RESEARCH PAPER

Lipoprotein(a), High-Sensitivity C-Reactive Protein, and Homocysteine as Emerging Biomarkers of Coronary Artery Disease Risk in the Indian Population: A Hospital-Based Case-Control Study

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Abstract

Background: Coronary artery disease (CAD) is the leading cause of cardiovascular mortality worldwide and poses a significant health burden in India. Emerging biomarkers such as Lipoprotein(a) [Lp(a)], high-sensitivity C-reactive protein (hs-CRP), and homocysteine may improve cardiovascular risk prediction beyond conventional risk factors.

Objective: To evaluate the association of serum Lipoprotein(a), hs-CRP, and homocysteine with coronary artery disease and assess their potential as biomarkers for cardiovascular risk stratification in the Indian population.

Methods: A hospital-based case-control study was conducted among 100 participants, including 50 angiographically confirmed CAD patients and 50 age- and sex-matched healthy controls. Serum Lipoprotein(a), hs-CRP, and homocysteine levels were measured using standardized laboratory methods. Statistical analysis included group comparisons, multivariable logistic regression, and receiver operating characteristic (ROC) curve analysis.

Results: Patients with CAD exhibited significantly higher serum Lipoprotein(a), hs-CRP, and homocysteine levels than controls (all $p < 0.001$). Elevated Lipoprotein(a) (adjusted OR 2.4, 95% CI: 1.3–4.5), hs-CRP (adjusted OR 3.1, 95% CI: 1.7–5.8), and homocysteine (adjusted OR 2.7, 95% CI: 1.5–4.9) were independently associated with CAD. Combined biomarker assessment demonstrated very good predictive performance (AUC = 0.91), outperforming individual biomarkers.

Conclusion: Lipoprotein(a), hs-CRP, and homocysteine may serve as complementary biomarkers for identifying individuals at increased risk of CAD. Their combined assessment has the potential to improve early cardiovascular risk stratification and support preventive clinical strategies. Further multicenter prospective studies are required to confirm these findings.

Keywords: Coronary artery disease; Lipoprotein(a); High-sensitivity C-reactive protein; Homocysteine; Cardiovascular biomarkers; Indian population.

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Introduction

Coronary artery disease (CAD) is the leading cause of cardiovascular morbidity and mortality worldwide and continues to represent one of the greatest public health challenges of the twenty-first century. According to recent global estimates, cardiovascular diseases account for nearly one-third of all deaths, with coronary artery disease constituting the largest proportion. In India, the rate of CAD prevalence has been alarmingly rising in the last three decades because of the rapid urbanization, sedentary living, dietary habits, rising obesity, diabetes mellitus, high blood pressure and tobacco use. Moreover, CAD is also more likely to be found at a younger age in Indians than in Western populations, which leads to significant socioeconomic impacts and higher healthcare costs. The early detection of high-cardiovascular-risk individuals remains among the

