Digital Twins for Predictive Modelling of Thrombosis and Stroke Risk: Current Approaches and Future Directions

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Abstract

Thrombosis drives substantial global mortality across atrial fibrillation, venous thromboembolism, and atherosclerosis. However, clinical scores treat risk as a static variable and omit evolving comorbidities, functional biomarkers, anatomy, and treatment exposure, leading to misclassification and preventable events. This statement advances a unified scientific agenda for patient-specific digital twins that dynamically integrate multimodal longitudinal data with mechanistic insight to predict thrombogenesis risks. We position these digital twins as hybrid models anchored in physics and data-driven algorithms that can simulate disease progression and therapy. The goal of this approach is to refine stroke and bleeding estimation beyond current clinical rules. Continuous updating from imaging data, laboratory test results, wearables, and electronic health records supports dynamic risk trajectories and adaptive care pathways, facilitating continuous risk reassessment. This statement analyzes gaps in data quality, calibration, validation, and uncertainty quantification that presently limit the clinical translation of this technology. Research priorities are then proposed for multiscale thrombosis modelling, physics-informed learning, probabilistic forecasting, and regulatory-compliant data stewardship. Finally, we outline

translation to in silico trials, regulatory alignment, and hospital workflows that link predictions to decisions. By articulating shared challenges across thrombosis-driven diseases and reframing risk as a time-varying measurable quantity, this statement lays a foundation for developing digital twin approaches that support a shift from population heuristics towards precise, timely thrombosis care. These advances are essential for translating digital twin technology from research to clinical practice, enabling dynamic risk prediction and personalized anticoagulation therapy.

Keywords
digital twins, computational modelling, computational fluid dynamics, thrombus, thrombosis, venous thromboembolism, deep vein thrombosis, stroke, atrial fibrillation, clinical risk prediction

1. Introduction

Thrombosis accounts for one-quarter of all death worldwide.[1] It underlies myocardial infarctions, strokes, and venous thromboembolism (VTE), and is strongly associated with widespread pathologies such as atrial fibrillation (AF), coronary artery disease and atherosclerosis, heart failure, and certain types of cancer (e.g., pancreatic, brain, and haematologic malignancies). To assess the risk of thromboembolic events, clinicians commonly utilize population-based risk scores. Examples include the CHA_2DS_2-VASc/CHA_2DS_2-VA score, a clinical risk stratification tool designed to estimate the likelihood of stroke in AF patients,[2] [3] and the Wells and Geneva scores used to predict risks of deep vein thrombosis (DVT) or pulmonary embolism (PE).[4]

However, these scores rely on a pre-defined set of demographic characteristics and comorbidities (e.g., CHA2DS2-VASc score) or on the subjective clinical judgement of a range of signs and symptoms (e.g., Wells score), overlooking the individualized risk factors of each patient and functional biomarkers. Also, most of these scores are determined at baseline while outcomes of interest occur many years later; hence, the lack of ability to address the dynamic nature of stroke risk.[5] As a result, these simple clinical risk scores have modest predictive value. Thus, they can exhibit suboptimal accuracy in stratifying patients, meaning some patients with “low” scores still suffer thrombotic events, whereas others at truly low risk may be overtreated with anticoagulants, exposing them to bleeding.[6]

Knowledge gaps in the pathophysiology of thrombosis, especially in the presence of different clusters of comorbidities and/or modifiable environmental factors, have so far prevented the development of a unified approach to individualized risk prediction despite the maturity of technology powered by computational modelling and artificial intelligence (AI). This is due to the complexity of modelling clot formation and its interplay with systemic health changes and the difficulty of integrating heterogeneous data, such as laboratory parameters, imaging data, and real-time physiological signals, into a coherent clinical framework. [Fig. 1] illustrates the main features underlying three of the major thrombosis-related diseases—AF, VTE, and atherosclerosis—from the perspective of the disease pathophysiology, current diagnostics, and emerging technologies. Physiologically, common factors such as inflammation, endothelial dysfunction, and blood stasis underlie the risks of thrombogenesis and stroke in all conditions. Medical diagnostics, therefore, also share common approaches, ranging from empirical risk scores to patient imaging. Future technologies should target these common clinical problems, utilizing digital twinning and data- and image-driven AI for patient-specific risk predictions.

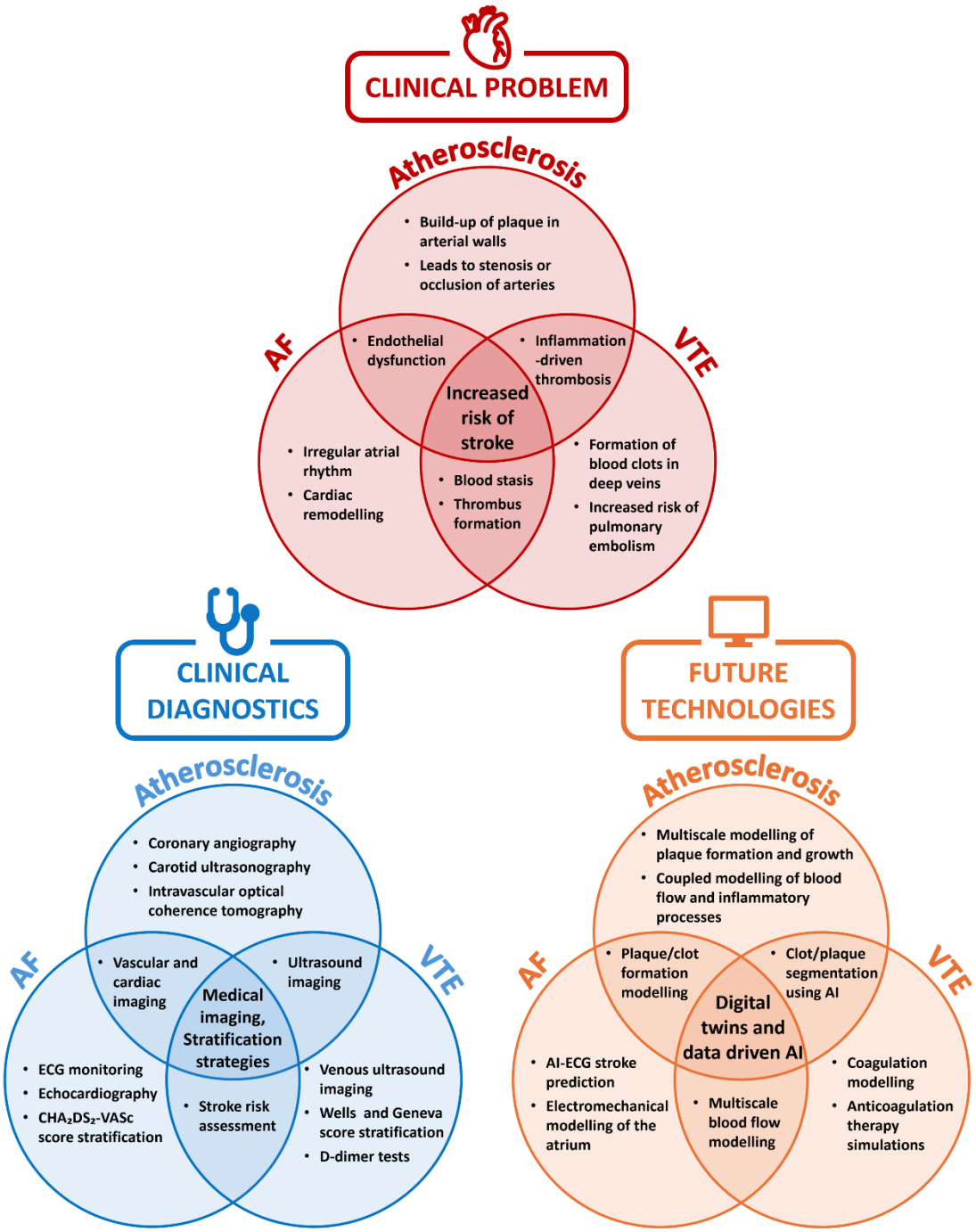


Fig. 1 Current strategies and emerging technologies for disease management. Venn diagrams illustrating the shared and distinct features of atrial fibrillation (AF), atherosclerosis, and venous thromboembolism (VTE) across three domains: clinical problems, diagnostic approaches, and emerging technologies.

Addressing these issues requires integrating mechanistic understanding with patient-specific data, a capability uniquely offered by digital twin technology. Digital twins are virtual representations of physical entities such as organs or systems of organs that integrate clinical, genomic, and imaging data to simulate disease progression.[7] [8] These data-driven models are further constrained by imposing adherence to physiological mechanisms, often via inclusion of conservation laws governing the behaviour of the system. This enables these so-called 'physics-based digital twins' to avoid unrealistic predictions, especially where training data are incomplete or sparse.

The core aim is to use patient-specific digital twins to achieve personalized predictions of disease trajectories in patients and refine diagnostic algorithms with unprecedented granularity. Digital twins can also be used to test different therapeutic interventions virtually to guide treatment.[9] Moreover, AI models can be embedded into the digital twins to facilitate fast (effectively real-time), patient-specific predictions. This approach has therefore strong potential to identify early risk indicators that conventional clinical scores might overlook.

However, challenges remain—from acquiring and harmonizing multiscale data, to validating the digital twins, to embedding real-time, explainable predictions into clinical workflows. Successful deployment of this technology at scale inevitably relies on multi-disciplinary research, where cutting-edge technology is developed to address the clinical needs and knowledge gaps that currently prevent early diagnosis and personalized treatment. Fulfilling this vision has the potential to transform thrombosis care from population-based heuristics to adaptive precision medicine.

2. Digital Twin Paradigm for Thrombus Prediction

2.1 Atrial Fibrillation and stroke risks

Atrial fibrillation (AF) is a common cardiac arrhythmia in which chaotic, rapid electrical impulses prevent the atria from contracting effectively. The resulting blood stasis (particularly within the left atrial appendage), as well as the dysfunction of the endothelium and an inflammation-driven hypercoagulable state, promotes thrombus formation. AF is therefore responsible for a 5-fold increase in ischaemic stroke incidence, with AF-related strokes typically more severe and disabling than other types.

2.1.1 Clinical challenges in thrombosis risk prediction and management in atrial fibrillation

Dynamic versus static risk. AF-related stroke risk is inherently dynamic, influenced by evolving comorbidities, functional biomarkers, and rhythm patterns. In particular, AF patients frequently present with comorbidities and blood property alterations whose interactions are not captured by static, population-based scores.[10] Another significant knowledge gap that has hindered precision medicine in this arena relates to understanding how risk changes with aging and incident comorbidities. In AF, the rhythm itself is also dynamic in nature, continuously changing and transitioning from paroxysmal to persistent or permanent AF. Hence, management strategies should also be responsive to the underlying pathophysiology associated with thromboembolism[11] and its changes over time.[12] Additionally, they should account for the risks associated with environmental factors that have been related to incident AF and AF-related complications.[13] [14] [15] These factors may trigger AF or worsen its complications and as such should be included in risk models. Finally, the genetic predisposition (and racial differences in AF-related risks and complications[16] [17] [18]) would need to be integrated into a learning system model.

However, the definition of new biomarkers to account for these complex aspects of risk is hindered by the lack of precise knowledge of the mechanisms linking AF to thrombus formation and subsequent stroke. There is, therefore, a critical need for physics-informed digital twin models that are capable of integrating these different streams of dynamic data to simulate how patients with complex phenotypes would behave, which is clearly related to prognosis and their responsiveness to clinical management.

Feasibility of patient-specific anticoagulation. Although current anticoagulation treatments have significantly reduced the risk of stroke in AF patients, the long-term risks of stroke recurrence and treatment-associated bleeding remain substantial. Balancing stroke prevention with bleeding risk is a perpetual clinical challenge in AF management. Although current guidelines emphasize that the benefit of stroke prevention in most patients outweighs the bleeding risk, in practice fear of bleeding complications frequently deters optimal therapy. Real-world data indicate that 25 to 30% of high-risk AF patients remain undertreated (i.e., not adequately anticoagulated) due to bleeding concerns or underestimation of risk. Like stroke risk, bleeding risk also depends on the interaction of modifiable and non-modifiable factors and is dynamic in nature.[19] AF patients are often elderly at high risk of bleeding

because of multimorbidity, polypharmacy, and frailty.[20] [21] Hence, we need to assess the net clinical benefit (NCB) of introducing oral anticoagulation (OAC) in these patients instead of pursuing other treatment options, such as the occlusion of the left atrial appendage. Although the NCB of OAC appears to be in favour of treatment in very elderly subjects at high bleeding risk,[22] [23] an important area where digital twin models could provide a tangible benefit is the identification of the patients who can (or cannot) benefit from OAC treatment given different and changing risk profiles.[6] Importantly, stroke prevention in AF is more than just OAC alone, and there is recognition of a residual risk of stroke and other cardiovascular events despite OAC use,[24] [25] with patient compliance to treatment also playing an important role. Hence, approaches such as the evidence-based Atrial fibrillation Better Care (ABC) pathway[26] have been developed to move towards an integrated care approach to AF management. The ABC pathway's pillars—Avoid stroke with Anticoagulation; Better management with patient-centered, symptom-directed rate or rhythm control; and Cardiovascular risk factor and comorbidity optimization – are supported by randomized trials,[27] [28] [29] observational cohorts,[30] [31] [32] and guidelines.[33] [34] Variants of the ABC acronym have been proposed, including the (untested) AF-CARE and SOS pathways.[33] [34] [35] [36] These frameworks provide an excellent opportunity to develop, test, and deploy digital twin models that are fully aligned with clinical needs.

