Biomarkers of Cardiovascular Disease

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Key Concepts

- A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."
- Biomarkers can be classified as predictive, diagnostic, prognostic, and representing pharmacodynamics or response to treatment; different types of biomarkers include genetic, imaging, and circulating biomarkers, with specific relevance at different points in the cardiovascular continuum. In this chapter we will focus on circulating biomarkers that represent biological processes.
- A clinically useful biomarker must show robust association with cardiovascular disease or risk, provide meaningful information about prognosis, and/or guide patient management beyond traditional risk factors or other measures that are already available in the clinical setting.

30.1 Introduction

Cardiovascular diseases (CVD) are the main cause of morbidity and mortality in the general population, a fact that underscores the importance of primary prevention [1]. However, the success of preventative measures depends in part on the accurate identification of individuals at risk of future cardiovascular events (risk prediction). In this regard hypertension, diabetes mellitus, obesity, smoking, and hypercholesterolemia, among others, are accepted as conventional risk factors for CVD and traditionally used as the main components of prediction models with clinical utility in the general population. Nonetheless, extensive research has revealed important limitations of such basic models. For instance, up to 20% of patients with coronary artery disease have no traditional risk factors, and 40% have only one. These data, as well as available results from other epidemiological studies [2], indicate that traditional risk factors do not fully explain the predisposition to CVD or how it evolves in different population groups and responds to treatment. Therefore, the incentive to improve upon current models with traditional risk factors has led to an increasing interest in discovering, validating, and translating to clinical practice novel biomarkers to better identify those individuals who will most likely experience cardiovascular events so that preventive measures can be applied.

Biomarkers generally represent a change at tissue or organ level that is associated with a physiological or pathological process. The National Institute of Health defines a biomarker as any "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Fig. 30.1). In addition, the World Health Organization proposes the following definition of a biomarker: "any substance, structure, or process that can be measured in the body or its products and influences or predicts the incidence of outcome or disease." On the whole, a biomarker should provide useful information to assist clinical decision-making and care, meeting at least one of the following criteria [3]:

1. Predict risk of developing clinically overt disease.
2. Diagnose and stage extent of disease.
3. Indicate disease prognosis.
4. Predict and/or monitor response to therapeutic intervention.

In addition, clinical usefulness of a biomarker requires that measurements render accurate and reproducible results in a standardized manner with high specificity and sensitivity. In biomarker development this often involves validation in independent populations and demonstration that the information provided adds meaningfully to already established clinical risk prediction tool or diagnostic tests. Biomarker data should not only be easily interpretable by clinicians but also cost-effective and thereby support implementation of affordable disease management strategies in the population [4]. It is important to note that biomarkers do not necessarily have to be more sensitive or specific than existing tools; it is the combination of performance parameters, ease of use, and costs that will ultimately inform clinical implementation.

Where these criteria are fulfilled, biomarkers can also be applied in clinical research and serve as endpoints in clinical trials. Substituting established "hard" clinical endpoints with surrogate markers is

