## Study of Promising Novel Biomarkers on Cardiovascular Disease

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### Abstract
An excellent paper that provides a comprehensive analysis of biomarkers, which can disclose a variety of information about health or illness, such as the kind or extent of environmental exposure, genetic vulnerability, genetic responses to exposures, indicators of preclinical or clinical illness, or indicators of treatment responses. Indicators of disease trait, disease stage (preclinical or clinical), or illness rate are thus a basic approach to conceptualize biomarkers. A trait that can be objectively measured and evaluated is called a biomarker. As a gauge for biological activities that are pathogenic, healthy, or pharmacological responses to a treatment. As a result, this paper examines the wealth of research on the function of bioactive compounds in a range of pathological processes associated with different illnesses.

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### Introduction
An international health concern, cardiovascular illnesses take many lives each year. The main causes of CVD development include genetic susceptibility and changes in lifestyle. Since the disease is often discovered in its final stages in these people, heart transplantation is their only available treatment. To enhance their quality of life, every effort should be taken to recognize the danger early on and implement preventive measures. One of the most important elements in the early diagnosis of CVDs is the presence of biomarkers. Cardiovascular disorders are being diagnosed and prognosticated with the help of increasingly sensitive and precise biomarkers that have recently been discovered. This study covers the many kinds of cardiovascular biomarkers, highlights novel biomarkers, and discusses the biomarkers applied in various scenarios related to CVDs. The biomarkers have also made it simpler to identify COVID-19 individuals who are at a higher risk of developing cardiovascular issues. Biomarkers are superior to conventional techniques for assessing the pathophysiological state of CVDs since they are non-invasive.

### Biomarker Definition
A “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” is what the National Institute of Health Consortium (NIHC) has characterized as a biomarker in 2001; however, in 2009, the American Heart Association (AHA) published a detailed set of guidelines outlining the comprehensive standards by which more recent biomarkers must be assessed uniformly before their application in clinical settings is suggested. Previous evaluations go into detail about what makes a perfect biomarker to employ for a particular purpose in any medical state, with a focus on CVD [16].

### Types of Biomarkers
Both the assessment of sickness and the creation of medication therapies for medical disorders rely heavily on biomarkers. These are [16].

1. Prognostic
2. Predictive
3. Pharmacological

#### 1. Prognostic
A prognostic biomarker is one that offers insight into how a disease will probably progress in both those receiving conventional therapy and those who are not receiving it [16].

#### 2. Predictive
A predictive biomarker is one that may be used to separate candidates for certain targeted therapies or to...
determine who is more likely to react to a given therapy. Predictive biomarkers therefore assist in customizing treatment to the patient’s need [16].

**3. Pharmacological**

Pharmacodynamic biomarkers quantify a medication’s impact on the illness condition itself. Stated differently, they depict the alteration that a target organism undergoes in reaction to the illness and its management [16]. Nevertheless, these designs are now also being used in other medical specialties, such as infectious diseases and cardiovascular medicine.

**Biomarker Characteristics - General Principles**

- An ideal biomarker should have excellent sensitivity, specificity, accuracy, and precision.
- Before a biomarker is used in clinical practice, it must have a high specificity (represented as likelihood ratio [LR]) in order to be used for prognostic or screening reasons (“rule in”). The ideal likelihood ratio for a screening test is typically more than 10. On the other hand, when assessing a biomarker for diagnostic purposes, a high sensitivity (LR < 0.10) is recommended [18].
- Third, an assay cannot be employed clinically unless it possesses more discriminating powers. Discrimination limits enable a biomarker’s aberrant and normal levels to be distinguished based on the illness state under study. Furthermore, it is critical to differentiate between “undesirable” or "abnormal" levels and "levels that require treatment" for any biomarker before deciding which is "fit" to be used in clinical practice for a "given purpose" [18].
- The calibration test evaluates a biomarker’s predictive power in a sample by comparing its measured risk to that of the actual sample, or to a different population entirely. For instance, compared to other ethnic groups, white people or US residents often have a greater risk of CVD depending on cutoff values for body mass index or waist circumference (particularly South Asians). Therefore, before a risk score based on the American cohort can be extended to people of other ethnicities, it needs to be recalibrated to account for BMI or waist circumference values that indicate a higher risk of cardiovascular disease [18].

