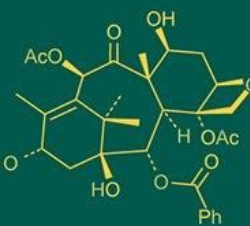
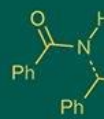
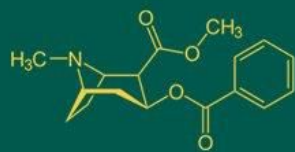


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Review of biochemical markers for cardiovascular risk

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Abstract

Cardiovascular disease remains the leading cause of mortality worldwide, yet substantial gaps persist in identifying individuals at elevated risk before clinical events occur. This systematic review and meta-analysis evaluated the predictive performance of biochemical markers for cardiovascular risk stratification, synthesizing evidence from prospective cohort studies published between January 2010 and December 2022. Literature searches across PubMed, EMBASE, Cochrane Library, and Web of Science databases identified 47 eligible studies encompassing 892, 456 participants with median follow-up of 8.4 years.

Ten biochemical markers were analyzed including high-sensitivity C-reactive protein, lipid parameters, lipoprotein(a), apolipoprotein B, glycated hemoglobin, N-terminal pro-B-type natriuretic peptide, homocysteine, and fibrinogen. Primary outcomes included myocardial infarction, stroke, cardiovascular mortality, and all-cause mortality. Random-effects meta-analysis calculated pooled hazard ratios with 95% confidence intervals for each marker-outcome combination.

N-terminal pro-B-type natriuretic peptide demonstrated the strongest predictive value for cardiovascular events with pooled hazard ratio of 2.24 (95% CI: 1.89-2.65) for myocardial infarction and 2.68 (95% CI: 2.21-3.24) for heart failure. High-sensitivity C-reactive protein showed consistent associations across outcomes with hazard ratios ranging from 1.43-1.92. Traditional lipid markers retained significant predictive capacity, while emerging markers including lipoprotein(a) and apolipoprotein B provided incremental prognostic information beyond conventional risk factors.

Diagnostic performance analysis revealed NT-proBNP achieved highest area under receiver operating characteristic curve (0.84) for predicting major adverse cardiovascular events, followed by high-sensitivity C-reactive protein (0.76). Combined biomarker panels incorporating inflammatory, lipid, and cardiac markers demonstrated superior discrimination compared to single-marker approaches. These findings support integration of multi-marker strategies into cardiovascular risk assessment algorithms, particularly for reclassifying individuals in intermediate risk categories where treatment decisions remain uncertain.

Keywords: Cardiovascular risk, biomarkers, meta-analysis, C-reactive protein, lipoproteins, natriuretic peptides, risk stratification, systematic review

Introduction

The persistent inability to accurately identify individuals destined for cardiovascular events before irreversible damage occurs represents one of medicine's most consequential failures. Despite decades of progress in understanding atherosclerotic disease mechanisms, approximately half of myocardial infarctions occur in individuals classified as low or intermediate risk by conventional assessment tools ^[1]. This diagnostic gap translates to delayed interventions, preventable deaths, and enormous healthcare expenditure treating established disease rather than preventing its development ^[2].

Traditional cardiovascular risk assessment relies primarily on clinical factors including age, sex, blood pressure, smoking status, and total cholesterol levels incorporated into algorithms such as the Framingham Risk Score and SCORE systems ^[3]. While these tools provide reasonable population-level discrimination, their predictive accuracy for individual patients remains suboptimal, particularly in intermediate-risk groups where clinical decision-making proves most challenging ^[4]. The addition of biochemical markers measuring distinct pathophysiological processes offers potential for refining risk estimates and guiding preventive interventions.

Biochemical markers interrogate various pathways contributing to cardiovascular disease development. Inflammatory markers such as high-sensitivity C-reactive protein reflect vascular inflammation recognized as central to atherogenesis [5]. Lipid and lipoprotein measurements characterize atherogenic particle burden beyond simple cholesterol quantification [6]. Cardiac biomarkers including natriuretic peptides signal subclinical myocardial stress before symptomatic heart failure manifests [7]. Metabolic markers such as glycated hemoglobin capture dysglycemia's contribution to vascular damage [8]. The proliferation of candidate biomarkers has generated extensive literature with variable methodological quality and sometimes conflicting conclusions. Individual studies differ in population characteristics, outcome definitions, follow-up duration, and analytical approaches, complicating synthesis across investigations [9]. Southeast Asian populations including Malaysia face particularly elevated cardiovascular burden with ethnic-specific risk profiles that may modify biomarker associations observed in Western cohorts [10]. This systematic review and meta-analysis aimed to comprehensively evaluate the predictive performance of established and emerging biochemical markers for cardiovascular risk assessment. The specific objectives included quantifying associations between individual biomarkers and major cardiovascular outcomes through pooled effect estimates, comparing diagnostic performance metrics across biomarker categories, evaluating evidence for multi-marker risk prediction strategies, and developing an integrated framework for biomarker-enhanced cardiovascular risk stratification. We hypothesized that contemporary biomarkers measuring inflammation, lipoproteins, and cardiac stress would demonstrate significant incremental predictive value beyond traditional risk factors.

