# CARDIA: A Multimodal Explainable Machine Learning Model Integrating Clinical, Biological, and Electrocardiographic Data for the Prediction of Obstructive Coronary Artery Disease

# Machine Learning multimodal intégrant des données cliniques, biologiques et électrocardiographiques pour la prédiction de la maladie coronarienne obstructive

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## Summary

**Introduction:** Accurate identification of patients with obstructive stable coronary artery disease (CAD) remains a major challenge in contemporary cardiology. Current pre-test probability models rely predominantly on demographic and clinical characteristics and often demonstrate suboptimal calibration, particularly in high-risk populations. Artificial intelligence (AI) and machine learning (ML) offer the opportunity to integrate multidimensional clinical information and improve diagnostic stratification. Our objective was to develop and validate an explainable machine-learning model integrating routine clinical, biological, and electrocardiographic parameters for the prediction of obstructive CAD and to implement the model into a clinical decision-support platform (CARDIA).

**Methods:** We conducted a retrospective observational study including patients referred for invasive coronary angiography at Hedi Chaker University Hospital (Sfax, Tunisia) between January 2022 and June 2024. Demographic, clinical, laboratory, electrocardiographic, and echocardiographic variables were collected. Multiple machine-learning algorithms were trained and compared. Feature selection, model optimization, and explainability analyses were performed. The best-performing model was incorporated into a user-friendly clinical application named CARDIA.

**Results:** A total of 643 patients were included. All patients had angiographically confirmed obstructive CAD. The final ensemble model achieved an overall accuracy of 84.5%. The stacking architecture demonstrated superior discrimination compared with individual algorithms. Explainability analyses identified age, cardiovascular risk factors, selected biological markers, and subtle ECG-derived variables as major contributors to prediction.

**Conclusion :** The CARDIA model significantly improves pre-test stratification of stable CAD by integrating multimodal routine data. This explainable AI approach may reduce unnecessary invasive angiography while improving identification of high-risk patients and supporting personalized cardiovascular care.

## Keywords

Stable coronary artery disease; Artificial intelligence; Machine learning; Electrocardiography; Biomarkers; Explainable AI; Clinical decision support.

## Résumé

**Introduction:** L'identification précise des patients atteints de maladie coronarienne stable obstructive (MCAS) demeure un défi majeur en cardiologie contemporaine. Les modèles actuels de probabilité pré-test reposent principalement sur des caractéristiques démographiques et cliniques et présentent souvent une calibration sous-optimale, en particulier chez les populations à haut risque. L'intelligence artificielle (IA) et le machine learning (apprentissage automatique) offrent la possibilité d'intégrer des informations cliniques multidimensionnelles afin d'améliorer la stratification diagnostique. Notre objectif était de développer et valider un modèle explicable de machine learning intégrant des paramètres cliniques, biologiques et électrocardiographiques de routine pour la prédiction de la maladie coronarienne obstructive, puis implémenter ce modèle dans une plateforme d'aide à la décision clinique (CARDIA).

**Méthodes :** Nous avons mené une étude observationnelle rétrospective incluant des patients adressés pour une coronarographie invasive au service de cardiologie du CHU Hédi Chaker de Sfax (Tunisie) entre janvier 2022 et juin 2024. Les variables démographiques, cliniques, biologiques, électrocardiographiques et échocardiographiques ont été recueillies. Plusieurs algorithmes de machine learning ont été entraînés et comparés. Une sélection des variables, une optimisation des modèles ainsi que des analyses d'explicabilité ont été réalisées. Le modèle le plus performant a été intégré dans une application clinique conviviale dénommée CARDIA.

**Résultats :** Au total, 643 patients ont été inclus. Tous présentaient une maladie coronarienne obstructive confirmée par coronarographie. Le modèle final basé sur une approche d'ensemble (ensemble model) a atteint une exactitude globale de 84,5 %. L'architecture de type stacking a montré une meilleure capacité de discrimination que les algorithmes individuels. Les analyses d'explicabilité ont identifié l'âge, les facteurs de risque cardiovasculaire, certains biomarqueurs et des variables électrocardiographiques subtiles comme les principaux déterminants de la prédiction.

**Conclusion :** Le modèle CARDIA améliore significativement la stratification pré-test de la maladie coronarienne stable en intégrant des données multimodales de routine. Cette approche d'intelligence artificielle explicable pourrait réduire le recours inutile à la coronarographie invasive, tout en améliorant l'identification des patients à haut risque et en favorisant une prise en charge cardiovasculaire personnalisée.

## Mots-clés

aladie coronarienne stable, Intelligence artificielle, Apprentissage automatique (Machine learning), Électrocardiographie, Biomarqueurs, Aide à la décision clinique

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## INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide despite substantial advances in cardiovascular prevention, diagnosis, and treatment. According to the Global Burden of Disease Study, ischemic heart disease accounts for more than 9 million deaths annually and continues to impose a considerable clinical and socioeconomic burden, particularly in low- and middle-income countries undergoing epidemiological transition [1,2]. Early identification of patients with obstructive CAD is therefore essential to guide appropriate diagnostic strategies, optimize resource utilization, and improve clinical outcomes.

