Clinical and Applied
Thrombosis/Hemostasis
Volume 31: 1-10
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DOI: 10.1177/10760296251347938
journals.sagepub.com/home/cat

Oral Anticoagulants in Women: What's the Difference? A Narrative Review

Elena Maria Faioni, M.D[1,2] and Barbara Scimeca, M.D[1]

Abstract

Gender sensitive medicine refers to the need to individualize epidemiology, diagnosis, knowledge of disease presentation, and therapy based also on sex and gender. An impressive amount of scientific literature deals now with sex and gender differences in disease. Not so much, yet, on individualized therapeutic approaches. Part of the reason lies in how studies that deal with the pharmacology, efficacy and safety of drugs are conducted. Often women are under-represented, and/or no gender specific analysis of outcomes is performed. As a consequence, in many fields of medicine, not as much is known about important and life-saving drug dosage, safety and efficacy in women as in men. Oral anticoagulants are not the exception, even if new regulations are operative regarding inclusion of women in all phases of drug studies. The result is that there are many areas of uncertainty or outright confusion regarding the efficacy and safety of oral anticoagulants in women that need to be addressed.

Keywords

anticoagulants, atrial fibrillation, bleeding, coumarins, direct oral anticoagulants, venous thromboembolism

Received: 1 February 2025; revised: 29 April 2025; accepted: 20 May 2025

Aims of the Review

Oral anticoagulants (OACs), either vitamin K antagonists (VKAs) (warfarin acenocoumarol, phenprocoumon) or direct oral anticoagulants (DOACs) (such as dabigatran, a thrombin inhibitor, and the activated factor X inhibitors rivaroxaban, apixaban and edoxaban), are employed in a number of clinical conditions associated with an increased risk of arterial or venous thrombosis or for the treatment of such events. Their indications for use do not completely overlap and are summarized, as well as their characteristics, in recent guidelines for arterial and venous thromboembolism.[1-3] Moreover, while DOACs have largely replaced VKAs in many clinical conditions, some patients cannot be treated with DOACs and still need VKAs: carriers of Ventricular Assist Device, patients with atrial fibrillation (AF) and moderate or severe mitral stenosis, previous anticoagulant failure while on DOACs, anti-phospholipid syndrome with triple anti-phospholipid positivity, severe renal insufficiency (at least in Europe), liver failure, inadequate adherence/persistence.[1-3]

A very large number of clinical trials on anticoagulation are concluded or ongoing so that indeed a lot is known concerning oral anticoagulants, their efficacy, safety and limitations and many evidenced-based guidelines are available. One might ask, therefore, why should there be a need to discuss anticoagulation efficacy and safety yet **again**. One reason is that far too little attention was and still is given to anticoagulated women and their specific problems. In an era when gender related issues are addressed by almost every field of medicine, this is rather puzzling. A Global Burden of Disease study demonstrated that more than 59 million individuals lived with (AF) (one of the main indications to anticoagulation) in 2019, overall equally divided between men and women, and current estimates indicate this number will substantially increase in

[1]Anticoagulant Clinic, Centro Cardiologico Monzino IRCCS, Milano, Italy
[2]Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

Corresponding Author:
Elena Maria Faioni, M.D., Department of Health Sciences, Università degli Studi di Milano, Milan, Lombardy, Italy.
Email: elena.faioni@unimi.it

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the next decades.[4] Also the incidence of venous thromboembolism (VTE), another important condition with an indication to anticoagulation, is increasing, and cumulative incidence of VTE is not different between men and women globally.[5,6] This translates into milions of patients worldwide who are on anticoagulants, approximately half of whom are women. Is there convincing evidence that anticoagulants behave equally in men and women and were developed and studied with sex and gender issues in mind? Did phase 1 and 2 studies, registrative trials and real world registries address this issue? An interesting collateral effect of looking at outcomes in women specifically is that it entails also looking at outcomes in men specifically, and both aspects are of conceptual as well as clinical relevance.

