

A European-multicenter network for the implementation of artificial intelligence to manage complexity and comorbidities of atrial fibrillation patients: the ARISTOTELES consortium

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide, contributing significantly to morbidity, healthcare costs, and resource utilization¹. Patients with AF face a higher mortality and morbidity from stroke, heart failure, dementia, and hospitalisations¹. Oral anticoagulants (OAC) are the cornerstone of AF management, as they substantially reduce the risk of stroke and mortality². Nevertheless, some residual risk still remains despite anticoagulation, with most AF-related mortality linked to cardiovascular causes and comorbidities rather than stroke alone^{2,3}.

AF is not a yes/no homogeneous diagnosis. AF patients are often elderly, multimorbid and frail, with associated polypharmacy, leading to 'clinically complex' phenotypes or clusters. As comorbidities often cluster in different patterns, these impact on the risk of adverse outcomes and management. In the prospective GLORIA-AF registry of AF patients, the presence of clinical complexity was associated with lower odds of being prescribed with OAC (odds ratio [OR] 0.50, 95% confidence interval [CI] 0.44-0.57), higher OAC discontinuation and with a higher risk of adverse events [hazard ratio [HR] 1.63, 95% CI 1.43-1.86)⁴. Indeed, 'high clinical complexity' patients defined using latent class analysis represented a prevalence of 6.6% among AF patients, and was associated with higher hazards of experiencing the primary composite outcome of all-cause death and major adverse cardiovascular events (HR 1.47, 95% 1.24-1.75)⁵. Comorbidities and polypharmacy have an important influence on decision making, by conditioning either lack of prescription of OAC in patients at risk or inappropriate dosing⁶⁻⁸.

Recognising that AF management is more than simply OAC alone, and requires a holistic and integrated care approach, contemporary guidelines globally on AF management have promoted this concept, based on the Atrial fibrillation Better Care (ABC) pathway, emphasizing Anticoagulation, Better symptom management with rate or rhythm control, and Comorbidity/lifestyle management⁹⁻¹¹. The ABC pathway is well supported by clinical trial and real-world evidence¹¹, whereby adherence to the ABC pathway is associated with a reduction in all cause and cardiovascular mortality, stroke and bleeding^{12,13}. Despite this, adherence to ABC-based management remains low, whereby a meta-analysis of 14 studies revealed that only 21% (95% CI 13-34%) of AF patients were managed in accordance with the ABC pathway¹². This perhaps highlights a critical gap in the implementation of comprehensive evidence-based care strategies. Of note, the 'ABC' acronym has been modified in US guidelines (as 'SOS', e. Stroke, Other Comorbidities, Rate or Rhythm control)¹⁴ and the 2024 ESC guidelines (as 'CARE', i.e. Comorbidities, Avoid stroke, Rate or rhythm control, Evaluation)¹⁵, although these new acronyms are untested in clinical trials¹¹.

Artificial intelligence in atrial fibrillation

Artificial intelligence (AI) is becoming a promising tool in modern clinical practice, particularly for managing complex conditions such as AF^{16,17}. Different types of AI, including machine learning (ML), deep learning (DL), and neural networks, allow for the analysis of vast datasets, including structured data like patient demographics, electrocardiograms (ECGs), and lab results, as well as unstructured data like imaging and clinical notes¹⁸. These systems can rapidly process information that is beyond human capacity, identifying patterns and correlations that may otherwise go unnoticed. Such data science approach can even create virtual twins of complex patient phenotypes with AF and stroke¹⁹.

This is important as with AF, we are dealing with comorbidities that are not static but dynamic in nature²⁰, and the rhythm itself is dynamic²¹. Also, adherence to the ABC pathway is dynamic over time, with implications for outcomes²². Thus, for AF management, the use of AI can integrate all these dynamic changes, as well as detect subtle abnormalities in ECGs, predict arrhythmias, and even assess future clinical risks²³. As part of a learning health system, AI tools can offer predictive analytics that help may enhance diagnostic accuracy, and speed up decision-making, allowing clinicians to provide timely interventions and personalized treatments tailored to the unique needs of each patient (Figure 1).