2.1.2 The paradigm shift towards Digital Twins for stroke risk prediction

Mechanistic Digital Twins. The CHA2DS2-VASc is a simple clinical score widely used for assessing thrombus risk in AF,[36] but only focuses on comorbidities and demographic factors, while neglecting cardiac morphology, electrophysiology, and haemodynamics.[37] Digital twins could shift this paradigm towards precision medicine by integrating multimodal data with governing laws of physics.[7] [38] Stroke digital twins can aid medical decisions involving different disciplines (e.g., neurology, cardiology).[39] [40] [41] [42] While multi-organ mechanistic digital twins would be overwhelmingly complex, models representing single organs can provide valuable insight in specific contexts. An example of this approach are the left atrial digital twins (LADTs) developed to address the risks of ischaemic strokes originating in the fibrillating atrium.[43] [44] LADTs are computational models that simulate how AF disrupts normal electrical activity, mechanical contraction, and blood flow, creating conditions that promote clot formation. They can have varying levels of fidelity depending on their dimensionality (e.g., 0D compartment models versus 3D anatomical models), biophysical representation, personalization (e.g., via imaging data, blood tests), and spatiotemporal resolution. [Fig. 2] illustrates general strategies of digital twin personalization using AF patient imaging data, with different modalities utilized to obtain information about patient-specific LA size, wall movement, and thrombus locations. High-fidelity twins then use computational fluid dynamics (CFD) models to solve the partial differential equations (PDEs) governing blood flow in a 3D domain representing the LA chamber.[44] [45] [46] [47] [48] [49] [50] [51] [52] [53] These models focus on the left atrial appendage (LAA), the most common site of thrombosis, and can provide metrics related to blood stasis or coagulation protein species concentration[11] (see [Video 1], available in the online version only). Some models also include PDEs for simulating electrical and mechanical activity of the myocardium to mimic wall motion.[54] [55] [56] [57]

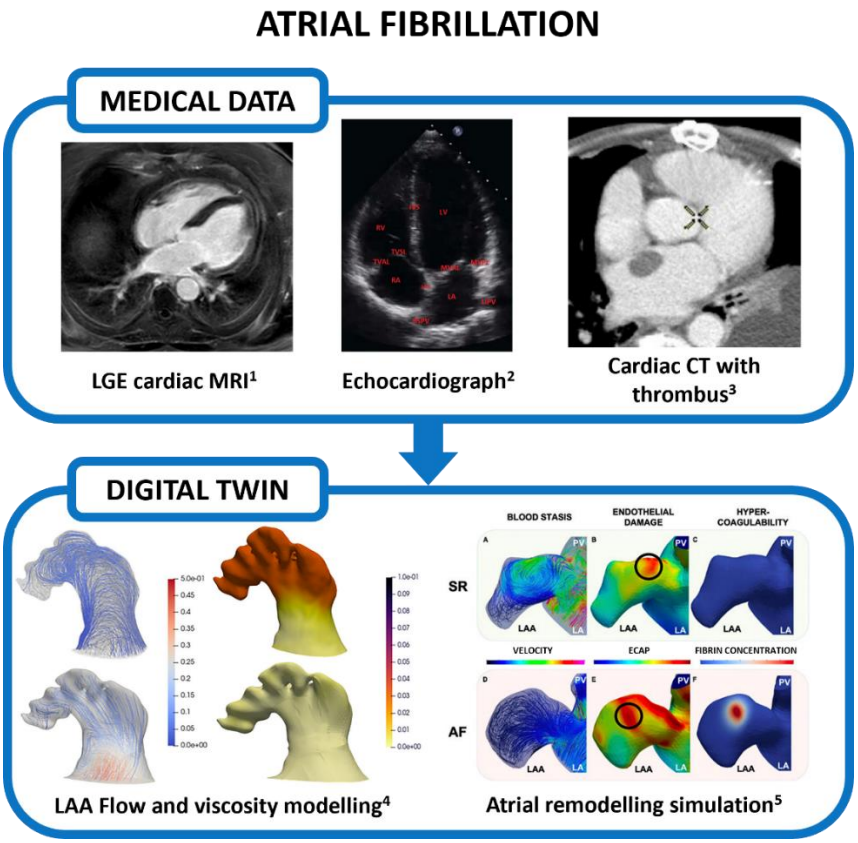
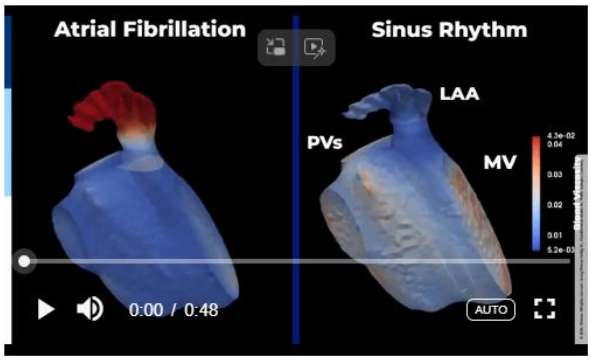


Fig. 2 From clinical data to personalised models: atrial fibrillation. Patient-specific digital twins integrate multiple imaging modalities to predict thrombosis risk: late gadolinium enhancement (LGE) MRI to identify fibrotic tissue,[202] echocardiography to capture wall motion abnormalities,[203] and CT scans to reveal anatomical variations.[204] These modalities are used to create predictive models of left atrial remodelling,[77] blood flow, and viscosity within the left atrial appendage,[69] aiding risk stratification and treatment planning. AF, atrial fibrillation; LA, left atrium; LAA, left atrial appendage; SR, sinus rhythm.



Video 1 Video of CFD simulations illustrating the thrombogenesis in the left atrium (LA). The simulations employ a non-Newtonian blood model to capture viscosity changes associated with red blood cell aggregation under conditions of blood stasis. The left panel depicts a patient with AF, while the right panel shows a patient in sinus rhythm. LA geometries and the mitral flows are provided by patient Cine MRI images and Doppler ultrasound, respectively. In AF, the absence of effective atrial contraction and the lack of an A wave in the mitral inflow led to blood stasis and increased viscosity, promoting the thrombus formation.

Current technological challenges. As the biophysical complexity of LADTs increases, so does their mechanistic level of detail, but their computational demands and parameterization become more challenging; the latter is particularly hindered by the LA's complex anatomy. Notably, the pulmonary veins and LAA exhibit frequent variants with disparate morphologies associated with LAA blood stasis and

stroke risk.[58] [59] [60] [61] [62] [63] [64] The diverse pathophysiology of AF and thrombosis further complicates the creation of comprehensive LADTs. Factors like epicardial fat, myocardial fibrosis, blood haematocrit, endothelial dysfunction, blood stasis, and hyper-coagulable state can all contribute to stroke risk, in the so-called Virchow's triad.[65] Caused by excess buildup of collagen fibres, myocardial fibrosis modifies electrical conduction, contractility, and stiffness.[66] [67] The secretome of epicardial adipose tissue promotes fibrosis and thrombosis.[68] Haematocrit affects blood viscosity, especially inside the LAA.[69] [70] [71] [72] Epicardial fat and myocardial fibrosis can be mapped with medical imaging, while haematocrit and coagulation factors can be measured from blood draws, as can inflammatory markers related to endothelial dysfunction. Although these data can deeply personalize LADTs, many associated model parameters are not directly measurable, and their inference requires solving ill-posed inverse problems. Novel machine learning methods have the potential to close this gap.[73] [74] [75] [76]

Next-generation mechanistic twins. The growing availability of anticoagulant drugs targeting diverse clotting factors presents new opportunities for LADTs in stroke prediction. LADT of thrombosis are however less developed than electromechanics, haemodynamics, or device implantation models due to their computational cost and labour-intensive personalization.[77] [78] [79] Recent advances have addressed these limitations. New 4D image segmentation workflows based on neural networks[80] leverage the increase in capacity of GPUs to bypass human labour almost completely. Neural networks trained on massive datasets from high-fidelity simulations can predict flow fields and haemodynamic metrics associated with thrombosis.[75] [81] GPU implementations of 3D PDE solvers achieve unprecedented speed for high-fidelity LADTs.[42] [82] [83] Reduced-order and multi-fidelity models of the coagulation cascade accelerate thrombosis simulations by orders of magnitude.[42] [84] In parallel, medical device and pharmaceutical companies already use digital twins of varying fidelities to accelerate product development.

All these advances are bringing us close to near-real-time execution in research settings. However, real-world impact can only happen when this technology is developed in hospital settings. Meeting these requirements will demand unprecedented resource investment, infrastructure and specialized personnel, interoperability between clinical and computation systems, protocol robustness, and close collaboration between technical, clinical, and regulatory stakeholders. In addition to model development, validation, verification, and uncertainty quantification following recognized standards (e.g., V&V40[85]) are essential to assess the adequacy of these twins. These tasks are performed at different levels, starting with model convergence, comparison with synthetic data or in vitro phantoms, and ultimately, validation versus clinical data.[86] [87]

AI-driven digital twins. Although mechanistic digital twins[53] [69] [78] [88] [89] [90] [91] can provide invaluable patient-specific simulations of thrombus formation, in many circumstances this approach is challenging due to limited knowledge of the system and the lack of data for a rigorous personalization. On the other hand, data-driven digital twins powered by AI can learn more complex, non-linear systems that cannot be easily/effectively modelled using differential equations alone. These AI-driven twins are therefore particularly valuable for incorporating comorbidities, genetic factors, lifestyle influences, and other variables that are difficult to model using mechanistic approaches.[8] [92] [93]

In this context, a hybrid modelling framework that anchors machine learning–based predictions in physics principles could detect complex interactions and subtle patterns that might be missed by traditional clinical assessments without the computational burden of mechanistic twins. These hybrid twins can enhance the personalization of the CHA2DS2-VASc score by incorporating patient-specific, real-time data beyond the standard binary risk factors, reflecting the unique risk profile of each individual. For example, the inclusion of dynamic parameters like disease progression rates and wearable-derived markers could allow for a dynamic stroke risk stratification and AF patient management, improving outcomes in a highly individualized manner.

Moreover, these twins can simulate the effects of adjustments in anticoagulation therapy or lifestyle modifications, enabling clinicians to identify optimal treatment pathways or refine current ones such as the ABC pathway. This vision is precisely the focus of extensive research programmes such as the EU project TARGET,[9] [94] which aims to harness AI-driven digital twins to transform the management of

stroke patients, from diagnosis to poststroke rehabilitation. One example from TARGET involves the development of personalized algorithms to assess the optimal point to initiate anticoagulation treatment after an acute ischaemic stroke against risks of early haemorrhagic transformation.[95] [96] Other important digital twin applications include the prediction of the haemodynamic impact of LAA occluder devices and their potential for device-induced thrombosis,[41] [43] or of LAA excision.[97]

Take-home message. AF twins should prioritize stroke prevention and individualized stroke versus bleeding trade-offs over the years, adjusting predictions dynamically based on incident comorbidities and changes in atrial function and coagulability. Another interesting area of impact for the digital twins is the prediction of time-varying risk under rhythm/rate control and simulation of anticoagulation treatment with net clinical benefit clearly quantified against current clinical risk scores.

2.2 Deep Vein Thrombosis and Pulmonary Embolism

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a vascular disease of considerable public health importance given that about 1 in 12 adults will be affected in their lifetime.[98] It remains the leading cause of in-hospital mortality[99] and can lead to long-term impact on health including a poorer quality of life.[100] Thus, DVT and PE are serious medical conditions that require prompt diagnosis and treatment to prevent complications. Awareness of the symptoms, risk factors, and preventive measures is crucial for managing and reducing the risk of these conditions.

2.2.1 Clinical challenges and knowledge gaps

Current clinical challenges in VTE. Symptoms and signs of a VTE event are not specific. For example, DVT can often be mistaken for trauma-related injury or cellulitis, leading to false negatives, while elevated D-dimer levels, which can be seen in various other conditions, may result in false positives. This can lead to delays in presentation, diagnosis, and initiation of potentially lifesaving treatment.[101] Although radiological imaging for VTE is the cornerstone to confirm diagnosis, these modalities are also subject to challenges related to motion artifacts or contrast timing (e.g., subsegmental emboli), operator dependency (e.g., differentiating chronic thrombi from acute DVT[102]), or safety and availability in patients who are otherwise high risk (e.g., during pregnancy or patients with renal insufficiency).[103]

After the first episode of VTE, there remains a persistent, elevated risk of recurrent events that is estimated to be over 50 times higher than in an individual without prior VTE.[104] However, the diagnosis of recurrent events can be challenging as symptoms and signs of chronic complications, such as post-thrombotic syndrome or valvular insufficiency, overlap with episodes of acute VTE making clinical differentiation difficult.[102] The use of clinical decision tools and laboratory tests that help predict pre-test probabilities, integrated with radiological tools, could overcome some of these challenges, but there remains a need for more advanced multimodal data analysis, protocol optimization, and decision support for the diagnosis of initial and recurrent VTE events to radically improve risk prediction.

Knowledge gaps. VTE risk depends on the interaction of multiple factors across different timescales, including:

Baseline factors: Demographics (age, sex), inherited thrombophilias (factor V Leiden, prothrombin mutations), acquired conditions (JAK2-mutated myeloproliferative neoplasms).

Dynamic factors: Medications (anticoagulants, hormonal contraception), laboratory parameters (platelet counts, coagulation profiles), disease progression (metastatic cancer).

Predicting VTE thus requires integrating these chronic and acute factors to estimate time-specific risk,[105] which is far from straightforward as clinicians need to account for several inputs to estimate the risk at any time point. Key examples of basal risk factors for DVT include demographics (e.g., age or biological sex), as well as underlying inherited genotypes such as hereditary thrombophilia (including factor V Leiden, prothrombin gene mutation, protein C, S and antithrombin deficiency) or acquired conditions like JAK2-mutated myeloproliferative neoplasms. This baseline risk is further compounded by

dynamic factors including medications (such as antiplatelets, anticoagulation, hormonal contraception), laboratory features (such as platelet counts or coagulation parameters), and progression of an underlying disease (such as metastatic cancer). Thus, risk calculators must integrate chronic and acute risk factors to predict an individual's risk for VTE at specific time points.[106] [107]

As in AF, anticoagulation remains the mainstay of VTE prevention but carries an inherent risk of bleeding that can itself be life threatening.[108] Current guidelines recommend that the choice of agent, dose, and duration of anticoagulation is tailored based on a patient's propensity to bleed, the severity of the thrombosis, as well as likely triggers for the index thrombosis that can predict the risk for recurrence.[109] [110] [111] Thus, these complex therapeutic decisions in VTE are high stakes and rely heavily on individual clinician expertise and experience, which are inherently highly variable.

