Review Article

Biomarkers of Cardiovascular Disease and Future Directions: A Review

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ABSTRACT

A major worldwide cause of death is cardiovascular disease (CVD), which continue to rise in prevalence as compared to previous decades due to ageing of the overall population. Progress in biomarker discovery and developments over the years associated with CVD have been the result of steadily responsive screening techniques, a greater focus on early detection and diagnosis and improvements in treatments that contribute to increasingly successful network clinical outcomes. This review focuses on a number of promising biomarkers which provide indicative and predictive data. The tissue-specific myocardial biomarker cardiac troponine, high sensitivity tests for cardiovascular troponine and the cardiovascular fatty acid binding protein are used in the early hours following the manifestation to evaluate myocardial infarction (MI). High-sensitivity C-sustainable protein, fibrinogen, and uric acid anticipate IM and extinction, including growth differentiation factor-15. The threat of acute coronary artery disease is pregnant-related plasma protein A, myeloperoxidase, and metalloproteinase matrix. Incidents and repeated cardiovascular events are predicted to occur with lipoprotein-related phospholipase A2 and secretive phospholipase A2. Finally, high natural peptides have all been accepted to predict death and cardiac insufficiency. For example, the assessment of micro-RNA is also investigated in increasingly increasing new areas. In any event, the use of biomarkers for different purposes in CVD continues to be a relevant field of research that researchers have been exploring over the years and many new innovations still exist.

Keywords: Cardiovascular disease, biomarkers, risk emerging, microRNAs.

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INTRODUCTION

Day by day, cardiovascular disorders increase excessive fat or genetic reason. It is a leading cause from infancy to old age of morbidity and mortality. While traditional risk prediction algorithm is made available in the presence of major cardiovascular risk factors in the ailing population, there is a lack of effective, accurate CVD biomarkers. It has delayed not only clinical diagnosis but also increased multiple risks and caused patients to die unplanned. In this respect, early detection and treatment of risk factors are important if disease prevention and disease improvement are to be accelerated.[1]

Many risk scores for cardiovascular danger have also been established. These scores depend on the overall significance of the major risk factors. As of today, several glucose-based physiological biomarkers have been reported as being associated with increased cardiovascular risks as well as hormone biomarkers. Some of them are historically basic, lipid profile and risk factors based biomarkers. The best cardiovascular risk biomarkers are plasma, serum and blood levels.[2] Cellular lipid interaction and physiological functions of serum lipid-carrying proteins shows the biomarkers which support clinical decision making and authenticated risk type. [3]

In developed countries, cardiovascular disease continues to remain a significant health issue, although recent trends of decreased incidences and improved results in acute myocardial infarction.[4] For example, cardiovascular disease remains at a broad margin the leading cause of death in the USA.[5] Improved strategies for the prevention of cardiovascular disease are therefore a priority for public health. A major problem is the cost-effective implementation of such techniques, the minimal forecast value of existing risk management models.

There are no typical risk factors for up to 20 percent of the coronary-disease patients and just 40% have one.[6, 7] Often, adults identified as low or moderate disease risk by conventional standards at a population level are responsible for much of the risk burden.[8] Hence the discovery of new risk markers of cardiovascular disease have found considerable potential to enhance selection of preventive strategies by individuals.

Biomarker definition:

A biomarker may be defined as any molecular, cellular, tissue or imaging measurement of a physiological, pathological or therapeutic response.[9] To be considered valuable, the following criteria must have accuracy and

therapeutic impact with early intervention [10].Based on the primary risk prediction of cardiovascular disease, it is important to provide an incremental information on an emerging biomarker over and above existing algorithms with proven clinical risk assessment models, such as the Framingham risk score.[11]

The classification of biomarkers is traditionally based on its intended application, such as screening, diagnosis and prognosis. The ideal features of a new biomarker that is planned to be used are shown in Fig. 1. A prognostic biomarker offers data on the possible course of an illness in an untreated person or in a person who receives traditional therapy. A predictive biomarker, on the other hand, may be used to classify those who will most frequently react to or distinguish candidates for specific targeted therapies.[12,13] Predictive biomarkers thus help to customise therapy for the needs of the patient. To date the assessment of biomarkers based on prognostic or predictive use has been restricted to the field of oncology; reversely, these clinical designs have also now started to be adopted by another field of medicine like cardiovascular medicine and infectious diseases.[14]

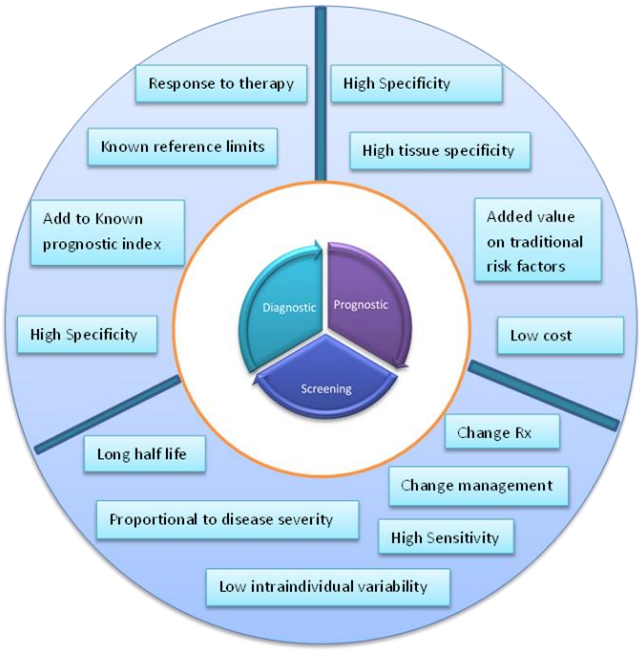

Figure 1: Ideal Properties of Biomarkers bestowing to their intended use.

