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Abstract

Atrial fibrillation (AF) is a complex condition caused by various underlying pathophysiological disorders and is the most common heart arrhythmia worldwide, affecting 2% of the European population. This prevalence increases with age, imposing significant financial, economic, and human burdens. In Europe, stroke is the second leading cause of death and the primary cause of disability, with numbers expected to rise due to ageing and improved survival rates. Functional recovery from AF-related stroke is often unsatisfactory, leading to prolonged hospital stays, severe disability, and high mortality.

Despite advances in AF and stroke research, the full pathophysiological and management issues between AF and stroke increasingly need innovative approaches such as artificial intelligence (AI) and machine learning (ML). Current risk assessment tools focus on static risk factors, neglecting the dynamic nature of risk influenced by acute illness, ageing, and comorbidities. Incorporating biomarkers and automated ECG analysis could enhance pathophysiological understanding.

This paper highlights the need for personalised, integrative approaches in AF and stroke management, emphasising the potential of AI and ML to improve risk prediction, treatment personalisation, and rehabilitation outcomes. Further research is essential to optimise care and reduce the burden of AF and stroke on patients and healthcare systems.

Keywords: Artificial Intelligence; Machine Learning; Personalised care; Atrial Fibrillation; Stroke; Digital Twins; Burden; Impact; Significance

1. Introduction

Atrial fibrillation (AF) is a heterogeneous condition caused by various underlying pathophysiological disorders. AF is the most common heart arrhythmia worldwide, affecting 2% of the European population (15 million patients) which increases with age, with approximately 18 million AF patients estimated by 2060 [1,2], and it imposes a high financial, economic and human burden.

In Europe, stroke is the second most common cause of death and the leading cause of disability [3], with more than 1 million new stroke cases in 2017 and 10 million stroke survivors. These numbers are expected to increase by 27% due to ageing and improved survival rates [4]. AF-related stroke (AFRS) accounts for 20% of ischaemic strokes, and the pathophysiology of AFRS is associated with severe neurological deficits due to larger clots, infarction of substantial cerebral areas and haemorrhagic transformation, a complication that significantly worsens prognosis [5]. Functional recovery from AFRS is often unsatisfactory, leading to longer hospital stays, severe disability and high mortality.

Despite extensive research on AF and its complications[6], and the advances in stroke prevention for AF patients, the precise pathophysiology linking AF to stroke remains unclear, highlighting the need for innovative approaches [6]. The long-term risks of stroke recurrence and bleeding from antithrombotic treatment remain substantial. Limited understanding of cellular and molecular mechanisms creates challenges in clinical practice, requiring complex decisions to balance reducing ischaemic events with minimising bleeding risk [7]. Hence, innovative approaches such as artificial intelligence (AI) and machine learning (ML) are becoming increasingly prominent [6].

Currently, risk assessment tools focus mainly on static risk factors and overlook the dynamic nature of risk, which changes with ageing, comorbidities, and during acute illness [7]. Including biomarkers related to cardiac or neurologic damage and automated ECG analysis would enhance pathophysiological insights. In this context, we define a ‘biomarker’ as any disease marker, including symptoms, signs, demographics, physical examination findings, and clinical investigation results, whether routinely measured or innovative parameters tested in urine, blood or imaging [8]. With temporal changes in biomarkers, a dynamic and personalised risk assessment approach is needed to reliably predict outcomes, incorporating a learning health system approach.

In stroke rehabilitation, the conventional approach based on the assessment of the patient’s cognitive and physical activities is through visual observation, clinical impression, tests and examination. Integration of biomarkers and their dynamic changes into treatment models may support the formulation of individualised recovery plans to help reduce disability and enhance quality of life. Despite AFRS having a major impact on health outcomes, few longitudinal studies have investigated the response to rehabilitation and associated prognosis, and further work is required to examine differences regarding initial needs for rehabilitation and the time course of recovery.

This review addresses the need for integrative personalised approaches for the enhanced and optimal management of AF and stroke patients across the patient ‘journey’ or ‘patient pathway’, which importance has been previously recognised [9–11] to overcome the limitations of current stroke management and rehabilitation. To this aim, we summarise the available evidence to highlight the research need for AF and stroke care personalisation, from prevention to rehabilitation, the role that AI/ML can play, and their potential impact and significance.

