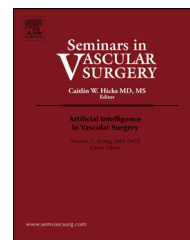


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Review article

Artificial intelligence–based predictive models in vascular diseases



Fabien Lareyre^{a,b}, Arindam Chaudhuri^c, Christian-Alexander Behrendt^{d,e}, Alexandre Pouhin^f, Martin Teraa^g, Jonathan R. Boyle^h, Riikka Tulamoⁱ, Juliette Raffort^{b,j,k,*}

^a Department of Vascular Surgery, Hospital of Antibes Juan-les-Pins, France

^b Université Côte d'Azur, INSERM U1065, C3M, Nice, France

^c Bedfordshire-Milton Keynes Vascular Centre, Bedfordshire Hospitals NHS Foundation Trust, Bedford, UK

^d Brandenburg Medical School Theodor-Fontane, Neuruppin, Germany

^e Department of Vascular and Endovascular Surgery, Asklepios Medical School Hamburg, Asklepios Clinic Wandsbek, Hamburg, Germany

^f Division of Vascular Surgery, Dijon University Hospital, Dijon, France

^g Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

^h Cambridge Vascular Unit, Cambridge University Hospitals NHS Trust and Department of Surgery, University of Cambridge, Cambridge, UK

ⁱ Department of Vascular Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

^j Institute 3IA Côte d'Azur, Université Côte d'Azur, France

^k Clinical Chemistry Laboratory, University Hospital of Nice, France

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ABSTRACT

Cardiovascular disease represents a source of major health problems worldwide, and although medical and technical advances have been achieved, they are still associated with high morbidity and mortality rates. Personalized medicine would benefit from novel tools to better predict individual prognosis and outcomes after intervention. Artificial intelligence (AI) has brought new insights to cardiovascular medicine, especially with the use of machine learning techniques that allow the identification of hidden patterns and complex associations in health data without any *a priori* assumptions. This review provides an overview on the use of artificial intelligence–based prediction models in vascular diseases, specifically focusing on aortic aneurysm, lower extremity arterial disease, and carotid stenosis. Potential benefits include the development of precision medicine in patients with vascular diseases. In addition, the main challenges that remain to be overcome to integrate artificial intelligence–based predictive models in clinical practice are discussed.

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* Corresponding author.

E-mail address: raffort-lareyre.j@chu-nice.fr (J. Raffort).

1. Introduction

Cardiovascular diseases are the leading cause of deaths in developed countries and represent a heavy burden on health care, economy, and society [1,2]. Aortic aneurysm, lower extremity arterial disease (LEAD), and carotid stenosis are the top three cardiovascular diseases that are being managed in daily vascular surgical practice. Despite technical advances and innovations in diagnostics and treatment, management of these vascular diseases is still challenging and patient outcomes are often associated with high rates of morbidity and mortality [3–6]. Novel tools to better predict individual prognosis and outcomes of interventions would help to develop personalized medicine and improve patient care.

Artificial intelligence (AI) has brought new insights to cardiovascular disease with the development of innovative techniques. AI is a broad domain and among the main fields, computer vision offers opportunities to enhance imaging analysis and natural language processing (NLP) brings new tools to improve the management of health data. Furthermore, smart devices are contributing to the development of new techniques to better detect, diagnose, classify, predict, or treat these diseases [7–9]. As a branch of AI, machine learning (ML) enables computer technology to learn from data. ML can be used to identify patterns among complex data, shrink a vast volume of information to a more meaningful level, and make predictions without being explicitly programmed and without specific a priori assumption. Although risk prediction in health care has so far been based on traditional statistical methods, they may present some limitations. Statistics methods are mainly based on inference and create probability models [10]. However, they allow the investigation of associations among a limited number of predefined parameters and they were designed for models with input variables and sample sizes that would be considered small to moderate today. Advances in technology and computer science have led to an exponential increase in health data, and appropriate methods, such as ML, can help to capture complex relationships among data [10]. ML-based prediction models for cardiovascular diseases are promising, especially in vascular surgery [7,9,11], as they have the potential to provide improved prognostic evaluation, guidance of therapeutic decision making, and contribute to enhanced precision medicine [7,9,11]. In this review, we aimed to summarize the main AI-based predictive models, focusing on aortic aneurysm, LEAD, and carotid stenosis. This review may serve as an update to provide a brief overview for an increasing number of research projects using these new technologies.