Pharmacokinetics are not the same in men and women, and neither are body fat distribution, metabolism, nutritional habits, social roles, inclusion in clinical trials, access to medications and health care, as discussed below. Furthermore, women are subject to hormonal variations throughout their fertile age, and to important changes during pregnancy, lactation and the menopause, or may need hormonal therapy. To administer the correct medication at the right dose for the appropriate time to a specfic patient, avoiding any adverse effects or worsening of the quality of life, are goals that all physicians should share, and yet a substantial number of women are anticoagulated with insufficient or contrasting evidence.

The aim of this narrative review is to address possible concerns related to the differences in outcome of anticoagulation in women (and men) by delving in what we already know and what is missing to encourage further studies, if needed. Throughout this review the term sex will refer to attributed sex at birth, while gender will be used to indicate the complex of acquired habits and traits which belong to men and women in different cultures and may influence various aspects of anticoagulation. The terms "men and women" will also be used when citing original work that employs these terms. Finally, in the context of anticoagulation, it is important to distinguish aspects that relate to anticoagulation in men and women alike, such as pharmacokinetics, efficacy, safety, inclusion in trials, sex- and gender-sensitive analysis of results, adherence and persistence, and aspects that are specific to women such as pregnancy, breastfeeding, hormonal therapy, menopause and abnormal uterine bleeding. In this review only the last-mentioned among the woman-specific aspects will be addressed, leaving issues related to anticoagulation and pregnancy, breastfeeding, hormonal therapy, or menopause to other ad hoc in-depth analyses.

Methods

The questions we wanted to address were:

Are different pharmacokinetics taken into account when studying drug development (cells and animals of both sexes, for example)? Are women included in anticoagulant trials equally to men or at least in a way that reflects prevalence of the disease by sex? Are gender issues taken into account? Is safety and efficacy really equivalent by sex and gender in registrative trials? And in the real world studies? When studies address directly safety and/or efficacy of anticoagulants by sex and gender with specific outcomes, what do we find?

To address these questions we interrogated Pub Med, scientific society sites and institutional health sites, with the following queries in mesh:

Vitamin K antagonists, direct oral anticoagulants, gender, sex, efficacy, safety, bleeding, stroke, hematuria, uterine bleeding, gastrointestinal bleeding, major bleeding, pharmacokinetics, adherence, metanalysis, systematic review, randomized clinical trials.

We did not establish a date limit, though when a choice was offered we chose more recent publications over older ones. We also navigated the reference list of the publications we included in the review.

Since narrative reviews may include a noncomprehensive and non-exhaustive sample of the literature on a specific topic,[7] we chose papers that in our opinion were relevant to the questions we were asking.

Pharmacokinetics

Women metabolize drugs differently from men and are under fluctuating hormonal influences, which vary monthly and also during their lifetime with ovulation and menstruation, pregnancy, breastfeeding and the menopause. Thus the differences between the male and female responses to medications are not simply related to average body size and composition (women have about 15% more body fat than a man of equal weight and height), but to fundamental metabolic and hormonal differences that may cause changes in both the pharmacokinetic and pharmacodynamic drug profiles.[8,9] A systematic review of population pharmacokinetics of warfarin concluded that gender had an impact on the clearance of warfarin, with women having a lower clearance than men thus needing lower doses for equivalent anticoagulation potency and efficacy.[10] Other studies showed similar results, although not all studies agree. A previous paper suggested that there is a sex difference in the anticoagulant effects of warfarin, and that this difference may be related to the estradiol levels in plasma.[11] The Authors suggested that 17β-estradiol may influence absorption, metabolism or excretion of vitamin K, resulting in an increase of vitamin K in the liver which might reduce the anticoagulant effect of warfarin.[11]

