ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2021: digital health and innovation

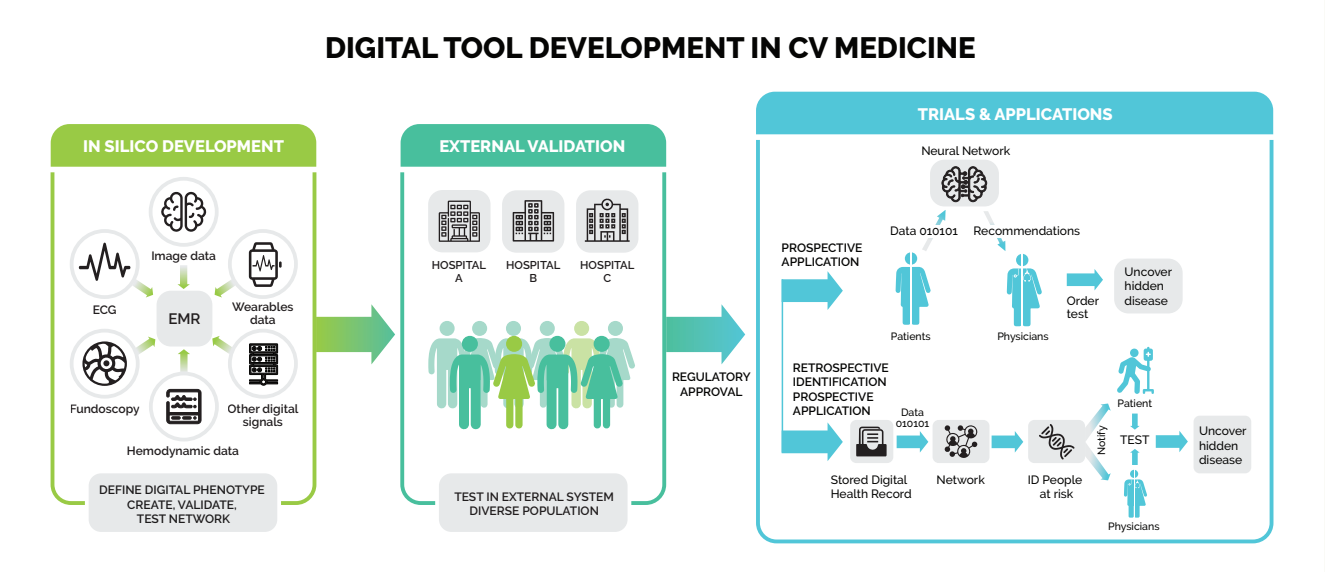
Panos E. Vardas[1,2*], Folkert W. Asselbergs[3,4], Maarten van Smeden[5], and Paul Friedman[6]

[1] *Heart Sector, Hygeia Hospitals Group, HHG, 5, Erithrou Stavrou, Marousi, Athens 15123, Greece*
[2] *European Heart Agency, ESC, Brussels, Belgium*
[3] *Department of Cardiology, Division of Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands*
[4] *Health Data Research UK and Institute of Health Informatics, University College London, London, UK*
[5] *Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands*
[6] *Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA*

Received Date: 13 October 2021; Revision received Date: 15 November 2021; Accepted Date: 23 November 2021

Reproduced from: Vardas PE, Asselbergs FW, van Smeden M, Friedman P. The year in cardiovascular medicine 2021: digital health and innovation. Eur Heart J 2022;43:271–279. https://doi.org/10.1093/eurheartj/ehab874, by permission of Oxford University Press on behalf of the European Society of Cardiology

*Corresponding author. Tel: +30 210 6867691/+30 210 686 7937, Fax: +30 210 6869926, E-mail: pvardas@hygeia.gr



Graphical Abstract Digital tool development in cardiovascular medicine

Abstract

This article presents some of the most important developments in the field of digital medicine that have appeared over the last 12 months and are related to cardiovascular medicine. The article consists of three main sections, as follows: (i) artificial intelligence-enabled cardiovascular diagnostic tools, techniques, and methodologies, (ii) big data and prognostic models for cardiovascular risk protection, and (iii) wearable devices in cardiovascular risk assessment, cardiovascular disease prevention, diagnosis, and management. To conclude the article, the authors present a brief further prospective on this new domain, highlighting existing gaps that are specifically related to artificial intelligence technologies, such as explainability, cost-effectiveness, and, of course, the importance of proper regulatory oversight for each clinical implementation.

Keywords: AI-ECG; AI-wearables; Digital health; Cardiovascular medicine; Big data; Machine learning

Introduction

Digital health, a broad-spectrum concept that has received a significant boost as a result of the COVID-19 pandemic, is growing exponentially, flexing its muscles with scientific breakthroughs and associated publications, while also driving trends and developments in industry.

For cardiovascular medicine in particular, during the last year, an impressive number of authoritative new publications have confirmed previous research findings and proposed new innovative ideas and practices related to the diagnostic and therapeutic management of cardiovascular diseases, with the promise of ground-breaking developments during the coming years, for both cardiovascular sciences and care.

In the year 2021, as in the years immediately preceding, the field of digital health has been flooded with publications referring to the diverse applications of artificial intelligence (AI), from supervised to unsupervised learning, focusing mainly on the diagnostic capabilities of this impressive new technology.

Furthermore, the role of machine learning algorithms in the development of clinical prognostic models for risk assessment and early warning systems represents a rapidly evolving field that may be expected to have a catalytic effect by improving the prediction of medium- and long-term clinical outcomes.

Indeed, the prospects seem to be excellent.

Nonetheless, some questions still remain. Apart from the *in silico* design and development, the explainability of the machine learning algorithms and their validation methodology need to be more solidly confirmed in well-designed longitudinal studies, as well as in clinical practice before these algorithms find their way into the guidelines.

Beyond the field of AI—though often closely connected with it—developments in wearable devices have commandeered a significant part of the recent scientific literature, highlighting emerging new possibilities for the fuller monitoring and treatment of cardiovascular diseases and their related risk factors.

The technological developments in wearables—especially as they expand to cover not only the needs of fitness but also those of diagnosis and monitoring of cardiovascular diseases—will obviously require more substantial regulation to ensure device reliability, backed by well-organized studies that will highlight their cost-effectiveness so

that insurance companies may be persuaded they should be reimbursable.

Artificial intelligence-enabled cardiovascular diagnostic tools, techniques, and methodologies

A new era in electrocardiogram analysis

The application of AI to the electrocardiogram (ECG) has seen significant advances recently and has developed in the following two broad categories: (i) tools to automate ECG interpretation, extending human capabilities via massive scalability, important as mobile form factors permit signal acquisition and (ii) algorithms to identify conditions not visible to human readers by training networks to identify multiple, complex, non-linear patterns in the ECG signal to find occult disease (confirmed using other tests such as imaging), or impending disease. In contrast to automation tools in which a human overread provides a gold standard, algorithms identifying occult or future conditions require additional patient information.

