ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–3
https://doi.org/10.1093/eurheartj/ehad738

EDITORIAL
Arrhythmias

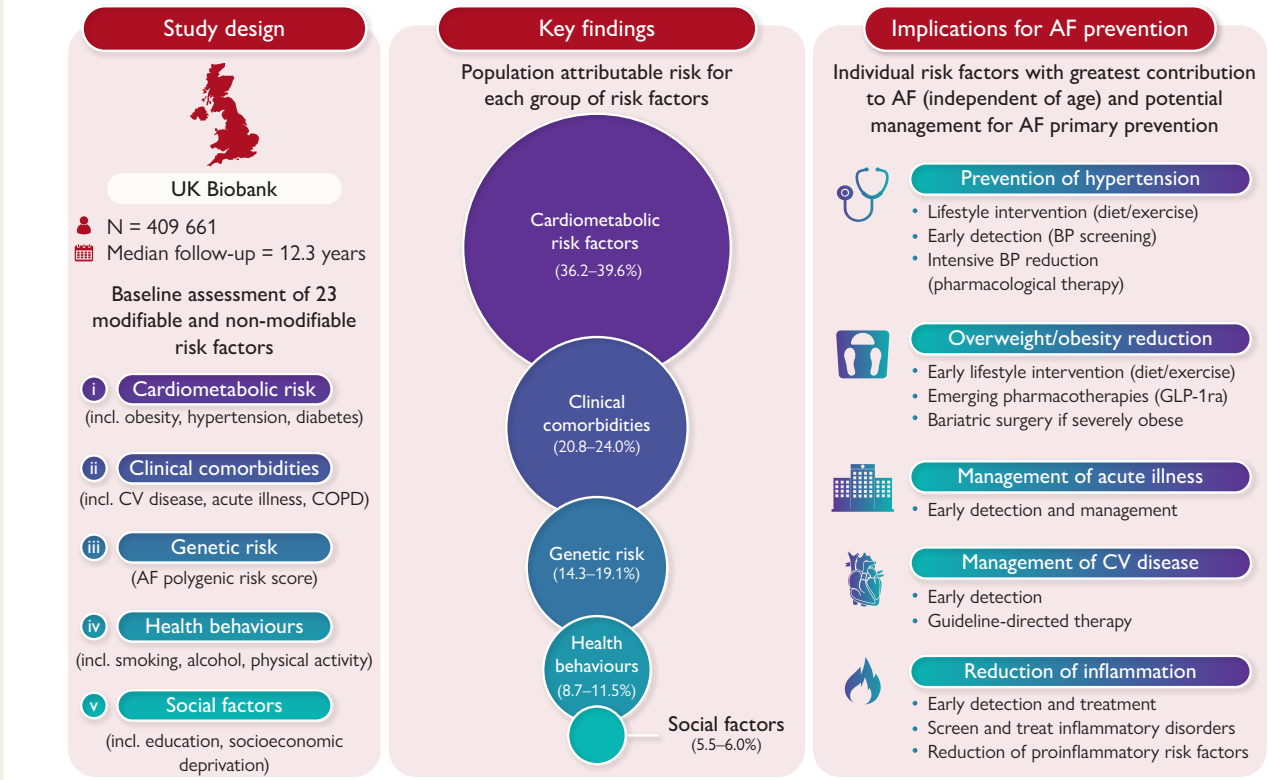
Prevention of atrial fibrillation: a call to action

Adrian D. Elliott [1]*, Emelia J. Benjamin [2,3], and Melissa E. Middeldorp [1]

[1]Centre for Heart Rhythm Disorders, University of Adelaide, South Australian Health & Medical Research Institute and Royal Adelaide Hospital, 5000, Adelaide, Australia; [2]Cardiovascular Medicine Sections, Department of Medicine, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA; and [3]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

This editorial refers to 'Acquired risk factors and incident atrial fibrillation according to age and genetic predisposition', by N. Wang *et al.*, https://doi.org/10.1093/eurheartj/ehad615.

