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*Review Article*

# Artificial Intelligence in Cardiology and Atherosclerosis in the Context of Precision Medicine: A Scoping Review

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Cardiovascular diseases remain the main cause of death worldwide which makes it essential to better understand, diagnose, and treat atherosclerosis. Artificial intelligence (AI) and novel technological solutions offer us new possibilities and enable the practice of individually tailored medicine. The study was performed using the PRISMA protocol. As of January 10, 2023, the analysis has been based on a review of 457 identified articles in PubMed and MEDLINE databases. The search covered reviews, original articles, meta-analyses, comments, and editorials published in the years 2009–2023. In total, 123 articles met inclusion criteria. The results were divided into the subsections presented in the review (genome-wide association studies, radiomics, and other studies). This paper presents actual knowledge concerning atherosclerosis, in silico, and big data analyses in cardiology that affect the way medicine is practiced in order to create an individual approach and adjust the therapy of atherosclerosis.

## 1. Introduction

The perception of a human being as a structure with numerous mathematical dependencies has been developed over the centuries. First examples can be found in antiquity and among Pythagoreans who investigated the nature of numbers and their relationship with the world exhaustively. It is suspected that the world-famous first computer, the Antikythera mechanism, was designed by Pythagoreans [1] and that the Lycurgus Cup made by the ancient Romans is the first example of the use of nanotechnology [2]. Today, the most important synthesis seems to have been published in "The fractal geometry of nature" by Kirkby [3]. It introduces the concept of fractals, connects dependencies that can be described by the Fibonacci Sequence, and have been discovered over a long time, such as the Julia set, the Cantor set, the Hausdorff dimension, the Sierpiński triangle, and the Sierpiński carpet. Similarly, the chromatin cell architecture is considered to be fractal, as well as other biological structures and processes [4]. Their description demands artificial intelligence (AI) because of its complexity which corresponds more to quantum than classical physics. Quantum physics, quantum computing, and AI are currently dynamically evolving fields of science. AI is a perfect candidate for quantum computing as its assumptions are mostly based on probabilistic elements, require huge amounts of data, and significantly increase the efficiency of already existing systems [5]. This is why quantum machine learning (ML) is gaining popularity.

Cardiovascular disease (CVD) remains the leading cause of death [6]. Together with the Fourth Industrial Revolution and AI solutions, new approaches are being proposed to expand the actual risk stratification, diagnosis, and treatment of CVD; to provide therapy tailored to an individual in the context of precision medicine; and to explain possible interactions affecting the pathophysiology of atherosclerosis. The amount of data collected to screen and then diagnose and treat an individual requires AI. In the case of atherosclerosis, optimal treatment is based not only on the experience of the physician but also on the individual characteristics of the atherosclerotic lesions in the body.

Table 1: Methodology.

| Criteria | Objectives |
|---|---|
| Inclusion criteria | Presence of AI solutions |
| | Application in personalized medicine |
| Exclusion criteria | Studies performed on animals |
| | Studies concerning cardiovascular risk stratification |
| | Verification of the methods impossible |
| Classification of articles | GWAS |
| | Radiomics |
| | Other studies |
| | Cardiovascular risk stratification (will be given in another article) |

This paper presents current knowledge on atherosclerosis, in silico, and big data analysis with AI, and AI performing other human functions that can be used in everyday medical practice to achieve better outcomes, speed up workflow, reduce costs, improve diagnostics and treatment solutions, and better understand a complex atherosclerotic disease. As atherosclerosis remains the leading cause of death, optimal diagnosis and treatment of patients are of paramount importance. Analyzed data will be used in the context of precision medicine and its potential application in personalized therapy.

## 2. Methodology

The study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.

*2.1. Inclusion Criteria.* The main inclusion criteria were the presence of AI solutions and the connection of the topic with personalized medicine.

*2.2. Exclusion Criteria.* Studies performed on animals and concerning cardiovascular risk stratification as well as those with no possibility of verifying applied methods were excluded from this review.

*2.3. Search Methodology.* PubMed and MEDLINE databases were searched using the Boolean operators "AND" and "OR." The following commands were used "artificial intelligence" OR "AI" AND "atherosclerosis" ($n = 4{,}458$); "artificial intelligence" OR "AI" AND "atherosclerosis" AND "cardiology" AND "GWAS" ($n = 110$); "artificial intelligence" OR "AI" AND "cardiology" AND "precision medicine" ($n = 352$); "artificial intelligence" OR "AI" AND "cardiology" AND "radiomics" ($n = 31$). For "artificial intelligence" OR "AI" AND "atherosclerosis," an additional filter was used to include papers published in the last 10 years. Two researchers conducted searches independently of each other. No automation tools were applied: (1) articles with similar contents were chosen by the publication date—the newest were included; (2) articles written by the same author and concerning the same issue—the newest were included. The results were divided into subsections presented in the review. The inclusion and exclusion criteria as well as organization of articles are presented in Table 1.

The authors identified 4,951 records. One hundred fifty nine records were removed due to duplication and 4,335 due to inconsistency with the topic. As of 10 January 2023, 457 articles were included for further analysis. Of the 457 articles, 11 were performed on animals, 73 involved cardiovascular risk stratification, 225 were inconsistent with the topic, and 18 were reviews. There were seven articles in which the authors could not verify the methods and decide whether they met the inclusion criteria. These articles were excluded. Finally, 123 studies were included. All articles have been divided into the following subsections presented in the article: genome-wide-association study, radiomics, and other applications.

The process is presented in Figure 1. Figure 2 presents an overview of the application of AI in the medical context.