2. Aortic aneurysm

2.1. Prediction of aortic aneurysm growth and risk of rupture

Aortic aneurysms are associated with high rates of morbidity and mortality. Aneurysm growth and risk of rupture are the main indications for aneurysm repair, therefore, effective and accurate tools to predict these events would be essential to

inform therapeutic decisions. Several ML models have been developed in this field and have demonstrated encouraging but preliminary results [12]. Among them, Kontopodis et al [13] tested several ML algorithms based on 29 input variables, including clinical, biological, morphometric, and biomechanical characteristics, to predict abdominal aortic aneurysm (AAA) growth rate and classify their growth rate as high or low. Based on a cohort of 40 patients with small AAAs, the XGboost (extreme gradient boosting) model achieved the highest area under the curve (AUC) in predicting growth rate (81.2%; 95% CI, 61.1%–100%) [13]. In this model, the most important predictive factors were maximum aneurysm diameter and neck diameter, tortuosity from the renal arteries to the aortic bifurcation, and maximum thickness of the intraluminal thrombus, highlighting the importance of anatomic characteristics of AAA to predict its progression [13]. Other investigators developed an ML algorithm to predict rupture using 45 features extracted from 66 patients [14]. Their results indicate that the BestFirst feature selection algorithm yielded the highest prediction accuracy (82% on the test set). These results suggest that a combination of several parameters that comprehensively capture AAA behavior may help to evaluate the risk of AAA-related events, such as rupture. However, the model performance needs to be improved and trained on larger cohorts of patients with iterative adjustments to improve accuracy and reliability. Indeed, another study used a much larger cohort of patients with descending aortic aneurysms ($n = 1,083$) to predict occurrence of rupture, dissection, or all-cause mortality and trained 6 ML models with 44 variables [15]. All of these models demonstrated better performance than simple descending aortic diameter measurement to predict these outcomes, showing the additional value of ML-based risk stratification to predict aneurysm-related complications [15]. These models could be of further interest to guide screening and follow-up strategies.

The variety and heterogeneity of available algorithms and subsequently derived models also emphasized that results may be prone to inflation bias to some degree. In addition, a main limitation in this research area is that it is difficult to obtain a standardized follow-up of patients with data regarding the outcomes (aneurysmal growth or rupture). Hence, it seems reasonable to strictly follow appropriate reporting standards and prespecify the basic study characteristics if possible.

2.2. Prediction of postoperative outcomes

Several studies have focused on ML to predict outcomes after aneurysm repair, including the risk of mortality and postoperative complications [12]. Endoleaks are the Achilles heel of endovascular aneurysm repair (EVAR) and influence long-term outcomes and reintervention rates. Therefore, several predictive models have been developed to better evaluate the risk of endoleaks [16–18]. Masuda et al [17] integrated patient characteristics, stent-graft configuration, and a selection of vessel lengths, diameters, and angles measured on the basis of preoperative computed tomography angiography (CTA) in an ML model to predict the occurrence of Type I and II endoleaks after EVAR [17]. The AUC of the predictive model was 0.88, with a sensitivity of 0.85 and a specificity of 0.91 [17]. Another study evaluated the performance of radiomic features derived from

