ESC European Society of Cardiology

European Heart Journal (2024) **00**, 1–14
https://doi.org/10.1093/eurheartj/ehae465

STATE OF THE ART REVIEW
Digital health and innovation

Artificial intelligence in cardiovascular medicine: clinical applications

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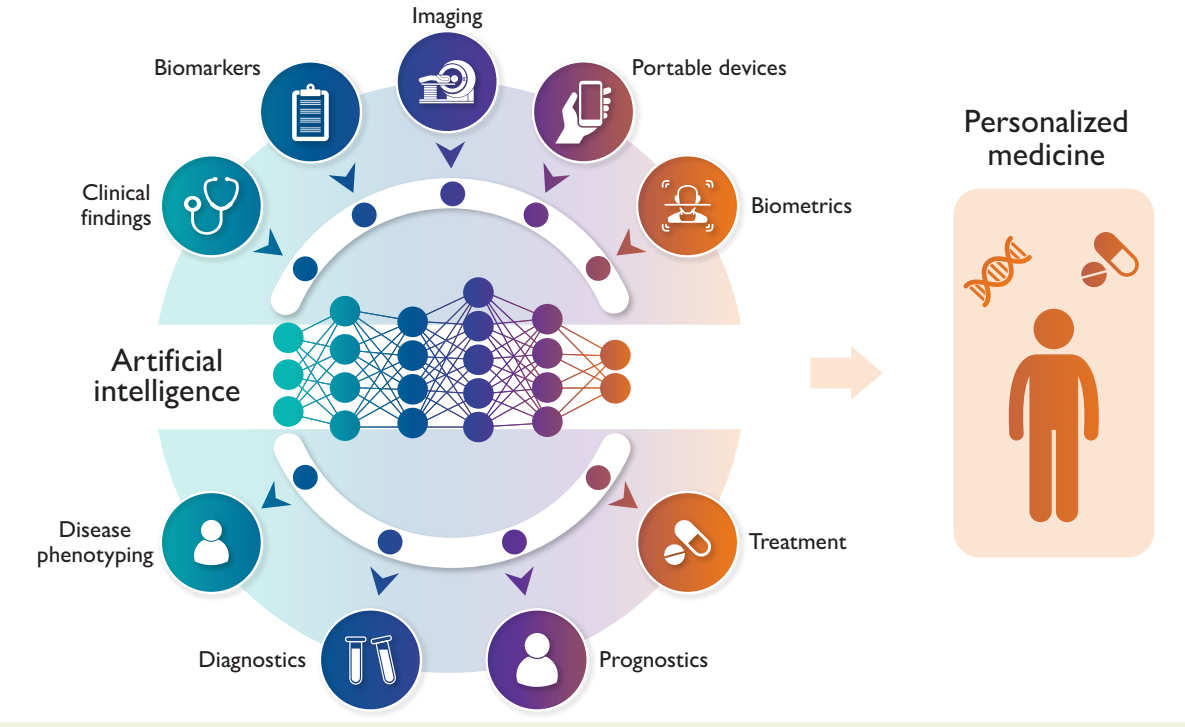
Received 18 March 2024; revised 7 June 2024; accepted 3 July 2024

Graphical Abstract



Clinical information including patient data, laboratory parameters, and results from clinical examination, large-scale data from (multi-)national registries, imaging data, and (patient) biometrical data can all be processed by artificial intelligence. Resulting models allow for disease phenotyping, enhance diagnostics, improve prognostication, and facilitate treatment decision-making, thus ultimately contributing to a more personalized therapy of patients with cardiovascular disease.

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Abstract

Clinical medicine requires the integration of various forms of patient data including demographics, symptom characteristics, electrocardiogram findings, laboratory values, biomarker levels, and imaging studies. Decision-making on the optimal management should be based on a high probability that the envisaged treatment is appropriate, provides benefit, and bears no or little potential harm. To that end, personalized risk–benefit considerations should guide the management of individual patients to achieve optimal results. These basic clinical tasks have become more and more challenging with the massively growing data now available; artificial intelligence and machine learning (AI/ML) can provide assistance for clinicians by obtaining and comprehensively preparing the history of patients, analysing face and voice and other clinical features, by integrating laboratory results, biomarkers, and imaging. Furthermore, AI/ML can provide a comprehensive risk assessment as a basis of optimal acute and chronic care. The clinical usefulness of AI/ML algorithms should be carefully assessed, validated with confirmation datasets before clinical use, and repeatedly re-evaluated as patient phenotypes change. This review provides an overview of the current data revolution that has changed and will continue to change the face of clinical medicine radically, if properly used, to the benefit of physicians and patients alike.

Keywords Artificial intelligence • Deep learning • Diagnostic algorithms • Face recognition • ECG • Imaging • Outcome prediction

Introduction

Intelligence is a feature of humans (*Homo sapiens sapiens*), which distinguishes us in part from other species. In evolution, human intelligence, together with the socialization in groups, markedly enhanced by the development of gesturing and speech, allowed us to survive despite an overall weak physical constitution. Indeed, intelligent thinking allowed mankind to use and create tools and weapons, develop agriculture, and eventually, modern technology and medicine. For centuries, there was consensus that human-level intelligence can only arise from biological human brains yet rapid technological advances in the recent years have led to exponential growth in the number of intellectual tasks that now can be solved by computer-based artificial intelligence (AI) (*Table 1*), putting this long-held believe into question.

With the development of computers after the Second World War, increasingly sophisticated programmes have been developed that eventually were able to handle ever-increasing amounts of data and finally to learn.[1] Such programmes have been rapidly adopted in medicine. Indeed, today's medicine is flooded by data that are difficult for a human brain to comprehend or analyse without the help of AI and machine learning (ML).

The data revolution

In recent decades, an ever-increasing amount of data has been collected in medicine, and cardiology in particular. As a consequence, epidemiology and data science have gained increasing importance in medicine and evolved into independent disciplines dedicated to the investigation of demographics, health status, and outcomes of large populations of healthy individuals and patients with different medical conditions.[2] While initially demographics and clinical parameters, as well as the electrocardiogram (ECG) and biomarkers have been recorded, more recently, genetic information and imaging with different modalities have been included. These enormous datasets required new analytical tools such as AI/ML algorithms for their use in the diagnosis, prognostication, and patient management.[3] This article reviews current applications of AI/ML in cardiovascular medicine.

Types of data

Different types of data can be analysed with AI, all being prone to specific sorts of errors that have to be carefully considered, largely deriving from modalities of data collection and storage (*Table 2*). Clinical characteristics such as patient age, gender, body mass index, and laboratory parameters constitute structured data (*Graphical Abstract*). Semi-structured data involve all sorts of text-based information such as medication use and dosage, as well as parameters collected on continuous scales as visual analogue scale scores. Imaging data are considered unstructured, given their large inter-individual variability. One way to reduce this variability is to collect this type of data in a standardized fashion, e.g. by using the same ECG device or identical cardiovascular magnetic resonance scanners with standardized imaging protocols. However, this would premise that the data analysed have either been collected within prospective trials, or that retrospectively ascertained data derive from tertiary centres applying standardized, up-to-date technologies. On the other hand, image-based AI models should—as any other AI model—be applicable to a broader patient population and in a meaningful clinical context, wherefore some sort of variability and data heterogeneity is even desired.[4]

In general, the more unstructured the data are that are processed with AI, the more pre-processing is usually required to reduce background 'noise'. On the other hand, advantages of AI, as outlined above, include their ability to potentially detect valuable associations within 'noisy' background information that usually remains concealed to humans.

Natural language processing

Many documents and data in medicine are still presented as free, unformatted texts, such as letters, reports, and alike. To analyse such information systematically, natural language analysis systems have been developed.