2.2.2 Engineering Perspective: Tailoring risk assessment

Digital Twins to enhance patient management. Digital twins can provide significant enhancements for managing DVT and PE in several ways. First, digital twins can be designed to learn the patient-specific balance of chronic and acute risk factors to adjust dynamic risk prediction from a patient-specific baseline calibrated on population-based data. Lifestyle factors can also be integrated to create a detailed risk profile of the patient that can adjust as new data become available (e.g., changes in mobility, onset of symptoms) to guide personalized rehabilitation plans and suggest preventive measures, such as the use of compression stockings, changes in medication, or increased physical activity. Second, digital twins can simulate the progression of DVT and PE under various scenarios using underlying mechanistic models or machine learning–based correlations, helping clinicians predict the likely course of the disease and identify potential complications early. Finally, digital twins can also be used to monitor patients for signs of recurrence, assess ongoing risk thanks to continuous data sources such as wearable devices, and recommend follow-up care as needed.

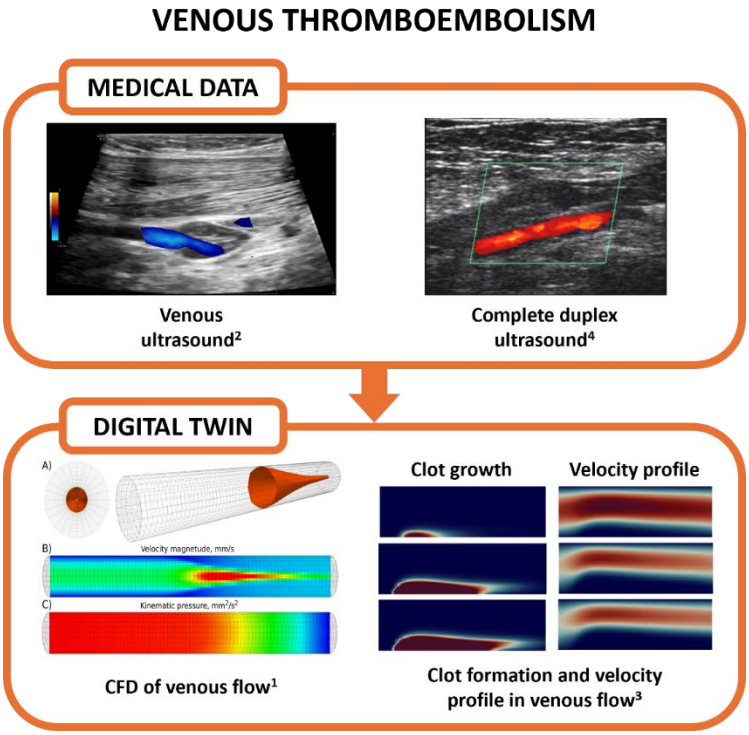


Fig. 3 From clinical data to personalised models: venous thromboembolism: venous thromboembolism. Venous[205] and complete duplex[206] ultrasound data support models that predict clot formation, simulate blood flow velocity,[117] and capture haemodynamics within the venous system via simulations to assist in clinical decision-making.[112] These models can be augmented by including simulation of biochemical reactions in the patient-specific blood flow using data from blood tests and clotting profiles.

Patient-specific predictions with AI. In VTE, mechanistic digital twinning involves the development of a 3D model of the patient's venous system using imaging data, to replicate the patient-specific anatomy and physiological conditions using CFD models. Patient-specific factors like blood viscosity, vessel elasticity, and flow rates can be incorporated in the model.[112] [113] [114] Physiological simulations of the blood flow dynamics,[115] clot formation, and dissolution processes[116] can then be applied to predict patient-specific responses to anticoagulant therapy under venous flow conditions. [Fig. 3] illustrates digital twin personalization strategies using VTE patient imaging data, with different ultrasound modalities utilized to obtain information about the vein structure and thrombus locations, and CFD models then applied to simulate haemodynamics underlying the clot formation.

However, digital twin simulations of the blood clotting and anticoagulation dynamics are computationally expensive, warranting the use of AI. The AI integration implies the development of machine learning algorithms using large datasets that include various patient responses to anticoagulant therapies.[117] [118] [119] These AI models can learn patterns and predict outcomes based on newly available patient data. This integration, however, relies on the ability to achieve fusion of information and comprehensive data curation and integration. Where real-world datasets are too messy or incomplete to be used, AI can be trained on the outcomes validated mechanistic simulations calibrated on in silico cohorts generated from image and clinical datasets. Such AI training can include additional factors such as different anticoagulant dosage, drug interactions, and individual patient risk factors. However, as for the LADT, the incorporation of in silico training is promising but inevitably relies on a rigorous validation of the mechanistic models it uses. Successful implementation therefore requires addressing challenges related to model validation and verification and data quality before clinical adoption is possible.

Take-home message. VTE digital twins should emphasize fast diagnostic and short- to medium-term management decisions. Because VTE symptoms are non-specific and recurrence is common, an area where this approach could provide clinical benefit is a tailored and accurate analysis of the recurrence risk that governs the duration of anticoagulation after thrombotic events, and a rapid diagnosis support under high uncertainty.

2.3 Stroke and Atherosclerosis

Atherosclerosis is characterized by the accumulation of lipid material within the arterial wall, with consequent progressive luminal stenosis by growth of plaques. Disturbed flow, characterized by low and oscillating shear stresses, predisposes to a cascade of events that lead to plaque formation.[120] In this context, branch points and bifurcations are especially prone to developing atherosclerotic lesions.[121] Additionally, in recent years, the role of inflammation in the initiation and progression of atherosclerosis has become increasingly recognized.[122]

2.3.1 Clinical challenges and knowledge gaps

Plaque growth mechanisms. The presence of atherosclerotic plaques has been documented in autopsy studies of young children dying from unrelated conditions. It is therefore evident that the disease process may start at a young age and progress throughout a person's life course; however, the rate at which it progresses is accelerated by risk factors, in particular smoking, hypercholesterolaemia, hypertension, diabetes mellitus, and overweight/obesity. All these conditions are characterized by endothelial dysfunction, which in turn is largely attributable to the proinflammatory state typical of these diseases. Endothelial dysfunction is associated with increased lipid uptake into the subintima, predominantly through the binding of blood-borne cholesterol in the form of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). In regions where the wall shear stress (WSS) exerted by the flow on the arterial wall is low and oscillating, the permeability of the intima to LDL increases, leading to pathological inflammation, monocyte recruitment, and growth of sub-endothelial plaque.[123] Platelets also play a crucial role in promoting inflammation through binding of leukocytes (so-called heterotypic aggregation) and in monocyte recruitment and infiltration into the arterial wall.[124] [125] When the lipid-rich core of the plaque is relatively small and the collagen-rich cap relatively thick, the plaque is stable. However, in

the reverse situation, it is unstable and prone to fissure or rupture, especially when the inflammatory cell burden is high, exposing the blood circulation to the lipid-rich material within, which is highly thrombogenic.[126] [127] Despite the mechanisms of plaque growth being well understood, plaque-level biology remains invisible to classical scores and risk calculators integrate systemic exposures (e.g., age, LDL) but cannot tell which artery harbours a vulnerable cap. There is also an inadequate ability to capture biomechanical triggers of rupture as most clinical datasets do not include CFD-derived stress fields. Further, sparse longitudinal cohorts and limited spatial omics impede an informed prediction of lesion initiation and progression velocities.

Patient data. Technological advances now allow much relevant patient data to be gathered and stored digitally. Different imaging modalities are used in different context, such as carotid or coronary plaques. These include:

1. Data from blood samples on monocyte and neutrophil counts, as well as on circulating levels of monocyte–platelet aggregates and monocyte phenotype;
2. Non-invasive carotid ultrasonography, to detect the presence of atherosclerotic plaque in large extracranial arteries, and evaluate the degree of stenosis and, to a limited degree, plaque composition. In the absence of overt plaque disease, it will also allow assessment of carotid intima–media thickness, which has been shown to predict future cardiovascular risk;
3. Invasive angiography (usually reserved for candidates to carotid surgery), to outline the distribution and severity of atherosclerotic disease in more detail than non-invasive ultrasonography;
4. Intravascular ultrasound scanning, to provide greater detail on the degree of stenosis and the internal anatomy of atherosclerotic plaques (e.g., volume of necrotic core versus fibrous cap);
5. Intravascular optical coherence tomography, to offer better resolution and visualization of the vessel lumen, degree of atherosclerosis, and internal plaque structure than intravascular ultrasound.

2.3.2 Engineering Perspective: mechanobiological models of atherosclerotic plaque

Blood dynamics plays a crucial role in creating the conditions that promote atherosclerosis. However, atherosclerosis is a process that develops within the vessel wall. Thus, in principle, an accurate prediction of plaque development should include the interaction between blood and vessel wall and the strong interplay between macroscopic and microscopic scales that characterizes plaque formation.[128] Specifically, a computational model for atherosclerosis should be able to accurately capture: (1) low and oscillating WSS, which provokes a cascade of events at the cellular level whose final consequence is plaque formation; and (2) blood vessel geometry, which determines both the precise location of regions of bifurcation and the nature of their interaction with low and oscillating WSS. This means that different patients, characterized by different vascular anatomy and molecular processes, may develop atherosclerosis differently. [Fig. 4] illustrates how patient-specific information, highlighted above under (1) and (2), can be obtained from various medical imaging modalities, with patient-specific simulations then applied to analyze the dynamics of plague growth and possible therapy response.

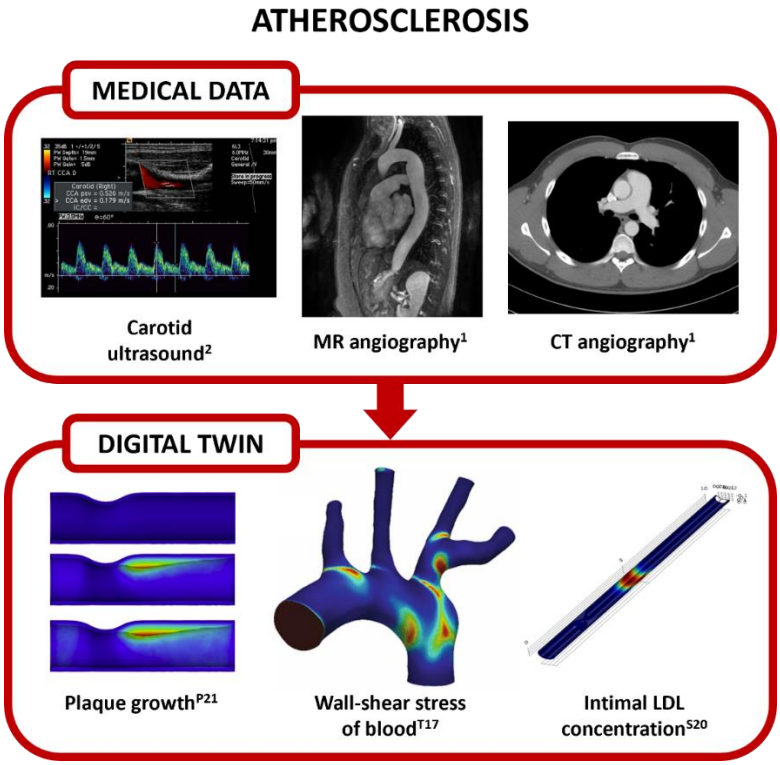


Fig. 4 From clinical data to personalised models: atherosclerosis. Carotid ultrasound,[207] MRI[208] and CT[209] angiography inform models that simulate plaque growth,[128] blood shear stress,[133] and LDL concentration,[132] providing insights into disease progression and therapeutic response.

Furthermore, WSS, being the result of blood fluid dynamics, is dominated by the short time scale of the cardiac cycle. However, the consequences on plaque formation occur over a time scale of many years, meaning mathematical models must also incorporate multiple temporal and spatial scales, as well as patient-specific morphology. Although image-based CFD simulations are widely used to model blood flow in the context of atherosclerosis,[129] [130] [131] [132] more recently models based on the solution of a fluid-structure interaction problem (FSI) for blood and vessel wall have been proposed to couple the macroscopic and microscopic models of plaque formation and growth.[128] [133] Coupled differential models have also been proposed to describe the inflammatory processes in the arterial wall.[134] [135] However, most studies introduce a macro-to-micro scales feedback by adopting a relationship linking WSS and the permeability of the endothelium[131] [135] or linking WSS and growth itself.[136] The micro-to-macro scales feedback has been described by means of phenomenological growth laws[130] [135] relating cellular concentrations to plaque thickness, or by including a growth tensor in the vessel wall dynamics.

None of these models however addresses thrombus progression specifically. One of the first models to include the effects of pro-thrombotic agents in blood, platelet adhesion, and thrombus growth was proposed in the study by Anand et al.[137] More recently a deposition potential driven by haemodynamics was successfully applied to patient-specific geometries,[138] and multiscale models that include platelet adhesion were proposed.[139] As with many other disease processes, digital twin technology is now at the point where it can model the progression of atherosclerosis with ever-increasing precision thanks to technological advances and a better understanding of underlying pathogenetic mechanisms. The goal for the next few years will be to demonstrate its capability to reliably predict outcomes, as well as the utility of specific treatments, in individual patients. The most important and challenging issue that now needs to be addressed by the digital twin community lies in the calibration of such models. Here, we underscore three new challenges in which we should invest. The first one is the collection of follow-up data for the same patients to incorporate information about the plaque and/or thrombus development over years, to assess the predictive capacity of the method. The second one is

the development of efficient and easily implementable numerical methods to solve the minimization problem arising during calibration, to provide patient-specific (or at least reasonable) values of the model parameters. Nowadays, this is often performed heuristically, by a trial-and-error strategy, since the most efficient strategies (for example, gradient-like methods) are today hardly applicable to very noisy data. Finally, the development and curation of standardized datasets at multiple scales is crucial to allow for model benchmarking and validation, and ultimately for the clinical translation of the digital twin concept.