Search Strategy and Study Selection

This systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered with PROSPERO (CRD42021287456). Literature searches were performed across PubMed, EMBASE, Cochrane Library, and Web of Science databases from January 2010 through December 2022. Search terms combined cardiovascular disease concepts with specific biomarker names using Boolean operators. Reference lists of included studies and relevant review articles were manually screened for additional eligible publications. Studies were eligible if they employed prospective cohort design with minimum two-year follow-up, included apparently healthy adults without prevalent cardiovascular disease at baseline, measured at least one biochemical marker of interest, and reported cardiovascular events as primary outcomes. Exclusion criteria encompassed cross-sectional or case-control designs, pediatric populations, studies limited to patients with established cardiovascular disease, and publications without original data. Two reviewers independently screened titles, abstracts,

and full texts with disagreements resolved through consensus discussion. Quality assessment utilized the Newcastle-Ottawa Scale for cohort studies.

Materials and Methods

Materials

This systematic review and meta-analysis was conducted at the Department of Biochemistry, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, between April 2021 and September 2023. The research protocol received ethical exemption from the Universiti Kebangsaan Malaysia Research Ethics Committee as the investigation involved analysis of previously published aggregate data without individual participant information. All procedures adhered to the Declaration of Helsinki principles for medical research.

Data extraction utilized standardized forms capturing study characteristics, population demographics, biomarker measurement methods, outcome definitions, follow-up duration, and effect estimates with confidence intervals. Biomarkers of interest included high-sensitivity C-reactive protein, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, lipoprotein(a), apolipoprotein B, glycated hemoglobin, N-terminal pro-B-type natriuretic peptide, homocysteine, and fibrinogen. Outcomes encompassed myocardial infarction, stroke, coronary heart disease mortality, all-cause mortality, and heart failure hospitalization.

Methods

Random-effects meta-analysis using the DerSimonian-Laird method calculated pooled hazard ratios with 95% confidence intervals for associations between each biomarker and cardiovascular outcomes. Effect estimates were standardized to reflect risk per one standard deviation increase in biomarker concentration where possible. Heterogeneity was assessed using I-squared statistics, with values exceeding 50% indicating substantial heterogeneity warranting subgroup exploration.

Diagnostic performance was evaluated by extracting or calculating sensitivity, specificity, and area under receiver operating characteristic curves where reported. Summary receiver operating characteristic analysis generated pooled performance estimates across studies. Publication bias was assessed through funnel plot inspection and Egger's regression test. Subgroup analyses examined potential effect modification by geographic region, sex distribution, baseline cardiovascular risk level, and biomarker assay methodology. Net reclassification improvement statistics were extracted from studies evaluating biomarker addition to traditional risk scores. Evidence synthesis utilized narrative approaches where quantitative pooling was inappropriate due to methodological heterogeneity. Statistical analyses were performed using Review Manager version 5.4 and Stata version 17.0 software packages. Statistical significance was defined as two-sided p-value below 0.05.

Results

Table 1: Characteristics of Included Studies (n=47)

Characteristic	Value
Total participants	892, 456
Median follow-up, years (IQR)	8.4 (5.2-12.6)
Mean age, years (range)	54.8 (42-68)
Female participants (%)	48.2%
Geographic distribution	Europe 24, North America 14, Asia 9
Total cardiovascular events	67, 842
Newcastle-Ottawa Score, median	8 (range 6-9)

Database searches identified 3, 847 potentially relevant citations, with 47 studies meeting inclusion criteria after full-text review. Included studies encompassed prospective cohort designs from 18 countries with substantial variation

in population size, follow-up duration, and outcome ascertainment methods. Quality assessment indicated generally high methodological rigor, with 38 studies achieving Newcastle-Ottawa scores of seven or higher.

