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Heart disease prediction using Machine learning and cardiovascular therapeutics development using molecular intelligence simulations: A perspective review

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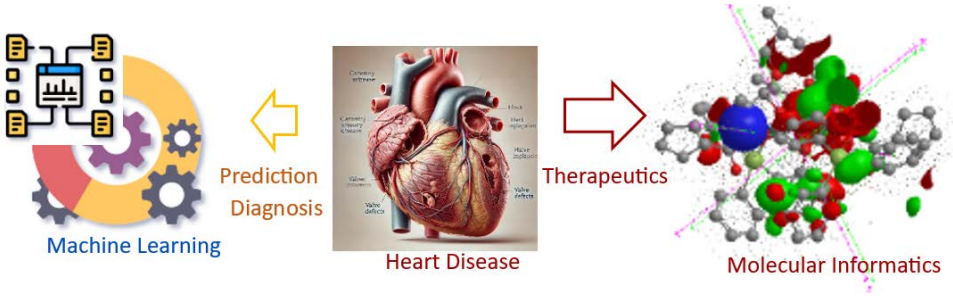
Review

ABSTRACT



Heart disease prediction using machine learning utilizes algorithms with patients' medical records to predict the possibility of particular cardiovascular ailment. The patients' records like age, cholesterol levels, blood pressure, and lifestyle habits are used to first train the machine models such as logistic regression, decision trees, support vector machines, or neural networks. These machine models, then are used to identify patterns and risk factors for probability of occurrence of heart disease. Besides heart disease prediction, the drug development process is assisted by computer simulations. Molecular modeling in cardiovascular drug design utilizes computational dockings and simulations to analyze the interactions between potential drug molecules and cardiovascular disease targets (key binding sites on proteins like enzymes or receptors). This virtual screening of potential drug molecules accelerates the drug discovery process in time saving statistics. This review delves in combined approach of machine learning and molecular simulation where the Machine learning aids early diagnosis, enabling timely interventions and personalized treatment plans, ultimately improving patient outcomes and reducing healthcare burdens while the Molecular modeling approaches reduce costs and time in drug development, thus, enabling precise design of therapies targeting conditions like hypertension, atherosclerosis, and heart failure.

Keywords: Heart diseases detection, machine learning algorithm, image classification, drug, cardiovascular, molecular modeling.

INTRODUCTION

Ischemic heart disease, or coronary artery disease and other cardiovascular diseases (CVDs) are biggest causes of morbidity and mortality globally. The CVDs are comprised of ailments in heart or blood vessels manifested as coronary artery disease, myocardial infraction, cardiac hypertrophy, and heart failure. In developed countries such as the United States, Canada, and many nations in the Western Europe, CVD is still the number one killer despite the significant advancement in healthcare technologies. In the United States, the heart disease claims about 697,000 lives every year, or nearly a quarter of the total 130 million people of which 18.2 million are due to coronary artery diseases among the people aged 20 and above, according to the Center of Disease Control and Prevention(CDC).[1] In 2020, the scale of CVD in terms of covering adults was 523 million and above.[2] From the Word Health Organization, CVDs are now responsible for over 31% of all deaths across the world. This translates to more than 17.9 million deaths per year, of which over 80 percent takes place in low and middle income countries (LMICs).[3] However, the rate of heart disease have either shown signs of coming down or have actually begun to come down especially in these regions due to increased prevention, early detection and control. On the other hand, LMICs especially in Asia, Africa and Latin America have seen increase in the burden of heart diseases. Many developing countries, including India, China, and Brazil, have recently experienced a marked increase in CVD incidence. For example, among Indian population, ischemic heart disease is the number one cause of mortality. Approximately 30 million people in India suffer from some form of heart disease and the figure is expected to rise, according to the Indian Council of Medical Research (ICMR).[4] Similarly, in Africa, CVDs are the second largest killer after infectious diseases such as HIV/AIDS and malaria. Most of the causes that lead to the development of heart disease are actually preventable, factors which call for prevention and early intervention. These risk factors include: hypertension, unhealthy

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eating habits, lack of exercise, tobacco use, obesity and diabetes, drinking alcohol, and heredity. Heart disease is a leading cause of death and those numbers are high, with occasional changes in regions. In many high-income countries the heart disease mortality rates have reduced during the past few decades due to recording early diagnosis and improved medical care in addition to increase in control of cholesterol and blood pressure.[5-8] To address the growing crisis of cardiovascular health, a multifaceted approach is essential. This includes improving healthcare infrastructure, promoting healthier lifestyles, and implementing public health campaigns aimed at reducing key risk factors such as smoking, poor diet, and physical inactivity. If successful, these efforts can significantly reduce the global burden of heart disease, saving millions of lives and alleviating the economic strain associated with cardiovascular conditions. However, fast-paced socio-economic changes pose significant challenges to the implementation of preventive measures, often delaying efforts to eliminate risk factors. Additionally, individual health conditions and personal fitness must be considered when designing strategies to improve overall health. This underscores the importance of leveraging modern scientific approaches, such as personalized medicine, to tailor solutions that address individual needs effectively.

AI has attracted a lot of interest in different sectors, particularly in medicine. Since the early period of the clinical medicine, especially from the 1960, machine learning algorithms such as deep learning, neural networks have been used.[9] The AI technology has a vast role to play in the field of healthcare systems. It may be possible to use data centric applications to discover additional phenotypes of frequently diagnosed diseases and promote cardiovascular drug development. New applications of AI-based systems appear in cardiovascular medicine such as cardiovascular imaging, assessing cardiovascular risk scores and discovery of novel therapeutic targets. These applications has better delineated and refined this viscoelastic property of active cardiac contraction and relaxation and offered a functional definition and dimensional analysis of progressive and reversible heart failure and congenital and acquired heart disease for treatment planning and drug delivery strategy selection throughout the course of CVD.[10] AI with genomic medicine, phenomapping of CVDs and with utilities as diagnostic imaging like echocardiograms and MRI/CT imaging can open a new horizon in early diagnosis and management of many CVDs.[11] However, due to possible bias in the results of both electronic health records (EHRs) and billing data, the interpretations that are obtained should be generalized with caution to the general population. The disadvantages, which clinical use and interpretation were subjected to include, data privacy, selection bias, and historical bias. Nevertheless, as AI infers without providing causation, besides the data, the clinical judgment, framework, and reasoning must take central stage when engaging with studies employing AI.

Traditional drug discovery approaches for CVDs required a lot of manpower and resulted in less-than-optimal success because of (a) poor understanding of the molecular mechanisms associated with disease, (b) high late-stage clinical trial failure rates, and (c) insufficient in vitro tools for predicting toxicity and off-target effects. Role of machine learning (ML) in cardiovascular therapeutics, a subpart of AI, lends an arm for the interested analysts in deriving the strongest tools for big data analyses, pattern extraction and predictions. Applications of ML in cardiovascular therapeutics include the following: (i) drug discovery and target identification, where the model is learned using deep learning and random forest approach to analyze omics datasets (genomics, proteomics, and transcriptomics) to discover novel drug targets, and with tools like Natural language processing (NLP) using delving into the literature to derive biological information from published scientific literature,[12] (ii) prediction of drug-protein interactions using graph-based ML models and convolutional neural networks (CNNs) approaches input to predictive modelling of ligand-protein interactions and then shows knowledge of understanding the mechanism of selective drug action into new and existing molecules in small-human studies for identifying drugs with very high specificity for cardiovascular biomarkers,[13] and (iii) toxicity prediction and safety profiling; organ-ADR is either cell or organ in effect adverse drug reactions (ADRs) have been a leading cause of failure of new drugs. ML models based on historical data can predict early on in the development process which compounds are risky with respect to cardiotoxicity and reduce the chance of failure during clinical trials.[14] For clinical trials, patient stratification through the identification of subpopulations most likely to respond to therapies enables efficient trial design through ML.

The molecular simulations use physics-based computational models to replicate and predict molecular interactions at an atomic level. These simulations complement ML in cardiovascular drug design (a) molecular docking and dynamics, (b) virtual screening of drug libraries, (c) structure-based drug design, and (d) multi-scale modeling.[15] Enhancing their integration in machine learning and molecular simulation hold the real potential between ML and molecular simulations: (I) *Enhanced prediction accuracy:* ML models trained on simulation data increase the precision of binding affinity and pharmacokinetic predictions. (II) *Data-driven refinement:* Simulation outputs become input features for ML models continuing to refine predictions concerning drug efficacy and toxicity. (III) *Automated workflows:* Automated pipelines take both ML and simulations, and merge them into iterative drug optimization while drastically reducing time and costs. For instance, however, drug development targeting the renin-angiotensin-aldosterone system (RAAS) system-hypertension[16] focuses on ML omics data in identifying critical pathway components, whereas simulation focuses on predicting inhibitor binding efficacy: example angiotensin-converting enzyme (ACE) blockers.

Predicting heart disease using machine learning and advancing cardiovascular therapeutics through molecular intelligent simulations present significant challenges, which include: (i) *Data limitations*: High-quality, annotated data is essential for the training of ML models. Data sharing and standardization play a critical role in overcoming such challenges. (ii) *Computational*

cost: Molecular simulations are resource-intensive. Advances in cloud computing and quantum computing will help mitigate these challenges. (iii) *Integration with clinical practice:* Bridging computational-prediction clinical applicability requires robust validation-regulatory frameworks. (v) *Ethical considerations*: ML algorithm transparency and bias mitigation are important for the fair therapeutic development.[17] Future directions include explainable AI (XAI) for transparent decision-making-federated learning for collaborative model training at institutions-harnessing real-world evidence sources from ethical health record (EHR) into ML Pipelines.[18] This convergence of machine learning with molecular intelligent simulations is transforming the entire antithrombotic therapeutics landscape in the global scheme. The development has a great potential to bring solutions towards the global burden of CVDs by unraveling complex mechanisms of diseases and accelerating drug discovery and personalized medicine. Onward innovation as well as interdisciplinary collaboration will usher in another wave of cardiovascular health breakthroughs.