AI tools can also provide valuable insights regarding the risk of AF progression, as well as the potential worsening or development of comorbidities (Figure 1). As is well known, AF progression is associated with poorer outcomes, worsening symptoms, or deterioration of heart failure, even in asymptomatic patients^{24,25}. Similarly, worsening renal function has significant implications for dosing OAC therapy and affects patient outcomes²⁶. Furthermore, incorporating biomarkers into AI tools could further refine risk stratification and enhance decision-making processes²⁷. In addition, AI's ability to continuously learn from new data ensures that treatment approaches evolve with advances in the medical field, offering ever-more refined risk assessments and therapy optimizations.

However, while AI offers considerable promise, clinical evidence demonstrating its long-term benefits in daily practice is still limited. Rigorous, large-scale clinical trials are needed to validate AI's effectiveness in improving patient outcomes, particularly in AF management, where comorbidities add layers of complexity.

ARISTOTELES project

To address the challenges of integrating AI into AF care, the European Union, under its Horizon Europe research programme, has funded the ARISTOTELES project (Grant Agreement no. 101080189). This project aims to develop AI-driven solutions for improving the diagnosis, treatment, and management of AF and its associated risks. The ARISTOTELES consortium consists of 18 leading academic institutions from 10 countries, forming a diverse network of experts in AI, cardiovascular medicine, and big data management.

The project's objective is to create a robust AI-based platform capable of analyzing real-world data from clinical records, biomarkers, genetic information, and imaging. These datasets will be harmonized and used to train AI models that can predict disease trajectories, identify early signs of comorbidities, and guide personalized treatment decisions. The AI models developed through the ARISTOTELES project will be rigorously tested in a randomized clinical trial (RCT) to assess their safety and efficacy in real-world clinical settings.

The ARISTOTELES project, launched in November 2023, is structured into eight work packages (WPs), each addressing different facets of the project (Figure 2). WP1 focuses on project management and coordination, while WP2, led by the University of Oslo, tackles the ethical, legal, and data protection issues associated with AI development and implementation. WP3 emphasizes stakeholder engagement, including collaboration with patients and healthcare providers, to ensure that the AI tools are practical, user-friendly, and relevant to real-world challenges.

Four key WPs—WP4, WP5, WP6, and WP7—form the research core of ARISTOTELES. WP4 will develop the data platform that integrates clinical, genetic, and imaging data. This platform will support WP5, which focuses on creating AI tools capable of predicting disease progression and assessing patient risks. WP6 will validate these AI models using *in silico* trials (simulated clinical trials), ensuring they are safe and effective before real-world application. WP7 will then test these AI tools in a large-scale randomized clinical trial, evaluating their impact on AF management and patient outcomes. The trial will compare an AI-supported intervention group with a usual care group. In the usual care group, patients will be managed according to AF guidelines, based on the ABC pathway²⁸, while other conditions will be managed according to their specific guidelines²⁹. In the AI-supported intervention arm, physicians will similarly rely on clinical judgment, but with AI tools providing additional support. Throughout the project, WP8 will focus on disseminating the project's findings to the broader scientific community and exploring pathways for the commercialization of the AI solutions developed.

The ARISTOTELES randomized controlled trial

As the ARISTOTELES project reaches its final phase, a cluster-randomized controlled trial (RCT) will be conducted to assess the effectiveness of AI-informed management for patients with AF. The RCT is a prospective, multicenter, open-label, cluster-randomized trial that will recruit patients with AF. ARISTOTELES RCT will include approximately 1200 patients. The key inclusion criteria will be a diagnosis of AF (qualifying event documented by 12-lead ECG, 24-hour ECG Holter, or other electrocardiographic methods within 12 months before enrollment) and the presence of at least one non-sex-related CHA₂DS₂-VASc score risk factor included (ie. CHA₂DS₂-VA³⁰). Exclusion criteria will include the presence of mechanical heart valves or moderate to severe mitral stenosis, serious diseases with a life expectancy inferior to 12 months.

Patients will be recruited from four participating countries: Italy, Spain, Romania, and Greece. National Coordinators in each country will identify a total of 30 centers each enrolling about 40 patients. These centres will be randomized in a 1:1 ratio to either the AI-supported intervention group or the usual care group. This ensures that 15 clusters will implement the AI-supported management strategy, while the remaining 15 will continue with usual care practices, with no active intervention needed. The selected centres will primarily be general hospitals with a minimum of 200 new AF referrals per year, ensuring an adequate patient volume for the study.

