Essa, H, Ortega-Martorell, S, Olier, I and Lip, GYH

Machine learning to identify phenotypic clusters of patients with atrial fibrillation

Machine learning to identify phenotypic clusters of patients with atrial fibrillation

Hani Essa[1], Sandra Ortega-Martorell[1,2], Ivan Olier[1,2], Gregory Y. H. Lip[1,3,4]

1. Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital; Liverpool, UK
2. Data Science Research Centre, Liverpool John Moores University, Liverpool, UK
3. Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
4. Department of Cardiology, Lipidology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland.

Correspondence:

Prof GYH Lip gregory.lip@liverpool.ac.uk

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide and is associated with significant morbidity and mortality, from stroke, heart failure, dementia and hospitalisations[1]. As a result, better efforts to identify patients at greatest risk, who would benefit most from appropriate management are needed.

Oral anticoagulation (OAC) can be used to ameliorate the risk of stroke in AF, but the management of AF is more than just OAC, given the recognised residual risks of major adverse events despite anticoagulation [2]. Indeed, AF is not a homogeneous single diagnosis, and over recent years, phenotypes of 'clinical complexity' associated with AF have been identified, with implications for prognosis and management[3].

The current management of AF has moved towards a more holistic or integrated care approach, initially proposed as the Atrial fibrillation Better Care (ABC) pathway[4]. The ABC pathway is supported by trial and real-world evidence[5], and variants of the 'ABC' acronym have been used in US guidelines (i.e. 'SOS', Stroke, Other Comorbidities, Rate or Rhythm control)[6] and 2024 European guidelines (as 'CARE', i.e. Comorbidities, Avoid stroke, Rate or rhythm control, Evaluation)[7].

Phenotypic clusters of AF patients identified by hierarchical cluster analysis show improved outcomes with ABC pathway adherence, but to a varying degree depending on their phenotype[3]. Adherence to the ABC pathway has been associated with a significant reduction in all-cause mortality, cardiovascular mortality, stroke and bleeding[8].

Turning to stroke risk, the more common and well-validated risk factors have been utilised to formulate stroke risk stratification schemes, of which, the most one used is the CHA_2DS_2-VASc score[9]. Whilst clinically useful to identify patients who may benefit from anticoagulation this is an oversimplification of a much more complex and dynamic scenario and hence only demonstrates a modest predictive performance of stroke risk. There is a clinically apparent need for better risk stratification strategies to identify patients who may benefit from anticoagulation.

Beyond hierarchical cluster analysis, other approaches such as latent class analysis have been used to phenotype patients with AF[10]. Nevertheless, artificial intelligence (AI) and Machine Learning (ML), a subset of AI, signal the emergence of tools that can help us leverage large data sets to identify clinically significant patterns that may not be easily identified by conventional methods, and this is demonstrated in dramatic growth in the numbers of publications in this field over the last few years[11].

In this issue of Heart Rhythm O^2, Hsu et al[12] used a statistical approach to identify distinct prognostic phenotypic clusters in a Taiwanese population of 5,002 patients with AF. In this analysis, the authors perform an unsupervised hierarchical cluster analysis based on the components of the CHA_2DS_2-VASc score, identifying four distinct clusters: Cluster I included 1,918 diabetic patients with heart failure preserved ejection fraction, and chronic kidney disease; Cluster II comprised 1006 older patients with low body mass index and pulmonary hypertension; Cluster III consisted of 1731 patients with metabolic syndrome and atherosclerotic disease; and Cluster IV included 347 patients with left heart dysfunction, including reduced ejection fraction.

The main outcomes measured across all clusters were the risk of ischemic stroke, heart failure hospitalisation, cardiovascular death, and all-cause mortality. First, they found significant differences in the risk of ischemic stroke independent of CHA_2DS_2-VASc score between clusters, with cluster IV demonstrating the lowest risk. Second, Cluster II was associated with the highest risk of heart failure hospitalisation, cardiac death and all-cause mortality. Finally, the data-driven algorithm identified heterogeneous risk profiles across different clusters, each associated with a varying risk of cardiovascular events. The study by Hsu et al identified distinct phenotypes that demonstrated a differential risk of stroke, independent of their CHA_2DS_2-VASc score. The authors further benefitted from a large sample size and a long duration of follow-up. Furthermore, these results were externally validated on a separate dataset lending creditability and demonstrating reproducibility of the findings.

Nonetheless, several limitations must be considered when interpreting these results. First, this is a retrospective study in a predominantly homogenous East Asian population and is therefore open to confounding factors that may explain these findings. Second, as a study dependent on data extraction from an administrative database (without a review of individual patient charts), there is a significant risk that data are subject to coding errors which can alter results. Lastly, even though their work is supported by external validation on a Taiwanese dataset, its applicability to non-Asian populations is uncertain, especially given the reported racial differences in AF-related outcomes such as stroke and bleeding[13, 14].