Machine learning in a CVD includes the use of algorithms that study patient information and estimate the chances of heart problems.[19] Different attributes like age, cholesterol, blood pressure or patterns of living are used for training models using logistic regression, decision tree, support vector machines etc or neural nets. These models establish relationships as well as influencing variables that define heart diseases. Model performance is improved by utilizing feature selection, and performance is measured by measurement indices such as accuracy, precision, and AUC-ROC (Area under the receiver operating characteristic curve). Computational methods applied in molecular modeling in cardiovascular drug design involve an analysis of the conformations of the molecules that may act a cardiovascular drug and the interaction of these molecules the possible cardiovascular targets. The aspects of the topic investigated in this paper include other elements that raise expectations of heart diseases based on machine learning. Further, the discussion includes the results about the treatment of heart diseases based on the molecular drug data analysis from the molecular intelligence simulations.

CARDIOVASCULAR THERAPEUTICS: CURRENT SCENARIO

Machine learning and cardiovascular therapeutics development using molecular intelligence simulations can solve this problem with great accuracy. This interdisciplinary approach integrates computational and data-driven algorithms into the design of faster and more efficient drug discovery and therapeutic optimization to predict patient responses for cardiovascular diseases (CVDs). These are myocardial infarction and its sequelae, heart failure, and hypertension, and they continue to be the most common causes of death worldwide. The complicated nature of these diseases can be attributed to the multifactorial influences of genetic, epigenetic, environmental, and lifestyle factors. CVDs are the number one killers in the world today and that is why there is a lot of emphasis on developing better ways of identifying, managing and even preventing the conditions.[20] One of the hottest fields of AI, branching out to healthcare, is the prediction of heart diseases and the creation of cardiovascular therapies. There is a growing use of ML to predict the risk of heart diseases while there has been progress in therapeutic interventions in different CVDs. For example, the market size of artificial intelligence in cardiovascular system treatment is estimated to grow from USD 1.91 billion in 2024 to USD 36.76 billion in 2034 at CAGR of 27.06%, with North American region at a CAGR of 34.52%.

Several classes of drugs are now used to treat CVDs aimed at the heart function and averting adverse outcomes. These include: anti-atherogenic drugs include statins, antiplatelet medications such as aspirin, beta blockers, drugs inhibiting formation of Angiotensin converting enzyme (ACE) inhibitors, and Diuretics; and drugs learning angiotensin receptor blockers (ARB).[21] Although these drugs greatly enhance the chances of heart disease patients, they are general drugs and do not consider the patient's genetics and environment, which is why more needs to be done. Artificial intelligence specifically termed machine learning has readily presented itself as an effective technique for heart disease prediction. There are so many dimensions to patient data, and experience shows that by employing ML algorithms instead of rudimentary analysis procedures, healthcare providers can find patterns and correlations that would otherwise escape their attention. Some key ML techniques applied in heart disease prediction include: Collecting data such as the patient history, lifestyle, and genetic makeup, as well as the basic biomarkers, the ML models can provide the probability of the development of heart conditions.[22] Some suggested algorithms like the Framingham heart study algorithm have been morphed into machine learning in order to effectively capture potential heart attack or stroke patients (Figure 1). This ability has been deployed on simple application such as echocardiograms and CT scans to identify early signs of heart diseases with the use of deep learning neural networks. Such models can detect the signs of structural heart disorders, plaques, and other patterns which may be unnoticed when using interpretation solely.

Risk stratification, machine learning is also being employed in a more accurate production of risk stratification helping those in the healthcare industry find out which clients need close or more intense observation according to their scores. They are also integrating genomically driven data with machine learning algorithms to detect genes that might have a link to heart disease conditions. This may lead to having different treatment programmes based on one's genotype. Using machine learning to predict heart diseases has elements that can help diagnose and prevent the illness at an earlier time than before. The new cardiovascular therapeutics is already being also discovered by conventional approaches and strategies using advanced technologies such as gene editing, nanotechnology, and regenerative medicine.[23]

Clinicians, by tradition, construct an encyclopedia that specifies the reasons and trends for the treatment and reaction prognosis. The machine learning algorithms will help clinical specialists with this work. Still, the new algorithms require clinician engagement to actively participate in their implementation.[24] The vast amounts of cardiovascular-relevant

patient data, such as electrocardiograms (ECGs), are available to yield larger amounts of data for ML models to ease the clinical work processes.[25]

A mounting form of literature has applied ML to cardiovascular medicine, where the algorithms have demonstrated outstanding utility and predictive capability.[26] The study by Raileanu G et.al.[27] reported the designing and tuning the artificial intelligence ECG algorithms with the intent to serve population-scale cardiovascular diagnosis for 15 prevalent diagnosis in parallel. Included in the analysis were 160,526 initial ECGs of 62,444 adults obtained in 84 EDs or hospitals in Alberta, Canada.[27] The study considered 15 CV diagnoses, as identified by the International Classification of Diseases, 10th revision (ICD-10) codes: The most common listed disorders include: Atrial fibrillation (AF), supraventricular tachycardia (SVT), ventricular tachycardia (VT), cardiac arrest (CA), atrioventricular block (AVB), unstable angina (UA), ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), pulmonary embolism (PE), hypertrophic cardiomyopathy The researchers used ResNet-based deep learning (DL) using ECG tracings and extreme gradient boosting (XGB) using ECG measurements.[28] The evaluation results for the diagnosis of the most common CV conditions showed satisfactory-to-high predictive validity. The areas under the receiver operating characteristic curves (AUROCs) of this DEHF for diagnosis of HFrEF values were 0.843 (95% confidence interval, 0.840–0.845) and 0.889 (0.887–0.891) for internal and external validation respectively, and significantly outperformed those of LR (0.800 [0.797–0.803], 0.847 [0.844–0.850]) and RF (0.807 [0.804–0.810], 0.853 [0.850–0.855]) analyses. The AUROCs of deep learning for identification of the secondary endpoint was as follows 0.821 (0.819–0.823) and 0.850 (0.848–0.852) for internal and external validation respectively; clearly outperformed by reports from the LR and RF analyses.[29]

The research integrates the methodology of multi-scale experimentation, simulation, high performance computing (HPC), and machine learning to develop a risk assessment map for drug safety assessment. This diagram helps map out new and existing drugs assigning them pro-arrhythmic risk exposure at 50% current block. By categorizing risk for 23 common drugs, the classifier establishes the basis for evidence-based criteria to foster science-driven criteria for drug advancement to minimize dangerous heart rhythm disorders and construct safer drugs. This study shows the capability of machine learning methods to emerging drugs' safety assessment.[30] More, there is hope with artificial intelligence and machine learning in cardiovascular medicine, but their use is not reasonable. LMIC's struggle to provide a complete care path for CVDs owing to the lack of funding and human resource. AI/ML has the potential of enhancing delivery of healthcare in these countries, but there is deficiency of research articles. It is vital to comprehend these challenges if we are to create AI/ML solutions for the patient's sake as well as for the economy.[31] AI in particular has been instrumental particularly in cardiovascular imaging by improving diagnostic precision and operations' effectiveness. Nevertheless, the technical specificity of such approaches as machine learning and deep learning causes legal and ethical issues.[32] These are being implemented in wearables, in ECG, in echocardiography, in angiography and in genetic. However, more stringent empirically-proven investigation on these scales is required for ascertaining their viability and stability.[33] The evolvement in cardiovascular therapeutics includes gene therapy and CRISPR (clustered regularly interspaced short palindromic repeats); for treating CVDS based on gene' mutation: Techniques like CRISPR-Cas9 are utilized for cardiogenetic diseases, including Familial hyper Cholesterolaemia or arrhythmogenic right ventricular cardiomyopathy (ARVC). These models help to increase the effectiveness of prediction, and therefore carry out the diagnosis at an early stage and individualize the process.

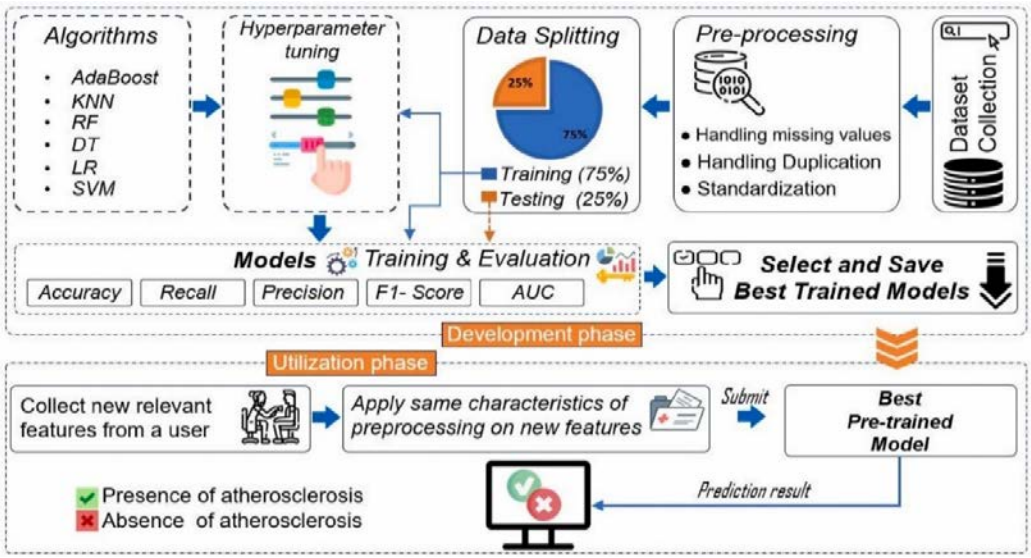


Figure 1. Flowchart of the medical projecting analysis using six ML algorithms. Reprinted (adapted) with permission from.[176]

However, current advancements in gene therapy, regenerative medical treatment, and molecular engineering should gradually lead to the transformation of heart diseases to chronic, easily treatable conditions in the future.

Scientists are also looking at the ability to fix damaged heart muscle using gene therapy after a heart attack. Heart disease has potential treatment through regenerative medicine: stem cell therapy and tissue engineering.[34] Scientists are looking for ways to utilize stem cells to replace worn out heart muscle or grow artificial heart muscle tissues for transplants or to patch up damaged tissue. Targeted drug development is being designed that affect a particular mechanism associated with CV diseases. For instance, drugs that act on proteins that cause atherosclerosis or therapies that regulate the immune system in autoimmune diseases of the heart are already in clinical trial.[35] Besides, the application of nanoparticles in drug delivery is another promising one. Cardiovascular drugs can be targeted to the site of plaque formation or inflammation using engineered nanoparticles and therefore the side effects of the drugs will be greatly reduced while their effectiveness will be greatly increased.[36] Machine learning is also being applied in drug discovery to predict the interactions of new compounds with cardiovascular targets. By analyzing large chemical databases of compounds and their interactions with cardiovascular tissues, AI can identify potential drugs more effectively and efficiently.