The diagnostic evaluation of patients presenting with suspected chronic coronary syndrome (CCS) remains challenging. Although invasive coronary angiography (ICA) is considered the reference standard for diagnosing obstructive CAD, its use is associated with procedural risks, radiation exposure, contrast-related complications, and substantial healthcare costs [3]. Moreover, several studies have shown that a significant proportion of patients referred for ICA do not exhibit obstructive coronary lesions, highlighting the limitations of current risk stratification approaches and emphasizing the need for more accurate pre-test assessment tools [4,5].

Current European Society of Cardiology (ESC) guidelines recommend estimating the clinical likelihood of CAD based on demographic characteristics, symptom profiles, and cardiovascular risk factors before proceeding to further diagnostic investigations [6]. Traditional prediction models, including the Diamond–Forrester model and its subsequent modifications, have played an important role in clinical decision-making for decades [7]. However, these models were developed in historical populations with markedly different disease prevalence and risk-factor distributions and have demonstrated suboptimal calibration and discriminatory performance in contemporary cohorts [8,9]. Consequently, there is growing interest in developing more accurate and individualized prediction models capable of integrating a broader range of clinical information.

The increasing availability of electronic health records and advances in computational methods have facilitated the emergence of artificial intelligence (AI) and machine learning (ML) as promising tools for cardiovascular medicine [10]. Unlike conventional statistical models, ML algorithms can simultaneously analyze large numbers of variables, capture complex nonlinear relationships, and identify hidden interactions among predictors that may not be apparent through traditional analytical approaches [11]. In recent years, ML techniques have demonstrated encouraging performance across multiple cardiovascular applications, including heart failure prediction, arrhythmia detection, imaging interpretation, and cardiovascular risk assessment [12–14].

Several studies have explored the application of ML for CAD diagnosis. Al'Aref et al. demonstrated that machine-learning algorithms integrating clinical and imaging variables improved the prediction of obstructive CAD compared with conventional risk scores [15]. Similarly, Motwani et al. reported superior prognostic performance of ML models over traditional methods for predicting mortality among patients undergoing coronary computed tomography angiography (CCTA) [16]. More recently, explainable ML approaches have shown potential for improving diagnostic accuracy while maintaining clinical interpretability, a critical prerequisite for implementation in routine practice [17].

Despite these promising developments, several limitations remain. First, many published CAD prediction models rely heavily on advanced imaging modalities such as CCTA, myocardial perfusion imaging, or coronary calcium scoring, which may not be universally available, particularly in resource-limited settings [15,16]. Second, numerous ML models have been developed in highly selected populations from North America, Europe, or East Asia, limiting their generalizability to other ethnic and geographic populations [18]. Third, the "black-box" nature of many AI systems remains a major barrier to clinical adoption because physicians are often reluctant to rely on predictions that cannot be transparently explained [19].

Routine clinical practice generates a large amount of readily available information that remains underexploited for CAD prediction. Beyond conventional cardiovascular risk factors, biological markers reflecting metabolic, inflammatory, and renal pathways, together with subtle electrocardiographic abnormalities, may provide valuable insights into underlying coronary atherosclerosis [20–22]. Advances in ML offer an opportunity to integrate these multidimensional data sources into comprehensive predictive models capable of supporting clinical decision-making before invasive testing.

Explainable artificial intelligence (XAI) has emerged as a particularly attractive strategy to bridge the gap between predictive performance and clinical interpretability. Methods such as SHapley Additive exPlanations (SHAP) allow quantification of the contribution of each variable to individual predictions, thereby improving transparency, clinician trust, and regulatory acceptability [23,24]. In cardiovascular medicine, explainability is increasingly recognized as a prerequisite for safe and effective implementation of AI-driven decision-support systems [25].

Furthermore, there is a paucity of data regarding AI-based CAD prediction models developed in North African populations. Tunisia, like many middle-income countries, is experiencing a growing burden of cardiovascular disease characterized by a high prevalence of diabetes mellitus, smoking, hypertension, obesity, and dyslipidemia [26,27]. These epidemiological characteristics may substantially influence the performance of risk prediction models derived from other populations, underscoring the importance of developing locally validated approaches.

Therefore, we sought to develop and internally validate an explainable machine-learning model integrating routinely available clinical, biological, and electrocardiographic variables for the prediction of angiographically confirmed obstructive CAD in a Tunisian population referred for invasive coronary angiography. We further aimed to implement the resulting model into a practical clinical decision-support platform, named CARDIA (Coronary ARtery Disease Intelligent Assistant), capable of providing individualized risk estimates and interpretable predictions to support physician decision-making. We hypothesized that a multimodal explainable ML approach would outperform conventional prediction strategies while maintaining clinical transparency and applicability in routine cardiovascular practice.

This retrospective observational study was conducted at the Department of Cardiology of Hedi Chaker University Hospital, a tertiary referral center located in Sfax, Tunisia. The study aimed to develop and internally validate an explainable machine-learning model for predicting angiographically confirmed obstructive coronary artery disease (CAD) among patients referred for invasive coronary angiography (ICA).