Risk Emerging in Cardiovascular Diseases:

Many cardiovascular risk markers have been identified based on clinical findings in relation to biomolecules, their structure and their functions. Innovative clinical causes at mini-and micro-level are supplemented by an elevated risk of developing heart disease. However, there are many physical variables that may serve as biophysical benchmarks, all of which, however, are inadequate for an assessment of disease and the status of risks in patients. Many of these biomarkers can be incorporated into risk prediction models by themselves or in combination to decide whether their addition has an effect on increasing the model's predictive skill. In addition, models for predicting various cardiovascular risks such as the integration of molecular and conventional risk factors, genetic immunology, imagery and biophysical factors for a more accurate, reliable cardiovascular risk assessment have been identified.

Coronary heart disease is related to mono-cytosis, high blood pressure, diabetes and chronic kidney conditions.[15] Homozygous familial hypercholesterolemia (HoFH) is usually accompanying with severe hypercholesterolemia and premature cardiovascular morbidity and mortality. Moreover, raised cardiovascular risk has likewise been linked with the existence of obesity, hypertriglyceridemia, chronic kidney disease, and augmented levels of Lp(a). In individual increased risk of CVD and mortality are generally due to hyperglycaemia or type 1 diabetes. Patients fronting type 1 diabetes exhibited increase of premature mortality, primarily from cardiovascular disease (CVD).[16] Atherosclerosis being the main cause of death in the world through causing ischemic heart disease (IHD). It is peripheral arterial disease (PAD), most prevalent, morbid, and mortal disease.[17] Depression in the old years and the rate of very high atherosclerosis is considered the most common disorders among elderly people.[18] In the case of atherosclerosis of individuals, novel biomarkers of myocardial reshaping formed to classify asymptomatic hypertensive people at risk for diastolic disorders and diastolic heart diseases.[19]

Depression in old age and the rates of high atherosclerosis are regarded as the most common disorders among older people, since it persists.[18] The formation of lipids, cholesterol, calcium and cellular waste on individual atherosclerosis is seen in intima walls of large and medium-sized arteries with endothelial disease, vascular swells.[19]

Novel cardiovascular biomarkers under evaluation:

Most commonly biomarkers can be grouped on the basis of disease specificity such as biomarkers of heart failure BNP, N-terminal prohormone of brain natriuretic peptide (NT- proBNP), atrial natriuretic peptide (ANP), ST-2,etcof atherosclerotic coronary disease (troponin T or I, creatinine phosphokinase-MB, etc.), or they can be grouped according to their use such as in acute changes (copeptin, high sensitivity Troponin, galectin-3,andST-2) versus in the chronic stage of CVD to estimate prognosis (coronary calcium by CT).

On the other hand, in accordance to the pathologic process VD biomarker scan be categorized as inflammation (e.g. C-reactive protein, interleukin6, fibrinogen, monocyte chemotactic protein-1, tumonecrosis factoralpha), metabolic (e.g. lipoprotein(a) low-density lipoproteins, high-density lipoprotein, ApoB100, lipoprotein-associated phospholipase A2, homocysteine, vitamin D, fibroblast growthfactor23, adiponectin, glycated hemoglobin, haptoglobin) and oxidative stress (e.g.,isoprostanes).

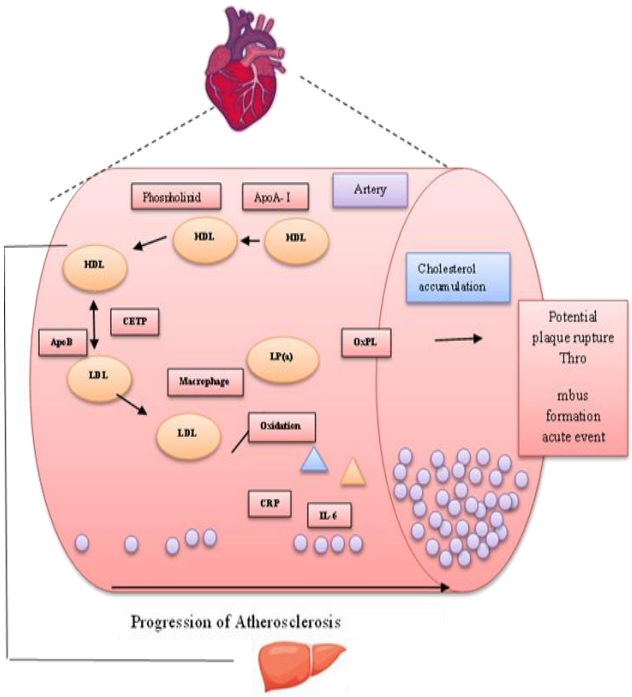

Figure 2: Connection of cholesterol and lipoproteins in atherosclerosis.

Figure 2 is an example of an artery showing the development of atherosclerosis. The development consists of deposition of cholesterol in the artery wall (by LDL), oxidation of LDL, inflammation (mediated by IL-6 and CRP), attraction of monocytes and/or macrophages and the development of plaques.

Abbreviations: ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CETP, cholesteryl ester transfer protein; CRP, C-reactive protein; Lp(a), lipoprotein(a); OxPL, oxidized phospholipids.

Key novel heart failure biomarkers:

The classification of biomarkers for heart failure has been suggested by investigators in conjunction with the pathological method. The biomarkers of heart failure are classified in Figure 3 according to the pathophysiological method. ProBNP is the primary product produced by myocardial stretch and further divided into BNP and NT-proBNP (inert form). The increased risk of heart failure diagnosis in patients who show higher levels of BNP in the blood in an emergency department is correlated with. In addition, higher levels of BNP are linked to increased patient-level mortality when admitted to the hospital. [47]

It is also found that NT-proBNP, which is a more stable type of BNP, predicts heart failure diagnosis. Medicines and other procedures are also known to effectively minimize BNP levels, with certain exceptions, in the course of treating a heart failure 48. Up to now, the study shows that MR-proANP may have an additional benefits in obese, elderly and renal disease patients compared with BNP in cardiac insufficiency diagnosis.[49] The prediction of cardiac failure is also measured for MR-proANP.