CURRENT PROCEDURES FOR THE DETECTION OF CARDIOVASCULAR DISEASE

Cardiovascular disease is a perennial cause of morbidity and mortality, hence there is need for early identification in order to minimize or prevent complications all together. CVD diagnosis has been established to require clinical evaluation alongside other tests and imaging procedures.[18] The current processes involved in detecting CVD are as follows: (a) *Clinical assessment and risk factors:* The diagnosis of CVD is done by clinical assessment of the patient's medical history and physiological factors. Risk factors evaluated in the healthcare setting include demography, gender, and family history, and smoking history, lack of exercise, hypertension, diabetes, hypercholesterolemia, and previous cardiac events. Therefore, based on these major factors, clinician may estimate the risk score of the patient towards CVD such as using Framingham risk score or ASCVD risk calculator.[37] (b) *Blood tests:* Blood tests are common preferred procedures to check the strength of the heart by measuring cholesterol, blood sugar, and inflammatory biomarkers.[38] Key blood tests include: (I) *Lipid profile*: Total cholesterol LDL cholesterol, HDL cholesterol, and triglyceride level. LDL and low HDL are indicators of atherosclerosis and heart diseases. (II) *High-sensitivity C-reactive protein (hs-CRP)*: This biomarker can also inform the presence of inflammation in arteries which might be linked a boost in cardiovascular episodes.[39] (c) *Natriuretic peptides (e.g., BNP, NT-proBNP)*: High amount of these biomarkers may indicate heart failure.[40] (d) *Electrocardiogram (ECG or EKG);* Electrocardiogram (ECG or EKG) is a type of cardiac test whereby the heart's electrical impulses are monitored non-invasively.[41] It is often used to diagnose arrhythmias, rhythm changes observed in patients after heart attack, as well as other infrequent pathological heart rhythms (fibrillation). A normal 12-lead ECG is a routine investigation or when a patient presents with chest pain, shortness of breath, palpitations or any other cardiovascular-related complaint. (e) *Echocardiogram:* Echocardiogram refers to a noninvasive test based on ultrasound that assists in imaging of the heart chambers and major blood vessels.[42] It is employed in diagnosing the functioning of the hearts chambers, valves, the volume and direction of blood. Echocardiograms are used for the evaluation of heart valve disorders, heart failure, birth defects of the heart and structural heart abnormalities. This procedure aid in determining the pumping capacity of the heart that is important in the diagnosis of any disease such as heart failure or cardiomyopathy. (f) *Stress testing*, Stress tests involve the use of treadmill or exercise electrocardiography which examines how the heart operates given a physical challenge. The patient walks or bikes (on a treadmill or stationary bicycle) during the electrocardiogram (ECG) to uncover signs of ischemic changes or arrhythmias.[43] (g) *Pharmacological stress* testing is also applied to patients who are incapable of exercising the use of medicines to induce the effect of exercise on the heart.[44] (1) *Exercise stress test:* Patients are taken through monitored exercises including walking with simultaneous monitoring of their blood pressure, pulse, and ECG. This test assists in diagnosing CAD (computer-aided design) since it measures the heart's performance when stressed. (2) *Stress echocardiography*: Joins an echocardiogram with a stress testing that invades the heart function while under stress in order to diagnose ischemia or other functional disorders. (h) *Cardiac imaging:* Technological developments are applied to diagnose CVDs and evaluate their severity more accurately;[45] (i) *Computed tomography (CT) angiography:* This test involves injection of contrast agents into the bloodstream followed by scanning by a CT scan to establish blockage or insulation of the coronary arteries because of atherosclerosis.[46] It is most helpful for those patient in intermediate risk who are thought to have coronary artery syndrome (CAS) or coronary artery disease. (1) *Magnetic resonance imaging (MRI):* Cardiac MRI can take pictures of the specific area of the heart and its functioning.[47] It is most effective in evaluating myocardial infarction- heart attack, cardiomyopathy, and congenital heart disease. It can also estimate perfusion and tissue ischaemia, That's why; (2) *Coronary angiography:* Historically seen as the reference standard for assessing ischemic heart disease, this is done through the use of a catheter and contrast to highlight limitations or obstruction in arteries.[48] It can also be done on its own but commonly as a procedure alongside an angioplasty or stent implantation if necessary. The brief Iowa implant card is as follows: *Coronary artery calcium (CAC) score*; A CAC score is utilized based on an abdominal CT scan to assess if there is any calcium deposition in the coronary arteries.[49] This test provides means of predicting other future cardiovascular incidents. Therefore, higher CAC score is associated with higher risk of CVD including heart disease in patients who may not necessarily be symptomatic. Other diagnostic tests are as follows: (I) *Holter monitor:* A portable ECG device that records electrical activity

of the heart for duration of 24-48 hours, useful in diagnosing availing arrhythmias that may not be revealed in routine ECG test.[50] (II) *Cardiac catheterization:* A technique involving the implantation of a catheter into the heart's blood vessels to check or at times treat heart diseases.[51] It permits measuring of pressures within the heart as well as evaluation of the blood flow.

Cardiovascular disease diagnosis entails an evaluation of the patient's risk, physical examination, chemical analysis and imaging technologies. Although conventional techniques like ECG, and echocardiogram still hold an important place, newer tools like coronary CT angiography, and cardiac MRI have become more widespread concerning diagnosis and counseling on the management.[52] Prompt identification of the disease is important so as to enhance the patients' prognosis, minimize the occurrence of heart attacks, stroke, and other complications, and achieve the required level of treatment.

MACHINE LEARNING TECHNIQUE

Cardiovascular disease is one of the major causes of death around the globe. Prevention is quite effective at minimizing the severity of its effects; in this context, machine learning provides effective solutions. In the context of heart disease diagnosis, use of big data to feed the ML algorithms allows for early and precise prediction of the likely outcome. Machine learning applies data available in the form of EHR's, medical pictures, wearable and clinical tests in order to forecast heart disease. Key benefits include: (1) *Analytical information*: There are hierarchies between variables that may include age, cholesterol, blood pressure, smoking status, and genes.[53] (2) *Early diagnosis*: Machines are able to identify primary signs of heart diseases better than by following standard manual diagnostic techniques; therefore timely actions can be taken.[54] (3) *Personalized medicine*: Implementation of the modern integration of data analysis allows identifying singularized risk levels presenting particular patients, therefore, prescribing unique prevention and treatment approaches.[55] Common ML techniques used are as follows: supervised learning: distance and logistic regression: both are linear models: where Distance measure can be used to classify a certain form of cancer, while logistic regression can be used to identify if a patient has heart disease or not. (1) *Random forest and decision trees:* It is also noticeable that these are amongst the most interpretable methods, which do not have difficulties capturing non-linear dependencies in the data.[56] (2) *Support vector machines (SVM):* Suitable for large data on which it is possible to distinguish between classes with a wide margin.[57,58] (3) *Unsupervised learning:* Examples of such methods include; clustering methods like K-means that groups patients according to risk characteristics or key behavior change indicators for specific interventions.[59] (4) *Deep learning:* Two common types of neural networks used in health care, convolutional neural networks (CNNs), and recurrent neural networks (RNNs), are particularly good at image analysis (for example, ultrasonic heart imaging such as an echocardiogram) and time-series analysis (for example, an electrocardiogram ECG).[60] ML models for heart disease prediction rely on diverse datasets and key features, such as: Clinical parameters include age, gender, body mass index (BMI), serum cholesterol and blood pressure. Behavioral factors: Smoking habits, alcohol consumption, and exercise frequency. (5) *Diagnostic tests:* Cardiac pacemaker information, ECG tracings, imaging studies, and stress test findings.[61] Genetic and biomarker data for more advanced forms of the predictive models.

The following performance parameters are used to evaluate the ML models, accuracy, precision, recall, F1-score, and area under the ROC curve. However, challenges remain, including: (a) *Data quality:* Patients' records showing variabilities in their entries hence distorting the outcome of the model.[62] (b) *Bias and fairness:* Ensuring the effectiveness and applicability of ML models to everyone.[63] (c) *Interpretability:* One of the largest challenges is the ability to distil complicated models between healthcare service providers and consumers.[64] Combining ML operation with wearable technology and connected devices including smartwatches can help track heart health in real time using wearable fitness tracker devices.[65] Bridging them with genomics or other aspects of precision medicine can enhance the risk prediction accuracy or individualized approaches, respectively. Appropriate cooperation between clinical practitioners, data analytical professionals as well as the policy makers is critical in order to foster the risks and advantages of utilizing ML in the assessment of probabilities of heart diseases so as to surmount the ethical and feasibility issues. By relating the information and foundations of machine learning, healthcare systems can now make a transition from a reactive approach to the proactive one, and therefore dramatically decrease the global rate of heart diseases.