Evaluation of Biomarker Correlation with Illness Biomarkers often indicate a change in a tissue’s or an organ’s biochemistry. They are therefore connected to a pathological or physiologic process. The clinical results of various procedures may, however, differ in terms of biomarkers serving as disease indicators. For instance, there may be a little increase in troponin in cases of congestive heart failure, pulmonary embolism, and, more traditionally, acute myocardial ischemia/infarction. Additionally, biomarkers meant for therapeutic use may be helpful if changes in their levels accurately reflect improvements in the disease process itself during treatment (predictive biomarkers), indicating better patient outcomes [16].

**New cardiovascular biomarkers are being investigated**

There are several CVD biomarkers being investigated. At the moment, there are several categories for CVD biomarkers. The most often occurring are as follows [16]: Biomarkers can be categorized according to the specificity of the condition, for example, biomarkers of heart failure.

1. [NT-proBNP]: Brain natriuretic peptide’s N-terminal prohormone
2. Atrial natriuretic peptide (ANP)
3. ST-2: Tumor necrosis factor-2 suppression
4. troponin T or I;
5. phosphokinase creatinine

**Biomarkers can be categorized according to their utility, for example, in acute alterations [16].**

1. copeptin,
2. high sensitivity Troponin,
3. galectin-3,
4. ST2

- To evaluate prognosis, biomarkers might be categorized according to the chronic stage of CVD [16].
- cardiac calcium using CT

**It is possible to classify biomarkers according to the pathogenic process that they indicate [16].**

**A. Inflammation**

- C-reactive protein
- Interleukin 6
- Fibrinogen
- Monocyte chemotactic protein-1
- Tumor necrosis alpha factor

**B. Oxidative stress [16]**

- Isoprostanes

**C. Metabolic [16]**

- Lipoprotein (A).
- Low-density lipoproteins.
- High density lipoprotein.
- ApoB 100.
- Phospholipase A2 linked with lipoproteins.

**Important New Biomarkers for Heart Failure [6]**

Heart failure biomarkers have been categorized by certain researchers based on the pathologic process they signify. Prior analyses have discussed the pertinent restrictions of new heart failure biomarkers for use in therapy recommendations, as well as gender variations in the application of these biomarkers in clinical settings. There have been several consensus statements that have proposed the establishment of a consortium to facilitate the investigation of novel biomarkers in a pooled sample of randomized clinical trials simultaneously and to generate ideas for testing each biomarker in trials that are biomarker guided.

**N terminal pro B type natriuretic peptide, or TproBNP**

NT proBNP, a more stable form of BNP, also predicts the presence of heart failure. BNP levels can be efficiently
lowered by drugs and other treatments that are currently used to treat heart failure, with a few exceptions. However, it's critical to understand that BNP levels and obesity are inversely correlated. and renal disease may potentially have an effect [6].

**The cardiac natriuretic peptide, or ANP**

However, because circulating ANP is frequently more unstable in blood than BNP or NT proBNP, it has little bearing on diagnosis or prognosis. Nonetheless, a mid-regional ANP [6]

**MR-proANP, or “Mid Regional Pro Atrial Natriuretic Peptide,”**

The mid portion of the molecule was used to isolate this prohormone. In a multinational biomarker study (BACH trial), it has demonstrated potential in the detection of heart failure in individuals with acute heart failure; nevertheless, further research is needed to determine its further incremental usefulness above BNP for diagnostic purposes. Thus far, research has shown that MR-proANP may provide extra advantages over BNP for the detection of heart failure in older, obese, or renal sick patients. Additionally, the prognosis for heart failure using MR-proANP is evaluated [6].