Regarding DOACs, a systematic review and clinical appraisal using exposure simulation showed that women were associated with a slight (< 25%) decrease in DOAC

clearance.[12] The Authors discussed that this would have minor clinical impact in itself, but that the accumulation of covariates with modest individual impact on exposure, could have a significant impact. These minor covariates, for example polymedication, metabolic genotypes and sex, are not usually factored in DOACs choice and dosage, since no models take them into account. The European Society of Cardiology issued a position paper on pharmacology and drug therapy which summarizes what is (not) known about the sex and gender-specific differences in pharmacology of cardiovascular drugs, including anticoagulants, and concluded that future pharmacological studies will need to take into account gender-related differences in pharmacokinetics and pharmacodynamics in order to better size the samples of males and females to be included.[13]

An additional obstacle to the generalization of results from studies on the pathophysiology of cardiovascular disease or pharmacodynamics and pharmacokinetics of experimental drugs is that animals employed in the early stages of these studies have long been preferentially male. A review including full articles published between July 2006 and June 2016 and reporting original data from in vivo experiments in nonhuman mammals on pathophysiology, genetics, or therapeutic interventions directly relevant to a specific cardiovascular disorder in humans found that the sex of the animals used was not reported in 20% of studies. Male animals were exclusively used in 71.6% of studies in which sex was reported, whereas females were exclusively used in 12.9% and both sexes in 15.5%. Sex matching of animals was reported in 17.1% of studies that included both sexes.[14]

Evidence from animal and human studies also shows that excipients (the inactive ingredients in drug formulations) could impact the bioavailability of drugs differently in women and men, with the potential to reduce efficacy. A study in rats[15] and one in human volunteers[16] showed that excipients modulate drug availability through different mechanisms, including intestinal transportation via P-glycoprotein. No studies specific to this aspect, to our knowledge, were conducted for AVKs and DOACs. They would be of interest, especially considering generic DOACs with different excipients are now marketed.

Equal Access to Clinical Trials, Specific Analysis of Outcomes by Sex and Gender, Adherence and Persistence, Equal Opportunity to Treatment

The Food and Drug Administration (FDA), a regulatory USA agency, in 1993 recommended the inclusion of more women in clinical trials,[17] in 2013 Health Canada issued a Guidance document to address the under representation of women in clinical trials[18] and the EU Clinical Trial Regulation No 536/2014 set out the legal conditions under which clinical trials have to be conducted in Europe.[19] This was subsequent to the observation that women were not enrolled in clinical trials in the same numbers as men and, if included, that the data were not analyzed and/or reported for women separately. It was recommended that in all phases of drug development women should be proportionally included, and that the population in phase 3 trials should equate disease prevalence in women and men to reflect as much as possible the real world population in a controlled setting. Unfortunately many studies reporting on sex disparities in trial enrollment, particularly older studies, do not account for the sex ratio of cases in the underlying population. Commentaries and analyses give a mixed-bag-of-cats view on how things really stand now, though a trend to amelioration is observed at least from a quantitative point of view. If we consider for example cardiovascular disease prevention trials, the proportion of women increased significantly over time, from 9% in 1970 to 41% in 2006.[20] Sheick et al showed that although women's enrollment increased over time (from 1986 to 2023), women remain underrepresented, in comparison to men, and notably, according to population cardiovascular disease prevalence.[21] A study evaluated 24 European Society of Cardiology guidelines from 2018 to 2023 and concluded that less than 50% of guidelines had a section dedicated to gender-specific medicine.[22]

Table 1 shows the percentage of women participating in the main randomized controlled studies on DOACs from 2009 to 2017.[23-35] While average participation is 41% (range 35%–47%), there is a slight trend towards improvement over time. In VTE registries, that include higher numbers of patients and better reflect real world epidemiology, enrollment of women is 50%,[36,37] while in AF registries it is lower (between 40% and 45% in three main registries).[38-40] The situation is not greatly changed in the recent concluded trials on the new anti factor XI(a) anticoagulants: average percent participation of women is 46% (range 31 to 49).[41-42] Several reasons are suggested to condition a lower participation of women in randomized controlled trials and earlier phase studies, and are listed in Table 2.[43-46]

