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Editorial

Beyond traditional risk scores: The emerging role of biomarkers in cardiovascular risk stratification

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, claiming approximately 17.9 million lives annually [1]. Traditional risk prediction models, including the Framingham Risk Score and the Pooled Cohort Equations, have formed the foundation of preventive cardiology for decades. While these tools have served clinicians well, they rely predominantly on conventional risk factors of age, sex, blood pressure, cholesterol, smoking, and diabetes, and provide only moderate discrimination, particularly among individuals at intermediate risk and in ethnic populations not well represented in their derivation cohorts [2]. The persistent burden of cardiovascular events despite widespread statin use and risk factor modification underscores the concept of "residual risk" and highlights a pressing need for refined approaches to risk stratification that capture the biological complexity of atherosclerosis.

In this issue of the *American Journal of Preventive Cardiology*, Uttarwar et al. [3] present a cross-sectional analysis from the MASALA (Mediators of Atherosclerosis in South Asians Living in America) cohort, examining associations between adipokine levels such as adiponectin, leptin, resistin, and composite indices, and prevalent cardiometabolic outcomes in nearly 900 South Asian American adults. Their findings that higher adiponectin was associated with lower odds of dyslipidemia in the overall population and diabetes in women, while the adiponectin-resistin index paralleled these associations, add to a growing literature positioning adipokines as phenotypic markers of adipose dysfunction. These descriptive observations, though limited by cross-sectional design, reinforce a broader and increasingly urgent theme in cardiovascular medicine: the potential for circulating biomarkers to illuminate pathways of risk that remain invisible to traditional scoring systems.

The concept of residual inflammatory risk has gained substantial traction since the landmark CANTOS trial demonstrated that targeting interleukin-1β with canakinumab reduced recurrent cardiovascular events by 15 % in patients with prior myocardial infarction and elevated high-sensitivity C-reactive protein (hsCRP), independent of any change in lipid levels [4]. This trial proved that inflammation is not merely a bystander but a causal driver of atherothrombosis. Equally important, CANTOS revealed that the magnitude of cardiovascular benefit correlated directly with the degree of hsCRP reduction, and that patients achieving on treatment hsCRP levels below 2 mg/L experienced substantially greater reductions in both cardiovascular and all-cause mortality. Subsequent analyses from CANTOS further demonstrated that modulation of the interleukin-6 signaling pathway was similarly associated with event reduction, reinforcing the central role of the IL-1β–IL-6–CRP axis in atherosclerotic disease [4]. The COLCOT and LoDoCo2 trials extended these findings into clinical practice, showing that low-dose colchicine reduced major adverse cardiovascular events by 23–31 % in patients with coronary artery disease, leading to FDA approval of colchicine for secondary cardiovascular prevention in 2023 [5].

These therapeutic advances have simultaneously validated hsCRP and IL-6 as actionable biomarkers, not merely prognostic indicators but tools that can guide treatment decisions and monitor therapeutic efficacy. This represents a paradigm shift: from biomarkers as passive risk predictors to biomarkers as active targets for intervention. Yet inflammation is only one dimension of residual risk. Other biomarker classes capture distinct pathophysiological pathways that traditional risk factors overlook (Table 1). Lipoprotein(a), a genetically determined and largely treatment-resistant risk factor, identifies individuals with inherited susceptibility to atherosclerotic and valvular disease. High-sensitivity cardiac troponins detect subclinical myocardial injury, while natriuretic peptides signal hemodynamic stress and incipient heart failure. Metabolomic markers such as trimethylamine N-oxide (TMAO) reflect the gut-microbiome-cardiovascular axis, and emerging proteomic platforms now enable simultaneous measurement of thousands of circulating proteins, offering unprecedented resolution of individual risk profiles [2,6].

The work by Uttarwar et al. [3] contributes to this landscape by examining adipokines, a biomarker class that bridges adiposity, inflammation, and metabolic dysregulation. Their finding that leptin's associations with cardiometabolic outcomes are attenuated after adjustment for BMI, while adiponectin retains significance, echoes observations from MESA and other multi-ethnic cohorts. Importantly, the study highlights that South Asian Americans exhibit distinctive patterns of adiposity and adipokine profiles, with lower adiponectin and higher resistin levels compared to other ethnic groups at comparable BMIs. This observation carries particular relevance given that traditional risk calculators systematically underestimate cardiovascular risk in South Asians, a population that develops cardiometabolic disease earlier and at lower BMI thresholds.

The challenge ahead is not the identification of individual biomarkers. Hundreds of biomarkers have demonstrated robust associations with cardiovascular events, but rather their integration into clinical workflows in ways that meaningfully improve patient outcomes. As Neumann et al. noted in a recent European Heart Journal review, the

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Table 1
Circulating biomarkers investigated for cardiovascular risk assessment.