Natural language processing (NLP) is a novel tool to process patient information such as history, results of examinations, and management for diagnostic and prognostic purposes. For instance, it may help to better diagnose heart failure with preserved ejection fraction (HFpEF). Indeed, accurate and timely diagnosis of HFpEF is crucial for proper patient management and treatment. In a single centre, retrospective cohort study, Wu *et al.* employed NLP to analyze electronic health records (EHR) and collected demographic, clinical, echocardiographic, and outcome data from the EHR of patients with heart failure (HF). Of 3727 consecutive patients with HF and left ventricular ejection fraction (LVEF) $\geq$ 50% on echocardiography, only 8.3% had a clinician-assigned diagnosis of HFpEF, although 75% met European

Table 1 Glossary of keywords

Keywords	Abbreviation	Brief explanation
Artificial intelligence	AI	AI is the technology that enables machines, in particular computer systems, to mimic human cognitive function. It integrates tasks like learning, reasoning, problem solving, perception, and understanding language, allowing computers to derive insights from data, make informed decisions, and solve complex problems.
Convolutional neural network	CNN	CNN represents a specialized architecture tailored for analysing visual imagery, within the broader category of DNN. They utilize convolutional layers that apply filtering operations to efficiently capture spatial patterns in the data. This makes CNN exceptionally skilled at tasks like image and video recognition, improving their ability to interpret intricate visual inputs.
Deep learning	DL	DL, a specialized area within ML, utilizes multi-layered neural networks to learn from vast datasets with little need for manual feature engineering. This approach is highly effective for complex tasks, including image and speech recognition, as it allows the networks to autonomously discern and analyse various data elements.
Deep neural network	DNN	DNN is a sophisticated DL structure in computational models, primarily designed to analyse and process complex data patterns similar to the human brain. This type of network utilizes multiple layers ('deep') of processing units to learn from vast amounts of data, enhancing its ability to make accurate predictions and decisions.
Large language model	LLM	LLM are advanced DL models, such as the Generative Pre-trained Transformer (GPT), trained on extensive text data. These models excel at generating human-like text and understanding natural language, allowing them to process and produce language effectively.
Machine learning	ML	ML, a branch of AI, focuses on creating algorithms and models that train computers to analyse data and make predictions. These algorithms are not explicitly programmed for each task; instead, they enhance their performance as they process more and more data, thereby enabling autonomous learning and decision-making.
Natural language processing	NLP	NLP is a field within AI aimed at enabling machines to understand, interpret, and respond to human languages in a way that is both meaningful and useful. This technology is crucial for developing applications such as language translation, sentiment analysis, and voice-activated systems. LLM is a type of DL algorithm designed to handle multiple NLP tasks.

Society of Cardiology (ESC) criteria of HFpEF. Patients with a diagnosis of HFpEF confirmed based on NLP analysis were hospitalized more frequently and those who met the ESC criteria had higher mortality. This study demonstrates that patients with undiagnosed HFpEF are a high-risk group with elevated mortality. It is possible to use NLP to identify likely HFpEF patients as well as other conditions from EHR data who could benefit from expert clinical review and complement the use of diagnostic algorithms.[5]

Clinical features

Face recognition

The surface, structure, and expression of our face changes with mood, health, and age considerably. For any physician, the facial characteristics of a patient, the assessment of their body shape and language, their position, and gait speed allow within a blink of an eye for a first basic, but often highly useful assessment of the overall health and frailty of a given patient. Facial recognition technology, used widely in various settings like airports, has also been applied to clinical settings in the form of patient face recognition analysis.

Particularly useful is face recognition for endocrine disorders (e.g. acromegaly, Cushing's syndrome, and hyperthyroidism) and genetic abnormalities (e.g. trisomy and Turner syndrome) and neuromuscular diseases (e.g. myasthenia and stroke).[6] Moreover, face recognition has been evaluated in the emergency room and in coronary artery disease (CAD). Forte *et al.* assessed whether a neural transfer convolutional neural network (CNN) for data augmentation trained on a dataset of simulated and augmented facial photographs reflecting acutely ill patients would be able to differentiate between healthy and lipopolysaccharide-infused, acutely ill individuals. In the external validation set, the four individual feature models of different parts of the face distinguished acutely ill patients with sensitivities ranging from 10.5% for the skin model to 89.4% for the nose model. Specificity ranged from 42.1% for the nose and 94.7% for skin. The stacked model combining all four facial features achieved a C-index of .67 and distinguished acutely ill patients with a sensitivity of 100% yet a low and specificity of only 42%.[7]

Several studies have shown that it is feasible to detect CAD and predicting outcomes based on a single facial photo with reasonable accuracy.[8] The algorithm examines hair structure and density, wrinkles on the forehead, around the eyes, and the chin and derives a comprehensive analysis of the obtained information and relates it to clinical outcomes (e.g. major adverse cardiovascular events) derived from large patient populations.[9] However, in a Chinese study evaluating 5796 patients from eight sites, the C-index was still modest with .73, but higher than that of the widely used Diamond–Forrester model and the CAD consortium clinical score (*Figure 1*).[8] Thus, this approach is promising, also due to its practicality, but requires improvements in sensitivity and particular specificity to be clinically truly useful.

Speech analysis

Intuitively, we notice changes in the voice of colleagues, friends, or family when they suffer for a common cold. However, voice characteristics

Table 2 Data sources and analytical aspects

Data source	Common analytical approaches	Potential	Challenges
Imaging data	• Deep learning • Convolutional neural networks • Image enhancement algorithms	• High accuracy in image analysis • Rapid processing of visual data • Efficient pattern detection • Advanced feature extraction capabilities	• Requires extensive computational resources • Privacy issues with personal data
Voice recordings	• Deep learning	• Patient convenience • Continuous health monitoring • Early detection of cardiac disease • Real-time alerting systems	• Background noise
ECG readings	• Deep neural network • Support vector machines	• Patient convenience • Continuous health monitoring • Early detection of cardiac disease • Real-time alerting systems	• Prone to interference and noise
Text data	• Natural language processing	• Insight extraction from unstructured data • Health care efficiency	• Ambiguity and context dependence • Language and cultural variations
Tabular data (e.g. clinical characteristics)	• Tree-based learning algorithms • Neural networks	• Efficient handling of complex non-linear interactions • Efficient handling of high-dimensional data • Broad applicability	• Overfitting to training dataset

do change in a more subtle way in many other conditions, particularly with arrhythmias, CAD, and HF. Voice has many physiologic inputs that can be impacted by disease, including an exquisite innervation, arterial and venous blood supply, tissue water content, and lung-generated airflow. Indeed, the recurrent laryngeal nerve travels between the left mainstem bronchus and great vessels such that cardiac disease such as mitral stenosis or aortic aneurysms that increase left atrial size can impinge on the nerve leading to hoarseness, first described by the Viennese cardiologist Norbert Ortner in 1897 (Ortner Sign). Language-independent cepstral analysis appears to permit early disease detection. Voice-based diagnostics would be particularly important with the increasing use of telephone consultations, particularly since the COVID-19 pandemic.

In one study focusing on atrial fibrillation (AF), pronounced vowels 'Ahh' and 'Ohh' were recorded synchronously with an ECG tracing in 158 patients with AF. The developed AF algorithm was reliable as its numerical value markedly decreased and became much more homogeneous both for 'Ahh' and 'Ohh' after cardioversion when sinus rhythm was reached. The area under the receiver operating characteristic curve (AUC) was >.98 and >.89 for 'Ahh' and 'Ohh,' respectively (*Figure 2*).[10] Thus, AI/ML-based voice recognition of AF episodes holds promise, but is currently based on initial small studies and will require verification in large, independent cohorts.

Impressively, automated speech analysis technology can detect voice changes reflecting HF decompensation, thus providing clinical value for outpatient follow-up. Indeed, acute decompensation of HF affects both larynx function and respiratory rate, and thereby the quality of speech.[11] Often, so-called mel-frequency cepstral coefficient (MFCC) features, used to model the human voice, as well as glottal features and their combination are used to differentiate between acute HF speech and healthy speech. In this context, MFCC features yielded even higher classification accuracies than glottal features.