primary objectives of preventive cardiology and can significantly decrease the burden of the disease by intervening early and modifying lifestyle **[1]**. Conventional cardiovascular risk factors such as age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, and family history are major risk factors of CAD. Nevertheless, these traditional predictors do not explain a considerable percentage of cardiovascular events. The normal or slightly abnormal lipid profiles of many patients who present with acute coronary syndrome underscore the importance of further biomarkers that can enhance risk prediction beyond the conventional factors. Recent developments in cardiovascular biology have highlighted the role of inflammatory mechanisms, genetic predisposition, endothelial dysfunction, oxidative stress, and lipid metabolic changes in the initiation and development of atherosclerosis **[2]**. Atherosclerosis is now considered a long-term inflammatory ailment, which is signified by endothelial injury, lipid deposition in the arterial wall, inflammatory cell infiltration, smooth muscle growth, and the development of plaque. Gradual increase in plaque instability ultimately culminates in thrombosis and heart attack. Many circulating biomarkers have thus been studied as predictors of vascular inflammation and vulnerability of the plaque. Lipoprotein(a), high-sensitivity C-reactive protein (hs-CRP) and homocysteine are some of them which have received significant interest due to their different but complementary roles in the pathogenesis of atherosclerotic disease **[3]**. Lipoprotein(a) Lp(a) is a genetically predetermined low-density lipoprotein-like particle that includes apolipoprotein(a), confers unique proatherogenic and prothrombotic capabilities. Increased Lp (a) facilitates cholesterol deposition in the walls of the arteries, promotes smooth muscle cell growth, suppresses fibrinolysis by structural similarity with plasminogen, and accelerates the growth of the plaque. In contrast to traditional lipids, serum Lp(a) levels are not affected by diet or lifestyle and are mainly controlled by genetics. Lp(a) has thus become a distinct cardiovascular risk factor in a number of epidemiological and genetic studies, especially in South Asian populations, where high levels are comparatively prevalent **[4]**. Inflammation is becoming a key element of coronary atherosclerosis. High-sensitivity C-reactive protein is an acute-phase reactant produced by hepatocytes in response to stimulation by interleukin-6 and other pro-inflammatory cytokines. However, in contrast to traditional CRP tests, hs-CRP is sensitive to extremely low levels of systemic inflammation, and has been shown to be a predictor of future cardiovascular events in seemingly healthy persons. An increase in hs-CRP is an indicator persistent vascular inflammation, endothelial dysfunction, and plaque instability and offers valuable prognostic data to traditional lipid measurements. A number of potential research studies have confirmed hs-CRP as a factor predictive of myocardial infarction, stroke and cardiovascular death by itself **[5]**. Homocysteine is a sulfuric acid amino acid that is produced in the metabolism of methionine. Hyperhomocysteinemia has been involved in endothelial dysfunction, oxidative stress, vascular smooth muscle proliferation, platelet activation, and thrombotic tendency. High homocysteine levels can be a consequence of nutritional deficiency of folate or vitamin B12, kidney failure, genetic polymorphism and lifestyle. Observational studies have indicated that homocysteine levels are associated with an increased risk of cardiovascular disease, but intervention trials with vitamin supplements have shown variable results. Despite this, homocysteine remains a biologically feasible biomarker of endothelial damage and vascular impairment **[6]**. The Indians have distinct genetic, metabolic, and environmental factors that predispose them to early coronary artery disease. This increased susceptibility is increased by higher levels of insulin resistance, central obesity, high levels of Lp(a), low levels of HDL cholesterol, and sustained low-grade inflammation. Therefore, biomarkers that have been proven to be valid in Western populations need to be assessed independently in cohorts of Indians before they can be used in routine clinical practice. The hospital-based studies on angiographically confirmed patients with CAD offer a possibility to test these biomarkers in the conditions of the real clinical practice **[7]**. Even though past studies have focused on Lp(a), hs-CRP, or homocysteine individually, few studies have been able to assess all three biomarkers in the same Indian population. As these biomarkers represent unique pathophysiological pathways such as lipid metabolism, inflammation and endothelial dysfunction, a combined measurement of these biomarkers may offer better risk stratification than any of these biomarkers individually. Combining various biomarkers can thus enable early detection of individuals at high risk, enhance preventive care, and provide personalized cardiovascular care **[8]**. The emerging developments in cardiovascular medicine are now increasing emphasize multi-marker techniques of disease prediction. Inflammatory, lipid-related and metabolic biomarker-based statistical models have been shown to be more discriminatory than traditional risk scores. The results of receiver operating characteristic (ROC) studies indicate that a combination of biomarkers is more effective in

enhancing sensitivity and specificity in the detection of clinically relevant coronary artery disease. These approaches can be especially useful in the resource-scarce health care environments where specific screening of the high-risk groups is a crucial procedure **[9]**. This case-control study was thus conducted in the hospital to assess the serum Lipoprotein(a), hs-CRP and homocysteine levels of angiographically proven coronary artery disease (CAD) patients and healthy controls. The research also aimed to establish the independent relation of these biomarkers with CAD and evaluate the diagnostic efficiency of these biomarkers in conjunction with each other in stratifying cardiovascular risks in the Indian population. The hypothesis was that concurrent evaluation of the biomarkers would provide a better predictive value than single measurements, and therefore justify their use in future cardiovascular risk assessment measures. **[10]**.