EMERGENCE OF MACHINE LEARNING TECHNIQUES IN THE DETECTION OF HEART DISEASES

Noninvasive imaging techniques including electrocardiogram, echocardiography and clinical scores are less sensitive or specific in several conditions. Enhancements in Machine learning (ML) techniques have provided novel methods for institution of accurate diagnostic methods from large and complicate datasets.[66–68] A part of AI, machine learning uses the concept of algorithms that gets trained in an environment where it ingests data and then makes particular decisions without being programmed to do so at all. Applications of ML in heart disease detection are as follows: ECG signal analysis of patients is the first test used in diagnosing clinical problems related to the heart.[69] Convolutional neural networks (CNN) with recurrent neural network (RNN) for the automatic interpretation of ECGs have been applied for the process of automating ECG interpretation techniques.[70] Such models are developed using large volumes of data to identify arrhythmia, acute myocardial infarction, and other heart conditions as effectively as practicing cardiac clinicians.[71,72]

For example, the MIT-BIH (Massachusetts Institute of Technology–Beth Israel Hospital) Arrhythmia database has been applied to ML approach to identify the heartbeats, and to distinguish the irregular rhythm patterns. (1) *Predictive risk models:* Current risk assessment tools include the Framingham risk score and more such tools are derived from only a few core

input parameters.[73] (2) *Random forest:* support vector machine (SVMs) and gradient boost algorithms allows for viewing high dimensional data and include genomics data, lifestyle data, and biomarkers to prediction risk profiles.[74] (3) *Imaging analysis:* Computer-aided techniques can be particularly useful in cardiothoracic imaging since recent developments in medical imaging have produced enhanced image resolution of the cardiac organ such as Cardiac MRI, CT angiography, which are difficult to analyze manually.[75] Artificial intelligence in medicine (AIM) techniques connected with deep learning have been used to categorize as well as diagnose these pictures in cases of coronary artery disease and heart failure and so on. For instance, to differentiate the edematous from abnormal contraction of the walls of the heart, CNN could sketch out the signature of the cardiac structures and evaluate the wall motion within a few seconds compared to the conventional manual analysis.[76] (4) *Integration of wearable technology*: Wearable gadgets like smartwatches, and fitness trackers have become another way of managing heart diseases because they provide personalized alerts.[77] Professional medical devices record clients' real-time data and ML algorithms are used to identify any abnormalities like atrial fibrillation or bradycardia. Through wearables, those with chronic diseases have had constant surveillance so that machine learning can amplify early diagnosis and prompt treatment.

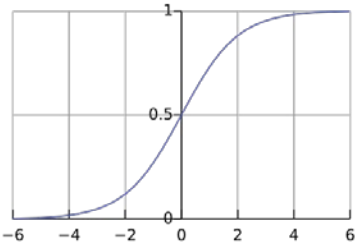
As notable, there is a challenge with applying ML in the detection of heart disease though the concept can greatly transform the field. Contrary to the general assumption that ML reduces costs and saves time, the complex computational training and deployment of the most advanced models pose the limitation of steep costs in environments with limited resources. More research should be directed towards creating more interpretable ML models, enlarging the types of datasets used and designing reliable systems for continuous analysis. The prospect of using ML with the other latest technologies like IoT devices and block chain in securely sharing data has the potential of enhancing heart disease diagnosis and control.[78] There is no doubt that the use of machine learning algorithms has signified the new era for diagnosing heart diseases. With the help of high level of differentiation and variety of data and algorithms used, ML has optimized diagnosis, risk prediction and constantly updated monitoring. The constant further development of ML and its application in clinical medicine can become the key to the reduction of the impact of heart disease and the improvement of the quality of life of patients around the world.

Machine Learning Techniques for Heart Disease Detection and Their Accuracy Levels

However, the machine learning (ML) approach is much advantageous to the diagnosis and detection of heart diseases. This is fundamentally the computational models that serve as the basis of sifting through a bulk dataset, the discovery of the underlying patterns and improvement of the diagnostic accuracy. The following are some machine learning techniques for detecting heart disease:

Logistic regression

Logistic regression is one of the highly used statistical ML models in solving binary classification problems like the prediction of heart diseases presence or absence. It is a statistical and machine learning method which gained prominence in heart disease prediction due to its simplicity, interpretability, and efficacy in binary classification problems. Unlike linear regression, which predicts continuous values, logistic regression predicts the probability of an event occurring based on one or more independent variables. Establishing linear relationships and well-defined models among a few variables provides better results of logistic regression (figure 2). Considering some less obvious risk factors such as blood pressure, cholesterol levels, and age, logistic regression gives a probabilistic expression of prediction about heart diseases. Studies indicated that the reported accuracy range falls within the interval of 75% to 85% depending on dataset and feature selection. Although it is straightforward and interpretable, LR never performs very well for high-dimensional data that show fine, complex, and non-linear patterns.[79]



$$f(x)^n = \frac{L}{1+e^{-k(x-x0)}}$$

Figure 2. A simplified logistic function or logistic curve is a common S-shaped curve with the given equation where L is the carrying capacity and supremum of the values of the function, is the logistic growth rate, the steepness of the curve; and is the value of the function's midpoint.

Decision trees

Decision trees (DT) are non-linear models that classify data by cutting them up based on feature threshold. The DT algorithms operate by recursively splitting the dataset based on feature thresholds, creating a tree-like structure of decision rules. Each node in the tree corresponds to a feature, and branches represent conditions that lead to different outcomes. Decision trees excel in handling non-linear relationships and interactions between features, which are often prevalent in medical data.

In the context of heart disease prediction, decision trees can incorporate diverse clinical parameters such as blood pressure, cholesterol levels, and lifestyle factors. Their interpretability allows clinicians to trace decision pathways, aiding transparency in predictions. Its simplicity and ability to interpret makes DT one of those models that are frequently adopted in the detection of heart diseases. It can over fit a model with small data sets as well. DT models in the different features achieved accuracies between 65-80% like that but much better with feature engineering and pruning techniques.[56] However, decision trees are prone to overfitting, especially with small datasets, and may require techniques like pruning or ensemble methods (e.g., random forests) to enhance generalizability.

Random forestry

Random forests are ensemble learning methods. Multiple decision trees are built together and their outputs combined together to produce robust predictions (figure 3).[80] This can adjust overfitting in individual decision trees, handling high dimensions very well. In heart disease prediction, random forests analyze a wide range of clinical and lifestyle variables by constructing a collection of decision trees on different subsets of the data. This approach reduces overfitting and improves the model's ability to generalize to unseen data. Random forests operate by averaging the predictions of individual trees, resulting in more stable and reliable outputs. They also provide feature importance metrics, helping to identify the most significant risk factors for heart disease. Random forests have shown a consistency of accuracies of detection of heart disease between 85%-92% because they are more adept at handling large datasets with so many miscellaneous features. The complexity of Random Forest can make them less interpretable than single decision trees. Despite this, their high accuracy and resilience to noisy data make random forests a popular choice in medical diagnostics and predictive modelling for heart disease predictions.[81]

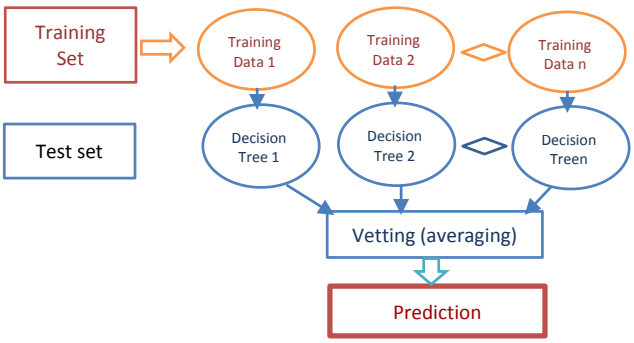


Figure 3. Random forest processing and prediction representation.

Support vector machines

Support vector machines (SVM) can be defined as a powerful classification model which makes use of hyperplanes that can segregate data points.[82] In terms of small datasets, these methods have proved potent because they get well-established non-linear relationships using kernel functions. SVMs work by finding the hyperplane that best separates data points of different classes in a high-dimensional space. By utilizing kernel functions, such as radial basis function (RBF) or polynomial kernels, SVMs can model complex, non-linear relationships between features and the target variable. In the context of heart disease prediction, SVMs analyze clinical and demographic features to identify individuals at risk. Their strength lies in their ability to handle high-dimensional data and outliers, making them suitable for medical datasets with diverse and noisy attributes. SVMs are also robust in avoiding overfitting, especially when the number of features exceeds the number of samples. The SVM models have been reported achieving accuracies ranging from 80% to 90% when Gaussian or radial basis function (RBF) kernels are used. The costs in computation increase with the size of the data set, however. The interpretability by SVM is limited compared to simpler models like logistic regression or decision trees. Despite this, the accuracy and flexibility of SVMs make them a valuable tool in predictive healthcare analytics.

K-*Nearest neighbors (KNN)*

KNN is one of the simplest instance-based learning algorithms because it predicts the class of newly given data points with respect to existing labeled points.[83] KNN operates by identifying the nearest data points to a query point in the feature space and using their majority class to classify the query. In heart disease prediction, KNN can analyze clinical data, such as cholesterol levels, age, and blood pressure, to determine the likelihood of an individual having heart disease. One of the strengths of KNN is

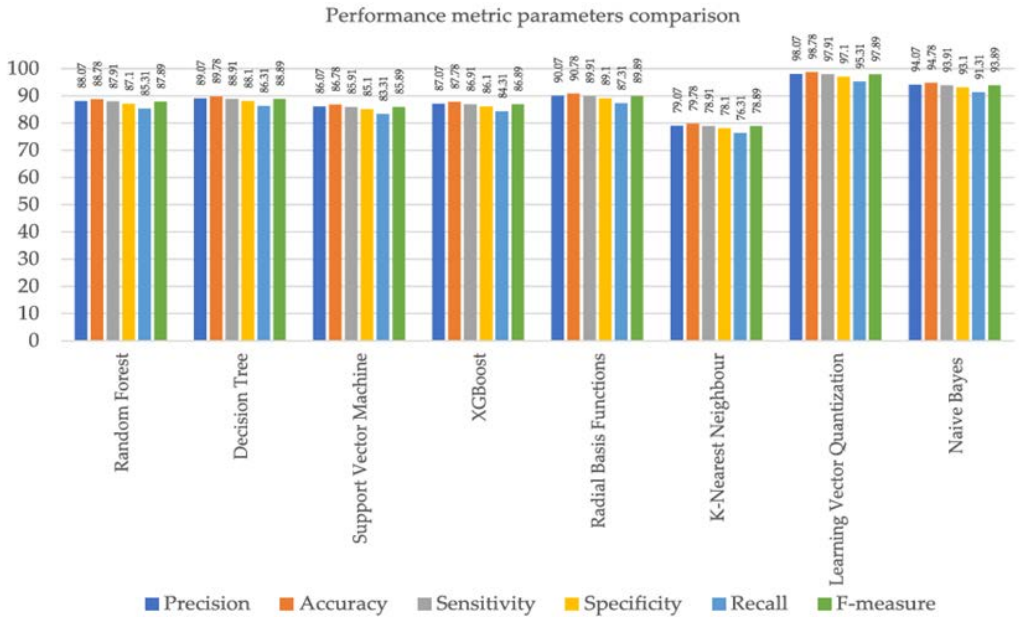


Figure 4. Arrangement of accuracy performance metric parameter comparison. Reprinted (adapted) with permission from.[177]

its non-parametric nature, which makes no assumptions about the underlying data distribution. This allows it to capture complex patterns in the data. Additionally, the algorithm is easy to implement and highly intuitive. Though KNN is very intuitive, but much relies on the quality of the selected k and the distance metric used to measure distance on the attribute space. Studies have shown that KNN has assigned accuracy levels between 70% and 85%; however, KNN performance crumbles under conditions of noisy or imbalanced datasets. KNN can be computationally expensive for large datasets, as it requires calculating distances to all training points for each prediction. Its performance is also sensitive to the choice of the distance metric, and the presence of noisy data. Despite these challenges, KNN remains a valuable tool, particularly when combined with feature selection and preprocessing techniques, for heart disease prediction tasks.