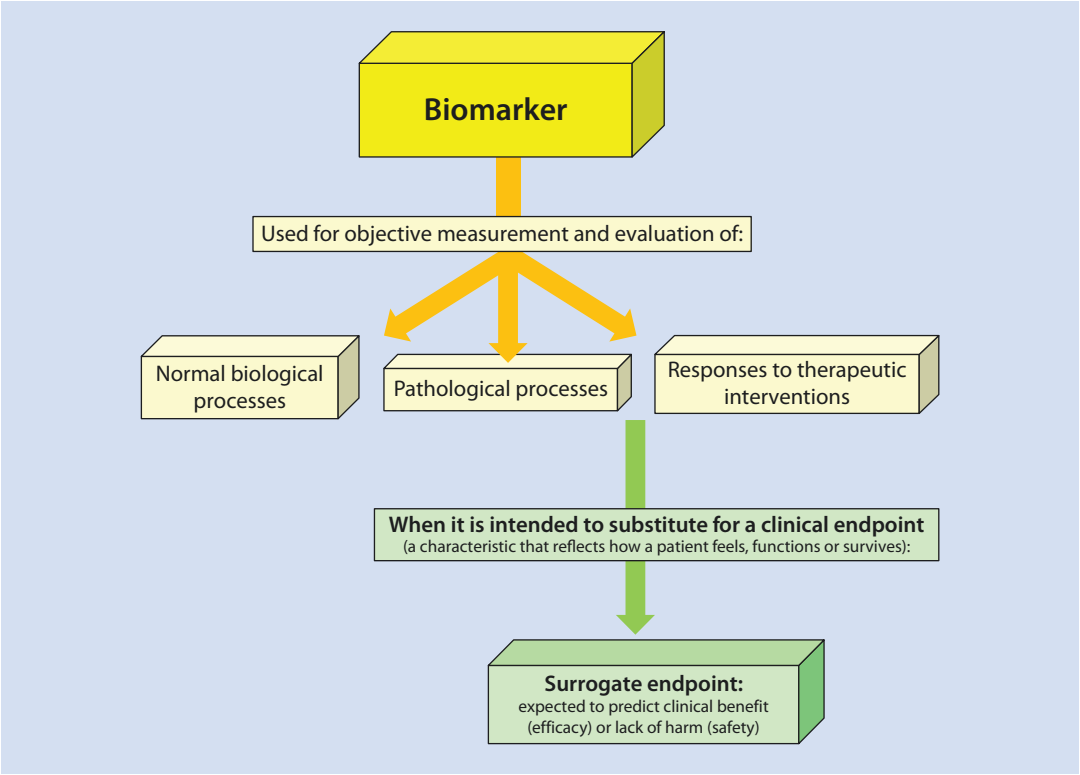

Fig. 30.1 Clinical applications of biomarkers

often more cost-effective and easier than assessing "true" endpoints (Fig. 30.1). These considerations play an important role in clinical trials where the use of surrogate endpoints that are closely linked to morbidity and mortality can result in smaller sample sizes, shorter duration of follow-up, and thereby more cost-effective trial designs. Biomarkers that are commonly used in the clinical trial setting include blood pressure, blood glucose levels, circulating markers of hemodynamic stress and cardiomyocyte injury, and echocardiographic parameters, all of which can help to evaluate the effects of drugs or other therapeutic regimens. However, it is important to note that surrogate endpoints are only useful in the context of specific disease mechanisms and depend on good understanding of disease pathophysiology.

30.2 Biomarker Types

Biomarkers are relevant to precision medicine, which according to the Precision Medicine Initiative is defined as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person" [5]. In this context, biomarkers are investigated as a source of information about a person's genes and proteins in order to prevent, diagnose, and treat disease. Thereby, biomarkers can be classified as predictive, diagnostic, prognostic, and reflecting pharmacodynamics.

A predictive biomarker can be used to estimate the risk of developing overt disease. Traditional risk factors such as blood pressure or body mass index are predictive biomarkers that provide reasonably exact information at population level. However, for individual risk, prediction markers that reflect specific disease processes have the potential to refine risk estimates and provide more precise information.

A *diagnostic biomarker* aids the diagnosis of a disease providing discrimination limits that allow separation of abnormal levels from normal levels for detecting the disease condition of interest. Ideally diagnostic markers should have both high sensitivity (low number of false-negative results) and high specificity (low number of false-positive results), but depending on the clinical context,

different performance characteristics can be accepted. This particularly applies to screening biomarkers that provide a first diagnostic step subsequently followed by further more specific confirmatory tests.

A *prognostic biomarker* provides information on the likely course of a disease or condition in an untreated or treated individual. Such markers may also identify individuals who are most likely to respond to a given therapy or help tailoring specific therapies to individuals depending on their biomarker profile. Changes in circulating levels of biomarkers that are intended to be used as prognostic tools in clinical practice should adequately reflect changes in mechanisms underpinning the disease of interest.

Biomarkers representing therapeutic response measure the effect of a drug or other interventions on the disease process itself. For instance, low-density lipoprotein (LDL) cholesterol is used as a pharmacodynamic biomarker where changes in its concentration are used to guide therapy with the ultimate aim of reducing the risk of future cardiovascular events.

For all types of biomarkers, derivation and validation of their use in a clinical context should be carried out in independent populations and different subsets of populations [6]. In an ideal scenario, a single biomarker can represent all of the above domains, i.e., predict risk, diagnose disease, and provide information about prognosis and response to treatment. However, complex diseases such as CVD develop over long periods of time, are multifactorial in origin, and involve different pathophysiological processes at different stages of disease. Therefore, biomarkers should be seen in the context of the development of disease, and while they may provide information during certain stages, they may not be universally useful.