Materials and Methods

Study Design and Participants: This was a case-control study done in a hospital in the Departments of Biochemistry and Medicine, ESIC Medical College & Hospital, Indore, Madhya Pradesh, India. There was a total of 100 participants in the study: 50 patients (coronary artery disease (CAD) with angiographic confirmation) and 50 controls (apparently healthy age- and sex-matched participants). The research was conducted within a specified study period after obtaining the consent of the Institutional Ethics Committee. All the participants were provided with written informed consent before enrolling. The research was conducted according to the ethical principles of the Declaration of Helsinki.

Inclusion Criteria: Patients aged 30–75 years of either gender who were diagnosed with coronary artery disease based on coronary angiography showing ≥50% stenosis in at least one major coronary artery were included in the case group. Individuals who presented to the hospital with stable angina, unstable angina, or previous history of myocardial infarction confirmed by angiographic evidence were eligible. Controls were age- and sex-matched individuals without clinical or angiographic evidence of coronary artery disease. Participants with stable hypertension or diabetes mellitus but without documented CAD were eligible, provided they had no acute inflammatory illness, chronic kidney disease, chronic liver disease, autoimmune disorders, malignancy, or other exclusion criteria.

Exclusion Criteria: Participants with chronic kidney disease, chronic liver disease, acute or chronic inflammatory disorders, autoimmune diseases, malignancy, thyroid dysfunction, or recent infections within the preceding three months were excluded from the study. Individuals on lipid-lowering drugs, vitamin B12 or folate supplementation, or anti-inflammatory medications were also excluded to avoid confounding effects on biomarker levels. Pregnant and lactating women were not included. Individuals with acute infection or hs-CRP concentrations >10 mg/L suggestive of acute systemic inflammation were excluded or reassessed after recovery.

Data Collection: A detailed clinical history was obtained from all participants using a structured questionnaire, including demographic data, lifestyle habits (smoking, alcohol consumption), dietary patterns, and family history of coronary artery disease. Anthropometric measurements such as height, weight, and body mass index (BMI) were recorded using standard procedures. Blood pressure was measured using a calibrated sphygmomanometer after a rest period of at least 10 minutes. Venous blood samples were collected from all participants after an overnight fasting period of 10–12 hours under aseptic conditions.

Biochemical Analysis: Approximately 5 mL of fasting venous blood was drawn from each participant. Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at −20°C until analysis. Serum Lipoprotein(a) levels were measured using an immunoturbidimetric assay. High-sensitivity C-reactive protein (hs-CRP) levels were estimated using a high-sensitivity immunoassay based on latex-enhanced turbidimetry. Serum homocysteine levels were measured using an enzymatic cycling assay. All biochemical analyses were performed in the Department of Biochemistry using the Cobas Integra 400 plus Fully Automatic Analyzer (Roche Diagnostics) following standardized protocols. The analyzer was calibrated according to the manufacturer's recommendations, and internal quality control as well as external quality assurance procedures were strictly followed to ensure the accuracy, precision, and reproducibility of the results.

Diagnosis of Disease: The diagnosis of coronary artery disease in cases was confirmed by coronary angiography performed in the Department of Cardiology. A significant coronary lesion was defined as ≥50% luminal narrowing in at least one major epicardial coronary artery. Patients were categorized based on clinical presentation and angiographic

findings, including stable angina, unstable angina, or prior myocardial infarction. Controls were confirmed to be free from CAD based on clinical evaluation, absence of symptoms, and normal electrocardiographic findings.

Statistical Analysis: Data distribution was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were compared using Student's independent t-test, whereas non-normally distributed variables were analyzed using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test, where appropriate.

Multivariable logistic regression analysis was performed using biomarker concentrations as continuous variables after standardization (per standard deviation increase). The variables included in the model (age, sex, body mass index, smoking status, hypertension, and diabetes mellitus) were selected a priori based on their established epidemiological association with coronary artery disease. The aim of the model was to determine whether Lipoprotein(a), hs-CRP and homocysteine had independent associations with traditional cardiovascular risk factors. Since this research was purely exploratory, with a small sample, the regression analysis was aimed at assessing relations, but not developing a predictive model. Adjusted odds ratios (ORs) and 95 percent confidence intervals (CIs) were obtained.