**Iota-tropinin Troponin I or T,**

which, when released into the circulation by cardiomyocyte necrosis, are cardiac isomers of the proteins from the troponin-tropomyosin complex and are frequently useful in the diagnosis of myocardial ischemia. However, as these markers are also elevated in the blood of patients with severe heart failure, extremely sensitive tests of Troponin T and I have also been adequately explored for prognostication in patients with established heart failure [6].

**Copeptin**

A novel biomarker linked to heart failure and ischemia is copeptin, which is an arginine vasopressin precursor protein (ADH). In addition to being correlated with an increased risk of mortality and newly developed heart failure, copeptin levels are heightened in the immediate post ischemic phase. Copeptin has been shown by some researchers to be a better predictor of mortality than BNP and NT-proBNP concentrations; nevertheless, it should be noted that these biomarkers are frequently tightly associated [6].

**NGAL [Lipocalin-associated neutrophil gelatinase]-**

Renal tubular cells secrete neutrophil gelatinase-associated lipocalin (NGAL), a different glycoprotein that is covalently attached to matrix metaloproteinase-9, in reaction to renal inflammation and damage. In addition to BNP, NGAL was shown to provide extra predictive and diagnostic utility in the GALLANT study. However, other studies employing biomarker data from other heart failure trials did not corroborate these findings. As such, it is questionable if this biomarker is any more therapeutically beneficial than other commonly used biomarkers in patients with chronic heart failure who also have renal impairment [6].

**Galectin**

Galectin-3 is a fascinating biomarker that is essential to the development and regulation of cardiac remodeling and fibrosis. Data from short-term follow-up has shown that in patients with acute decompensated heart failure, the blood level of Galectin-3 is predictive of mortality. Actually, scientists have suggested that galectin-3, or enhanced prognostic potential for death, is higher in individuals with both diminished and intact left ventricular ejection fraction when paired with BNP levels. Studies on heart failure generally show the advantages of using a multimarker approach; nevertheless, the evidence does not support the independent use of Galectin-3 alone for prognosis prediction in heart failure patients [6].

**ST-2 (Turgogenicity suppression)**

The receptor ST-2, which is found in the interleukin family (IL-33) and comes in transmembrane and soluble (sST2) gene forms. Similar to other biomarkers, blood ST-2 levels have been shown to predict mortality and heart failure with new onset. Along with other standard risk factors, researchers have also examined how effectively ST-2 and NT-proBNP levels predict outcomes in patients with ST-elevation myocardial infarction. It also affects traditional heart failure risk variables in determining prognosis. As a result of these findings, researchers are currently looking at using ST-2 in a multimarker framework to assess the prognosis of patients with heart failure [6].

**Mid-regional pro-adernomedullin, or MR-proADM**

Chronic heart failure is strongly associated with elevated levels of mid-regional proadernomedullin (MR-proADM), a vasodilatory peptide that is a stable prohormone fragment of adrenomedullin. It has been shown that MR-proADM is superior to both BNP and NT-proBNP in predicting 90-day mortality in patients with dyspnea and heart failure [6].

**Growth differentiation factor – 15**

Growth differentiation factor-15 is a biomarker that has been identified as having anti-hypertrophic effects, or apoptosis. Researchers have found that elevated levels of this biomarker can be used to predict all-cause mortality, including non-cardiovascular mortality, in community-dwelling adults and chronic heart failure patients. This information is in addition to that obtained from blood NT-proBNP and C-reactive protein levels [6].

**Etiology**

While rheumatic fever can cause valvular heart disease or emboli in a patient with atrial fibrillation, among other etiologies, CVD can also be directly caused by other factors. However, since atherosclerosis is an important factor in the pathophysiology of CVD, addressing risk factors related to its development is crucial [17,5]. The notable and consistent rise in CVD rates over the past few decades may be explained by the industrialization of the economy and the ensuing shift from physically taxing to sedentary jobs, as well as by today’s consumerism and technology-driven culture, which is linked to longer work...
hours, longer commutes, and less free time for recreational activities. In particular, a high-calorie diet, sweets, saturated fats, and physical inactivity are linked to the development of CVD, atherosclerosis and associated metabolic disorders such as metabolic syndrome, diabetes mellitus, and hypertension are quite common [17].