CTA to differentiate aggressive from benign Type II endoleaks post EVAR [16]. Patients were divided into two groups according to changes in aneurysm sac dimensions, differentiating aggressive from benign Type II endoleaks. In this study, two supervised ML algorithms (support vector machines [SVM] classifiers) were developed to predict the aneurysm sac dimension changes at 1 year, using radiomic features at 1- and 6-month CTAs. These SVM classifiers trained on 1- and 6-month radiomic features were able to predict sac expansion at 1 year with an AUC of 89.3% and 95.5%, respectively. Hence, ML models might not only be of interest to predict the occurrence of Type II endoleaks, but are also able to predict its impact on aneurysm sac expansion and therefore guide therapeutic decision making. In addition to endoleaks, other serious EVAR-related adverse events can occur, such as iliac limb occlusion or restenosis, stent-graft migration, aneurysm sac expansion, or AAA rupture. Several studies have reported the role of ML to predict these outcomes [18,19]. In their study, Wang et al [19] included 493 patients for the development and comparison of multimodal models (optimized morphologic feature, deep learning [DL], and radiomic models) to predict EVAR-related severe adverse events [19]. The radiomic model based on logistic regression demonstrated better predictive performance (AUC = 0.93) than the other models. Together these results support the future use of ML-based predictive models to evaluate the prognosis of patients with AAA and enhance precision medicine through evaluation of the balance between risk of AAA growth and rupture and risks related to potential postoperative complications.

2.3. Lower extremity arterial disease

2.3.1. Prediction of systemic cardiovascular events and mortality

LEAD is a major problem in health care, as it affects more than 237 million people worldwide and is associated with high rates of morbidity and mortality [4,20]. LEAD is associated with systemic atherosclerosis and patients are at high risk of developing cardiovascular events. Several studies demonstrated the potential role of ML models to predict the risk of major adverse cardiac and cerebrovascular events [21,22]. ML was also used to predict the risk of mortality [23]. In a cohort of 1,755 patients with LEAD, several ML algorithms using clinical, imaging, and genomic information were built and tested to predict future mortality. The performances of the ML models tended to be higher compared with logistic regression models (AUC = 0.76 v 0.65; $P = .10$), showing encouraging results for developing new tools to evaluate the prognosis of patients with LEAD [23].

Furthermore, patients with LEAD are often treated with antithrombotic or anticoagulant drugs and the balance between prevention of atherosclerosis-related complications and risk of bleeding events remains difficult to evaluate [24]. In this context, using a LASSO (least absolute shrinkage and selection operator) approach, a novel risk score (OAC3-PAD risk score) was recently built to predict the risk of major bleeding events 1 year after hospitalization for LEAD [25]. The score was developed from data derived from Germany's second largest health insurance fund and the cohort included 81,930 patients. The score was composed of 8 items and exhibited ade-

quate calibration and discrimination between four risk groups of major bleeding ($c = 0.69$; 95% CI, 0.67–0.71). External validation was performed in a prospective cohort of 5,479 patients and confirmed the performance of the OAC3-PAD bleeding risk score (discrimination using Harrell's c -statistic = 0.61; 95% CI, 0.43–0.80) [26]. As the first internally and externally validated pragmatic bleeding score in the LEAD field, this could be useful to support clinical guidelines and potentially develop patient-centered decisions regarding use of antithrombotic treatments.

2.3.2. Prediction of limb-related and post-intervention outcomes

In addition to medical treatment, revascularization is a cornerstone of LEAD treatment and can be proposed on the basis of the stage of disease. However, the risk of postoperative complications remains difficult to predict [4,27] and AI-based models have been proposed in this setting [28]. As an example, some authors investigated whether ML could predict the 2-year major adverse limb event-free survival after percutaneous transluminal angioplasty and stenting for LEAD [29]. In a cohort of 392 patients, demographic, medical, and imaging data were used to develop an ML model. The artificial neural network (ANN) model achieved an AUC of 0.80 (95% CI, 0.68–0.89) and significantly outperformed the logistic regression model to predict event-free survival. This study points to the potential use of ML to guide therapeutic decision making.

Better prediction of amputation risk in LEAD may also help to optimize treatment decisions. Based on the American College of Surgeons National Surgical Quality Improvement Program database including 14,444 patients who underwent endovascular procedures for LEAD, a random forest ML model was built to predict 30-day amputation [30]. The model achieved an AUC of 0.81, and although external validation is required, it offers interesting perspectives to optimize clinical decision making for patients with LEAD [30]. Furthermore, wound healing after amputation is another concern and is very difficult to predict. A novel wound multispectral imaging system was developed to help predict healing after amputation and was tested in 25 patients with various levels of amputation (ie, toe, transmetatarsal, below-knee, or above-knee) [31]. Using patients' clinical risk factors combined with preoperatively obtained imaging of the lower limb, the ML algorithm had a sensitivity of 91% and a specificity of 86% for predicting non-healing amputation sites [31].