To compare the diagnostic performance of Lipoprotein(a), hs-CRP, and homocysteine, receiver operating characteristic (ROC) curve analysis was conducted. The predicted probabilities of the multivariate logistic regression model of all three biomarkers were used to construct a combined biomarker model. Since there was no independent validation cohort, ROC estimates are apparent performance and can be subject to optimism bias. The Youden Index was used to calculate sensitivity and specificity. A p-value of <0.05 was considered statistically significant. The SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) was used to conduct statistical analyses.

Results

A total of 100 participants were enrolled in the study, including 50 patients with angiographically confirmed coronary artery disease (CAD) and 50 age- and sex-matched healthy controls. The demographic and clinical characteristics of the study population are summarized in **Table 1**.

The mean age of the CAD group was 56.8 ± 9.4 years compared with 55.2 ± 8.7 years in the control group, with no statistically significant difference ($p = 0.38$). Similarly, the proportion of male participants was comparable between the two groups (68% vs. 64%, $p = 0.67$). However, patients with CAD had a significantly higher mean body mass index (27.6 ± 3.8 vs. 25.9 ± 3.2 kg/m², $p = 0.02$). The prevalence of conventional cardiovascular risk factors, including smoking (44% vs. 18%, $p = 0.01$), hypertension (52% vs. 20%, $p < 0.001$), and diabetes mellitus (46% vs. 22%, $p = 0.01$), was also significantly greater among CAD patients than controls **(Table 1)**.

Serum concentrations of all three biomarkers were significantly elevated in patients with CAD compared with healthy controls (**Table 2**). Mean Lipoprotein(a) levels were approximately two-fold higher in the CAD group (42.6 ± 15.3 mg/dL) than in controls (21.4 ± 9.8 mg/dL) ($p < 0.001$). Likewise, mean hs-CRP levels were markedly increased in CAD patients (4.8 ± 1.9 mg/L) compared with controls (1.6 ± 0.8 mg/L) ($p < 0.001$). Serum homocysteine concentrations were also significantly higher among cases (18.7 ± 6.2 µmol/L) than controls (10.3 ± 3.4 µmol/L) ($p < 0.001$), indicating a strong association between elevated biomarker levels and the presence of coronary artery disease **(Table 2)**.

To determine whether these biomarkers were independently associated with CAD, multivariable logistic regression analysis was performed after adjustment for age, sex, body mass index, smoking status, diabetes mellitus, and hypertension (**Table 3**). All three biomarkers remained significant independent predictors of CAD. Elevated hs-CRP demonstrated the strongest association with disease (adjusted odds ratio [OR] 3.1, 95% confidence interval [CI]: 1.7–5.8; $p < 0.001$), representing the effect per standard deviation increase in biomarker level, followed by homocysteine (adjusted OR 2.7, 95% CI: 1.5–4.9; $p = 0.001$) and Lipoprotein(a) (adjusted OR 2.4, 95% CI: 1.3–4.5; $p = 0.004$) **(Table 3)**.

Receiver operating characteristic (ROC) curve analysis demonstrated good discriminatory ability for each individual biomarker and further improvement when all three biomarkers were combined (**Table 4**). Among the individual biomarkers, hs-CRP showed the highest diagnostic performance with an area under the curve (AUC) of 0.84, followed by homocysteine (AUC = 0.80) and Lipoprotein(a) (AUC = 0.78). The combined biomarker model yielded an AUC of 0.91, with a sensitivity of 88% and specificity of 84%,

indicating excellent discrimination between CAD patients and healthy controls **(Table 4)**.

Comparison of predictive models further demonstrated the incremental value of incorporating these biomarkers into cardiovascular risk assessment (**Table 5**). A model based solely on traditional cardiovascular risk factors achieved a moderate predictive performance (AUC = 0.72), whereas individual biomarkers produced AUC values ranging from 0.78 to 0.84. In contrast, the combined biomarker model achieved the highest diagnostic accuracy (AUC = 0.91), suggesting that simultaneous assessment of Lipoprotein(a), hs-CRP, and homocysteine provides superior discrimination of CAD risk compared with conventional risk factors or any single biomarker alone **(Table 5)**.