## 3. Genome-Wide Associated Studies (GWAS) and Artificial Intelligence in Atherosclerosis

Genetics is a field of medicine that connects mathematics, physics, and biology. It is complicated character and the fact that the majority of traits are created by an interplay of various genes resulting in a particular phenotype makes it difficult to find a pattern for their distribution in a general population. A theory of infinitesimal model assumes that the continual discovery of new genes affecting particular trait contribute to a smaller causality in each of them [7]. Precision medicine's goal is to tailor an individualized therapy based on, among other things, genetic profiling, and to assess if there exists an increased risk for a particular disease or a severe variant. Tools used by precision medicine are genome-wide associated studies (GWAS) that enable the identification of single-nucleotide polymorphisms (SNPs), and exome sequencing. Surprisingly, these important particles of the human genome mostly reside in its noncoding part and are often not linked to particular genes. Therefore, it is difficult to determine the significance of some mutations [8, 9]. It was proven that many loci susceptible to particular disease fall within enhancers specific to disease-relevant types of cells, for example, the 1p13 locus, rs12740374, altering SORT1 gene hepatic expression with minimal effect in other cells [10]. However, it is still possible that even the most important loci have small effect sizes which explains only a part of genetic variation. This phenomenon is called the mystery of "missing heritability" and was partially solved by analyses concerning SNPs [11].

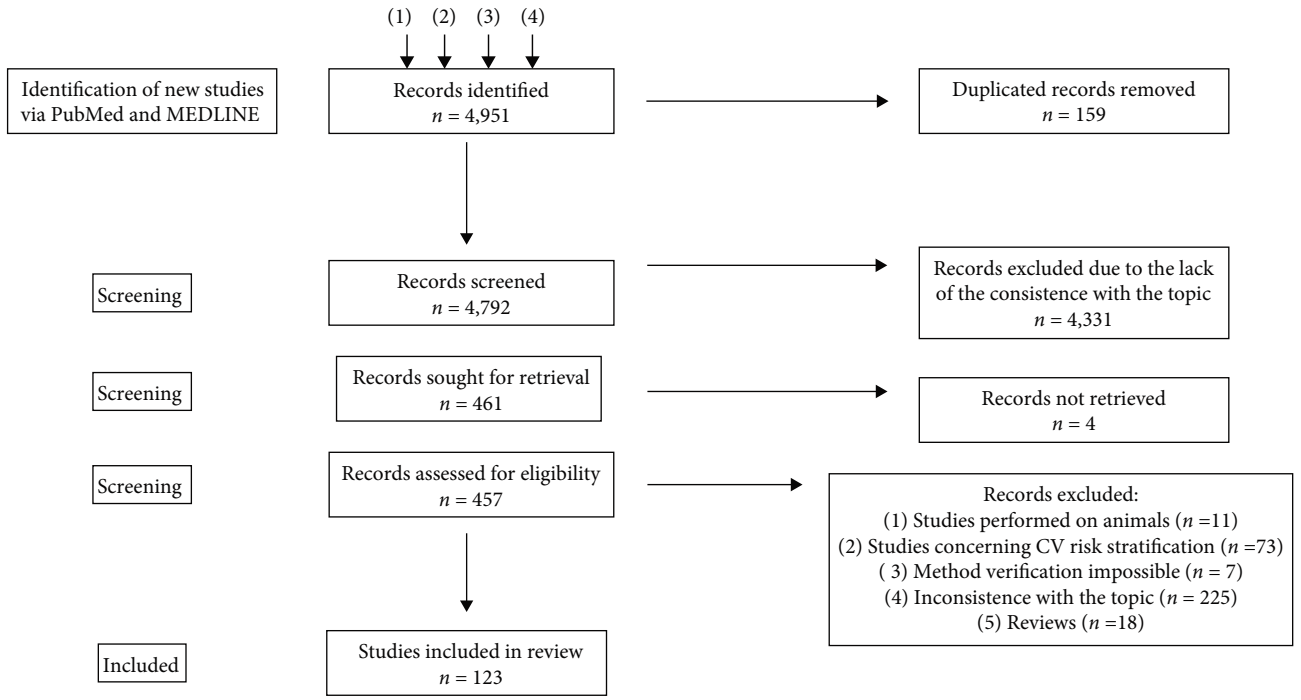


Figure 1: Identification of studies search: (1) "artificial intelligence" OR "AI" AND "atherosclerosis" (last 10 years) $n = 4{,}458$; (2) "artificial intelligence" OR "AI" AND "atherosclerosis" AND "cardiology" AND "GWAS" $n = 110$; (3) "artificial intelligence" OR "AI" AND "cardiology" AND "precision medicine" $n = 352$; and (4) "artificial intelligence" OR "AI" AND "cardiology" AND "radiomics" $n = 31$.

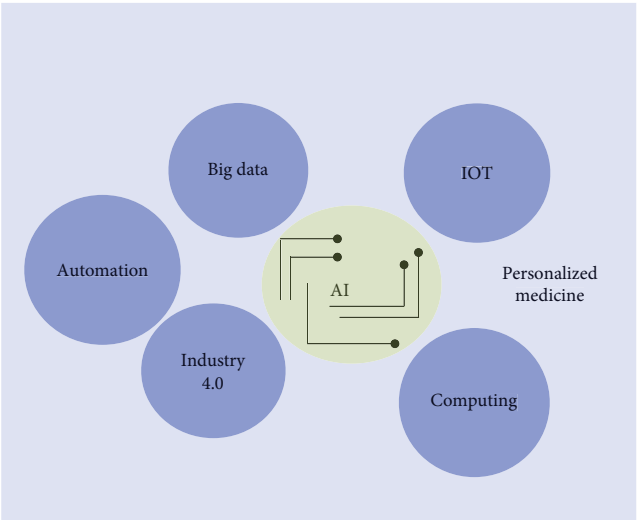


Figure 2: Artificial intelligence and its application in medical context.