Each patient will have a minimum follow-up period of 1 year. Follow-up visits for patients will be scheduled at 3, 6, 12. During these visits, the following data will be collected: updated clinical status, any adverse events, clinical outcomes, new interventions, and ongoing or new concomitant medications.

The primary endpoint of the study will be a composite of all-cause death or hospitalization for any cause. The secondary objectives of the trial will further explore AI's impact by examining its ability to reduce the rates of fatal and non-fatal ischemic strokes, transient ischemic attacks (TIA), major bleeding events, and cardiovascular or all-cause death. Additionally, the trial will assess improvements in quality of life, therapy adherence, and the development of new comorbidities over the follow-up period. By focusing on these secondary endpoints, the trial will provide a broader understanding of how AI can enhance not only patient outcomes but also the overall quality of AF management.

Conclusions

The ARISTOTELES project represents a significant step toward integrating AI into the management of atrial fibrillation and its comorbidities. By leveraging the expertise of a multinational consortium, the project will develop and test AI tools that can improve the prediction and treatment of AF. Through a rigorous, large-scale RCT, the project will provide critical data on the effectiveness of AI in real-world clinical settings. If successful, ARISTOTELES has the potential to revolutionize AF care, making treatments more personalized, efficient, and effective, while setting the stage for AI-driven innovations across other areas of cardiovascular medicine.

References

1. Linz D, Gawalko M, Betz K, et al. Atrial fibrillation: epidemiology, screening and digital health. *Lancet Reg Health Eur*. Feb 2024;37:100786. doi:10.1016/j.lanepe.2023.100786
2. Lip GYH, Proietti M, Potpara T, et al. Atrial fibrillation and stroke prevention: 25 years of research at EP Europace journal. *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*. Aug 2 2023;25(9)doi:10.1093/europace/euad226
3. Ishiguchi H, Abdul-Rahim AH, Huang B, et al. Residual Risks of Thrombotic Complications in Anticoagulated Patients with Atrial Fibrillation: A Cluster Analysis Approach from the GLORIA-AF Registry. *Journal of general internal medicine*. Sep 25 2024;doi:10.1007/s11606-024-09045-6
4. Romiti GF, Proietti M, Bonini N, et al. Clinical Complexity Domains, Anticoagulation, and Outcomes in Patients with Atrial Fibrillation: A Report from the GLORIA-AF Registry Phase II and III. *Thromb Haemost*. Dec 2022;122(12):2030-2041. doi:10.1055/s-0042-1756355
5. Romiti GF, Corica B, Mei DA, 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*. Apr 08 2024;22(1):151. doi:10.1186/s12916-024-03373-4
6. Guenoun M, Cohen S, Villaceque M, et al. Characteristics of patients with atrial fibrillation treated with direct oral anticoagulants and new insights into inappropriate dosing: results from the French National Prospective Registry: PAFF. *Europace*. Oct 05 2023;25(10)doi:10.1093/europace/euad302
7. Grymonprez M, Petrovic M, De Backer TL, Steurbaut S, Lahousse L. The Impact of Polypharmacy on the Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Thrombosis and haemostasis*. Feb 2024;124(2):135-148. doi:10.1055/s-0043-1769735
8. Zheng Y, Li S, Liu X, Lip GYH, Guo L, Zhu W. Effect of Oral Anticoagulants in Atrial Fibrillation Patients with Polypharmacy: A Meta-analysis. *Thrombosis and haemostasis*. Jul 3 2023;doi:10.1055/s-0043-1770724
9. Wang Y, Guo Y, Qin M, et al. 2024 Chinese Expert Consensus Guidelines on the Diagnosis and Treatment of Atrial Fibrillation in the Elderly, Endorsed by Geriatric Society of Chinese Medical Association (Cardiovascular Group) and Chinese Society of Geriatric Health Medicine (Cardiovascular Branch): Executive Summary. *Thrombosis and haemostasis*. Oct 2024;124(10):897-911. doi:10.1055/a-2325-5923
10. Chao TF, Joung B, Takahashi Y, et al. 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. *Thrombosis and haemostasis*. Jan 2022;122(1):20-47. doi:10.1055/s-0041-1739411
11. Potpara T, Romiti GF, Sohns C. The 2024 European Society of Cardiology Guidelines for Diagnosis and Management of Atrial Fibrillation: A Viewpoint from a Practicing Clinician's Perspective. *Thrombosis and haemostasis*. Oct 24 2024;doi:10.1055/a-2434-9244
12. Romiti GF, Pastori D, Rivera-Caravaca JM, 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*. Mar 2022;122(3):406-414. doi:10.1055/a-1515-9630
13. Treewaree S, Lip GYH, Krittayaphong R. Non-vitamin K Antagonist Oral Anticoagulant, Warfarin, and ABC Pathway Adherence on Hierarchical Outcomes: Win Ratio Analysis of the COOL-AF Registry. *Thrombosis and haemostasis*. Jan 2024;124(1):69-79. doi:10.1055/s-0043-1772773
14. Joglar JA, Chung MK, Armbruster AL, 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*. Jan 2 2024;149(1):e1-e156. doi:10.1161/CIR.0000000000001193
15. Van Gelder IC, Rienstra M, Bunting KV, 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*. Aug 30 2024;doi:10.1093/eurheartj/ehae176
16. Hygrelle T, Viberg F, Dahlberg E, et al. An artificial intelligence-based model for prediction of atrial fibrillation from single-lead sinus rhythm electrocardiograms facilitating screening. *Europace*. Apr 15 2023;25(4):1332-1338. doi:10.1093/europace/euad036
17. Svennberg E, Caiani EG, Bruining N, et al. The digital journey: 25 years of digital development in electrophysiology from an Europace perspective. *Europace*. Aug 25 2023;25(8)doi:10.1093/europace/euad176

