**EDITORIAL**

**Revisiting the Dynamic Risks of Incident Atrial Fibrillation: Does the Use of Nonsteroidal Anti-Inflammatory Drugs Contribute to Risk?**

Stephanie L. Harrison1 PhD

Martin O’Flaherty2 MD, PhD

Gregory Y. H. Lip1,3 MD

1Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

2Department of Public Health and Policy, University of Liverpool, Liverpool, United Kingdom

3Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Correspondence:

Prof Gregory Y. H. Lip Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, Liverpool, L7 8TX United Kingdom gregory.lip@liverpool.ac.uk

In this issue of the journal, Chokesuwattanaskul *et al*. publish a systematic review and meta-analysis to determine risk of incident atrial fibrillation (AF) associated with use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).1 This important review examined four case-control and four cohort studies including over 14.8 million patients. The authors concluded that compared to no use of NSAIDs, using NSAIDs was associated with a higher risk of AF (Risk Ratio (RR) of AF 1.29; 95% Confidence Interval (CI): 1.19-1.39).

NSAIDs are used widely for a range of conditions to relieve pain and reduce inflammation. It is difficult to examine long-term risk associated with use of NSAIDs due to heterogeneity in the patients who use NSAIDs (e.g. age, co-morbidities) and duration of use and adherence. Categorising participants at baseline based on their use of NSAIDs and then examining outcomes years later is problematic because in that time frame exposure to NSAIDs could have changed multiple times (from exposed to not exposed and vice versa). Furthermore, AF can be difficult to detect and extended monitoring may enhance the detection of AF; therefore, heterogeneity in the measurements used for incident AF are also important to consider.

The consistent association between NSAIDs and incident AF in the studies included in the review by Chokesuwattanaskul *et al*.1 should give compelling evidence for future studies to further explore this association. Risk is not a static concept and this should be considered when adjusting for confounding factors. The included studies in the review varied in what factors were adjusted for, but most adjusted for baseline factors including sex, age, certain co-morbidities and medications e.g. antihypertensives. Further studies could examine the association between NSAIDs and AF with cohort data with repeated measurements on the exposure and potential confounders.2 Duration of use and changes in exposure to NSAIDs should be examined and studies could adjust for time-varying factors such as co-morbidities and inflammatory markers.

Observational studies with long-term follow-up provide evidence that cannot be examined in a randomised controlled trial. However, NSAIDs are frequently used for people with inflammatory conditions and as inflammation is important for the initiation of AF, this potential confounding needs to be carefully considered when examining the association between NSAIDs and AF. Although NSAIDs are anti-inflammatory, Chokesuwattanaskul *et al*. propose underlying mechanisms such as inhibition of cyclooxygenase (COX) enzymes and hyperkalemia caused by NSAIDs may explain the association between NSAIDs and higher risk of AF.1

A recent review including 32 cohort studies of over 20 million participants found similarities and differences in risk factors for AF and other cardiovascular disease.3 Higher levels of the inflammatory biomarker C-reactive protein was one risk factor consistently associated with incident AF.3 No medications have been designed to target inflammation in patients with AF or as primary prevention for patients at high-risk of AF. Yet, the inflammatory pathway is an important potential therapeutic target for AF prevention due to the role of inflammation in the initiation of AF.4

Several risk prediction models for AF have been developed, for example the C2HEST score,5 the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF score6 and the Framingham score7 for AF. Further development of risk prediction models for AF could lead to routine use in clinical practice to identify patients at “high-risk” and target extended monitoring for AF to detect AF as early as possible, enabling AF prevention through public health strategies and targeted primary prevention. Current risk prediction models for AF do not consider medication use apart from hypertension treatment. Further exploration considering medication use could be a potential avenue when examining methods to improve risk prediction models for AF. Detecting AF as early as possible is important to implement integrated care pathways: ‘easy as ABC …’, i.e. ‘A’ Avoid stroke with Anticoagulants; ‘B’ Better symptom management with individualised rhythm or rate control; ‘C’ Cardiovascular risk and comorbidity management.8 The care pathway should be discussed with the patient and appropriate treatments and lifestyle modifications implemented.9 Furthermore, the fact that many of these factors are modifiable suggest that there is potential to reduce AF incident risk by targeting them through individual and population level interventions.10

To conclude, the inflammatory pathway may be an important target for reducing risk of AF, but current evidence suggests the use of NSAIDs is associated with a higher risk of AF. Future studies should consider how use of NSAIDs changes over time amongst individuals and decipher the associations between duration of use and risk of incident AF for different subgroups of people considering time-varying risk factors for AF.

**References**

1. Chokesuwattanaskul R, Chiengthong K, Thongprayoon C, Lertjitbanjong P, Bathini T, Ungprasert P, et al. Nonsteroidal Anti-Inflammatory Drugs and Incidence of Atrial Fibrillation: A Meta-Analysis. QJM-Int J Med. 2019.

2. Doosti-Irani A, Mansournia MA, Collins G. Use of G-methods for handling time-varying confounding in observational research. Lancet Glob Health. 2019;7(1):e35.

3. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R, Schilling R, et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. Thromb Haemost. 2017;117(5):837-50.

4. Hu Y-F, Chen Y-J, Lin Y-J, Chen S-A. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol. 2015;12:230.

5. Li YG, Pastori D, Farcomeni A, Yang PS, Jang E, Joung B, et al. A Simple Clinical Risk Score (C2HEST) for Predicting Incident Atrial Fibrillation in Asian Subjects: Derivation in 471,446 Chinese Subjects, With Internal Validation and External Application in 451,199 Korean Subjects. Chest. 2019;155(3):510-8.

6. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc. 2013;2(2):e000102.

7. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Sr., et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009;373(9665):739-45.

8. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Sung JH et al. Improved Population-Based Clinical Outcomes of Patients with Atrial Fibrillation by Compliance with the Simple ABC (Atrial Fibrillation Better Care) Pathway for Integrated Care Management: A Nationwide Cohort Study. Thromb Haemost. 2019; 19(10):1695-1703.

9. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiology. 2017;14(11):627-8.
10. Isakadze N, B P, B S, Patel R, Baer J, Isiadinso I, et al. Life's Simple 7 Approach to Atrial Fibrillation Prevention. Journal of atrial fibrillation. J Atr Fibrillation. 2018;11(3):2051.