Finally, chronic limb-threatening ischemia (CLTI) has a significant impact on quality of life, with high rates of morbidity and mortality [32]. Prognostic tools would aid in clinical decision making. Several CLTI prediction models have been developed using statistical methods, such as those derived from the BASIL (Bypass versus Angioplasty in Severe Ischaemia of the Leg), FINNVASC (Finland National Vascular registry), PREVENT III (Prevention of Infringuinal Vein Graft Failure) [32]. However, external validation in other cohorts found that all these models performed poor to fair in predicting mortality and amputation, with an AUC ranging from 0.60 to 0.71 for the latter [32]. To develop new stratification models in patients with CLTI, some investigators used ML models (supervised

topic model cluster analysis) using cohort data from the PREVENT III randomized clinical trial to predict 1-year CLTI-free survival, defined as a composite of survival with remission of ischemic rest pain, wound healing, and freedom from major lower-extremity amputation [33]. Interestingly, three distinct clusters were identified within the cohort, with distinct 1-year CLTI-free survival rates (82.3% for stage 1, 61.1% for stage 2, and 53.4% for stage 3) [33]. Although further studies are required for validation, this approach could improve risk stratification in patients with CLTI because of its ability to incorporate a wider variety of features compared with other previously published stratification schemes. In addition, this method has the advantage of malleability, and it can adjust as the prevalence and severity of risk factors change over time within the disease.

3. Carotid stenosis

Carotid stenosis is another manifestation of atherosclerosis that carries a risk of cerebrovascular event, such as acute ischemic stroke or transient ischemic attacks, which is a major cause of long-term disability and the second leading cause of death worldwide [5,6]. In 2020, almost 30% of the global population aged 30 to 79 years had increased carotid intima-media thickness [34]. The treatment of carotid stenosis aims to reduce the future risk for plaque-related ischemic stroke, but interventional therapies are associated with potential complications. Patients would benefit from tools to measure an optimal balance between the risk of cerebrovascular events and intervention-related complications. AI may help optimize care via developing predictive models to improve treatment selection.

3.1. Plaque characterization and identification of predictive patterns of stroke risk

Carotid plaque characterization and classification of carotid plaque may help to better predict the risk of cerebrovascular events and assist in the clinical decision making for revascularization [35]. Atherosclerosis of carotid arteries is characterized by a focal accumulation of lipids, fibrous elements, and calcification, which results from complex mechanisms involving endothelial activation and a related chronic low-grade inflammatory process. Thus, characterization and determining the nature of carotid plaques are challenging, as they are composed of various components formed at different stages during plaque formation, progression, and remodeling [35]. Several imaging techniques are available [36] and a recent review summarized the main types of AI models that were used to analyze carotid plaques and identified patterns associated with symptomatic disease and plaque vulnerability based on magnetic resonance imaging, computer tomography, or ultrasound (US) [35].

As US is non-invasive, inexpensive, and easily available, it is not surprising that studies published so far mainly used this imaging technique to classify carotid plaques and develop predictive models of stroke risk [35]. Symptomatic plaques are often hypoechoic due to a large lipid core, minimal col-