Not without meaning is the importance of AI as it enables the integration of all collected high-dimensional data based on multiomic studies. The number of analyses concerning CVDs, mostly caused by complex and heterogeneous factors like multiple genetic, environmental, and behavioral factors, is constantly growing. Not least because CVD is globally the leading cause of mortality and morbidity [6]. The nascent amount of data gathered by various institutions to improve the quality of healthcare, increase cost-effectiveness, workflow, and adopt rising precision medicine assumptions needs special measures, such as ML. In the light of these findings, new methods of big data analysis, such as variant-Set Test for Association using Annotation infoRmation (STAAR) or JACUSA software (implemented for detection of SNPs), have been proposed [12, 13].

It should be mentioned that most genetic studies are based on Mendelian randomization and GWAS. These are methods that do not fit into the strict definition of AI that exists today. They are used as hybrid methods, mostly in big data analysis, i.e., statistics or protein–protein interaction [14]. Yet, they yield such an amount of data that is hard and time-consuming to analyze without AI application. Nowadays, questions arise as to whether these newly described loci are of biological importance, and which mechanisms are connected with their action and disease-relevant function. Below we present the most relevant studies performing their analyses in silico or using AI approaches and big data analyses.

Studies of human atheroma plaques have been performed for years but have hardly resulted in the most important knowledge during recent years. Depuydt et al. [15] exhaustively analyzed the cellular landscape of human atheroma identifying 14 main cell populations with an in silico method. They found a predominance of T-cells in the lymphocyte population and confirmed that the CD4 + CD28 null line plays an important role in patients with CVD, as well as found pro- and anti-inflammatory cells, distinct endothelial cells (this can be proof for the endothelial to mesenchymal cell transition), and evaluated the cellular interplay within the plaque. The authors additionally integrated GWAS data to

find cell-specific loci responsible for CVD and to determine potential individual targets for drug intervention. Single-cell RNA sequencing and cytometry by time of flight gave a new insight into the macrophage population within the plaque and their function [16]. Another study examined 7,000 human atherosclerotic cells and exploited GWAS as a source to reveal how specific cell types participate in particular diseases, identify cell- and tissue-specific enhancers, and genes that are likely to be influenced by the noncoding genome, describe transcription factors that could play an important role in smooth muscle cell differentiation, as well as describe super-enhancers (defined as those driving the expression of genes important for cell identity and function) in lesion cell types, in the context of atherosclerosis [17].

Recent years have brought important knowledge of noncoding RNAs (ncRNAs) as cardiovascular risk factors and regulators of human cells. They can be divided into long noncoding RNAs (lncRNAs), micro-RNAs (miRNA), and small interference RNAs (siRNAs) [18, 19]. Imprinting represents epigenetic marks common to genes requisite for early development and growth of the placenta. Its loss leads to the expression of miRNA-regulated genes. MicroRNAs, small noncoding single-stranded molecules repressing gene expression at the posttranscriptional level, are not less important in the pathophysiology of atherosclerosis. An epigenomic study of altered DNA methylation was performed finding a hypomethylated imprinted chromosomal locus 14q32 encoding over 60 mRNAs and 70 snoRNAs. The most relevant seems to be the RTL-1 gene (RTL1AS encodes for the hsa-mir-431, -433, -127, -432, and -136) and has-mir-127 as both are upregulated in atherosclerotic plaques and may become potential drug targets [20]. Other studies try to identify new pharmacological targets for CVDs [21, 22]. The influence of monocyte ncRNA on the underlying cardiovascular disorders, including atherosclerosis, was evaluated in a study by Pérez-Sánchez et al. [23] gathering patients with antiphospholipid syndrome. Studies using AI to describe the pathophysiology of atherosclerosis have been performed, i.e., to analyze the impact of ncRNA on the immune response, and find out that the immune system and smooth muscle cell cytoskeleton dysregulation accelerate atherosclerosis progression [24].

Since 2007 and the breakthrough discovery of 9p21 locus by four independent groups of researchers, over 163 loci have been identified and another 300 are suspected to be connected with coronary artery disease (CAD) risk. They implicate the same pathways in atherosclerosis etiology-vascular tone, blood pressure, low-density lipoprotein (LDL-C), triglyceride-rich lipoproteins, inflammation, cellular migration, smooth muscle cell proliferation, and vascular remodeling, lipoprotein (a), neovascularization and angiogenesis, and NO/cGMP signaling. Moreover, a lot of CAD risk loci exhibit an association with other diseases and traits and are designated as pleiotropic. It is estimated that combined they are responsible for 30%–40% of CAD heritability but particular mechanisms remain unknown [25, 26].

Locus 8q24, containing the gene TRIB1, has been associated with the therapeutically beneficial lipid profile and seems to play a key role in plasma lipid homeostasis [27–29]. PHACTR1 gene regulation was proven to have a huge impact on the severity of vascular calcifications in a murine model [30] and the impact of genetic variation can be seen in vascular smooth muscle cells function [31].

A study by Meng et al. [32] presented potential key genes (C3AR1, CCR1, CCR2, CD33, CD53, CXCL10, CXCL8, CXCR4, CYBB, FCER1G, FPR2, ITGAL, ITGAM, ITGAX, ITGB2, and LILRB2) for atherosclerosis pathology that may become potential drug targets. Additionally, a thorough analysis indicated immunity, chemokines, and cell adhesion molecules as the most important biological factors in atherosclerosis.