30.3 Biomarkers and CVD

Extensive research within the cardiovascular context has evaluated new biomarker strategies in the "apparently healthy" general population and in patients with overt CVD [6]. These biomarker approaches include, among others, demographic features, imaging biomarkers, and proteomic, metabolomic, and genetic biomarkers, although in the context of CVD, the term biomarker is most often applied to circulating serum or plasma analytes beyond those used in routine hematology and biochemistry tests. As mentioned above, which of these biomarkers are most informative depends on the stage of the disease process. For instance, subclinical CVD can be present for decades before clinical symptoms are evident. In this regard, *imaging biomarkers* may detect the presence of subclinical CVD but are of limited utility for characterizing the very early stages at which not even subclinical changes in organ structure or function are present. In contrast, *genetic biomarkers* provide information about disease susceptibility, although without indication of whether or not subclinical disease has developed. *Circulating biomarkers* (and other biomarkers present in body fluids such as urine or saliva) may provide information at early or late stage of the disease process, with some reflecting activation of biological pathways that precede disease and others being influenced by the presence of subclinical CVD. Each of these biomarker categories should exhibit certain characteristics that determine their clinical usefulness (Fig. 30.2).

DNA transcription into RNA and translation into proteins that then regulate the metabolism often exert complementary actions to perform certain biological functions. Such synergistic interactions between omic layers can be captured by integrating genomics and transcriptomics as well as proteomics and metabolomics (Fig. 30.3).

Following this model, we will describe genetic, proteomic, and metabolomic biomarkers before we move on to imaging biomarkers and finally provide examples of biomarkers representing specific aspects of cardiovascular pathophysiology.

30.3.1 Genomic Biomarkers

Genetic factors play an important role in the development of CVD. Identification of new genetic susceptibility variants has contributed to the understanding of the pathophysiological processes underlying CVD. Although genetic factors are not influenced by environmental factors, gene-environment interactions will often determine transcription and translation of genes into RNA and proteins and thereby the development of disease. A key difference between genetic biomarkers and other circulating or imaging biomarkers is that the systemic genome itself remains largely unchanged throughout the lifespan, thereby allowing for risk

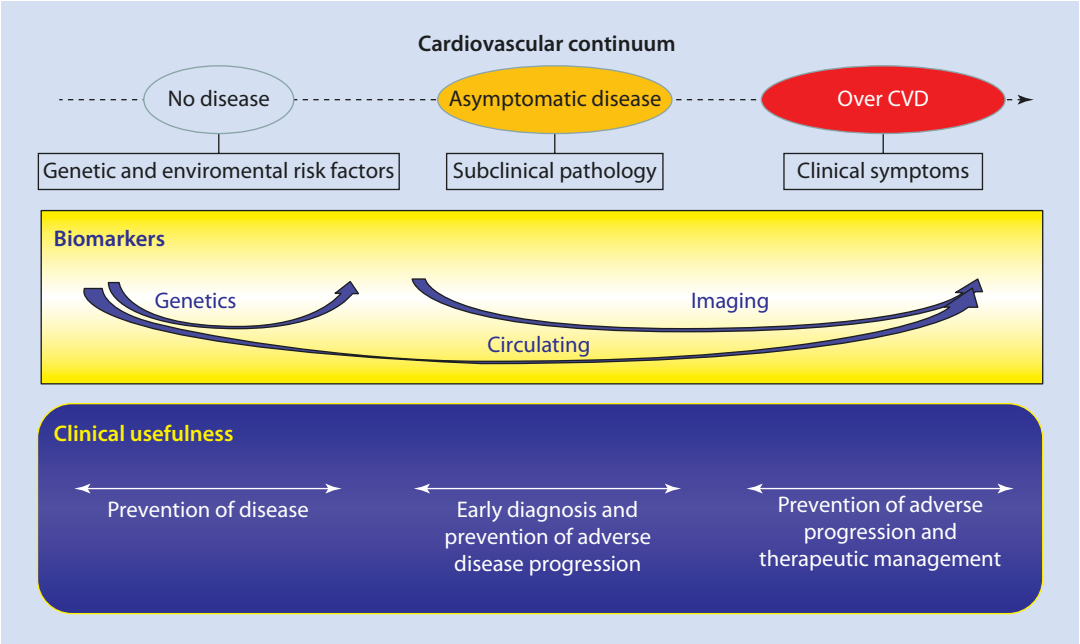

Fig. 30.2 Clinical usefulness of different types of biomarkers along the stages of the CVD continuum