The work conducted by Hsu et al. is timely and contributes to the expanding role of data-driven approaches in the management of AF[11]. Moving forward, phenotyping clinically complex AF patients can deploy more ML sophisticated approaches, such as generative topographic mapping, as recently published by our group[15]. AI/ML has the potential to be able to provide a continuous ‘real-time’ assessment of individual risk in AF outperforming traditional stroke risk stratification schemes[16]. This is augmented by the growth in methodologies such as digital twins, currently applied in extensive research programmes to improve diagnosis, risk prediction, peri-stroke management and post-stroke rehabilitation[17, 18].

However, risk factors and comorbidities in AF patients are not static but dynamic in nature, and the arrhythmia per se is also dynamic, changing in patterns over time[19, 20]. Furthermore, we have adherence to the ABC pathway that is also dynamic, and adherence/non-adherence over follow-up can impact outcomes[21].

Novel ML approaches could help identify phenotypic clusters of AF patients, who have a high risk of ischemic stroke, despite being deemed low risk by traditional risk scores such as CHA_2DS_2-VASc and randomising these patients to ABC pathway-based management versus conventional treatment. The ability to identify these high-risk individuals who would otherwise be missed, could allow a tailored approach to decision-making and improve overall patient care. Ultimately, we may utilise AI/ML to create an algorithm that incorporates conventional patient data used in normal risk stratification schemes combined with non-conventional and dynamic data for the identification of which patients may benefit from anticoagulation (Figure 1).

In conclusion, the growth in AI/ML yields promising results for the identification of high-risk patients who may otherwise be missed via conventional stroke stratification schemes. Integrating AI/ML into the diagnostic and treatment processes for AF has the potential to mitigate current limitations and optimise care. The 'rise of the machines' is clearly evident in healthcare.

Declarations

HE reports no conflict of interest

SOM is the Principal Investigator of the TARGET project on health virtual twins for personalised management of atrial fibrillation and stroke (grant agreement no. 101136244) and senior investigator in the ARISTOTELES project on artificial intelligence for the management of chronic long-term conditions (grant agreement no. 101080189), both funded by the EU's Horizon Europe Research & Innovation programme. She is also a member of the board of the ART (Ageing Research Translation) of Healthy Ageing Network funded by the Biotechnology and Biological Sciences Research Council (BBSRC).

IO is the methodological lead of the TARGET project on health virtual twins for personalised management of atrial fibrillation and stroke (grant agreement no. 101136244) and partner lead in the ARISTOTELES project on artificial intelligence for the management of chronic long-term conditions (grant agreement no. 101080189), both funded by the EU's Horizon Europe Research & Innovation programme.

GYHL is a National Institute for Health and Care Research (NIHR) Senior Investigator. He is Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos (No fees are received personally). He is co-PI/lead of the AFFIRMO project on multimorbidity in AF (grant agreement No 899871), TARGET project on digital twins for personalised management of atrial fibrillation and stroke (grant agreement No 101136244) and ARISTOTELES project on artificial intelligence for management of chronic long term conditions (grant agreement No 101080189), which are all funded by the EU's Horizon Europe Research & Innovation programme.

References

1. Burdett, P. and G.Y.H. Lip, *Atrial fibrillation in the UK: predicting costs of an emerging epidemic recognizing and forecasting the cost drivers of atrial fibrillation-related costs.* Eur Heart J Qual Care Clin Outcomes, 2022. **8**(2): p. 187-194.
2. Liu Y, et al., *Residual Risk Prediction in Anticoagulated Patients with Atrial Fibrillation Using Machine Learning: A Report from the GLORIA-AF Registry Phase II/III.* European Journal of Clinical Investigation, 2024. DOI: 10.1111/eci.14371
3. Krittayaphong, R., et al., *Clinical phenotype classification to predict risk and optimize the management of patients with atrial fibrillation using the Atrial Fibrillation Better Care (ABC) pathway: a report from the COOL-AF registry.* QJM, 2024. **117**(1): p. 16-23.
4. Lip, G.Y.H., *The ABC pathway: an integrated approach to improve AF management.* Nat Rev Cardiol, 2017.
5. Potpara, T., G.F. Romiti, and C. Sohns, *The 2024 European Society of Cardiology Guidelines for Diagnosis and Management of Atrial Fibrillation: A Viewpoint from a Practicing Clinician's Perspective.* Thromb Haemost, 2024.
6. Joglar, J.A., et al., *2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* Circulation, 2024. **149**(1): p. e1-e156.
7. Van Gelder, I.C., et al., *2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS).* Eur Heart J, 2024.
8. Romiti, G.F., et al., *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**(3): p. 406-414.
9. Lip, G.Y., et al., *Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation.* Chest, 2010. **137**(2): p. 263-72.
10. Romiti, G.F., et al., *Patterns of comorbidities in patients with atrial fibrillation and impact on management and long-term prognosis: an analysis from the Prospective Global GLORIA-AF Registry.* BMC Med, 2024. **22**(1): p. 151.
11. Olier, I., et al., *How machine learning is impacting research in atrial fibrillation: implications for risk prediction and future management.* Cardiovasc Res, 2021. **117**(7): p. 1700-1717.
12. Hsu, J.-C., et al., *Phenotypes of Atrial Fibrillation in a Taiwanese Longitudinal Cohort: Insights from an Asian Perspective.* Heart Rhythm O2.
13. Kang, D.S., et al., *Racial Differences in Bleeding Risk: An Ecological Epidemiological Study Comparing Korea and United Kingdom Subjects.* Thromb Haemost, 2024. **124**(9): p. 842-851.
14. Kang, D.S., et al., *Racial Differences in Ischemic and Hemorrhagic Stroke: An Ecological Epidemiological Study.* Thromb Haemost, 2024. **124**(9): p. 883-892.
15. Bellfield, R.A.A., et al., *AI-based derivation of atrial fibrillation phenotypes in the general and critical care populations.* EBioMedicine, 2024. **107**: p. 105280.
16. Lip, G.Y.H., et al., *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**(1): p. 142-150.
17. Ortega-Martorell, S., et al., *TARGET: A Major European Project Aiming to Advance the Personalised Management of Atrial Fibrillation-Related Stroke via the Development of Health Virtual Twins Technology and Artificial Intelligence.* Thromb Haemost, 2024.