Table 1: Baseline Characteristics of Study Participants

Parameter	CAD Cases (n=50)	Controls (n=50)	p-value
Age (years, mean ± SD)	56.8 ± 9.4	55.2 ± 8.7	0.38
Male gender (%)	68%	64%	0.67
BMI (kg/m²)	27.6 ± 3.8	25.9 ± 3.2	0.02*
Smokers (%)	44%	18%	0.01*
Hypertension (%)	52%	20%	<0.001*
Diabetes mellitus (%)	46%	22%	0.01*

***Significant at p < 0.05**

Table 2: Comparison of Biomarkers Between Cases and Controls

Biomarker	CAD Cases (Mean ± SD)	Controls (Mean ± SD)	p-value
Lipoprotein(a) (mg/dL)	42.6 ± 15.3	21.4 ± 9.8	<0.001*
hs-CRP (mg/L)	4.8 ± 1.9	1.6 ± 0.8	<0.001*
Homocysteine (µmol/L)	18.7 ± 6.2	10.3 ± 3.4	<0.001*

Table 3: Independent Predictors of Coronary Artery Disease

Variable	Adjusted OR	95% CI	Adjusted for
Lp(a)	2.4	1.3–4.5	Age, sex, BMI, smoking, diabetes, hypertension
hs-CRP	3.1	1.7–5.8	Age, sex, BMI, smoking, diabetes, hypertension
Homocysteine	2.7	1.5–4.9	Age, sex, BMI, smoking, diabetes, hypertension

Odds ratios represent the change in risk per standard deviation increase in biomarker levels.

Table 4: ROC Curve Analysis of Biomarkers

Biomarker	AUC (95% CI)	Sensitivity (%)	Specificity (%)
Lipoprotein(a)	0.78 (0.69–0.87)	72	70
hs-CRP	0.84 (0.76–0.92)	80	76
Homocysteine	0.80 (0.71–0.89)	74	72
Combined Model	0.91 (0.85–0.97)	88	84

Table 5: Comparative Predictive Performance

Model	AUC	Diagnostic Accuracy
Traditional risk factors only	0.72	Moderate
Biomarkers individually	0.78–0.84	Good
Combined biomarkers	0.91	Excellent

Overall, patients with coronary artery disease demonstrated significantly higher serum Lipoprotein(a), hs-CRP, and homocysteine concentrations than healthy controls. All three biomarkers remained independently associated with CAD after adjustment for conventional cardiovascular risk factors. Furthermore, the Combined biomarkers demonstrated very good discriminatory performance (AUC = 0.91), indicating improved diagnostic accuracy compared with individual biomarkers or traditional risk factors alone **(Tables 2–5)**.

Discussion

The present hospital-based case-control study demonstrates that serum Lipoprotein(a), high-sensitivity C-reactive protein (hs-CRP), and homocysteine are significantly elevated in patients with angiographically confirmed coronary artery disease (CAD) compared to healthy controls. More importantly, all three biomarkers were found to be independently associated with CAD even after adjustment for conventional cardiovascular risk factors, highlighting their potential role as complementary indicators of atherosclerotic risk. The combined biomarker model showed very good diagnostic performance (AUC = 0.91), indicating strong apparent discrimination between CAD cases and controls.

Lipoprotein(a) is a genetically determined lipoprotein particle that is structurally similar to low-density lipoprotein, but it carries apolipoprotein(a), which imparts prothrombotic and proatherogenic capability. High Lp(a) facilitates deposition of cholesterol in the arterial wall, enhances the growth of smooth muscle, and interferes with the fibrinolytic system by competing with the activation of plasminogen. In the current research, high levels of Lp(a) were significantly associated with CAD (adjusted OR 2.4), which is consistent with previous findings that Lp(a) is an independent cardiovascular risk factor. Massive genetic and epidemiological investigations have also shown that Lp(a) is an additive source of residual cardiovascular risk in statin-treated individuals, which supports its clinical importance in risk prediction programs **[11]**.

Inflammation is a key factor in the development and disease progression of atherosclerosis, with hs-CRP, a sensitive systemic inflammatory biomarker, significantly increasing in CAD patients and being the most significantly associated of the biomarkers studied (adjusted OR 3.1). This observation confirms the concept that vascular inflammation is not just a by-product but a cause of atherosclerotic disease. hs-CRP has been demonstrated to be indicative of endothelial dysfunction, plaque instability and increased cardiovascular risk even in apparently healthy persons. The findings of this study are consistent with earlier large prospective studies, which have shown that hs-CRP is an independent predictor of myocardial infarction and cardiovascular mortality **[12]**.

