

# Stroke in women: anticoagulation in a complicated puzzle

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## ABSTRACT

Stroke is the third leading cause of death and the most important reason for disability. It is worth noting that 60% of all stroke deaths involve women. This review aims to revise the prothrombotic hemostatic alterations in hypertension along with the often-overlooked role of depression and the job strain of the homemakers' condition proven to be risk factors for stroke. Moreover, the impact of atrial fibrillation and the related oral anticoagulation with either vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC) in women will be discussed. Another point is that women are treated less with anticoagulants than men. Underdosing is also frequent. In our opinion, defensive medicine represents the basic bias, which plays a major role in this contest. The main reasons are the overlooking of the increased cardioembolic risk in women, the fear of an increased bleeding risk, and the wrong concept regarding a hypothetical higher frailty. In conclusion, from a practical point of view, thrombosis centers should consider all these factors when a woman shows a bad quality of anticoagulation with VKA or a poor adherence to DOAC treatment. Underdosing should also be carefully avoided. We hope that the sex gap in terms of inadequate treatment and inclusion in clinical trials will be covered in the future. Lastly, defensive medicine should be strongly discouraged.

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## Introduction

Stroke is the third leading cause of death and the most important reason for disability. It is worth noting that 60% of all stroke deaths involve women who suffer from stroke events because of their longer life expectancy and older age.<sup>1-3</sup> In a series of 1,316 patients with stroke, women were older (mean age 76±0.6 vs. 72±0.6, P<0.01) and had a more severe ischemic event than men (44% vs. 36%, P=0.01). Even 28-day mortality was higher in women (32% vs. 21%, P<0.001).<sup>4</sup> In addition to traditional vascular risk factors (hypertension, diabetes, dyslipidemia, and atrial fibrillation), some sex-specific conditions are to be taken into account: age at menarche, use of hormonal contraception, pregnancy, post-partum, menopause, and hormonal replacement.<sup>5,6</sup> Furthermore, in menopause, the number of estrogenic receptors tends to decrease, provoking the generation of an inflammatory milieu secondary to increased production of cytokines, especially in the cerebral vascular system.<sup>7</sup> This further leads to a hypercoagulable state.<sup>8</sup> This review aims to revise the prothrombotic hemostatic alterations in hypertension, the often-overlooked role of depression, and the job strain of the homemakers' condition as risk factors for stroke.

Moreover, the impact of atrial fibrillation and the related oral anticoagulation in women will be discussed. Finally, we will give some suggestions to the thrombosis centers on the management of women, underlying some practical aspects that could help improve the quality of the anticoagulation, especially in patients with poor control and low adherence to the therapy with either vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs).

## Methods

We examined the MEDLINE database without temporal limits up to February 2024, considering the following keywords:

stroke and women AND hypertension AND depression AND job strain AND atrial fibrillation AND anticoagulation.

The search was limited to papers published in English without limiting the article type, publication year, and geography. They were considered relative to the review aspects and were published in peer-reviewed journals. Screening was carried out by reading titles and abstracts. Then, a further critical review of the texts of the articles was conducted based on the evaluation of the possible impact on the review topics. Subsequent critical assessment of the selected full-text articles was determined based on the assessment of the relevance of topics, clinical questions, study methodology, and reported findings.