Graphical Abstract



Cardiometabolic risk factors, most notably obesity and hypertension, have the greatest population-attributable risk (PAR) for atrial fibrillation (AF). The five individual risk factors with the highest PAR for AF were hypertension, obesity, acute illness, cardiovascular disease, and inflammation. We propose five key strategies to manage these risk factors for the primary prevention of AF.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +61 883139000, FaX: +61 883622273, Email: adrian.elliott@adelaide.edu.au

For over three decades, there has been substantial evidence that atrial fibrillation (AF) is promoted in the presence of a broad range of modifiable and non-modifiable risk factors.[1] The incidence of AF is rising, driven by an ageing population, increased surveillance,[2] and global increases in lifestyle-based risk factors such as hypertension and obesity.[3] Every year, our understanding of risk factors deepens as we uncover additional known risks and incorporate newly identified factors that have emerged from large population studies, including genetic susceptibility, ancestry, and social determinants of health.[4,5] Similar to other major health conditions, the list of likely causative mechanisms may be apparent, but how we can reconcile this information and initiate population-wide interventions to reduce AF incidence is largely unknown.

In this issue of the *European Heart Journal*, Wang *et al.*[6] utilize the UK Biobank to provide us with insights into the relative contribution of social factors, health behaviours, cardiometabolic risk factors, and clinical comorbidities to the incidence of AF across individuals stratified by age and genetic risk. This approach has the potential advantage of enabling prioritization of primary prevention and screening strategies to manage the increasing trends in AF that promise to pressure healthcare systems globally and substantially increase cardiovascular disease morbidity and mortality.

The authors have leveraged the UK Biobank cohort, with the assessment of clinical comorbidities, cardiometabolic risk factors, social and behavioural factors, alongside genetic risk quantified using AF-specific polygenic risk scores. Using these factors, the authors have quantified the population-attributable risk (PAR) for each risk factor amongst the 409 661 individuals who were followed for a median of 12.3 years. The contribution of each risk factor was assessed within participants grouped by age and genetic risk to determine if the PARs for each group of risk factors differed.

There are several key findings worth highlighting: cardiometabolic factors, notably hypertension and obesity, carried the greatest PAR when stratified either by age or by genetic risk tertile. The contribution of genetic risk was greatest in participants within the younger age group (40–49 years), whilst the contribution of cardiometabolic factors and clinical morbidities declined slightly with increasing genetic risk. In younger participants, the contribution of clinical comorbidities was also greater than in older participants. In the UK Biobank cohort, the relative contribution of social factors (education, socioeconomic deprivation, and air pollution) was modest across all age and genetic risk groups.

There are obvious strengths in this analysis, which utilizes a comprehensive combination of risk factors. It is firmly established that AF is promoted by multiple risk factors which, when combined into a clinical risk score, provide reasonable predictive value for the development of AF. The current analysis advances this by assessing all available risk factors simultaneously and exploring the potential for differing contributions across age and genetic risk groups. The authors also conducted several sensitivity analyses, including adjusting for the competing risk of death, and multiple imputation for missing data. Collectively, the study findings may guide the prioritization of initiatives to reduce risk factors and potentially refine models to predict which individuals may be most likely to have AF detected on targeted screening.

The findings by Wang *et al.* highlight and reinforce that the key to AF prevention is through the reduction of prevalent cardiometabolic risk factors, particularly hypertension and obesity (*Graphical Abstract*). In the UK Biobank, 30%–35% of incident AF diagnoses could be attributed to hypertension and obesity alone, data that are consistent with other cohort studies.[7] With reproducible estimates on the contribution of these risk factors, we can look towards the evidence in favour of risk factor reduction. In the SPRINT trial of patients with hypertension, intensive blood pressure (BP) reduction (<120 mmHg systolic BP) reduced incident AF events compared with standard BP targets (<140 mmHg).[8] Similarly, strict BP lowering reduced new-onset AF in the Cardio-Sis trial when compared with standard BP targets.[9] There are fewer data on weight loss for primary prevention of AF. In patients with high body mass index, observational studies have reported that bariatric surgery was associated with a significant reduction in incident AF.[10] We eagerly await the results from primary prevention trials using newer pharmacotherapies, such as glucagon-like peptide-1 (GLP1) receptor agonists.