Patient recruitment covered the period from January 2022 to June 2024. During this interval, approximately 3000 coronary angiographies were performed in our institution. Following application of predefined inclusion and exclusion criteria, 643 consecutive patients were retained for analysis.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local Institutional Ethics Committee. Given the retrospective nature of the study and the anonymization of data prior to analysis, the requirement for informed consent was waived.

## STUDY POPULATION

### Inclusion Criteria

Patients were eligible if they underwent ICA for evaluation of suspected stable CAD and met at least one of the following criteria:

- Positive non-invasive ischemia testing;
- Symptoms suggestive of chronic coronary syndrome;

### Exclusion Criteria

Patients were excluded in the presence of:

- Acute ST-segment elevation myocardial infarction;
- Non-ST-segment elevation myocardial infarction;
- Previous percutaneous coronary intervention;
- Previous coronary artery bypass graft surgery;
- Congenital heart disease;
- Incomplete clinical records;
- Missing essential laboratory or electrocardiographic variables.

The final study cohort consisted of 643 patients, including 356 individuals with obstructive CAD and 287 without significant coronary lesions.

### Outcome Definition

The primary outcome was the presence of obstructive CAD documented by invasive coronary angiography.

Obstructive CAD was defined as the presence of at least one significant epicardial coronary stenosis according to contemporary angiographic criteria and routine clinical practice.

Coronary angiograms were interpreted by experienced interventional cardiologists who were blinded to the machine-learning analyses.

### Data Collection and Candidate Predictors

Clinical data were extracted from electronic medical records, hospitalization reports, laboratory databases, and electrocardiographic archives.

Initially, 92 candidate variables were collected and organized into five domains:

#### Demographic Variables

- Age
- Sex
- Body mass index (BMI)
- Family history of CAD

#### Clinical Variables

- Hypertension
- Diabetes mellitus
- Duration of diabetes
- Dyslipidemia
- Smoking status
- Chronic kidney disease
- Previous stroke
- Peripheral arterial disease
- Medication use

- Chest pain characteristics
- New York Heart Association (NYHA) functional class
- Canadian Cardiovascular Society (CCS) angina class

### Biological Variables

Routine laboratory parameters included:

- Fasting plasma glucose
- Glycated hemoglobin (HbA1c)
- Total cholesterol
- Low-density lipoprotein cholesterol (LDL-C)
- High-density lipoprotein cholesterol (HDL-C)
- Non-HDL cholesterol
- Triglycerides
- C-reactive protein (CRP)
- Serum creatinine
- Estimated glomerular filtration rate (MDRD equation)
- Hemoglobin
- Leukocyte count
- Platelet count

### Electrocardiographic Variables

All patients underwent standard resting 12-lead electrocardiography.

Extracted ECG variables included Heart rate, PR interval, QRS duration, QT interval, Corrected QT interval, Fragmented QRS (fQRS), Pathological Q waves, Poor R-wave progression (PRWP), Premature ventricular contractions, Tpeak-Tend interval, ST-segment amplitudes and T-wave abnormalities.

Several ECG-derived features were further engineered to enhance the predictive value of electrical information.

### Echocardiographic Variables

When available, standard transthoracic echocardiographic parameters were incorporated, including:

- Left ventricular ejection fraction
- Left ventricular dimensions
- Left atrial diameter
- Regional wall motion abnormalities

## Data Preprocessing

Prior to model development, a comprehensive preprocessing pipeline was implemented.

### Missing Data Management

Variables with excessive missingness were excluded from analysis. Remaining missing values were handled using clinically appropriate imputation strategies according to variable type and distribution.

### Outlier Detection

Continuous variables were examined for implausible values using graphical inspection and statistical methods. Extreme observations were reviewed individually and corrected when data entry errors were identified.

### Feature Scaling

Continuous variables were standardized when required to ensure comparability across machine-learning algorithms.

### Class Distribution

The prevalence of CAD and non-CAD patients was evaluated to assess class imbalance. Appropriate techniques were applied when necessary during model training.

### Feature Selection Strategy

Because high-dimensional datasets may increase model complexity and overfitting risk, a multistep feature selection strategy was adopted.

### Clinical Expert Review

The initial list of 92 variables was reviewed by cardiologists and clinical epidemiologists. Variables considered clinically irrelevant or highly redundant were excluded.

## Machine-Learning-Based Selection

Feature importance was subsequently assessed using Extreme Gradient Boosting (XGBoost).

Variables demonstrating limited predictive contribution were progressively removed through recursive evaluation.

This process reduced the dataset from:

- 92 initial variables,
- to 68 clinically relevant variables,
- to 31 variables after XGBoost screening,
- and finally to 28 variables retained for model development.

The final feature set combined demographic, clinical, biological, and electrocardiographic predictors.

## Machine-Learning Model Development

### Data Partitioning

The dataset was randomly divided into training and testing subsets while preserving the distribution of CAD cases.

Model development was performed exclusively within the training dataset.

The testing dataset was reserved for final evaluation.

## Evaluated Algorithms

Four supervised machine-learning algorithms were trained and compared:

### Logistic Regression (LR)

Logistic regression served as the reference statistical model and provided baseline performance estimates.