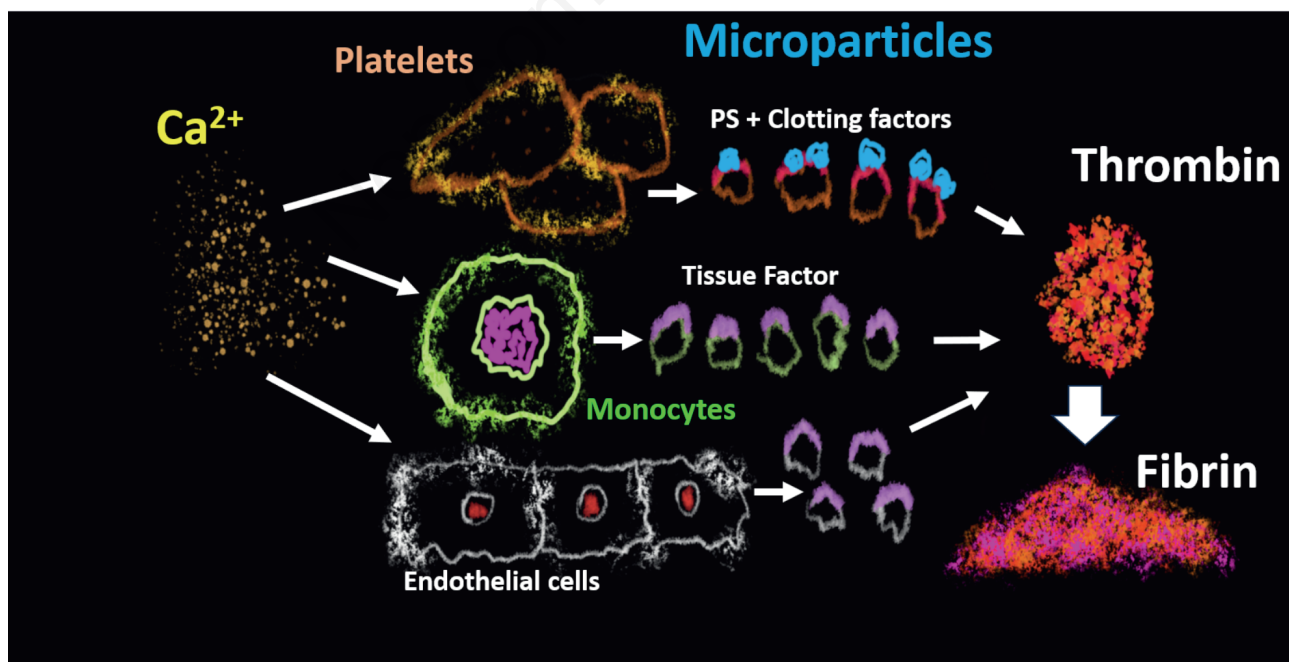
## Hypertension

Hypertension occurs more frequently in women than in men, resulting in an increased risk for cardiovascular diseases.<sup>9,10</sup> We briefly summarise here how hypertension is the basis for the development of major cardiovascular events such as myocardial infarction and stroke through the involvement of several cell lines, which develop a hypercoagulable state. Hypertension leads to cellular dysfunction because of an increase in the  $Ca^{2+}$  influx. High concentration of the intracellular  $Ca^{2+}$  induces the release of microparticles by the endothelial cells, monocytes, platelets, and red blood cells.<sup>11</sup> In particular, angiotensin II has been found to provoke the formation of microparticles from monocytes *in vitro*.<sup>12</sup> All these cells produce microparticles, which carry on their membrane phosphatidylserine and tissue factor. The first allows the adsorption, via the gamma-carboxyglutamic acid (GLA) residues, of clotting factors (VII, IX and X, and prothrombin). GLA

residues provide a bridge with the platelet phospholipids via the  $Ca^{2+}$  while tissue factor forms a complex with factor VII, leading to the activation of factors IX and X, thus producing thrombin generation. In other words, the two systems are bilaterally integrated (Figure 1).<sup>13</sup> Several markers of a hypercoagulable state have been found to be related to both systolic and diastolic arterial pressure,<sup>14</sup> thus indicating that fibrin deposition does occur in the vessels of hypertensive patients, leading to atherosclerosis and its macrovascular complications such as stroke and myocardial infarction. Nevertheless, the involvement of microparticles in the initiation and progression of atherosclerosis has been proven to occur by activating even other mechanisms such as increased endothelial permeability, inflammation and chemo-attraction of leukocytes, foam cells formation, neovascularization, and muscle cells proliferation and migration.<sup>15</sup>

## Depressive disorders

Major depression, dysthymia, recurrent brief depression, and depressive personality represent the different types of depression disorders (DD),<sup>16</sup> which confer an increased risk of developing acute myocardial infarction, heart failure, or stroke, as stated by the Committee of the Council on Cardiovascular Disease in the Young. In particular, major depressive and bipolar disorder among youth are to be considered as a moderate risk condition for developing atherosclerosis and its early vascular complications. A number of reasons have been identified such as: oxidative stress, endothelial dysfunction, sedentary lifestyle, abnormal nutrition, tobacco, substance abuse, and II generation of antipsychotic drugs.<sup>17</sup> Some years ago, a meta-analysis and systematic review



**Figure 1.** In a hypertensive milieu,  $Ca^{2+}$  influx induces the release of microparticles carrying phosphatidylserine and tissue factor. The former allows the adsorption of clotting factors while the second triggers coagulation. Both provoke thrombin generation which in turn produces fibrin (handmade by FM using I-PAD Pro and Procreate software).