Another important issue is lack of anticoagulant prescription. For example in non valvular AF, underprescription of oral anticoagulants is still very common in both men and women. The GARFIELD-AF registry showed that in patients at high risk (CHA_2DS_2-VASc score ≥ 2), 35.4% of men and 38.4% of women did not receive an anticoagulant[47] similarly to what is reported for other registries taken together[48] and a survey based on electronic health record data from 88 health systems in the United States from 2011 to 2020.[49] Other studies showed that women have a reduced chance of being anticoagulated compared to men,[50-51] at all levels of the CHA_2DS_2-VASc score.[52] Women have also a greater chance of

Table 1. Percentage of Women Enrolled in major Phase 3 Clinical Trials on DOACs Between 2009 and 2017.

Authors and Year (Reference Number in Manuscript)	Trial Name	Drug Comparison and Clinical Setting	% Women Enrolled
Connolly et al, 2009 [23]	RE-LY	Dabigatran versus warfarin AF	32
Shulman et al, 2009 [24]	RE-COVER Study Group	Dabigatran versus warfarin in VTE	42
EINSTEIN Investigators, 2010 [25]	EINSTEIN	Rivaroxaban versus warfarin in VTE	43
Patel et al, 2011 [26]	ROCKET-AF	Rivaroxaban versus warfarin in AF	40
Granger et al, 2011 [27]	ARISTOTLE	Apixaban versus warfarin in AF	35
EINSTEIN–PE Investigators, 2012 [28]	EINSTEIN-PE	Rivaroxaban versus warfarin in PE	47
Giugliano et al, 2013 [29]	ENGAGE AF-TIMI 48	Edoxaban versus warfarin in AF	38
Agnelli et al, 2013 [30]	AMPLIFY	Apixaban versus warfarin in VTE	41
Hokusai-VTE Investigators, 2013 [31]	HOKUSAI-VTE	Edoxaban versus warfarin in VTE	43
Agnelli et al, 2013 [32]	AMPLIFY-EXT	Apixaban for extended treatment of VTE	43
Shulman et al, 2013 [33]	RE-MEDY & RE-SONATE	Extended use of dabigatran, versus warfarin or placebo in VTE	42
Shulman et al, 2014 [34]	RE-COVER II	Dabigatran versus warfarin in VTE and pooled analysis	39
Weitz et al, 2017 [35]	EINSTEIN CHOICE	Rivaroxaban or Aspirin for Extended Treatment of VTE	45

(VTE = venous thromboembolism; PE = pulmonary embolism; AF = atrial fibrillation).

Table 2. Obstacles to Participation of Women in Clinical Trials Suggested in Scientific Literature Dealing with This Topic.[43-46]

Obstacles
Perceived higher risk of harm from trial participation than men
Caregiver for family, little time available
Lower socio-economic position
Perceived risk, by researchers, of exposing fetus or of confounding due to hormonal changes
Cultural dependance (for example, need to ask permission)
Burden that trial participation can impart on study subjects (visits, blood-letting, phone calls etc)
Eligibility criteria that disproportionately exclude women (for example age cut-off)

inappropriate dosing of DOACs, especially of reduced dosage compared to evidence based indications: for example lower than reccomended dosage was observed in 61.5% women *versus* 56.3% men in a prospective observational cohort study.[53] This is probably related to physician evaluation of reduced weight and mass, perception of increased frailty and fear of increased bleeding, similarly to what happens with older patients, both men and women.

Adherence and persistence to medications are other important aspects that are reported to be dissimilar between men and women: women are considered at risk of poor adherence and persistence to chronic treatments, though agreement between studies is not high.[54] A multivariate analysis of risk factors for non adherence and persistence in a population of DOACs and VKAs users in the Netherlands identified young age, female sex, no concomitant drug use and non-adherence as predictors for non-persistence of DOACs.[55] A cohort study of 123,250 people who initiated DOACs, (46.9% women and 53.1% men) showed higher adherence and persistence of women compared to men in the first year.[56] Another population-based retrospective cohort study of 17,920 patients showed low persistence in older women and in patients, men and women, who had experienced bleeding.[57]

Adherence and persistence are influenced by many different patient factors: type of disease and its perception, culture, habits, age, polymedication, previous or feared adverse events and possibly sex and gender are just a few. Consequently, it is not surprising that available studies reach different conclusions since they involve different populations, medications, and diseases, as well as definitions of adherence and persistence.