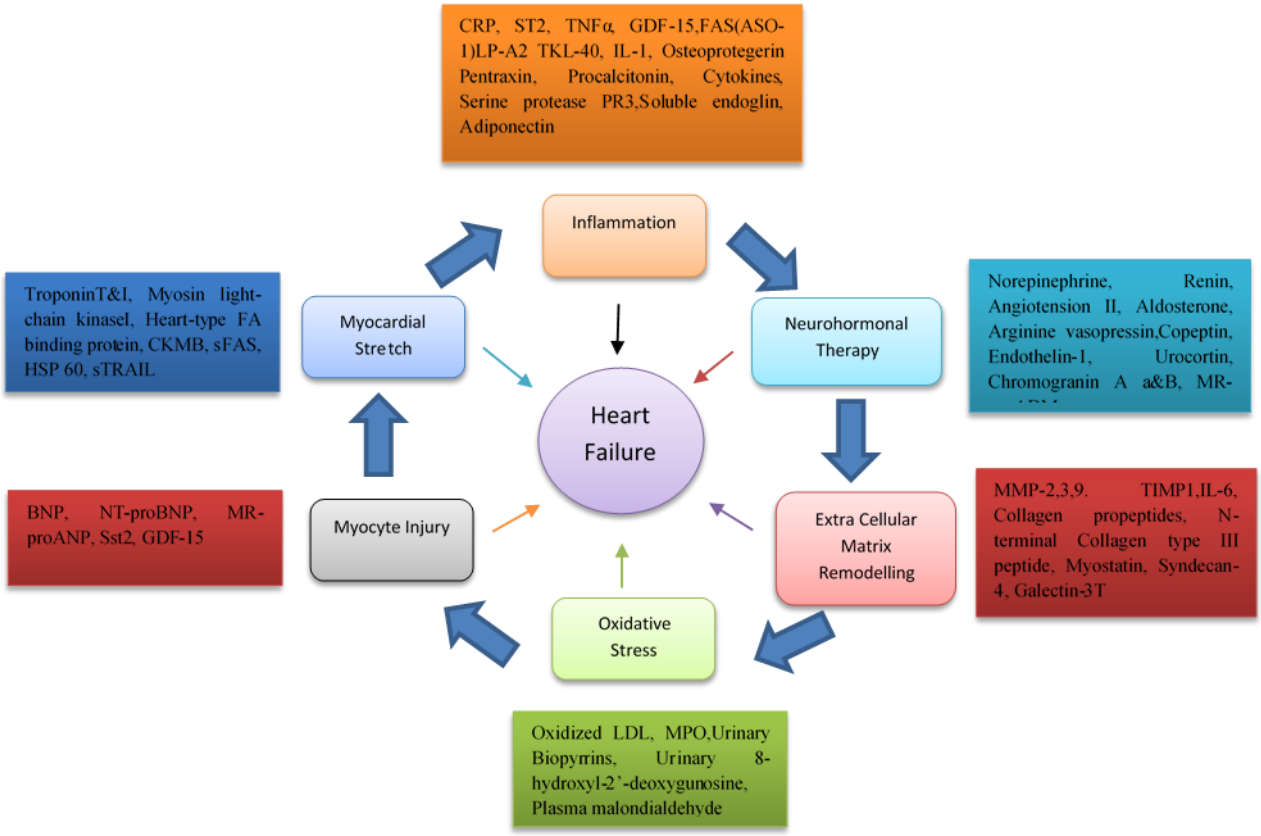

Figure 3: Classification of heart failure biomarkers according to pathophysiologic processes

Troponin I or T (cardiac protein isomers) are released from troponin-tropomyosin complex and are typically convenient for detecting myocardial ischemia in a person's blood circulation.[50] Copeptin is an arginine vasopressin (ADH) precursor protein. In an immediate post-is chemical period, copeptin levels are elevated and also contribute to higher death risk and new-onset heart failure. Galectin-3 is an amazing biomarker with a significant role in cardiac fibrosis production and regulation.[51] The amount of galectin-3 blood indicated a prognosis of mortality for short-term follow-up in patients diagnosed with acute decompensated cardiac failure. Subsequent biomarkers for disease assessment are now being investigated as biomarkers with implications for extracellular matrix markers such as collagen degradening metalloprosteins, metalloprotein specific tissue inhibitors (TIMPs), procollagen type III amino-terminal propeptide (PIINP) or procollagene type I carboxy terminal peptides (PICP) historically related to hypertensive heart disease.[52]

In addition, higher levels of acute-phase procalcitonin in blood were associated with a greater risk of infection in heart failure patients. Mid-regional pro-adrenomedullin (MR-proADM), the receptor of the interleukin family (IL-33) with two gene-soluble forms (sST2) and transmembrane shape, is a stable prohormone fragment of adrenomedule, and the vasodilatory peptide is closely linked to the existence of chronic heart disease. In the last position, small non-coding microRNAs53 RNAs are considered to play a significant role in the regulation of cardiac hypertrophy (e.g. microRNA-133).[53]

Thus, in some studies, microRNA could become an attractive bio-marker for potential heart failure therapy in association with cardiac fibrosis and hypertrophy. Thus, in some studies, microRNA could become an attractive bio-marker for potential heart failure therapy in association with cardiac fibrosis and hypertrophy54. However, in broader, non-selected populations some of these have not yet been thoroughly explored in relation to heart failure.