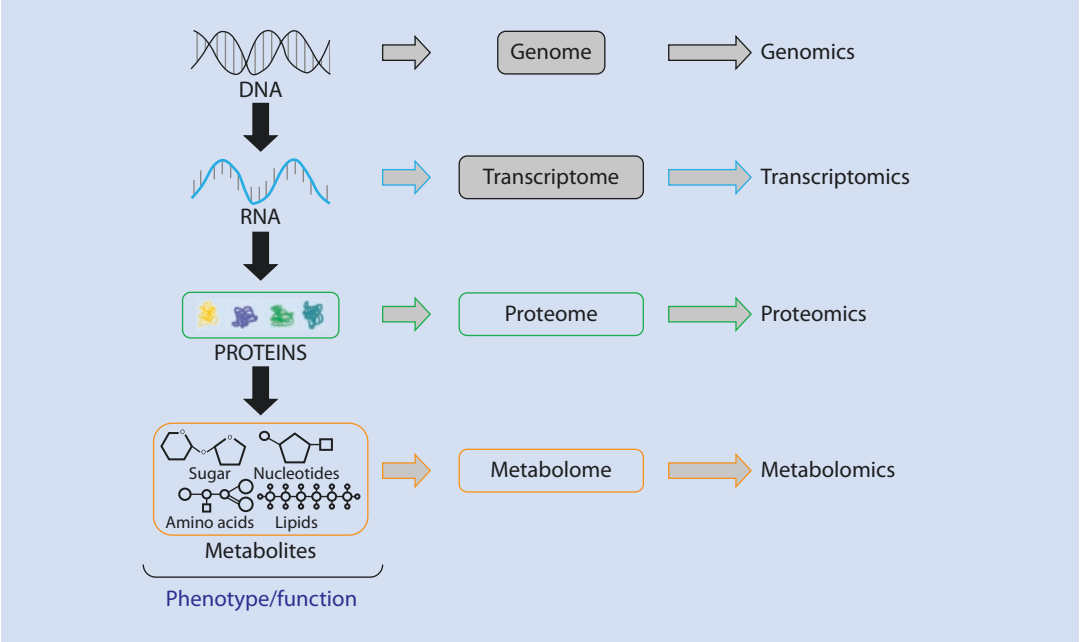

Fig. 30.3 Diagram depicting the flow of information from genes to metabolites and the "omic" sciences

prediction and primary prevention at early stages. In fact, recent genetic studies have shown some consistent loci or genes independently associated with CVD risk factors and with a higher risk of developing CVD. For instance, certain changes in the DNA sequence and epigenetic modifications resulting in altered gene expression and phenotypes have been associated with adverse cardiovascular phenotypes [7]. These properties allow genetic information to be evaluated to guide drug

therapy based on the presence or absence of markers associated with cardiovascular outcomes. Several pharmacogenomic assays are now approved by the FDA for clinical use to assess risk of adverse events and mode of drug action and to predict the response to treatment. Importantly, the sequencing of the human genome in the past decade has enabled genome-wide association studies, a popular experimental design that surveys the whole genome to create single-nucleotide polymorphism (SNP) maps and databases [8]. More details about the genetic makeup of CVDs are provided in ▶ Chap. 16 of this book. The field of proteomics in human pathology is still young, and defining the proteome in different cardiovascular diseases still awaits extensive research.