Take-home message. Atherosclerotic stroke twins should focus on the characterization of lesion phenotype and growth to predict system-wide risk evolution. Multiscale coupling of patient-specific haemodynamics and wall/plaque biology can inform lipid lowering and antiplatelet strategies, and revascularization choices (e.g., carotid stenosis) within a multi-year trajectory.

3 Current Barriers and New Frontiers of Digital Twin Technologies

3.1 Calibration and validation: data and computational requirements for AI

Data limitations. Training data for the coagulation dynamics are often limited, sparse, or heterogeneous. Large, comprehensive datasets of spatio-temporal clot formation encompassing both the macro and the micro scale are rare and confined to research settings. Similarly, experimental data often consist of only a few summary metrics (e.g., clotting times) at sparse time points, rather than full continuous observations of all species, and present various degrees of experimental noise. These factors significantly limit the quality of training data, which can be further compromised by variations in measurement protocols and batch effects. A lack of a unified approach to data collection also makes it difficult to align datasets derived from different sources or using different technologies.

Technological solutions. To address these data limitations, computational modelling must employ advanced strategies. These include data imputation techniques, uncertainty quantification frameworks, and robust training procedures capable of handling imperfect real-world datasets. Techniques like transfer learning, physics-informed neural networks (PINNs), and Bayesian calibration methods can alleviate some of these issues by embedding biophysical domain knowledge into the training process: for example, PINNs encode conservation of mass and momentum in the blood flow and biochemical advection–reaction–diffusion equations into their loss function, while Bayesian calibration incorporates biophysically plausible priors into the model.

Validation strategies. Validation of model-based thrombosis models must involve rigorous comparison with empirical evidence at multiple scales. Although summary metrics like clotting time and peak thrombin levels provide a coarse reference point, more granular data are needed to evaluate model performance. Recent microfluidic, chip-based vascular devices for mimicking thrombosis provide invaluable resources to calibrate and validate multiscale computational models.[140] [141] [142] These experimental phantoms enable reproducible strategies for both model calibration and validation, addressing these limitations. Co-developing digital twins with organ-on-chip or other in-vitro vascular platforms will thus enable a much-needed bidirectional workflow, where models guide hypothesis-driven experiments, and experimental results serve as benchmark for model accuracy. These initial steps are key before progressing to in-vivo validation of model predictions against clinical outcomes.

Take-home message. Digital twins for thrombosis face a common bottleneck: real-world clinical data are sparse, noisy, and heterogeneous across scales. Credible twin models therefore need physics-aware learning, Bayesian calibration with explicit uncertainty, and robust verification and validation. Microfluidic/organ-on-chip platforms provide an excellent benchmark for calibration that is currently under-utilized by the modelling community.

3.2 Integration of machine learning and multi-scale modelling

A common issue across all types of thrombosis modelling and prediction is the need to account for multiscale processes. However, multiscale modelling alone often struggles with efficiently leveraging

large, diverse datasets, and its computational costs can be prohibitively high. Combining ML techniques with physics-based multiscale models can yield more efficient workflows for patient-specific predictions. While ML identifies correlations in large multimodal data, multiscale modelling can determine the causality in these relationships and uncover underlying mechanisms in a deterministic fashion. Instead of using either in isolation (which can lead to non-physiological predictions or inability to use large datasets), new approaches should integrate both. This complementary interaction opens up new challenges and opportunities in the development of predictive digital tools.[143]

Physics-based models (often in the form of PDEs with patient-specific boundary conditions)[11] [77] can be used to regularize ML approaches, enabling them to learn from limited and noisy data that vary across time and space. In Gaussian process regression, the PDEs can be used to generate physiologically acceptable prior distributions, while in PINNs they are incorporated in the cost function of the network to enforce known physical constraints while learning from data. The result is a “best of both worlds” model that can predict an individual's thrombus formation dynamics under various conditions, grounded in physiological knowledge and informed by patient data. Moreover, such models can be continuously updated. These approaches have been used to tackle a range of applications in fluid dynamics, cardiac electromechanics, and drug development.[69] [144] [145] [146] [147]

Although this integration holds great promise, significant open challenges remain. Biological systems are governed by complex spatio-temporal interactions that are only partially understood. Traditional multiscale modelling requires well-defined boundary conditions that are difficult to derive from real-world biological data, leading to ill-posed problems or incorrect simplifications. Although physics-informed ML models can approximate the behaviour of high-fidelity simulations at a fraction of the computational cost, they are still informed by physical constraints in the underlying multiscale model, and thus rely on its accuracy. These models also have inherent limitations due to their mathematical formulations, such as the difficulty of capturing sharp gradients or the lack of generalizability in complex spatial domains.

A critical question moving forward is how to ensure these AI-driven digital twins can be generalized across different biological contexts. Answering this question requires a better understanding of the underlying multiscale mechanisms and the establishment of validation workflows to span vastly different scales. For example, in multiscale cardiac modelling, it is often unclear whether observed inaccuracies in simulations arise from missing cellular-level mechanisms, organ-level anatomical features, or using inaccurate constitutive equations. ML models, e.g., variational autoencoders and generative adversarial networks, could help fill these gaps by learning latent representations of biological systems and suggesting missing parameters or interactions that are not adequately captured by existing data.[148] Future studies should therefore explore how generative AI modelling techniques can be used in conjunction with multiscale modelling to infer unknowns systematically.

Take-home message. ML approaches coupled to multiscale biophysics models allow exploiting data rapidly, while keeping physiology and causality notions. However, tackling sharp gradients, boundary uncertainty, and complex domains demands hybrid approaches. A key challenge is to ensure that these sophisticated twins can generalize both across anatomical domains and patient populations.

3.3 Risk as a dynamic variable that evolves in time

Modelling risk involves not only capturing high-dimensional phenomena across different spatial scales, but also approximating their temporal evolution. Most current digital twins provide an individualized risk assessment at the specific time point when the dataset was acquired. However, it is now increasingly recognized that the concept of risk is not static, as the interactions between comorbidities, anatomical and functional factors, and blood biomarkers are constantly evolving. Capturing the time-varying aspect of risk is therefore essential for effective patient monitoring and classification.

This can be achieved by updating the digital twins using continuous or near-continuous data streams, for example, from wearables or home-testing devices. The latter are well established for monitoring patients on anticoagulation therapy using warfarin, e.g., Roche CoaguChek Systems to measure PT/INR from a finger-stick blood sample or Abbott i-STAT 1 to perform rapid point-of-care coagulation tests. While these portable monitors are widely used for medical purposes, wearable devices that detect changes in clotting status are still largely in the research space. Next-generation biosensors will include flexible patches or skin-adhesive sensors that track biomarkers (e.g., fibrinogen levels, platelet function) continuously.

Data-driven technologies have been developed to assess the risk "snapshots" at fixed time frames and then extrapolate risk profiles in time. These approaches include probabilistic approaches (e.g., dynamic Bayesian networks[149]) and deep learning (DL) networks. Notably amongst the latter, architectures that treat time as an additional input parameter were proposed to allow for precise predictions over time periods, comparable to those in the training data (e.g., Deep Operator Networks[150]). However, these DL approaches assume the system's dynamics remain consistent—yet processes like fibrin formation, platelet deposition, and fibrinolysis can introduce longer timescales not seen in training data. Other recent developments include DL networks that can extract a compact set of latent variables encoding the system state and learn a differential equation governing how these variables evolve in time to predict dynamic states (e.g., latent dynamics networks[151]).

Thrombus formation spans across vastly different timescales: milliseconds for individual heartbeats, seconds to minutes for platelet activation and thrombin generation, hours to days for clot development, and months to years for disease progression. Capturing this range within a single predictive model presents significant algorithmic challenges. Future research will thus need to address the integration of multiple temporal scales, potentially through hybrid ML/DL–mechanistic approaches (see "Integration of machine learning and multi-scale modelling") that capture these disparate timescales within a single dynamic digital twin.

Take-home message. Twins of thrombosis risk must learn thrombus formation dynamics across disparate timescales. More sophisticated mechanistic–ML approaches are needed to bridge milliseconds-to-months behaviour. Continuous or near-continuous streams (home testing, emerging wearables) provide a unique source of data to enable these new developments.

3.4 Bayesian inference models

For digital twin technology to be translated into clinically applicable tools, quantifying uncertainty in risk estimates is essential. Given thrombosis can have life-threatening outcomes, every decision-support tool must provide an estimation of the confidence in the prediction. To address this issue, Bayesian inference has emerged as a foundational approach in risk models. By treating model parameters and outputs as probability distributions rather than fixed values, Bayesian methods naturally incorporate uncertainty arising from noisy data, patient variability, and model limitations. A formal Bayesian framework provides a principled way to account for both measurement errors and model inaccuracies in complex biomedical models. This is especially relevant for thrombosis, where certain risk factors might be unknown or not measurable: Bayesian models can incorporate prior knowledge (e.g., from population studies or mechanistic models) and update beliefs about a patient's risk as new patient data become available.

Recent studies have applied Bayesian techniques for model calibration and selection in medical contexts and for propagating uncertainties through simulations using Gaussian process emulators.[152] [153] The outcome is not a single risk score, but a probabilistic forecast: for example, a model might predict a 20% probability of a clot forming within 6 months with a 95% credible interval of 15 to 25%. Such probabilistic risk predictions are extremely important for clinical decision-making, as they convey confidence levels and enable risk–benefit analysis for interventions. Moreover, Bayesian approaches can guide adaptive data collection: if a model exhibits high uncertainty about a particular patient, it can suggest what new test or information should be performed to reduce that uncertainty.

Take-home message. Embedding principles of Bayesian inference in the digital twins thus adds a layer of rigour and transparency to individualized risk modelling. This approach addresses a current limitation of

many AI models—the lack of insight into their confidence—and moves the field towards more trustworthy and clinically useful predictions.

3.5 Inferring causal pathways with AI: state of the art

Inferring causal pathways related to thrombosis and stroke risks using AI involves utilizing advanced ML algorithms to decode the complex mechanisms underlying these conditions. AI models, particularly those using causal discovery methods like Bayesian networks, can process large, multi-dimensional datasets to reveal how factors such as blood clotting, vascular health, and patient-specific genetic or lifestyle factors interact to influence the likelihood of thrombosis or stroke. These models move beyond simple correlation, identifying not just associated risk factors, but also the specific causal pathways that contribute to disease development.[154] This is crucial in understanding how the blood dynamics and conditions like AF and hypertension converge to increase the risk of stroke and thrombosis, enabling more targeted interventions.

The state of the art in AI-driven causal inference for thrombosis and stroke risk is rapidly advancing.[155] For example, Chahine et al[156] discuss how causal discovery methods are being applied to large-scale health data to identify pathways that predict stroke events, while Paul and Masood[157] illustrate the shift from correlation to causation in AI models applied to cardiovascular disease (CVD). Richens et al[158] have also demonstrated how causal AI can improve the interpretability and reliability of risk prediction models, which could help clinicians better understand the specific factors driving CVD in individual patients.

However, several barriers to inferring causal pathways for thrombosis and stroke remain. A key challenge is the interpretability of complex AI models, particularly DL, which often functions as a “black box,” obscuring how conclusions about causal pathways are reached. This lack of transparency makes it difficult for clinicians to fully trust AI-generated insights.[159] Another challenge is the need for large, high-quality datasets, as many causal inference models require rich temporal and physiological data that are not always available in clinical settings. To overcome these challenges, future research should focus on integrating explainable AI techniques, which aim to make AI decisions more transparent, and hybrid models that combine AI's data-driven capabilities with mechanistic insights into CVD.[160] [161] These advances could enhance the clinical utility of AI in predicting and managing stroke and thrombosis risks.

Take-home message. Causal AI can capture pathological mechanisms without the need for time-intensive mechanistic models. However, lack of transparency poses a significant barrier to clinical trust and adoption; explainability techniques leveraging causal AI should thus be incorporated in the twins.

3.6 Enabling in-silico trials to enhance trial design and save costs

How do digital twins fit into the in silico trial (IST) paradigm? They are effectively two sides of the same coin. Where digital twins are focusing on developing patient-specific models that can inform treatment of an individual, ISTs develop virtual populations (digital twins of a group of individuals). These virtual populations do not have to mirror individuals but instead are statistically representative of a population of individuals, hence making them easier to develop and deploy.

Modern clinical trials are expensive, take many years to run, and regularly fail due to the inability to recruit enough subjects to power the trial. They are also often not ecologically valid due to the controlled inclusion and exclusion criteria to prove the efficacy of the drug or device. ISTs can overcome these problems. At each stage of clinical trials (from preclinical to phase III onwards), ISTs can be used for early proof-of-concept in drug development through to running multiple ISTs with different treatment paradigms to improve the chance of real-world trial success.[162] ISTs can also improve the diversity of the patient population, as virtual patients with different demographics can be recruited with relative ease.

Recent work has demonstrated the use of ISTs in ischaemic stroke, simulating thromboembolisms, tissue death, and treatment via thrombectomy and thrombolysis.[39] [163] [164] [165] Populations of brain geometries were developed along with simulations of cerebral oedema post-stroke.[166] [167] These ISTs also went beyond what is clinically measurable by simulating the impact of clot fragmentation and micro-emboli occluding distal vessels post stroke treatment.[168] [169] [170] Eventually, once fully validated in a real-world clinical trial, these ISTs of stroke can be used for the development of new thrombolytic drugs and novel stent designs. Another area where ISTs can provide benefit is in retinal diseases.[162] Numerous conditions ranging from thromboembolic events, like retinal vein occlusion, diabetic retinopathy, and age-related macular degeneration, along with the advancement of micro-resolution imaging, make retinal conditions ideal for the development of ISTs. Although still lagging behind organs like the heart and brain, retinal ISTs and digital twins are rapidly developing, with thromboembolic conditions likely to be the first to be tackled.