BIOMARKERS OF MYOCARDIAL INJURY

Cardiac troponin

Troponin is a complex of three globular contractile regulatory proteins (troponin T, I and C) located in the thin striated-muscle filament that prevents contraction by blocking actin and myosine interaction[55].Cardiac troponin I (cTnI) and T (cTnT) are heart-unique proteins that constitute complex and responsive biomarthritis[56]. In skeletal and cardiac muscles, cTnT and cTnI are different to allow for their use as a cardiac biomarker. However, the troponin C that is found in type 2 fibers of the skeletal muscle and the cardiac muscle are identical. It is therefore not easy to use it as a cardiac-specific marker.

In the case of acute myocardial infarction (AMI), necrotic myocardial infarction releases cTnI and cTnT in terms of proteins and decaying materials. Cardiac troponins were more responsive than creatine kinase due to its CK-MB (CMB) and myoglobin, as well as to its more basic cardiomyocyte injury markers. Where the clinical appearance is consistent with myocardial ischemia, AMI is specified by a complex increase in cardiac troponin above the 99th percentile of healthy persons[57]. However, the major drawback of traditional cTn tests shows poor sensitivity when the AMI is presented, as there is a pause in the circulatory increase in cTn and a need for serial sampling for 6–9 hours in many patients.

High-sensitivity cardiac troponin(hs-cTn)

With technical advances, the ability to diagnose and measure cardiomyocyte injury was refined in cTnexperiments. A new generation of troponin tests has recently become possible with improved sensitivity. There are two separate features, one being cTn's sensing in a large number of healthy people and the other a more detailed description of the 'average level' (the 99th percentile) with a more accurate assay, which differentiates from traditional cTn assays[58].

Data from many major multi-center studies have consistently shown that responsive cTn and hs-cTn led at the time of the emergency department to improve the diagnosis accuracy[59].

In a recent study the correlation among patients with diabetes mellitus and stable coronary artery disease (CAD) between high sensitivity troponin and 5-year results was further increased demonstrates a strong and steady association between the baseline level of the moving cTnT and the death, stroke, myocardial and cardiac insufficiency hazard in people suffering both from type 2 diabetes and from a healthy CAD. These findings showed that the hs-cTn test is an excellent method for risk stratification of patients with diabetes and CAD[60].

Heart-type fatty acid binding protein(H-FABP)

The cytoplasmic FABP belonging to the family of transportation proteins permits the transportation of fatty acids across the membrane. The tissue specifics of FABP are the liver type FABP (L-FABP), the bowel-type FABP (BFABP) and the cardiovascular FABP (H-FABP)[61]. H-FABP consists of 132 amino acids, which are a low molecular protein and are involved in the metabolism of the fatty acid myocardium. It is normal in cardiomyocytes abundant and is present in small amounts in the brain, kidney and skeletal tissues, and its levels can be increased as a result of acute ischemic strokes and vigorous exercise. In AMI, H-FABP is released early in the cytosol.

According to the results, H-FABP is either greater to or contributes an increment value for troponin in the initial diagnosis of acute coronary syndrome (AAC), as indicated by ROC analyses[62,63]. H-FABP sensitivity was significantly higher than that of cTnI (18.8%) and CK-MB (12.5%) in the AMI patients with a symptom starting within four hours[64].

The specificity, however, was just 23. 53%, comparatively lower than that of cTnI (66. 67%) and CK-MB (100%).

The H-FABP sensitivity during 4–12 hours of starting symptoms was 86.96%, comparable to the cTnI (90,9%) and the CK-MB (77,3%), with species of 60% in the 4–12 hour class, comparable to cTnI (50%) or CK-MB (50%).In addition, H-FABP is an independent risk factor for all forms of cardiovascular deaths and causes and has high levels of cardiovascular risk factors related to many others. H-FABP may also be a useful predictor to identify high-risk individuals in the general population early[64].

BIOMARKERS OF INFLAMMATION

High-sensitivity C-reactive protein (hsCRP)

C-reactive protein (CRP), recognised as a nonspecific inflammatory marker, as part of the pentraxin family's innate immune response protein, has been used extensively under research in CVD[65].

Studies such as the Women's Health Study and the Physician's Health study have shown that CPR and cardiovascular events connotations are not linked to other risk factors of cardiovascle[66]. Under the Class IIb guidelines for hsCRP (ESC), hsCRP is characterized as a recommendation that hsCRP can be assessed in patients with uncommon or moderate cardiovascular risk profiles as part of the refined risk evaluation[68].

Therefore, it is easy to interpret the hsCRP results: concentrations < 1 mg / L are necessary and they represent low systemic inflammatory status and lower atherosclerotic risk; levels from 1 to 3 mg / L are moderately vascular; levels > 3 mg / L are higher vascular risk in comparison to other risk factors and the value > 10 mg / L are expressed in transient infection or other acute phase response[69].

Growth-differentiation factor-15(GDF-15)

Divergent members of the transforming growth factor β-cytokine superfamily and expressed by activated macrophages are GDF-15, also referred to as macrophage-inhibitory cytokine-1[70]. Connotations of cell oxidative stress, ischemia and stress are uncertain; but it is unknown if GDF-15 involves causally CVD pathologies or has a cellular defense function[71].

During the surveillance of knockout mice, GDF-15, which directly affects leucocyte integration activations inhibiting leukocyte arrest and extravasation has become a major role in the regulation of inflammatory cell recruitment. The findings show that the recruitment of leucocytes in the heart has a GDF-15 inhibitor.GDF-15 is a good indicator of all-cause, cardiovascular and non-cardiovascual mortality in the elderly population and adds added importance to the standard risk factors and levels of CRP, thereby demonstrating a crucial role in the biological processes of aging[72,73].