Several groups have used large, labelled data sets to train neural networks to accurately apply diagnostic codes to single-lead and multiple-lead ECGs. Hannun *et al*.[1] used 91 232 single-lead ECGs from a wearable patch to train a network to provide 12 rhythm classes and found that the network outperformed the average cardiologist's read. Subsequently, two mega trials using smart watches based on photoplethysmography technology enrolled 419 297 and 246 541 patients to screen for atrial fibrillation (AF) in under 9 months.[2,3]

These trials confirmed the ability to massively enrol subjects and acquire data, at the cost of high rates of early dropout and a low yield of disease (<0.5% in both studies), and with limited clinical characterization of the study subjects. Ongoing trials will assess these tools in the context of patients selected for arrhythmia risk. Finally, there have been recent reports of interesting research that aimed to develop and validate an AI-enabled ECG algorithm capable of comprehensive 12-lead ECG analysis comparable to that of practising cardiologists.[4]

Furthermore, the AI-ECG has identified occult and manifest cardiac conditions, including ventricular dysfunction,[5] peripartum cardiomyopathy,[6] amyloid heart disease,[7] and pulmonary hypertension,[8] as well as non-cardiac conditions such as hyperkalaemia and cirrhosis.[9,10] In addition, special algorithms have been used for the early diagnosis of valvular diseases such as asymptomatic or oligosymptomatic severe aortic stenosis and mitral regurgitation,[11–13] left ventricular hypertrophy,[14,15] myocardial infarction,[16,17] and a number of other conditions. Common findings in these studies include a strong clinical performance [area under the curve (AUC) often >0.90] and detection of disease months to years ahead of the clinical diagnosis.

The significance of these findings remains to be evaluated, taking into account the scalability of electrocardiography, and hence the contribution of AI to its further and more substantial utilization.

The ECG is an ever-present diagnostic tool that has served medical practitioners for more than a century. With the support of deep learning AI techniques, it is clearly entering a new era, in which it may prove to be a powerful detector of subclinical and clinical cardiac diseases, going beyond the boundaries of human observation. There can be no doubt that when the previous capabilities of the ECG are combined with the evolving features of wearable devices such as smartphones, the chances of a much broader and pluralistic diagnostic process will increase rapidly.

Artificial intelligence-electrocardiogram and clinical trials

Clinical trials are essential to demonstrate the ability of novel digital tools like the AI-ECG to improve human health. Factors to consider in evaluating the quality of AI-ECG studies are listed in *Table 1*. A framework for the assessment of how well AI-ECG clinical trials can predict meaningful outcomes, based on whether the trials are single-centre or multicentre, prospective or retrospective, is shown in *Table 2*. It is likely that Level 3 or higher would be required for regulatory approval, allowing for variation in specific tests and regional differences. There is a pressing need for additional clinical trials to assess

Table 1 Factors to consider in evaluating artificial intelligence-electrocardiogram studies

1. Data label accuracy: robustness of data labels used for training and testing
   a. Proxy labels (EMR report of 'chest pain') vs. gold standard labels (physician-described angina, troponin levels, serial ECGs)
   b. Number of subjects for whom labels available
   c. Absence in labels of false distractors (e.g. all ECGs from patients with condition taken at one hospital, using an acquisition system different than that used in controls, so that network may identify differences in ECG machines rather than disease)
2. Risk of bias: cohort creation and controls
   a. Controls not identical to cases in all conditions except the desired AI differentiator, most commonly in demographics (example: using adult controls for paediatric ECGs with WPW to train a network)
   b. Controls and cases taken from public data sets (difficult to know details regarding the absence/presence of conditions, poor phenotyping)
   c. Use of only subsets of larger data sets, introducing potential bias—need for racial, ethnic, and geographic diversity in data sets (example: initial face recognition AI, trained using only Caucasians, mislabelled African Americans as primates).
   d. Inappropriate exclusion of data at the patient or signal feature level will bias results (examples: exclusion of signals on the basis of artefact of those same exclusions will not be used in real-world implementation; or exclusion of patients with hypertension when creating an AI-ECG screen for hypertension)
   e. Temporal shifts—training using data acquired in the remote past and application to recent data sets
   f. Commercial interest and backgrounds of engineers creating AI tools (potential bias)
3. Overfitting/lack of generalizability
   a. Overly complex AI-ECG network with a small number of samples (the results are not generalizable to other populations)
   b. Most data sets for AI-ECG training number in the tens of thousands or more, although exceptions exist

Table 2 Proposed categories of clinical trials to assess the artificial intelligence-electrocardiogram

Study category	Description of population used to test an AI-ECG network	Study design	Strengths	Limitations
1	Public data set	Retrospective	Inexpensive, rapid	Unreliable phenotyping, high risk of bias, limited clinical utility
2	Single centre: same hospital/clinic used to acquire data, but different patients	Retrospective	Rich data sets to phenotype patients, rapid, relatively inexpensive, robust proof-of-concept approach	Risk of bias, under-representing important populations
3	Multicentre: different hospital systems used to test AI, than one used to create	Retrospective	Lower risk of bias, potential for greater diversity among subjects, test types, potential to rapidly and meaningfully assess tests	Need to confirm labels assessed in systematic, similar manner across sites (example: assessment of EF by echo)
4	Single centre: same hospital used to test AI, different patients	Prospective	Assesses AI, impact on workflow, adoption by clinicians, clinical impact	Greater technical infrastructure required, more expensive, greater time requirement
5	Multicentre	Prospective (may use retrospective ECGs to prospectively enrol patients)	Prospective trial but with accelerated enrolment, by screening large data set of stored ECGs; potential for portal/email study invitations and pragmatic design, statistical robust, potential to minimize bias	Greater technical requirements, time, expense

AI-ECG tools. A search of clinicaltrials.gov on 8 October 2021, for trials utilizing the terms 'artificial intelligence' and 'ECG' returned 27 studies, with only 5 completed.

The first AI-ECG prospective trial published, the Eagle study,[18] demonstrated how digital, pragmatic trials can effectively and rapidly enrol subjects, and how the AI-ECG can positively impact clinical practice. It randomized 120 primary care teams from 45 clinics or hospitals in Minnesota and Wisconsin to an intervention arm (clinicians have access to AI-ECG results screening for left ventricular dysfunction when routinely ordering a clinical ECG) or a control arm (no AI results). Despite the development of the pandemic, >22 000 patients were enrolled in 8 months, and the AI-ECG increased the diagnosis in the overall cohort [odds ratio (OR) 1.32, $P=0.007$]. The test performance (AUC = 0.92) matched that of the initial retrospective cohort (0.93).[19] Interestingly, the overall utilization of echocardiography was similar in both groups but in the intervention group, more echocardiograms were ordered for patients with a positive AI-ECG (38.1% control vs. 49.6% intervention, $P<0.001$), suggesting that the AI-ECG did not lead to more echocardiograms, but to better selection of patients to undergo imaging.