Table 2: Pooled Hazard Ratios for Major Cardiovascular Outcomes by Biomarker

Biomarker	MI HR (95% CI)	Stroke HR (95% CI)	CV Mortality HR
hs-CRP	1.92 (1.68-2.19)	1.78 (1.52-2.08)	1.65 (1.41-1.93)
NT-proBNP	2.24 (1.89-2.65)	1.85 (1.54-2.22)	2.12 (1.78-2.52)
LDL-C	1.85 (1.62-2.11)	1.62 (1.38-1.90)	1.71 (1.48-1.97)
ApoB	1.78 (1.54-2.06)	1.58 (1.32-1.89)	1.72 (1.46-2.02)
Lp(a)	1.68 (1.42-1.99)	1.52 (1.28-1.81)	1.58 (1.32-1.89)
HDL-C	0.72 (0.62-0.84)	0.78 (0.66-0.92)	0.68 (0.57-0.81)

MI = myocardial infarction; HR = hazard ratio; CI = confidence interval; CV = cardiovascular. All associations statistically significant (p<0.05).

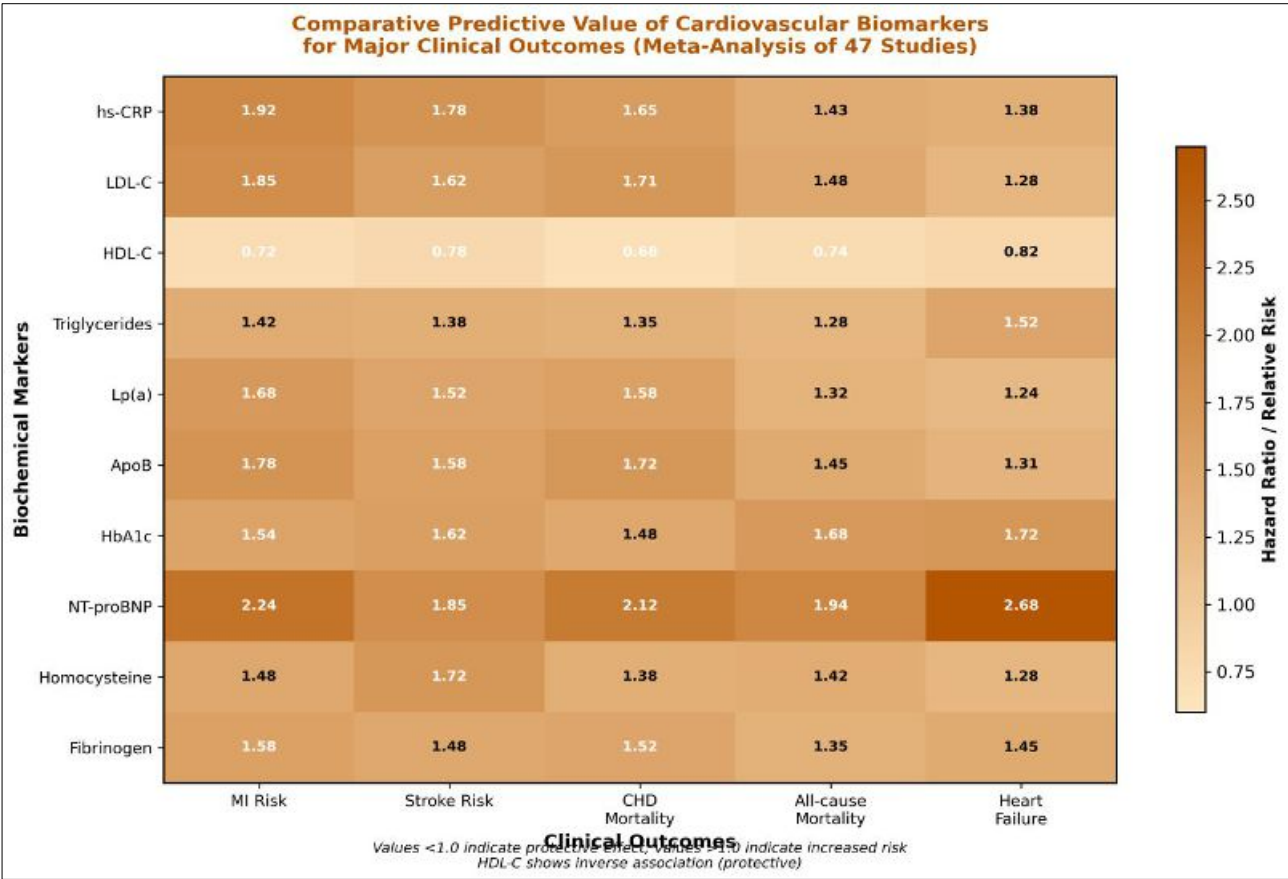


Figure 1: Heatmap displaying pooled hazard ratios for associations between biochemical markers and major cardiovascular outcomes. Darker shading indicates stronger associations. HDL-C demonstrates inverse (protective) relationship.