Homocysteine, a sulfur-based amino acid in the metabolism of methionine was also found to be significantly high in CAD patients. Hyperhomocysteinemia has been reported to cause endothelial damage by oxidative stress, decreased nitric oxide bioavailability, platelet activation, and smooth muscle proliferation. In this research, homocysteine showed a strong independent association with CAD (adjusted OR 2.7), which confirms the fact that it is a modifiable metabolic risk factor. In spite of the inconclusive outcomes of clinical trials of homocysteine-lowering therapy, the relationship between this treatment and atherosclerotic disease burden is observed in the case of observational studies **[13]**.

The best finding of this research is the high predictive ability of the combined biomarker model (AUC = 0.91), which was significantly better than single biomarkers. This observation indicates that CAD is a multifactorial disease that is driven by the interaction of pathways that include lipid metabolism, inflammation and endothelial dysfunction. Thus, the integration of several biomarkers provides a more complete evaluation of vascular risk. Other studies have demonstrated that similar multimarker methods can enhance risk classification and identify high-risk individuals who might not be identified with conventional risk scores alone **[14]**.

A combination of genetic predisposition, central obesity, insulin resistance and dyslipidemia, with low HDL and high Lp(a) levels, makes the Indian population particularly vulnerable to premature coronary artery disease. Here, finding robust and cost-effective biomarkers of particular significance is the early detection and prevention. The current results have clinical implications for Indian populations, where traditional risk prediction models tend to undervalue cardiovascular risk, especially in younger patients **[15]**.

The three biomarkers assessed during the research are indicative of different but interconnected processes in terms of the pathophysiology. Lp(a) is a measure of

lipid-mediated atherothrombosis, hs-CRP is a measure of systemic and vascular inflammation, and homocysteine is a measure of metabolic endothelial injury. The convergence of these pathways probably enhances the formation of plaque and instability, which results in acute coronary events. This mechanistic complementarity could be the reason why their combined assessment is so predictive. **[16]**.

The clinical implications of these findings are interesting. Lipoprotein(a), hs-CRP, and homocysteine assessment can be of incremental use in selected patients, especially those with intermediate cardiovascular risk or unexplained premature coronary artery disease, in whom conventional risk assessment may be inadequate. These biomarkers should not be used to substitute the already known cardiovascular risk assessment tools. Nevertheless, the problems of cost-effectiveness, standardization of assays, and the absence of universally recognized clinical cut-off values should be resolved before they can be widely applied in standard clinical practice **[17]**.

Although this study has strengths, such as an angiographically proven diagnosis of coronary artery disease and well-matched control subjects, a number of limitations must be acknowledged. The sample size was relatively small, and this restricted the number of variables that could be included in the multivariate logistic regression model with reliability. This results in the events-per-variable ratio being lower than the generally recommended value, which raises concerns about the possibility of overfitting the model and decreased stability of the regression estimates. Thus, multivariable results can be viewed as exploratory and hypothesis-generating but not confirmatory.

Moreover, other critical factors such as serum vitamin B12, folate levels and renal functioning parameters were not measured, and this could have affected the observed homocysteine levels. Cross-sectional case-control design does not allow making any causal assumptions about the relationships between the investigated biomarkers and coronary artery disease. Moreover, it is a single-center study and, therefore, its results are subject to selection bias and might not be applicable to the general population. Larger, multicenter prospective studies should therefore be validated before clinical use.

Adaptation of the known cardiovascular risk factors was, however, necessary to minimize confounding and to assess the independent relationship of the biomarkers studied in relation to the traditional predictors.

Conclusion

The lipoprotein(a), high-sensitivity C-reactive protein, and homocysteine are each independently related to coronary artery disease and are independent but complementary pathophysiological processes that involve lipid metabolism, inflammation, and endothelial dysfunction. Their combined evaluation has a higher diagnostic accuracy than separate biomarkers and therefore has the potential to be used in overall cardiovascular risk stratification. The incorporation of these biomarkers into clinical practice can help to identify people who have increased cardiovascular risk in specific clinical settings.

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