Retinal diagnostics

Although fundoscopy has traditionally been recommended in the work-up of patients with hypertension or diabetes, in clinical routine, it is rarely done as it requires time, expertise, and experience or a referral to a specialist. Artificial intelligence holds promise to facilitate this diagnostic task. Artificial intelligence and machine learning-based algorithms can identify, localize, and quantify pathological features in almost every macular and retinal disease. Recently, fully automated AI-based systems have been approved for screening of diabetic retinopathy. In a study comparing general ophthalmologists, retina specialists, and the EyeArt AI system in 521 diabetics, the algorithm correctly identified those with retinopathy with a sensitivity of 97% and specificity of 88%. Of note, the AI system showed higher sensitivity for detecting mild diabetic retinopathy than either general ophthalmologists or retina specialists compared with the clinical reference standard.[12] Similar results have been obtained in the diagnosis of hypertensive retinopathy.[13]

Furthermore, the retinal feature, Reti-cardiovascular disease (CVD) identified individuals with intermediate- and high-risk for cardiovascular disease consistent with existing risk assessment tools using 48 260 participants of the UK Biobank and 6810 from the Singapore Epidemiology of Eye Diseases study. Reti-CVD identified intermediate- and high-risk groups with a sensitivity, specificity, and positive and negative predictive value of 82.7%, 87.6%, 86.5%, and 84.0%, respectively. Thus, a retinal photograph may, if confirmed in larger cohorts, be used by ophthalmologist to identify patients requiring referral to a cardiologist for further assessment.[14]

Electrocardiogram

After the stethoscope, the ECG is the oldest cardiac examination tool used by physicians worldwide billions of times per year in patients with various health conditions. The interpretation of ECG readings belongs

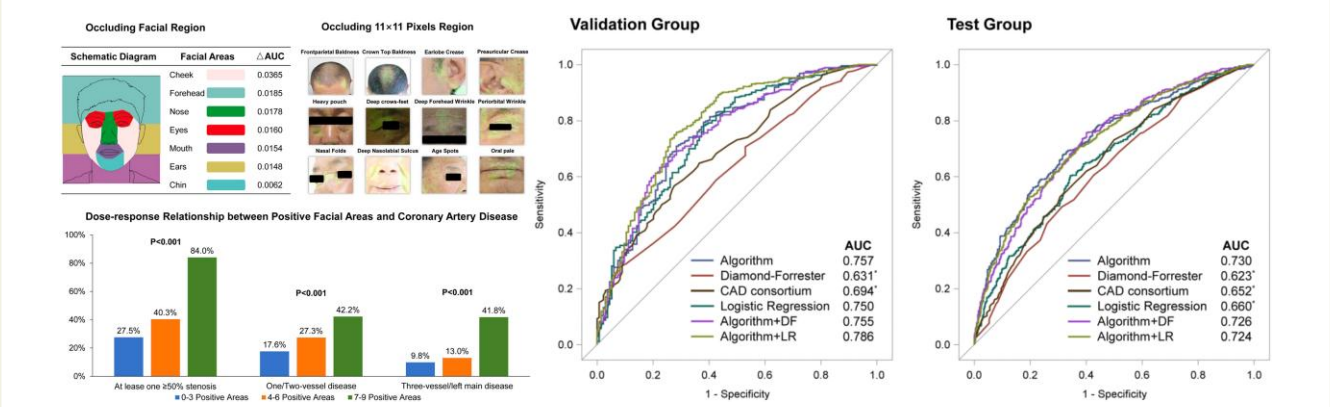

Figure 1 Predicting outcomes based on a single facial photograph is feasible with clinically helpful accuracy. CAD, coronary artery disease; DF, Diamond–Forrester; LR, logistic regression[8]

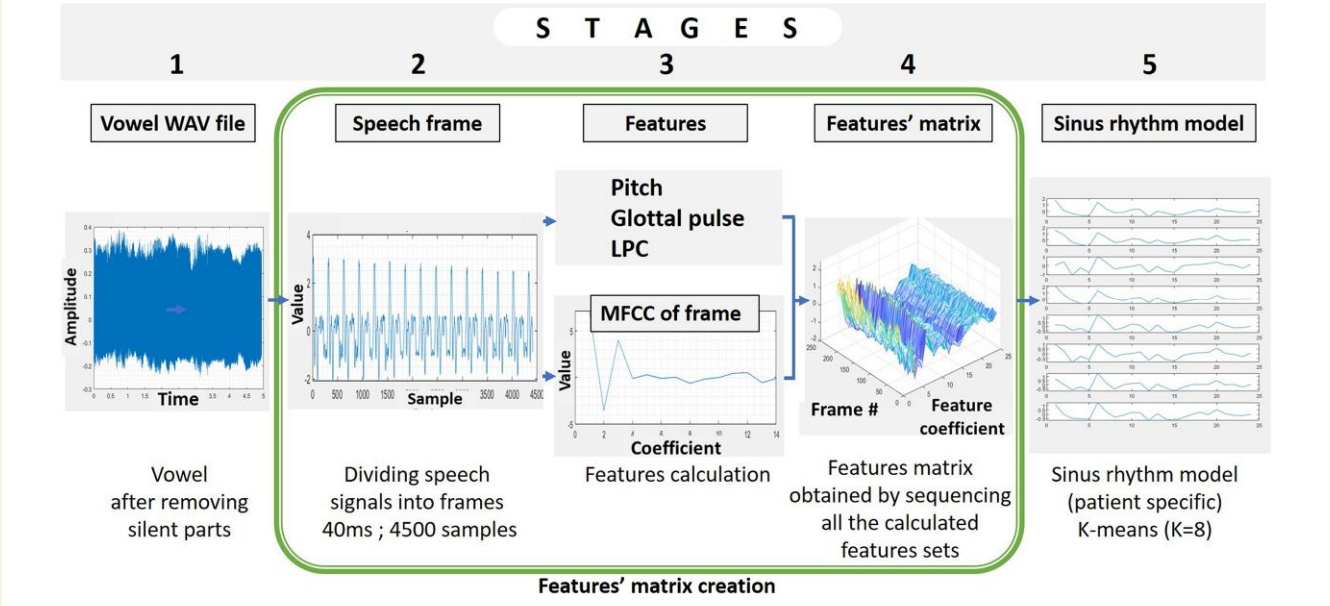

Figure 2 Creation of the AI-enhanced 'sinus rhythm model' for voice-based recognition of atrial fibrillation. The patient sinus rhythm specific model was created in five stages using recordings of sinus rhythm. LPC, linear prediction coefficient; MFCC, mel-frequency cepstral coefficient[10]

to the basic skills of physicians and cardiologists, in particular. However, the paper version of the ECG conceals a large amount of information contained in the electronic vector ECG that can be analysed further by AI/ML in large cohorts. The Mayo Clinic has pioneered this field by analysing more than 650 000 ECGs of patients with various cardiac conditions, allowing for the development of AI/ML algorithms deriving clinically useful information.[15] For example, only based on a few heartbeats, the AI/ML algorithm is able to determine whether a patient is male or female, what his or her biological age is, and whether there is evidence of left ventricular dysfunction.[16]

Electrocardiogram diagnosis of left ventricular dysfunction

Using paired 12-lead ECG and echocardiogram data, including the LVEF of 44 959 patients, they trained a CNN to identify patients with left ventricular dysfunction as defined by an LVEF ≤ 35%, using the ECG data alone. When tested on an independent set of 52 870 patients, the model yielded an AUC of .93 (*Figure 3*).[16] In those without LVEF > 35%, those with a positive AI screen were at risk of developing future left ventricular dysfunction with a hazard ratio of 4.1.

