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# Biological Clues in a Silent Epidemic: Cardiovascular Disease Burden and the Role of Biological Markers

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## ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for more than 20 million deaths annually and nearly one-third of all global deaths. The burden is disproportionately higher in low- and middle-income countries, including Sri Lanka, where rapid urbanization, demographic transition, and lifestyle changes have significantly increased disease prevalence. Despite major advances in pharmacological therapy, interventional cardiology, and preventive strategies, early detection remains suboptimal due to the silent and progressive nature of disease development. Biological markers, or biomarkers, have emerged as powerful tools for identifying subclinical disease, improving risk stratification, and enabling personalized therapeutic strategies. These markers provide insight into underlying pathophysiological processes such as inflammation, oxidative stress, endothelial dysfunction, and metabolic dysregulation. This oration explores the global and regional burden of cardiovascular disease, integrates findings from local research conducted in Sri Lanka, and discusses the evolving role of traditional and emerging biomarkers, particularly in acute coronary syndrome (ACS). Special emphasis is placed on oxidative stress and inflammatory biomarkers, their clinical relevance, and their potential to transform cardiovascular care from reactive treatment to preventive medicine.

*Keywords: Cardiovascular disease, Biomarkers, Acute coronary syndrome, Oxidative stress, Sri Lanka*

## INTRODUCTION

Cardiovascular disease is widely recognized as a silent epidemic, characterized by a prolonged asymptomatic phase during which pathological processes evolve unnoticed. Over several decades, vascular injury accumulates through complex interactions between metabolic abnormalities, chronic inflammation, oxidative stress, and genetic susceptibility. Endothelial dysfunction, lipid accumulation, and progressive plaque formation develop gradually, often without producing symptoms. This silent progression represents one of the greatest challenges in cardiovascular medicine, as opportunities for early intervention are frequently missed.

Despite remarkable advances in diagnostic modalities, pharmacological therapies, and interventional techniques, many patients continue to present only after the occurrence of major clinical events such as myocardial infarction or stroke. This pattern highlights a critical limitation in current healthcare systems—the inability to



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identify disease at an early and reversible stage. Consequently, there is an increasing emphasis on preventive strategies aimed at detecting disease before irreversible damage occurs.

Biomarkers offer a promising solution to this challenge. These measurable indicators of biological processes can reflect disease activity at a molecular level, often preceding structural or functional abnormalities. By identifying individuals at high risk and enabling early intervention, biomarkers have the potential to transform cardiovascular care from a reactive model focused on treatment to a proactive approach centered on prevention.

**Global Burden of Cardiovascular Disease**

Cardiovascular disease represents a major global health challenge, affecting more than 500 million individuals and accounting for approximately one-third of all deaths worldwide. According to the World Health Organization, nearly 18 million deaths occur annually due to cardiovascular diseases, with over three-quarters occurring in low- and middle-income countries. This disproportionate burden reflects disparities in access to healthcare, preventive strategies, and socioeconomic conditions.

The economic impact of cardiovascular disease is substantial, with global costs exceeding one trillion US dollars annually. These costs include direct healthcare expenditures as well as indirect costs related to lost productivity and long-term disability. As populations age and risk factors become more prevalent, the economic burden is expected to increase further.

Coronary artery disease remains the leading contributor to cardiovascular mortality worldwide. In South Asia, the burden is particularly severe, with individuals developing disease at a younger age and experiencing more aggressive clinical courses. Genetic predisposition, combined with environmental and lifestyle factors, contributes to this increased risk.

Rapid urbanization in countries such as Sri Lanka has led to significant changes in lifestyle, including reduced physical activity, increased consumption of processed foods, and rising prevalence of obesity and diabetes. These factors have contributed to a steady increase in cardiovascular disease prevalence over recent decades (1). Unlike developed countries, where incidence rates have declined due to effective preventive strategies, developing countries continue to experience rising trends.