18. Olier I, Ortega-Martorell S, Pieroni M, Lip GYH. How machine learning is impacting research in atrial fibrillation: implications for risk prediction and future management. *Cardiovascular research*. Jun 16 2021;117(7):1700-1717. doi:10.1093/cvr/cvab169
19. Ortega-Martorell S, Olier I, Ohlsson M, Lip GYH, Consortium T. 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. *Thrombosis and haemostasis*. Nov 7 2024;doi:10.1055/a-2438-5671
20. Krittayaphong R, Winijkul A, Methavigul K, Chichareon P, Lip GYH. 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. *Journal of thrombosis and thrombolysis*. Jul 9 2024;doi:10.1007/s11239-024-03007-9
21. Imberti JF, Bonini N, Tosetti A, et al. Atrial High-Rate Episodes Detected by Cardiac Implantable Electronic Devices: Dynamic Changes in Episodes and Predictors of Incident Atrial Fibrillation. *Biology (Basel)*. Mar 15 2022;11(3)doi:10.3390/biology11030443
22. Krittayaphong R, Chichareon P, Methavigul K, Treewaree S, Lip GYH. 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*. May 24 2024;doi:10.1093/ehjqcco/qcae039
23. Zhao Y, Cao LY, Zhao YX, et al. Harnessing Risk Assessment for Thrombosis and Bleeding to Optimize Anticoagulation Strategy in Nonvalvular Atrial Fibrillation. *Thrombosis and haemostasis*. Sep 19 2024;doi:10.1055/a-2385-1452
24. Vitolo M, Proietti M, Imberti JF, et al. Factors Associated with Progression of Atrial Fibrillation and Impact on All-Cause Mortality in a Cohort of European Patients. *Journal of clinical medicine*. Jan 18 2023;12(3)doi:10.3390/jcm12030768
25. Boriani G, Bonini N, Vitolo M, et al. Asymptomatic vs. symptomatic atrial fibrillation: Clinical outcomes in heart failure patients. *Eur J Intern Med*. Sep 25 2023;doi:10.1016/j.ejim.2023.09.009
26. Ding WY, Potpara TS, Blomström-Lundqvist C, et al. Impact of renal impairment on atrial fibrillation: ESC-EHRA EORP-AF Long-Term General Registry. *Eur J Clin Invest*. Jun 2022;52(6):e13745. doi:10.1111/eci.13745
27. Toprak B, Brandt S, Brederecke J, et al. Exploring the incremental utility of circulating biomarkers for robust risk prediction of incident atrial fibrillation in European cohorts using regressions and modern machine learning methods. *Europace*. Mar 30 2023;25(3):812-819. doi:10.1093/europace/euac260
28. Imberti JF, Mei DA, Vitolo M, et al. Comparing atrial fibrillation guidelines: Focus on stroke prevention, bleeding risk assessment and oral anticoagulant recommendations. *European journal of internal medicine*. Jul 2022;101:1-7. doi:10.1016/j.ejim.2022.04.023
29. Boriani G, Venturelli A, Imberti JF, Bonini N, Mei DA, Vitolo M. Comparative analysis of level of evidence and class of recommendation for 50 clinical practice guidelines released by the European Society of Cardiology from 2011 to 2022. *Eur J Intern Med*. May 09 2023;doi:10.1016/j.ejim.2023.04.020
30. Lip GYH, Teppo K, Nielsen PB. CHA2DS2-VASc or a non-sex score (CHA2DS2-VA) for stroke risk prediction in atrial fibrillation: contemporary insights and clinical implications. *European heart journal*. Sep 1 2024;doi:10.1093/eurheartj/ehae540