Cardiovascular imaging

Imaging has been the frontrunner in the application of AI in healthcare, because of the repetitive nature of imaging processing and evaluation. Artificial intelligence may improve imaging quality—and thereby scan and dose time—and assist in segmentation, processing, and analysis.[20] Furthermore, most data are retrieved from a single standardized data source, making it more accessible for large-scale analyses. During the pandemic, critics were pointing out that, despite massive efforts, AI had no impact on the care of COVID-19 patients, while simple straightforward randomized controlled trials did save lives.[21] However, this clearly shows only one side of the coin. The pandemic led to a greater burden on radiology resources, as computerized tomography (CT) scans were carried out routinely in all patients. Artificial intelligence is key in all parts of the imaging pipeline, including acquisition, processing, and analyses.[22,23] Furthermore, a plethora of papers have been published during the pandemic, showing the prognostic value of calcium score measurements in COVID-19 chest CT scans.

Those measurements can be automated using deep learning,[24] providing clinicians with information, not only about the pulmonary status of COVID-19 patients, but also their cardiovascular risks.[25] Artificial intelligence will enable automated analyses of routine chest CT examinations for opportunistic cardiovascular screening, allowing early preventive treatment. All these developments, together with the notable Food and Drug Administration clearance of a new technology to identify strokes on brain CT scans enabled by AI, hold out the prospect of a bright future in medical diagnostics.[26,27]

Retinal photography to detect cardiovascular disease

Another imaging application that can determine risk across a wide range of diseases is retinal photography. Retinal photography is a non-invasive imaging modality that aides in the diagnosis and treatment of major eye diseases, but can also provide information on the human vasculature jand therefore cardiovascular disease. Prior manually coded studies have shown that retinal vascular abnormalities are predictive for cardiovascular disease.[28] Deep learning can extend this knowledge through the automation and detection of more subtle signs that are not clearly visible to the human eye. Several large-

-scale studies have been published recently, focusing on the predictive value of features extracted from retinal photographs. Studies have shown that deep learning algorithms can predict levels of biomarkers such as haemoglobin to detect anaemia,[29] as well as age, sex, body composition, and creatinine levels,[30] although external validation is warranted before this can be widely adopted in population screening. Another interesting study investigated the predictive capability of deep-learning--enabled coronary artery calcium (CAC) scores derived from retinal scan data.[31] Computerized tomography scans and retinal measurements were performed on the same day and the score derived from retinal images showed an AUC of 0.74 for predicting CAC > 0. Although higher than other single risk factors, such as age, sex, and cholesterol, the added predictive value in the multivariable clinical model was limited (AUC from 0.782 to 0.784). However, the CAC score derived from retinal scans showed a similar performance in predicting cardiovascular outcomes to CAC measured by CT scan (both AUC 0.71). Furthermore, the authors showed in the UK Biobank that this retinal-based CAC score could improve risk stratification in those with borderline or intermediate risk.

However, this method has certain disadvantages. Home-based tests are not yet available, and images with poor quality were excluded in the reported analyses, which is likely to limit the external validity. Real-world data are necessary to estimate the added value in population screening, and the development of mobile applications for self-tests is needed[32] before implementation on a large scale. These deep learning applications are, however, already useful in those who already undergo regular retinal scans, such as diabetic patients, to screen for retinopathy.[33]

To end this section, at least a brief mention should be made of the diagnostic capability and cost-effectiveness of the combined imaging approach, where the use of AI and magnetic resonance imaging yields the atheroma index of the coronary arteries or peripheral vessels as a by-product of the primary diagnostic evaluation of other organs.[34]

Automation of imaging processing

While the application of AI in cardiovascular imaging for clinical decision-making is still in its infancy, the use of AI to automate imaging processing in other fields, such as ophthalmology as discussed above, oncology, and dermatology, has already matured. However, several promising studies using different imaging modalities have recently been published and have shown that cardiology is able to catch up with the other disease domains. A large international collaborative study showed that the coefficient of variation in measuring left ventricular wall thickness by cardiovascular magnetic resonance was significantly lower for machine learning in comparison to human experts.[35] This study involved a cohort of patients with hypertrophic cardiomyopathy, where variations in wall thickness measurements directly impact clinical decision--making by affecting the calculation of sudden death risk and thereby the indication for preventive implementation of an implantable cardioverter defibrillator (ICD).

Another recent example of automation is the International Society for Heart and Lung Transplantation's grading of endomyocardial biopsies in heart transplant patients.[36] The authors compared histological grading performed by expert pathologists with a computer-assisted automated pipeline and showed similar performance of the Computer-Assisted Cardiac Histologic Evaluation (CACHE) grader in comparison to the pathologist (*Figure 1*). Moreover, they showed only limited attenuation of the performance when it was applied to an external validation data set, indicating good generalizability across different scanning and tissue preparation protocols. International collaborative efforts in the field of transplant research have been hampered by variations in grading by individual centres, which increase the noise-to-signal ratio in the detection of biologically meaningful results when data sets from individual centres are merged. CACHE-enabled automated grading can play an instrumental role in advancing the field of transplant research.

Finally, AI will increasingly be applied in the field of echocardiography. Prior studies have shown that AI can identify different echo views, segment cardiac structures, estimate ejection fraction,[37,38] and diagnose diseases such as cardiac amyloidosis.[39] Recently, a study from Stanford also showed that deep-learning algorithms are able to detect pacemaker or ICD leads and, interestingly, are able to predict age, sex, height, and weight based on echo images.[40] Furthermore, they used gradient-based sensitivity mapping methods to highlight the regions of interest for human interpretation. Visualization methods to unlock the so-called black box algorithms are essential if healthcare professionals are to fully adopt the results generated by AI models. These algorithms will support untrained professionals with the interpretation of echocardiograms when cardiological expertise is of limited availability. A recent study showed that deep learning can even help untrained nurses to perform limited echocardiograms for standard evaluation of the left and right ventricular size and pericardial effusion, enabling the use of echocardiograms in non-cardiological settings, such as primary care, COVID wards, or remote areas.[41] However, before its widespread implementation, additional studies regarding safety and generalizability are warranted.