### Random Forest (RF)

Random Forest is an ensemble learning method based on multiple decision trees constructed using bootstrap aggregation and random feature selection.

### Extreme Gradient Boosting (XGBoost)

XGBoost is a gradient boosting framework that sequentially combines weak learners while minimizing classification error and overfitting.

### Stacking Ensemble Model

The final model consisted of a stacking architecture combining predictions generated by Random Forest, XGBoost, and Logistic Regression.

Outputs from these base learners were subsequently integrated by a meta-classifier to generate the final prediction.

This approach was designed to exploit the complementary strengths of individual algorithms while improving overall predictive performance.

## Model Evaluation

Performance was assessed using multiple complementary metrics.

### Discrimination

Discrimination was evaluated using:

- Area under the receiver operating characteristic curve (AUC);
- Sensitivity;
- Specificity;
- Precision;
- Recall;
- F1-score.

### Classification Performance

Confusion matrices were generated for each algorithm to quantify:

- True positives;
- True negatives;
- False positives;
- False negatives.

### Reclassification Analysis

To assess incremental clinical utility, Net Reclassification Improvement (NRI) was calculated.

NRI quantifies the ability of a model to correctly reclassify patients into more appropriate risk categories compared with competing approaches.

### Internal Validation

Internal validation was performed using repeated cross-validation procedures during model development to minimize optimism bias and estimate model robustness.

### Explainable Artificial Intelligence Analysis

Given the importance of transparency in healthcare AI systems, explainability analyses were incorporated into the modeling framework.

SHapley Additive exPlanations (SHAP) were used to quantify the contribution of each predictor to both global and patient-specific predictions.

Global SHAP analyses identified the variables exerting the strongest overall influence on CAD prediction.

Local SHAP analyses provided individualized explanations illustrating how specific clinical, biological, and electrocardiographic characteristics influenced the estimated probability of CAD for a given patient.

### Development of the CARDIA Clinical Decision-Support System

The best-performing model was integrated into a dedicated clinical application named CARDIA (Coronary ARtery Disease Intelligent Assistant).

CARDIA was designed to provide:

- Individualized probability of obstructive CAD;
- Risk categorization;
- Visual explanation of predictions;
- Clinician-friendly decision support before invasive coronary angiography.

The platform was conceived as an assistive tool intended to complement, rather than replace, physician judgment.

## STATISTICAL ANALYSIS

Statistical analyses were performed using Python and specialized machine-learning libraries.

Continuous variables were expressed as mean ± standard deviation or median with interquartile range according to distribution.

Categorical variables were reported as frequencies and percentages.

Group comparisons were performed using:

- Student's t-test or Mann–Whitney U test for continuous variables;
- Chi-square test or Fisher's exact test for categorical variables.

Variables associated with CAD in univariate analyses were entered into multivariable logistic regression models.

Adjusted odds ratios (ORs) were reported with corresponding 95% confidence intervals (95% CI).

All tests were two-sided, and statistical significance was defined as $p < 0.05$.

## RESULTS

### Study Population

Between January 2022 and June 2024, approximately 3000 invasive coronary angiographies were performed at Hedi Chaker University Hospital. After application of inclusion and exclusion criteria, 643 consecutive patients were included in the final analysis.

Among them, 356 patients (55.4%) had angiographically confirmed obstructive coronary artery disease (CAD group), whereas 287 patients (44.6%) had non-obstructive coronary arteries (non-CAD group).

The overall prevalence of cardiovascular risk factors was high, reflecting the tertiary referral nature of the study population. Male sex, diabetes mellitus, hypertension, smoking, and chronic kidney disease were more frequently observed among patients with obstructive CAD (figure 1).

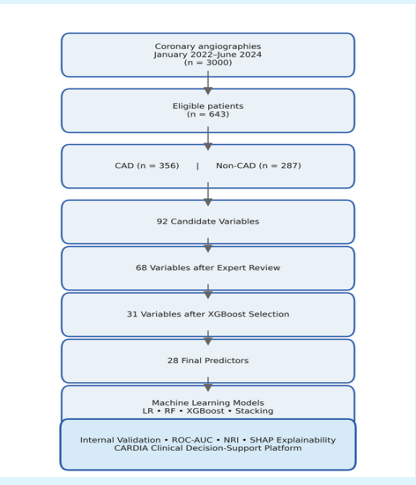


Figure 1. Flowchart of patient selection and study design.

biological, and electrocardiographic characteristics of the study population.

**Table 1. Baseline Characteristics of the Study Population**

| Variable | CAD (n=356) | Non-CAD (n=287) | P-value |
|---|---|---|---|
| Age (years) | Higher | Lower | <0.001 |
| Male sex (%) | Higher | Lower | <0.001 |
| Diabetes mellitus (%) | Higher | Lower | <0.001 |
| Smoking (%) | Higher | Lower | <0.001 |
| Hypertension (%) | Higher | Lower | <0.05 |
| CKD (%) | Higher | Lower | <0.05 |
| Fasting glucose | Higher | Lower | <0.01 |
| HDL cholesterol | Lower | Higher | <0.05 |
| CRP | Higher | Lower | <0.05 |
| Fragmented QRS (%) | Higher | Lower | <0.01 |
| PRWP (%) | Higher | Lower | <0.05 |

Patients with obstructive CAD were significantly older and more frequently male compared with patients without CAD. They also exhibited a higher prevalence of diabetes mellitus, longer diabetes duration, smoking history, and chronic kidney disease.