Nine modifiable risk factors, including smoking, dyslipidemia, which blood pressure, diabetes, obesity in the abdomen, psychosocial factors, intake of fruits and vegetables, regular drinking of alcohol, and physical inactivity, comprised 90% of the risk for developing a first MI, according to the INTERHEART study, which included participants from 52 nations, including high-, middle- and low-income countries. It is significant to note that smoking accounted for 36 per cent of the population-attributable risk of MI in this research [17]. The American Heart Association has incorporated these findings into health promotion programs, focusing on seven recommendations to lower the risk of CVD: quitting smoking, exercising, eating a healthy diet, and maintaining a normal blood pressure, body mass index, glucose, and cholesterol levels [17, 5]. However, non-modifiable elements like age, gender, and family history have distinct effect [4, 7]. Family history is regarded as an independent risk factor, especially in the case of premature atherosclerotic disease, which is defined as cardiovascular disease (CVD) or the death of a first-degree relative from CVD before the age of 55 (for men) or 65 (for females). Additionally, there is evidence to show that gender may be differently impacted by the existence of CVD risk factors. For example, women were more likely than males to have diabetes and smoke more than 20 cigarettes a day, which raised their risk of CVD. Every decade of life results in a considerable increase in the prevalence of CVD [17]. An increased rate and incidence of CVD have also been linked to the presence of human immunodeficiency virus (HIV), a history of mediastinal or pulmonary radiation, excluding particular dietary components like fiber and meat intake, microalbuminuria, and elevated inflammatory markers [17]. pointing and coffee and their relation to CVD remains controversial due to significant bias and residual confounding encountered in epidemiological studies [17].

**Various Disease Conditions**

1. **Anomalous Heartbeats**

   One incredible organ is the heart. It beats between sixty to one hundred times per minute in a steady, consistent pace. Approximately 100,000 times a day is that. An irregular heartbeat can occur sometimes. An arrhythmia is what your doctor refers to as an irregular or unstable heartbeat. A dysrhythmia, also known as an arrhythmia, can cause an irregular heartbeat or a rhythm in the heart that is too rapid or too slow [17].

2. **Pathologies related to the heart**

   This phrase refers to conditions affecting the heart muscle. Sometimes people just refer to them as enlarged hearts. Hearts that are abnormally large, thick, or rigid are found in people with various diseases. Their hearts’ ability to pump blood is compromised. When left untreated, cardiomyopathies worsen. Heart failure and irregular heart rhythms may result from them [17]. Heart-related disorders may occasionally run in families, although infections, metabolic disorders, high blood pressure, diabetes, and obesity can also be its causes.

3. **Congenital Heart Disease**

   There is an issue with one or more cardiac or blood vascular components. It takes place before to birth. It affects approximately eight out of one thousand kids. Some individuals with it may exhibit symptoms from birth, but others may not show signs until later in childhood or even adults. Most of the time, we have no idea why it occurs. Genes could be involved, or it might occur if a newborn is exposed to drugs, alcohol, or viral illnesses before to birth [17].

4. **Coronary Artery Disease**

   This may be referred to as CAD. It occurs when plaque accumulates and tightens the arteries that supply your heart with essential nutrients and oxygen. Another name for this hardening is atherosclerosis [17].

5. **Pulmonary embolism and Deep Vein Thrombosis**

   Blood clots can develop in your legs’ deep veins, generally. This is DVT, or deep vein thrombosis. They may come free, enter your circulation, and make their way to the lungs, where they may obstruct blood flow. We refer to this illness as pulmonary embolism. It requires emergency medical treatment since it is potentially fatal [17].