Big data and prognostic models for cardiovascular risk prediction

Machine learning for risk prediction

Clinical risk prediction modelling based on machine learning has been an active field of research. During the first months of the pandemic, hundreds of such models were developed.[42] Clinical prediction models are commonly developed to inform physicians about the probability of a certain disease being present (diagnosis), or to predict a certain health state in the future (prognosis), for individual patients, and to use that knowledge in the care of those patients.[43] By applying machine learning techniques that can use complex data relationships between predictors and outcome without the need for the modeller to pre-specify them, the expectation is that the accuracy of predictions will improve compared with traditional risk

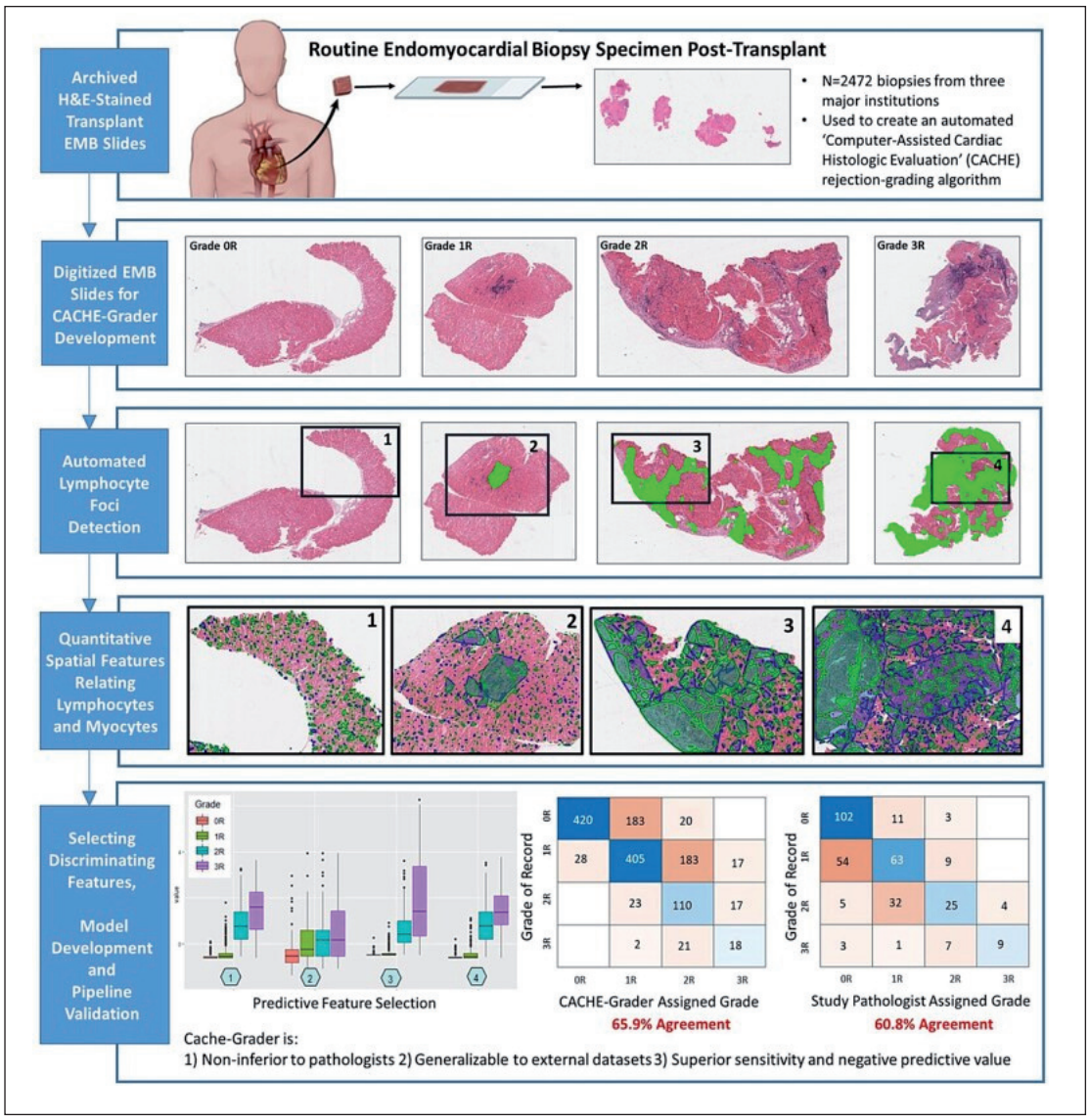


Figure 1 An overview of the 'Computer-Assisted Cardiac Histologic Evaluation (CACHE)-Grader' multicentre validation experiment. The CACHE-Grader's performance was compared with both the grade of record and independent pathologists performing re-grading, demonstrating non-inferiority to expert pathologists, generalizability to external data sets, and excellent sensitivity and negative predictive value. Reproduced by permission from Peyster *et al.*,[36] by permission of OUP on behalf of ESC.

prediction modelling approaches, and that its application will be less labour-intensive at the bedside.

Improvements in predictive accuracy are, however, not guaranteed.[44] For instance, a study that developed machine learning models to predict the risk of death after acute myocardial infarction (AMI) found that machine learning models were not uniformly superior to a traditional logistic regression approach in a cohort of 755 402 AMI patients.[45] In fact, of the three models used, two were superior to the logistic regression model for risk stratification. In addition, those two models were much better calibrated across patient groups based on age, sex, race, and mortality risk, and thus better suited for risk prediction. In contrast, the third model, based on a neural network, was found to be inferior to the logistic regression model used in the study. There may be pragmatic reasons for this inferiority, but they are probably related to the methodology used and in particular the sample sizes of each of the study's populations.

Nonetheless, in other settings, machine learning approaches have yielded promising results. One such study developed models to predict the risk of death, myocardial infarction, and major bleeding after an acute coronary syndrome (ACS). The machine-learning-based models were developed from a cohort with 19 826 adult ACS patients and were shown to predict the risk with high AUCs on external validation, at 1 year (AUCs: 0.81–0.92) and 2 years (AUCs: 0.84–0.93).[46]

Early warning systems

Early warning systems are prognostic predictive models that aim to inform physicians about important future health outcomes. Often, these early warning systems are used to monitor patients and to update these pre-

dictions over time. For instance, to predict circulatory failure in patients admitted to intensive care, a machine learning model was developed that made a new prediction for every patient every 5 min.[47] The early warning systems developed were shown to yield high AUCs, between 0.88 and 0.94. However, these models also produced two to three alarms per patient per day. This may result in the so-called alarm fatigue, which can lead to inadequate responses and may even impact patient safety.[48] Hence, for these early warning systems and other risk prediction models used to guide clinical decisions, it is essential to ensure safety and effectiveness in improving patient outcomes, for instance, through a randomized controlled trial (RCT) comparing the early warning system to standard of care. One such RCT evaluated a machine-learning-based early warning system for pending intraoperative hypotension.[49] This early warning system updates every 20 s the probability of a hypotensive event in the next 15 min (warning when estimated probability >85%) based on the arterial pressure waveform.[50] In an RCT with 60 adult elective non-cardiac surgery patients, the early warning system, in combination with a haemodynamic diagnostic guidance and treatment protocol, reduced the median total time of hypotension per patient from 32.7 min under standard of care to 8 min.