18. Ortega-Martorell, S., et al., *A European network to develop virtual twin technology for personalized stroke management in atrial fibrillation: the TARGET consortium.* Eur Heart J, 2024.
19. Krittayaphong, R., et al., *Clinical outcomes of patients with atrial fibrillation in relation to multimorbidity status changes over time and the impact of ABC pathway compliance: a nationwide cohort study.* J Thromb Thrombolysis, 2024.
20. Imberti, J.F., et al., *Atrial High-Rate Episodes Detected by Cardiac Implantable Electronic Devices: Dynamic Changes in Episodes and Predictors of Incident Atrial Fibrillation*. Biology (Basel), 2022. **11**(3).
21. Krittayaphong, R., et al., *Relation of changes in ABC pathway compliance status to clinical outcomes in patients with atrial fibrillation: A report from the COOL-AF registry.* Eur Heart J Qual Care Clin Outcomes, 2024.

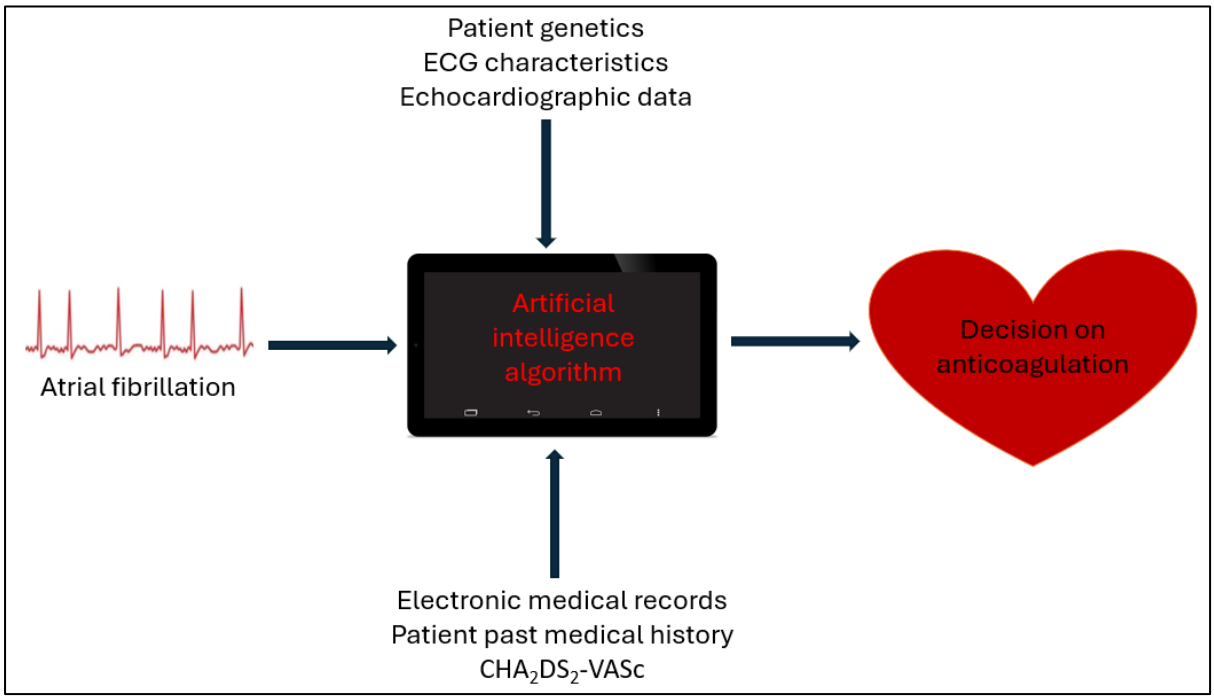

Figure 1 – The potential role of artificial intelligence and machine learning in decision making for anticoagulation