In 2021, Levin et al. [33] presented a large study identifying 116 SNPs associated with stroke, 107 with CAD, and 105 with peripheral artery disease (PAD). In their study, authors suggest that smoking had an atherogenic effect in all the vascular beds as well as show that the genetic liability for smoking can influence other, already identified cardiovascular risk factors [33].

Lipoprotein A level is linked to atherosclerosis, although its atheroprotective role is still being discussed [34]. A study by Zekavat et al. [35] showed that knowledge of particular lipoprotein A genotype enables more specific CVD risk prediction and that the heritability is high in European and African American populations (75% and 85%, respectively). Recently, APOH was identified as a novel locus for lipoprotein A encoding ß2-glycoprotein I [36]. Another study performed GWAS analysis of 441,016 UK Biobank participants to find out that apolipoprotein B has the highest correlation with coronary heart disease of all studied lipid particles [37]. Holliday et al. [38] found an extensive genetic overlap between large artery atherosclerosis and small vessel ischemic stroke which suggests a potential shared genetic pathogenesis, based on GWAS of 12 389 ischemic stroke patients. Awan et al. [39] investigated genetics of familial hypercholesterolemia.

Among 8,536 patients of African and European ancestry with type 2 diabetes mellitus a GWAS study has been performed. Diabetic patients tend to have higher coronary artery calcification (CAC) and common carotid intima-media thickness (cIMT). The authors have identified a new locus rs8000449 near CSNK1A1L at 13q13.3 for association with CAC, two other loci have been confirmed for CAC and one for cIMT. Locis rs2891168 near CDKN2B-AS1 at 9p21 and rs11170820 near FLJ12825 at 12q13.13 for CAC; rs7412 near APOE at 19q13.32 for cIMT have been correlated with a CAD [40].

Last but not least is the analysis of big data described by Shendre et al. [41] who performed GWAS of 682 HIV-positive and 288 HIV-negative black women and measured carotid intima-media thickness to define whether European ancestry and SNPs may affect the cIMT. The study showed a possible influence of the local European ancestry on atherosclerosis, yet did not define particular SNPs associations with cIMT. Two SNPs within the ryanodine receptor (RYR3) gene were associated with cIMT among HIV patients treated with highly active antiretroviral therapy [42]. Table 2 presents studies included in this analysis.

Table 2: Studies included in the GWAS-section analysis and AI methods applied.

| References | Method of data analysis | AI approaches |
|---|---|---|
| Musunuru et al. [10] | SPSS | Machine learning |
| Shi et al. [11] | HAPGEN | Transfer learning |
| Li et al. [12] | STAAR | Machine learning |
| Piechotta et al. [13] | JACUSA | Machine learning |
| Yazdani et al. [14] | — | Bayesian causal network |
| Depuydt et al. [15] | Custom R scripts, Seurat | Machine learning |
| Örd et al. [17] | HOMER | Support vector regression |
| Aavik et al. [20] | Ingenuity | Machine learning |
| Folkersen et al. [21] | PLINK | Machine learning |
| Plens-Galaska [22] | GraphPad Prism | Machine learning |
| Pérez-Sánchez [23] | Ingenuity | Machine learning |
| Liu et al. [24] | R package | Machine learning |
| Zekavat et al. [35] | WGS, logistic regression | Machine learning |
| Nelson et al. [26] | CARDIoGRAMplusC4D | Machine learning |
| Manichaikul et al. [28] | SMARTPCA, KING | Machine learning |
| Aherrahrou et al. [30] | GraphPad Prism | Machine learning |
| Aherrahrou et al. [31] | PLINK, R package, GraphPad Prism | Machine learning |
| Meng et al. [32] | R package, Cytoscape | Machine learning |
| Karjalainen et al. [34] | CARDIoGRAMplusC4D | Machine learning |
| Richardson et al. [37] | CARDIoGRAMplusC4D | Machine learning |
| Hoekstra et al. [36] | PLINK | Machine learning |
| Holliday et al. [38] | PLINK, METAL | Machine learning |
| Awan et al. [39] | R package, MCODE | Machine learning |
| Lu et al. [40] | LDhat package, METAL | Machine learning |
| Shendre et al. [41] | LAMPLD, PLINK | Machine learning |
| Shrestha et al. [42] | PLINK | Machine learning |

## 4. Radiomics and Artificial Intelligence in Atherosclerosis

A standard in cardiologic procedures includes visualization of the heart, coronary arteries, and aorta with echocardiography, computed tomography, and magnetic resonance.

Echocardiography is a method of visual estimation of the heart—muscle, valves, and aorta—and it does not only depend on precise calculation. It owes its status as a basic diagnostic tool in cardiology mostly to modern AI-based solutions. The road from the PipieLined Image Processing Engine (PIPE) in 1985 through automated strain measurements 20 years later to the current multichamber automatic analyses has been long. ML was introduced to assess the ejection fraction (EF) and longitudinal strain [43, 44]. In heart failure (HF), ML was applied to diagnose HF with preserved EF, classify symptomatic, and asymptomatic patients using strain technology, predict hospitalization risk, exercise tolerance, E/e' measurements, define isolated diastolic dysfunction, and left ventricle filling pressure [45, 46]. Madani et al. [47] presented an algorithm to classify echocardiogram images with a 97.8% accuracy and no overfitting. No less important is the application of ML-based methods in the detection of wall motion abnormalities, assessment of the response of the cardiac muscle to the resynchronization therapy, prediction of major adverse cardiac events (MACEs) or coronary artery calcium (CAC), recognition, and assessment of valvular heart disease, classification of echocardiograms, differentiation of hypertrophic cardiomyopathy (HCM) and physiological hypertrophy of the athletes, or restrictive cardiomyopathy (RCM), and constrictive pericarditis [43, 48–51].