30.3.2 Proteomic Biomarkers

Proteins play an important role in almost every physiological process of cellular life; therefore it is not surprising that dysregulation in protein expression and activity can result in pathology. Mass spectrometry (MS) has become one of the most powerful technologies in recent years to examine peptide and protein expression in a variety of biological samples such as blood, urine, or tissues. This methodology has been utilized in the past two decades to evaluate the association between a wide range of proteins and CVDs [9, 10]. In particular, MS has been used to create large-scale databases of proteins that inform experimental studies to characterize changes in protein expression associated with adverse cardiovascular phenotypes. By studying large numbers of proteins in an unbiased approach, proteomic techniques can support the characterization of pathophysiological pathways and ultimately the assessment of the CVD risk. In addition, the large amount of information provided by proteomic techniques facilitates further progress in drug discovery and therapeutic approaches in different CVDs [10].

30.3.3 Metabolomic Biomarkers

Metabolomic techniques allow identification and quantification of small molecules that provide information about the state of the organisms at a certain time. Recently developed high-throughput metabolomic profiling technologies allow the quantification of hundreds of circulating metabolites that may help identify metabolic changes preceding irreversible organ damage and symptomatic disease. Characterization of the interrelation between identified metabolites can contribute to the identification of individuals at high CVD risk and provide a "fingerprint" of disease and preclinical disease states and a better understanding of the pathophysiological mechanisms involved in development of CVD. In particular, metabolites such as acylcarnitines, dicarboxylacylcarnitines, and TMAO, several amino acids such as phenylalanine and glutamate, and several lipid classes have been associated with CVD risk. Of interest, some of these metabolites (e.g., branched-chain amino acids) have been found to be associated with obesity, insulin resistance, and diabetes mellitus through underlying processes such as inflammation and oxidative stress. Although comprehensive metabolomics profiling applied to CVD is still in its infancy, metabolomics is currently considered as a tool that holds considerable promise for the search of novel biomarkers in the CVD context [11].

30.3.4 Imaging Biomarkers

Currently, several imaging-based techniques have been developed to study CVD progression. For instance, the assessment of carotid intima-media thickness (cIMT) by ultrasonography is a simple and noninvasive technique that allows characterization of early atherosclerotic changes and thereby visualizes more advanced consequences of the atherosclerotic disease process. cIMT has been found to be correlated with clinical outcomes, making it an attractive biomarker of atherosclerosis and CVD risk. However, although data support the use of cIMT as a valuable tool in clinical atherosclerosis research, it remains unclear how exactly assessment of cIMT can inform clinical decision-making and if changes in cIMT over time that result from a particular therapy correlate with future clinical events [12].

Cardiac magnetic resonance (CMR) is another imaging tool which is increasingly being used to differentiate the etiology of cardiomyopathies but also to assess the structure and function of blood vessels. CMR allows accurate measurement of

cardiac morphology and function due to its three-dimensional nature with excellent spatial resolution and high tissue contrast. In particular, late gadolinium enhancement is the reference imaging procedure for noninvasive assessment of the myocardial scar and focal fibrosis, facilitating differentiation between ischemic versus non-ischemic cardiomyopathy. However, this technique does not allow detection of diffuse fibrosis. In this regard, parametric mapping methods, such as native and post-contrast T1 mapping, have shown potential to detect and quantify both focal and diffuse alterations in myocardial structure, with promising results as novel biomarkers to support diagnostic, therapeutic, and prognostic decision-making in cardiac patients [13].

30.3.5 Circulating Biomarkers

Several systems exist to classify circulating biomarkers of CVD. Most commonly, biomarkers have been grouped based on disease specificity such as biomarkers of heart failure (HF) or cardiomyocyte injury. They have been also classified according to their use in acute versus chronic disease stages or as prognostic biomarkers. In addition, they may be categorized according to the pathophysiological process they represent, such as inflammation, oxidative stress, or myocardial fibrosis (an overview of these categorizations is shown in ◘ Table 30.1). In this section, examples of traditional and novel biomarkers that are currently being investigated for different pathophysiological processes involved in CVD are presented.

30.3.5.1 Biomarkers of Myocardial Stress

Natriuretic peptides are the most commonly used biomarkers to support the diagnosis of heart failure in patients with dyspnea. They are a closely related family of ring-shaped peptides involved in sodium and water balance and regulation of vascular tone, with several structurally similar natriuretic peptides identified: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP). Of these, ANP and BNP are produced in the myocytes of the atria and ventricles, respectively. In conditions of myocardial strain, induction of the BNP gene results in the production and secretion of the prohormone, which is cleaved into the biologically more stable N-terminal pro-B-type natriuretic peptide (NT-proBNP). Natriuretic peptides are also produced in other organs, especially the kidney.