Electrocardiogram diagnosis of aortic stenosis

Artificial intelligence and machine learning-based ECG analysis was further successful in the identification of patients with aortic stenosis. Cohen-Shelly *et al.* analysed 258 607 adults with an echocardiography and an ECG. Moderate to severe aortic stenosis was present in 3.7%. Model training was performed in 129,788, validation in 25,893, and testing in 102 926 randomly selected subjects. In the test group, the

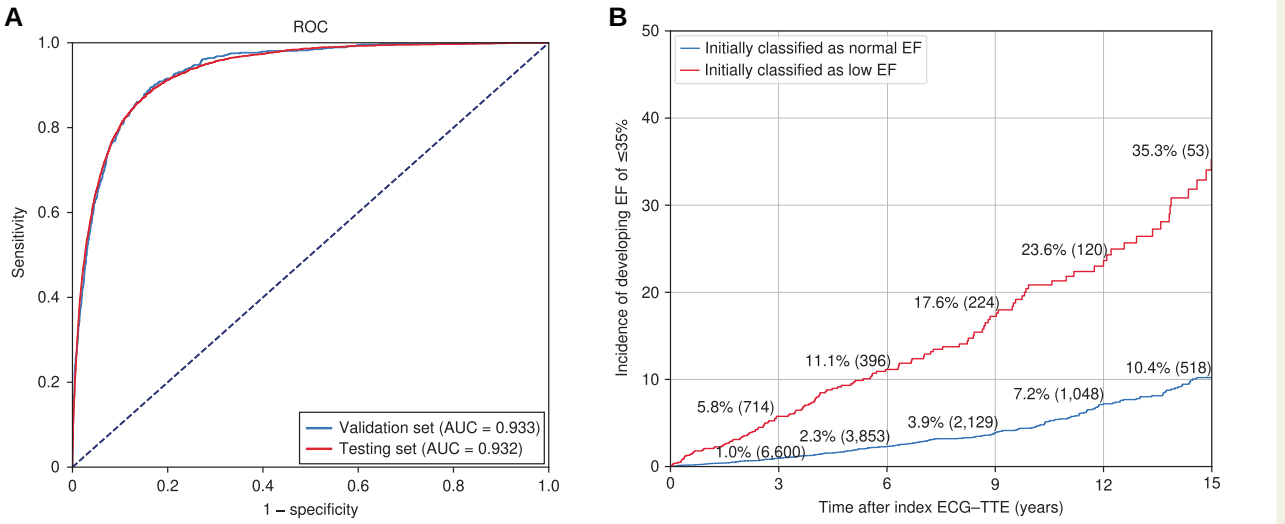

Figure 3 AI/ML-enabled diagnosis of LV dysfunction based on ECG readings. (*A*) Area under the curve (AUC) of detection of reduced LVEF in the validation and testing sets. (*B*) The long-term outcomes of patients with an echocardiographic EF of ≥50% at the time of initial classification are categorized based on the initial network classification. The vertical axis shows the cumulative incidence of developing a low EF (≤35%), and the horizontal axis represents the years since the initial ECG–TTE evaluation. Patients whose ECG was classified as abnormal by the AI algorithm had a four-fold increased risk of developing a future low EF (age- and sex-adjusted HR: 4.1, $P < .001$) compared to those with an initially normal EF who were classified as normal by the ECG network. The numbers along the cumulative incidence curves indicate the estimated cumulative incidence (with the number at risk in parentheses) for each group at the time points shown on the axis. AI, artificial intelligence; ECG, electrocardiogram; EF, ejection fraction; HR, hazard ratio; TTE, transthoracic echocardiography[16]

AI-ECG labelled 3.7% as positive with an AUC of .85. The sensitivity, specificity, and accuracy were 78%, 74%, and 74%, respectively, with the sensitivity increasing and specificity decreasing as age increased. Women exhibited lower sensitivity, but higher specificity compared to men. Performance slightly increased when age and sex were added to the model (AUC .87), particularly in patients without hypertension (AUC .90). Patients with false-positive AI-ECGs had double the risk for developing moderate or severe aortic stenosis 15 years later compared with true negative AI-ECGs with a hazard ratio of 2.18.[17] Overall, this algorithm appears promising in screening for aortic stenosis at the general practitioner level, if confirmed in a large cohort outside the original institution.

Electrocardiogram diagnosis of arrhythmias

The diagnosis of arrhythmias is primarily based on the analysis of an ECG at rest, during exercise, over several days, or in the electrophysiology lab. Under all circumstances, AI/ML is most helpful.[18] Impressively, an ECG algorithm developed by the Mayo Clinic Group is able to identify prior episodes of AF in patients who are in sinus rhythm at the time of the examination.[19] Of note in the Mayo study, over 600 000 patients with previously acquired and digitally stored ECGs were screened, allowing a subset to be remotely enrolled in the study, at a fraction of the cost of traditional enrolment. While the algorithm is in clinical use at the Mayo Clinic, widespread availability awaits approval by the Food and Drug Administration (FDA). This obviously has important clinical implications in patients presenting with stroke or transient ischaemic attacks and may guide physician to consider a non-vitamin K oral anticoagulants (NOACs) before a stroke occurs. It remains to be shown whether the algorithm is able to distinguish between atrial high-rate episodes in which NOACs are harmful[20] and subclinical AF where they reduces stroke or systemic embolism.[21]

Arrhythmia classification has been well studied. A deep neural network (DNN) to classify 12 rhythm classes using 91 232 single-lead ECGs from 53 549 patients wearing a single-lead ambulatory ECG monitoring device was used. When validated against an independent test dataset annotated by a consensus committee of board-certified practicing cardiologists, this DNN achieved an average concordance (C)-index of .97. The average F1 score, which is the harmonic mean of the positive predictive value and sensitivity, for the DNN (.837) exceeded that of general cardiologists (.780). Thus, an end-to-end deep learning (DL) approach can classify a broad range of distinct arrhythmias from a single-lead ECG with high diagnostic performance similar to that of cardiologists.[22]

Imaging

Echocardiography

Echocardiography is the diagnostic working horse of cardiology, as it is widely available, easy to apply in hospitals and surgery alike, and provides important real-time information on cardiac structure and function. However, the technique is largely operator dependent, and the quality of the images largely varies depending not only on the user's experience but also on anatomical characteristics of the patient. Developing DL approaches for automated segmentation and image interpretation is therefore challenging, and requires large, annotated training datasets. However, such algorithms are already developed and are built in many commercially available equipment including handheld versions; they transform image interpretation, allowing for faster and more accurate diagnoses. Indeed, a ML algorithm was trained on a database of over 50 000 echocardiographic studies, to automatically