ISTs will likely become a part of the regulator's evidence requirements, with the FDA leading the way in developing guidelines for submission of digital evidence from ISTs.[171] A recent publication from the FDA details a workflow for assessing the credibility of a medical device IST, and is a first step to standardize IST submissions.[172] In the short term, ISTs will primarily be used for repurposing of already approved devices in new environments, as well as testing minor modifications to approved devices. In the medium term, there is an industry-driven push for the use of data-driven longitudinal virtual populations to replace control arms in real-world clinical trials.[173] This augmentation of a real-world trial with virtual subjects aims to reduce the number of subjects required for recruitment, hence reducing cost and risk of failure.

The long-term vision of ISTs is one where computational and AI models are used at every step of the regulatory process, speeding up the time-to-market and reducing the cost of discovery and development. Academically, there is a huge push in developing robust models of human physiology and treatment, ranging from AF in the heart[174] to treatment of stroke and aneurysms[175] to virtual populations for retinal diseases.[176] These models, once validated, can become the testing grounds for the next generation of ISTs in tandem with industry and regulators.

Take-home message. In silico trials enable virtual cohort studies to de-risk design and costs of clinical trials. Initial applications include augmentation of control arms and testing of device modifications, with emerging regulatory workflows highlighting the need for probabilistic and transparent evidence.

3 Breaking the barriers to clinical adoption: confidence in the Twins' predictions, uncertainty quantification in models

Currently, treatment decisions rely on general population data from clinical trials, which is inadequate given the wealth of real-time patient data available and advancements in computational power. Although personalized digital twins hold great promise for enhancing clinical practices, fully realizing their potential remains challenging.[177] [178] Effective deployment of digital twins warrants a robust representation of individual health, which requires rigorous validation and uncertainty quantification (UQ).[179] [180] Physicians often face uncertainty in clinical decision-making due to incomplete data, patient variability, and evolving medical knowledge. Predictive modelling and digital twins do not eliminate uncertainty, and it is crucial that these tools enhance physicians' decision-making capabilities rather than hinder them. Therefore, UQ is essential for building trust in digital twins. Uncertainties should be tracked throughout the entire modelling process, facilitating real-time interaction between digital and physical systems.

Unlike traditional models based on static, well-curated datasets, digital twins require continuous data availability to adapt to dynamic personal changes and ensure long-term model integrity. These dynamic updates cannot be limited to routine clinical check-ups, as such an approach could fail to capture the complex and evolving nature of human physiology. Historically, healthcare has focused on computational models that simulate typical physiological processes, with advancements over time only in modelling complexity. However, advanced digital twins must be continuously recalibrated, receive regular updates, and facilitate interactive feedback from users. Recent developments in cardiac electrophysiological modelling and AI[181] [182] [183] [184] [185] have illustrated this by integrating medical imaging data for

personalized predictions that can help diagnose and treat conditions such as AF, a major precursor of stroke. As these virtual representations adapt to new extensive information, practices for validation and UQ must also evolve. Same as the digital twins themselves, the UQ processes must be tailored to incorporate data from physical counterparts to effectively calibrate their virtual representations.

The quality, consistency, and availability of patient data directly influence the suitability of the digital twin's design. Calibration processes can range from simple statistical techniques to sophisticated AI training, depending on the model and data quality.[186] Additionally, data processing is crucial as errors or uncertainties can also emerge during this stage. Bayesian inference methods, Kalman filters, and Monte Carlo simulations have been employed to quantify these uncertainties in a range of medical applications, such as inferring clinical haemodynamic parameters[69] [187] and identifying targets for AF treatment by catheter ablation[161] [185] from the underlying patient imaging data.

The final crucial component of clinical adoption of digital twins involves the transfer of information from the digital realm back to the physical environment, resulting in actionable predictions relevant to clinical decision-making, health trajectory forecasting, and optimized treatment strategies.[188] [189] Generating these predictions may appear straightforward, but complexities can arise in communicating them effectively, necessitating a focus on building trust. Uncertainty at various stages, from model to physical data, must be carefully conveyed alongside predictions. The assumptions behind digital twin predictions should also be clearly communicated to earn the confidence of both clinicians and patients. Engaging a diverse group of stakeholders, including the patients, medical professionals, and legal and regulatory bodies within the digital twin ecosystem will be crucial in facilitating their efficient clinical adoption.

Take-home message. Personalized digital twins can move care beyond population averages. However, they must be designed as living, transparent models and rigorously validated. Future developments should focus on achieving continuous updates and rigorous uncertainty quantification and propagation. Clinician and patient dialogue is crucial in the design process to guide the translation of the twins' predictions into clinical actions.

5. Privacy, security and route to regulatory approvals: responsible and safe AI in the ethical landscape of highly personalised health data use

Digital twins are subject to varying regulatory frameworks depending on their architectural design. Systems relying exclusively on physics-based models are governed by existing legacy software and medical device regulations. In contrast, digital twin systems that incorporate AI, such as image segmentation during data preprocessing, must adhere to region-specific AI regulations. The regulation of AI remains fragmented across countries and regions. Although many governments prioritize rapid AI adoption as a source of economic growth, there are still concerns from both governmental bodies and the public about the detrimental consequences of limited oversight of this new technology, especially in high-risk areas like healthcare.[190] In the United States (US) and the United Kingdom (UK), neither has enacted comprehensive national or federal regulation specifically targeting AI, to aid acceleration of AI adoption—hence, digital twin software (with or without AI) will adhere to the same regulation.

This fragmentation is reflected in the differing regulatory approaches to AI-based digital twin software across jurisdictions ([Table 1]). In the UK, regulation is based on the Medical Devices Regulations 2002 and the UK General Data Protection Regulation (UK GDPR) 2018. The UK GDPR includes protections against fully automated decision-making (Article 22; Recital 71).[191] [192] Proposed reforms under the Data Protection and Digital Information Bill may relax some of these restrictions.[193] In parallel, the Medicines and Healthcare products Regulatory Agency is leading initiatives to modernize oversight of AI-assisted medical software.[194] In the US, no comprehensive federal framework governs AI in healthcare. Regulation instead combines oversight by the US Food and Drug Administration with state-level legislation. For example, California requires disclosure when generative AI communicates clinical information to patients.[195] It also mandates physician-led decision-making in certain health insurance contexts.[196] As a result, regulatory requirements vary across states. By contrast, the EU has adopted a harmonized, risk-based approach through the EU AI Act (2024), building on the EU GDPR (2018). Under

this framework, AI-enabled medical devices and clinical decision support systems are typically classified as high risk. These systems are subject to stringent conformity assessments and post-market surveillance. AI systems employing "social scoring" to determine access to health benefits are explicitly prohibited as an unacceptable risk.[197]

Table 1. Comparative overview of regulatory frameworks governing AI-based digital twin software in healthcare across the UK, US, and European Union, including current legislation, AI-specific rules, and key medical device software requirements

Jurisdiction	Current framework	AI-specific rules	Key requirements (incl. medical device software policy)
United Kingdom (UK)	Medical Devices Regulations 2002 UK General Data Protection Regulation (2018), incl. Article 22 and Recital 71	Medicines and Healthcare products Regulatory Agency (MHRA) Software as a Medical Device (SaMD)/AI as Medical Device Regulatory Reform Program Data Protection and Digital Information Bill (proposed)	**Medical device software policy:** Software (including AI and digital twins) that performs diagnostic, monitoring, or therapeutic functions is treated as a medical device and requires UK Conformity Assessed marking and MHRA conformity assessment. **Additional requirements:** Human oversight for automated decisions; transparency and data minimization; algorithm change management under forthcoming MHRA reforms.
United States (US)	Food and Drug Administration regulation (FDA) of SaMD Health Insurance Portability and Accountability Act (HIPAA)	State-level rules (e.g., California AB 3030 and SB 1120 requiring disclosure and human clinical authority)	**Medical device software policy:** FDA classifies many AI-enabled digital twins as SaMD; requires safety/effectiveness evidence, real-world performance monitoring, and may require Predetermined Change Control Plans for adaptive AI. **Additional requirements:** State-driven variations in oversight; disclosures when AI communicates clinical information; HIPAA-compliant data practices.
European Union (EU)	Medical Device Regulation (MDR 2017/745) EU General Data Protection Regulation (2018)	EU AI Act (2024): risk-based classification (unacceptable, high, limited, minimal risk)	**Medical device software policy:** Under Medical Device Regulation, software for diagnosis or therapeutic decision support is classified as a medical device; requires Conformité Européenne marking, clinical evaluation, and post-market surveillance. **Additional requirements:** High-risk (medical) AI must undergo conformity assessment; transparency and human oversight obligations; robust risk management and data governance.

Data privacy and security in digital twin systems are also governed by regional legislation, such as the UK/EU GDPR. This presents a significant challenge for AI-based digital systems in particular, due to the inherent difficulties in collecting and managing data across different sources. Federated learning (FL) has emerged in recent years as a technique to address this challenge. It enables the implementation of AI models across distributed data environments, allowing model training to occur locally at multiple data sources without the need for centralized collection or direct access to raw training data.[198] In FL, local nodes train a shared AI model while keeping data and computation on-site. Only model updates (e.g., model parameters or gradients) are exchanged, enhancing privacy by ensuring raw data remains local and reducing the risk of sensitive data exposure.[199] Due to these benefits, FL has been proposed as a solution for implementing AI in healthcare.[200] However, FL is not inherently compliant with the UK and EU GDPR requirements.[201] Hence, when applying FL to AI-based digital twin systems for the purpose of ensuring data privacy and security, careful attention must be paid to regulatory compliance.

Take-home message. Digital twins face patchwork regulation shaped by computational/AI models' architecture and geography. To ensure compliance, twins should be built from the outset using a "regulatory-by-design," accounting for transparency, human oversight, and privacy.

6. Digital Twins in a hospital of the future

As healthcare needs and systems around the world evolve, the role and design of hospitals are also changing. Some of the most common challenges faced by healthcare systems are overcoming workforce shortages, improving remote access to healthcare, and reducing variability in the standard of healthcare delivery. Digital twins can address these issues by efficiently storing and updating patient data and making fast, technology-driven predictions that accelerate and democratize clinical decision-making. Such

predictions will be explainable, mechanistically transparent, and compliant with the current legal and ethical regulations. The integration of digital twins in standard clinical care will inevitably rely on our ability to build models that are generalizable beyond a single site and able to ingest real-world multimodal data, as shown in the conceptual flowchart in [Fig. 5]. In our case, they will include assessing risk of thrombogenesis and stroke from multimodal patient data (e.g., electronic health records, medical imaging, genetics and population data) and selecting personalized treatments specific to the evolving patient profile and disease state (AF- or VTE-related thrombogenesis, atherosclerosis). With the digital twin and AI technologies used for monitoring, prediction, and care delivery both in real and "virtual" hospitals, healthcare will become more accessible. Moreover, early predictions will enhance the focus on patients' well-being and disease prevention, facilitating the shift from sick-care to true personalized healthcare. In this context digital twin implementation could deliver tangible clinical benefits:

- Reduce stroke rates through earlier identification of high-risk patients
- Decrease bleeding complications via personalized anticoagulation dosing
- Shorter hospital stays by optimizing treatment timing
- Lower healthcare costs through prevention rather than emergency intervention
- Improve equity by providing expert-level risk assessment in resource-limited settings

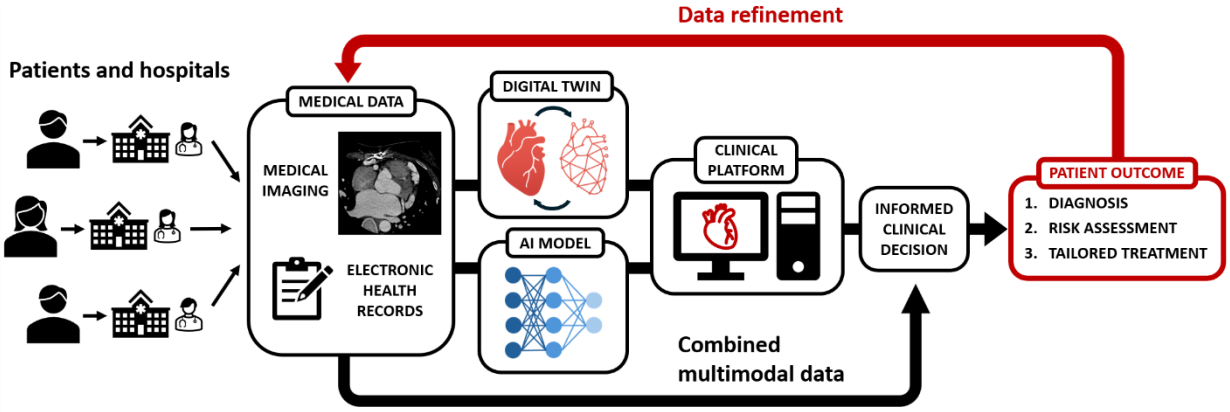


Fig. 5 The hospital of the future. Conceptual flowchart of the hospital of the future, illustrating the integration of digital twins and AI. Data from multiple healthcare centres, including medical imaging and electronic health records, is used to create predictive simulations and outcome forecasts. These insights are delivered to clinicians via a clinical platform, supporting more accurate diagnosis, personalised treatment, and improved risk assessment. Patient outcomes are fed back to continuously refine the models.

Policy makers and executives worldwide should consider how they can build upon the acceleration of digital twin and AI innovations today and plan for a better future.

Conclusion

Digital twin technologies for thrombosis measure risk as a dynamic quantity that can be monitored and acted upon across AF, VTE, and atherosclerotic disease. These models must be multiscale and have the ability to capture vastly different timescale via a single predictive engine. Delivering this vision hinges on robust, reproducible, and regulated workflow. Immediate priorities (0–2 years) are therefore validation studies, shared regulatory standards, and efficient integration with electronic health records and imaging data. Medium-term goals (2–5 years) should focus on multi-centre clinical trials, real-time model updating, and the development of causal AI frameworks that link mechanisms to outcomes. The long-term vision (5–10 years) is routine deployment of digital twins in hospital workflows and extension to other thrombo-inflammatory diseases. Achieving these goals will enable transparent, continuously learning systems that support equitable and preventive thrombosis care.