The innovative promising biomarker for risk assessment is associated with the GDF-15 with CVD, such as ACS, stable CAD, and HF, an independent of other established risk biomarkers reported two cut-offs for GDF-15 [74,75]. GDF-15 is non-commonly present in a number of malignancies (prostate, colon, glial), and not CVD-specific. However, GDF-15 is a possible method to mitigate risks and make therapeutic decisions for positive clinical trial outcomes.

Fibrinogen

Prominent concentrations of fibrinogen are linked with an increased CVD risk.The association of fibrinogen concentration and the risk of both main vascular and non-vascular was studied using FSC studies on the outcome of 15,4211 individual patient data without known CVD from 31 prospective studies [76].

The findings showed that the concentration of fibrinogen is the risk factor for CAD, stroke and mortality. The ERFC research analyses data from 53 forward-looking studies, involving 246,669 CVD historians. The assessment of CRP or fibrinogenic level in persons with an intermediate risk of a cardiovascular event may help to avoid one additional event over a 10-year period for 400 to 500 person's screened[77].

In addition, fibrinogen contains two sets of three polypeptide chains. Aα, Bβ, and μ are composed of 8±15 percent of fibrinogen which flow to a healthy population. Recent studies have shown that α fibrinogen is positively related to CAD, ischemic stroke, peripheral artery disease, HF, and cardiovascular death.

This observation has suggested that causal risk factor for CVD is γA/γ' fibrinogen. In both in vitro and in vivo studies, a global imbalance in redox and marked fibrinogenic carbonylation is found to be correlated with changed coagulation function in patients who suffer from post-AMI[78].These structures may help an improved vision in acute cardiovascular events on the pathophysiology of fibrinogen. Therefore, in the form of risk evaluation for patients with a rarity or a medium cardiovascular risk, the European Society's Cardiology Recommendations for CVD anticipation in clinical practice permit the use of fibrinogen measurements.

BIOMARKERS OF PLAQUEINSTABILITY/RUPTURE

Pregnancy-associated plasma protein-A(PAPP-A)

Pregnancy-referred plasma protein A is a metalloproteinase, a zinc-binding matrix belonging to the metalloproteinase metzincin superfamily. It was made in placenta and found in women who were pregnant. PAPP-A contributes to insulin growth factor-1 (IGF-1) activation which in turn promotes inflammation and lipid uptake that can be used to subsidise atherogenesis and plaque volatility[81].

Together with the repeated is chemical event in individuals with assumed ACS, independent of TnI, the concentration of PAPP-A was identified in two early studies. Then some clinical trials showed that high PAPP-A levels are related to greater cardiovascular risk in individuals with stable and dysfunctional CADs. In the prospective research it is shown in a contemporary responsive test for cTnI that an important association between PAPP-A and cardiovascular death or re-current ischemic events in 3782 individuals with ACS is involved[82]. Therefore, PAPP-A is a biomarker capable

of stratifying the ACS risk. The latest 3-vessel, IVUS research has shown for the first time that higher PAPP-A levels in patients with CAD are associated with higher3-vessel thin-cap fibroatheroma burden. PAPP-A can therefore be a useful serum biomarker for growing fibroatheroma and plaque instability in the coronary thin cap [83].

Myeloperoxidase (MPO)

Myeloperoxidase formed in a heme peroxidase family by polymorphonuclear leukocytes, neutrophil and monocytes. MPO is articulated with MMP macrophages, which inhibit TIMP, oxidation of low-density lipoprotein (LDL) induces the production of hypochloric acid, induces ApoA-I oxidation, and reduces the ability of cholesterol efflux. MPO is well-considered to contribute to plaque formation and breakdown[84].It was found that in people with stable and unstable angina pectoris MPO levels have an important reverse correlation to levels of paraoxonase 1 linked with high density liposure proteins (HDL), which indicated that the incoherence between prooxidants and antioxidants could contribute to the development of coronary plaque instabilities.

In a second-perspective study in the European Prospective Investigation on Cancer and Nutrition (EPIC)-Norfolk study we investigated the relation between the levels of MPO and CAD in an initially well-healthy population[85]. Placing MPO as the circulating inflammatory marker in ACS, HF and CAD is also shown by subsequent forward and cross-sectional studies. The explored risk of stratification of various markers strategies and explored the prognostic information of circulating MPO concentrations in 1090 patients with ACS is shown in the CAPTURE trial[86].

In contrast,[87] MPO concentrations were extrapolative of cardiovascular events up to 16 h after chest pain. It seems that, regardless of the primary process of leukocyte activation and MPO release, it is only likely to employ MPO for risk stratification in the early phase from the onset of chest pain. Recently, a large long-term study like Ludwigshafen Risk and Cardiovascular Health inspected 3036 applicants (median follow-up of 7.75 years) and demonstrated that MPO concentrations but not genetic variants at the MPO locus were independently linked with risk for total and cardiovascular mortality in CAD. Collectively, recent verdicts do not provide any indication for a direct causality of MPO in the risk of adverse clinical outcomes, thus the role of MPO in recognizing individuals at risk for MI is limited.

Matrix metalloproteinases (MMPs)

Endopeptidase, the different inflammatory and tumor cells as zymogens and subsequently activated by the proteinase, MMPs belong to this family. Counteracting roles of MMPs in intimal thickening leading to plaque rupture by regulating plaques and likewise destroys the extracellular matrix[88]. The MMPs are congregated into interstitial collagenases that worsen fibrillar collagen (MMP-1, -8, -13, and -14), gelatinases that degrade denatured collagen (MMP-2 and -9), stromelysins that have a broader specificity (MMP-3, -7, -10, and -11), and macrophage elastase (MMP-12) that primarily cleaves elastin[89].