**Evidence from Local Research**

Local research conducted at Teaching Hospital Peradeniya has provided important insights into the epidemiology and clinical characteristics of cardiovascular disease in Sri Lanka. A study involving approximately 300 patients with acute coronary syndrome demonstrated a mean age of 61.3 ± 12.6 years, with a significant predominance of male patients. Statistical analysis revealed that male sex was significantly associated with all types of ACS ($P = 0.001$). Lifestyle factors were strongly associated with disease presentation. Smoking was significantly more prevalent among STEMI patients compared to NSTEMI and unstable angina patients, demonstrating a strong association with acute plaque rupture ($P = 0.017$). Alcohol consumption was also significantly associated with STEMI ($P = 0.006$). In contrast, hypertension was more commonly associated with NSTEMI and unstable angina ($P = 0.008$), suggesting differing pathophysiological mechanisms between ACS subtypes (2).

A subsequent study involving 780 ACS patients further highlighted the role of metabolic risk factors. The prevalence of overweight and obesity was significantly higher than in the general population. Female patients demonstrated a higher prevalence of obesity, while males exhibited a higher prevalence of overweight. Anthropometric measures such as waist circumference and waist-hip ratio were significantly elevated, indicating increased risk of metabolic syndrome and cardiovascular complications (3).

Community-based studies conducted in the Sabaragamuwa Province revealed a high prevalence of dyslipidemia, affecting more than 60% of adults. Risk factors included increasing age, physical inactivity, poor dietary habits, and elevated body mass index. Behavioral risk factors such as smoking and alcohol use were particularly

prevalent among men, while women demonstrated lower levels of physical activity (4,5).

A comparison of cardiovascular risk prediction models revealed significant discrepancies between the Framingham Risk Score and WHO/ISH charts. The Framingham model identified a higher proportion of individuals as high-risk, highlighting the need for locally validated risk prediction tools tailored to the Sri Lankan population (6).

**Hypertension and Cardiovascular Risk**

Hypertension is one of the most important modifiable risk factors for cardiovascular disease, affecting approximately 1.28 billion individuals worldwide. Nearly half of affected individuals remain unaware of their condition, and less than 20% achieve adequate blood pressure control. Hypertension contributes significantly to cardiovascular morbidity and mortality, including myocardial infarction, stroke, and chronic kidney disease.

The global burden of hypertension has increased significantly over recent decades, particularly in low- and middle-income countries. This increase is driven by population growth, ageing, unhealthy lifestyle behaviors, and disparities in access to healthcare (7).

In South Asia, hypertension prevalence ranges between 18% and 33%, with low levels of awareness and control. Factors such as high salt intake, increasing obesity, and sedentary lifestyles contribute to this burden (8). In Sri Lanka, prevalence is estimated at approximately 20.9%, although regional variations exist.

Local studies demonstrate that hypertension is frequently asymptomatic at presentation. A significant proportion of patients report no symptoms, reinforcing its designation as a “silent killer.” Improved public awareness, screening programs, and early intervention strategies are essential to reduce disease burden (9,10).

**Pathophysiology of Atherosclerosis and Acute Coronary Syndrome**

Atherosclerosis is a chronic inflammatory disorder involving lipid accumulation, endothelial dysfunction, and immune activation. The disease begins with endothelial injury, which increases vascular permeability and allows infiltration of low-density lipoprotein (LDL) particles into the arterial wall.

Oxidative stress plays a central role in this process. Reactive oxygen species (ROS) promote oxidation of LDL, forming oxidized LDL, which is highly pro-inflammatory. This triggers recruitment of monocytes and their differentiation into macrophages, leading to formation of foam cells and fatty streaks. Over time, these lesions progress to fibrous plaques. Chronic inflammation weakens the fibrous cap, increasing the risk of rupture. Plaque rupture leads to thrombus formation and acute coronary syndrome (11).

**Biomarkers in Cardiovascular Disease**

Biomarkers serve as measurable indicators of biological processes and have become essential tools in cardiovascular medicine. Traditional biomarkers such as troponins, C-reactive protein, and natriuretic peptides have significantly improved diagnosis and management. However, these markers primarily detect established disease rather than early pathological changes.

**Biomarkers in Acute Coronary Syndrome**

The diagnosis of acute coronary syndrome (ACS) remains a significant clinical challenge, particularly in the early phase of presentation. Although electrocardiography (ECG) is a fundamental and widely available diagnostic tool, its sensitivity is limited, especially in patients without ST-segment elevation. Similarly, cardiac troponins, while highly specific for myocardial injury, may not become detectable until several hours after the onset of ischemia. This diagnostic window creates uncertainty in early clinical decision-making, particularly in emergency settings where rapid risk stratification is essential.