dedicated to depression and stroke considered 28 prospective cohort studies (for 317,540 participants).<sup>18</sup> Stroke was reported in 8,478 cases for a follow-up period lasting up to 29 years. The pooled hazard ratio (HR) was 1.25 [95% confidence interval (CI), 1.11-1.40] for ischemic stroke and 1.45 (95% CI, 1.29-1.6) for total stroke. The authors concluded that the increased risk of total stroke was associated with depression across most subgroups. The authors explained their findings by further several mechanisms such as the sympathetic nervous system activation, the activation of the adrenocortical axis, and the development of an inflammatory condition. As a matter of fact, C-reactive protein, interleukin (IL)-1, and IL-6 have been found to be associated with DD.<sup>19</sup> On the other hand, high IL levels are known to be associated with an increased risk for stroke.<sup>20</sup> DD are often under-recognized and more prevalent in women than men. The large Women's Health Initiative Observational Study considered 93,676 postmenopausal women followed for 4.1 years. Risks of cardiovascular disease (CVD) were computed by means of Cox proportional hazard models adjusted for demographic, clinical, and risk factor covariates. A high percentage of around 16% was discovered during the screening process for depressive symptoms. Depression was significantly associated with cardiovascular risk and comorbidity [odds ratios (OR) from 1.12 for hypertension to 1.60 for history of stroke or angina].<sup>21</sup> Even in women with a negative history of CVD, depression resulted to be an independent predictor of CVD death (relative risk, 1.50) and all-cause mortality [relative risk (RR), 1.32] after adjustment for age, ethnicity, education, income, diabetes, hypertension, smoking, high cholesterol level, body mass index, and physical activity. An important finding was that antidepressant drugs did not reveal any impact on the depression-associated risks. Bucciarelli *et al.* recently focussed attention on the association between depression and stroke in women.<sup>22</sup> They reported other mechanisms involved in this topic such as abnormal behavioral habits (smoking, lack of physical activity, and patchy rest) along with poor adherence to pharmacological treatment. The latter could be of paramount importance in chronic conditions such as atrial fibrillation in which oral anticoagulation is almost mandatory. Finally, they stated that DD may be present in 20-25% of women throughout their life, a figure not always well known (Figure 2). When 563,255 participants (73% women) were analyzed,<sup>23</sup> depressive symptoms were found to be associated with CVD incidence, even considering lower levels than those indicative of DD. It is worth noting that this association remained after adjustment for several cardiovascular risk factors on one hand and that the spectrum of depressive symptoms was wide including people with low mood. These findings, although of modest significance, highlight the difficulty in discovering patients characterized by mild depressive symptoms. Another important issue is that referred to a poorer quality of life of women after a stroke in comparison with men. A more severe stroke and a pre-stroke depression have been found to characterize this critical scenario.<sup>24</sup>

## Job strain

An often-unrecognized risk factor is the job strain of women. In other words, how much do women work? In 1979, Karasek introduced the concept of how the job, in general, could be evaluated.<sup>25</sup> A combination of job demand, *i.e.*, the quantitative workload and job control, known to be the enabling factors to

make decisions on one's job, along with the possibility of learning to develop new skills, may lead to different jobs. The association of high demand and low control, as it happens, for instance, in manual and repetitive jobs, leads to a high-strain job, which confers a significant high physical and mental stress.<sup>26</sup> The results of a longitudinal study showed that people submitted to a persistently high job strain (high demand, low control) were at a higher risk of developing major depression than those who experienced a low job strain.<sup>27</sup> High job strain is, therefore, *per se* associated with an increased risk of stroke, especially in women (RR 1.33, 95% CI 1.04-1.69), as shown by a meta-analysis which considered six prospective cohort studies including 138,782 people.<sup>28</sup> Several mechanisms could explain these findings. First, work-related stress can encourage unhealthy behavior such as smoking, limited physical activity, bad eating habits, metabolic syndrome,<sup>29</sup> diabetes, and obesity.<sup>30</sup> Second, as reported for DD, high job strain can elicit an elevated inflammatory response as reported by Emeny *et al.*<sup>31</sup> In their study, people with high job strain showed higher monocyte chemoattractant protein-1, IL-8, and IL-18 in comparison with those without high job strain. Similar results were obtained as far as high-sensitivity C-reactive protein, IL-6, and soluble intercellular adhesion molecule-1. From a clinical point of view, job strain resulted associated with incident coronary events using a Cox proportional hazard models (HR=2.57, 95% CI 1.09-6.07) substantially confirmed after adjustment for CHD risk factors (2.35, 1.003-5.49). This study is important since the results come from an average follow-up of 12 years although the final sample size was small (114 cases with high job strain and 913 controls). In addition, a high-strain job was associated with