Bibliography

1 Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res 2016; 118 (09) 1340-1347

2 Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. 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 (02) 263-272

3 Teppo K, Lip GYH, Airaksinen KEJ. et al. Comparing CHA_2DS_2-VA and CHA_2DS_2-VASc scores for stroke risk stratification in patients with atrial fibrillation: a temporal trends analysis from the retrospective Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) cohort. Lancet Reg Health Eur 2024; 43: 100967

4 Le Gal G, Righini M, Roy PM. et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006; 144 (03) 165-171

5 Chang TY, Lip GYH, Chen SA, Chao TF. Importance of risk reassessment in patients with atrial fibrillation in guidelines: assessing risk as a dynamic process. Can J Cardiol 2019; 35 (05) 611-618

6 van den Ham HA, Klungel OH, Singer DE, Leufkens HGM, van Staa TP. Comparative performance of ATRIA, $CHADS_2$, and CHA_2DS_2-VASc risk scores predicting stroke in patients with atrial fibrillation: results from a national primary care database. J Am Coll Cardiol 2015; 66 (17) 1851-1859

7 Corral-Acero J, Margara F, Marciniak M. et al. The “digital twin” to enable the vision of precision cardiology. Eur Heart J 2020; 41 (48) 4556-4564

8 Ortega-Martorell S, Olier I, Ohlsson M, Lip GYH. TARGET Consortium. Advancing personalised care in atrial fibrillation and stroke: the potential impact of AI from prevention to rehabilitation. Trends Cardiovasc Med 2025; 35 (04) 205-211

9 Ortega-Martorell S, Olier I, Ohlsson M, Lip GYH. TARGET Consortium. 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 2025; 125 (01) 7-11

10 Bellfield RAA, Olier I, Lotto R. et al. AI-based derivation of atrial fibrillation phenotypes in the general and critical care populations. EBioMedicine 2024; 107: 105280

11 Qureshi A, Lip GYH, Nordsletten DA, Williams SE, Aslanidi O, de Vecchi A. Imaging and biophysical modelling of thrombogenic mechanisms in atrial fibrillation and stroke. Front Cardiovasc Med 2023; 9: 1074562

12 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 2025; 11 (03) 239-248

13 Zhang J, Luo L, Chen G. et al. Associations of ambient air pollution with incidence and dynamic progression of atrial fibrillation. Sci Total Environ 2024; 951: 175710

14 Kurasz A, Lip GYH, Święczkowski M, Tomaszuk-Kazberuk A, Dobrzycki S, Kuźma Ł. Air quality and the risk of acute atrial fibrillation (EP-PARTICLES study): a nationwide study in Poland. Eur J Prev Cardiol 2025; zwaf016

15 Święczkowski M, Lip GYH, Kurasz A. et al. Association between exposure to air pollution and increased ischaemic stroke incidence: a retrospective population-based cohort study (EP-PARTICLES study). Eur J Prev Cardiol 2025; 32 (04) 276-287

16 Kim MH, Yang PS, Kim D. et al. Racial differences and similarities in atrial fibrillation epidemiology and risk factors in UK Biobank and Korean NHIS-HEALS cohort studies. Heart Rhythm 2025; 22 (08) e277-e284

17 Kang DS, Yang PS, Kim D. et al. Racial differences in bleeding risk: an ecological epidemiological study comparing Korea and United Kingdom subjects. Thromb Haemost 2024; 124 (09) 842-851

18 Kang DS, Yang PS, Kim D. et al. Racial differences in ischemic and hemorrhagic stroke: an ecological epidemiological study. Thromb Haemost 2024; 124 (09) 883-892

19 Serna MJ, Rivera-Caravaca JM, López-Gálvez R. et al. Dynamic assessment of CHA_2DS_2-VASc and HAS-BLED scores for predicting ischemic stroke and major bleeding in atrial fibrillation patients. Rev Esp Cardiol (Engl Ed) 2024; 77 (10) 835-842

20 Soler-Espejo E, Zazo-Luengo BÁ, Rivera-Caravaca JM. et al. Poor clinical outcomes associated to multimorbidity, frailty and malnutrition in patients with atrial fibrillation. J Nutr Health Aging 2025; 29 (01) 100430
21 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. J Thromb Thrombolysis 2025; 58 (01) 97-108
22 Chao TF, Chan YH, Chiang CE. et al. Stroke prevention with direct oral anticoagulants in high-risk elderly atrial fibrillation patients at increased bleeding risk. Eur Heart J Qual Care Clin Outcomes 2022; 8 (07) 730-738
23 Chao TF, Liu CJ, Lin YJ. et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. Circulation 2018; 138 (01) 37-47
24 Liu Y, Chen Y, Olier I. et al; GLORIA-AF Investigators. Residual risk prediction in anticoagulated patients with atrial fibrillation using machine learning: a report from the GLORIA-AF registry phase II/III. Eur J Clin Invest 2025; 55 (03) e14371
25 McCabe JJ, Cheung Y, Foley M. et al. Residual risk of recurrent stroke despite anticoagulation in patients with atrial fibrillation: a systematic review and meta-analysis. JAMA Neurol 2025; 82 (07) 696-705
26 Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol 2017; 14 (11) 627-628
27 Chu M, Zhang S, Gong J. et al; MIRACLE-AF Investigators. Telemedicine-based integrated management of atrial fibrillation in village clinics: a cluster randomized trial. Nat Med 2025; 31 (04) 1276-1285
28 Guo Y, Lane DA, Wang L. et al; mAF-App II Trial Investigators. Mobile health technology to improve care for patients with atrial fibrillation. J Am Coll Cardiol 2020; 75 (13) 1523-1534
29 Romiti GF, Guo Y, Corica B, Proietti M, Zhang H, Lip GYH. mAF-App II trial investigators. Mobile health-technology-integrated care for atrial fibrillation: a win ratio analysis from the mAFA-II randomized clinical trial. Thromb Haemost 2023; 123 (11) 1042-1048
30 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. Thromb Haemost 2024; 124 (01) 69-79
31 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 2022; 122 (03) 406-414
32 Krittayaphong R, Treewaree S, Yindeengam A, Komoltri C, Lip GYH. Latent class analysis for the identification of phenotypes associated with increased risk in atrial fibrillation patients: the COOL-AF registry. Thromb Haemost 2025; . Epub ahead of print
33 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. Thromb Haemost 2022; 122 (01) 20-47
34 Wang Y, Guo Y, Qin M. et al; Expert Reviewers. 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. Thromb Haemost 2024; 124 (10) 897-911
35 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 2024; 149 (01) e1-e156
36 Van Gelder IC, Rienstra M, Bunting KV. et al; ESC Scientific Document Group. 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; 45 (36) 3314-3414
37 Sun Y, Ling Y, Chen Z. et al. Finding low CHA_2DS_2-VASc scores unreliable? Why not give morphological and hemodynamic methods a try?. Front Cardiovasc Med 2023; 9: 1032736
38 Sel K, Osman D, Zare F. et al. Building digital twins for cardiovascular health: from principles to clinical impact. J Am Heart Assoc 2024; 13 (19) e031981
39 Luraghi G, Rodriguez Matas JF, Dubini G. et al; INSIST investigators. Applicability assessment of a stent-retriever thrombectomy finite-element model. Interface Focus 2021; 11 (01) 20190123

40 Hoekstra AG, Marquering H. on behalf of the GEMINI consortium. Towards a generation of digital twins in healthcare of ischaemic and haemorrhagic stroke. In: Franco L, de Mulatier C, Paszynski M, Krzhizhanovskaya VV, Dongarra JJ, Sloot PMA. eds. Computational Science – ICCS 2024. ICCS 2024. (Lecture Notes in Computer Science; vol 14834). Springer, Cham; 2024: 239-245
41 Albors C, Mill J, Olivares AL, Iriart X, Cochet H, Camara O. Impact of occluder device configurations in in-silico left atrial hemodynamics for the analysis of device-related thrombus. PLOS Comput Biol 2024; 20 (09) e1011546
42 Guerrero-Hurtado M, Garcia-Villalba M, Gonzalo A. et al. Haemodynamics affects factor XI/XII anticoagulation efficacy in patient-specific left atrial models. Preprint posted online August 28, 2024
43 Aguado AM, Olivares AL, Yagüe C. et al. *In silico* optimization of left atrial appendage occluder implantation using interactive and modeling tools. Front Physiol 2019; 10: 237
44 García-Villalba M, Rossini L, Gonzalo A. et al. Demonstration of patient-specific simulations to assess left atrial appendage thrombogenesis risk. Front Physiol 2021; 12: 596596
45 Zhang LT, Gay M. Characterizing left atrial appendage functions in sinus rhythm and atrial fibrillation using computational models. J Biomech 2008; 41 (11) 2515-2523
46 Koizumi R, Funamoto K, Hayase T. et al. Numerical analysis of hemodynamic changes in the left atrium due to atrial fibrillation. J Biomech 2015; 48 (03) 472-478
47 Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart 1999; 82 (05) 547-554
48 García-Isla G, Olivares AL, Silva E. et al. Sensitivity analysis of geometrical parameters to study haemodynamics and thrombus formation in the left atrial appendage. Int J Numer Methods Biomed Eng 2018; 34 (08) e3100
49 Bosi GM, Cook A, Rai R. et al. Computational fluid dynamic analysis of the left atrial appendage to predict thrombosis risk. Front Cardiovasc Med 2018; 5: 34
50 Feng L, Gao H, Griffith B, Niederer S, Luo X. Analysis of a coupled fluid-structure interaction model of the left atrium and mitral valve. Int J Numer Methods Biomed Eng 2019; 35 (11) e3254
51 Masci A, Barone L, Dedè L. et al. The impact of left atrium appendage morphology on stroke risk assessment in atrial fibrillation: a computational fluid dynamics study. Front Physiol 2019; 9: 1938
52 Sanatkhani S, Nedios S, Menon PG, Bollmann A, Hindricks G, Shroff SG. Subject-specific calculation of left atrial appendage blood-borne particle residence time distribution in atrial fibrillation. Front Physiol 2021; 12: 633135
53 Bäck S, Skoda I, Lantz J. et al. Elevated atrial blood stasis in paroxysmal atrial fibrillation during sinus rhythm: a patient-specific computational fluid dynamics study. Front Cardiovasc Med 2023; 10: 1219021
54 Telle Å, Kassar A, Chamoun N. et al. Systematic computational assessment of atrial function impairment due to fibrotic remodelling in electromechanical properties. Preprint posted online June 27, 2025
55 Viola F, Meschini V, Verzicco R. Fluid–structure-electrophysiology interaction (FSEI) in the left-heart: a multi-way coupled computational model. Eur J Mech B Fluids 2020; 79: 212-232
56 Bucelli M, Zingaro A, Africa PC, Fumagalli I, Dede' L, Quarteroni A. A mathematical model that integrates cardiac electrophysiology, mechanics, and fluid dynamics: application to the human left heart. Int J Numer Methods Biomed Eng 2023; 39 (03) e3678
57 Gonzalo A, Augustin CM, Bifulco SF. et al. Multi-physics simulations reveal haemodynamic impacts of patient-derived fibrosis-related changes in left atrial tissue mechanics. *bioRxiv*. Published online October 17, 2024
58 Di Biase L, Santangeli P, Anselmino M. et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol 2012; 60 (06) 531-538
59 Yamamoto M, Seo Y, Kawamatsu N. et al. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. Circ Cardiovasc Imaging 2014; 7 (02) 337-343
60 Yaghi S, Chang AD, Akiki R. et al. The left atrial appendage morphology is associated with embolic stroke subtypes using a simple classification system: a proof of concept study. J Cardiovasc Comput Tomogr 2020; 14 (01) 27-33