Efficacy and Safety of Oral Anticoagulants in Men and Women

The number of women enrolled in a study is not the only variable to influence generability of conclusions. Gender-sensitive analysis of outcomes should be included in clinical trials. In most of the DOACs and AVKs studies some pre-specified subgroup analysis was performed and reported, however details of the events (for example type and site of bleeding or thrombosis) by sex were not provided by all studies. With this as background, results of metanalyses of efficacy and safety from available trials could only provide mixed results, which are summarized in Table 3.[58-67] As shown, metanalyses results differ both in safety and efficacy end-points in AF and VTE, albeit individual studies they included did not show

Table 3. Reported Differences by sex and Gender in Bleeding and Thrombosis from Metanalyses and ad hoc Studies of DOACs.

Authors and Year	Numerosity	Type of Study	Main Findings
Ruff et al, 2014 [58]	71,683	metanalysis	DOACs were equally effective and safe in men and women treated for AF
Dentali et al, 2015 [59]	71,580 AF + 26,872 VTE	Systematic review and metanalysis	DOACs were equally effective and safe in men and women treated for AF or VTE
Loffredo et al, 2016 [60]	16,372	systematic review and metanalysis of double blind randomized control trials in patients treated with DOACs for VTE	compared to men, women had a higher incidence of major bleedings plus clinically relevant minor bleedings (approximately a third more).
Proietti et al, 2017 [61]	71,511	systematic review and metanalysis on gender differences of patients treated with DOACs for AF	men were more protected from stroke/systemic embolism and women from major bleeding events
Raccah et al, 2018 [62]	66,389	systemic review and network metanalysis in AF	women treated with DOACs had a lower rate of major bleeding and higher rate of stroke and systemic emboli compared with men
Emdin et al, 2016 [63]	4,371,714	systematic review and meta-analysis of 30 cohort studies on AF	higher risk of all cause mortality in women and a significantly stronger risk of stroke, cardiovascular mortality, cardiac events and heart failure
Nielsen et al, 2020 [64]	239,671	Danish National Patient Registry on AF	female sex was a prognostic factor for stroke in patients with atrial fibrillation overall, but also a risk modifier, since the excess risk for women was especially evident among those with ≥2 nonsex-related stroke risk factors
Pancholy et al, 2014[65]	26,260 warfarin 26,791 DOACs	meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation	women taking warfarin were at a significantly greater residual risk of cardiovascular adverse events compared with men (approximately 30% more) No gender difference in residual risk of cardiovascular adverse events was noted in patients with AF receiving DOACs and major bleeding was less frequent in women with AF treated with DOACs
Alotaibi et al, 2013 [66]	9417	a sex-based meta-analysis	no difference in the primary efficacy outcome of recurrent VTE between men and women, however, men had less major bleeding with DOACs compared to women (approximately 20% less)
Law et al, 2018 [67]	9806	cohort study of patients starting either warfarin or DOACs for a recent AF diagnosis	no difference between men and women regarding stroke incidence or gastrointestinal bleeding in DOACs users compared to warfarin, while women had a decreased incidence of intracerebral hemorrhage and of all-cause mortality compared to warfarin, but not men

(AF = atrial fibrillation; VTE = venous thromboembolism).

meaningful differences. This could be due to the increased power of pooling studies together in metanalyses, to different methodology with which they were conducted or to yet not identified reasons. Furthermore, the difference observed in bleeding events in women between AF trials and VTE trials could be related to the different median age of women included, younger in the VTE trials and thus more affected by abnormal uterine bleeding (see below). A few studies, also reported in Table 3, addressed directly differences between anticoagulated men and women in disease oucomes. Also in this case differences between men and women are identified and, once again, results are mixed in both safety and efficacy.[63-67]