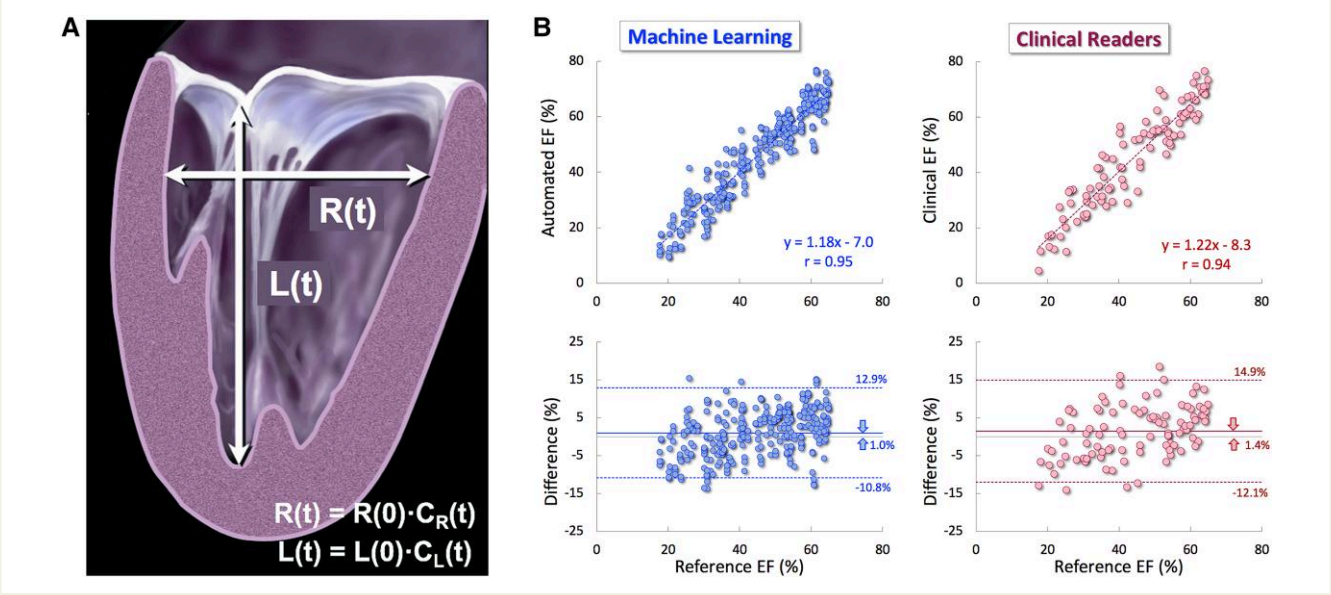

Figure 4 AI-enhanced calculation of LVEF from echocardiographic images. Schematic representation of the left ventricle showing its longitudinal and radial dimensions, L and R, which vary over time from their initial values, L(0) and R(0), according to time-dependent contraction coefficients CL(t) and CR(t). These coefficients are used to compute the ejection fraction (A). The agreement between machine learning-based automated ejection fraction (EF; B) measurements (left side of B) and clinical measurements (right side of B) is evaluated against reference values averaged from a panel of three experts. The analysis includes linear regression (top of B) and Bland–Altman plots (bottom of B). EF, ejection fraction[23]

estimate LVEF.[23] This algorithm was trained using multiple apical two- and four-chamber views and proved consistent and similar to human expert measurements with a mean deviation of 2.9% and sensitivity .90 and specificity .92 for detection of ejection fraction ≤ 35%, which is very similar to the between-human operators variability (*Figure 4*).[23]

Working in the same direction, Elwazir *et al.* have recently developed a fully automated ML workflow to label mitral inflow Doppler images, detect the envelope of the signal and extract E- and A-wave flow velocities and deceleration time. They trained CNN models on 5544 images of 140 patients for predicting 24 image classes and obtained an impressive overall accuracy of .97. E and A wave velocity analysis showed excellent correlation of .99 and .98 with operator values, respectively, while deceleration time showed lower correlation with an R value of .82.[24] Obviously, these algorithms rely on the image quality, a limitation which can be eliminated as more data derived from different hardware and clinical settings become part of the training dataset.

Furthermore, AI may not only perform automated measurements of cardiac function and structure but could also interpret findings leading to 'best clinical diagnosis'. Indeed, DL models can diagnose conditions such as aortic stenosis using two-dimensional and Doppler echocardiographic features that differ from patients with structurally normal aortic valves. In a cohort of 256 patients, AI closely matched human measurement of aortic valve peak velocity ($r = .97$), mean pressure gradient ($r = .94$), aortic valve area ($r = .88$), stroke volume index ($r = .79$), left ventricular outflow tract velocity-time integral ($r = .89$), aortic valve velocity-time integral ($r = .96$), and left ventricular outflow tract diameter ($r = .76$).[25] Although not perfect yet, AI/ML-based algorithms hold promise in automizing echocardiographic diagnostics.

Due to cardiovascular side effects of novel cancer therapies, monitoring of cardiac function is pivotal in such patients. However, they are still mainly seen in oncology services. Artificial intelligence may facilitate acquisition of optimal images and automated LVEF calculation. Using an already commercially available AI-enabled hand-held ultrasound device, 115 cancer patients were scanned by oncology staff to calculate LVEF. Correlation between DL derived LVEF and that obtained by cardiologists was excellent with small underestimation of LVEF by the DL. These findings might expedite the clinical workflow for cancer patients and accelerate a referral to cardiology services when necessary.[26]

Computed tomography

Computed tomography (CT) is a cross-sectional imaging modality with high resolution and excellent contour detection enabling 3D reconstruction of the acquired images. As the images are standing frames, CT lends itself particularly well to automated analysis with or without the help of AI/ML.

Deep learning is currently used to automatically segment cardiac and vascular structures, in a way that often exceeds the accuracy and the reproducibility of human operators. Recent examples include automated calcium scoring,[27] coronary plaque quantification,[28] or epicardial adipose tissue segmentation and quantification.[29] This is expected to drastically reduce the reporting time for clinical cardiovascular CT imaging in the coming years, allowing faster and better delivery of these clinical services worldwide.[30] This is becoming particularly relevant given that CT coronary angiography (CTCA) is now considered as a first-line investigation for chest pain,[31] a paradigm shift that brings significant pressure to the healthcare systems who are forced to expand their cardiac CT capabilities (including the installed base of CT scanners, but also expansion of local reporting expertise and service delivery manpower).[32]

Beyond automating image analysis and interpretation, ML can be used to extract from the CT scans information non-visible to the human eye. Indeed, the introduction of the fat attenuation index (FAI) score, an AI-based CT analysis that measures changes in the

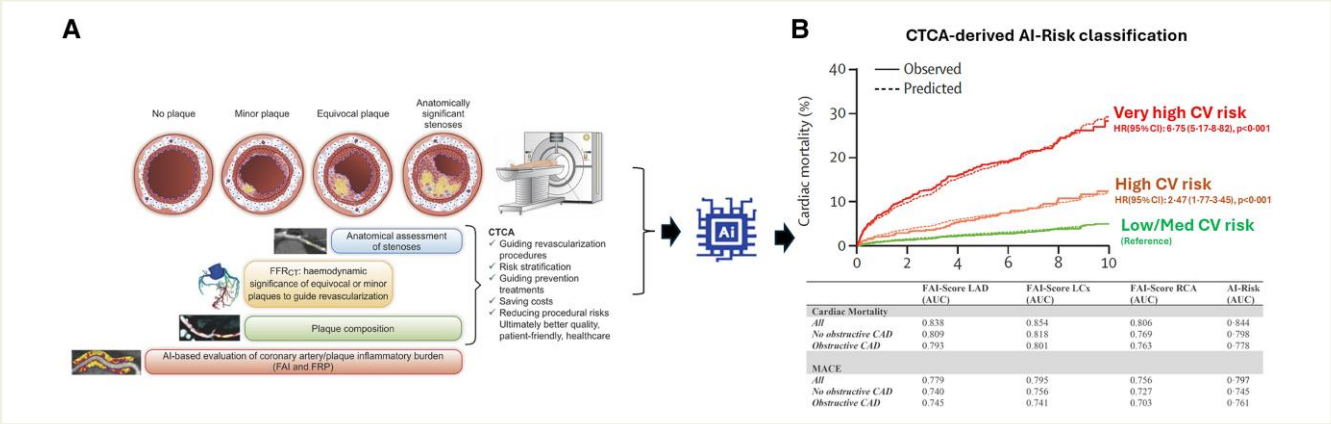

Figure 5 AI-based CTCA analysis. CTCA is increasingly becoming a 'one-stop shop' for evaluating patients with stable chest pain. (*A*) As CTCA usage grows globally, several patient categories will frequently be encountered: those with no detectable atherosclerosis, those with minor atherosclerosis, those with atherosclerosis of uncertain hemodynamic significance, and those with obstructive disease clearly visible on anatomical assessment. FFRCT will likely be most beneficial for patient management and resource optimization in the minor and ambiguous stenosis categories, where it can serve as a gatekeeper for invasive procedures. For patients with no atherosclerosis, new AI-based technologies such as the FAI score will enhance the value of CTCA by improving risk stratification, and these technologies can be applied throughout all stages of disease. (*B*) Using an AI-risk assessment model to integrate FAI score with information about atherosclerotic plaque on top of the patient's clinical risk factors can result in very high precision in predicting future cardiovascular events. AI, artificial intelligence; CTCA, computed tomography coronary angiography; FAI, fat attenuation index; FFR_{CT}, fractional flow reserve computed tomography; FRP, fat radiomic profile[35,36]