Big data: representativeness and algorithmic fairness

Access to large and diverse databases with electronic health records creates important new research opportunities. Such large databases include the Clinical Practice Research Datalink (CPRD), with highly detailed data from >5 million individuals representative of the UK population. Using the CPRD data, one interesting study developed and validated several machine-learning-based risk prediction models for predicting the risk of familial hypercholesterolaemia in primary care patients.[51] These prediction models were shown to have high AUCs of around 0.89. The large scale and representativeness of large databases also allows for studying specific groups that may otherwise be difficult to study. For instance, one study compared cardiovascular disease incidences and outcomes in homeless individuals using a linkage between CPRD, hospital episode statistics, and the Office of National Statistics for mortality data.[52] This study showed that homeless individuals have a 1.8 times higher risk of developing cardiovascular disease and are 1.6 times more likely to die within 1 year after cardiovascular disease diagnosis, compared with similar individuals who are not homeless. Finally, large and diverse databases, where minority groups are also well represented, are essential to ensure that the algorithms developed are fair,[53] i.e. do not systematically disadvantage certain groups of individuals. This requires evaluation of the performance of the algorithms in important subgroups. For instance, a recent study on atherosclerotic cardiovascular disease risk prediction showed a comparable performance of existing pooled cohort equations and newly developed machine-learning-based models in Asian and Hispanic subgroups, for which the performance was so far uncertain.[54]

Wearable devices in cardiovascular risk assessment, cardiovascular disease prevention, diagnosis, and management

Wearables in atrial fibrillation risk assessment and management

The role of physical activity as a modifiable risk factor for the development of AF was studied recently in a well-organized prospective study,[55] which included 93 669 participants from the UK Biobank prospective cohort, without a prevalent history of AF, who wore a wrist-based triaxial accelerometer for 1 week. The sensor captured acceleration at 100 Hz with a dynamic range of ±8 g. The primary outcome of the study was incident AF.

According to the findings of the study, greater accelerometer-derived physical activity is associated with a lower risk of incident AF and stroke, after adjustment for clinical risk factors (*Figure 2*). Wearable sensors may enable both objective assessment of physical activity and modification of AF risk through targeted feedback. The authors consider that future preventive efforts to reduce AF risk may be most effective if they target adherence to objective activity thresholds.

Another study[56] that aimed to investigate the association between changes in physical activity and the onset of AF reported similar findings. A total of 1410 participants from the general population were studied (46.2% women, mean age 74.7 ± 4.1 years), with risk factors but with no prior AF diagnosis, who underwent continuous monitoring for AF episodes along with daily accelerometric assessment of physical activity, using an implantable loop recorder, over an average period of 3.5 years.

According to the findings of the study, intra-individual changes in physical activity were associated with the onset of AF episodes, as detected by continuous monitoring, in a high-risk population. For each person, a 1 h decrease in daily physical activity during the previous week increased the odds of AF onset the next day by ~25%, while the strongest association was seen in the group with the lowest activity overall.

Apart from these two recent and revealing studies of the relationship between a person's physical activity and the occurrence of AF, a significant number of ongoing or recently published studies have evaluated the capabilities of wearables, focusing on the relationship between the individual clinical outcome and the burden of recorded episodes of clinical or subclinical AF.[57]

Wearables in heart failure assessment and management

Heart failure (HF), a fast-growing disease internationally, also has a long-standing affinity with wearable technology, since the pathophysiology of the disease and its clinical consequences require close and continuous long-term monitoring. Indeed, wearables offer a unique opportunity to assess patients' status and a number of indicators closely, outside the classical settings. In patients with HF, data from consumer wearables, such as physical activity step count or heart rate, but also more intense monitoring of such factors as pulmonary artery pressure or fluid retention, have long been the target of these evolving devices.

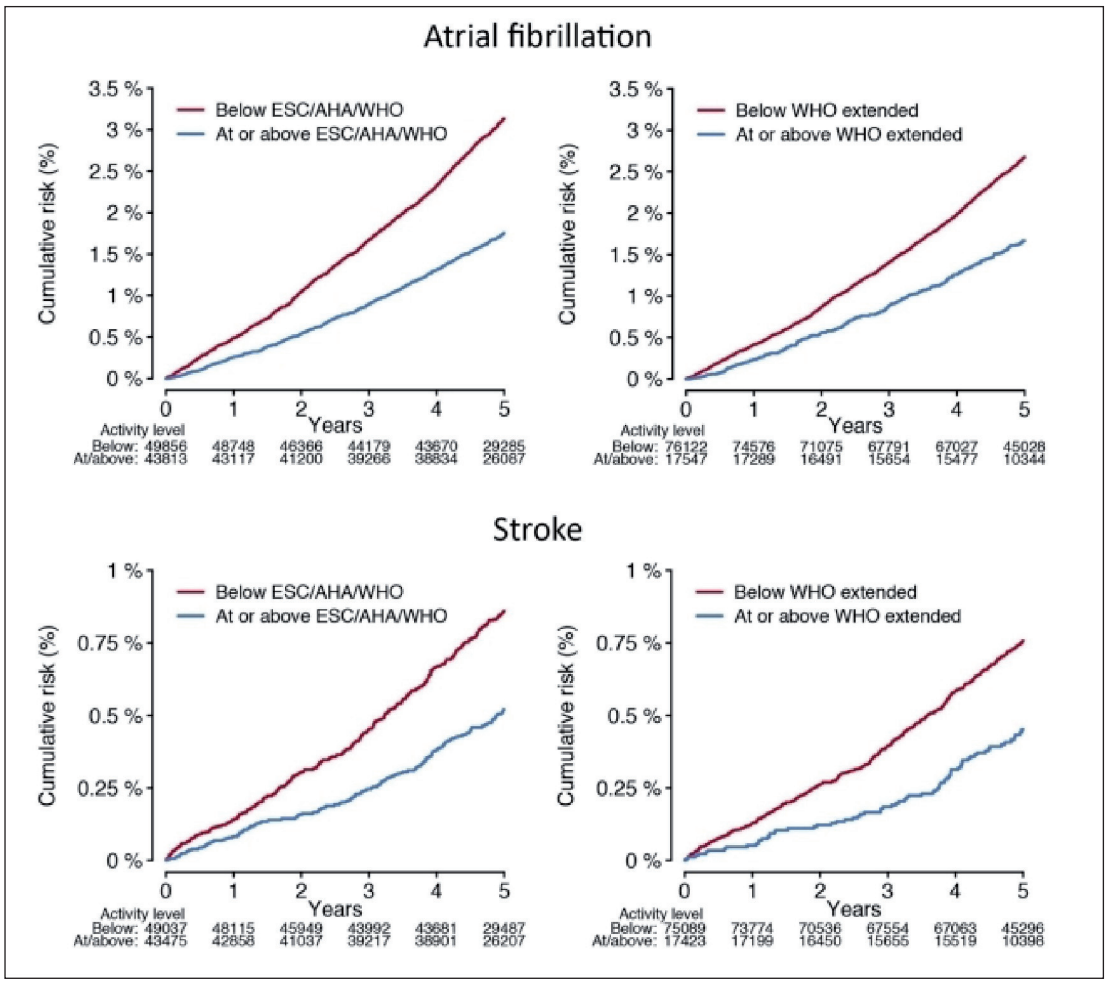


Figure 2 **Cumulative risks of atrial fibrillation (upper panel) and stroke (lower panel) stratified by adherence to physical activity recommendations, as validated by accelerometer-derived physical activity. Reproduced by permission from Khurshid *et al.*,[55] by permission of OUP on behalf of ESC.**