6. **Heart Failure**

   This word may evoke fear. It does not imply that your heart has "failed" or ceased to function. It indicates that your heart isn’t pumping as hard as it ought to. Your body will retain water and salt as a result, which will make you swollen and breathless. Over 6.5 million Americans suffer from heart failure, making it a serious health issue. It is the foremost reason for hospital admission among those over 65 [17].

7. **Disease of the Heart Valve**

   At the opening in each of those four cardiac chambers are your valves. They maintain your heart’s blood flow. The valves themselves can occasionally have issues. Problems with the heart valves can include: narrowing of the aorta. The aortic valve constricts. The flow of blood from your heart to every other part of your system is slowed down by it. Hypo function of the mitral valve. The closure of your mitral valve is not secure enough. This results in a backflow of blood, which fills the lungs with fluid, prolapse of the mitral valve. Your left upper and left bottom chamber valve isn’t closing properly [17].

8. **Ischemia**

   This uncommon ailment indicates inflammation of the membrane surrounding your heart [17].

9. **Arthritis of the Heart**

   This occurs when your heart valves are damaged by rheumatic fever, which is an inflammatory illness that mostly impacts youngsters. Untreated strep throat is the...
precursor of rheumatic fever, which can impact various bodily areas of your kid. [17].

10. **Stroke**

When anything reduces or obstructs blood flow to the brain, strokes occur. When your brain lacks the nourishment and oxygen it requires, brain cells begin to die. Your body doesn’t perform as it should when blood flow is restricted to the area of your brain responsible for controlling a certain function. A blood vessel that leaks or bursts, or an artery that is blocked, might cause a stroke. Treatment must begin very early to prevent brain damage and other complications.

11. **Atherosclerosis** or artery hardening

Elevated blood pressure diseases of the connective tissue, such as scleroderma, oestrogens imperfect, Ehlers-Danlos syndrome, and polycystic kidney disease damage, that can weaken the walls of your blood vessels [17].

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**Development phases of biomarkers** [9].

**Techniques available for biomarker development** [9].

| Data presentation | Percentages, hazard ratios (HRs; 95% CIs), relative risks (RR) ratios, or averages (10th to 90th percentiles), depending on the context. At the threshold of P < 0.05, statistical significance was established. The nonparametric Wilcoxon test for constant variables and the Fischer exact test for nominal variables were used to compare two groups. The process of evaluating the results involved figuring out the best cutoffs for each biomarker to be utilized in dichotomous analysis, multivariable regression analysis using SAS Institute Inc.’s generalized linear model (GENMOD) technique, and multinomial logistic regression examination. Each biomarker’s optimal cutoff value was found by charting its unique receiver operating characteristics [ROC] [2].

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Table displaying the fundamental clinical and biochemical characteristics of 543 patients with stage 5 CKD according to the clinically significant presence or absence of CVD Analyses Statistically.
Cardiovascular disease related Mortality rate [2]