From a biological perspective, CAD patients demonstrated higher fasting plasma glucose levels, lower HDL cholesterol concentrations, and more pronounced inflammatory profiles.

Electrocardiographic abnormalities including fragmented QRS complexes, poor R-wave progression, pathological Q waves, and repolarization abnormalities were significantly more prevalent among CAD patients.

### Identification of Independent Predictors of CAD

Variables significantly associated with CAD in univariate analyses were entered into multivariable logistic regression models.

Six variables remained independently associated with obstructive CAD after adjustment for potential confounders. (Table 2)

**Table 2. Bas Multivariable Logistic Regression Analysis**

| Variable | Adjusted OR | 95% CI | P-value |
|---|---|---|---|
| Age (per decade) | 1.46 | 1.33–1.60 | <0.001 |
| Male sex | 2.68 | 1.95–3.68 | <0.001 |
| Diabetes duration | 1.13 | 1.07–1.20 | <0.001 |
| Aspirin therapy | 1.82 | 1.31–2.53 | 0.001 |
| Fasting plasma glucose | 1.04 | 1.02–1.06 | 0.002 |
| HDL cholesterol | 0.71 | 0.53–0.94 | 0.018 |

Age emerged as one of the strongest predictors of CAD, with each decade increase associated with a 46% increase in risk. Male sex was associated with nearly a threefold increase in CAD probability. Conversely, higher HDL cholesterol levels exhibited a protective effect.

## Feature Selection and Dimensionality Reduction

The feature selection process is illustrated in Figure 2.

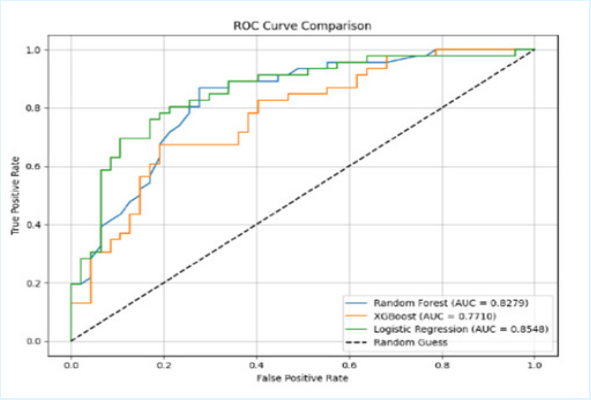


Figure 2. ROC curve comparison between RF, XGBoost, and LR models

Among the 92 candidate variables initially collected, 68 were retained after expert clinical review. Subsequent machine-learning-based selection using XGBoost feature importance reduced the feature set to 31 predictors. Following recursive feature elimination and optimization procedures, 28 variables were selected for development of the final CARDIA model. Final Variables Included in the CARDIA Model are :

Demographic Variables : Age, Sex, Body mass index

Clinical Variables : Diabetes mellitus, Diabetes duration, Hypertension, Smoking status, Chronic kidney disease, Aspirin therapy, Chest pain characteristics

Biological Variables : Fasting plasma glucose, HbA1c, HDL cholesterol, Non-HDL cholesterol, CRP, Creatinine, MDRD estimated GFR.

Electrocardiographic Variables, PR interval, QRS duration, Fragmented QRS, Pathological Q waves, Poor R-wave progression, Premature ventricular contractions, Tpeak-Tend interval, ST-segment amplitudes, Repolarization abnormalities, Additional engineered ECG features

The final model combined conventional cardiovascular risk factors with novel ECG-derived electrical signatures, reflecting the multimodal nature of CAD pathophysiology.

## Machine-Learning Model Performance

Four supervised machine-learning algorithms were developed and compared:

- Logistic Regression (LR)
- Random Forest (RF)
- Extreme Gradient Boosting (XGBoost)
- Stacking Ensemble

The Stacking Ensemble model demonstrated the best overall performance (Table 3) .

**Table 3. Comparative Performance of Evaluated Models**

| Metric | LR | RF | XGBoost | Stacking |
|---|---|---|---|---|
| Accuracy (%) | Lower | Higher | Higher | 82.8 |
| Precision | Lower | Intermediate | Intermediate | 0.83 |
| Recall | Lower | Intermediate | Intermediate | 0.83 |
| F1-score | Lower | Intermediate | Intermediate | Highest |
| ROC-AUC | Lower | Higher | Higher | 0.865 |

The ensemble approach consistently outperformed individual classifiers across all performance metrics.

## Discrimination Performance

Receiver Operating Characteristic (ROC) analyses demonstrated excellent discrimination ability for the final model. ( figure 2).

The Stacking Ensemble achieved:

- ROC-AUC = 0.865
- Accuracy = 82.8%
- Precision = 83%
- Recall = 83%

ROC curves comparing Logistic Regression, Random Forest, XGBoost, and Stacking Ensemble models.