Protease like MMP-2, MMP-8, and MMP-9 have been known that contribute to atherosclerotic plaque rupture and clinical events by degenerating structural components of the plaque matrix. MMP activity is inhibited antagonists called tissue inhibitor of MMP (TIMPS). Although, cardiovascular death, HF, or both are associated with TIMP-1 and MMP-9 but, they are not linked with recurrent MI. MMP-2 is independent predictor of all-cause mortality in post-ACS and elevated post-MI. A raised MMP-2 activity in plaques is linked with a higher rate of consequent ischemic cerebrovascular events. In contrast to MMP-2, increased MMP-8 levels in the carotid plaque are linked with an unstable plaque phenotype. Occurrence of a systemic cardiovascular outcome during the follow-up are linked up with raisedMMP-8 levels in the carotid plaque. Recently[90] it was identified that the plasma levels of MMP-7 and -12 are elevated in type 2 diabetes mellitus and that the elevated levels are linked with more serious atherosclerosis and a high incidence of coronary events.

MARKERS OF PLATELETACTIVATION

Lipoprotein-associated phospholipase A2(Lp-PLA2)

Lp-PLA2 is a member of the phospholipase A2 super- family and is also known as platelet-activating factor acetylhydrolase. In general, they are formed by monocytes and macrophages. Due to the ability of Lp-PLA2 to change the surface of LDL particles in the phospholipid hydrolysis process, it increases their vulnerability to oxidation[91]. Following LDL oxidation, Lp-PLA2 triggers the release from the inflammatory case of lysophosphatidylocholine and oxidized acids. Following LDL oxidation, Lp-PLA2 triggers the release from the inflammatory case of lysophosphatidylo choline and oxidised acids.

The Coronary Preventative Study from the west of Scotland was the first study to demonstrate the correlation of high LP-PLA2 and cardiovascular events[92]. Further studies showed that operation of Lp-PLA2 is an autonomous CAD interpreter and its typical risk factors have been stroked by large-scale people. In 2012, American and European Guidelines suggested the use of Lp-PLA2 in the cardiovascular risk evaluation of patients[93].Therefore the causal role of Lp-PLA2 in cardiovascular events must continue to be determined.

Secretory phospholipase A2(sPLA2)

It belongs to the enzyme consisting 10 disulfide-rich isoenzyme which is the biggest of the family of enzymes. They are of various type likesPLA2-IB, -IIA, -IIC,-IID,-IIE, -IIF, -III, -V, -X, and -XIIA, and these isoenzymes are involved in a variety of biological processes[94].Some of them are found in atherosclerotic lesions and myocardial regions which have sustained ischemic injury likesPLA2s, sPLA2-IIA, sPLA2-V, and sPLA2-X. This enzyme can contribute to atherogenesis and inflammation by promoting the retention of lipoprotein with vascular proteoglycans, activating the platelet via prostanoids and facilitating LDL oxidation[95,96].

The association between higher circulating levels and sPLA-IIA activity and increased risks of cardiovascular injuries and chronic events has been shown through observational studies (cardiovascular death, AMI, and stroke). However the risk for frequent cardiovascular events in persons with ACS was not reduced, the risk of MI was significantly increased and randomised controlled trials of Mendelian and PHASE III focused on the probability of causal function[97]. A major increase was observed in the sPLA2 inhibitor varespladib. Consequently, the clinical importance of sPLA2 is uncertain [98,99].

Soluble CD40 ligand(sCD40L)

Tumor necrosis superfamily in a family of different cell types, including immune cells (such as lymphocytes, dendritic cells, neutrophils, and macrophages) and non-immune cells (such as epithelial, smooth, and endothelial cells).For immunomodulating properties, the interaction of CD40L with its CD40 receptor is especially significant. As a consequence the platelet's surface can be too binding and activating the CD40, which contributes to its activation and further secretion in a complex modulation cycle.[100]

The prospective studies analogue to Trial CAPTURE [101] and Test Women's Health [102] provide both the CAD individual and healthy person with a prognostic value of CD40L as a biomarker. Recently, 3044 serials had been investigated in the Acute Nondisabling Cerebrovasclic events trial (CHANCE), which showed that increased sCD40L levels predicted recurrent stroke independently in persons with a small stroke and a temporary ischemical attack. However, literature findings about the diagnostic accuracy of sCD40L were problematic in patients with AMI and some researchers showed that sCD40L is not linked to unfatal, potentially lethal, or recurring events with MI. Moreover an acute decrease in sCD40L has been found in the settings of early AMI and the explanation for this is speculative. Assessment of people with suggestive ischemic cardiovascular symptoms needs some additional research to presume an exact function of sCD40L [103].

BIOMARKERS OF NEUROHORMONALACTIVATION

Copeptin

It is part of the C-terminal of the precursor pre-provaspressin (pre-proAVP) and released in equal volume as AVP. Copeptin, aglycosylated 39-amino-acid peptide. It is stable and has a half-life of days in plasma, as related to 5–20 min for AVP. It was then known as an irresponsible biomarker for heart failure and an interpreter of death instead of AVP. The stimulation of the hypothalamus-pituitary-adrenal-axis is assumed to be a recent hallmark[104]. Recently, it has been found that both diabetics and non-diabetics could predict CAD development and cardiovascular mortality. Increased probability of death from CAD for people at the top versus the lower quartile of copeptin[105]. In the case of individuals with an AMI, but not direct cardiac releasing into the coronary circulation in AMI, there was a substantial rise in copeptin. Therefore it remains a matter of debate whether the heart still contributes to copeptin release [106].

Mid-regional-pro-adrenomedullin (MR-proADM)

A52-amino acid ringed peptide with C-terminal amidation, was first seen in pheochromocytoma cells in the adrenal medulla. Being a potent vasodilator and synthesized in the adrenal medulla, vascular endothelial cells, the heart, and else where in response to physical stretch and specific cytokines. It levels in the heart will increased as a result of pressure and volume over- load. It is tough to measure plasma ADM levels due to its short half-life and the existence of binding proteins[107].