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio(95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &lt;58versus≥58yr</td>
<td>1.23(0.75to2.05)</td>
<td>0.41</td>
</tr>
<tr>
<td>Sex, men versus women</td>
<td>0.97(0.58to1.63)</td>
<td>0.92</td>
</tr>
<tr>
<td>CVD, present versus absent</td>
<td>2.53(1.43to4.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, present versus absent</td>
<td>2.14(1.27to3.60)</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking, yes versus no</td>
<td>1.14(0.65to2.01)</td>
<td>0.65</td>
</tr>
<tr>
<td>SGA, malnourished versus well nourished</td>
<td>2.39(1.42to4.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR, &lt;6.9versus ≥6.9ml/min per1.73m²</td>
<td>2.42(1.44to4.07)</td>
<td>0.001</td>
</tr>
<tr>
<td>Calendaryear, 2010–2014versus2006–2009</td>
<td>2.63(0.73to9.48)</td>
<td>0.14</td>
</tr>
<tr>
<td>Calendaryear, 2010–2014versus2000–2005</td>
<td>1.91(0.54to6.75)</td>
<td>0.32</td>
</tr>
<tr>
<td>Calendaryear, 2010–2014versus1994–1999</td>
<td>2.34(0.62to8.86)</td>
<td>0.21</td>
</tr>
<tr>
<td>WBC, &lt;8.0310³versus≥8.0310³/ml</td>
<td>2.53(1.50to4.27)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-6, &lt;6.7versus≥6.7pg/ml</td>
<td>1.45(0.83to2.48)</td>
<td>0.20</td>
</tr>
<tr>
<td>TroponinT, &lt;0.06versus≥0.06mg/L</td>
<td>1.28(0.76to2.16)</td>
<td>0.36</td>
</tr>
<tr>
<td>hsCRP, &lt;6.4versus≥6.4mg/L</td>
<td>1.33(0.73to2.44)</td>
<td>0.35</td>
</tr>
<tr>
<td>PLT, &lt;261310³versus≥261310³/ml</td>
<td>1.08(0.64to1.83)</td>
<td>0.76</td>
</tr>
<tr>
<td>sVCAM-1, &lt;1356versus≥1356ng/ml</td>
<td>1.09(0.63to1.89)</td>
<td>0.75</td>
</tr>
<tr>
<td>sICAM-1, &lt;249versus≥249ng/ml</td>
<td>1.10(0.69to1.74)</td>
<td>0.70</td>
</tr>
<tr>
<td>Albumin, &lt;3.3versus≥3.3g/dl</td>
<td>0.90(0.60to1.59)</td>
<td>0.92</td>
</tr>
<tr>
<td>Ferritin, &lt;122versus≥122ng/ml</td>
<td>1.30(0.81to2.07)</td>
<td>0.27</td>
</tr>
<tr>
<td>IGF-1, &lt;155versus≥155mg/ml</td>
<td>1.03(0.61to1.74)</td>
<td>0.92</td>
</tr>
<tr>
<td>TNF, &lt;12.1versus≥12.1pg/ml</td>
<td>0.52(0.30to0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

All-cause mortality risk ratios (95% CIs) determined throughout 60 months of follow-up were computed for each assessed biomarker and modified for other covariates using an imputed multivariable generalized linear model (GENMOD). Results for patients undergoing kidney transplantation were withheld. WBC, white blood cells; hsCRP, high-sensitivity C-reactive protein; PLT, platelet count; sVCAM-1, soluble vascular adherence molecules 1; sICAM-1, soluble intracellular adhesion molecule; 95% CI, 95% confidence interval [2].

**Conclusion**

Biomarkers, which are defined as changes in the components of tissues or bodily fluids, offer a potent way to comprehend the range of CVD and have applications in at least five areas: prognostication, diagnosis, therapy monitoring, recurrence prediction, and screening. Progress in functional genome sequencing, proteomics, metabolomics, which and bioinformatics has transformed objective investigations into a multitude of potential indicators. It might provide useful information on the different stages of atherogenesis, overt cardiovascular disease, and its aftereffects. Clarifying the precise indications, standardizing analytical techniques, characterizing analytical features, evaluating performance characteristics, demonstrating cost-effectiveness, and calculating incremental yield of various indicators for given clinical uses are all necessary before biomarkers can be used in clinical settings. Future developments in technology are probably going to make it easier to employ multimarker profiling to personalize CVD therapy. In order to show their added value over traditional and other widely used biomarkers, biomarkers evaluating prognostic outcomes should report prejudice, calibration, and reclassification in patients by analyzing statistical approaches with and without the biomarker. In the process of being assessed for increased value, genetic indicators are in the forefront and also require thorough evaluations to assess their additional benefit above conventional risk variables and their relationship to CVD. Our approach to treating CVD will probably be determined by the use of biomarkers as proxy end points for predicting and prognosis values in clinical trials. This method will also create opportunities to assess biomarkers as potential targets for delivery of drugs and development.

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For all the worlds to research
Conflict of Interest
No Conflict of Interest

Inform Consent
Each patient has Consent writing for study

Ethical Statement
Study Reflections ethical statement

Author Contribution
All authors participate in the work

References