Yet, some limitations cannot be omitted. First, echocardiography is a subjective test. Second, the problem of repeatability is created by the fact that input data are highly dependent on the person performing an examination. Third, AI can detect and characterize valvular and anatomic pathology as well as enhance the quality of existing echocardiograms but is certainly unable to accurately assess all cardiac pathologies that could be noticed and described by a clinician [52].

The importance of cardiovascular computed tomography (CCT) has grown since the 1990s when it was used to assess stenotic regions of arteries and occlusion of bypass grafts. Nowadays, with new diagnostic methods and AI, it has become possible to create visual simulations helpful in planning surgeries, assessing postsurgical complications, predicting outflow tract obstruction, and other hemodynamic complications, or identifying the high-risk phenotype of left ventricular hypertrophy [53, 54]. Computational fluid dynamics (CFD) and finite element (FE) simulations have been used in transcatheter aortic valve replacement, transcatheter mitral valve implantation, thoracic endovascular aortic repair, left atrial appendage occlusion, and to assess myocardial strains

[55–59]. All simulations have been helpful to make personal predictions and assumptions concerning treatment. However, ML does not need CFD or FE simulations to result in excellent outcomes.

Studies by Hu et al. [60] and Gupta et al. [61] proposed a radiomic tool to improve the diagnostic performance of cardiovascular computed tomography angiography (CCTA). Atkov et al. [62] diagnosed CAD based on clinical and laboratory data combined with SNPs and CCTA with 64%–94% accuracy. CT and AI solutions have been applied in the identification of hemodynamically significant coronary artery stenosis, also by computing fractional flow reserve (FFR) [63] which is arising as a noninvasive alternative in diagnosing chest pain. Recently, culprit lesions have been studied using ML models based on CCTA of 60 patients with an acute myocardial infarction. The authors have shown that culprit lesions and severe stenosis present some characteristic features [64].

ML–FFR was found to be a better tool than CCTA to detect and quantify CAC [44]. Interestingly, a performance test between CFD-FFR and ML-FFR was found to be equal [65]. Prediction of obstructive CAD was performed by Al'Aref et al. [66] based on 35,281 patients from the CONFIRM registry. ML was also applied in CCTA to assess volumes of ventricles and atria, detect plaques and identify culprit lesions in acute coronary syndromes (ACS), measure CAC, prepare and segmentation CT images, phenotype coronary plaques, and predict cardiovascular risk [43, 67–69]. As an alternative, a ML method with intravascular ultrasound (IVUS) was proposed to assess FFR in intermediate coronary lesions [70] or to classify the components of an atherosclerotic plaque [71]. Interestingly, the action connective matrixes have been developed to extract potentially invisible features from IVUS images and reduce the image noise [72].

In the recent years, the role of perivascular adipose tissue (PVAT) has been connected with an increased cardiovascular risk. Hypotheses concerning the influence of the inflammatory process within PVAT on worsened CVD outcomes have been broadly discussed in the literature [73]. Thus, it is of high importance to create appropriate and repetitive tools to assess the plaque-associated risk. Oikonomou et al. [74] presented an AI-based tool, the fat radiomic profile (FRP), to assess cardiovascular risk based on CT scans of periadventitial fat. The FRP enabled observation of changes that are dynamic and reversible, including fibrosis, vascularity, and tissue homogeneity. These factors influence adipose tissue health in obesity as well and altogether have created a noninvasive tool to assess the cardiovascular risk better than already established risk factors like age, sex, diabetes, systolic blood pressure, body mass index, obstructive CAD, total cholesterol level, high-density lipoprotein level, and Agatston calcium calcification score (CCS) [74]. A study by Commandeur et al. [75] proposed an AI approach to quantify epicardial and thoracic adipose tissue based on non-contrast CT scans. Eisenberg et al. [76] stated that the epicardial adipose tissue volume is positively correlated with an increased risk of major adverse cardiovascular events (MACE), while attenuation was inversely associated.

Cardiac magnetic resonance (CMR) was highly affected by technological advancements which have boosted its diagnostic and risk stratification capabilities [43]. According to the ESC guidelines, it is the gold standard to assess volumes, mass, and EF of both the left and right ventricles [77]. Together with ML, it was used to assess ventricular volumes, strain, filling, and ejection rate, predict an all-cause death in HF patients, analyze and describe cardiac structures, scars in HCM patients, diagnose HCM, differentiate HCM and hypertensive heart disease, diagnose pulmonary artery hypertension, predict outcomes in newly diagnosed pulmonary hypertension, segmentate, and diagnose carotid atherosclerosis [43, 77–82].

Another approach used CMR in patients with ST-elevation myocardial infarction (STEMI) and stated that radiomics could provide higher diagnostic accuracy for detecting microvascular obstruction [83] as well as become a new tool to predict MACEs [84]. However, the first clinical application of ML-based algorithms in everyday practice might be an algorithm estimating volumes of the left ventricle in CMR [62].