2. The need for personalised care across the disease pathway

The need for personalisation of care in AF and stroke arises from the heterogeneity of patient populations and the variable responses to treatments and interventions. AF is a complex arrhythmia associated with diverse risk factors and comorbidities, leading to variability in disease progression, complications, and treatment outcomes among individuals. Similarly, stroke, a common complication of AF, presents with varying degrees of severity, aetiologies, and prognoses across patients.

There are also sex differences in AF and stroke across the disease pathway, including in rehabilitation – see Supplementary Material (SM), section S1. Hence, personalising care in AF and stroke (see Figure 1) involves preventive measures, tailoring treatment strategies, and interventions based on individual patient characteristics, preferences, and risk profiles. By adopting a personalised approach, healthcare providers can optimise therapeutic efficacy, minimise adverse events, and improve patient outcomes in the management of AF and stroke.

2.1 Risk prediction of AF and stroke

AF, especially short AF episodes which convert spontaneously into sinus rhythm often remains undetected until cerebral ischaemia has already occurred. To date, risk prediction models of AF have many limitations, and simple clinical risk scores only have modest predictive value for identifying high-risk subjects who sustain events [5]. Many clinical risk scores use baseline factors that would change with ageing and incident comorbidities, and may not fully account for risk differences by race [12,13] and gender [14,15]. Also, many simple clinical risk scores assign equal weight to some component, potentially overlooking the varying degrees of importance of individual risk factors in predicting bleeding events.

As an illustrative example, current guidelines globally [16–18] use well-established stroke risk assessment tools such as the CHA_2DS_2-VASc score [19]. However, these conventional methods have been designed to be sufficiently reductionist so they can be easily applied in everyday clinical practice. Hence, they are constrained by their modest predictive efficacy as they do not consider many stroke risk factors such as renal impairment, inflammation, atrial remodelling, and pertinent cardiac and cerebrovascular biomarkers, thereby potentially limiting their prognostic utility. Moreover, these established tools predominantly consider static risk factors and fail to fully accommodate the dynamic nature of risk [20,21], which can fluctuate in response to acute illness, ageing processes, and the presence of comorbidities.

Consequently, there exists a pressing need to augment existing risk prediction methodologies with a more comprehensive understanding of the diverse array of risk factors influencing AFRS, encompassing both static and dynamic variables.

2.2 Diagnosis and management of stroke

During the acute phase, stroke aetiology is identified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST [22]) classification system, which includes clinical evaluation of different data sources (mainly clinical history, laboratory testing, ECG and neuroimaging data). A standard ECG, blood pressure, and heart rate are measured within the first hour in patients presenting with stroke. Multimodal neuroimaging (e.g., a non-contrast computerised tomography (NCCT), in some cases CT-angiography (CTA) and CT-perfusion (CTP)) is performed to identify patients who will benefit from reperfusion therapies. Indeed, acute treatment with thrombolysis and thrombectomy has revolutionised stroke care and the personalisation of these approaches has been one of the major challenges in stroke management (to facilitate personalised maximum delay, targeting specific types of clots, etc).

Risk factors or demographic variables associated with poor stroke outcomes are known, but as discussed above, current models to predict prognosis perform modestly and do not account for dynamic changes in risk profile. Drug treatment, particularly with anticoagulants, is also a challenge in AFRS, as an early initiation is potentially associated with an increased rate of haemorrhagic transformation, while a delayed initiation may result in a recurrent ischaemic stroke.

2.3 Stroke rehabilitation

Rehabilitation aims to restore/improve functional capacity to perform activities in daily life. After discharge from the stroke unit, post-acute inpatient care services offer intensive therapy programs, where healthcare professionals aim to identify patients' functional outcomes using screening tools and scales, covering three main domain areas: cognitive and occupational, activity and motor functioning, and swallowing and speech. Patients treated in organised stroke units and post-stroke rehabilitation facilities have better functional outcomes and higher return rates to community living than those in general wards or long-term care hospitals [23–26].

There is a notable increase in responsiveness to training within the first three months post-stroke, highlighting the importance of utilising this critical time window for rehabilitation. Understanding how to effectively modulate the mechanisms of increased plasticity during this period is crucial, with the intensity and nature of therapeutic activities playing a pivotal role in promoting functional recovery. While stroke recovery progresses relatively rapidly in the initial month post-stroke, the pace slows between 3 and 6 months [27], with only minor improvements in motor function occurring beyond 6-month [28]. Consequently, clinicians must accurately predict patients' motor function at or beyond the 6-month threshold to determine the ongoing necessity of orthotic interventions.