61 Dueñas-Pamplona J, García JG, Castro F, Muñoz-Paniagua J, Goicolea J, Sierra-Pallares J. Morphing the left atrium geometry: a deeper insight into blood stasis within the left atrial appendage. Appl Math Model 2022; 108 (10) 27-45
62 Musotto G, Monteleone A, Vella D. et al. Fluid-structure interaction analysis of the thromboembolic risk in the left atrial appendage under atrial fibrillation: effect of hemodynamics and morphological features. Comput Methods Programs Biomed 2024; 246: 108056
63 Lantz J, Gupta V, Henriksson L. et al. Impact of pulmonary venous inflow on cardiac flow simulations: comparison with in vivo 4D flow MRI. Ann Biomed Eng 2019; 47 (02) 413-424
64 Mill J, Harrison J, Saiz-Vivo M. et al. The role of the pulmonary veins on left atrial flow patterns and thrombus formation. Sci Rep 2024; 14 (01) 5860
65 Ding WY, Gupta D, Lip GYH. Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020. Heart 2020; 106 (19) 1463-1468
66 Daccarett M, Badger TJ, Akoum N. et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. J Am Coll Cardiol 2011; 57 (07) 831-838
67 Boyle PM, Del Álamo JC, Akoum N. Fibrosis, atrial fibrillation and stroke: clinical updates and emerging mechanistic models. Heart 2021; 107 (02) 99-105
68 Iacobellis G. Epicardial adipose tissue in contemporary cardiology. Nat Rev Cardiol 2022; 19 (09) 593-606
69 Melidoro P, Sultan ARA, Qureshi A. et al. Enhancing stroke risk stratification in atrial fibrillation through non-Newtonian blood modelling and Gaussian process emulation. J Physiol 2024; . Epub ahead of print
70 Black IW, Chesterman CN, Hopkins AP, Lee LCL, Chong BH, Walsh WF. Hematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. J Am Coll Cardiol 1993; 21 (02) 451-457
71 Gonzalo A, García-Villalba M, Rossini L. et al. Non-Newtonian blood rheology impacts left atrial stasis in patient-specific simulations. Int J Numer Methods Biomed Eng 2022; 38 (06) e3597
72 Melidoro P, Sabry M, Sultan ARA. et al. Comparing left atrial spontaneous echo contrast intensity with Gaussian process emulator predictions. In: Camara O. et al, eds. Statistical Atlases and Computational Models of the Heart. Workshop, CMRxRecon and MBAS Challenge Papers. STACOM 2024. (Lecture Notes in Computer Science; vol 15448). Springer, Cham; 2025: 443-452
73 Ruiz Herrera C, Grandits T, Plank G, Perdikaris P, Sahli Costabal F, Pezzuto S. Physics-informed neural networks to learn cardiac fiber orientation from multiple electroanatomical maps. Eng Comput 2022; 38: 3957-3973
74 Caforio F, Regazzoni F, Pagani S. et al. Physics-informed neural network estimation of material properties in soft tissue nonlinear biomechanical models. Comput Mech 2025; 75 (02) 487-513
75 Morales Ferez X, Mill J, Juhl KA. et al. Deep learning framework for real-time estimation of *in-silico* thrombotic risk indices in the left atrial appendage. Front Physiol 2021; 12: 694945
76 Saiz-Vivó M, Mill J, Iriart X. et al. Digital twin integrating clinical, morphological and hemodynamic data to identify stroke risk factors. NPJ Digit Med 2025; 8 (01) 369
77 Qureshi A, Melidoro P, Balmus M. et al. MRI-based modelling of left atrial flow and coagulation to predict risk of thrombogenesis in atrial fibrillation. Med Image Anal 2025; 101: 103475
78 Qureshi A, Darwish O, Dillon-Murphy D. et al. Modelling left atrial flow and blood coagulation for risk of thrombus formation in atrial fibrillation. Comput Cardiol 2020; 47
79 Qureshi A, Balmus M, Ogbomo-Harmitt S. et al. Modelling blood flow and biochemical reactions underlying thrombogenesis in atrial fibrillation. In: Bernard O, Clarysse P, Duchateau N, Ohayon J, Viallon M. eds. Functional Imaging and Modeling of the Heart. FIMH 2023. (Lecture Notes in Computer Science; vol 13958). Springer, Cham; 2023: 435-444
80 Isensee F, Jaeger PF, Kohl SAA, Petersen J, Maier-Hein KH. nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. Nat Methods 2021; 18 (02) 203-211
81 Liu X, Lin H, Liu X. et al. LAFlowNet: a dynamic graph method for the prediction of velocity and pressure fields in left atrium and left atrial appendage. Eng Appl Artif Intell 2024; 136: 108896
82 Laha S, Fourtakas G, Das PK, Keshmiri A. Graphics processing unit accelerated modelling of thrombus formation in cardiovascular systems using smoothed particle hydrodynamics. Phys Fluids 2025; 37 (02) 021902

83 Viola F, Del Corso G, De Paulis R, Verzicco R. GPU accelerated digital twins of the human heart open new routes for cardiovascular research. Sci Rep 2023; 13 (01) 8230
84 Guerrero-Hurtado M, Garcia-Villalba M, Gonzalo A. et al. Efficient multi-fidelity computation of blood coagulation under flow. PLOS Comput Biol 2023; 19 (10) e1011583
85 Viceconti M, Pappalardo F, Rodriguez B, Horner M, Bischoff J, Musuamba Tshinanu F. In silico trials: verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods 2021; 185: 120-127
86 Kjeldsberg HA, Albors C, Mill J. et al. Impact of left atrial wall motion assumptions in fluid simulations on proposed predictors of thrombus formation. Int J Numer Methods Biomed Eng 2024; 40 (06) e3825
87 Khalili E, Daversin-Catty C, Olivares AL, Mill J, Camara O, Valen-Sendstad K. On the importance of fundamental computational fluid dynamics toward a robust and reliable model of left atrial flows. Int J Numer Methods Biomed Eng 2024; 40 (04) e3804
88 Qureshi A, Balmus M, Lip GYH. et al. Mechanistic modelling of Virchows triad to assess thrombogenicity and stroke risk in atrial fibrillation patients. Eur Heart J Digit Health 2022; 3 (04) ztac076.2788
89 Qureshi A, Balmus M, Nechipurenko D. et al. Left Atrial Appendage Morphology Impacts Thrombus Formation Risks in Multi-Physics Atrial Models. In: 2021 Computing in Cardiology (CinC). IEEE; 2021: 1-4
90 Qureshi A, Balmus ME, Williams S. et al. Modelling Virchow's Triad to Improve Stroke Risk Assessment in Atrial Fibrillation Patients. In: Computing in Cardiology. 2022. Vol 49.
91 Valvez S, Oliveira-Santos M, Piedade AP, Gonçalves L, Amaro AM. Computational flow dynamic analysis in left atrial appendage thrombus formation risk: a review. Appl Sci (Basel) 2023; 13 (14) 8201
92 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. Cardiovasc Res 2021; 117 (07) 1700-1717
93 Viceconti M, De Vos M, Mellone S, Geris L. Position paper From the digital twins in healthcare to the Virtual Human Twin: a moon-shot project for digital health research. IEEE J Biomed Health Inform 2023; PP (01) 491-501
94 Ortega-Martorell S, Olier I, Lip GYH. TARGET consortium. A European network to develop virtual twin technology for personalized stroke management in atrial fibrillation: the TARGET consortium. Eur Heart J 2025; 46 (03) 229-232
95 Paciaroni M, Agnelli G, Corea F. et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 2008; 39 (08) 2249-2256
96 Andrade JBC, Mohr JP, Lima FO. et al. The role of hemorrhagic transformation in acute ischemic stroke upon clinical complications and outcomes. J Stroke Cerebrovasc Dis 2020; 29 (08) 104898
97 Albors C, Terreros NA, Saiz-Vivó M. et al. In silico estimation of thrombogenic risk after left atrial appendage excision: towards digital twins in atrial fibrillation. Comput Biol Med 2025; 194: 110483
98 Bell EJ, Lutsey PL, Basu S. et al. Lifetime risk of venous thromboembolism in two cohort studies. Am J Med 2016; 129 (03) 339.e19-339.e26
99 Henke PK, Kahn SR, Pannucci CJ. et al; American Heart Association Advocacy Coordinating Committee. Call to action to prevent venous thromboembolism in hospitalized patients: a policy statement from the American Heart Association. Circulation 2020; 141 (24) e914-e931
100 Winter MP, Schernthaner GH, Lang IM. Chronic complications of venous thromboembolism. J Thromb Haemost 2017; 15 (08) 1531-1540
101 Elliott CG, Goldhaber SZ, Jensen RL. Delays in diagnosis of deep vein thrombosis and pulmonary embolism. Chest 2005; 128 (05) 3372-3376
102 Rodger MA, Miranda S, Delluc A, Carrier M. Management of suspected and confirmed recurrent venous thrombosis while on anticoagulant therapy. What next?. Thromb Res 2019; 180: 105-109
103 Huisman MV, Klok FA. Current challenges in diagnostic imaging of venous thromboembolism. Blood 2015; 126 (21) 2376-2382
104 White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107 (23, Suppl 1): I4-I8
105 Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. Nat Rev Cardiol 2023; 20 (04) 248-262

106 van Es N. Dynamic prediction modeling for cancer-associated venous thromboembolism. J Thromb Haemost 2020; 18 (06) 1276-1277
107 Lee D, Kim S, Lee S. et al. Deep learning-based dynamic risk prediction of venous thromboembolism for patients with ovarian cancer in real-world settings from electronic health records. JCO Clin Cancer Inform 2024; 8: e2300192
108 Piran S, Schulman S. Treatment of bleeding complications in patients on anticoagulant therapy. Blood 2019; 133 (05) 425-435
109 Ortel TL, Neumann I, Ageno W. et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020; 4 (19) 4693-4738
110 Stevens SM, Woller SC, Baumann Kreuziger L. et al. Executive summary: antithrombotic therapy for VTE disease: second update of the CHEST Guideline and expert panel report. Chest 2021; 160 (06) 2247-2259
111 Konstantinides SV, Meyer G, Becattini C. et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020; 41 (04) 543-603
112 Bouchnita A, Terekhov K, Nony P, Vassilevski Y, Volpert V. A mathematical model to quantify the effects of platelet count, shear rate, and injury size on the initiation of blood coagulation under venous flow conditions. PLoS One 2020; 15 (07) e0235392
113 Ratto N, Bouchnita A, Chelle P. et al. Patient-specific modelling of blood coagulation. Bull Math Biol 2021; 83 (05) 50
114 Bouchnita A, Volpert V, Kozulinas N, Belyaev AV, Panasenko G. Multiphase patient-specific simulations to study fibrillation-induced thrombosis in the left atrial appendage. Phys Fluids 2024; 36 (07)
115 Bessonov N, Sequeira A, Simakov S, Vassilevskii Yu, Volpert V. Methods of blood flow modelling. Math Model Nat Phenom 2016; 11 (01) 1-25
116 Belyaev AV, Dunster JL, Gibbins JM, Panteleev MA, Volpert V. Modeling thrombosis in silico: frontiers, challenges, unresolved problems and milestones. Phys Life Rev 2018; 26-27: 57-95
117 Bouchnita A, Nony P, Llored JP, Volpert V. Combining mathematical modeling and deep learning to make rapid and explainable predictions of the patient-specific response to anticoagulant therapy under venous flow. Math Biosci 2022; 349: 108830
118 Bouchnita A, Mozokhina A, Nony P, Llored JP, Volpert V. Combining computational modelling and machine learning to identify COVID-19 patients with a high thromboembolism risk. Mathematics 2023; 11 (02) 289
119 Bouchnita A, Yadav K, Llored JP, Gurovich A, Volpert V. Thrombin generation thresholds for coagulation initiation under flow. Axioms 2023; 12 (09) 873
120 Faxon DP, Fuster V, Libby P. et al; American Heart Association. Atherosclerotic vascular disease conference: writing group III: pathophysiology. Circulation 2004; 109 (21) 2617-2625
121 Zarins CK, Giddens DP, Bharadvaj BK, Sottiurai VS, Mabon RF, Glagov S. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. Circ Res 1983; 53 (04) 502-514
122 Libby P. Inflammation in atherosclerosis. Nature 2002; 420 (6917) 868-874
123 Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. Arteriosclerosis 1985; 5 (03) 293-302
124 Lievens D, von Hundelshausen P. Platelets in atherosclerosis. Thromb Haemost 2011; 106 (05) 827-838
125 Woollard KJ, Geissmann F. Monocytes in atherosclerosis: subsets and functions. Nat Rev Cardiol 2010; 7 (02) 77-86
126 Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014; 114 (12) 1852-1866
127 Fuster V, Badimon J, Chesebro JH, Fallon JT. Plaque rupture, thrombosis, and therapeutic implications. Haemostasis 1996; 26 (Suppl. 04) 269-284

128 Pozzi S, Redaelli A, Vergara C, Votta E, Zunino P. Mathematical modelling and numerical simulation of atherosclerotic plaque progression based on fluid-structure interaction. J Math Fluid Mech 2021; 23 (03) 74
129 Chalmers AD, Cohen A, Bursill CA, Myerscough MR. Bifurcation and dynamics in a mathematical model of early atherosclerosis: how acute inflammation drives lesion development. J Math Biol 2015; 71 (6-7): 1451-1480
130 Cilla M, Peña E, Martínez MA. Mathematical modelling of atheroma plaque formation and development in coronary arteries. J R Soc Interface 2013; 11 (90) 20130866
131 Corti A, Chiastra C, Colombo M, Garbey M, Migliavacca F, Casarin S. A fully coupled computational fluid dynamics—agent-based model of atherosclerotic plaque development: multiscale modeling framework and parameter sensitivity analysis. Comput Biol Med 2020; 118: 103623
132 Silva T, Jäger W, Neuss-Radu M, Sequeira A. Modeling of the early stage of atherosclerosis with emphasis on the regulation of the endothelial permeability. J Theor Biol 2020; 496: 110229
133 Thon MP, Hemmler A, Glinzer A. et al. A multiphysics approach for modeling early atherosclerosis. Biomech Model Mechanobiol 2018; 17 (03) 617-644
134 El Khatib N, Génieys S, Volpert V. Atherosclerosis initiation modeled as an inflammatory process. Math Model Nat Phenom 2007; 2 (02) 126-141
135 Calvez V, Houot JG, Meunier N, Raoult A, Rusnakova G. Mathematical and numerical modelling of early atherosclerotic lesions. ESAIM Proceedings 2010; 30: 1-14
136 Liu B, Tang D. Computer simulations of atherosclerotic plaque growth in coronary arteries. Mol Cell Biomech 2010; 7 (04) 193-202
137 Anand M, Rajagopal K, Rajagopal KR. A model for the formation and lysis of blood clots. Pathophysiol Haemost Thromb 2005; 34 (2-3): 109-120
138 Di Achille P, Tellides G, Humphrey JD. Hemodynamics-driven deposition of intraluminal thrombus in abdominal aortic aneurysms. Int J Numer Methods Biomed Eng 2017; 33 (05)
139 Xu Z, Chen N, Kamocka MM, Rosen ED, Alber M. A multiscale model of thrombus development. J R Soc Interface 2008; 5 (24) 705-722
140 Lin J, Chen S, Zhang C. et al. Recent advances in microfluidic technology of arterial thrombosis investigations. Platelets 2024; 35 (01) 2316743
141 Govindarajan V, Rakesh V, Reifman J, Mitrophanov AY. Computational study of thrombus formation and clotting factor effects under venous flow conditions. Biophys J 2016; 110 (08) 1869-1885
142 Colace TV, Muthard RW, Diamond SL. Thrombus growth and embolism on tissue factor-bearing collagen surfaces under flow: role of thrombin with and without fibrin. Arterioscler Thromb Vasc Biol 2012; 32 (06) 1466-1476
143 Alber M, Buganza Tepole A, Cannon WR. et al. Integrating machine learning and multiscale modeling-perspectives, challenges, and opportunities in the biological, biomedical, and behavioral sciences. NPJ Digit Med 2019; 2 (01) 115
144 Smine Z, Melidoro P, Qureshi A. et al. Global sensitivity analysis of thrombus formation in the left atrial appendage of atrial fibrillation patients. In: Camara O. et al. Statistical Atlases and Computational Models of the Heart. Regular and CMRxRecon Challenge Papers. STACOM 2023. (Lecture Notes in Computer Science; vol 14507). Springer, Cham; 2024: 55-65
145 Costabal FS, Matsuno K, Yao J, Perdikaris P, Kuhl E. Machine learning in drug development: characterizing the effect of 30 drugs on the QT interval using Gaussian process regression, sensitivity analysis, and uncertainty quantification. Comput Methods Appl Mech Eng 2019; 348: 313-333
146 Longobardi S, Lewalle A, Coveney S. et al. Predicting left ventricular contractile function via Gaussian process emulation in aortic-banded rats. Philos Trans A Math Phys Eng Sci 2020; 378 (2173) 20190334
147 He X, Wang Y, Li J. Flow completion network: inferring the fluid dynamics from incomplete flow information using graph neural networks. Phys Fluids 2022; 34 (08)
148 Ballard JL, Wang Z, Li W, Shen L, Long Q. Deep learning-based approaches for multi-omics data integration and analysis. BioData Min 2024; 17 (01) 38
149 Polotskaya K, Muñoz-Valencia CS, Rabasa A, Quesada-Rico JA, Orozco-Beltrán D, Barber X. Bayesian networks for the diagnosis and prognosis of diseases: a scoping review. Mach Learn Knowl Extr 2024; 6 (02) 1243-1262