When we look at the findings and messages of the most recent relevant studies, those of the LINK-HF multicentre study by Stehlik *et al.*,[58] which evaluated the accuracy of non-invasive remote monitoring in predicting rehospitalization for HF, were quite revealing. This was a study of 100 patients with HF, aged 68.4 ± 10.2 years (only 2% female). The investigators showed that multivariate physiological telemetry from a wearable sensor, in combination with machine learning analytics, can accomplish accurate early detection of impending rehospitalization with a predictive accuracy comparable to that of implantable devices. The authors emphasize, however, that the clinical efficacy and generalizability of this low-cost non-invasive approach to rehospitalization mitigation still needs further testing.

Looking at the issues more broadly, apart from the use of modern electronic technology for continuous haemodynamic monitoring in HF patients, it has become clear that such technology can and should be used for education and support in these patients' therapeutic management.[59]

The EPIC-HF study (Electronically Delivered Patient-Activation Tool for Intensification of Medications for Chronic Heart Failure with Reduced Ejection Fraction) evaluated patients from a diverse health system who had HF and reduced ejection fraction, randomizing them to usual care vs. patient activation tools. The tools—a 3 min video and a one-page checklist—encouraged patients to work collaboratively with their clinicians to 'make one positive change' in their HF medication.

The findings were clear. A patient activation tool delivered electronically before the cardiology clinic visit enhanced clinicians' intensification of guideline-directed medical therapies.

ST-segment elevation myocardial infarction

The vast majority of wearable devices currently offer single-lead ECG recording, which allows the detection of AF and, more rarely, other arrhythmias to a satisfactory extent. However, such ECG recordings cannot reliably detect ST/T changes due to regional myocardial ischaemia. Nevertheless, a good many expectations have been invested in this possibility, as ECG recording by wearables, backed by telemonitoring to detect the early signs of myocardial ischaemia, could limit its often destructive effects.

Muhlestein *et al.*,[60] in their relatively recent publication, reviewed the feasibility of combining serial smartphone single-lead recordings to create a virtual 12-lead ECG capable of reliably diagnosing ST-elevation myocardial infarction. The study included 200 subjects (mean age 60 years, 43% female).

For all interpretable pairs of smartphone ECGs, compared with standard 12-lead ECGs ($n = 190$), the sensitivity, specificity, and positive and negative predictive values for ST-segment elevation myocardial infarction (STEMI) or STEMI equivalent (left bundle branch block) achieved by the smartphone were 0.89, 0.84, 0.70, and 0.95, respectively. The authors concluded that a 12-lead equivalent ECG constructed from multiple serial single-lead recordings from a smartphone can identify STEMI with a good correlation to a standard 12-lead ECG.

Similar to the previous study, a prospective study[61] also investigated the feasibility and accuracy of a smartwatch in recording multiple electrocardiographic leads and detecting ST-segment changes associated with ACS, compared with a standard 12-lead ECG. A commercially available smartwatch was used in 100 participants. The watch was placed in different body positions to obtain nine bipolar ECG tracings (corresponding to Einthoven leads, II and III, and precordial leads, V1–V6), which were compared with a simultaneous standard 12-lead ECG.

To a significant extent, there was an agreement between the findings of the smartwatch tracings and the standard ECGs for the identification of a normal ECG, ST-segment changes, and no ST-segment elevation.

The findings of the two previous studies give cause for optimism that, in the near future, the technical difficulties will be overcome, so that the recording of wearable devices will gain sufficient reliability for the recording of ischaemic changes on the ECG.

Conclusions

Digital health stands poised to transform cardiovascular medicine, much as echocardiographic imaging has upended stethoscope-based auscultation for diagnosis. Work published in 2021 has advanced this hope, and engaged an ever-widening group of stakeholders, critical to ensure proper evaluation of this important technology that may touch so many lives. Digital health's great promise in no small measure stems from its ability to endow extant medical tests (ECG, fundoscopy, and imaging) and electronic health record data, which are known to practitioners and integrated into workflows, with new superpowers, and to draw massively scalable data from wearables into the fold. This integration will accelerate adoption and impact care.

Before the promise of digital health can bear fruit to improve human health, a major gap must be addressed—the paucity of clinical trials to address outcomes. The 'black box' issue and lack of explainability are widely discussed concerns that may not be solved in the short term, but may be mitigated or overcome with robust evidence from prospective clinical trials. Data management processes to prevent overwhelming an already taxed healthcare system are mandatory. Further development of novel hybrid regulatory strategies, recognizing software as a medical device coupled to consumer hardware, are pre-requisites to exponentially driving data availability. With broad input from clinicians, industry, regulators, and patients; attention to privacy and human rights; diligent testing, validation and oversight; and prospective trial data, digital health promises an exciting and healthy future, as opposed to a brave new world.

Acknowledgements

The authors thank the following for their contributions to the preparation of the manuscript: Dr Anastasia Xintarakou, Mr Philip Lees, and Ms Alexandra Kourlampa. Thanks also to Professors E. Peyster and S. Khurshid for permission to use the figures.

Conflict of interest: P.E.V. has received teaching fees from Servier International and consultancy fees from Hygeia Hospitals Group, HHG, and ESC/European Heart Agency, Brussels. P.F. is the co-inventor of AI-ECG algorithms, and he and Mayo Clinic may benefit from their commercialization. F.W.A. is supported by UCL Hospitals NIHR Biomedical Research Center. M.v.S. has nothing to declare.