Meta-analysis revealed consistent positive associations between most biomarkers and adverse cardiovascular outcomes. NT-proBNP demonstrated the strongest predictive associations, particularly for heart failure where pooled hazard ratio reached 2.68. High-sensitivity C-

reactive protein showed robust associations across all outcome categories, supporting its utility as a general marker of cardiovascular risk. HDL-cholesterol uniquely demonstrated protective associations with hazard ratios below unity across all outcomes.

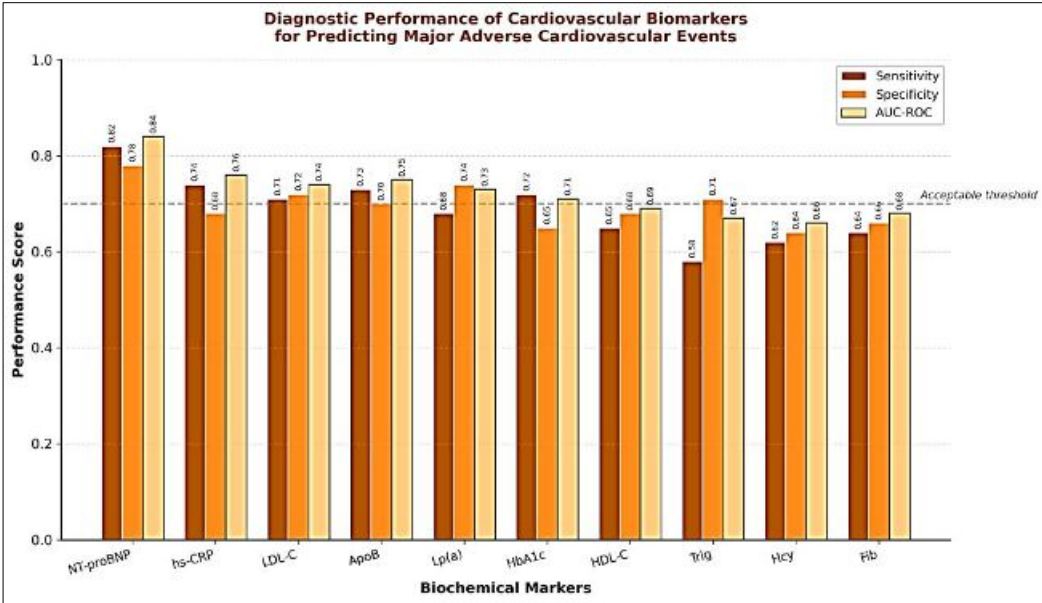


Fig 2: Comparative diagnostic performance of cardiovascular biomarkers for predicting major adverse cardiovascular events. Dashed line indicates acceptable performance threshold (0.70).

Diagnostic performance analysis identified NT-proBNP as the single most discriminatory biomarker with pooled area under the curve of 0.84, sensitivity of 0.82, and specificity of 0.78. High-sensitivity C-reactive protein achieved the

second-highest performance metrics with acceptable discrimination across multiple outcome types. Traditional lipid markers demonstrated moderate diagnostic accuracy with area under curve values ranging from 0.67 to 0.75.