150 Lu L, Jin P, Pang G, Zhang Z, Karniadakis GE. Learning nonlinear operators via DeepONet based on the universal approximation theorem of operators. Nat Mach Intell 2021; 3 (03) 218-229
151 Regazzoni F, Pagani S, Salvador M, Dede' L, Quarteroni A. Learning the intrinsic dynamics of spatio-temporal processes through Latent Dynamics Networks. Nat Commun 2024; 15 (01) 1834
152 Madireddy S, Sista B, Vemaganti K. A Bayesian approach to selecting hyperelastic constitutive models of soft tissue. Comput Methods Appl Mech Eng 2015; 291: 102-122
153 Sahli Costabal F, Perdikaris P, Kuhl E, Hurtado DE. Multi-fidelity classification using Gaussian processes: accelerating the prediction of large-scale computational models. Comput Methods Appl Mech Eng 2019; 357: 112602
154 Olier I, Zhan Y, Liang X, Volovici V. Causal inference and observational data. BMC Med Res Methodol 2023; 23 (01) 227
155 Wu X, Peng S, Li J. et al. Causal inference in the medical domain: a survey. Appl Intell 2024; 54 (06) 4911-4934
156 Chahine Y, Magoon MJ, Maidu B, Del Álamo JC, Boyle PM, Akoum N. Machine learning and the conundrum of stroke risk prediction. Arrhythm Electrophysiol Rev 2023; 12: e07
157 Vision Paul V, Masood JAIS. Exploring predictive methods for cardiovascular disease: a survey of methods and applications. IEEE Access 2024; 12: 101497-101505
158 Richens JG, Lee CM, Johri S. Improving the accuracy of medical diagnosis with causal machine learning. Nat Commun 2020; 11 (01) 3923
159 Plecko D, Bareinboim E. Causal fairness for outcome control. arXiv 2023
160 Armoundas AA, Narayan SM, Arnett DK. et al; American Heart Association Institute for Precision Cardiovascular Medicine, Council on Cardiovascular and Stroke Nursing, Council on Lifelong Congenital Heart Disease and Heart Health in the Young, Council on Cardiovascular Radiology and Intervention, Council on Hypertension, Council on the Kidney in Cardiovascular Disease, and Stroke Council. Use of artificial intelligence in improving outcomes in heart disease: a scientific statement from the American Heart Association. Circulation 2024; 149 (14) e1028-e1050
161 Ogbomo-Harmitt S, Muffoletto M, Zeidan A, Qureshi A, King AP, Aslanidi O. Exploring interpretability in deep learning prediction of successful ablation therapy for atrial fibrillation. Front Physiol 2023; 14: 1054401
162 Hernandez RJ, Roberts PA, El-Bouri WK. Advancing treatment of retinal disease through in silico trials. Prog Biomed Eng (Bristol) 2023; 5 (02) 022002
163 Konduri PR, Marquering HA, van Bavel EE, Hoekstra A, Majoie CBLM. INSIST Investigators. *In-silico* trials for treatment of acute ischemic stroke. Front Neurol 2020; 11: 558125
164 Józsa TI, Padmos RM, Samuels N, El-Bouri WK, Hoekstra AG, Payne SJ. A porous circulation model of the human brain for *in silico* clinical trials in ischaemic stroke. Interface Focus 2021; 11 (01) 20190127
165 Petkantchin R, Padmos R, Boudjeltia KZ, Raynaud F, Chopard B. INSIST investigators. Thrombolysis: observations and numerical models. J Biomech 2022; 132: 110902
166 Józsa TI, Petr J, Payne SJ, Mutsaerts HJMM. MRI-based parameter inference for cerebral perfusion modelling in health and ischaemic stroke. Comput Biol Med 2023; 166: 107543
167 Chen X, Wang J, van Kranendonk KR. et al. Mathematical modelling of haemorrhagic transformation in the human brain. Appl Math Model 2023; 121: 96-110
168 Xue Y, El-Bouri WK, Józsa TI, Payne SJ. Modelling the effects of cerebral microthrombi on tissue oxygenation and cell death. J Biomech 2021; 127: 110705
169 El-Bouri WK, MacGowan A, Józsa TI, Gounis MJ, Payne SJ. Modelling the impact of clot fragmentation on the microcirculation after thrombectomy. PLOS Comput Biol 2021; 17 (03) e1008515
170 Graff BJ, Payne SJ, El-Bouri WK. The ageing brain: investigating the role of age in changes to the human cerebral microvasculature with an *in silico* model. Front Aging Neurosci 2021; 13: 632521
171 FDA. Assessing the Credibility of Computational Modelling and Simulation in Medical Device Submissions. 2023 . Accessed at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modelling-and-simulation-medical-device-submissions
172 Pathmanathan P, Aycock K, Badal A. et al. Credibility assessment of in silico clinical trials for medical devices. PLOS Comput Biol 2024; 20 (08) e1012289

173 Fisher CK, Smith AM, Walsh JR. Coalition Against Major Diseases, Abbott, Alliance for Aging Research, Alzheimer's Association, Alzheimer's Foundation of America, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Critical Path Institute, CHDI Foundation, Inc., Eli Lilly and Company, F. Hoffmann-La Roche Ltd, Forest Research Institute, Genentech, Inc., GlaxoSmithKline, Johnson & Johnson, National Health Council, Novartis Pharmaceuticals Corporation, Parkinson's Action Network, Parkinson's Disease Foundation, Pfizer, Inc., sanofi-aventis. Collaborating Organizations: Clinical Data Interchange Standards Consortium (CDISC), Ephibian, Metrum Institute. Machine learning for comprehensive forecasting of Alzheimer's Disease progression. Sci Rep 2019; 9 (01) 13622
174 Roney CH, Sim I, Yu J. et al. Predicting atrial fibrillation recurrence by combining population data and virtual cohorts of patient-specific left atrial models. Circ Arrhythm Electrophysiol 2022; 15 (02) e010253
175 Payne S, Józsa TI, El-Bouri WK. Review of in silico models of cerebral blood flow in health and pathology. Prog Biomed Eng (Bristol) 2023; 5 (02) 022003
176 Hernandez RJ, Madhusudhan S, Zheng Y, El-Bouri WK. Linking vascular structure and function: image-based virtual populations of the retina. Invest Ophthalmol Vis Sci 2024; 65 (04) 40
177 Sel K, Hawkins-Daarud A, Chaudhuri A. et al. Survey and perspective on verification, validation, and uncertainty quantification of digital twins for precision medicine. NPJ Digit Med 2025; 8 (01) 40
178 National Academies of Sciences, Engineering, and Medicine, National Academy of Engineering, Division on Earth and Life Studies, Division on Engineering and Physical Sciences, Board on Atmospheric Sciences and Climate, Board on Life Sciences, Computer Science and Telecommunications Board, Committee on Applied and Theoretical Statistics, Board on Mathematical Sciences and Analytics, Committee on Foundational Research Gaps and Future Directions for Digital Twins. Foundational Research Gaps and Future Directions for Digital Twins. Washington DC: National Academies Press; 2024
179 Mirams GR, Niederer SA, Clayton RH. The fickle heart: uncertainty quantification in cardiac and cardiovascular modelling and simulation. Philos Trans A Math Phys Eng Sci 2020; 378 (2173) 20200119
180 Tunedal K, Ebbers T, Cedersund G. Uncertainty in cardiovascular digital twins despite non-normal errors in 4D flow MRI: identifying reliable biomarkers such as ventricular relaxation rate. Comput Biol Med 2025; 188: 109878
181 Roy A, Varela M, Chubb H. et al. Identifying locations of re-entrant drivers from patient-specific distribution of fibrosis in the left atrium. PLOS Comput Biol 2020; 16 (09) e1008086
182 Muffoletto M, Qureshi A, Zeidan A. et al. Toward patient-specific prediction of ablation strategies for atrial fibrillation using deep learning. Front Physiol 2021; 12: 674106
183 Corrado C, Roney CH, Razeghi O. et al. Quantifying the impact of shape uncertainty on predicted arrhythmias. Comput Biol Med 2023; 153: 106528
184 Liu CM, Chang SL, Chen HH. et al. The clinical application of the deep learning technique for predicting trigger origins in patients with paroxysmal atrial fibrillation with catheter ablation. Circ Arrhythm Electrophysiol 2020; 13 (11) e008518
185 Trayanova NA, Prakosa A. Up digital and personal: how heart digital twins can transform heart patient care. Heart Rhythm 2024; 21 (01) 89-99
186 Bhagirath P, Strocchi M, Bishop MJ, Boyle PM, Plank G. From bits to bedside: entering the age of digital twins in cardiac electrophysiology. Europace 2024; 26 (12) euae295
187 Lal R, Nicoud F, Bars EL. et al. Non invasive blood flow features estimation in cerebral arteries from uncertain medical data. Ann Biomed Eng 2017; 45 (11) 2574-2591
188 Eloranta S, Boman M. Predictive models for clinical decision making: deep dives in practical machine learning. J Intern Med 2022; 292 (02) 278-295
189 Amirahmadi A, Ohlsson M, Etminani K. Deep learning prediction models based on EHR trajectories: a systematic review. J Biomed Inform 2023; 144: 104430
190 Zaidan E, Ibrahim IA. AI governance in a complex and rapidly changing regulatory landscape: a global perspective. Humanit Soc Sci Commun 2024; 11 (01) 1121
191 McGrath CP. The state and values of AI governance in UK healthcare. In: Research Handbook on Health, AI and the Law. Edward Elgar Publishing; 2024: 291-310
192 Mourby M, Ó Cathaoir K, Collin CB. Transparency of machine-learning in healthcare: The GDPR & European health law. Comput Law Secur Rev 2021; 43: 105611

193 Donelan M, Camrose V. Data Protection and Digital Information Bill. UK Parliament; 2024
194 Medicines and Healthcare products Regulatory Agency. Impact of AI on the regulation of medical products. 2024; available at: https://www.gov.uk/government/publications/impact-of-ai-on-the-regulation-of-medical-products
195 Calderon. Assembly Bill No. 3030–Health Care Services: Artificial Intelligence. California State Assembly; 2024
196 Becker. Senate Bill No. 1120 - Health Care Coverage. Utilization Review; 2024; available at: https://calmatters.digitaldemocracy.org/bills/ca_202320240sb1120
197 van Kolfschooten H, van Oirschot J. The EU Artificial Intelligence Act (2024): implications for healthcare. Health Policy 2024; 149: 105152
198 McMahan BH, Moore E, Ramage D, Hampson S, Aguera y Arcas B. Communication-efficient learning of deep networks from decentralized data. In: McMahan HB, et al. Communication-Efficient Learning of Deep Networks from Decentralized Data. International Conference on Artificial Intelligence and Statistics. 2016
199 Khan M, Glavin FG, Nickles M. Federated learning as a privacy solution—an overview. Procedia Comput Sci 2023; 217: 316-325
200 Rieke N, Hancox J, Li W. et al. The future of digital health with federated learning. NPJ Digit Med 2020; 3 (01) 119
201 Truong N, Sun K, Wang S, Guitton F, Guo Y. Privacy preservation in federated learning: an insightful survey from the GDPR perspective. Comput Secur 2021; 110: 102402
202 Feger J, Baba Y, Elfeky M. Late gadolinium enhancement. In: Radiopaedia.Org. Radiopaedia.org; 2020.
203 Carroll D, Murphy A, Bell D. Transthoracic echocardiography. In: Radiopaedia.Org. Radiopaedia.org; 2018.
204 Radswiki T, Hacking C, Feger J. Intracardiac thrombus. In: Radiopaedia.Org. Radiopaedia.org; 2010.
205 English K. Upper extremity deep vein thrombosis. In: Radiopaedia.Org. Radiopaedia.org; 2023.
206 Gaillard F, Knipe H, Silverstone L. Deep vein thrombosis. In: Radiopaedia.Org. Radiopaedia.org; 2008.
207 Weerakkody Y, Kogan J, Feger J. Internal carotid artery stenosis (classification). In: Radiopaedia.Org. Radiopaedia.org; 2010.
208 Di Muzio B. MR angiography of the thoracic aorta. In: Radiopaedia.Org. Radiopaedia.org; 2015.
209 Murphy A, Foster T, Knipe H. CT angiography of the chest (protocol). In: Radiopaedia.Org. Radiopaedia.org; 2019.