References

1. Hannun AY, Rajpurkar P, Haghpanahi M, Tison GH, Bourn C, Turakhia MP, et al. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. *Nat Med* 2019;25:65–69.
2. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* 2019;381:1909–1917.
3. Guo Y, Wang H, Zhang H, Liu T, Liang Z, Xia Y, et al. Mobile photoplethysmographic technology to detect atrial fibrillation. *J Am Coll Cardiol* 2019;74:2365–2375.
4. Kashou AH, Ko W-Y, Attia ZI, Cohen MS, Friedman PA, Noseworthy PA. A comprehensive artificial intelligence–enabled electrocardiogram interpretation program. *Cardiovasc Digit Health J* 2020;1:62–70.
5. Adedinsewo D, Carter RE, Attia Z, Johnson P, Kashou AH, Dugan JL, et al. Artificial intelligence-enabled ECG algorithm to identify patients with left ventricular systolic dysfunction presenting to the emergency department with dyspnea. *Circ Arrhythmia Electrophysiol* 2020;13:e008437.
6. Adedinsewo DA, Johnson PW, Douglass EJ, Attia IZ, Phillips SD, Goswami RM, et al. Detecting cardiomyopathies in pregnancy and the postpartum period with an electrocardiogram-based deep learning model. *Eur Heart J - Digit Health* 2021: ztab078.
7. Grogan M, Lopez-Jimenez F, Cohen-Shelly M, Dispenzieri A, Attia ZI, Abou Ezzedine OF, et al. Artificial intelligence–enhanced electrocardiogram for the early detection of cardiac amyloidosis. *Mayo Clin Proc* 2021;96:2768–2778.
8. Kwon J-M, Kim K-H, Medina-Inojosa J, Jeon K-H, Park J, Oh B-H. Artificial intelligence for early prediction of pulmonary hypertension using electrocardiography. *J Heart Lung Transplant* 2020;39:805–814.
9. Kwon J-M, Jung M-S, Kim K-H, Jo Y-Y, Shin J-H, Cho Y-H, et al. Artificial intelligence for detecting electrolyte imbalance using electrocardiography. *Ann Noninvasive Electrocardiol* 2021;26:e12839.
10. Galloway CD, Valys AV, Shreibati JB, Treiman DL, Petterson FL, Gundotra VP, et al. Development and validation of a deep-learning model to screen for hyperkalemia from the electrocardiogram. *JAMA Cardiol* 2019;4:428–436.
11. Kwon J-M, Lee SY, Jeon K-H, Lee Y, Kim K-H, Park J, et al. Deep learning–based algorithm for detecting aortic stenosis using electrocardiography. *J Am Heart Assoc* 2020;9:e014717.

12. Cohen-Shelly M, Attia ZI, Friedman PA, Ito S, Essayagh BA, Ko W-Y, et al. Electrocardiogram screening for aortic valve stenosis using artificial intelligence. *Eur Heart J* 2021;42:2885–2896.
13. Kwon J-M, Kim K-H, Akkus Z, Jeon K-H, Park J, Oh B-H, et al. Artificial intelligence for detecting mitral regurgitation using electrocardiography. *J Electrocardiol* 2020;59:151–157.
14. Attia ZI, Kapa S, Noseworthy PA, Lopez-Jimenez F, Friedman PA. Artificial intelligence ECG to detect left ventricular dysfunction in COVID-19: a case series. *Mayo Clin Proc* 2020;95:2464–2466.
15. Kwon J-M, Jeon K-H, Kim HM, Kim MJ, Lim SM, Kim K-H, et al. Comparing the performance of artificial intelligence and conventional diagnosis criteria for detecting left ventricular hypertrophy using electrocardiography. *Europace* 2020;22:412–419.
16. Cho Y, Kwon J-M, Kim K-H, Medina-Inojosa JR, Jeon K-H, Cho S, et al. Artificial intelligence algorithm for detecting myocardial infarction using six-lead electrocardiography. *Sci Rep* 2020;10:20495.
17. Makimoto H, Höckmann M, Lin T, Glöckner D, Gerguri S, Clasen L, et al. Performance of a convolutional neural network derived from an ECG database in recognizing myocardial infarction. *Sci Rep* 2020;10:8445.
18. Yao X, Rushlow DR, Inselman JW, McCoy RG, Thacher TD, Behnken EM, et al. Artificial intelligence–enabled electrocardiograms for identification of patients with low ejection fraction: a pragmatic, randomized clinical trial. *Nat Med* 2021;27:815–819.
19. Attia ZI, Kapa S, Lopez-Jimenez F, McKie PM, Ladewig DJ, Satam G, et al. Screening for cardiac contractile dysfunction using an artificial intelligence–enabled electrocardiogram. *Nat Med* 2019;25:70–74.
20. Antoniades C, Oikonomou EK. Artificial intelligence in cardiovascular imaging—principles, expectations, and limitations. *Eur Heart J* 2021:ehab678.
21. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
22. Shamout FE, Shen Y, Wu N, Kaku A, Park J, Makino T, et al. An artificial intelligence system for predicting the deterioration of COVID-19 patients in the emergency department. *npj Digit Med* 2021;4:80.
23. Shi F, Wang J, Shi J, Wu Z, Wang Q, Tang Z, et al. Review of artificial intelligence techniques in imaging data acquisition, segmentation, and diagnosis for COVID-19. *IEEE Rev Biomed Eng* 2021;14:4–15.
24. Eng D, Chute C, Khandwala N, Rajpurkar P, Long J, Shleifer S, et al. Automated coronary calcium scoring using deep learning with multicenter external validation. *npj Digit Med* 2021;4:88.
25. Zeleznik R, Foldyna B, Eslami P, Weiss J, Alexander I, Taron J, et al. Deep convolutional neural networks to predict cardiovascular risk from computed tomography. *Nat Commun* 2021;12:715.
26. Oren O, Gersh BJ, Bhatt DL. Artificial intelligence in medical imaging: switching from radiographic pathological data to clinically meaningful endpoints. *Lancet Digit Health* 2020;2:e486–e488.
27. Chilamkurthy S, Ghosh R, Tanamala S, Biviji M, Campeau NG, Venugopal VK, et al. Deep learning algorithms for detection of critical findings in head CT scans: a retrospective study. *Lancet* 2018;392:2388–2396.
28. Seidelmann SB, Claggett B, Bravo PE, Gupta A, Farhad H, Klein BE, et al. Retinal vessel calibers in predicting long-term cardiovascular outcomes: the atherosclerosis risk in communities study. *Circulation* 2016;134:1328–1338.
29. Mitani A, Huang A, Venugopalan S, Corrado GS, Peng L, Webster DR, et al. Detection of anaemia from retinal fundus images via deep learning. *Nat Biomed Eng* 2020;4:18–27.
30. Rim TH, Lee G, Kim Y, Tham Y-C, Lee CJ, Baik SJ, et al. Prediction of systemic biomarkers from retinal photographs: development and validation of deep-learning algorithms. *Lancet Digit Health* 2020;2:e526–e536.
31. Rim TH, Lee CJ, Tham Y-C, Cheung N, Yu M, Lee G, et al. Deep-learning-based cardiovascular risk stratification using coronary artery calcium scores predicted from retinal photographs. *Lancet Digit Health* 2021;3:e306–e316.
32. Tran T, Huang NT, Montezuma SR. Smartphone funduscopy - How to use smartphone to take fundus photographs. https://eyewiki.aao.org/Smartphone_Funduscopy_-_How_to_Use_Smartphone_to_Take_Fundus_Photographs (2 March 2018, date last accessed).
33. Bora A, Balasubramanian S, Babenko B, Virmani S, Venugopalan S, Mitani A, et al. Predicting the risk of developing diabetic retinopathy using deep learning. *Lancet Digit Health* 2021;3:e10–e19.
34. Canton G, Hippe DS, Chen L, Waterton JC, Liu W, Watase H, et al. Atherosclerotic burden and remodeling patterns of the popliteal artery as detected in the magnetic resonance imaging osteoarthritis initiative data set. *J Am Heart Assoc* 2021;10:e18408.
35. Augusto JB, Davies RH, Bhuva AN, Knott KD, Seraphim A, Alfarih M, et al. Diagnosis and risk stratification in hypertrophic cardiomyopathy using machine learning wall thickness measurement: a comparison with human test-retest performance. *Lancet Digit Health* 2021;3:e20–e28.
36. Peyster EG, Arabyarmohammadi S, Janowczyk A, Azarianpour-Esfahani S, Sekulic M, Cassol C, et al. An automated computational image analysis pipeline for histological grading of cardiac allograft rejection. *Eur Heart J* 2021;42:2356–2369.
37. Zhang J, Gajjala S, Agrawal P, Tison GH, Hallock LA, Beussink-Nelson L, et al. Fully automated echocardiogram interpretation in clinical practice: feasibility and diagnostic accuracy. *Circulation* 2018;138:1623–1635.
38. Madani A, Ong JR, Tibrewal A, Mofrad MRK. Deep echocardiography: data-efficient supervised and semi-supervised deep learning towards automated diagnosis of cardiac disease. *npj Digit Med* 2018;1:59.
39. Goto S, Mahara K, Beussink-Nelson L, Ikura H, Katsumata Y, Endo J, et al. Artificial intelligence-enabled fully automated detection of cardiac amyloidosis using electrocardiograms and echocardiograms. *Nat Commun* 2021;12:2726.
40. Ghorbani A, Ouyang D, Abid A, He B, Chen JH, Harrington RA, et al. Deep learning interpretation of echocardiograms. *npj Digit Med* 2020;3:10.
41. Narang A, Bae R, Hong H, Thomas Y, Surette S, Cadieu C, et al. Utility of a deep-learning algorithm to guide novices to acquire echocardiograms for limited diagnostic use. *JAMA Cardiol* 2021;6:624–632.
42. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ* 2020;369:m1328.
43. van Smeden M, Reitsma JB, Riley RD, Collins GS, Moons KGM. Clinical prediction models: diagnosis versus prognosis. *J Clin Epidemiol* 2021;132:142–145.
44. Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, Van Calster B, et al. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol* 2019;110:12–22.
45. Khera R, Haimovich J, Hurley NC, McNamara R, Spertus JA, Desai N, et al. Use of machine learning models to predict death after acute myocardial infarction. *JAMA Cardiol* 2021;6:633–641.
46. D'Ascenzo F, De Filippo O, Gallone G, Mittone G, Deriu MA, Iannaccone M, et al. Machine learning-based prediction of adverse events following an acute coronary syndrome (PRAISE): a modelling study of pooled datasets. *Lancet* 2021;397:199–207.
47. Hyland SL, Faltys M, Hüser M, Lyu X, Gumbsch T, Esteban C, et al. Early prediction of circulatory failure in the intensive care unit using machine learning. *Nat Med* 2020;26:364–373.
48. Wilken M, Hüske-Kraus D, Klausen A, Koch C, Schlauch W, Röhrig R. Alarm fatigue: causes and effects. *Stud Health Technol Inform* 2017;243:107–111.
49. Wijnberge M, Geerts BF, Hol L, Lemmers N, Mulder MP, Berge P, et al. Effect of a machine learning-derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: the HYPE randomized clinical trial. *JAMA* 2020;323:1052–1060.