Rehabilitation programmes post-stroke include exercise prescriptions and other interventions to reduce risks and comorbidities and encourage lifestyle improvements. However, there is no consensus on the most effective protocol after acute stroke, nor a well-established personalised method based on functional outcomes in AFRS patients. Consequently, patients who would have benefited from inpatient rehabilitation and associated functional achievements and post-discharge quality of life may be excluded. Conversely, admitting patients for rehabilitation who do not benefit from it could cause emotional distress to patients (due to lack of meaningful improvement) and could also waste scarce healthcare resources (including beds, staff, and equipment). The challenges associated with stroke rehabilitation studies vary between countries and healthcare systems in terms of structural barriers to the recruitment and retention of participants.

3. The role of AI in transforming AF and stroke care

3.1 AI and digital twins in healthcare

In recent years, AI has emerged as a promising tool in stroke medicine, facilitating the efficient analysis of large-scale datasets and enabling personalised and precision medicine approaches. Unlike traditional prognostic scores, which often rely on predefined baseline variables and linear models, AI algorithms can analyse vast and complex datasets, uncovering intricate patterns and relationships that may elude human perception. By integrating diverse patient data, including clinical parameters, biomarkers, imaging findings, and genetic information, AI models can outperform conventional logistic regression models [29] and generate personalised risk predictions tailored to individual patient profiles.

AI models have exhibited remarkable accuracy in tasks such as imaging analysis, subtype diagnosis, risk stratification, medical treatment guidance, and patient prognosis prediction. Moreover, AI algorithms can adapt and refine predictions over time, incorporating new patient data as it gets collected. This dynamic and data-driven approach enables AI to offer more accurate and granular prognostic insights, surpassing the limitations of conventional prognostic scores and enhancing clinical decision-making [30].

Coupled with AI, digital twins (which in healthcare refer to the digital representation of individuals based on their specific characteristics, and medical and health status history) aim to improve patient outcomes by enabling more accurate diagnoses, more personalised treatment plans, and more efficient resource allocation. Digital twins in healthcare [31] are patient-specific computer models that can use detailed knowledge of disease progression and the underlying pathology to predict difficult-to-measure factors, offering precise clinical decision support [32]. Developing digital twins requires a complete understanding of the mechanisms governing their real counterparts.

The use of digital twins in healthcare began to gain traction in the mid-2010s, and they have found their way into clinical applications only in a limited number of cases. A key characteristic of digital twins in healthcare is that they model individual patients, distinguishing them from population models [32]. They are expected to have a real-time component, where the twin is informed by and updated with the individual patient data. They enable personalised models to provide a comprehensive view of a patient's health by integrating data from multiple organs and organ systems.

AI has revolutionised digital twin technology by significantly expanding its capabilities, allowing for more accurate and dynamic simulations [33]. For example, digital twin models have been used to simulate left atrial appendage thrombus formation in AF patients, using thrombogenic mechanisms based on Virchow's triad [34]. In healthcare, AI-powered digital twins can now simulate complex disease progression with enhanced precision as it enables the integration of real-time patient data, and the simulation of a wider range of simulations of scenarios and treatments (see Figure 2). Applied to AF and AFRS, AI and digital twin technology can help optimise the trajectory of clinical care of patients at different disease stages, facilitate precision medicine approaches and inform clinical trials. Still, the implementation of digital twins in healthcare faces several challenges that limit their adoption and integration into clinical practice [32,35]– see SM, section S2.

3.2 Personalised stroke care today: how far have we come?

To survey the literature on advances in personalised approaches to stroke care, searches were conducted in PubMed/MEDLINE and SCOPUS – see SM, section S3. A large proportion of these studies (8 out of 14) relied on private datasets (see Table S1, SM), which poses significant challenges for reproducibility. The use of proprietary or restricted-access data hinders the ability of other researchers to validate findings, conduct further analysis, or build upon the work, and the broader impact and applicability of the research are ultimately constrained by this lack of transparency and accessibility.

One of the studies [36] proposes a method based on computational spiking neural networks (SNN) for the identification of causal associations between clinical and environmental time series data to predict individual stroke events at least one day in advance. Unfortunately, the proposed methodology has potential data leakage as the modelling time windows are selected based on the stroke onset. It is also unclear how the associations found are deemed causal. SNNs have also been previously used [37] to detect cerebral ischaemia from temporal electroencephalographic (EEG) data.