Naive bayes (NB)

The feature independence and the predictions that will happen by using probabilistic methods by the classifiers of Naive Bayes are the main assumptions that form the basis of NB.[84] Strong independence, however, does still allow NB to be appropriate for small and structured datasets. It has been shown that models based on naive Bayes have achieved between 70% and 80% accuracy in detecting heart diseases. Thus, making them a better option as a baseline model due to their simplicity.

Artificial neural networks (ANNs)

The general idea of neural structures resembling human brain organization is that neurons, in their interconnectivity, can form networks of nodes in layers and carry out the modeling of intricate patterns.[85] One important branch of ANN is deep learning, which has shown remarkable efficiency in analyzing unstructured data, including ECG signals and medical images. ANNs attain some of the highest accuracies from 90% to 97%, depending on the architecture and data preprocessing. But they give rise to the "black box" problem whereby the results are not interpretative.

Gradient boosting algorithms

These algorithms like XGBoost, LightGBM, and CatBoost have started becoming popular due to their effectiveness in capturing complex relationships and also handling missing data.[86] These algorithms build trees iteratively through minimizing the error from the prediction. The gradient boosting algorithms possess accuracy levels of 88%-95% and outperform most other traditional methods (Table 1, Figure 4). The use of advanced gradient boosting algorithms XGBoost, LightGBM, and CatBoost has shown significant improvement in heart disease prediction. These methods leverage the principles of gradient boosting to construct ensemble models that sequentially minimize errors by learning from previous iterations.

1. **XGBoost:** XGBoost (Extreme Gradient Boosting) is known for its high efficiency and scalability. In heart disease prediction, XGBoost has been widely adopted due to its ability to handle missing data, regularization techniques to prevent overfitting, and the inclusion of advanced tree-based learning. Studies have reported high accuracy rates and robust performance when using XGBoost to analyze complex cardiovascular datasets.
2. **LightGBM:** LightGBM (Light Gradient Boosting Machine) is optimized for speed and performance, particularly with large datasets. Its unique leaf-wise tree growth approach allows it to capture intricate patterns in heart disease risk factors more effectively than traditional boosting methods. LightGBM also excels in handling categorical variables, making it highly suitable for datasets with mixed data types.
3. **CatBoost:** CatBoost specializes in handling categorical data without requiring extensive preprocessing. This feature is particularly advantageous in heart disease prediction, where many attributes, such as smoking status and family history, are categorical. CatBoost's noise robustness and efficient analysis has made it suitable for application with large medical data sets.

Table 1: Comparative analysis of accuracy levels.

Technique	Accuracy Range (%)	Advantages	Limitations
Logistic Regression[79]	75 - 85	Simple, interpretable	Limited to linear relationships
Decision Trees[87]	65 - 80	Easy to understand	Prone to overfitting
Random Forest[88]	85 - 92	Robust, handles high-dimensional data	Computationally intensive
Support Vector Machines[89]	80 - 90	Effective for small datasets	High computational cost for large data
K-Nearest Neighbors[90]	70 - 85	Simple to implement	Sensitive to noisy data
Naive Bayes[91]	70 - 80	Fast, works with small datasets	Assumes feature independence
Artificial Neural Networks[92]	90 - 97	Models complex patterns	Computationally expensive, less interpretable
Gradient Boosting[93]	88 - 95	Handles missing data, robust	Can over fit with improper tuning

While existing ML techniques have demonstrated remarkable accuracy, further advancements are needed to address current limitations: (a) *Improved interpretability*: Techniques like SHAP (SHapley Additive explanations) and LIME (Local Interpretable Model-agnostic Explanations) can make complex models like ANNs more transparent to clinicians.[94] (b) *Integration with real-time data*: Incorporating real-time data from wearable devices can enhance prediction accuracy and enable timely interventions.[95] (c) *Personalized medicine*: ML models should focus on personalized risk prediction by incorporating genetic, lifestyle, and environmental factors.[85] (d) *Generalization*: Developing models that perform well across diverse populations and settings will increase the clinical utility of ML techniques.[84]

The application of machine learning techniques in heart disease detection has demonstrated high accuracy and potential for improving diagnostic outcomes. While simpler models like logistic regression and decision trees offer interpretability, advanced methods such as ANNs and gradient boosting provide superior accuracy in complex datasets. By addressing challenges

related to interpretability, data quality, and computational costs, ML techniques can further revolutionize cardiac diagnostics and patient care.

DRUG DEVELOPMENT RESEARCH FOR CARDIOVASCULAR DISEASES AND USE OF COMPUTATIONAL METHODS: MOLECULAR DOCKING, AND SIMULATIONS

The approaches to drug discovery and development in CVDs include an understanding of the very complex pathophysiological mechanisms through molecular targets identification as well as high-efficacy, low-side-effect designing of therapeutics.[96] Among several computational methods, molecular docking and molecular dynamics simulations are very essential for modern drug development, for they give efficiency, precision, and cost-effectiveness. CVDs and their therapeutic challenges, include conditions such as coronary artery disease, heart failure, hypertension, and arrhythmias. Their pathogenesis is multifactorial, involving the dysregulation of lipid metabolism, inflammation, oxidative stress, and inherited predispositions.[97] Drug development in CVDs is the most challenging for the following reasons: (a) patient population is highly heterogeneous; (b) drugs are taken chronically with very few side effects; and (c) use of highly conserved molecular targets increases chances of off-target effects. It tends to be tedious and cost prohibitive.

Traditional drug discovery methods such as high-throughput screening and lead optimization are time-consuming. This has completely changed by computational techniques, which are now putting an end to this sheer agony by facilitating fast and rational drug discovery through the idea of targeted approach. Traditional drug discovery has to be seen as resource- and time-consuming, and new approaches fully shifted foundations. This regard molecular docking as procedural change, which offers excellent advantages in rational design and development of cardiovascular drugs. Cardiovascular diseases pose a therapeutic challenge. Pathophysiology of these diseases involves a number of processes such as:(1) Dysregulated lipid metabolism; (2) Oxidative stress with endothelial dysfunction; (3) Inflammation; and (4) Renin-angiotensin-aldosterone system (RAAS) dysregulation.[97] However, they exert their effects with high specificity for the development of very effective therapies with less side effects. Long term treatment, resistance against drugs and off-target-effects invite development of drugs by rational and precise approaches-a field where molecular docking offers great promise.[98–100]

Biomolecular dynamics simulations serve as an important complement to docking and provide insights into the dynamic behavior of biomolecular interactions under physiological conditions. They enable researchers to assess the stability of ligand-protein complexes over time; understand conformational changes of targets and ligands; and explore the effects of solvent and ionic conditions on drug efficacy.[97] For example, MD simulations were utilized for improvement in the statins that have long been used for cholesterol management. By studying the interaction of statins with the HMG-CoA reductase enzyme, it can enhance the good activity of medicines and minimize the side effect. This methodology divided into two categories.

(A) Molecular Docking: A Core Tool in Cardiovascular Drug Discovery

Molecular docking refers to a computational method to simulate and predict the preferred orientation and affinity or interaction of small molecules (ligands) to their target proteins.[101–106] Along with the structural basis for understanding the ligand-target interaction, it paves the paths for the design of new therapeutic agents. These are the key steps for molecular docking in CVD drug development: (1) *Target identification and validation:* Proteins like ACE, β-adrenergic receptors, or HMG-CoA reductase have been identified and validated as critical CVD drug targets and have specific protein structure data through X-ray crystallography or cryo-electron microscopy needed for accurate docking studies.[107] (2) *Ligand preparation:* Preparing chemical libraries of potential candidates for drug development: Types of molecule included within these natural and synthetic compounds are optimized to docking.[108] (3) *Docking simulations*: Using algorithms, scan ligands virtually to see their ability to bind to the target. Popular docking software such as AutoDock, Glide, and DOCK predicts the best binding conformation and calculates binding-affinity score.[109,110] (4) *Interaction analysis*: The interaction between ligand and target will be analyzed for key residues in binding elucidating SARs calls into the part of drug design.[111] (5) *Lead optimization*: Good candidates will be optimized on basis of docking to boost binding affinity, specificity, and pharmacokinetic properties.[112]

The targets of CVDs for drug development are:

(a) *Development of ACE inhibitors*: ACE has catered to the treatment of hypertension and heart failure for quite some time; the molecular docking paradigm has contributed to the design of effective ACE inhibitors like captopril **1** and enalapril **2**. Docking studies make it possible to select ligands based on strong hydrogen bonding and hydrophobic interactions at the active site, which enhance efficacy.[113] Molecular docking has been a key player in the design of very efficient ACE inhibitors, such as captopril **1** and enalapril **2**.[114] Docking simulation studies of natural peptides and synthetic compounds with ACE revealed some of the crucial binding interactions-including coordination to the zinc ion at the active site.[115] The drug lisinopril, for instance, came into being through the employment of the docking information for maximizing occupancy at the active site.