**Figure 2.** Depression is often overlooked but it is a risk factor for ischemic stroke in women (handmade by Nicolò Meloni, 9 years old).

female sex, lower education, and working outside the workplace. In women, the higher proportion of high job strain makes them more susceptible to negative health-related outcomes.<sup>32</sup> Homemakers had a higher hazard for CVD compared with full-time workers (HR=2.34, 95% CI 1.35 to 4.04), as demonstrated by a study carried out in the Netherlands in 2022.<sup>33</sup> In this study the baseline data of 18,058 participants without CVD from the population-based, multi-ethnic Healthy Life in an Urban Setting study (Amsterdam, the Netherlands) were linked to CVD incidence data in 2013-2018. They studied the association of time spent on household work, doing home repairs, and working in a male or female-dominated occupation with CVD incidence. Interestingly, employed women had a lower risk of mortality than homemakers (HR=0.65, 95% CI 0.49-0.86).<sup>34</sup> The findings of this study were later confirmed by Carson *et al.*, who showed that women working outside their homes had a decreased risk of CHD (HR=0.70; 95% CI 0.56-0.86) and ischemic stroke (HR=0.62; 95% CI 0.47-0.84) in comparison with homemakers.<sup>35</sup> These results again point out the condition of the homemakers, especially if elderly. Higher domestic workload was reported to be associated with increased psychological distress, suboptimal self-rated health, and cardiovascular health risks thus further reducing the quality of life of women. The results of a study from Sweden further sustain all these concepts:<sup>36</sup> women living in an unbalanced condition related to an unequal distribution of household duties showed significantly higher levels of stress, fatigue, physical/psychosomatic symptoms, and work-family conflicts in comparison with women living in a more equal environment. All these negative observations are to be added to the other two difficult situations, *i.e.*, those linked to childbearing and the caregiver's activity. While the presence of children improves psychological fatigue,<sup>37</sup> the latter confers a high-stress condition which has a negative impact on the quality of life.<sup>38</sup> If we consider that caregivers in daily life are almost always women, this has one more negative impact that contributes to high job strain. Consequently, it appears paramount to consider the effects of domestic work and work-family conflicts, attempting to improve the quality of their life. Therefore, a strategy to reduce domestic work stress is warranted by remodeling the gender roles at home. The support of families is to be encouraged by clearly explaining the risk of cardiovascular diseases in these women.<sup>39</sup>

## Atrial fibrillation

### Non-anticoagulated patients

Atrial fibrillation (AF) is a cardiac arrhythmia which represents an important risk factor for stroke and thromboembolic events.<sup>40</sup> In non-anticoagulated patients, ischemic stroke rates were higher in women than in men, as reported by a large Swedish study: 6.2% vs. 4.2% per year,  $P < 0.0001$ .<sup>41</sup> The HR was 1.47 (96% CI 1.40 to 1.54) when women were compared with men, thus indicating a significant increase of stroke (45%) in women. However, when age  $< 65$  years and a CHADS<sub>2</sub> score between 0 and 1 (*i.e.*, CHA<sub>2</sub>SDS<sub>2</sub>-VASc 2 or less because in this score, female sex is included) were considered, the risk remained higher in women but was no longer statistically different in comparison with men (0.7 vs. 0.5%,  $P = 0.09$ ). In another large national Danish study, only women aged  $\geq 75$  years showed a significantly increased risk of stroke (1.20, 95% CI 1.12-1.28).<sup>42</sup> In addition, two