Although databases containing medical information are still being discussed in the ethical context of sensitive data, their need has been highlighted in many fields [85]. Also, nuclear cardiology expressed the proposition of building large image databases which could help to speed up the workflow, reduce costs, and create appropriate prognostic models [85, 86]. Artificial neural networks have been used to detect myocardial ischemia using 99mTc-methoxyisobutylolisonitryle myocardial perfusion images [86]. In the case of nuclear cardiology, AI has been applied to assess cardiac perfusion, predict obstructive CAD, early revascularization, and MACEs, as well as automatically localize the mitral valve plane to prevent image artifacts. Moreover, implemented methods can outperform current clinical approach results [62, 86–92].

The basic goal of radiomics is to present clinically important features incorporated in medical images. Implemented to support genomic data with an AI-based analysis yields precise radiogenomic results. Although it has mostly been applied with outstanding success in oncology, it can be implemented into practice in most medical disciplines, including cardiology [85, 92]. Table 3 presents studies included in this analysis.

## 5. Artificial Intelligence and Atherosclerosis in Other Studies

Zhao et al. [99] proposed a tool for ECG autodiagnosis of ST-elevation myocardial infarction (STEMI). His algorithm achieved results highly comparable with those achieved by an experienced cardiologist and better than medical doctors [99]. Similarly, a deep learning-based algorithm to recognize myocardial infarction by Makimoto et al. [100] was tested in comparison to physicians. Another idea from the Mayo Clinic enabled the prediction of whether the patient is in danger of AF during a sinus rhythm [101]. Recently, Sakli et al. [102] have presented an AI-based tool to classify 27 ECG features, and Elias et al. [103] have proposed a method to identify aortic stenosis, regurgitation, and mitral regurgitation in ECG. Implementation of AI-based ECG analysis does not

Table 3: Studies included in the radiomics-section analysis and AI methods applied.

| References | Method of data analysis | AI approaches |
|---|---|---|
| Huang et al. [44] | — | Convolutional neural networks |
| Sanchez-Martinez et al. [46] | — | Machine learning, clustering |
| Madani et al. [47] | — | Convolutional neural networks |
| Soto et al. [48] | — | Deep learning |
| Duffy et al. [49] | — | Deep learning |
| Yuan et al. [50] | — | Deep learning |
| Liu et al. [51] | — | Deep learning |
| Kay et al. [54] | — | Machine learning, logistic regression |
| Hu et al. [60] | — | Logistic regression |
| Gupta et al. [61] | — | Deep neural network |
| Atkov et al. [62] | — | Deep neural network |
| Lin et al. [64] | — | Machine learning |
| Coenen et al. [65] | — | Machine learning |
| Al'Aref et al. [66] | — | Machine learning |
| von Knebel Doeberitz et al. [68] | — | Deep learning |
| Lee et al. [70] | — | Machine learning |
| Bajaj et al. [71] | — | Machine learning |
| Amato et al. [72] | — | Unsupervised machine learning |
| Oikonomou et al. [74] | — | Machine learning |
| Commandeur et al. [75] | — | Deep learning |
| Eisenberg [76] | — | Deep learning |
| Chen et al. [78] | — | Unsupervised machine learning |
| Wu et al. [79] | — | Deep neural networks |
| Antonopoulos et al. [80] | — | Machine learning |
| Sengupta et al. [81] | — | Machine learning |
| Sparapani et al. [82] | — | Bayesian additive regression trees |
| Ma et al. [83] | — | Machine learning |
| Durmaz et al. [84] | — | Machine learning |
| Laudicella et al. [86] | — | Deep neural networks |
| Nakajima et al. [87] | — | Deep neural networks |
| Hu et al. [88] | — | Machine learning |
| Betancur et al. [89] | — | Deep learning |
| Betancur et al. [90] | — | Machine learning |
| Arsanjani et al. [92] | — | Machine learning |
| Lin et al. [93] | — | Machine learning |
| Baumann et al. [94] | — | Machine learning |
| Suinesiaputra et al. [95] | — | Deep neural networks |
| Lossnitzer et al. [96] | — | Machine learning |
| Lossnitzer et al. [97] | — | Machine learning |
| Lee et al. [70] | SPSS | Machine learning (binary class L2 penalized logistic regression, deep neural networks, random forest, AdaBoost, CatBoost, and support vector machine) |
| Ji et al. [98] | SPSS | Deep learning |

only concern these cases. It has also helped to analyze if patients suffer from asymptomatic HF and to detect antiarrhythmic drugs and abnormal electrolyte levels, ventricular extrasystoles, atrial fibrillation, and left ventricular hypertrophy [104–108].

Antiplatelet therapy is important for cardiology patients who have undergone percutaneous coronary intervention (PCI). A population of 541 patients was studied to compare the effectiveness of treatment with ticagrelor or clopidogrel. Using a ML approach, the researchers found no difference in major adverse events, rehospitalization, or bleeding. However, ticagrelor showed better effects in patients with single-vessel disease [109].

Over 12,000 Caucasian patients were analyzed to determine the influence of aspirin intake on the prevalence of STEMI. Aspirin was connected with a decreased incidence

of STEMI in patients with hypertension, hypercholesterolemia, and in smokers but not among patients with diabetes [110].

It is expected that atherosclerotic tissue presents different biomechanical properties than healthy tissue. An AI-based study by Karimi et al. [111] presented a model to biomechanically characterize atherosclerotic coronary arteries. Fuzzy logic was used to prepare a risk score for the onset of ischemic chronic leg ulcers in PAD patients and natural language processing to better diagnose PAD patients [112, 113]. AI methods have also been used among patients suffering from PAD to link them with potential limitations and symptom severity [114]. ML has been implemented to diagnose PAD based on gait analysis [115]. Age, diabetes mellitus and its complications, congestive HF, comorbidities, and earlier revascularisation are factors increasing an in-hospital mortality in PAD [116].