perivascular space, has provided new insights into the coronary inflammatory status of patients undergoing CTCA (*Figure 5*).[33,34] From basic science, it is known that inflamed arteries (in the presence or absence of atherosclerotic plaques) release cytokines and chemokines which are diffused in the perivascular space initiating lipolysis and stalling adipogenesis in perivascular adipose tissue, changes that can be captured by the so-called perivascular FAI (*Figure 2*).[37,38] Measurement of coronary inflammation using peri-coronary FAI score has striking prognostic value for cardiac death and major adverse cardiovascular events,[39,40] as confirmed in the recently published external validation of the technology.[35,77] Cardiovascular risk assessment using this AI-enhanced algorithm is now being used in clinical practice for risk stratification of patients undergoing CTCA, integrated into prognostic models together with information about coronary plaque and clinical risk factors.[34–36,41,42] Recent evidence suggests that guiding prevention treatments based on this AI-enhanced risk assessment strategy applied to routine CTCA triggers change of management in ~45% of the patients undergoing the test, and it is particularly useful in those with no or minimal coronary atherosclerosis.[35] The introduction of 3D texture radiomics goes beyond FAI score, enabling advanced characterization of atherosclerotic plaques[43] and the perivascular space.[38] This deep characterization helps identify inflammatory processes driving atherogenesis[44] even before visible signs of atherosclerosis appear.[38] The emerging field of radio transcriptomics, which uses RNA sequencing from tissue biopsies to train radiomic signatures, could revolutionize tissue characterization and interpretation of medical images in the future.[45] This advancement may transform CTCA from a diagnostic test for coronary stenosis into a prognostic tool for guiding personalized therapeutic strategies.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) is a highly complex imaging procedure based on signals from magnetically induced changes in the atomic structure of various tissues. In cardiology, structure and function as well as perfusion of the heart muscle, cardiac chambers, and valves can be obtained. Cardiac contrast perfusion MRI can assess not only cardiac volumes and wall thicknesses with high accuracy but also myocardial texture, coronary perfusion, and the presence or absence of myocardial ischaemia. Late gadolinium enhancement allows for precise detection and quantification of myocardial scars and, when combined with novel automated image analysis software, can also help to visualize myocardial oedema.

In the past, the quantitative analysis of MRI scans was rather cumbersome and time consuming; however, with AI/ML algorithms, cardiac volumes, and volume changes, as well as ejection fraction are now calculated within seconds, by algorithms already built in many commercially available MRI equipment, allowing for more rapid and highly standardized image analysis. Specifically, DL models enable automated segmentation of cardiac structures, limiting the need for experienced expert users for the interpretation of these scans.[46] Functional assessment of myocardial function[47] as well as automated diagnosis of conditions like myocardial fibrosis/inflammation[48] are also recent developments that change the way we report and interpret cardiac MRI in clinical practice.[46] Deep learning models allow also more advanced phenotyping of cardiac and pericardial texture and composition, and it was recently demonstrated that radiomic profiling of the myocardium[49] or even the pericardial adipose tissue may offer new opportunities for the diagnosis and risk stratification of HF.[50]

Artificial intelligence and machine learning in interventional cardiology

Artificial intelligence and machine learning may be helpful in the catheterization laboratory in (i) preparing the procedure (risk assessment,

non-invasive imaging), (ii) early treatment planning (coronary anatomy, lesion characteristics, regional ischaemia), (iii) lesion detection, characterization, and functional flow assessment during the procedure, and eventually (iv) guiding robotic procedures.

Artificial intelligence and machine learning-enhanced coronary CT already provides essential information for planning such coronary anatomy, lesion detection and characterization (calcium content, inflammation using the FAI), fractional flow reserve to define haemodynamically significant lesions. Indeed, CT may eventually substitute diagnostic invasive angiography.[51] Furthermore, integration of demographic, laboratory, and clinical parameters might provide better risk assessment before and after the procedure. During the intervention, the integration of angiographic and optical coherence tomography allows for better definition of lesion size, vessel diameter, and in turn selection of stent size and length. However, most studies so far are small commonly single centre and mostly without external and independent validation.[52] Further, algorithms providing support during percutaneous coronary intervention would need to be tested for superiority in randomized controlled trials.

Diagnostic algorithms

Diagnoses are commonly made based on visual inspection, clinical examination, laboratory values, ECG, and imaging. Artificial intelligence and machine learning has the potential to integrate these findings in a comprehensive manner and to provide probabilities for the presence of different conditions. A very important clinical decision in the emergency setting is the correct assessment of patients presenting with chest pain or dyspnoea, i.e. symptoms compatible with acute coronary syndromes (ACS), acute HF, pulmonary embolism, lung infections, or other medical conditions.

Acute coronary syndromes

Clinical practice guidelines recommend defined cardiac troponin thresholds for the diagnosis of ACS; however, plasma concentrations of this myocardial necrosis marker are markedly dependent on age, sex, comorbidities, and time of symptom onset to presentation. Machine learning has the potential to integrate cardiac troponin plasma concentrations at presentation or upon serial testing with clinical features. The Collaboration for the Diagnosis and Evaluation of Acute Coronary Syndrome (CoDE-ACS) score was developed to provide a patient's probability of ACS. Doudesis *et al.* trained data from 10 038 female and male patients, and externally validated their algorithm on data obtained from 10 286 patients of seven cohorts. CoDE-ACS had excellent discrimination for ACS with a C-index of .953 also across subgroups and improved prediction of ACS above fixed cardiac troponin thresholds with a similar negative predictive value. Of note, at 30 days, patients with low predicted probability of ACS had a lower rate of cardiac death than those with intermediate or high probability. Thus, ML-based decision tools may reduce hospital admissions of patients with chest pain and a clinical suspicion of ACS to the benefit of patients and healthcare providers.[53]

Diagnosis of chronic conditions

Artificial intelligence-clinical decision support systems (AI-CDSS) have the potential to assist physicians in diagnosing for instance HF. In a retrospective cohort of 1198 patients with and without HF, Choi *et al.*[54] tested their AI-CDSS algorithm in a prospective clinical pilot study of 97 patients with dyspnoea, then in a training dataset of another 600 HF patients and a validation set of 598 HF patients and compared its diagnostic accuracy with that of physicians not specialized in HF. In the test dataset, concordance was 98.3%. The concordance in HF with reduced ejection fraction, with mid-range ejection fraction, with HFpEF, or absence of HF was 100%, 100%, 99.6%, and 91.7%, respectively. Thus, AI-CDSS may be useful for the diagnosis of HF, especially in general practice where HF specialists are not available.

Artificial intelligence-based outcome prediction

Despite numerous studies on AI-based outcome prediction tools in cardiovascular medicine, conventional risk models remain the 'gold standard'. However, ML models offer significant advantages, including the ability to analyse vast amounts of medical data, uncover hidden patterns, and generate prediction tools applicable across diverse patient populations. Additionally, AI excels in analysing imaging data with high accuracy.

In classical statistics, regression models are commonly used for clinical outcome prediction. However, they often rely on specific assumptions such as linear and time-independent relationships,[55] necessitating hypothesis testing before reliable application.[56] Artificial intelligence surpasses traditional statistical models by overcoming limitations related to non-linear and time-dependent influences on outcomes, particularly relevant in cardiovascular disease prediction.[55]

Types of outcomes analysed

Outcome prediction in cardiovascular research can be based on dichotomous measures (e.g. event occurring yes/no) or time-to-event data. Conventional regression modelling selects variables based on their association with the outcome, clinical/scientific rationale, availability, utility, and epidemiological considerations.[55] Multivariable logistic or Cox regression models provide clinicians with interpretable relative effect estimates, such as odds ratios and hazard ratios, enabling the calculation of relative event risks. However, conventional regression modelling may overlook certain factors and risk model overfitting, especially for rare events.[55] In contrast, AI-based prediction models offer a data-driven approach considering variable interactions, changing impacts over time, and non-linear effects.