years later, a systematic review found an increased risk for stroke in women with AF, especially in patients aged  $\geq 75$  years.<sup>43</sup> Thereafter, Nielsen *et al.*, analysing three nationwide registries (239,671 patients), demonstrated that female sex is a modifier risk factor for thromboembolism in AF rather than an independent one.<sup>44</sup> Consequently, they asked for not removing the sex component (Sc) from the CHA<sub>2</sub>DS<sub>2</sub>-VASc score,<sup>45</sup> as recommended by the guidelines from Australia and New Zealand (the CHA<sub>2</sub>DS<sub>2</sub>-VA score),<sup>46</sup> to avoid an underestimation of the whole thromboembolic risk in women,<sup>47</sup> further favouring the underuse of anticoagulation in this category of patients with AF. Following all these correct and wise observations, a European Heart Rhythm Association position paper stated that the female sex is to be evaluated as a modifier risk in the presence of other components of the CHADS<sub>2</sub>VA factors and not as an independent risk factor for stroke.<sup>48</sup> Therefore, AF patients aged  $< 65$  years, with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 due to female sex only, have an annual stroke rate of  $< 1$  and are not to be prescribed anticoagulation. On the contrary, females with AF and  $> 1$  additional stroke risk factor (*i.e.*, with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$ ) should be considered for anticoagulation. Why are women at increased risk of AF? A difference between women and men is likely because female sex hormones exert a protective action toward AF. This could explain why the incidence of AF is increased in post-menopausal women, as suggested by Tse *et al.*<sup>49</sup> who demonstrated a menopause effect in atrial electrophysiologic changes secondary to rapid atrial pacing and an increased atrial pressure. Another possible risk factor has been proposed: the different expression of fibrosis-related genes in women, which could explain why AF catheter ablation shows reduced success in comparison with men.<sup>50</sup>

### Anticoagulated patients

A large meta-analysis dealing with sex differences in stroke in patients with atrial fibrillation analyzed 44 studies comprising 993,603 patients (48.9% women).<sup>51</sup> After pooling the data, an increased risk for stroke was found in women in comparison with men (HR=1.24, 95% CI 1.14-1.36). The HR reached a statistical significance when women aged more than 65 years were considered. Conversely, it decreased concomitantly with the increasing use of oral anticoagulants, becoming not significant only when the use of the drugs was greater than 42%.<sup>52</sup> Another large meta-analysis of randomized controlled trials (RCT) considered both VKAs (warfarin) and DOACs. Women treated with warfarin showed a significantly higher residual risk of cardio-embolism when compared with men (OR 1.27, 95% CI 1.11-1.47) but a not significant difference as for bleeding (OR 0.92, 95% CI 0.81-1.05).<sup>52</sup> The results related to DOAC, instead, showed that there was no difference between women and men in terms of residual risk of cardio-embolism (OR 1.14, 95% CI 0.97-1.35) while bleeding was less present in women (OR 0.84, 95% CI 0.74-0.95). The disappointing results of warfarin's use may be explained by the less time spent by women within the therapeutic range (TTR), as we already reported.<sup>53</sup> In that experience, the women's TTR was related to regular vegetable intake (92% vs. 74%,  $P = 0.02$ ), assumption of other drugs (91% vs. 72%,  $P = 0.02$ ), and intercurrent disease (92% vs. 76%,  $P = 0.04$ ) in comparison with men. More recently, Avarello *et al.* confirmed our findings demonstrating a lower TTR in women. The explanation was not based on differences in age or comorbidity.<sup>54</sup> During the anticoagulation

with VKA, even the overdoses have been found to be more frequent in women than in men.<sup>55</sup> On that occasion, from January 2004 to December 2020, 1,230 patients with venous thromboembolism or atrial fibrillation were considered. Age, sex, type of VKAs, clinical indications, INR values and bleeding events were recorded. TTR was computed considering the entire period of treatment. The median amount of over-anticoagulation per year was significantly higher in females (0.39-year) than in males (0.28-year). The episodes of over-anticoagulation per year were found to be significantly associated with female sex, atrial fibrillation, warfarin therapy, follow-up length longer than four years, and TTR <73%, but not with bleeding episodes. These findings can further explain the lower TTR in women. Interestingly, the recovery of INR was achieved faster in patients treated with acenocoumarol, thus suggesting that it could replace warfarin in patients who present several episodes of over-anticoagulation. This phenomenon can be explained by the shorter half-life of acenocoumarol compared to that of warfarin. However, it should be recalled that acenocoumarol has an effect that is approximately twice that of warfarin.<sup>56</sup> Despite women with AF having a higher cardioembolic risk, they appear to be significantly less treated with oral anticoagulants (56.7% vs. 61.3%;  $P < 0.001$ ), whatever the  $CHA_2DS_2$ -VASc score. This is what the PINNACLE National Cardiovascular Data Registry found analyzing the records from 2008 to 2014.<sup>57</sup> Even with the increasing use of DOAC, women continue to be less treated with anticoagulants in comparison with men. The authors tried to explain these findings by the bias in following the guidelines on managing AF, overlooking the increased cardioembolic risk, the fear of an increased bleeding risk, and the wrong concept regarding a hypothetical higher frailty. Moreover, a large Spanish cohort study on 123,250 people starting oral anticoagulation found that women were more often underdosed with DOAC [39% of women vs. 27.4% of men ( $P < 0.001$ )] despite having a higher risk of stroke than men at baseline ( $CHA_2DS_2$ -VASc 3.9+1.4 vs. 2.6+1.6).<sup>58</sup>