The aortic diameter might be connected with an occlusive vascular disease [117, 118]. Pirruccello et al. [119] presented GWAS of thoracic aorta describing 104 new loci and their association with aortic aneurysm or dissection. The study was performed on 39,688 individuals from a UK Biobank and is definitely a new direction in identifying asymptomatic patients at risk for an acute aortic syndrome.

Plasma lipids are a modifiable risk factor for CAD. Guo et al. [120] presented a novel marker—the atherogenic index of plasma (AIP)—that may become a novel predictor of CAD in Chinese postmenopausal women. Interestingly, the ILLUMINATE study of torcetrapib, a cholesterol ester transfer protein inhibitor, was closed after 550 days because of the increased rate of cardiovascular events (1.2%) and mortality (0.4%). Artificially created nanoparticles may be helpful in a new drug development [121]. The study of Williams et al. [122] was designed to analyze and explain the harmful mechanism of the drug and to determine whether it would have been possible to predict such outcomes earlier. Proteomics, the protein-based risk score, turned out to be a proper tool to predict the harm within 3 months. Benincasa et al. [123] proposed a digitalized way to individualize the treatment of dyslipidemia and Tsigalou et al. [124] presented a ML method to assess LDL plasma levels. Another study created a method to identify patients with familial hypercholesterolemia [125]. Interestingly, nondiabetic patients with chronic kidney disease may present a hidden proatherogenic lipid profile [126]. Stem cells play an important role in the pathogenesis of atherosclerosis. Their release into the bloodstream during acute myocardial infarction results in atherosclerosis progression. Li et al. [127] designed Atherosclerosis-risk Modules to better understand the pathophysiology of atherosclerosis from the perspective of the system's biology. Connecting AI, gene expression and human networks (signaling and inflammatory pathways) derived valuable information from a stem cell point of view. Biological networks were also investigated by other authors [128, 129]. Dan–Shen–Yin (DSY), a traditional Chinese formula comprising Salvia Miltrorrhiza, Fructus Amomi, and sandalwood, is broadly used in diabetes and CAD; however, the mechanism of action remains unknown. The study proposed integration of biology, proteomics, and experimental pharmacology to understand its influence on atherosclerosis [128]. Molecular understanding of pathophysiological pathways and genes with bioinformatics was performed in other studies as well [130–133]. They can be also used to identify new biomarkers for atherosclerosis [134–138], biomarkers connected with a particular ischemic stroke type [139], and determine if the plaque is rupture-prone [140]. Serum markers for diabetes, CAD, and diabetes associated with CAD were studied using AI as well [141]. The topic of AI in pediatric cardiology has also been raised [142, 143].

The role of the opportunistic imaging concept has also been raised in the literature. Examinations of knee MRI of osteoarthritis patients [144] and standardized knee MRI [145] were a focus of a study of atherosclerosis development within the popliteal artery using ML. AI-based studies which investigated plaque distribution and composition predicted the plaque progression [146, 147]. Table 4 presents studies that are included in this analysis.

## 6. Discussion

Precision phenomapping and ML will constantly gain in popularity. Crosstalk between various "omic" fields shows new paths that may be helpful in better understanding and treating CVDs. The multiomic approach generates big data impossible to analyze without AI solutions as most genetic studies are being conducted with combined methods, using software and other programs incorporating AI. Big data has been called the greatest untapped resource of mankind [85]. AI-based algorithms have made a substantial impact in better understanding of atherosclerosis, genetics, diagnosing CAD, and cardiovascular imaging. Some of them are descriptive studies that create a problem of repeatability of what was already mentioned above.

These new omic fields have been developed to better understand the genomic causes of atherosclerosis. New genes (inherited and de novo mutations) are still being discovered. Similarly, the extraction of radiomic features based on CT or MRI images to build AI-based systems dedicated to speeding up the workflow and providing accurate diagnosis is of paramount importance. Other analyses related to lipidology, PAD, drug discovery, and their interactions are included in the multiomic fields. Attempts are being made to overcome the problem of the black box phenomenon. Other ethical issues such as the "human factor" or the subjectivity and experience of a physician are currently being discussed. Will AI take over human tasks? These are the questions that have been raised, and there is still no proper and unequivocal answer. A simplified schema of intelligent data processing is presented in Figure 3.

## 7. Limitations

In the era of big data, special measures are required. There are also questions of boundaries with other areas, not strictly classified as AI and presented in this review. Some reviews concerning AI solutions implemented in the cardiovascular system are available [42, 46, 53]. However, the authors of this work aimed to present a broader point of view and included studies implementing AI in data analysis. For example,

Table 4: Studies included in the other studies-section analysis and AI methods applied.