It is also established that MR-proADM is a prominent biomarker and has robust prognostic value for mortality and morbidity in patients with HF after an AMI and is higher to risk prediction of NT-proBNP[108].Prospectively investigated the prognostic performance of different biomarkers In emergency department in unselected older patients (aged 81 ± 6 years) prognostic performance of different biomarkers was found that xMR-proADM was the only predictor of cardiovascular deaths. Additionally, MR-proADM is positively linked with brachial pulse pressure and carotid intima-media thickness[109]. Thus, MR-proADM looks to be a prominent prognostic biomarker for early atherosclerotic plaque development and subclinical CAD. Likewise, it designates that even though MR-proADM did not have any clinical use in early AMI diagnosis, it affords predictive value for all-cause mortality. While it is prominent for predicting short-termprognosis, more data is necessary before MR-proADM is to be considered ready for prime-time clinical use[110].

BIOMARKERS OF MYOCARDIAL DYSFUNCTION OR STRESS

Natriuretic peptides

In the sodium and water balance, natural peptides are used by the family of ring-shaped peptides. Natriuretic peptides are types of the atrial natriuretic peptides (ANP), Natriuretic peptides type B (BNP), Natriuretic peptides of type C (CNP), and Dendroaspis Natriuretic peptides (DNP) types. In particular, ANP and BNP are transcribed and developed primarily in the atrium and ventricular myocytes. In conditions such as myocardial stretch, BNP induction contributes to prohormone production and secretion, which is leavened into the more biologically stable N-terminal proB nature peptide.[111]

sIn addition to the conventional risk factors, also among obese individuals, ARIC study showed that NT-proBNP is independently correlated with incidence of HF and enhances HF risk prediction. Furthermore, 5592 participants in the multiethnic atherosclerosis study (MESA) viewed NTproBNP as an independent CAD and CVD incident indicator outside clinical risk factors among asymptomatic individuals of several civilizations.

Additional foretelling information can be provided by an amendment to NT-proBNP. A fragment of natriuretic peptide type A is produced by cardiomyocyte in response to pressure or fluid overload in the mid-regional, pro-Atrial Natriuretic Peptide (MR-PROANP).In aorta and pulmonary arteries, which is consistent with cardiac output and

eventually represents atrial pressure or transmural stress, the highest plasma concentrations were found.MR-proANP, in the research epitopes on the proANP molecules, is a slightly stabler peptide than N-ANP and ANP[112].

Just like NT-proBNP, MR-proANP is predictive for an adverse outcome in patients with acutely decompensated heart failure. Karakas, *et al.*[113] observed that MR-proANP was independently associated with recurrent cardiovascular events after adjustment for established risk factors. When both NT-proBNP and MR-proANP were assessed, the results indicated that MR-proANP was futile in providing additional prognostic information to NT-proBNP in the population studied. In the present European guidelines, the peptides are considered as equal for the diagnosis of both chronic heart failure (CHF) and AHF [114].

ST2

ST2 falls into the family of interleukin-1 receptors. The transmembrane (ST2L) and a soluble decoy receptor are available in two different ways. The downstream effects of the cells include T-helper type 2 (Th2) and Th2-related cytokines production[115].

Dieplinger, *et al.*[116] revealed that increased levels of sST2 was an independent predictor of long-term all-cause mortality and provided corresponding prophetic information to hs-cTnT and NT-proBNP for stable CAD. The Dallas Heart Study investigated a low-risk population, and it was found that sST2 is in association with increased all-cause and cardiovascular mortality. Nonetheless, it remains unclear the appropriate upper reference limit of ST2 in order to predict risk in patients with suspected or proved ACS. Data from MERLIN-TIMI 36 recommend that the conventional value of 35 ng/mL might be acceptable, but it is not convincingly known whether gender-based thresholds should be considered[117]. The recommended cut-off for sST2 in CHF is 35 ng/mL[118].

Endothelin-1(ET-1)

ET1, 21-aminic acid peptide, is a heavy vasoconstrictor and pro-fibrotic hormone secreted with the association of shear strain and pulmonary artery pressure119 by vascular endothelial cells. Higher ET-1 levels are related to short-term clinical results in hospitals and 180-day mortality AHF patients.ET-1 provides additional prognostic information that was in increment to that yielded by NT-proBNP. The therapeutic use of neurohormones is however limited due to plasma instability. The more stable type of ET1 is the pro-Endothelin-1 C/terminal segment (CTproET1), which eventually tests endothelial system function.CT-proET-1 was found to be correlated with cardiovascular death and HF in both healthy CAD and AMI patients regardless of clinical variables and showed a pronostic value comparable to BNP or NT-proBNP[120].

Galectin-3(Gal3)

Gal3 is a glycoprotein-binding measurement approximately 26 kDa is a familial lectin protein secreted by activated macrophages. It plays a key role in atherogenesis by increasing phagocytosis and demonstrates the inducible synthesis of nitricide oxide to arginase in plaques[121].