The diagnostic strength of natriuretic peptides, and in particular of NT-proBNP, is their high sensitivity for heart failure, which is more likely as the value of this biomarker increases [14]. Natriuretic peptides have powerful negative predictive value at low levels. However, as with any other biomarker, there are caveats to the interpretation of circulating levels of natriuretic peptides. For instance, natriuretic peptide levels may be elevated in non-heart failure cardiac diseases such as tachycardia and myocarditis where they reflect ventricular stress rather than a clinical diagnosis of heart failure, as well as in non-cardiac diseases such as advanced chronic kidney disease where circulating levels are increased due to reduced renal clearance.

30.3.5.2 Biomarkers of Myocardial Injury

Cardiac troponin I and T, as proteins unique to the heart, are specific and sensitive biomarkers of myocardial damage. Troponin is a complex of three globular contractile regulatory proteins (troponin T, I, and C) that reside in the thin filament of striated muscle and inhibit contraction by blocking the interaction of actin and myosin. In contrast to troponin C, which is identical in type 2 fibers of the skeletal muscle and the cardiac muscle, troponins T and I are different between skeletal and cardiac muscle and are therefore preferred as cardiac-specific biomarkers.

The detection of cardiac troponins in peripheral blood is used as an estimate of cardiomyocyte damage. Technological advances have led to a refinement in troponin assays, improving its sensitivity to detect cardiomyocyte injury. In addition, these high-sensitivity troponin assays have expanded the role of cardiac troponins from biomarkers only used in the diagnosis of acute cardiac damage (e.g., myocardial infarction) to indicators of myocardial injury in chronic cardiac conditions (e.g., those evolving with HF). Interestingly, detectable levels of cardiac troponins have been observed in apparently healthy subjects from the general population as well as in asymptomatic individuals with stable CVD and predict future cardiovascular events [15]. Moreover, cardiac troponin levels have been found to be associated with

Table 30.1 Circulating biomarkers of pathophysiological processes involved in cardiovascular diseases

Pathophysiological processes associated with cardiovascular disease								
Vascular damage				Cardiac damage				
Inflammation/endothelial dysfunction	Plaque instability	Platelet activation	Oxidative stress	Neurohormonal activation	Myocardial injury	Myocardial stress	Myocardial fibrosis	
							Collagen characteristics	Other
ICAM-1	PAPP-A	sPLA2	Ox LDL	ADM	Troponin T	BNP	PICP	OPN
VCAM-1	MPO	Lp-PLA2	MPO	MR-proADM	Troponin I	NT-proBNP	PIIINP	MMP-2
E-selectin	MMPs	sCD40L	BOM	Copeptin	H-FABP	sST2	CITP:MMP-1	MMP-3
CRP	IL-6	PF4	F2-IsoPs		MLCK	Gal-3		MMP-8
sCD40L	Lp-PLA2	CXCL5	8-OHdG		CK-MB	GDF-15		MMP-9
IL-18	IL-18	CXCL7	pMDA		sFAS	ET-1		TIMP-1
MCP-1	sPLA2	CXCL8 (IL-8)			HSP 60	NRG-1		TIMP-4
Fibrinogen	OPN	CXCL12			sTRAIL			Myo-statin
MPO	OxApo A-I	MIP-1α						Syn-decan-4
FFA	PGF	CCL5						
	MCP-1	IL1β						
	OxLDL							
	TMAO							