In the paper by Zheng et al [38], an AI model for triage was proposed to recognise the early signs of ischemic stroke on individualised patient profiles, which was developed using XGBoost, with the use of eXplainable Artificial Intelligence (XAI) techniques such as local interpretable model-agnostic explanations (LIME) and SHapley Additive exPlanations (SHAP) to explain the black-box model. Another study developed an approach based on a variational autoencoder to simulate patient trajectories and forecast disease progression in stroke patients, generating synthetic samples resembling the original input data, which the authors called digital twins [39], although they do not exhibit a real-time component as previously defined [32].

Half of the selected articles addressed personalisation for the rehabilitation stage. Winner et al [40] show personalisation is achieved through the development of a data-driven and generative modelling approach that captures the individualised gait dynamics of individuals. Reinforcement learning was used by Lee et al [41] in an interactive hybrid approach that integrated expert knowledge for personalised rehabilitation assessment. Additionally, a game-based therapy [42] and an AI-driven framework [43] have been proposed to predict cognitive impairment, which could help optimise rehabilitation treatment. However, it is important to note that all these rehabilitation studies have been conducted on very small sample sizes, which presents a significant limitation, as it raises concerns about the generalisability of their findings.

Overall, AI has been applied to different aspects of cardiovascular care, but no overarching study has been conducted to personalise stroke and AF care at the different stages of the patient journey. Regarding tools and devices, several AI-based decision support tools have been developed for the AF and stroke pathways. However, they are mostly proprietary, do not predict risk and are not personalised.

Numerous systems and devices are purporting to be AF tools, including medical devices, e.g. Qardio and Bardy DX, or consumer wearables devices from various companies such as Apple Watch, AliveCor Kardia Band, Huawei, Fitbit, etc. [44]. However, these are AF detection or confirmation systems (i.e., the individual needs to be in AF or have suffered AF episodes to be identified). Another important limitation is that these devices can generally detect arrhythmic events, which may or may not be AF. With some devices, AF is diagnosed by physicians who may disagree among themselves on whether a particular ECG recording indicates AF or some other condition. Regardless of whether these devices are detecting AF or any other arrhythmic events, they are not risk prediction tools.

There are several AI-based decision support tools developed for the diagnosis and management of stroke, e.g., Viz.ai, which analyses brain imaging data in real-time to help diagnose and triage patients with suspected large vessel occlusion strokes [45]; and StrokeViewer, which analyses brain scans to provide automated assessments of stroke severity and potential treatment options [46]. There are also AI-based solutions that have been implemented in stroke care and research for image analysis, as well as decision-making with therapeutics and interventions, such as for the management of transient ischemic attack (TIA) and intracerebral haemorrhage (ICH) [47]. Many of these solutions are not personalised, and the integration of vast amounts of clinical, proteomic, and genomic data to tailor patient care remains a challenge. Future developments in this area may see advances in AI solutions for assessing the risk of drug interactions or side effects, patient suitability for treatments (e.g. reperfusion therapy), and predicting stroke mechanisms [47].

In stroke rehabilitation, hand rehabilitation is core to helping stroke survivors regain activities of daily living and give back some autonomy to the user, with several systems available in the market that use advanced brain-computer interface technology [48]. The MyoPro arm and hand orthosis device works by reading faint nerve signals (myoelectric signals) from the surface of the skin and then activating small motors to move the limb as the user intends [49]. There are also examples of AI-based solutions for gait analysis, providing measured parameters with better accuracy and increasing consistency across healthcare professionals (since observational gait is subjective and relies on the observer's experience) [50]. These and many other tools promise to revolutionise stroke rehabilitation, although their use in clinical settings is not yet well leveraged, and many of them are proprietary (which makes them less accessible).

4. Impact and significance of personalised approaches in AF and stroke care

4.1 Expected technological, scientific and societal impacts

The development of novel, secure and ethical personalised tools for AF and AFRS, as diseases with substantial financial, economic and human burdens, would have a major technological impact. These models could be integrated into existing monitoring devices, such as bedside monitoring or medical wearable devices, as part of a new generation of patient monitoring systems. This in turn will enable provider organisations to develop a range of new workflows, pathways and service delivery models (personalised medicine, diagnostic and therapeutic) that address falling staff-to-patient ratios, improve efficiencies, and deliver higher acuity care outside the hospital, facilitating long-term follow-up and the adoption of more proactive, data-driven processes and methods to prevent hospital admissions and readmissions for stroke patients. Such technology could also be integrated into medical devices and nonmedical wearables, including sports and fitness devices, potentially impacting a wider population.