Outcome prediction in cardiovascular disease benefits from AI-based analysis of large-scale datasets. Increasing availability of large dataset from clinical trials or nationwide registries including predictor variables (e.g. socio-economic features, comorbidities, and treatment) and clinical outcomes (e.g. mortality and major adverse cardiovascular events) paves the way to the application of AI-based prediction models in cardiovascular medicine.

Prediction of in-hospital outcomes

Due to the still considerable mortality of patients with different forms of ACS, in particular in those at risk or presenting with cardiogenic shock due to ACS,[57] HF, valvular heart disease, or Takotsubo syndrome (TTS), risk assessment is of utmost importance for personalized management. The Global Registry of Acute Coronary Events (GRACE) 2.0 score was developed for risk assessment in patients with ACS and validated predominantly in male patient populations. Wenzl *et al.* assessed its sex-specific performance and developed an improved GRACE 3.0 score using ML in 420 781 consecutive patients with non-ST-elevation ACS (NSTE-ACS) in contemporary nationwide cohorts from the UK and Switzerland.[58–60] Machine learning models for

predicting in-hospital mortality were informed by the GRACE variables and developed in sex-disaggregated data from 386 591 patients from England, Wales, and Northern Ireland split into a training and a validation cohort. External validation of the GRACE 3.0 score was performed in 20 727 patients from Switzerland.

While discrimination of in-hospital death by the GRACE 2.0 score was good in male patients with an AUC of .86, it was notably lower in females with a value of .82. In addition, underestimation of in-hospital mortality risk by GRACE 2.0 in females favoured their incorrect stratification to the low-to-intermediate risk group for which the score did not recommend an early invasive treamtent strategy. Accounting for sex differences in the NSTE-ACS phenotype, GRACE 3.0 showed superior discrimination and good calibration with an AUC of .91 in males and .87 in females with NSTE-ACS in an external validation cohort. GRACE 3.0 led to a significant reclassification of female patients to the high-risk group with important clinical implications (*Figure 6*).[58,60] The GRACE 3.0 score is among the first CV aritificial intelligence tools endorsed by international guidelines.[61,62]

Takotsubo syndrome is an acute cardiac condition, primarily affecting postmenopausal women and is associated with a substantial rate of major adverse cardiac events.[63] De Filippo *et al.* developed a ML-based model to predict the risk of in-hospital death in TTS patients with different risk profiles. They developed a ridge regression-based ML model to predict in-hospital death in a cohort of 3482 TTS patients randomly split in a training and a validation cohort. Further, they evaluated their algorithm in an external validation cohort of 1037 TTS patients. Ten of 31 clinical variables were most relevant and in-hospital mortality was 5.2%. Their model provided an impressive C-index of .89 for in-hospital mortality with a sensitivity of .85 and a specificity of .76 in the internal validation and a C-index of .82 with a sensitivity of .74 and a specificity of .79 in the external cohort.[64] This information will be particularly relevant for the design of future randomized trials on treatment strategies in TTS which so far is mainly managed based on clinical experience.

Prediction of long-term outcomes

The prediction of outcomes after hospital discharge is of utmost importance in guiding management strategies, particularly in secondary prevention. Of note, many established risk models, which rely on conventional statistics fail to account for non-linear and potentially high-dimensional relationships of patient features and provide limited predictive performance. Thus, there is a significant unmet medical need to improve risk prediction. Leveraging a broad range of parameters, including clinical examination data, facial features, ECG readings, biomarkers, laboratory results, and imaging findings, rather than relying solely on basic demographics and a few cardiovascular risk factors, holds significant promise for advancing future risk models.[57,65,66] Similar to the GRACE 3.0 score,[58] the Prediction of Adverse Events Following an Acute Coronary Syndrome (PRAISE) risk models developed in the PRAISE registry predict events following hospital discharge after an ACS with reasonable accuracy.[67] In particular, the prediction based on ML was accurate regarding bleedings, which is particular in line with the conceptual model of AI. Indeed, bleeding events after ACS depend on clinical features often not recorded by datasets conceived by cardiologists (like prior gastrointestinal haemorrhages) but which may be captured by non-linear relationship appraised by supervised or not-supervised algorithm. The integration of much more patient data, considering the context and the information available, may enhance future risk models. Integrating AI/ML with clinical decision-making can transform care, making clinical practice more efficient, faster, personalized, and effective as it has the potential to explore large amounts of information automatically and systematically.[68]

Artificial intelligence-assisted clinical decision-making

Google recently developed a large language model (LLM) powered by AI for conducting medical interviews.[69] Like humans in evolution, advanced AI/ML models developed to understand and produce speech to directly interact with patients. In a study comparing its performance with human doctors, 20 actors simulated patient scenarios for 149 clinical cases. The AI, known *as* Articulate Medical Intelligence Explorer (AMIE), matched or exceeded the diagnostic accuracy of board-certified clinicians in all scenarios across six medical specialties. While this study does not involve real patients and requires cautious interpretation, it underscores the potential of AI-based systems for diagnosing using LLMs.[70] With a vast database of patient histories, such systems could potentially streamline the diagnostic process by screening patients before doctor visits. However, they do require randomized controlled trials proving superiority as compared to physicians or at least in terms of the time spent to reach a diagnosis in a real-world setting.

Challenges in the development, validation, and implementation of artificial intelligence and machine learning

Artificial intelligence and machine learning algorithms must comply with the highest quality standards as they are increasingly used for the clinical management of patients. Such standards are related to (i) clear intended use, (ii) data quality, (iii) adequate sample size, (iv) representativeness for patient population (e.g. males and females, different ethnicities, and age groups), (v) appropriate external validation of developed algorithms, (vi) openness of data and software, and (vii) ongoing adaptations as patient phenotypes and diagnoses change over time.[71] Data must be as complete, solid, and representative of the disease and patient spectrum focusing as possible. In general, the bigger the cohort (e.g. >10 000–100 000 and beyond), the more reliable the trained modes get provided the data quality is appropriate. Furthermore, validation in a completely independent large cohort, ideally from another institution or even different country is essential before clinical use. Finally, changes in the patient phenotypes over time such as changing age, (pre-)treatments should be considered as the algorithm be open for further testing once in use.[72] Compliance with such standards is essential as almost two-thirds of published AI-based prediction tools in cardiovascular medicine lack these quality features or are not validated at all.[73] As imprecise risk models may cause harm to patients, only properly validated ones should be integrated into clinical practice.[74] Finally, evaluation of quality of evidence should also be applied to AI models, although it is not still be largely achieved. Recently, a systematic review demonstrated that only few randomized controlled trials are published in this field, while observational studies, as those not applying ML models, are prone to a relevant risk of bias.[75]

Authorities around the globe do require registration of AI/ML tools whether as standalone or embedded into a medical device prior to medical use. For instance, the EU Artificial Intelligence Act that will come into force later in 2024 considers AI/ML a device that has to undergo a conformity assessment procedure prior to be approved through notified

