolism compared with that in male. Female gender, by virtue of their lean body weight, especially our elderly Medicare population, have decreased creatinine clearance compared with male and may attain higher serum levels of DOACs predisposing them to bleed more. Furthermore, differences in sex hormones between sexes may influence variability in hemostasis and vascular reactivity ²⁵. It

is also possible that sex gaps in access to care may contribute to bleeding differences between male and female.

CONCLUSIONS

Sex differences are possible in the effectiveness of DO-ACs. Elderly female tended to bleed more with DOACs compared with warfarin, although the risk of bleeding in male was similar for DOACs and warfarin. To this regard, Rengo et al recommend that warfarin could be preferred in patients with high thromboembolic risk ²⁸. Rivaroxaban may be more effective for stroke prevention compared with dabigatran and warfarin in men, but all 3 drugs seem to provide similar stroke prevention in female ²⁷. Further studies are needed to understand whether lower rates of OAC use in the elderly female are associated with differences in clinical outcomes, and if so, action is needed to eliminate unnecessary differences in OAC use by sex.

CONFLICT OF INTEREST

The Authors declare to have no conflicts of interest.

References

- ¹ Heeringa J. *Atrial fibrillation: is the prevalence rising?* Europace 2010;12:451-2.
- ² Cacciatore F, Testa G, Langellotto A, et al. *Role of Ventricular rate response on dementia in cognitively impaired elderly subjects with atrial fibrillation: a 10-year study.* Dement Geriatr Cogn Disord 2012;34:143-8.
- ³ Cacciatore F, Abete P, de Santi D, et al. Mortality and blood pressure in elderly people with and without cognitive impairment. Gerontology 2005;51:53-61.
- ⁴ Pancholy SB, Sharma PS, Pancholy DS, et al. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. Am J Cardiol 2014;113:485-90.
- ⁵ Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death the Framingham Heart Study. Circ 1998;98:946-52.
- ⁶ Di Pasquale G, Mathieu G, Maggioni AP, Fabbri Ge al; ATA-AF Investigators. 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.
- ⁷ Politi C, Martignoni A, Giovi I, et al. Gender medicine: an uptodate. IJM 2013:96-106.
- ⁸ Kirchhof P, Benussi S, Kotecha D, et al. ESC guidelines for the management of atrial fibrillation developed in collaboration with eacts: the task force for the management of atrial fibrillation of the european society of cardiology (esc) Developed with the special contribution of the european

heart rhythm association (ehra) of the escendorsed by the european stroke Organisation (esO). Eur Heart J 2016;50:e1-88.

- ⁹ 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;49:572-7.
- ¹⁰ Shehab A, Zubaid M, Bhagavathula AS, et al.; on behalf of the Gulf Survey of Atrial Fibrillation Events (Gulf SAFE) investigators. Sex differences in management and outcomes of patients with atrial fibrillation in the Middle East: Gulf survey of atrial fibrillation events (Gulf SAFE). PLos One 2017;12:e0175405.
- ¹¹ Riesgo A, Sant E, Benito L, et al. Sex differences in the treatment of patients with atrial fibrillation: population-based study in a local health district. Rev Esp Cardiol 2011;64:233-6.
- ¹² Lane DA, Lip G. Female gender is a risk factor for stroke and thromboembolism in atrial fibrillation patients. Thromb Haemost 2009;101:802-5.
- ¹³ Stewart S, Hart CL, Hole DJ, et al. 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.
- ¹⁴ Corbi G, Simeon V, Conti V, et al. *Clinical, drugs interactions and pharmacogenetics evaluation of warfarin treatment in an elderly patients: a case report.* Journal of Gerontology and Geriatrics 2016;64:70-2.
- ¹⁵ Gomez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, et al. Causes of death in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 2016;68:2508-21.
- ¹⁶ Palamaner Subash Shantha G, Mentias A, Inampudi C, et al. Sex-specific associations of oral anticoagulant use and cardiovascular outcomes in patients with atrial fibrillation. J Am Heart Assoc 2017;6:e006381.
- ¹⁷ Shantsila E, Wolff A, Lip G, et al. Gender differences in stroke prevention in atrial fibrillation in general practice: using the GRASP-AF audit tool. Int J Clin Pract 2015;69:840-5.
- ¹⁸ Thompson LE, Maddox TM, Lei L, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR) PINNACLE Registry. J Am Heart Assoc 2017;6:e005801.

- ¹⁹ Falsetti L, Viticchi G, Buratti L, et al. *From head to toe: sex and gender differences in the treatment of ischemic cerebral disease.* Pharmacol Res 2017;121:240-50.
- ²⁰ Andersson T, Magnuson A, Bryngelsson I-L, et al. Patients with atrial fibrillation and outcomes of cerebral infarction in those with treatment of warfarin versus no warfarin with references to CHA2DS2-VASc score, age and sex – A Swedish nationwide observational study with 48.433 patients. PLos One 2017;12:e0176846.
- ²¹ Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. *Rivaroxaban versus warfarin in nonvalvular atrial fibrillation*. N Engl J Med 2011;365:883-91.
- ²² Palamaner Subash Shantha G, Bhave PD, Girotra S, et al. Sex-specific comparative effectiveness of oral anticoagulants in elderly patients with newly diagnosed atrial fibrillation. Circulation 2017;10. pii: e003418.
- ²³ Connolly SJ, Ezekowitz MD, Yusuf S, et al. *RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation.* N Engl J Med 2009;361:1139-51.
- ²⁴ Alotaibi GS, Almodaimegh H, McMurtry MS, et al. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sexbased meta-analysis. Thromb Res 2013;132:185-9.
- ²⁵ Lauffenburger JC, Farley JF, Gehi AK, et al. *Effectiveness* and safety of dabigatran and warfarin in real-world US patients with non-valvular atrial fibrillation: a retrospective cohort study. J Am Heart Assoc 2015;4:e001798.
- ²⁶ Maura G, Blotière PO, Bouillon K, et al. Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists: a French nationwide propensity-matched cohort study. Circulation 2015;132:1252-60.
- ²⁷ Avgil Tsadok M, Jackevicius CA, Rahme E, et al. Sex differences in dabigatran use, safety, and effectiveness in a population- based cohort of patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2015;8:593-9.
- ²⁸ Rengo G, Pagano G, Squizzato AL, et al. Oral anticoagulation therapy in heart failure patients in sinus rhythm: a systematic review and meta-analysis. PLos One 2013;8:1.

How to cite this article: Ciarambino T, Corbi G, Filippelli A, et al. *Anticoagulant drugs and gender: what is in the elderly? A minireview.* Journal of Gerontology and Geriatrics 2019;67:123-6.