Regarding VKAs, it is known that women have a worse TTR (ie time in therapeutic range) than men,[68] though not everyone agrees. TTR is correlated with safety and efficacy of AVK therapy: the lower the TTR, the worse the outcomes such as increased bleeding and thrombosis risks. The reason for the difference in TTR between men and women is not known. Lower TTR according to some studies is independent of age and ethnicity, and could be due to different nutritional habits in women (relevant to daily

vitamin K intake), to social aspects (less time dedicated to self health) or to dissimilar pharmacokinetics, as mentioned above. Some studies report that women have a similar risk of stroke compared with men in atrial fibrillation when anticoagulated with VKAs, independent of TTR, but a lower risk of major bleeding,[69] while others conclude that women have a higher risk of stroke also when anticoagulated with VKAs and a lower risk of bleeding overall and of major bleeding compared with men.[70]

Gastrointestinal bleeding (GIB) is increased with DOACs use compared with VKAs, even if agreement on this topic is at best moderate. A population-based retrospective analysis on linked administrative claims of 15,338 (55% women) DOACs and 44,542 (50% women) VKAs users, showed that women treated with DOACs have an approximately 50% increase in risk of GIB versus male patients; this difference was not observed in VKA patients.[71] When evaluating independent risk factors for GIB in patients on DOACs, however, Lv et al identified 11 independent risk factors, and sex was not one of them.[72] Other reports do not confirm increased GIB for most DOACs, or do not address sex as a variable. For example an analysis of 3347 matched pairs of new DOACs and new warfarin users after propensity score matching, concluded that the risk of GIB in new DOACs users was comparable to that in new warfarin users and that the risk of GIB was not significantly different between the two groups according to sex.[73]

Gross or visible hematuria is common in anticoagulated patients (reported between 2% and 24%). Association with urologic cancer is found in approximately one quarter to one third of cases.[74] A systematic review including 175,114 patients (number of women was not provided) from 22 eligible articles reported that visible hematuria was more frequent with antiplatelet agents and DOACs compared to AVKs.[74] The overall probability of visible hematuria in patients on OACs was 26.7%.[74] Ording et al,[75] analyzed a population of 2615 patients (6.1% women) with active urologic cancer or a history of urologic cancer initiating OACs, and they reported a similar incidence of hematuria in patients treated with DOACs or AVKs (4.8 and 4.7% per year, respectively).[75]

Few specific studies addressed sex- and gender-related differences in visible hematuria. A population-based, retrospective cohort study including all citizens in Ontario, Canada, aged 66 years and older, showed that 808,897 individuals (53% women) who received at least one antithrombotic drug prescription over the study period had a 44% increase in hematuria-related complications (for example emergency department visits) compared to individuals not exposed.[76] On multivariable analysis increasing age, male sex, and increasing comorbidity were significantly associated with rates of hematuria-related complications.[76] A prospective study of 66 anticoagulated patients (34% women) showed that gross hematuria was more common in men, while its recurrence was higher in women (52 vs 33%, respectively).[77]

Two recent prospective observational studies looked at the relationship between steady-state plasma levels of DOACs and subsequent bleeding or thrombotic events at one-year follow-up in 1657 (45.9% women) newly anticoagulated patients with non valvular AF.[78,79] Regarding bleeding, 50 events were observed in patients with higher plasma levels of DOACs, of these 10 major bleeds and 10 clinically relevant non major bleeding events were in women. Prevalence of bleeding events was not increased in women compared to men. Two events were vaginal bleeding.[78] Regarding thrombosis in patients with the lower plasma levels of DOACs, 57% of events in women compared to 14% in men were ischemic stroke.[79]