## Discussion

This review aimed to focus on one aspect of an important issue: stroke in women. We hoped to report here not only the pathophysiology of some risk factors in women, such as hypertension and atrial fibrillation but also to highlight two overlooked risk factors, such as depression and job strain. Both seem to be linked because depression may come from a difficult and poor quality of life characterized by a high job strain. Both can put women in a risk zone for stroke, as we reported above. These women deal with their husbands, sons, and nephews along with their homemakers' "duties", such as cooking and taking care of all the other housework (Figure 3). Depression and a high job strain should be carefully considered by the thrombosis centers when a woman shows a bad quality of anticoagulation with VKA or poor adherence to DOAC treatment. Some simple questions could be used to obtain information on a possible depressive condition as suggested by Bucciarelli *et al.*<sup>20</sup> and the European Society of Cardiology:<sup>59</sup> "Do you feel down, depressed or hopeless?" and "Have you lost interest and pleasure in life?". It could also be added: "How many hours do you work daily at home?" Another point we have reported is that women are less treated with anticoagulants than men. In our opinion, the basic bias is represented by defensive medicine, which plays a major role in this contest. Defensive medicine is characterized by the behaviour of physicians toward ordering redundant and useless tests, procedures, and visits, along with the avoidance of managing patients thought to be at high risk of bleeding far from evidence-based medicine.<sup>60</sup> The aim of this blameworthy behaviour is to limit malpractice liability. On the other hand, defensive medicine is very expensive and may lead patients to either complications due to unnecessary tests and procedures or the lack of appropriate care.<sup>61</sup> Efforts should be made to limit defensive medicine as much as possible. Doctors should be encouraged to be empathic since patients like



**Figure 3.** Homemakers are exposed to a high job strain and depression. Both can confer an increased risk for stroke (handmade by Marzia Barcellona using I-PAD Pro and Procreate software).

to be listened to on the one hand and discuss their problems on the other without feeling that their time is somewhat limited.<sup>62</sup> Nevertheless, a better organization of the health structures should be pursued by supporting doctors to be closer to evidence-based medicine and to discuss the patients' problems with other colleagues, especially if the decision-making process is difficult.<sup>63</sup> The underrepresentation of women in the most important clinical trials, both in the warfarin and DOAC arms, is a further relevant criticism.<sup>48</sup> A recent meta-analysis reported that the median enrolment rate of women in 300 RCT, addressed to several specialties, was 41% [interquartile range (IQR) 27-54%]. This percentage was even lower for women  $\geq 63$  years (33%, IQR 20-46%).<sup>64</sup> Low inclusion rates of women in RCT, especially if elderly, may lead to missing important information about the adverse effects and the pros and cons of any given treatment. Drug activities may differ between women and men, particularly in terms of pharmacokinetics and/or pharmacodynamics.<sup>65</sup> This may lead to non-correct dosing of the anticoagulants. It is worth noting that in the USA, the National Institutes of Health have developed an Outreach Notebook to facilitate the enrolment of women in clinical trials and better address the research on women's health.<sup>66</sup>

This review has some limitations, which deserve some comments. First, not all risk factors of stroke in women have been discussed because we chose to favour some aspects often overlooked in daily clinical practice. The readers are referred to the reviews on these topics cited in the Introduction. We chose to include in this review the most important issues, especially those often overlooked, such as depression and joint strain. Second, we report only the results of two meta-analyses related to both warfarin and DOAC. Reporting phase four studies was outside the scope of the present review. Third, we did not suggest any intervention to improve the quality of life of women treated with anticoagulants. In our opinion, these are topics that dedicated specialists should address.

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## Conclusions

This review aims to revise some aspects related to the increased risk of stroke in women, focussing on the most important risk factors. Depression and job strain were also included since we believe that the thrombosis centers should expand their skills in the management of oral anticoagulants. We hope that the sex gap in terms of inadequate treatment and inclusion in clinical trials will be covered in the future. Lastly, defensive medicine should be strongly discouraged.

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