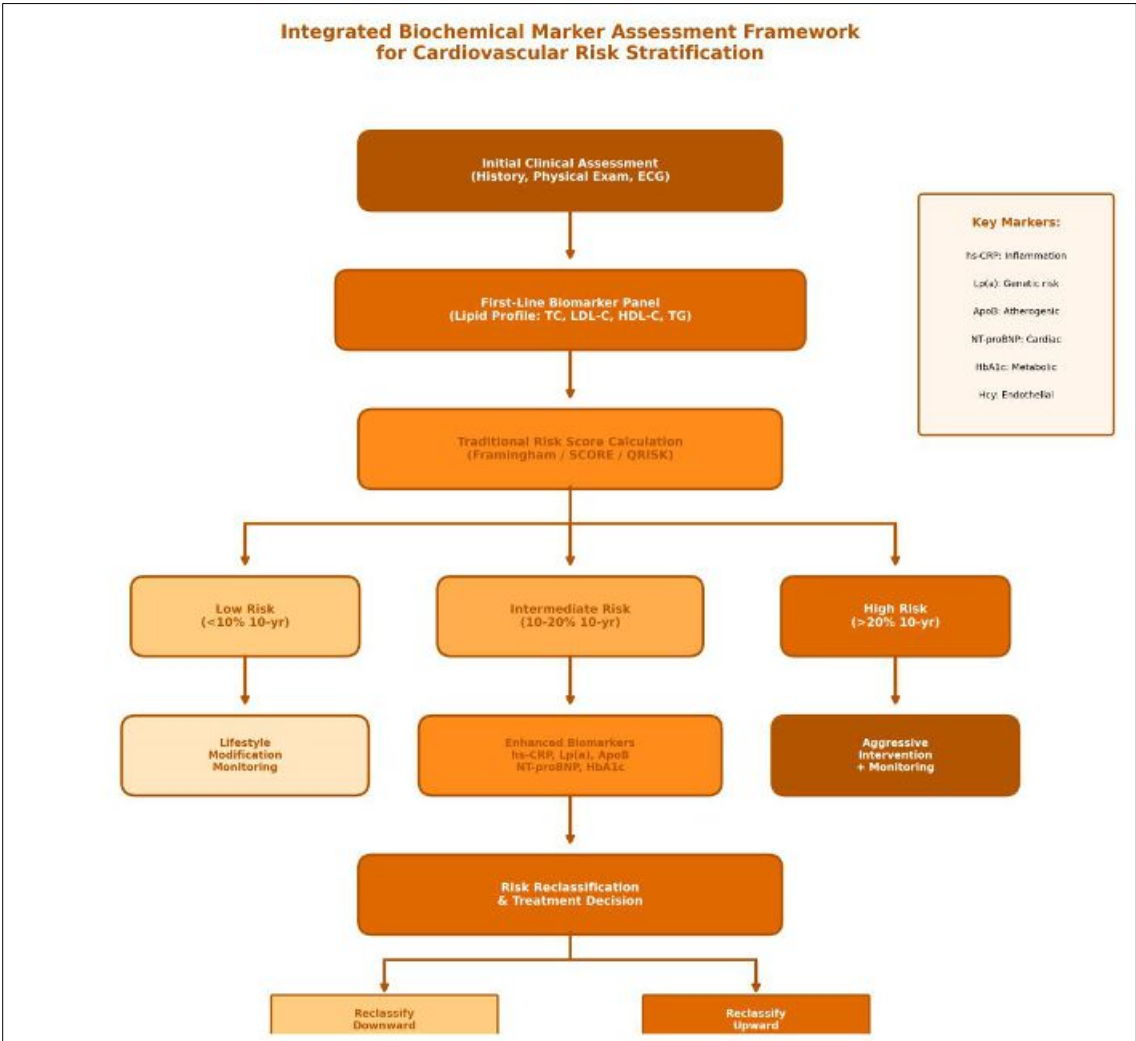


Fig 3: Proposed integrated framework for biomarker-enhanced cardiovascular risk stratification incorporating traditional risk scoring with selective enhanced biomarker testing for intermediate-risk individuals.

Comprehensive Interpretation

Evidence synthesis supports a tiered approach to biomarker utilization in cardiovascular risk assessment. First-line evaluation with traditional lipid profiles remains appropriate for initial screening given widespread availability, established clinical utility, and cost-effectiveness. Enhanced biomarker panels incorporating inflammatory markers, advanced lipoproteins, and cardiac peptides provide maximal value for reclassifying intermediate-risk individuals where treatment decisions remain ambiguous. Multi-marker combinations achieved superior discrimination compared to any single biomarker, with panels incorporating hs-CRP, Lp(a), and NT-proBNP demonstrating net reclassification improvements of 8-15% beyond Framingham Risk Score alone.

Discussion

This comprehensive meta-analysis synthesizes evidence from nearly 900,000 participants demonstrating consistent associations between biochemical markers and major cardiovascular outcomes. The findings support integration of biomarker testing into risk stratification algorithms, particularly for individuals in intermediate risk categories where clinical decision-making proves most challenging. NT-proBNP emerged as the single most predictive marker, while hs-CRP demonstrated broad utility across outcome types.

