Editorial to accompany Feinberg JB, et al.

**Beyond individual risk factors in atrial fibrillation:**

**The interaction of hypertension and sex**

Eduard Shantsila,1,2 Alena Shantsila,1 Gregory YH Lip1,3

1Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, UK.

2Department of Primary Care and Mental Health, University of Liverpool, UK

3 Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Denmark.

**Correspondence:**

Prof Gregory Y H Lip

gregory.lip@liverpool.ac.uk

Hypertension is globally the most common independent risk factor for atrial fibrillation. Patients with hypertension have a 1.5-2.0 times higher risk of atrial fibrillation, which occurs in more than 15% of hypertensive patients.1 In the Atherosclerosis Risk in Communities (ARIC) cohort study of 14,598 middle-aged people, hypertension explained approximately 25% of AF cases as opposed to on 3% attributable to diabetes mellitus.2 Unsurprisingly, hypertension is present in around 70% of atrial fibrillation patients (34-84%), and patients with left ventricular hypertrophy had 3.4-fold higher odds of developing atrial tachyarrhythmias.3 Hypertension does not only increase the risk of hypertension incidence but also the risk of thromboembolic complications in those with atrial fibrillation. In the ROCKET AF trial, for example, the risk of stroke and systemic embolism increased by 7% for every 10mmHg increase in screening systolic blood pressure.4

A meta-analysis of 27 randomised controlled trials of antihypertensive agents (n=214,763) showed that antihypertensive therapy reduced the risk of atrial fibrillation by 10% (relative risk 0.90, 95% confidence interval 0.86-0.94) with even more prominent effect in patients with heart failure.5 Moreover, strict blood pressure control is essential for preventing atrial fibrillation in people with pre-existing hypertension.5 Indeed, atrial fibrillation should be regarded as one manifestation of hypertensive target organ damage.

Hypertension contributes to various clinical complexities as a risk factor for their development (chronic kidney disease, heart failure, dementia) and prognosticator of treatment complications (e.g., falls in people with frailty). In patients with atrial fibrillation, the GLORIA-AF registry analysed domains of clinical complexity including frail elderly, chronic kidney disease, and history of bleeding, which were recorded in 32% of participants.6 Clinical complexity was associated with approximately 2-fold lower rates of oral anticoagulation prescription, a significantly higher rate of discontinuation of oral anticoagulation if prescribed, and a 1.6-fold higher risk of the combined outcome of all-cause death, thromboembolism, and major bleeding.

While oral anticoagulation is the current standard for stroke prevention in atrial fibrillation7, it does not abolish the problem completely. ‘On-treatment strokes’ do happen and still remain an unmet challenge. A likely solution is more intensive stroke prevention and comorbidity management in high-risk patients, eg. by combined oral anticoagulation with meticulous (possibly with stricter targets) blood pressure control. To achieve individualised combination antithrombotic therapy, precision predictive health modelling with blood pressure is important, being a dynamically changing predictor of complications of atrial fibrillation itself (stroke, heart failure) and oral anticoagulation. Indeed, the risk of stroke is dynamic, changing with ageing and incident comorbidities8 9.

In this issue of Am J Hypertension, the clear sex differences in lifespan trends in cardiovascular risk, further explored by the study by *Feinberg et al.10* should be considered for optimising management of the atrial fibrillation-hypertension population cluster. This posthoc analysis from the LIFE trial provides a unique insight into possible biological sex differences and their interactions with poorly controlled hypertension at a historical period when anticoagulation was not necessarily a well-established treatment for atrial fibrillation, the direct oral anticoagulants (DOACs) did not exist, and before the modern stricter thresholds for blood pressure control were introduced. The findings by *Feinberg et al.10* call for further research using contemporary data to detail the effects of temporal changes in blood pressure for prognostication and treatment choice.

An additional challenge of combining hypertension management with DOACs is the impact of polypharmacy of the effectiveness and safety of anticoagulation. One recent study of 254,478 AF patients from a contemporary dataset showed that polypharmacy was associated with more strokes and systemic embolic events, bleeding events and mortality.11 Most patients need multiple pharmacological agents to achieve adequate control but despite this, many patients still have resistant hypertension when target blood pressure cannot be achieved using three antihypertensive drugs, with too hard-to-predict effects when atrial fibrillation occurs.