FIGURES

Figure 1. Potential application of artificial intelligence among AF patients

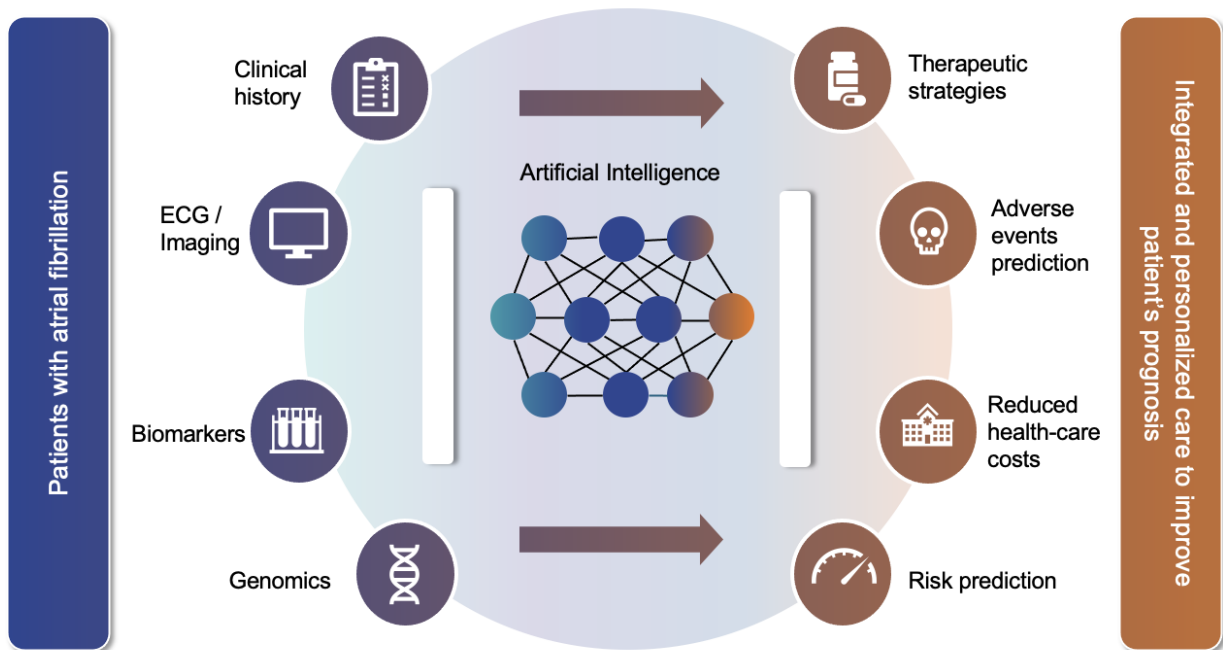


Figure 2. Work Packages (WP) of the ARISTOTELES project