(b) β-*adrenergic receptor antagonists*: β-blockers act on β-adrenergic receptors responsible for their major clinical application in arrhythmias and heart failure, and docking studies help in fine-tuning the selectivity of such β-blockers to avoid, for example, the β2 receptor-related side effect of bronchoconstriction.[116117118]

(c) *Cholesterol-lowering drugs*: Molecular docking was instrumental in the optimization of statins inhibiting HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase, an important enzyme for de novo synthesis of cholesterol. Docking simulations afford insights into the molecular interactions stabilizing the statin-enzyme complex.[119]

(d) *Natural product screening*: Many natural substances, for example, polyphenols, have been reported to have cardioprotective effects.[120] The screening of such compounds against cardiovascular disease-related targets will accelerate the discovery of bioactive molecules by docking studies.[121]

(B) Molecular Dynamic Simulations

MD simulations utilize Newtonian physics to model the motions of atoms in a biomolecular system over time.[122] In simulating the dynamic behavior of drug-target complexes, MD provides insight into binding stability, conformational changes, and interaction mechanisms. (1) *Coarse-grained simulations:* These types of simulations include a simplification of molecular models and have been applied to analyze larger-scale interactions such as lipid membrane dynamics or protein-protein interactions in cardiovascular pathways.[123] (2) *Steered molecular dynamics* (SMD): SMD uses external forces to imitate the process during which a drug binds to or unbinds from a drug target in order to calculate binding free energies and explain the pathways of dissociation.[124] (3) *Quantum mechanics/molecular mechanics* (QM/MM): This kind of hybrid approach considers quantum mechanics for the active site of a particular protein and classical molecular mechanics for its surrounding environment, hence supporting detailed studies of enzyme catalysis as well as drug binding.[125]

Applications of MD simulations in cardiovascular drug development includes: (a) *Drug binding and stability analysis:* The MD simulations help to determine the physiological-based stability weights in terms of binding affinities and interactions between proteins and drugs, among others.[126] MD have been used in statin optimization experiments focusing on the aspects of hydrogen bond and hydrophobic interactions between statins and HMG-CoA reductase. (b) *Understanding changes in conformation:* CVD-related proteins, for example ion channels and GPCRs (G-protein-coupled receptor), undergo great conformational change during their activation or inhibition.[127] Simulations enable investigation of such dynamics and therefore help in the rational drug designing by targeting specific conformations. (c) *Devising allosteric modulators:* Construction from molecular simulation provides the platforms for the identification of the possible allosteric sites, that is, other than active sites modulating protein function.[128] This application of MD study has been efficient in discovering allosteric modulation in β-adrenergic receptors. (d) *Interactions between membrane and protein:* Many cardiovascular-related targets including GPCRs and ion channels are embedded in lipid membranes.[129] Thus, it would be necessary to study drug interaction with these sites within the native environment of the membrane. (e) *Toxicity prediction and off-target effects:* Simulations predict potential off-target interactions and toxicity through the study of how drugs behave once interacting with unintended 111 proteoproteins or pathways such as the hERG (human ether-a-go-go related gene) potassium channel, a common off-target of cardiotoxicity.[130]

The selected Cardiovascular drug development case studies are: (a) *β-Adrenergic receptor agonists and antagonists:* The use of MD simulation to examine the dynamic binding of selective β1-blockers to β1-adrenergic receptors and optimizing the selectivity to avoid β2-related side effects, such as bronchoconstriction.[131] (b) *Ion channel modulators:* Kv1. 5 is a determinant of human B cell proliferation and migration, potassium channels are potentially valuable targets for the treatment of atrial fibrillation.[132] Molecular simulations are now used to identify inhibitors that stabilize specific conformations of the channels, so as to improve efficacy and to avoid the potential for arrhythmogenicity. (c) *Improvement of statin efficacy:* In silico statin-HMG-CoA reductase binding studies enabled optimizations in the interaction profiles for drugs such as atorvastatin and translated into a consequent enhancement of effect in cholesterol lowering.[133]

Future directions include: (1) *Integration with artificial intelligence:* Introducing AI algorithms to analyze simulated data would demonstrate patterns and possibilities for prediction, thus adding efficiency to the simulation overall.[134] (2) *Personalized medicine:* Simulations would take specific patient data for designing therapies.[135] (3) *Quantum computing:* Expected to lead exponential acceleration of simulations and facilitate exploration of larger biomolecular systems.[136]

The merger with AI and machine learning with molecular docking and MD simulation makes possible the following AI-enabled features: (a) More accurately predicts potential binding sites and druggable areas: (b) Ligand structure optimizations through learning through iterations and (c) Integration of genomics and proteomics into personalized medicine by large datasets.[137] Machine learning techniques have been combined with molecular docking to predict novel β-blockers with enhanced selectivity towards β1 adrenoceptors, thus minimizing any negative effects associated with β2-receptor interactions. In current scenario, following methods are now considered as novel in drug discovery, such as (1) *Multi-target drug designing:* Most CVDs are multifactorial. Considering that computational approaches are more directed toward developing drugs that modulate many targets at once, increasingly, this is much more likely being achieved.[138] (2) *Cardiovascular personalized medicine:* Computational models develop patient-specific therapy based on genetic, proteomic, and metabolic data.[139] (3) *Quantum computing:* New algorithms promise to achieve exponentially higher speed for docking and other simulation studies, opening up to completely new areas in drug discovery.[136] In silico methods, such as molecular docking and molecular dynamics simulations, have advanced the field of cardiovascular drug discovery. They have opened avenues toward rapid and safe treatments for CVDs because they elucidate molecular interactions and streamline the development processes when bringing a drug to the market. The innovations with integration of AI and computational advances would further facilitate precision medicine.

CARDIOVASCULAR DISEASE DRUG DEVELOPMENT: DOCKING STUDIES OF DIFFERENT DRUGS AND OTHER COMPOUNDS

The protein targets as highlighted previous paragraphs in CVD are: *Angiotensin-converting enzyme-I (ACE-I):* vital for the regulation of blood pressure and fluid balance;[140] *HMG-CoA reductase:* serves as a site for statins in cholesterol therapy;[141] *Beta-adrenergic receptors:* contribute to cardiac output and regulation of rhythm;[142] *Ion channels, eg, K^+, Na^+ and Ca^{2+}:* regarded as essential ones in cardiac electrophysiology.[143]

Docking studies for synthetic drugs are as follows: (1) *ACE inhibitors*, also known as captopril **1** and enalapril **2**, have proved to be quite effective as antihypertensive.[144] (2) *Beta-blockers*: Beta-blockers, such as propranolol **3**, act on beta-adrenergic receptors thereby decreasing the heart rate and workload of the heart.[145] Docking studies led to the discovery of selective beta-1 adrenergic blockers from non-selective beta-blockers and thereby reduced the risk of bronchospasm associated with non-selective beta-blockers. (3) *Statins:* Lower Cholesterol levels using HMG-CoA reductase inhibitors.[146] (4) *Flavonoids and polyphenols:* Binding analyses indicated their linkages into several important targets like ace and HMGCoAR (3-hydroxy-3-methylglutaryl-CoA reductase) reductase and gave clues for regulation of blood pressure and lipid lowering mechanism.[147] (5) *Alkaloids:* Berberine **4**, an alkaloid possess antihyperlipidemic and antidiabetic activity. It has also been a subject of much research through molecular docking studies (Figure 5).[148] Berberine **4** showed a high degree of binding affinity for targets linked to lipid metabolism and glucose regulation. Hence it has the potential for bringing in an intervention in metabolic syndrome involvement with CVD. A bright new avenue made possible by docking studies is the design of novel multi-target drugs for the polygenic nature of CVDs. Molecular docking changed the drug development scenario in CVD: it fast-tracked the identification and optimization of drug candidates.[149]

Kamal Dev et al. reported docking of target proteins involved in cardiovascular disorders: using phytocompounds of *Terminalia arjuna*.[150] These findings reported that this plant has about nineteen phytochemicals that are very useful in the development of cardiotonic therapies and treatment of other disorders. The phytochemicals display excellent cardioprotective activity without any cytotoxic activities and were screened using molecular docking and drug-likeness study. Arjunic acid, arjungenin, and terminic acid were found to meet all the ADMET (absorption-distribution-metabolism-excretion-toxicity)
parameters and showed lower autotoxicity. Thus, they appeared to be probable agents for developing broad-spectrum medicines against CVD. *Mingquan Guo et. al.* reported recent developments in molecular docking for research and discovery of prospective marine pharmacophores.[151] Diverse marine drugs approved by the Food and Drug Administration (FDA) depend on efficacy induced through protein-ligand interactions.

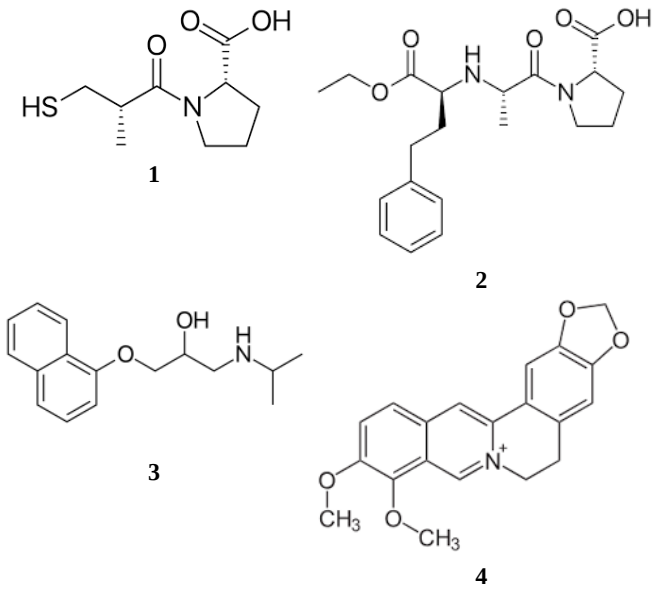


Figure 5. Chemical structures of captopril, enalapril, propranolol, and berberine.

However, complex components and simple bio-active chemical bases are the stumbling blocks in drug discovery and development. *Isaac Asiamah et. al.* have discussed molecular docking application in drug discovery based on natural products.[152] Natural products are mostly used to manage diseases, especially in developing countries. Traditional drug discovery mostly relies on crude extraction. *Chung-Der Hsiao et. al.* described that the studies of cardiotoxicity of ligands for ion channels in zebrafish have included cardiac rhythm studies and molecular docking.[153] The zebrafish, therefore, is a model that can serve to screen libraries of drugs that have intrinsic cardiotoxicity, thus meeting the criteria of the 3Rs: replacement, reduction, and refinement. Seven ion channel ligands were screened with a method based on ImageJ, and strong cardiotoxicity by in vivo definitions was revealed by 6 compounds. In silico-based molecular docking simulations were performed to elucidate five compounds that might interact with the Danio rerio L-type calcium channel, a well-known arrhythmia target. *Soliman, Mahmoud et. al.* testified the theory and applications of covalent docking in drug discovery: benefits and pitfalls.[154] Drug discovery and design are concerned with irreversible inhibitors such as covalent inhibition that act through time-dependent interactions with targets. Covalent inhibitors are effective in targeting rare residues and shallow binding cleavage proteins.