Biomarker	Pathway / Category	Role in CV Risk Assessment	Key Evidence
hsCRP	Inflammation	Identifies residual inflammatory risk; guides anti-inflammatory therapy	CANTOS, JUPITER, hsCRP <2 mg/L linked to lower CV mortality
IL-6	Inflammation	Upstream mediator of CRP; correlates with CV event reduction under IL-1β inhibition	CANTOS secondary analyses; RESCUE trial rationale; outcomes testing is in ZEUS
hs-Cardiac Troponins (hs-cTnI/T)	Myocardial injury	Detects subclinical myocardial injury; reclassifies intermediate-risk individuals	ARIC, Framingham Heart Study; improves NRI for incident CHD
NT-proBNP / BNP	Hemodynamic stress	Identifies subclinical ventricular dysfunction and incident heart failure risk	FHS, ARIC; independent predictor of HF and CV mortality
Lipoprotein(a)	Atherogenic lipoproteins	Genetically determined risk factor for ASCVD and aortic stenosis; identifies inherited risk	Copenhagen studies, UK Biobank; targeted therapies in trials (e.g., HORIZON)
Adiponectin	Adipokine / Metabolic	Inversely associated with insulin resistance, diabetes, and dyslipidemia; reflects adipose dysfunction	MESA, MASALA, Jackson Heart Study; sex-specific associations
Leptin	Adipokine / Metabolic	Marker of total adiposity; associations attenuated by BMI adjustment	MESA, REGARDS; stronger role in populations with ectopic fat
Resistin	Adipokine / Inflammatory	Linked to insulin resistance and atherosclerosis; sex-divergent associations	MASALA, European cohorts; linked to inflammation, insulin resistance, and atherosclerotic risk
GDF-15	Cellular stress / Aging	Associated with oxidative stress and adverse CV outcomes	FHS, BIOSTAT-CHF; independent predictor of CV mortality
Galectin-3	Fibrosis / Remodeling	Predicts new-onset HF and adverse prognosis in established HF	Framingham Heart Study, DEAL-HF
sST2	Myocardial stress	Prognostic in HF and post-MI settings; reflects myocardial fibrosis	BIOSTAT-CHF, Framingham Offspring Study
TMAO	Gut microbiome / Metabolomic	Reflects gut microbial metabolism; associated with incident ASCVD events	Cleveland Clinic cohorts; diet-modifiable risk factor
Lp-PLA2	Vascular inflammation	Marker of plaque inflammation; associated with coronary and cerebrovascular events	ARIC, Rotterdam Study; darapladib trials (neutral for events)
ApoB	Atherogenic lipoproteins	Counts atherogenic particles; may outperform LDL-C for risk prediction	INTERHEART, AMORIS; recommended/ recognized in guidelines for discordance assessment
Cystatin C	Renal function / Vascular	Predicts CV events beyond creatinine-based eGFR; improves calibration of risk models	SMART cohort, UK Biobank; stronger prediction in women
Fibrinogen	Hemostasis / Inflammation	Independently associated with MI and stroke; reflects thrombotic and inflammatory activation	Fibrinogen Studies Collaboration meta-analysis
Homocysteine	Metabolic	Associated with ASCVD risk; elevated in South Asians due to B12 deficiency	SHARE, HOPE-2 (supplementation neutral for CV events)
MicroRNAs (e.g., miR-21, miR-126)	Gene regulation / Emerging	Reflect cellular stress and plaque instability; potential for early detection of subclinical disease	Emerging clinical validation studies; not yet guideline-recommended

Abbreviations: hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; BNP, brain natriuretic peptide; Lp(a), lipoprotein(a); GDF-15, growth differentiation factor-15; sST2, soluble suppressor of tumorigenicity-2; TMAO, trimethylamine N-oxide; Lp-PLA2, lipoprotein-associated phospholipase A2; ApoB, apolipoprotein B; NRI, net reclassification improvement; ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; CV, cardiovascular; MI, myocardial infarction; AR, adiponectin-resistin.

incremental value of individual biomarkers added to conventional risk models has generally been modest in terms of model performance metrics [2]. However, this may reflect the limitations of how we measure improvement rather than the biological relevance of the markers themselves. Multi-biomarker panels and proteomic approaches that simultaneously assess inflammatory, metabolic, myocardial, and hemodynamic pathways may achieve what single biomarkers cannot: a comprehensive, personalized map of individual cardiovascular risk.

For prevention practice, several priorities emerge. First, hsCRP should be more widely adopted as a tool for identifying residual inflammatory risk, particularly in patients already on optimized lipid-lowering therapy. The availability of colchicine as an affordable, FDA-approved anti-inflammatory option makes this assessment directly actionable. Second, population-specific biomarker profiles as illustrated by the MASALA findings for adipokines in South Asians, deserve attention in risk stratification algorithms that currently lack ethnic granularity. Third, the field must move beyond cross-sectional associations toward prospective, outcome-driven studies that validate whether biomarker-guided strategies reduce cardiovascular events and improve survival. The ongoing ZEUS trial investigating ziltivekimab (an IL-6 ligand inhibitor) in patients with chronic kidney disease and elevated hsCRP exemplifies this next phase of targeted, biomarker-guided therapy [7].

In summary, the era of cardiovascular biomarkers has evolved from prognostic curiosity to therapeutic reality. The MASALA adipokine data from Uttarwar et al., viewed alongside the anti-inflammatory revolution catalyzed by CANTOS and colchicine trials, reinforces that atherosclerotic cardiovascular disease is a multi-pathway process requiring multidimensional risk assessment. As we stand at the intersection of precision medicine and preventive cardiology, the integration of biomarkers such as hsCRP, IL-6, adiponectin, Lp(a), and cardiac troponins into routine clinical practice holds transformative potential not merely to predict who is at risk, but to guide personalized interventions that move us

closer to eliminating residual cardiovascular risk.

Author statement

All authors have approved this work. There are no relevant COI or financial disclosures for Erfan Tasdighi or Anandita Kulkarni.

CRediT authorship contribution statement

Erfan Tasdighi: Writing – review & editing, Writing – original draft. **Anandita Kulkarni:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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