8-OHdG 8-hydroxydeoxyguanosine, *ADM* adrenomedullin, *BNP* B-type natriuretic peptide, *BOM* bilirubin oxidative metabolites, *CCL* chemokine ligand, *CITP:MMP-1* carboxy-terminal telopeptide of collagen type I to matrix metalloproteinase-1 ratio, *CK-MB* creatine kinase MB isoenzyme, *CXCL* CXC chemokine ligand, *CRP* C-reactive protein, *ET1* endothelin-1, *F2-IsoPs* F2-isoprostanes, *FFA* free fatty acids, *Gal-3* galectin-3, *GDF-15* growth-differentiation factor-15, *H-FABP* heart-type fatty acid-binding protein, *HSP* heat shock protein, *ICAM-1* intercellular adhesion molecule-1, *IL* interleukin, *MCP-1* monocyte chemoattractant protein-1, *MIP* macrophage inflammatory protein, *MLCK* myosin light-chain kinase, *MMP* metalloproteinase, *MPO* myeloperoxidase, *MR-proADM* adrenomedullin precursor, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *NRG-1* neuregulin-1, *OPN* osteopontin, *PAPP-A* pregnancy-associated plasma protein-A, *PGF* placental growth factor, *PICP* carboxy-terminal propeptide of procollagen type I, *PIIINP* amino-terminal propeptide of procollagen type III, *pMDA* plasma malondialdehyde, *sCD40L* soluble CD40 ligand, *sFAS* soluble FAS ligand, *sST2* soluble form of suppressor of tumorgenicity, *sTRAIL* soluble tumor necrosis factor-related apoptosis induced ligand, *TIMP-1* tissue inhibitor of metalloproteinase-1, *TMAO* trimethylamine-N-oxide, *VCAM-1* vascular cell adhesion molecule-1

established heart failure risk factors, including diabetes mellitus, left ventricular hypertrophy, chronic kidney disease, and elevated natriuretic peptide levels, independently of prior myocardial infarction. In fact, troponins evaluated with high-sensitivity assays exhibit prognostic value in patients with established heart failure [16].

30.3.5.3 Biomarkers of Myocardial Fibrosis

The myocardial extracellular matrix consists of an intricate weave of (predominantly) collagen fibrils that play a crucial role in maintaining the structural and functional integrity of the heart, among other organs. Imbalance between synthesis and degradation of collagen types I and III results in myocardial fibrosis, a lesion characteristic of more advanced stages of cardiac diseases. Importantly, the functional impact of myocardial fibrosis is not just a matter of the quantity (i.e., severity of deposition) but also of the quality (i.e., degree of cross-linking among collagen fibrils) of the collagen fibers. Therefore, it is proposed that the assessment of these characteristics of collagen fibers may help to identify cardiac patients vulnerable to adverse clinical outcome [17].

Among the many circulating molecules proposed as biomarkers of myocardial fibrosis in humans, only two collagen-derived serum peptides have been shown to be associated with the quantity of collagen fibers in the myocardium: the carboxy-terminal propeptide of procollagen type I (PICP), formed during the extracellular conversion of procollagen type I into mature fibril-forming collagen type I by the enzyme procollagen type I carboxy-terminal proteinase, and the amino-terminal propeptide of procollagen type III (PIIINP), formed during the extracellular conversion of procollagen type III into mature fibril-forming collagen type III by the enzyme procollagen type III amino-terminal proteinase. Serum PICP levels have been found to be highly correlated with the abundance of collagen fibers in the myocardium of patients with hypertensive heart disease. In addition, serum PIIINP has been found to be highly correlated with extent of collagen type III deposition in the myocardium of HF patients with ischemic heart disease or idiopathic dilated cardiomyopathy [17].

On the other hand, a more rigid and stiffer collagen fiber due to excessive cross-linking may be more resistant to degradation by matrix metalloproteinase-1 (MMP-1), resulting in diminished cleavage of a small carboxy-terminal telopeptide of the collagen type I fiber (CITP). In accordance with this, low serum levels of the CITP:MMP-1 ratio have been found to be independently associated with high myocardial cross-linking [17]. Recent findings suggest that the biochemical phenotyping of myocardial collagen cross-linking may be useful to guide anti-fibrotic therapies in patients with HF [18].

In addition, the biomarkers galectin-3 (Gal-3) and soluble suppression of tumorigenicity (sST2) are markers of myocardial fibrosis which have been endorsed by the American College of Cardiology (ACC)/AHA HF guidelines, with potential interest for additional stratification of HF patients [19]. Gal-3 is a beta-galactosidase-binding protein implicated in diverse biological processes and expressed in multiple tissues and in different types of cells, including macrophages, eosinophils, neutrophils, and mast cells. Plasma levels of Gal-3 are increased in patients with heart failure showing additional prognostic value to NT-proBNP levels [20]. ST2 is a member of the interleukin-1 family and exists in two forms, a transmembrane receptor (ST2L) as well as a soluble receptor (sST2). Several clinical studies have shown elevated sST2 levels in plasma from patients with both acute and chronic heart failure, with predictive value for heart failure outcomes. sST2 is produced by cardiomyocytes and cardiac fibroblasts although elevated plasma levels have been also observed in diseases other than those cardiac-related such as gastric and breast cancer, nephropathy, and liver disease [20]. The inclusion of these novel biomarkers in guidelines supports their potential value over and beyond established risk factors, although their exact potential to inform clinical decisions remains vague. In general, circulating biomarkers can derive from multiple and also non-cardiovascular sources and should be interpreted with caution; they may be influenced by systems other than those directly involved in CVD.