Hussam aly sayed murad et.al. published article covering in-silico molecular docking, molecular dynamics and pharmacokinetic/toxicity prediction studies on interactions of selected cardiovascular active natural compounds with CXCR4 (C-X-C motif chemokine receptor 4), and CXCR7 (Chemokine Receptor CXCR7) receptors.[155] This investigation has considered the molecular docking interactions of four of the most popular natural products with cardiovascular activity-curcumin, resveratrol, quercetin, and eucalyptol-with the receptors

CXCL12 (C-X-C Motif Chemokine Ligand 12), CXCR4, and CXCR7. The authors hypothesize that those compounds might modulate the CXCL12/CXCR4/CXCR7 pathway, thus possibly turning to some benefits for patients with coronary artery disease. All docking scores of the different compounds showed effective interaction with the receptors, and curcumin had the best binding with active sites. The compounds held drug-like characteristics, but eucalyptol showed the chances of weak cardiotoxicity. This is the very first attempt for binding interactions of such natural agents with the receptors CXCR4 and CXCR7, and even their druggability is predicted.

Zainab Shahzadi et. al. explored network pharmacology and molecular docking that defined convergent computational protocols to identify comprehend antihypertensive prospective derivatives of Fabaceae species.[156] Hypertension is a public health problem that affects 25% of adults. However, synthetic medications are available for treatment, which usually have side effects and long-term therapy requirements. This research aims to find new antihypertensive compounds from Cassia fistula, Senna alexandrina, and Cassia occidentalis using a network pharmacology and molecular docking approach. Six compounds identified effective agents. Most of them are non-toxic and have greater bioactivity scores. The higher binding affinities have been found in compounds Dihydrokaempferol, Flavan-3-ol, and Germichrysone. *Rokayya Sami et. al.* reported the characterization of the binding process of the key phyto-compounds against serotonin 5-HT2A (5-hydroxytryptamine (serotonin) receptor 2A) receptors through estimation of molecular properties, drug-likeness and cardiotoxic risk, liability profile, and molecular docking studies.[157] This study applied bioinformatics to predict the molecular characteristics, medicinal chemistry attributes, and potential cardiotoxicity and adverse liability profiles of four compounds in Centaurea tougourensis. Here, 4 compounds were designated and termed, separately, 2,5-monoformal-l-rhamnitol (compd **5**), cholest-7-en-3.beta.,5.alpha.-diol-6.alpha.-benzoate (compd **6**), 7,8-epoxylanostan-11-ol, 3-acetoxy- (compd **7**), and 1*H*-pyrrole-2,5-dione, 3-ethyl-4-methyl- (compd **8**). Results showed compounds **5** and **8** were non-cardiotoxic, with compd **5** having a higher level of confidence. *Yan Li et. al.* explored network pharmacology and molecular docking based medicines analysis on bioactive anticoronary heart disease compounds in *Trichosanthes kirilowii Maxim* and *Bulbus Alli Macrostemi* translation. [158] These studies aim to evaluate the potential effects of Gualou Xiebai decoction (GLXB), a well-known traditional Chinese herbal combination that focuses exclusively on coronary heart disease. As a result, 18 compounds and 21 action targets were identified, which indicated that effects induced by GLXB are primarily related to signaling pathways involved in the mechanism of action of tumor necrosis factor, nuclear factor-kappa B, and hypoxia-inducible factor-1, in addition to arachidonic acid metabolism and insulin resistance. Lavish real active compounds such as quercetin, naringenin, β-sitosterol, ethyl linolenate, ethyl linoleate, and prostaglandin B1. These could compose new recipes for treating coronary heart disease (Figure 6).

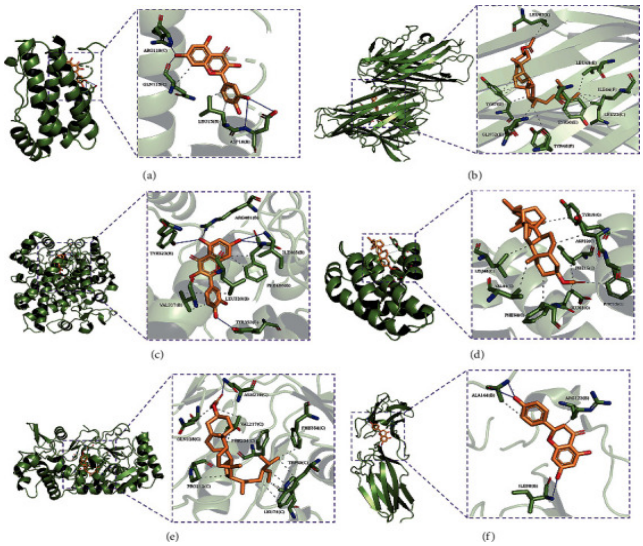


Figure 6. Representative docking of selected compounds (a-f) with targets. Molecular docking analysis identifies components with the highest affinity. (a) Interleukin 6 and quercetin, affinity = −6.3 kcal/mol. (b) Tumour necrosis factor and *β*-sitosterol, affinity = −8.3 kcal/mol. (c) Prostaglandin-endoperoxide synthase 2 and quercetin, affinity = −9.7 kcal/mol. (d) B-cell leukaemia/lymphoma 2 and *β*-sitosterol, affinity = −7.6 kcal/mol. (e) Nitric oxide synthase 3 and *β*-sitosterol, affinity = −9 kcal/mol. (f) Vascular cell adhesion molecule-1 and naringenin, affinity = −6.6 kcal/mol. Solid blue lines represent hydrogen bonds, while dotted grey lines represent hydrophobic interactions. Reprinted (adapted) with permission from.[158]

Bonifasius Putera Sampurna et. al. examined the cardiac rhythms and molecular docking studies of ion-channel ligands targeted toward cardiotoxicity in zebrafish.[153] The zebrafish model is a promising candidate for screening a library of potentially cardiotoxic drugs and adhering to the principle of 3Rs-replacement, reduction, and refinement. Here, 70 ion channel ligands were evaluated using an ImageJ-based method. Out of these 70 compounds, six were found to be extremely cardiotoxic in vivo and were put through in silico molecular docking simulations to reveal five compounds that may interact with Danio rerio L-type calcium channel, a recognized target for arrhythmia.[159]

Ibrahim F. Halawani et. al. elucidated new succinimide derivatives synthesis, molecular docking, and preclinical evaluation for cardioprotective, hepatoprotective, and lipid-lowering effects.[160] A study is currently undergoing preclinical investigation that would shed light on the histopathological impact of a newly synthesized succinimide derivative ((2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-3-(4-isopropylphenyl)-2-methylpropanal) compd **9**) into myocardial and hepatic tissues, within the framework of biochemical impacts on cardiac biomarkers, hepatic enzymes, and lipid profiles. This study involved albino rats and the administration of a single dose of 5-FU (5-Fluorouracil). From the results obtained, it was observed that while the incorporation of the compound had significant cardioprotective, hepatoprotective, and lipolytic activities against

5-FU toxicity, it was also reported that all the aforementioned toxic manifestations had been reversed post-administration of compd **9** at the doses administered. Compd **9** showed dose-dependent evidence, being most effective at the dose of 10 mg/kg body weight. *Junaidin et. al.* discussed ligand-based pharmacophore modeling, molecular docking, and molecular dynamic studies of HMG-CoA-reductase inhibitors.[161] Hyperlipidaemia, increased levels of plasma lipids, is one of the major risk factors for CVDs. 3-Hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase is an important enzyme in the synthesis of cholesterol. In silico studies revealed four compounds with lower docking values, along with some strong binding interactions with HMG-CoA reductase. One of them, stood out in results as having potential to be an HMG-CoA reductase inhibitor.

Yunfeng Yu et. al. offered an analysis of the mechanism of action for the treatment of coronary artery disease with colchicine based on network pharmacology and molecular docking technologies.[162] The databases utilized included TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform), Swiss Target Prediction, PharmMapper, GeneCards, OMIM (Online Mendelian Inheritance in Man), Therapeutic Target Database, DrugBank, and DisGeNET to gain a list of predicted drug targets. The outcome of all the studies shows that colchicine may be treating coronary heart disease by targets such as Cytochrome c, Myeloperoxidase, and Histone deacetylase 1. The mechanism could be in line with the response of a cell to a chemical stimulus.

Qunhui Zhang et. al. explored network pharmacology combined with molecular docking discloses the mechanism of *Wuwei Yuganzi San* (WYS; originated from MaDiYiZhuXuanJi, a famed book) in treating coronary heart disease.[163] By means of network pharmacology and molecular docking experiments, this study ascertained the mechanism of action on the drug Wuwei Yuganzi San (WYS) in the treatment of coronary heart disease (CHD). The main active components, target genes, and common targets were mined from databases including Traditional Chinese Medicine Systems Pharmacology, OMIM, GeneCards, and NCBI Gene Expression Omnibus DataSets. The compound-target-disease network as well as protein-protein interaction network were constructed and the gene ontology enrichment and the KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment pathway have been performed. Consequently, the study came to pinpoint principal ingredients that are related to 59 targets in CHD, which include including a disintegrin and metalloprotease 17 (ADAM17), aldo-keto reductase family 1 member C2 (AKR1C2), albumin (ALB), protein kinase B (AKT1), and alcohol dehydrogenase 1C (ADH1C). *Lucas Caruso et. al.* explained multi-target drug design for the treatment of cardiovascular diseases-multiple benefits from one drug.[164]

Xiaojie Xu et. al. have discussed CVDHD (cardiovascular disease herbal database) an herbal database for drug discovery and network pharmacology in CVDs.[165] The CVDHD is intended to be a complete database, which will facilitate the drug discovery from the natural products isolated from the medicinal herbs for their significance in diseases related to the cardiovascular system. Currently, the database has more than 35230 differentiated molecules along with their identification information, molecular properties, docking results, and 2395 target proteins. The database comprises medicinal herbs and natural products, CVD-related target proteins, docking results, diseases, and clinical biomarkers. The CVDHD simplifies drug/lead discovery processes and explores action mechanisms of medicinal herbs using virtual screening and network pharmacology. *Amandeep Kaur et. al.* expounded computational pharmacokinetics and molecular docking studies for FXa inhibitors as thrombolytics.[166]

Monjur Ahmed Laska et. al. explained docking and quantitative structure-activity relationship (QSAR) evaluations of some naturally available or naturally occurring diterpenes as inhibitors of ACE with reference to CVDs.[167] This research examines the adenine effect of naturally occurring diterpenes over the ACE, which is a relevant enzyme in the course of many CVDs. The diterpene Ent-kaur-16-en-15-one-19-oic acid was found to be non-toxic and Lipinski's compliant.[168] The docking study shows a greater affinitive binding within the active site of the drug target, whereas QSAR analysis shows significant IC50 values. This indicates that these diterpenes may act as a novel potential drug for treating CVDs.