lagen, and a heterogeneous fibrous cap, while asymptomatic plaques are hyperechoic and often calcified [35]. Using DL algorithms, several investigators developed computer-aided diagnostic systems for tissue classification and characterization based on US images [35]. As an example, Guang et al [37] evaluated the performance of their DL-based detection and classification system for carotid plaques on US compared with two experienced radiologists who manually classified plaque vulnerability. In a cohort of 205 patients, the DL system demonstrated a better AUC (0.84 v 0.69; $P < .01$ and 0.87 v 0.66 in the training and validation cohorts, respectively) [37]. Other investigators used transfer-learning-based DL models to classify symptomatic and asymptomatic plaques [38]. They augmented and optimized 11 AI models using a transfer-learning approach and showed the potential of the method for plaque characterization [38]. Characterization of plaque composition including the amount of lipid core, fibrous tissue, and calcification based on US images is challenging due to image noise and complexity of lesions [39]. Some investigators developed a fully automatic characterization for these features, using convolutional neural network, and found a correlation of approximately 0.90 with the clinical assessment [39], which supports its potential use in clinical practice. Finally, several studies integrated imaging to non-imaging features to assess plaque vulnerability and identify high-risk patients [35]. For example, Huang et al [40] built a nomogram using US-based radiomics and clinical features to identify symptomatic carotid plaques. This model outperformed the clinical and conventional US model, with an AUC of 0.93 and 0.92 in the training and test cohorts (v 0.723 and 0.580), respectively [40].

Other imaging techniques were also used to develop AI-based plaque characterization. Le et al [41] aimed to evaluate the robustness and reproducibility of radiomic features from carotid CTA to identify culprit carotid arteries in patients who had prior cerebrovascular events. In a cohort of 41 patients who had a stroke or transient ischemic attack (comprising 41 culprit and 41 non-culprit carotid arteries), the authors determined the robustness of 93 radiomic features to identify culprit and non-culprit arteries using ML [41]. After selection of the 10 top non-redundant robust radiomic features, their model achieved an AUC of 0.73 and an accuracy of 69%. Although these results need to be confirmed in prospective cohorts, this study found encouraging results to use carotid radiomic features to improve stroke prediction. Other investigators built a magnetic resonance imaging-based model using radiomics features and ML for differentiating symptomatic from asymptomatic carotid plaques [42]. From a cohort of 162 patients with carotid stenosis, the model achieved an AUC of 0.99 in the test cohort [42]. Another study aimed to develop an ML-based algorithm to segment carotid plaque components from a magnetic resonance scanner with both traditional multicontrast vessel wall magnetic resonance sequences and three-dimensional simultaneous non-contrast angiography and intraplaque hemorrhage sequence [43]. Several ML algorithms were tested and demonstrated their interest to segment and characterize plaque components, including lipid rich/necrotic core, calcifications, and fibrous tissue [43].

3.2. Prediction of outcomes of patients after carotid intervention

Several techniques can be used to treat carotid stenosis, including carotid endarterectomy (CEA) or carotid artery stenting (CAS) [5,6]. Both techniques carry a risk of serious postoperative complications, and development of new prognostic tools may help clinicians to better anticipate and prevent them.

For instance, Matsuo et al [44] built 5 ML algorithms to predict the risk of ischemic stroke within 30 days after carotid intervention (CEA or CAS). From a cohort of 165 consecutive patients, 17 clinical factors were used as input data in an XG-Boost model, which demonstrated an accuracy of 86.2% to predict postoperative ischemic stroke [44]. In this study, internal carotid artery peak systolic velocity, low-density lipoprotein cholesterol, and the type of procedure (ie, CEA or CAS) were identified as the most contributing factors of the predictive model. Although further studies are required, these results indicate the potential value of AI-based outcome prediction models to guide decision making and patient selection for CEA or CAS [44].

Other studies focused on the prediction of postoperative outcomes after CAS. In a cohort of 317 patients, some investigators used an ANN to evaluate the risk of major adverse cardiovascular events [45]. Based on input features composed of 13 clinical risk factors, the ANN model predicted the occurrence of major adverse cardiovascular events with a sensitivity of 85.8%, specificity of 60.8%, and accuracy of 80.8% [45]. Another study aimed to predict the risk of persistent hemodynamic depression after CAS using ANN, multiple logic regression, and SVM models [46]. In the test cohort, the ANN model demonstrated better performances to correctly classify and predict the outcome, with an AUC of 0.95 (*v* 0.80 for multiple logic regression and 0.89 for SVM) [46]. Finally, ML was also used for prediction of the risk of unplanned 30-day readmission after CAS [47]. From the US Nationwide Readmission Database, 16,745 patients who underwent CAS were identified, of whom 7.4% were readmitted within 30 days. A total of 42 clinical variables were used to develop the deep neural network and the model produced an accuracy of 87.43%, showing a proof of concept that ML-derived models may be of interest to identify high-risk patients that may require a closer follow-up.