In recent studies, Maiolino, *et al.*[122] reported that plasma Gal-3 can predict cardiovascular death in high-risk patients bring up for coronary angiography. In addition, Lisowska, *et al.*[123] perceived that Gal-3 being independent risk factor of CAD occurrence, and a concentration more than 8.7 ng/mL considered to be prophetic indicator of increased risk of all-cause mortality during mid-term follow up in MI patients. Inflammatory cascade interrelated to the following cardiac injury byGal-3 may have functions and pathways that regulate cardiac contractility. Prior studies estimated that galectin-3 expression is up-regulated in HF and it may be used as a biomarker for the diagnosis and prognosis of HF. Likewise, Gal-3 is a useful biomarker for the diagnosis of HF in patients with preserved ejection fraction[123]. Elevated Gal-3 levels are related with mortality in both AHF and CHF. In AHF patients, the diagnostic odds ratio of Gal-3 in predicting mortality in CHF patients was 2.36 (95% CI: 1.71–3.26) and 2.30 (95% CI: 1.76–3.01). Moreover, in 2010 US Food and Drug Administration (FDA) approved Gal-3 as a new biomarker in the risk stratification of heart failure. Though, current evidence does not support the sole use of Gal-3 for the prognosis evaluation of HF.

Neuregulin-1(NRG-1)

NRG-1 is a paracrine growth factor which is released from endothelial cells in order to promote cell survival and maintenance and bonds to a family of ErbB receptors on near-by heart myocytes[124]. Currently over 15 various protein products have been identified, encoded by the gene NRG-1.The ErbB (ErbB2, ErbB3,ErbbB4) family of tyrosine kinase receptors exerts its influence in a paracrine manner. The expression of NRG-1 is activated by various cardiovascular factors, including ischemia, exercise, and oxidative stress. Therefore, NRG-1/ErbB4 paracrine signalling in a cardiac adaptation to different physiological stresses proposes this system.

Advanced heart failure phases correlated to higher NRG-1 concentrations and indicated a weaker pronostics among CAD HF patients. In an Observational CAD cohort study, NRG-1 circulating was inversely associated with CAD intensity, which was shown to be more extreme in stress test patients who were positive about ischaemia.[125]. Even in patients with HF, elevated serum NRG levels have been interconnected with poor outcomes. Like NT-proBNP, high NRG serum levels could be a poor physiological reaction to cardiovascular injury, and exogenous administration of NRG could enhance cardiovascular function in cars. The hypothesis that Myocardial NRG-1 is stimulated in response to ischemia is reliable with those findings. Further studies are needed on the potential of NRG-1 as a valued CVD biomarker.

BIOMARKERS OF MICRORNAs(miRNAs)

MiRNAs has recently gained interest in cardiovascular disease pathophysiology. They are short non-encoding RNA molecules (22 nucleotides).They work through the seed region, a sequence of six to eight nucleotides binding to

messenger ribonucleic acid (mRNA), known as miRNA.[126].They usually control post-expression translation and prevent translational repression of the gene expression and mRNA degradation through two key pathways. The quantitative polymerase chain reaction was considered a keystone in miRNA quantification in real time and remains the most reliable method of comparing miRNA expressiveness levels quantitatively. Numerous pathways, such as lipids, glucose homeostasis, vascular integrity, and endothelial cell activity, which are highly involved in CVD are affected by miRNA regulation.

MiRNAs are stable, and detectable in the circulation. Several cardiac miRNAs tends to be detectable in blood early after MI, and hence potentially reducing time to diagnosis. Karakas, *et al*.[127] found an astonishingly strong correlation of single miRNAs with the risk of cardiovascular death and showed their prognostic value in second prevention. Bye, *et al*.[128] and Zampetaki, *et al*.[129] put forward the combined usefulness of a miRNA panel that improved the predictive power of traditional Framingham risk models, even so no single miRNA convened a clinically significant change in risk of acute MI. In recent times, miRNAs can serve as a novel biomarker for platelet reactivity and hence can be affected by antiplatelet therapy administration. Their platelet origin may be especially useful for circulating miRNAs in the sense of the CVD. Nevertheless, the clinical advantages of miRNA detection techniques are not obvious, as they take time and do not allow for rapid diagnosis in MI patients.[130-133]

CARDIOVASCULAR BIOMARKERS: FUTURE DIRECTIONS

Overall, the biomarker industry is expected to grow and prosper rapidly in the near future. As biomarker research increases, it forces a hierarchical data organisation to use structured taxonomies to allow biomarker metadata online to be shared with researchers.

Wide epidemiological and clinical studies are required to determine the cost-effectiveness of biomarkers. Only those that have outstanding performance characteristics are likely to be helpful in primary care settings with a small health care budget. It is possible that a variety of biomarkers will be used as over-the-counter checks, as the public is aware of its own health issues. Precious biomarkers would probably survive this rivalry in order to escape late CVD squeezes. This allows for the speedy collection of the most appropriate medicine and the titration of medication to prevent secondary consequences, as well as to make therapeutic results most appealing for the clinicians, including pharmacogenetic medicines. Concurrent improvement in physician education must be followed by the creation of biomarkers so the range of these can be used to enable clinicians to better order and deduce tests properly.

In health information systems, in the procedures of quality control within clinical laboratories and in the interpretation of biomarker tests, equivalent improvement must be made. A number of ethical and regulatory problems have been developed in conjunction with the advent of genomic biomarkers. The evolution of biomarkers of CVD would, in due course, represent concerted and definitive efforts in the collaboration of fundamental statisticians, Federal and industrial sponsors, science regulators, physicians, technology experts and epidemiologists.

CONCLUSION

Biomarkers, identified as tissue and body fluid changes in compounds, offer a good tactic for understanding the spectrum of CVDs in at least 5 areas: screening, diagnosis, prognosis, prediction of recurrence of diseases and therapeutic monitoring. Advances in functional genomics, proteomics, metabolomics and bioinforms have revolutionised equitable research into multiple alleged markers that can be informative of the different phases, including unconcealed CVD and its sequelae, of atherogenesis.

A description of particular indications, standardisation of analytical processes, characterisation of analytical features, evaluation of performance characteristics, incremental findings of different markers of the clinical indices and evidence of cost-effectiveness are a prerequisite for clinical use of biomarkers. Possibly, technical advances would help to personalise potential CVD care by using multimarker profiling.

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