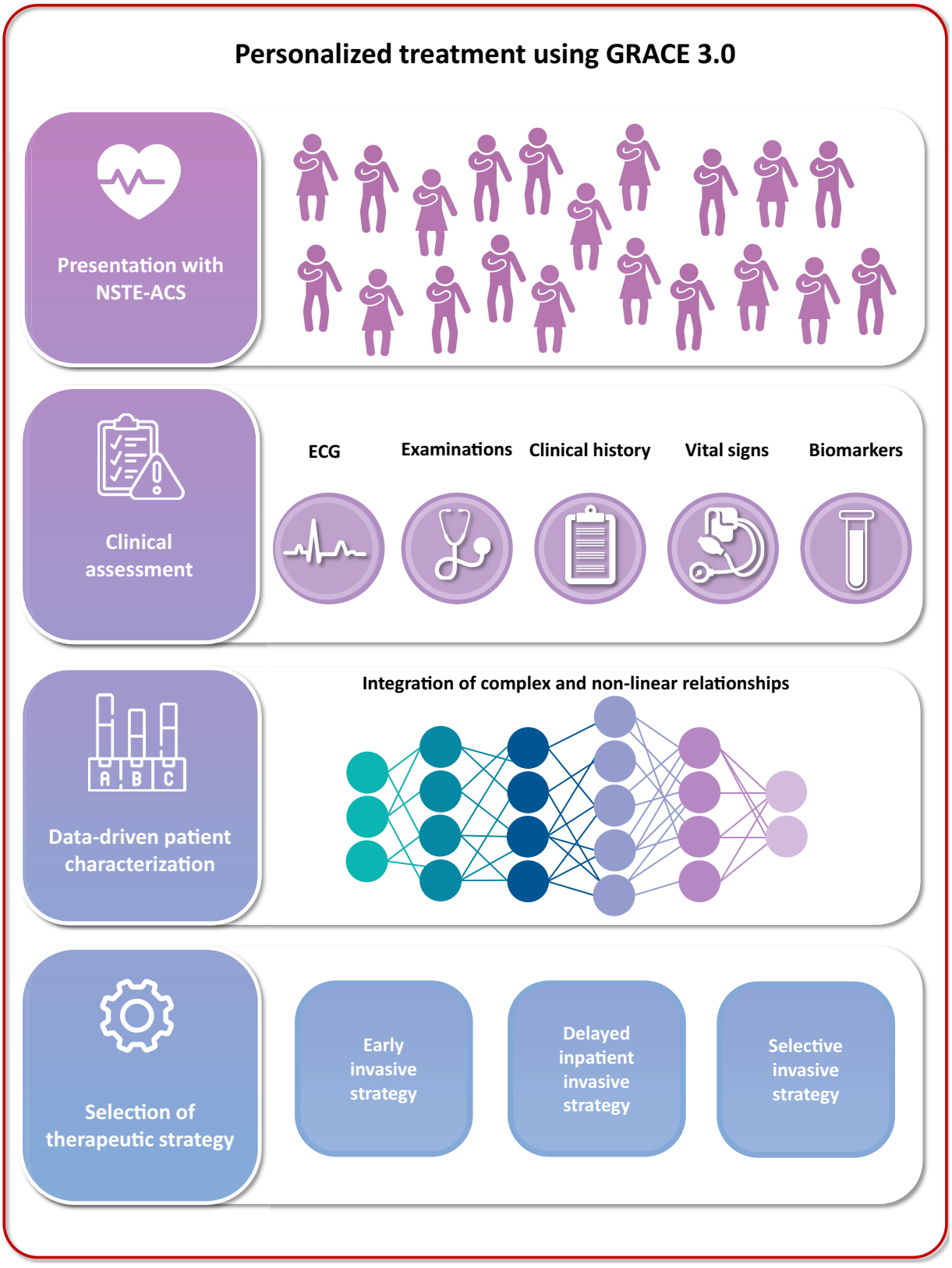

Figure 6 Machine learning-based risk assessment for personalized care of patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) using the Global Registry of Acute Coronary Events (GRACE) 3.0 score available under https://www.grace-3.com.[58–60] Based on clinical, electrocardiographic and laboratory parameters GRACE 3.0 considers complex non-linear relationships and sex differences for highly accurate risk prediction and early treatment stratification.

bodies. The draft EU Regulation on AI proposes rules applicable across industry sectors, while for devices the Medical Device Regulation also applies. In the Coordinating Research and Evidence for Medical Devices (CORE-MD) project, definitions and initiatives made by professional consensus groups, regulators, and standardization bodies are currently reviewed. The level of clinical evidence required should be determined according to each application, its risks category (i.e. minimal, limited, high, and unacceptable).[76] However, the requirements for approval are still in development as are definitions for legal and methodological factors that contribute to risk, including accountability, transparency, and interpretability. To date EU guidance has not yet specified the clinical evidence required for medical AI software. The FDA has approved over 700 AI/ML-enabled medical devices, primarily for use in image analysis.[77]

Finally, there are legal issues related to the use of AI/ML in medicine. Who is responsible in case of medical malpractice? The provider or the physician using it? Although jurisdiction is still unclear in this field, it will become an important issue as AI/ML is increasingly implemented into clinical practice.

The future of medicine in the age of artificial intelligence and machine learning

It is very likely that AI/ML will massively change the practice of medicine. First, it will make medicine more precise and faster. Indeed, as outlined above, AI/ML algorithms provide information not accessible for the clinician, particularly in imaging and ECG analysis ('see what you can't see'). This way, risk prediction is more precise as documented by the AI/ML-enabled GRACE 3.0 score, among others. And thirdly, AI/ML-enabled information is much faster. As a consequence, physicians will have better information and more time to discuss management options with their patients. Indeed, AI/ML-provided information on diagnostics and guideline-based therapeutic options are provided comprehensively and timely. Lastly, in contrast to humans, AI/ML cannot yet provide the same degree of empathy, personal interaction, and trust as good physicians.

Will we need less physicians for our health services? It is very likely that the required number of physicians involved in imaging analysis (e.g. radiologists, histopathologists, dermatologists, and alike) will be much lower. Routine monitoring of patients with chronic conditions will be more and more delegated to advanced nurse practitioners supported by AI/ML algorithms and supervised by physicians. Given the global shortage of physicians due to shorter working hours and increasing part-time commitments, this will help to maintain quality of care. On the other hand, manual activities such as catheter interventions and surgery will for a long time be supported, but not substitutable by AI/ML-enabled robotics. Finally, physicians with specialization in Digital Health, AI/ML, and Data Science will be more and more required providing new professional options for the next generation.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

T.F.L. has no conflicts of interest related to this manuscript, but has received educational and research grants from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Daichi-Sankyo, Novartis, Novo Nordisk, Sanofi, and Vifor and transfers all honoraria from pharmaceutical industry activities to a charity. F.A.W. does not report any conflicts of interest related to the present work but but reports support from the Fonds zur Förderung des akademischen Nachwuchses of the University of Zurich, Research Funding for excellent research by the University of Zurich, the Theodor und Ida Herzog-Egli Foundation, the Kurt und Senta Herrmann Foundation, the Foundation for Cardiovascular Research – Zurich Heart House, the European Society of Cardiology, the Swiss Society of Cardiology, the Swiss Heart Foundation, the Medical University of Graz, Amgen Switzerland, Roche Diagnostics, the Critical Care Clinical Trialists Consortium, the Sphingotec GmbH, the 4TEEN4 Pharmaceuticals GmbH, and the PAM Theragnostics GmbH., and IT-related positions outside this work. F.D. reports no conflicts of interest related to this work. P.A.F. has developed AI algorithms which have been licensed to Anumana, Ekohealth, and AliveCor via his employer, Mayo Clinic. C.A. declares several patents (US10,695,023B2, PCT/GB2017/053262, GB2018/1818049.7, GR20180100490, GR20180100510) licensed to Caristo Diagnostics. C.A. is the immediate past Chair of the British Atherosclerosis Society, as well as Founder, shareholder, and director of Caristo Diagnostics, a University of Oxford Spinout company. C.A. declares past honoraria from Amarin, Silence Therapeutics, and Caristo Diagnostics. C.A. declares funding from the British Heart Foundation (CH/F/21/90009 and RG/F/21/110040), and the British National Institute of Health Research Oxford Biomedical Research Centre (BRC).

Data Availability

No data were generated or analysed for this manuscript.

Funding

All authors declare no funding for this contribution.

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