In response to these limitations, considerable research has focused on identifying novel biomarkers that can detect myocardial ischemia at an earlier stage, prior to irreversible myocardial injury. Among these, ischemia-modified albumin (IMA) has emerged as a promising early marker of myocardial ischemia. IMA is formed when the N-

terminus of albumin is altered under conditions of oxidative stress and ischemia, reducing its ability to bind transition metals such as cobalt. Importantly, IMA levels rise within minutes of ischemic insult, preceding the elevation of troponin, and therefore may serve as a useful marker for early diagnosis or exclusion of ACS.

Myeloperoxidase (MPO), an enzyme released by activated neutrophils and macrophages, is another important biomarker reflecting inflammatory activity and oxidative stress within atherosclerotic plaques. Elevated MPO levels have been associated with plaque instability and increased risk of adverse cardiovascular events. Unlike troponin, which reflects myocardial necrosis, MPO provides insight into the underlying inflammatory processes that contribute to plaque rupture, thereby offering complementary diagnostic and prognostic information.

Copeptin, the C-terminal portion of the arginine vasopressin precursor, has also gained attention as an early biomarker in ACS. It is released rapidly in response to endogenous stress and hemodynamic changes, and its levels increase within the first few hours of symptom onset. When used in combination with cardiac troponin, copeptin has been shown to improve early rule-out strategies for myocardial infarction, enabling more rapid and safe discharge of low-risk patients from emergency departments.

In addition to these markers, other emerging biomarkers such as pregnancy-associated plasma protein-A (PAPP-A), intercellular adhesion molecule-1 (ICAM-1), galectin-3, and high-sensitivity C-reactive protein have been investigated for their roles in reflecting plaque instability, endothelial dysfunction, and systemic inflammation. These markers highlight the multifactorial nature of ACS, which involves not only myocardial injury but also complex interactions between thrombosis, inflammation, and oxidative stress.

A key concept in modern cardiovascular diagnostics is the use of multi-marker strategies, where combinations of biomarkers reflecting different aspects of disease pathophysiology are used together to improve diagnostic accuracy. For example, combining markers of myocardial injury (troponin), ischemia (IMA), inflammation (MPO), and stress response (copeptin) may provide a more comprehensive assessment of patients presenting with chest pain.

Despite their promise, the clinical integration of these novel biomarkers requires careful consideration. Factors such as assay availability, cost, standardization, and validation in diverse populations must be addressed before widespread implementation. Nevertheless, these emerging biomarkers represent an important step toward earlier diagnosis and more precise risk stratification in acute coronary syndrome (12,13).

**Emerging and Future Biomarkers**

Advances in molecular biology and high-throughput analytical technologies have led to the identification of a new generation of cardiovascular biomarkers that extend far beyond traditional indicators of myocardial injury and inflammation. Genetic markers, including single nucleotide polymorphisms and polygenic risk scores, have emerged as important tools in identifying individuals with a lifelong predisposition to cardiovascular disease. These markers provide insights into inherited susceptibility and allow early risk stratification even before the onset of conventional risk factors. In particular, genome-wide association studies have identified multiple loci associated with coronary artery disease, enabling the development of predictive models that may guide preventive interventions.

In addition to genetic determinants, epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNA regulation have been increasingly recognized as critical contributors to cardiovascular pathophysiology. Among these, microRNAs (miRNAs) have gained particular attention due to their role in post-transcriptional gene regulation. These small, non-coding RNA molecules are involved in key processes such as endothelial function, inflammation, lipid metabolism, and myocardial remodeling. Circulating microRNAs have shown promise as minimally invasive biomarkers for early detection, disease monitoring, and prognostication in cardiovascular disease.