50. Hatib F, Jian Z, Buddi S, Lee C, Settels J, Sibert K, et al. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. *Anesthesiology* 2018;129:663–674.
51. Akyea RK, Qureshi N, Kai J, Weng SF. Performance and clinical utility of supervised machine-learning approaches in detecting familial hypercholesterolaemia in primary care. *npj Digit Med* 2020;3:142.
52. Nanjo A, Evans H, Direk K, Hayward AC, Story A, Banerjee A. Prevalence, incidence, and outcomes across cardiovascular diseases in homeless individuals using national linked electronic health records. *Eur Heart J* 2020;41:4011–4020.
53. Mhasawade V, Zhao Y, Chunara R. Machine learning and algorithmic fairness in public and population health. *Nat Mach Intell* 2021;3:659–666.
54. Ward A, Sarraju A, Chung S, Li J, Harrington R, Heidenreich P, et al. Machine learning and atherosclerotic cardiovascular disease risk prediction in a multi-ethnic population. *npj Digit Med* 2020;3:125.
55. Khurshid S, Weng L-C, Al-Alusi MA, Halford JL, Haimovich JS, Benjamin EJ, et al. Accelerometer-derived physical activity and risk of atrial fibrillation. *Eur Heart J* 2021;42:2472–2483.
56. Bonnesen MP, Frodi DM, Haugan KJ, Kronborg C, Graff C, Højberg S, et al. Day-to-day measurement of physical activity and risk of atrial fibrillation. *Eur Heart J* 2021;42:3979–3988.
57. Bonnesen MP, Diederichsen SZ, Isaksen JL, Frederiksen KS, Hasselbalch SG, Haugan KJ, et al. Atrial fibrillation burden and cognitive decline in elderly patients undergoing continuous monitoring. *Am Heart J* 2021;242:15–23.
58. Stehlik J, Schmalfuss C, Bozkurt B, Nativi-Nicolau J, Wohlfahrt P, Wegerich S, et al. Continuous wearable monitoring analytics predict heart failure hospitalization: the LINK-HF multicenter study. *Circ Heart Fail* 2020;13:e006513.
59. Allen LA, Venechuk G, McIlvennan CK, Page RL, Knoepke CE, Helmkamp LJ, et al. An electronically delivered patient-activation tool for intensification of medications for chronic heart failure with reduced ejection fraction: the EPIC-HF trial. *Circulation* 2021;143:427–437.
60. Muhlestein JB, Anderson JL, Bethea CF, Severance HW, Mentz RJ, Barsness GW, et al. Feasibility of combining serial smartphone single-lead electrocardiograms for the diagnosis of ST-elevation myocardial infarction: smartphone ECG for STEMI Diagnosis. *Am Heart J* 2020;221:125–135.
61. Spaccarotella CAM, Polimeni A, Migliarino S, Principe E, Curcio A, Mongiardo A, et al. Multichannel electrocardiograms obtained by a smartwatch for the diagnosis of ST-segment changes. *JAMA Cardiol* 2020;5:1176–1180.