30.3.5.4 Biomarkers of Inflammation

Among all circulating inflammatory markers of the atherosclerotic process, C-reactive protein (CRP) has been most extensively studied. CRP is a member of the pentraxin family of innate immune response proteins and its secretion is stimulated in the liver by cytokines such as IL-1

and IL-6. Among other properties, the fact that the largest set of data in terms of cardiovascular biomarkers have been obtained from studies evaluating CRP may be in part explained by ease of measurement using reliable and affordable technology. In recent years, the role of CRP as a proatherogenic factor has emerged. In particular, it has been proposed that CRP has a role in modulating the network between the endothelium and both inflammatory and smooth muscle cells of the arterial wall, a mechanism that probably favors the atherosclerotic process [21]. In the general population, CRP is associated with cardiovascular events independent of other CVD risk factors.

However, despite the robust statistical association, several studies indicate that CRP measurements provide only modest improvements in predictive accuracy, raising the issue of whether CRP is merely a marker of itself or a causal factor for CVD [22]. In this regard, Mendelian randomization analyses evaluating the association between CRP and coronary heart disease indicate that CRP concentration itself is not a causal factor in this condition [23]. Nonetheless, results from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) demonstrate that targeting the interleukin-1β to interleukin-6 to CRP signaling pathway in patients with a history of myocardial infarction and high levels of circulating hs-CRP (≥2 mg/L) is beneficial for the secondary prevention of CVD, being this benefit independent of the cholesterol levels [24].

Other inflammatory biomarkers that hold promise in the context of atherosclerosis include advanced glycation endpoints, oxidized LDL, heat shock proteins, lipoproteins, tumor necrosis factors, interleukins 1 and 6, platelet-derived activation products, and myeloperoxidase [25]. These biomarkers have been comprehensively reviewed in ► Chap. 21 of this book.

Conclusion and Clinical Perspectives

Numerous cardiovascular biomarkers have been evaluated for their use in the clinical setting as predictive, diagnostic, prognostic, and therapy guidance tools. Importantly, a biomarker must reflect a pathophysiological mechanism and help making decisions on patient management, providing information beyond the clinical tools already available. More specifically, the prognostic value of a given biomarker should include improved discrimination, calibration, and reclassification with respect to standard variables already implemented in the clinical setting. In addition, biomarkers of CVDs have to be robustly validated in independent cohorts prior to approval for clinical practice. They should exhibit adequate precision and optimal intraindividual reproducibility, be easy to measure preferably at a point of care over a short time period, and demonstrate cost-effectiveness. These evaluation processes are needed to establish noninvasive tools as surrogate measures to be used for predictive and prognostic purposes in clinical trials, contributing to improve future precision medicine strategies in CVD treatment.

Gaps in Knowledge

- More reliable methods for diagnosis and guided clinical management of patients with CVD are needed.
- Limited reproducibility of proteomic data has been reported repeatedly. This may originate directly from the biology of protein expression: gene expression is highly variable even in healthy people, and disease changes expression of and diversity within protein families.
- Even if a protein is correctly identified as a potentially useful biomarker, it may be technically impossible to quantify it by affordable techniques (e.g., ELISA), precluding its use in the clinical setting. Current research based on methodological adjustments and multidimensional approaches is addressing these limitations so that the heterogeneity and diversity of biomarkers within proteomic approaches can be taken into account [26].
- A novel biomarker should add incremental information about a condition of interest, above and beyond traditional risk or disease factors. However, several studies suggest that many of the biomarkers currently used in the clinical setting, including multimarker models, may not consistently and substantially improve risk prediction or diagnosis of CVD compared to established criteria [6, 27].

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