The study of Wang *et al.* provides important data on the interaction between genetic risk and other risk factors in the development of AF. Notably, the contribution of genetic risk declined from 19.1% at 40–49 years to 14.3% at 60–69 years of age, a finding that is consistent with previous analyses in which adding genetic predisposition to existing clinical risk scores provided the most value for younger individuals.[11] However, Wang *et al.* reported that across all genetic risk groups, the three factors that contribute most to the PAR incident AF are hypertension, obesity, and acute illness. Most individual risk factors did not demonstrate any statistically significant interaction with genetic risk. In the take-home message that accompanies their graphical abstract, the authors state that targeting modifiable risk factors is most feasible in people with low genetic risk rather than high genetic risk. We respectfully counter this statement, given that across all genetic risk groups, the PAR for cardiometabolic factors suggests that these largely modifiable risk factors account for >1 in 3 of all incident AF diagnoses. Therefore, it is our firm view that prioritizing risk factor reduction for the primary prevention of AF and its complications should not differ based on the underlying genetic risk. Similarly, there is little evidence that adding genetic risk to existing clinical risk scores makes any substantial improvement to AF risk estimation.[11] Although we commend the advances in evaluation of underlying genetic predisposition to AF, we should not be distracted in our focus on underlying modifiable risk factors for AF screening and prevention.

Despite the strengths of this study, there are notable caveats that are critical for its interpretation. As the authors note, recruitment was limited to individuals ≤70 years of age, restricting the ability to detect age-related variations in risk factors. Many of the risk factors were assessed by self-report upon study enrolment. Baseline self-report probably results in reporting bias, as well as an inability to account for time-dependent changes in risk factor profile. Ascertainment of AF was undertaken through linkage to primary care, hospital records, and national death registers across the UK, which is likely to underestimate AF incidence given the high proportion of subclinical AF, particularly amongst higher risk individuals,[12] such as those with a higher burden of social factors. The authors also did not assess the interaction between sex and risk factor profile, which may have yielded differing risk factor contributions to incident AF between men and women.

Finally, the study by Wang *et al.* is limited in its ability to examine the contribution of social factors to the global burden of AF beyond the UK Biobank. In this study, socioeconomic deprivation was assessed using the Townsend Index, which is based on aggregate information for the postcode in which an individual resides. The index misses individual-level data such as household income or employment status, all of which may potentially influence underlying lifestyle-based risk factors, or AF incidence directly.[5] In addition, the burden of social risk factors in a volunteer cohort in the UK is likely to be more modest than in the general population, and in other countries, which may have resulted in lower

estimation of their contribution to AF risk. Furthermore, social factors predispose to health behaviours, cardiometabolic factors, and clinical comorbidities; hence, multivariable models may have underestimated the upstream contribution of social risk factors to AF incidence. There is also evidence that rurality may influence AF incidence, which is likely to be less of an issue in the UK with a smaller area and higher population density than other countries such as the USA, Australia, or China. As noted by the authors, the UK Biobank participants are predominantly White (~90%), which limits extension of these findings to other regions with greater diversity across racial and ethnic groups. In the Multi-Ethnic Study of Atherosclerosis, the incidence of hospitalized AF was lower amongst Hispanics, Chinese, and Black individuals when compared with White individuals.[13] Of relevance was the observation that the PARs of risk factors including hypertension, obesity, smoking, and diabetes differed substantially by race. We therefore recommend caution in extrapolating these findings to other regions where the contribution of risk factors may differ.