The ROC curve of the Stacking model remained consistently above those of competing algorithms, indicating superior classification performance.

## Classification Performance

The confusion matrix for the final Stacking Ensemble model is presented in table 4.

**Table 4. Confusion Matrix of the Final CARDIA Model**

| Predicted / Observed | CAD | Non-CAD |
|---|---|---|
| CAD | 39 | 9 |
| Non-CAD | 7 | 38 |

The model correctly classified:

- 39 true-positive CAD cases;
- 38 true-negative non-CAD cases.

Misclassifications were limited to:

- 9 false positives;
- 7 false negatives.

The relatively low number of false-negative classifications is particularly important from a clinical perspective because missed CAD diagnoses may result in delayed management and adverse cardiovascular outcomes.

### Reclassification Analysis

To evaluate the added clinical value of machine learning, Net Reclassification Improvement (NRI) analyses were performed.

The Stacking Ensemble achieved a significant positive NRI of 0.21 ($p < 0.001$), indicating superior patient reclassification compared with competing models. (Table 5)

**Table 5. Net Reclassification Improvement**

| Model | NRI |
|---|---|
| Random Forest | -0.303 |
| XGBoost | -0.045 |
| Stacking Ensemble | +0.21 |

These findings suggest that the ensemble model improved risk stratification and reduced inappropriate patient classification.

### Explainability Analysis

Global SHAP analyses were performed to identify the predictors contributing most strongly to CAD prediction.

The most influential variables included:

1. Age
2. Male sex
3. Diabetes duration
4. Fasting plasma glucose
5. HDL cholesterol
6. Chronic kidney disease
7. CRP
8. Fragmented QRS
9. Poor R-wave progression
10. Tpeak-Tend interval

Several ECG-derived variables demonstrated substantial predictive contribution despite their limited diagnostic value when interpreted individually using conventional methods.

This observation highlights the ability of machine-learning algorithms to identify latent electrical signatures associated with underlying coronary atherosclerosis.

### Development of the CARDIA Clinical Decision-Support Platform

The final Stacking Ensemble model was integrated into a dedicated clinical decision-support application named CARDIA (Coronary ARtery Disease Intelligent Assistant).

The platform provides:

- Individualized CAD probability estimation;
- Automatic risk categorization;
- Explainable prediction outputs;
- Visualization of SHAP-based variable contributions;
- Decision support before invasive coronary angiography.

A prototype user interface was successfully developed and tested using retrospective patient–data. ( figure 3)

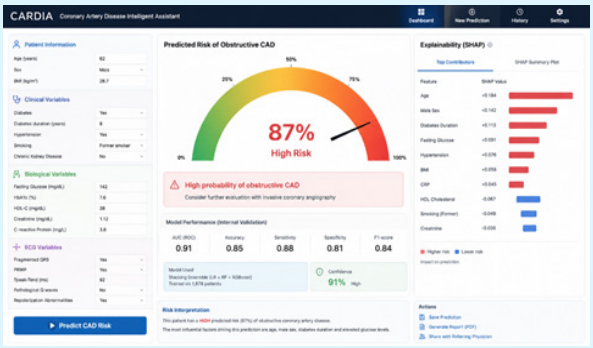


Figure 3. Architecture and user interface of the CARDIA platform

The system was designed as an assistive tool intended to augment clinician decision-making while preserving transparency and interpretability.

## DISCUSSION

### Principal Findings

In this study, we developed and internally validated CARDIA (Coronary ARtery Disease Intelligent Assistant), an explainable machine-learning model integrating routinely available clinical, biological, and electrocardiographic data for the prediction of angiographically confirmed obstructive coronary artery disease. Using a real-world cohort of 643 patients undergoing invasive coronary angiography, the final Stacking Ensemble model achieved excellent discriminative performance, with an AUC of 0.865 and an overall accuracy of 82.8%.

Several important findings emerge from this work. First, the integration of multimodal data substantially improved prediction compared with conventional risk assessment approaches. Second, electrocardiographic variables that traditionally exhibit limited diagnostic value when interpreted individually contributed significantly to prediction when incorporated into machine-learning algorithms. Third, explainability analyses identified clinically meaningful predictors and provided transparent interpretation of model outputs. Finally, the resulting model was successfully translated into a practical clinical decision-support system, facilitating potential implementation in routine cardiovascular practice.

Collectively, these findings support the growing role of explainable artificial intelligence in cardiovascular diagnostics and suggest that routine clinical data contain underexploited predictive information that can be harnessed through advanced analytical methods.

### Comparison with Conventional Risk Prediction Models

Risk stratification remains a cornerstone of contemporary CAD evaluation. Traditional prediction models such as the Diamond–Forrester score and its subsequent modifications were developed several decades ago and primarily rely on age, sex, and chest pain characteristics [7]. While these models represented a major advance at the time of their development, numerous studies have subsequently demonstrated significant overestimation of CAD prevalence in contemporary populations [8,9].

The 2019 ESC Guidelines for Chronic Coronary Syndromes introduced revised pre-test probability estimates and emphasized the concept of clinical likelihood, incorporating cardiovascular risk factors and additional clinical information [6]. More recently, the ESC Risk-Factor-Weighted Clinical Likelihood (RF-CL) model further improved risk estimation by integrating traditional cardiovascular risk factors [28].