| References | Method of data analysis | AI approaches |
|---|---|---|
| Zhao et al. [99] | — | Deep neural networks |
| Makimoto et al. [100] | SPSS | Deep neural networks |
| Attia et al. [101] | — | Deep neural networks |
| Sakli et al. [102] | — | Deep neural networks |
| Elias et al. [103] | — | Deep neural networks |
| Sangha et al. [105] | — | Deep neural networks |
| Chang et al. [106] | — | Deep neural networks |
| Liu et al. [107] | — | Machine learning (decision tree, K-means, back propagation neural network) |
| Tutuko et al. [108] | — | Deep neural networks |
| Xue et al. [109] | — | Decision tree |
| Burgiardini et al. [110] | SPSS | Supervised machine learning (k nearest neighbor algorithm) |
| Karimi et al. [111] | — | Deep neural networks |
| Serra et al. [112] | — | Fuzzy logic |
| Weissler et al. [113] | — | Natural language processing |
| Baloch et al. [114] | — | Supervised machine learning |
| Al Ramini et al. [115] | — | Machine learning |
| Zhang et al. [116] | — | Machine learning |
| Laughlin et al. [117] | SPSS | Machine learning |
| Pirruccello et al. [119] | — | Deep learning |
| Guo et al. [120] | SPSS | Machine learning |
| Williams et al. [122] | Ingenuity | Machine learning |
| Tsigalou et al. [124] | — | Machine learning |
| Paragh et al. [125] | — | Deep neural networks (natural language processing-word2vec) |
| Bermudez-Lopez et al. [126] | — | Machine learning (random forest analysis) |
| Li et al. [127] | — | Human signaling networks, ClusterONE |
| Yang et al. [128] | Cytoscape, MCODE | Machine learning |
| Wang et al. [129] | DAVID, SPSS | Machine learning |
| Tan et al. [130] | Cytoscape, MCODE | Machine learning |
| Zhang et al. [131] | Cytoscape, MCODE | Machine learning |
| Nai et al. [132] | Cytoscape, R package | Machine learning |
| Huang et al. [134] | Cytoscape | Machine learning |
| Yagi et al. [135] | GeneSpring | Machine learning |
| Liu et al. [136] | Cluster 3.0 genes, Python | Machine learning |
| Johno et al. [137] | — | Machine learning |
| Wei and Quan [138] | DAVID | Machine learning |
| Wang et al. [139] | Clustering, DAVID, Cytoscape, MCODE | Machine learning |
| Wang et al. [140] | DAVID, R package, Cytoscape, MCODE | Machine learning |
| Adela et al. [141] | — | Random forest analysis |
| Canton et al. [144] | — | Deep neural networks |
| Chen et al. [145] | — | Deep neural networks |
| Jurtz et al. [146] | — | Deep learning |
| Kigka et al. [147] | — | Machine learning |
| Wang et al. [148] | — | Machine learning |
| Xu et al. [149] | — | Machine learning |
| Forrest et al. [150] | — | Machine learning |
| Yang et al. [151] | — | Machine learning |
| Sharma et al. [152] | — | Machine learning |
| Chen et al. [153] | — | Machine learning |
| Jones et al. [154] | — | Machine learning |
| Jiang et al. [155] | — | Machine learning |

Table 4: Continued.

| References | Method of data analysis | AI approaches |
|---|---|---|
| Ross et al. [156] | — | Machine learning |
| Fan et al. [157] | — | Machine learning |
| Cox et al. [158] | — | Machine learning |
| Gao et al. [159] | — | Machine learning (logistic regression, random forest) |
| Kumar and Priya [160] | — | Machine learning (support vector machine, kernel radial basis function) |
| Park et al. [161] | — | Machine learning |
| Dai et al. [162] | — | Supervised convolutional neural network |
| Afzal et al. [163] | — | Natural language processing |

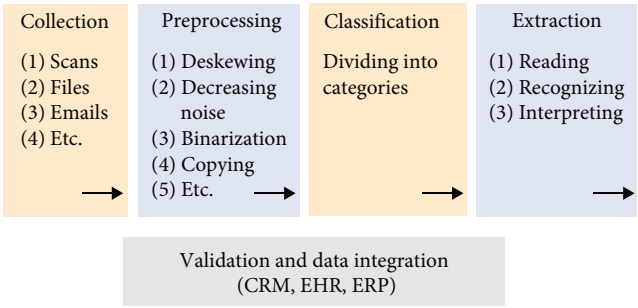


Figure 3: Simplified schema of intelligent data processing.

Depuydt et al. [15] presented big data analysis with the R 3.5 environment and Seurat 3.0 [15, 33]. "R" is a free software for statistical analysis and graphics and the R method is widely used in new-style AI, involving ML. Seurat uses ML for cell classification. Also, other studies implement SPSS [94, 110], PLINK [31, 38, 41, 42], CARDIoGRAMplusC4D [26, 34, 37], or Ingenuity [20, 23, 112] that are strictly correlated with AI. The search biases are unavoidable as well and the authors are aware of this. Moreover, the topic is extensive so the decision was made to exclude papers concerning an AI-based cardiovascular risk stratification as this will be given in another article. Also, the implementation of AI in PAD could be discussed more broadly [164]. Recently, an article raising a topic of AI in atherosclerosis has been published [165]. The article above however, discusses the problem more exhaustively, has been carefully planned and additionally focuses on precision medicine. Other articles present an insight into AI itself [166–170], discuss an application of a "Digital Twin" [171, 172] or an AI-application in various medical fields like nuclear medicine [173], genetics of CVDs [174], cardio-oncology [175–178], oncology [179], electrophysiology [180], assessment of a valvular heart disease [181], chronic diseases [182], and Alzheimer's [183]. This review was not reported and has no official protocol.

## 8. Conclusions

Personalized diagnostics and therapy have already changed the way we practice medicine. The potential of applying AI to the already overburdened healthcare system, with ever-increasing amounts of big data, seems inevitable. This article shows that the application of AI solutions in the light of the 4th industrial revolution has already begun. However, many complications need to be overcome. Not only cardiovascular risk stratification but also therapy and reduced time to diagnosis have become the benchmark in the diagnosis and treatment of atherosclerosis. This branch is still being developed.

## Data Availability

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Oliwia Kolaszyńska and Jacek Lorkowski contributed to methodology, review of literature, preparation of the original draft of the article, and review and editing.

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