From the scientific viewpoint, personalised models can help identify combined biomarkers which in turn can aid the further understanding of AF and AFRS, and pave the way to develop multi-scale, dynamic and personalised risk and outcome prediction scores, enhancing patient management. AF research, specifically, will benefit from the enhanced understanding (causality) of the drivers (key biomarkers) of disease onset and their impact on disease progression, at the level of the individual, facilitating the exploration and validation of diagnostic modalities and treatments that could be tailored to each patient. Also, the use of personalised models and tools in clinical practice would represent an advance in the field of neurology, providing key information for decision-making in acute AFRS management, such as resuming oral anticoagulation therapy. Importantly, these methodological approaches could be extended to other stroke aetiologies and health conditions, with the promise to improve care for a wider patient population.

More importantly, from the societal viewpoint, providing better monitoring strategies via personalised approaches has the potential to reduce the burden on patients, and personalisation of care promises to deliver improved treatment, better rehabilitation, less long-term disability, and better quality of life for patients and caregivers. A previous study showed the effectiveness of a nurse-led in-hospital monitoring protocol with mobile ECG was found to improve the rate of AF detection and was recommended for the monitoring of post-stroke patients during initial hospitalisation to complement routine care [51].

Therefore, the use of new strategies for personalisation of care will widen an important care system's path impacting the well-being of patients and their families/carers, representing a significant step forward in patient care. These approaches can also be extended to ambulatory care, home monitoring and long-term follow-up of high-risk patients; and can lead to improved care in the rehabilitation process, resulting in greater satisfaction of patients/caregivers with a realistic adjustment of expectations and better adaptation to disability and quality of life. Personalised approaches have the potential to empower patients and their families to support and better manage the patients' physical health and well-being.

4.2 Estimated costs and economic significance

In 2017, the total cost of stroke in Europe was estimated at €60 billion annually, with healthcare systems bearing €27 billion (45%) of this expense [3]. In the US, the cost to the healthcare system was estimated at €20 billion [3]. In 2050 there will be approximately 180K stroke patients due to a 2.2-fold increase in the number of AF patients compared to 2005 [52], with a significant increase in economic burden [53]. Adherence to holistic or integrated care management approaches based on the Atrial fibrillation Better Care (ABC) pathway translates to reductions in death (up to 80K in the UK in 2040), strokes (18K) and bleeding (26K), potentially leading to substantial healthcare costs saved (up to £720 million for the year in the UK) [53].

Burdett and Lip [54] reported that targeted screening and treatment of AF would substantially reduce the health and social care costs of AFRS, estimating that they would reduce stroke cases by 64% in patients over 65. If at least 20% of those strokes are avoided with the introduction of personalised approaches to patient care, supporting patient management approaches such as the ABC pathway, it will represent over €12 billion of total annual savings, with €5.4 billion of those to healthcare systems in Europe (estimated as 20% of €60 billion and €27 billion, respectively, reported for 2017 [3]).

Regarding rehabilitation, centralised specialist stroke care can improve the use of evidence-based care in the first few hours after a stroke, estimating the 90-day saving to healthcare of €2K per patient (adjusted by population increase), and the 10-year saving of €10K per patient [55]. This implies that: 1) the expected reduction of 20% of cases would mean a 90-day saving of €72 million and a 10-year saving of around €360 million, and 2) rehabilitation interventions may have a significant impact on healthcare costs, hence we could expect that personalised rehabilitation tools could further reduce costs. In addition to the significant reduction of costs due to better monitoring, treatment and rehabilitation, there is a bigger impact on the lives saved and the better quality of life for patients, benefits to families and carers, and a reduction in rehabilitation requirements and long-term care needs.