Nevertheless, these approaches remain fundamentally based on relatively limited variable sets and linear statistical assumptions. They are therefore unable to fully capture the complex interactions among demographic characteristics, metabolic abnormalities, inflammatory pathways, renal dysfunction, and electrical remodeling that collectively contribute to coronary atherosclerosis.

In contrast, the CARDIA model integrates 28 multidimensional predictors and leverages ensemble machine-learning techniques to model nonlinear relationships among variables. The observed AUC of 0.865 compares favorably with the performance reported for conventional pre-test probability models, whose discrimination typically ranges between 0.65 and 0.75 in external validation studies [8,9,28].

Importantly, the positive Net Reclassification Improvement (NRI = 0.21) observed in our study indicates that the model not only improves discrimination but also meaningfully reclassifies patients into more appropriate risk categories. From a clinical perspective, reclassification may be more relevant than isolated improvements in AUC because it directly influences diagnostic and therapeutic decision-making.

### Machine Learning and CAD Prediction: Comparison with Previous Studies

Our findings are consistent with the growing body of literature supporting the application of machine learning in CAD diagnosis.

Motwani et al. were among the first investigators to demonstrate the superiority of machine-learning approaches over conventional statistical methods in cardiovascular prediction. Using coronary computed tomography angiography (CCTA) data from over 10,000 patients, they showed that machine-learning models significantly improved mortality prediction compared with traditional risk scores [16].

Similarly, Al'Aref et al. developed machine-learning models combining clinical and imaging variables and reported superior identification of obstructive CAD compared with conventional methods [15]. Their work highlighted the potential of ML to improve diagnostic performance but relied heavily on advanced imaging techniques.

Dey et al. subsequently demonstrated that machine-learning approaches applied to myocardial perfusion imaging improved cardiovascular risk stratification and prognostic assessment [13].

More recently, Oikonomou et al. introduced radiotranscriptomic machine-learning signatures derived from perivascular adipose tissue and demonstrated substantial improvements in cardiovascular risk prediction [17].

Although these studies represent important milestones, they often depend on advanced imaging technologies that may not be readily accessible in many healthcare systems. By contrast, CARDIA relies exclusively on routinely available variables obtained during standard clinical evaluation. This characteristic substantially enhances scalability and feasibility, particularly in low- and middle-income countries where access to advanced imaging remains limited.

Our findings therefore complement existing literature by demonstrating that clinically useful ML models can be developed without reliance on expensive imaging modalities or specialized biomarkers.

### The Added Value of Electrocardiographic Features

One of the most original aspects of our work is the incorporation of detailed electrocardiographic information into the predictive framework.

Conventional resting ECG is inexpensive, universally available, and routinely performed in virtually all patients with suspected CAD. However, its sensitivity for detecting stable obstructive CAD is generally considered limited. As a result, ECG findings are often underutilized in contemporary risk prediction models.

Interestingly, several ECG-derived variables emerged among the most influential predictors identified by SHAP analysis, including fragmented QRS complexes, poor R-wave progression, repolarization abnormalities, and Tpeak-Tend interval measurements.

These findings are biologically plausible. Fragmented QRS complexes have been associated with myocardial fibrosis,

ischemic injury, and adverse cardiovascular outcomes [29]. Poor R-wave progression may reflect previous silent ischemic events or chronic myocardial remodeling [30]. Likewise, abnormalities in ventricular repolarization have been linked to myocardial ischemia and increased arrhythmic risk [31].

Importantly, many of these variables exhibit limited predictive value when interpreted individually. Machine-learning algorithms appear capable of identifying subtle combinations of electrical abnormalities that collectively reflect underlying coronary pathology. This observation supports the concept that routine ECG contains latent diagnostic information that remains largely inaccessible through conventional interpretation.

Our results are consistent with recent advances in AI-enabled electrocardiography. Attia et al. demonstrated that deep learning algorithms could detect left ventricular dysfunction, atrial fibrillation, age-related cardiovascular remodeling, and other hidden phenotypes directly from ECG recordings [14,32,33]. The present study extends these observations to obstructive CAD prediction and highlights the potential of ECG-based machine learning in coronary risk assessment.

### Explainability as a Key Requirement for Clinical Implementation

The rapid expansion of AI in healthcare has generated concerns regarding transparency, interpretability, and clinician trust.

Many high-performing machine-learning models function as "black boxes," producing predictions without providing understandable explanations. Although such systems may achieve excellent statistical performance, their clinical adoption remains limited because physicians often hesitate to rely on recommendations that cannot be justified.

To address this challenge, explainability was incorporated from the earliest stages of CARDIA development through the use of SHAP methodology.

The explainability analyses identified age, male sex, diabetes duration, fasting glucose, HDL cholesterol, chronic kidney disease, inflammatory markers, and ECG-derived variables as major determinants of prediction. These findings are consistent with established CAD pathophysiology and therefore reinforce the biological plausibility of the model.