4. Challenges and perspectives

The studies presented in this review illustrate the increasing popularity, high potential, and areas of applications of AI in modern management of vascular diseases. ML models have shown their potential to predict outcomes of patients with vascular diseases, including complications related to the disease itself and complications potentially related to medical, surgical, and endovascular treatments (Fig. 1). Taken together, these models can help to evaluate survival and risk of complications and rehospitalization. In addition, the balance between outcomes related to the disease and its treatment might help to guide therapeutic decision making and patient-

tailored management. Although ML-based predictive models hold great promise, several challenges remain.

4.1. Accuracy of ML models and datasets used

ML algorithms are dependent on the availability, quality, and volume of data used for the training. The performances of the models can therefore be limited, especially for rare diseases or rare events and complications. Data used in the studies were very diverse (including clinical, biological, and imaging) and study designs were heterogeneous from small single-center studies to large retrospective national and administrative databases. A large heterogeneity regarding types, sources, formats, structures, quality, protocol of data acquisitions, storage, sharing, transfer, and analysis is a field reality. Standardization of data architecture is a critical and complex process to accurately extract the data and bring them into a common and digestible format to allow collaborative research and development of AI/ML applications. Standardization is essential and additionally the process must guarantee patient privacy, data protection, and legal conformity regarding ethics regulation. Multicenter and multidisciplinary collaboration is crucial to build efficient and large-scale databases that can serve to train and test AI models [48]. International vascular registries (such as VASCUNET, European Vascular Research Collaborative, International Consortium of Vascular Registries, or Society for Vascular Surgery Vascular Quality Initiative) have been very dynamic toward federating and coordinating research among health institutions to better study the outcomes of patients and build guidelines for clinical practice [48–50]. In addition to vascular registries, which are mainly based on clinical and administrative data, international consortia are currently initiated to put efforts together to build large-scale data repositories for vascular diseases (including imaging data). The European Research Hub was also recently created and endorsed by the European Society for Vascular Surgery to evaluate and facilitate the development of multicenter and multinational studies among European researchers [51]. These approaches truly have the potential to bring major insights to the development of AI models.

4.2. Explainability and validation of AI models

The vast majority of ML-based predictive models for vascular diseases have been developed and tested on retrospective data. Most studies do not provide a detailed description of the raw data, source codes, and algorithms developed, making it difficult to assess the robustness of the methodology and hindering reproducing and testing the method. In addition, AI-based decision-making process, prediction, and classification are hard to explain, as they function as a “black-box” process, meaning that the output is achieved without providing explanations on how it was reached. Given the complexity of the models, robust and standardized methods to prove the accuracy, efficiency, and safety of the models are required to gain trust among health care professionals and patients. External validation in other cohorts is required and randomized controlled trials would be of interest to assess the clinical benefits and medico-economic impact of the AI models. The generalizability of the predictive models is a key point that remains

