Artificial Intelligence in patients with atrial fibrillation to manage clinical complexity and comorbidities: the ARISTOTELES project

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Atrial fibrillation (AF) is the most common arrhythmia worldwide, contributing significantly to mortality and morbidity, as well as healthcare costs, and resource utilization[1]. Patients with AF are at a notably higher risk of stroke—a major complication associated with the condition—often leading to disability, dementia, and mortality[2]. The cornerstone of AF management is treatment with oral anticoagulants, which significantly reduces stroke risk[1]. However, this therapy comes with an increased risk of bleeding, which can difficult to predict given the risk reflects the interaction of modifiable and non-modifiable bleeding factors[3,4].

The management of AF is further complicated by the interplay of various comorbidities such as heart failure, diabetes, kidney disease and hypertension, which can exacerbate the disease and negatively affect the outcome, with important challenges for decision making on the appropriate treatments[5], especially since some guidelines do not provide evidence-based recommendations[6,7].

Comorbidities and multimorbidity (defined as the presence of ≥2 chronic long-term conditions) place a high burden on individuals, their families, communities, and health services, and are strongly associated with structural and functional decline, decreased quality of life, and higher mortality[8]. For increasingly elderly patients with AF, management of comorbidities, aligned with holistic or integrated care management, as endorsed by guidelines[7,9], is currently a cornerstone of appropriate care in the long term.

In this context, Artificial Intelligence (AI) tools are increasingly being used in clinical practice to detect or predict disease states and improve patient outcomes[10]. However, the application of AI to inform patient management remains sparsely explored. AI - specifically causal machine learning (ML) - offers a powerful approach to co-explore disease mechanisms and clinical outcome variations in multimorbidity, identifying important trajectories through integrated analysis of data from multiple sources (including clinical, anthropometric, genetic, biomarker, and laboratory data). There is therefore the potential for AI to support clinicians and optimize care in complex disease states, with a positive impact both patient management and health system resources.

In response to this, the European Union, under its Horizon Europe research programme, has funded the “Applying ARtificial Intelligence to Define clinical trajectorieS for personalized predicTiOn and early deTEctiOn of comorbidiTy and muLtimorbidiTy pattErnS” (ARISTOTELES) project (Grant Agreement no. 101080189) to evaluate the impact of AI tools into clinical management of AF and associated comorbidities. The consortium brings together the diverse expertise of 18 leading academic institutions located in ten countries, forming a strategic multidisciplinary research community of world-leading researchers and healthcare professionals in AI, big data management, cardiovascular biology, and medicine (Figure 1). The partners have established track records of relevant projects and scientific publications in the fields of AI and cardiovascular

research, both in observational, diagnostic, and interventional contexts. The project is co-led by experienced Principal Investigators from the University of Modena and Reggio Emilia (UniMoRe) and University of Liverpool.

ARISTOTELES will build a comprehensive multinational platform that integrates data from various real-world databases, combining different types of information, such as clinical records, biomarker data, imaging results, and genetic information. These data will be harmonized into a single platform that will be used to train AI models, allowing the system to learn from diverse patient populations and disease states. The trained AI models will then be used and tested in randomized clinical trials (RCTs) to ensure their efficacy in real-world clinical settings. This innovative approach will enable the development of personalized predictive tools that can be applied across different healthcare environments, providing a robust framework for individualized treatment strategies.

The ARISTOTELES project, which started in November 2023, is structured around eight work packages (WPs) to be delivered over five years (Figure 2). The project activities are coordinated and managed by WP1 under the scientific leadership of Prof. Giuseppe Boriani (Principal Investigator, UNIMORE) and Prof. Gregory Y H Lip (Co-Principal Investigator, UoL).

In parallel, WP2, led by the University of Oslo, is dedicated to addressing the ethical, legal, and data protection challenges associated with the development and implementation of AI-driven solutions. This ensures compliance with international standards and safeguards patient privacy and data security.

WP3 focuses on another crucial element of ARISTOTELES: engaging stakeholders, including patients, healthcare providers, and public health authorities. By involving them from the early stages of the project, the consortium aims to ensure that the AI tools being

developed are not only scientifically robust but also user-friendly and clinically relevant. During this phase, patient needs, and clinician feedback will be central to the refinement of the AI algorithms, guaranteeing that the solutions developed address real-world challenges.

At the core of the project are the combined efforts of four key work packages (WP4, WP5, WP6, and WP7), each playing a crucial role in achieving our objectives. WP4 will focus on developing a comprehensive data platform designed to harmonize and integrate clinical, genetic, biomarker, and imaging data from various sources. This platform will serve as the backbone for the subsequent work packages.

Building on this foundation, WP5 will develop advanced AI tools capable of predicting disease progression, assessing patient risk, and recommending personalized therapeutic strategies based on each patient's unique health profile. WP6 will introduce an innovative aspect of the project by subjecting these AI tools to in silico trials—a cutting-edge approach that simulates clinical trial scenarios to validate the models before any real-world application.

The final phase, led by WP7, will involve testing the AI tools in a large-scale, multicenter randomized clinical trial. This 2-arm, prospective, cluster-randomized controlled trial will enroll 1200 patients with AF, comparing adaptive AI-supported patient management versus usual care. Patients will be recruited from primary and secondary care facilities in four European countries (Italy, Spain, Romania, and Greece). Randomization will occur in a 1:1 ratio, with intervention centers utilizing an adaptive AI tool for personalized patient care, while control centers continue with usual care. The trial is expected to conclude within two years, with at least one year of follow-up for the last enrolled patient.

Throughout all phases of the project, WP8 will focus on disseminating and exploiting the results. This includes sharing findings with the wider scientific community, healthcare providers, and policymakers, while also exploring potential pathways for the commercial adoption and implementation of the AI-driven solutions developed by ARISTOTELES.

Through this comprehensive structure, ARISTOTELES aims to implement the management of AF and multimorbidity by integrating advanced AI models into clinical practice. By providing clinicians with personalized decision-support tools and improving the precision of therapeutic interventions, the project has the potential to significantly enhance patient outcomes and optimize healthcare resources across Europe. Considering the epidemiological profile and healthcare impact of AF[1] the results of ARISTOTELES will provide important inputs for improving the management of patients with AF, using the most advanced AI tools.

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ARISTOTELES consortium

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FIGURES

Figure 1. Panel A Europe map representing the ARISTOTELES consortium. Panel B Work Packages (WP) of the ARISTOTELES project