Metabolomics and proteomics represent further advancements in biomarker discovery, enabling comprehensive profiling of metabolic and protein

signatures associated with disease states. These approaches provide a systems-level understanding of cardiovascular disease by identifying complex biochemical pathways involved in disease initiation and progression. For example, alterations in lipid metabolites, amino acids, and oxidative stress markers can reveal early metabolic disturbances that precede clinical disease. Similarly, proteomic analyses can identify novel protein biomarkers that reflect vascular injury, inflammation, and thrombosis.

The role of the gut microbiome has also emerged as an important frontier in cardiovascular research. Microbiota-derived metabolites, such as trimethylamine N-oxide (TMAO), have been strongly associated with atherosclerosis, thrombosis, and adverse cardiovascular outcomes. These findings highlight the complex interplay between diet, microbial metabolism, and host physiology, opening new avenues for therapeutic intervention.

Collectively, these emerging biomarkers support the transition toward precision medicine, where risk assessment, diagnosis, and treatment are tailored to individual biological profiles. By integrating genomic, molecular, and environmental data, future approaches to cardiovascular care will move beyond population-based strategies toward more personalized and predictive models (14).

**Challenges and Future Directions**

Despite the remarkable progress in biomarker research, several challenges continue to limit their widespread adoption in clinical practice. One of the most significant barriers is the high cost associated with advanced biomarker assays, particularly those involving genomic, proteomic, and metabolomic technologies. These costs can be prohibitive in low- and middle-income countries, where healthcare resources are already constrained.

Another major challenge is the lack of standardization across different biomarker assays. Variability in measurement techniques, laboratory protocols, and reference ranges can lead to inconsistencies in results, limiting their reliability and comparability. Furthermore, many emerging biomarkers have not yet been validated in large, diverse populations, particularly in South Asian and Sri Lankan contexts. This lack of validation raises concerns regarding their generalizability and clinical applicability.

Accessibility also remains a critical issue. Advanced biomarker testing is often limited to specialized centers, making it difficult to implement on a large scale, particularly in rural or resource-limited settings. In addition, the interpretation of complex biomarker data requires specialized expertise and advanced analytical tools, which may not be readily available in all healthcare environments.
Ethical considerations also arise, particularly in the context of genetic and predictive biomarkers. Identifying individuals at high risk of disease may have psychological, social, and insurance-related implications, especially when effective preventive interventions are not readily accessible.

Looking forward, integration of biomarkers with digital health technologies and artificial intelligence offers promising opportunities to overcome these challenges. Machine learning algorithms can analyze large datasets, identify patterns, and generate predictive models that enhance risk stratification and clinical decision-making. Combining biomarker data with clinical, imaging, and lifestyle information may further improve diagnostic accuracy and enable truly personalized care.

Future research should focus on validating biomarkers in diverse populations, developing cost-effective assays, and integrating multi-marker strategies into routine clinical practice. Strengthening translational research and fostering collaboration between basic scientists, clinicians, and public health experts will be essential in bridging the gap between discovery and implementation.

**CONCLUSION**

Cardiovascular disease remains a silent epidemic, characterized by a prolonged asymptomatic phase that often culminates in sudden and life-threatening clinical events. Despite significant advances in treatment, the global burden of cardiovascular disease continues to rise, particularly in low- and middle-income countries such as Sri Lanka. This underscores the urgent need for strategies that prioritize early detection and prevention.

Biomarkers provide a powerful approach to addressing this challenge by offering insights into the underlying biological processes that drive disease development. From traditional markers of myocardial injury to advanced molecular and genetic indicators, biomarkers enable clinicians to detect disease at an earlier stage, improve risk stratification, and guide individualized therapeutic interventions. In particular, biomarkers related to inflammation and oxidative stress, as highlighted in this work, play a critical role in understanding the pathogenesis of acute coronary syndrome and offer potential for early diagnosis.

However, the successful integration of biomarkers into clinical practice requires careful consideration of cost, accessibility, standardization, and ethical implications. Addressing these challenges will be essential to ensure that advances in biomarker science translate into meaningful improvements in patient care.

The future of cardiovascular medicine lies in the integration of biological insights with clinical practice. By combining advances in molecular biology, data science, and public health, it is possible to shift the paradigm from reactive treatment to proactive prevention. Such an approach holds the promise of reducing the burden of cardiovascular disease and improving health outcomes for populations worldwide.

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