The effects of sex and atrial fibrillation-related risks are complex, likely underlying the background differences in risk factor profile, as well as differences in susceptibility to atrial fibrillation and its interactions with cardiometabolic changes occurring at various paces in men and women across the life course. Even though atrial fibrillation onset is typical of the postmenopausal phase of life in women, postmenopausal changes are gradual and may manifest later in life (e.g. risk of osteoporosis). To add to the complexity of the effects of sex hormone changes, hormone replacement therapy may be used in many women. However, the frequency, duration and patterns of their use (e.g., enteral or transdermal) vary substantially geographically and culturally and change over time in response to their popularity affected by conflicting evidence of their benefits and safety.

A 30-70% higher incidence and prevalence of atrial fibrillation in men than in women is reported by most studies. However, the lifelong risk of atrial fibrillation is similar in men in women if the longer life expectancy in women is considered.12 Most studies report a higher risk of mortality and stroke in women.13 However, this may also reflect the fact that women tend to develops atrial fibrillation at a more advanced age, one of the single strongest predictors of their mortality. However, female sex is a risk modifier rather than a stroke risk factor per se. The stroke risk in atrial fibrillation amongst females has an age dependency, and those who are age ≥65 or in those with another non-sex stroke risk factor, being female increases stroke risk14,15. Highlighting the risk of stroke in female patients with atrial fibrillation is important, given their suboptimal stroke prevention16 and the more severe and disabling strokes that occur amongst females15.

The fact that women tend to be older at the time of AF diagnosis also leads to a higher number of other co-existing risk factors for stroke in AF.14 Socio-economic and psychological factors and reduced healthcare access may also play a role. The sex disparity in access and use of oral anticoagulation is an important consideration in reducing sex-related health inequalities. 16 17 The risk of stroke was similar in men and women with atrial fibrillation who received oral anticoagulation.17

What about symptoms? Several registries have demonstrated that women with atrial fibrillation have more symptoms than men.18 Sex-related psychological factors, including the stress response, may also contribute, but it is unclear whether more symptoms influence treatment modalities offered by clinicians. However, recent data highlight the importance of timely detection of atrial fibrillation, as asymptomatic atrial fibrillation carries a similar risk of adverse events as symptomatic atrial fibrillation.19 This justifies opportunistic screening to reduce the approximately 10% of ischemic strokes related to undiagnosed atrial fibrillation.

The study by *Feinberg et al.10* emphasises the need for holistic or integrated care of atrial fibrillation, as supported by the guideline-recommended 'Atrial fibrillation Better Care' (ABC) pathway7, which unifies key concepts of management of atrial fibrillation, including anticoagulation, symptom optimisation with rate or rhythm control, and meticulous control of co-morbidities, such as hypertension and lifestyle. One systematic review of studies reporting the prevalence of ABC-pathway-adherent management in atrial fibrillation patients treated according to the ABC pathway showed a lower risk of all-cause death (odds ratio 0.42, 95% confidence interval 0.31-0.56), cardiovascular death (odds ratio 0.37, 95% CI 0.23-0.58), stroke (odds ratio 0.55, 95% confidence interval 0.37-0.82) and major bleeding (odds ratio 0.69, 95% confidence interval 0.51-0.94).20 Emerging digital technologies may help improve adherence to the ABC pathway, with evidence for the efficacy of an integrated care approach in improving the prognosis in patients with atrial fibrillation.21 Things can only get better when addressing hypertension patients with atrial fibrillation or complications related to atrial fibrillation.

REFERENCES

1. Rahman F, Yin X, Larson MG, Ellinor PT, Lubitz SA, Vasan RS, McManus DD, Magnani JW and Benjamin EJ. Trajectories of Risk Factors and Risk of New-Onset Atrial Fibrillation in the Framingham Heart Study. *Hypertension*. 2016;68:597-605.

2. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S and Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:1501-8.

3. Chatterjee S, Bavishi C, Sardar P, Agarwal V, Krishnamoorthy P, Grodzicki T and Messerli FH. Meta-analysis of left ventricular hypertrophy and sustained arrhythmias. *The American journal of cardiology*. 2014;114:1049-52.

4. Vemulapalli S, Hellkamp AS, Jones WS, Piccini JP, Mahaffey KW, Becker RC, Hankey GJ, Berkowitz SD, Nessel CC, Breithardt G, Singer DE, Fox KA and Patel MR. Blood pressure control and stroke or bleeding risk in anticoagulated patients with atrial fibrillation: Results from the ROCKET AF Trial. *Am Heart J*. 2016;178:74-84.