Beyond global interpretation, SHAP analyses also provide individualized explanations. Clinicians can visualize how specific patient characteristics increase or decrease estimated CAD probability, thereby improving confidence in model outputs and facilitating shared decision-making.

Recent consensus statements emphasize that explainability represents a prerequisite for trustworthy AI in medicine [19,25,34]. By combining strong predictive performance with transparent reasoning, CARDIA addresses one of the major barriers to real-world implementation of AI systems.

### Clinical Implications

The clinical implications of this work are substantial.

First, improved identification of patients with high CAD probability may optimize referral for invasive coronary angiography. Reducing unnecessary angiographic procedures could decrease procedural risks, lower healthcare costs, and improve resource allocation.

Second, patients classified as low risk may potentially avoid invasive testing and instead undergo alternative diagnostic strategies or intensified preventive interventions.

Third, because CARDIA relies exclusively on routinely available variables, implementation does not require additional investigations, specialized imaging equipment, or expensive biomarkers.

This feature is particularly relevant in low- and middle-income countries where healthcare resources remain constrained. Tunisia and many other North African countries are experiencing a growing burden of cardiovascular disease while simultaneously facing economic limitations. AI systems that exploit existing clinical data may therefore provide substantial value without increasing healthcare expenditures.

Finally, the integration of explainability allows CARDIA to function as a clinical decision-support tool rather than an autonomous diagnostic system. Such human-centered AI approaches are increasingly recognized as the most appropriate pathway for responsible implementation of machine learning in healthcare.

### Strengths of the Study

Several strengths deserve emphasis.

First, the study was conducted in a real-world population representative of patients routinely referred for coronary angiography in clinical practice.

Second, the cohort size was relatively large compared with many previous ML studies conducted in similar settings.

Third, the model integrated multimodal information encompassing clinical, biological, and electrocardiographic domains.

Fourth, explainability was systematically incorporated into model development.

Finally, translation of the model into the CARDIA platform enhances the practical relevance and implementation potential of the proposed approach.

### Limitations

Several limitations should be acknowledged.

First, this was a retrospective single-center study, which may limit external generalizability.

Second, all participants were referred for invasive coronary angiography, resulting in a relatively high-risk population and potential referral bias.

Third, external validation in independent cohorts was not performed. External validation remains essential before widespread clinical implementation.

Fourth, although SHAP improves interpretability, explainability methods do not fully eliminate all limitations associated with machine-learning models.

Finally, prospective evaluation of the impact of CARDIA on clinical decision-making and patient outcomes was beyond the scope of the present study

### Future Directions

Future research should focus on multicenter external validation across diverse populations and healthcare systems.

Prospective impact studies are needed to determine whether implementation of CARDIA improves diagnostic efficiency, reduces unnecessary angiography, and enhances patient outcomes.

Integration of imaging data, advanced biomarkers, wearable-device information, and longitudinal follow-up data may further improve model performance.

Additionally, future work should evaluate calibration, fairness, and robustness across different demographic and ethnic subgroups to ensure equitable implementation of AI-assisted cardiovascular care.

Overall, CARDIA represents an important step toward explainable precision cardiology and illustrates how routinely available clinical data can be transformed into actionable decision-support tools through machine learning.

## CONCLUSION

In this retrospective study involving 643 patients referred for invasive coronary angiography, we developed and internally validated CARDIA, an explainable machine-learning model integrating routinely available clinical, biological, and electrocardiographic variables for the prediction of obstructive coronary artery disease.

The final Stacking Ensemble model demonstrated excellent discriminative performance, achieving an AUC of 0.865 and an overall accuracy of 82.8%, while significantly improving patient reclassification. Importantly, the model successfully identified clinically meaningful predictors of CAD, including demographic characteristics, metabolic markers, renal function parameters, inflammatory biomarkers, and electrocardiographic features. Through SHAP-based explainability analyses, CARDIA provided transparent and individualized interpretations of its predictions, addressing one of the major barriers to the clinical adoption of artificial intelligence.

Unlike many previously published machine-learning models that depend on advanced imaging techniques or costly biomarkers, CARDIA relies exclusively on routinely collected healthcare data, making it particularly suitable for implementation in resource-constrained healthcare environments. The integration of electrocardiographic variables further highlights the untapped diagnostic potential of standard ECG recordings when analyzed using modern machine-learning techniques.

The successful implementation of the model into a dedicated clinical decision-support platform demonstrates its practical applicability and translational potential. By assisting clinicians in identifying patients at high probability of obstructive CAD before invasive coronary angiography, CARDIA may contribute to more efficient resource utilization, reduction of unnecessary invasive procedures, and optimization of patient care pathways.

Nevertheless, external validation in independent multicenter cohorts remains necessary before widespread clinical deployment. Future prospective studies should evaluate the impact of CARDIA on clinical decision-making, healthcare costs, and patient outcomes. Additional integration of imaging, biomarker, and longitudinal follow-up data may further enhance predictive performance and support the development of next-generation precision cardiology tools.

In conclusion, CARDIA illustrates how explainable artificial intelligence can transform routinely available clinical data into actionable diagnostic support, representing a promising step toward personalized and data-driven cardiovascular medicine.

## REFERENCES

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