Abnormal uterine bleeding in the setting of anticoagulation consists mostly of heavy menstrual bleeding, intermenstrual bleeding, prolonged menstrual bleeding or postmenopausal bleeding. It can be psychologically, socially and medically disabeling: bleeding is associated with major or clinically relevant non major events and it translates in time away from work and social activities as well as an increased risk of thrombosis due to witholding of anticoagulation. For example a prospective study on 76 women on rivaroxaban and 45 patients on VKA showed a two-fold risk of abnormal uterine bleeding and an associated increased risk of recurrent VTE in women on DOACs compared to those on VKAs.[80] In a post-hoc analysis of the EINSTEIN-CHOICE study, compared with 10 mg rivaroxaban or aspirin, full dose 20 mg rivaroxaban showed numerically more often increased menstrual flow duration and intensity.[81] A study on bleeding events on a random Medicare sample of 1302 dabigatran users and 8102 warfarin users who initiated anticoagulants, showed that dabigatran was associated with a more than twofold hazard rate of vaginal bleeding events relative to warfarin.[82] Similarly, a post-hoc analysis of the Hokusai-VTE study showed that abnormal vaginal bleeding occurred more frequently in women treated with edoxaban than with warfarin (15%/year vs 9%/year, respectively),[83] though none of the reported bleeding was major. Perhaps not all DOACS behave equally: for example apixaban was associated with less than half uterine bleeding events compared with rivaroxaban in a prospective registry.[84] Summary of findings suggests that premenopausal or early menopausal women are more at risk for abnormal uterine bleeding, that a great number of women who experience uterine bleeding while on oral anticoagulants do not have gynecological reasons for this, and that DOACs that require a loading dose for treatment of VTE are associated with the highest incidence of abnormal uterine bleeding.[85]

Treatment of abnormal uterine bleeding is challenging and is not within the scope of this narrative review.

Concluding Remarks: What are We Missing?

Overall, studies addressing specifically efficacy and safety outcomes by sex and gender in the field of anticoagulation are very few, compared with the global number of studies that involve anticoagulation, notwithstanding regulatory rules. Though this attitude is slowly changing, at present there is little and contrasting evidence to measure diretly safety and efficacy of oral anticoagulants by sex and gender (Table 3 for a summary). On average the percentage of women included in the studies is not extremely low but then again it is always below 50% and the trend to improvement is discontinuous. Analysis by sex is at best perfunctory in most studies, and almost none by gender. Yet, we do believe that anticoagulants work also for women, as a whole. In times of individualized medicine and therapies, it would be nice to know a little more, for example concerning the interaction of hormonal changes, both physiological and medication-induced, with anticoagulants and their efficacy, or about gastro-intestinal bleeding, or abnormal uterine bleeding (it would be nice to know, for example, which women are more at risk, so that we can avoid a traumatic period of bleeding at the start of therapy by appropriate management and counselling), or yet again what we can do and what works to increase participation of women in clinical trials and especially in early phase trials of drug development. Finally, it would be useful to know with some grade of confidence whether or not women are equally protected from stroke and other thrombotic adverse events when adequately anticoagulated for non valvular AF.

To include an adequate number of women and to analyze results based on sex and gender in studies throughout the development phases of drugs is not a waste of money and time: it can prevent adverse events, which have been known to sprout from incomplete research starting from pre-clinical and phase 1 and 2 trials. Several recent commentaries and papers underline the need to focus on gender sensitive issues in cardiovascular medicine because (still) not enough scientific studies address them.[22,43,44,86,87]

A number of reasons prevent an equal participation of women and men in clinical trials, not last the very low number of women research leaders.[45] It is also the responsibility of scientific societies to promote culture and sensibility on this topic, and of scientific journals to favour dissemination of gender-sensitive scientific work. Health institutions have rules in place regarding drug development and sex and gender issues, as mentioned above, so it's really up to us, physicians and researchers, to exploit this concern and translate it into hard facts and practice guidelines. The European Society of Cardiology in 2021 published a call to action on the importance of achieving sex- and gender based equity in cardiovascular clinical trials and so did the American Heart Association in 2022.[88-89] Perhaps also scientific societies that deal with venous thromboembolism, anticoagulation, and hemostasis, should follow this example.

ORCID iD

Elena Maria Faioni https://orcid.org/0000-0001-8731-6531

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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