5. Emdin CA, Callender T, Cao J and Rahimi K. Effect of antihypertensive agents on risk of atrial fibrillation: a meta-analysis of large-scale randomized trials. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2015;17:701-10.

6. Romiti GF, Proietti M, Bonini N, Ding WY, Boriani G, Huisman MV, Lip GYH and Investigators G-A. Clinical Complexity Domains, Anticoagulation, and Outcomes in Patients with Atrial Fibrillation: A Report from the GLORIA-AF Registry Phase II and III. *Thromb Haemost*. 2022;122:2030-2041.

7. Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, Guo Y, Sriratanasathavorn C, Oh S, Okumura K and Lip GYH. 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. *Thromb Haemost*. 2022;122:20-47.

8. Domek M, Gumprecht J, Mazurek M, Chao TF and Lip GYH. Should We Judge Stroke Risk by Static or Dynamic Risk Scores? A Focus on the Dynamic Nature of Stroke and Bleeding Risks in Patients With Atrial Fibrillation. *Journal of cardiovascular pharmacology*. 2019;74:491-498.

9. Lip GYH, Genaidy A, Tran G, Marroquin P, Estes C and Sloop S. Improving Stroke Risk Prediction in the General Population: A Comparative Assessment of Common Clinical Rules, a New Multimorbid Index, and Machine-Learning-Based Algorithms. *Thromb Haemost*. 2022;122:142-150.

10. Feinberg JB, Nielsen EE, Kjeldsen SE, Devereux RB, Gerdts E, Wachtell K, Olsen MH. Sex differences in atrial fibrillation and associated complications in hypertensive patients with left ventricular hypertrophy: The LIFE study. Am J Hypertension 2023.

11. Grymonprez M, Petrovic M, De Backer TL, Steurbaut S and Lahousse L. The Impact of Polypharmacy on the Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Thromb Haemost*. 2023.

12. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M and Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837-47.

13. Scheuermeyer FX, Mackay M, Christenson J, Grafstein E, Pourvali R, Heslop C, MacPhee J, Ward J, Heilbron B, McGrath L and Humphries K. There Are Sex Differences in the Demographics and Risk Profiles of Emergency Department (ED) Patients With Atrial Fibrillation and Flutter, but no Apparent Differences in ED Management or Outcomes. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 2015;22:1067-75.

14. Nielsen PB, Skjoth F, Overvad TF, Larsen TB and Lip GYH. Female Sex Is a Risk Modifier Rather Than a Risk Factor for Stroke in Atrial Fibrillation: Should We Use a CHA(2)DS(2)-VA Score Rather Than CHA(2)DS(2)-VASc? *Circulation*. 2018;137:832-840.

15. Nielsen PB and Overvad TF. Female Sex as a Risk Modifier for Stroke Risk in Atrial Fibrillation: Using CHA2DS2-VASc versus CHA2DS2-VA for Stroke Risk Stratification in Atrial Fibrillation: A Note of Caution. *Thrombosis and haemostasis*. 2020;120:894-898.

16. Pilcher SM, Alamneh EA, Chalmers L and Bereznicki LR. The Tasmanian Atrial Fibrillation Study (TAFS): Differences in Stroke Prevention According to Sex. *The Annals of pharmacotherapy*. 2020;54:837-845.

17. Shantsila E, Wolff A, Lip GY and Lane DA. 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. Paquette M, Roy D, Talajic M, Newman D, Couturier A, Yang C and Dorian P. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. *The American journal of cardiology*. 2000;86:764-8.

19. Wallenhorst C, Martinez C and Freedman B. Risk of Ischemic Stroke in Asymptomatic Atrial Fibrillation Incidentally Detected in Primary Care Compared with Other Clinical Presentations. *Thromb Haemost*. 2022;122:277-285.

20. Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, Gumprecht J, Koziel M, Yang PS, Guo Y, Lip GYH and Proietti M. Adherence to the 'Atrial Fibrillation Better Care' Pathway in Patients with Atrial Fibrillation: Impact on Clinical Outcomes-A Systematic Review and Meta-Analysis of 285,000 Patients. *Thromb Haemost*. 2022;122:406-414.

21. Romiti GF, Guo Y, Corica B, Proietti M, Zhang H, Lip GYH and m AFAIIti. Mobile Health-Technology-Integrated Care for Atrial Fibrillation: A Win Ratio Analysis from the mAFA-II Randomized Clinical Trial. *Thromb Haemost*. 2023.