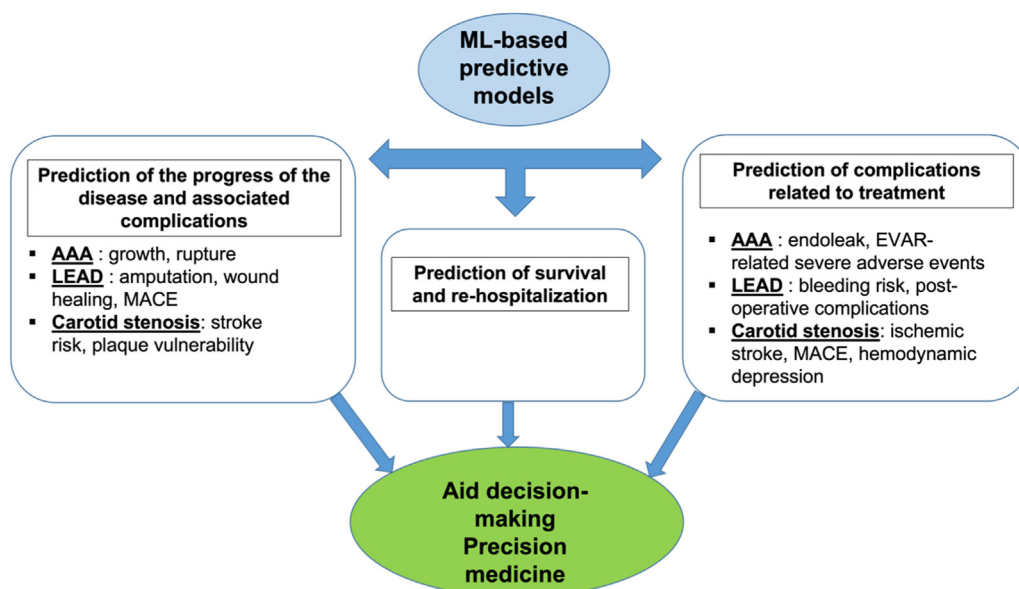


Fig. 1 – Artificial intelligence–based predictive models in vascular diseases. Machine learning (ML) models focused on the prediction of three main risks associated with vascular diseases: prediction of the progress of the disease and associated complications, prediction of survival and rehospitalization, and prediction of complications related to treatment. Together, ML-based predictive models offer new tools to guide decision making and develop precision medicine. AAA, abdominal aortic aneurysm; EVAR, endovascular aortic aneurysm repair; LEAD, lower extremity arterial disease; MACE, major adverse cardiovascular event.

to be explored, as it is possible that algorithm performances can vary depending on demographic, ethnic, geographic, and socioeconomic disparities.

4.3. Implementation of AI predictive models in clinical practice

Although evidence of the accuracy and benefits of ML-based predictive models is a necessary condition, additional factors are at stake. First, AI models can be computationally expensive, which can limit their deployment, depending on the infrastructure and technical support available in health institutions. Second, it is important to think about how the model can be integrated into the clinical workflow. Patients with vascular diseases can have acute and severe conditions, requiring decision making and urgent interventions. Computational time should be studied carefully and fit with the intended use. Management of vascular diseases is constantly evolving, with variations of patient’s characteristics over time, advancements in imaging analysis, and technical innovation for vascular interventions. AI models have the potential to evolve and improve over time, with adjunction and continuous updating from large and dynamic datasets. Hence, it can be expected that the AI methods will continue to improve over time with continuous updating. In addition, feedback from end users associated with regular performance monitoring will help to build real-time prognostication and personalized therapy guidance. Adherence to, and health care professionals’ and patients’ perceptions of, AI solutions are key points that should be taken seriously. AI-based predictive models developed to enhance care of patients with vascular diseases

can be considered as applications in the field of “narrow AI.” As opposed to “general AI,” the applications are built for a highly focused set of tasks. They are not meant to replace humans, but they are intended to be used by humans as a complementary technology to improve care in a process during which health care professionals keep their entire responsibilities for medical expertise and decision making in accordance with the patients’ wishes. The perception of AI can be associated with fears of misuse or misconduct. The European Commission is currently building regulatory frameworks elaborated by multidisciplinary groups of experts to promote trustworthy, transparency, ethics, and equity within AI. Appropriate education and communication with a large audience are mandatory to avoid misconception or misuse of these new technologies [52].

5. Conclusions

There are various innovative AI-driven tools to predict the progress of vascular disease as well as treatment outcomes and intervention-related complications. Although ML predictive models hold great promise, their heterogeneity, the often-limited sample size, and the paucity of external validation emphasize the remaining challenges for future implementation in daily clinical practice. Although the road ahead is still long, it appears reasonable to be open-minded as both clinicians and researchers, and keep working toward safe, efficient, and accurate innovative applications that are likely to aid the clinicians in the future in the decision-making process and personalized medicine.

Declaration of Competing Interest

The authors declare no competing interest

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