We close by reinforcing that this work strengthens the demand for population-wide initiatives that address modifiable factors that promote the development of AF, particularly hypertension and obesity. As with the secondary prevention of AF, which benefits from weight loss and aggressive risk factor reduction,[1,14] the primary prevention of AF demands the prioritization of those factors most responsible for its development.[15] Until meaningful reduction in the prevalence of these risk factors is achieved, the global burden of AF will continue to rise, and we will continue to count the cost through excess cardiovascular morbidity and mortality, impaired quality of life, surging hospitalizations, and escalating healthcare demands.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Funding

A.D.E. is supported by a Future Leader Fellowship from the National Heart Foundation of Australia. E.F.B. is supported in part by the National Institutes of Health R01HL092577 and the American Heart Association AHA_18SFRN34110082.

References

1. Elliott AD, Middeldorp ME, Van Gelder IC, Albert CM, Sanders P. Epidemiology and modifiable risk factors for atrial fibrillation. *Nat Rev Cardiol* 2023;**20**:404–417. https://doi.org/10.1038/s41569-022-00820-8
2. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, *et al.* 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154–162. https://doi.org/10.1016/S0140-6736(14)61774-8
3. Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, *et al.* Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* 2021;**398**:957–980. https://doi.org/10.1016/S0140-6736(21)01330-1
4. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, *et al.* Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet* 2018;**50**:1225–1233. https://doi.org/10.1038/s41588-018-0133-9
5. Essien UR, Kornej J, Johnson AE, Schulson LB, Benjamin EJ, Magnani JW. Social determinants of atrial fibrillation. *Nat Rev Cardiol* 2021;**18**:763–773. https://doi.org/10.1038/s41569-021-00561-0
6. Wang N, Yu Y, Ying S, Zhang H, Wang Y, Chen C, *et al.* Age-specific and genetic predisposition-specific risk factor profiles associated with incident atrial fibrillation. *Eur Heart J* 2023;**44**:ehad615. https://doi.org/10.1093/eurheartj/ehad615
7. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, *et al.* 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**:1501–1508. https://doi.org/10.1161/CIRCULATIONAHA.110.009035
8. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, *et al.* Effect of intensive blood pressure lowering on the risk of atrial fibrillation. *Hypertension* 2020;**75**:1491–1496. https://doi.org/10.1161/HYPERTENSIONAHA.120.14766
9. Verdecchia P, Staessen JA, Angeli F, De Simone G, Achilli A, Ganau A, *et al.* Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet* 2009;**374**:525–533. https://doi.org/10.1016/S0140-6736(09)61340-4
10. Pontiroli AE, Centofanti L, Le Roux CW, Magnani S, Tagliabue E, Folli F. Effect of prolonged and substantial weight loss on incident atrial fibrillation: a systematic review and meta-analysis. *Nutrients* 2023;**15**:940. https://doi.org/10.3390/nu15040940
11. Khurshid S, Mars N, Haggerty CM, Huang Q, Weng LC, Hartzel DN, *et al.* Predictive accuracy of a clinical and genetic risk model for atrial fibrillation. *Circ Genom Precis Med* 2021;**14**:e003355. https://doi.org/10.1161/CIRCGEN.121.003355
12. Healey JS, Alings M, Ha AC, Leong-Sit P, Birnie DH, de Graaf JJ, *et al.* Subclinical atrial fibrillation in older patients. *Circulation* 2017;**136**:1276–1283. https://doi.org/10.1161/CIRCULATIONAHA.117.028845
13. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC Jr, *et al.* Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the multi-ethnic study of atherosclerosis. *Ann Epidemiol* 2015;**25**:71–76. https://doi.org/10.1016/j.annepidem.2014.11.024
14. Middeldorp ME, Ariyaratnam J, Lau D, Sanders P. Lifestyle modifications for treatment of atrial fibrillation. *Heart* 2020;**106**:325–332. https://doi.org/10.1136/heartjnl-2019-315327
15. Segan L, Canovas R, Nanayakkara S, Chieng D, Prabhu S, Voskoboinik A, *et al.* New-onset atrial fibrillation prediction: the HARMS2-AF risk score. *Eur Heart J* 2023;**44**:3443–3452. https://doi.org/10.1093/eurheartj/ehad375