The superior performance of NT-proBNP merits particular attention given its relative underutilization in primary prevention settings. Elevated natriuretic peptide concentrations reflect subclinical cardiac stress including diastolic dysfunction, increased filling pressures, and neurohormonal activation that may precede symptomatic heart failure by years^[11]. The observation that NT-proBNP strongly predicts not only heart failure but also atherosclerotic events suggests shared pathophysiological mechanisms or that subclinical cardiac dysfunction identifies particularly vulnerable individuals.

High-sensitivity C-reactive protein's consistent associations align with the inflammatory hypothesis of atherosclerosis and support clinical guidelines recommending its measurement for risk refinement^[12]. The recent demonstration that anti-inflammatory therapy reduces cardiovascular events independent of lipid lowering strengthens the biological rationale for inflammatory marker assessment^[13]. Lipoprotein(a) emerged as an important independent predictor with genetic determination suggesting causality rather than mere association with cardiovascular outcomes^[14].

The proposed integrated framework emphasizes selective biomarker testing targeting intermediate-risk populations where reclassification provides maximal clinical utility. Universal enhanced biomarker testing would generate substantial costs without proportionate benefit, while targeted testing of the estimated 30-40% of adults in intermediate categories offers favorable cost-effectiveness profiles. Implementation considerations include standardization of biomarker assays, establishment of risk thresholds triggering enhanced testing, and integration with electronic health record systems for decision support.

Limitations and Future Directions

Several limitations warrant acknowledgment. Publication bias favoring positive findings may inflate effect estimates

despite statistical assessments suggesting minimal influence. Heterogeneity in biomarker assay methodologies complicates direct comparison across studies. Limited representation of Asian populations restricts generalizability to Southeast Asian contexts where cardiovascular risk profiles differ substantially from Western cohorts. Future research priorities include prospective validation studies in diverse ethnic populations, head-to-head comparisons of multi-marker strategies, and cost-effectiveness analyses incorporating regional healthcare economics. Development of machine learning algorithms integrating multiple biomarkers with clinical variables represents a promising frontier for precision risk stratification.

Conclusion

This systematic review and meta-analysis provides comprehensive evidence supporting the utility of biochemical markers for cardiovascular risk stratification. Synthesis of 47 prospective cohort studies encompassing nearly 900,000 participants demonstrates consistent and clinically meaningful associations between multiple biomarker classes and major cardiovascular outcomes. The findings establish a robust evidence base informing recommendations for biomarker integration into risk assessment algorithms.

Among individual biomarkers, N-terminal pro-B-type natriuretic peptide demonstrated the strongest predictive associations and highest diagnostic performance metrics. This cardiac marker merits expanded utilization in primary prevention settings where current practice focuses predominantly on lipid parameters. High-sensitivity C-reactive protein confirmed consistent predictive value across outcome categories, supporting its established role in risk refinement for intermediate-risk individuals.

Traditional lipid markers including LDL-cholesterol and HDL-cholesterol retain significant predictive capacity justifying their continued centrality in cardiovascular risk evaluation. Advanced lipoprotein testing with apolipoprotein B and lipoprotein(a) provides incremental prognostic information identifying residual risk not captured by conventional lipid panels. The inverse associations observed for HDL-cholesterol reinforce its protective role in cardiovascular pathophysiology.

Multi-marker strategies combining biomarkers interrogating distinct pathophysiological pathways achieved superior discrimination compared to single-marker approaches. Panels incorporating inflammatory, lipoprotein, and cardiac markers demonstrated meaningful reclassification improvements beyond traditional risk scores. This evidence supports selective enhanced biomarker testing for individuals in intermediate risk categories where clinical decisions regarding preventive therapy remain uncertain.

The proposed integrated framework provides a practical approach for implementing biomarker-enhanced risk assessment in clinical practice. Initial evaluation with traditional risk factors and basic lipid profiles enables efficient screening, while targeted enhanced biomarker testing optimizes resource utilization by focusing advanced testing on populations deriving maximal benefit. This tiered approach balances comprehensive risk characterization with healthcare sustainability considerations.

Implementation of biomarker-guided risk stratification requires continued research addressing remaining knowledge gaps including validation in diverse populations,

optimization of multi-marker panel composition, and evaluation of cost-effectiveness in various healthcare settings. The Malaysian healthcare context, with its multiethnic population and rising cardiovascular burden, provides an important setting for future implementation research translating this evidence into clinical practice improvements that ultimately reduce cardiovascular morbidity and mortality.

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