PERSPECTIVE DISCUSSION

In the medical field, specifically in heart diseases, machine learning has turned out to be a revolutionizing element in the diagnosis of the condition during recent years. It can analyze large amounts of data, find out different kinds of patterns, and feed indications, often exceeding common statistical methods. One of the strongest capabilities of machine learning for detecting heart disease is its ability to handle complex multidimensional data, data that would otherwise include clinical information (for example, the patient's history, blood pressure, and cholesterol) imaging data (including echocardiograms and CT scans), and live monitoring information transmitted from wearable devices.[169] For instance, convolutional neural networks have excelled in identifying abnormal structures in the heart, such as hypertrophy or stenosis, from medical images. Time-series data sourced from electro-cardiograms can be processed for arrhythmic and other cardiac event detections using recurrent neural networks and long short-term memory models.

Although it seems promising, the application of ML in heart disease diagnostics has constraints. The two common challenges are data quality and accessibility. Medical databases are, most of the time, incomplete, imbalanced, or polluted by noise, which affects the performance of the developed models. Furthermore, the lack of standard protocols for data sharing and integration across healthcare systems makes ML solutions less scalable. These issues drive researchers towards the development of stronger preprocessing routines, transfer learning models, and federated learning frameworks to generalized models. Interpretability is another great challenge that comes with ML applications in healthcare. The black-box models, although accurate, are not able to give any insights to clinicians on what does that mean other than its predictions. Techniques such as

SHAP (SHapley Additive explanations) and LIME (Local Interpretable Model-agnostic Explanations) thus bridge this gap through "visage" into how the models decide and encourage "domestication" in terms of how these will fit with clinical expertise.[170] For its future capabilities, ML technologies during the diagnosis of heart diseases have certain challenges. Data quality and availability obstacles are still two main roadblocks to its application. Medical datasets are usually fragmented, imbalanced, or noisy, which affect the performance of models. Limiting scalability of ML solutions is the lack of standardized protocols for sharing and integrating data across healthcare systems. To add, researchers were focusing on developing robust preprocessing techniques and federated learning frameworks and transfer learning models in order to further improve the generalizability of models-in these cases. This is other significant aspects of ML applications in health-care, such as interpretability. It lacks, therefore, the actionable clinical reasoning that justifies its prediction, yet accurate "black-box" model predictions offer.[171] Such gap, therefore, is being closed using techniques such as SHAP (SHapley additive explanations) and LIME (Local interpretable model-agnostic explanations) where glimpses to how decisions are made by models is ensured toward the model's alignments with clinical expertise.

Molecular docking is a computational method for predicting the binding orientation and affinity of small molecules (ligands) for their target proteins. Its application in cardiovascular drug design is invaluable for identifying new candidate therapeutic agents to modulate specific pathological molecular pathways involved in heart disease. Cardiovascular diseases are often characterized by the dysregulation of signaling pathways, including the renin-angiotensin-aldosterone system (RAAS) and platelet aggregation mechanisms.[171] Using molecular docking in research permits researchers to screen huge chemical libraries with compounds interacting with important proteins in these pathways. For instance, it has been chiefly instrumental in the development of ACE (angiotensin-converting enzyme) inhibitors affecting hypertension and heart failure. With improvements in the 'molecular docking' algorithms, the accuracy and efficiency of these techniques have also increased. The traditional mode of operation, rigid docking, treated both ligand and protein statically. However, the recent advances in flexible docking have enabled one to consider the dynamic nature of molecular interactions and, consequently, improve the reliability of predictions. Along with other software such as AutoDock and Schrödinger's Glide, protein-ligand docking program, GOLD (Genetic Optimization for Ligand Docking) has a well-developed set of scoring functions for estimating binding affinities and thus enabling retention of the promising candidates for drug testing.[172] The introduction of machine learning to this technology has allowed for further breakthroughs in molecular docking. Currently, ML models can be trained to predict binding affinities directly, bypassing some of the traditionally computationally intensive procedures in docking. Other deep learning architectures like graph neural networks represent molecular structures as graphs, thus encompassing the complex spatial relationships between atoms. This combined approach facilitates the rapidity of the drug discovery pipeline while providing access to new opportunities in exploring novel chemical spaces.

ML and molecular docking would potentiate the cardiovascular drug discovery. These two areas will complement each other toward developing a more integrated framework for drug discovery. High-throughput screening data can be subjected to ML algorithms that can help in determining ligand-protein interactions, thus making docking experiments more promising.[173] Similarly, the docking result can also serve as training data for the ML models, thus making it more refined via its prediction (Figure 6). This includes the most interesting application identification of biomarkers and drug targets for precision medicine. Such data from omics (genomics, proteomics, and metabolomics) can be analyzed by ML and novel drug targets can be derived that could be associated with heart disease, leading to the possible exploration using molecular docking to design concrete-specific inhibitors or activators that pave the way for personalized therapeutics.[174]

Future developments will be seen in the road to or toward the ability to integrate techniques both in quantum computing and advanced AI as well as multi-omics data with the aim of enhancing both ML and molecular docking simulation.[175] Such improvements will be good not just in the enhancement of both efficiency and accuracy in the prognosis and diagnosis but also in the new ways to revolutionize the wider field of cardiovascular research. In brief, therefore, machine learning and molecular docking are complementary weapons in the armory of modern medicine against CVDs. Each plays its unique strength, as well as relying upon its respective weaknesses, thereby adding great power to how one can diagnose, treat, and eventually even prevent heart disease.

CONCLUSION

Artificial intelligence (AI) and machine learning (ML) are driving significant advancements in precision medicine, particularly in the areas of risk prediction for heart diseases and evaluating the success of drugs. These technologies utilize complex, interacting variables to enable early identification and tailored interventions. When effectively integrated, AI and ML can improve patient care, reduce healthcare delivery costs, and transform cardiology into a more science-based specialty. However, further work is required to optimize data usage, enhance model robustness, and address the ethical dimensions of AI applications.

Traditional diagnostic methods for cardiovascular diseases (CVD), such as clinical examination, imaging modalities, laboratory tests, and functional assessments, aid in identifying atheromatous structures, plaque load, and ischemic changes. However, these methods often rely on sophisticated equipment and invasive procedures, limiting their practicality in resource-poor settings. Complementary strategies, including molecular diagnostic tests, wearable devices, and machine learning, offer the potential for reliable, portable, and early detection of CVD, thereby reducing the global disease burden. The ability of ML to process and interpret complex datasets makes it particularly useful in CVD management, employing supervised and

unsupervised learning models for risk prediction, early diagnosis, imaging analysis, and personalized treatment planning.

The benefits of ML in CVD include increased diagnostic accuracy and early identification of high-risk individuals. However, challenges persist, such as data quality, model interpretability, and ethical considerations. Addressing these issues, along with fostering interdisciplinary collaboration and leveraging clean datasets, could revolutionize CVD detection and management.

Molecular docking and molecular simulations have greatly enhanced drug discovery for CVDs. These computational techniques are cost-effective and time-efficient, facilitating the screening and optimization of potential therapeutic compounds. Molecular docking provides insights into the binding affinities and orientations of small molecules with target proteins, while molecular dynamics (MD) simulations offer detailed information about the properties of biomolecules. These approaches have proven effective in advancing the development of treatments for hypertension, atherosclerosis, and heart failure. The integration of computational methods with high-throughput experimentation and machine learning is expected to further improve the efficiency of cardiovascular drug discovery.

Molecular docking studies have become indispensable in modern drug development, enabling the identification of potential inhibitors and modulators for key CVD targets. These studies also facilitate structural optimization, drug repurposing, and the evaluation of bioactive compounds from natural resources for next-generation therapeutics.

ML methodologies are emerging as transformative tools in cardiovascular healthcare, enabling the analysis of abundant data to support decision-making processes. Supervised and unsupervised techniques have enhanced diagnostic accuracy and reliability, particularly in big data applications. AI-powered non-invasive diagnostic tools, such as wearable devices and remote monitoring systems, have further advanced CVD management. However, limitations remain, including model interpretability, data quality, and ethical considerations.

As ML advances and interdisciplinary collaboration grows, the detection and management of heart diseases are poised for revolutionary changes. Techniques such as logistic regression, decision trees, support vector machines (SVM), k-nearest neighbors (KNN), and ensemble methods have been applied to heart disease detection. Deep learning architectures, including convolutional neural networks (CNNs) and recurrent neural networks (RNNs), have shown promise in handling imaging data and patient records. The performance of these models, however, depends on dataset size, feature selection, and data preprocessing. Future efforts should focus on improving model generalization, explainability, and data clarity.

Innovative computational techniques and experimental analyses are expanding the scope of docking studies in CVD drug discovery. The integration of ML and molecular docking is enhancing both heart disease diagnosis and drug development processes. Reinforcement learning systems play a pivotal role in hypothesis generation and pattern analysis, advancing treatment strategies. Molecular docking expedites the identification of drug candidates by predicting binding sites on target proteins, saving time and resources. However, the approach requires high-quality structural data and robust validation. Combining big data, computational tools, and experimental evaluation could pave the way for personalized medicine, significantly reducing the prevalence of CVDs.

AUTHORS CONTRIBUTION

BSC, SK conceptualized and supervised, RK composed, JS, AC included revisions and updates.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest, financial or otherwise.

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