5. Conclusions

AF and stroke management requires a holistic, comprehensive, personalised approach that integrates dynamic risk assessment and innovative technologies. Despite progress, the complex mechanisms underlying AF-related stroke remain insufficiently understood, posing challenges in clinical practice. Recent advances in AI and ML offer promising avenues for enhancing risk prediction and treatment personalisation, however, only a few studies have attempted to develop personalised approaches, and no overarching study has been conducted to personalise stroke and AF care at the different stages of the patient journey. By leveraging biomarkers and their temporal changes, healthcare providers can develop individualised treatment plans and rehabilitation programmes, potentially reducing disability and improving quality of life for stroke survivors.

This paper underscores the critical need for continued research and the adoption of integrative strategies to optimise AF and stroke care, ultimately aiming to mitigate the substantial burden these conditions impose on patients and healthcare systems. This research need is what gave origin to projects such as TARGET: "Health virtual twins for the personalised management of stroke related to atrial fibrillation" (€10M project funded by the EU Horizon Programme)[56,57].

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List of figures:

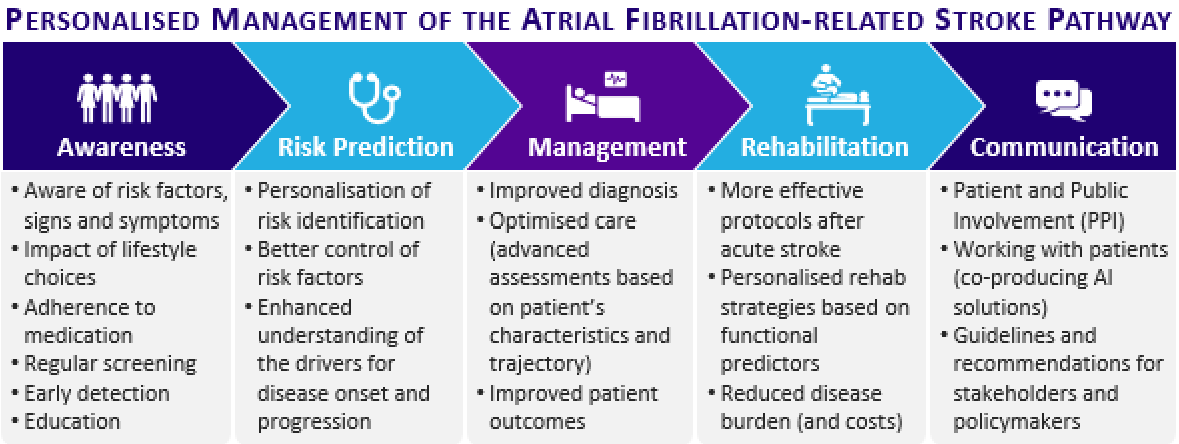

Figure 1. Benefits of personalisation of care across the disease pathway, starting from awareness, risk prediction, management, rehabilitation, and further communication.

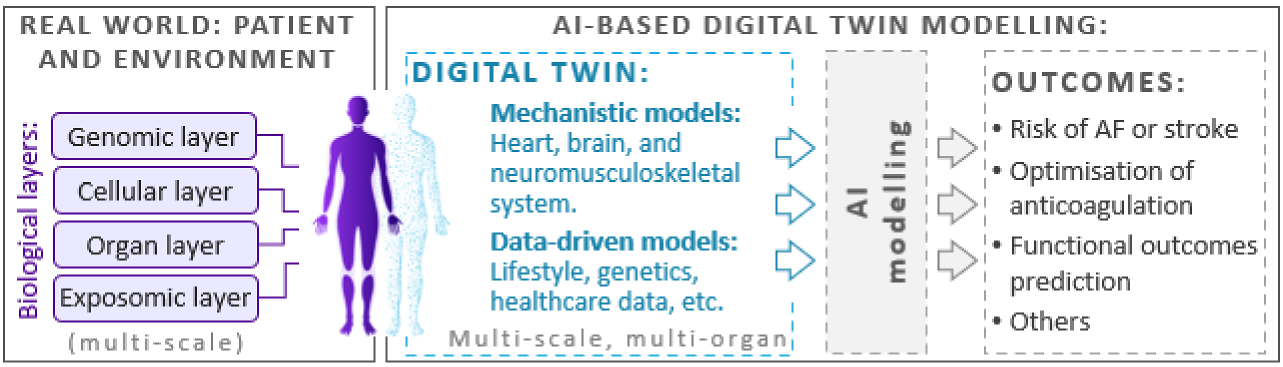

Figure 2. Personalised AI-based modelling of adverse outcomes using digital twin technology.