Hypertension Research (2023) 46:893–895
https://doi.org/10.1038/s41440-023-01187-0

COMMENT

Era of biomarker-based disease risk management

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Keywords Biomarker · Framingham risk score · Vascular function

Received: 20 December 2022 / Revised: 28 December 2022 / Accepted: 29 December 2022 / Published online: 20 January 2023

Hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, and aging are known to cause serious organ complications in the brain, heart and kidneys. Large clinical trials have shown that intervention for subjects with cardiovascular risks significantly reduces the incidence of cardiovascular disease and mortality [1, 2]. Atherosclerosis develops and progresses with vascular endothelial dysfunction as the initial step [3]. Further progression leads to cardiovascular complications such as angina pectoris, myocardial infarction, heart failure, stroke, and renal failure. Therefore, it is clinically important to accurately evaluate vascular function even before the onset of atherosclerosis to assess the degree of progression of atherosclerosis and the effectiveness of treatment. Many noninvasive as well as invasive vascular function tests have been performed [4]. In addition, measurements of chemical biomarkers including blood pressure, lipid profile, and glucose have been established for detecting cardiovascular risks and events [5, 6]. In the next era, there is an urgent need to evaluate the most appropriate biomarkers in each disease and use them to reduce the target organ damage and incidence of cardiovascular events (Fig. 1).

The ideal assessment of vascular function such as endothelial function (e.g., strain-gauge plethysmography, flow-mediated vasodilation and reactive hyperemia index (RHI)) and arterial stiffness (e.g., pulse wave velocity, cardio ankle vascular index, augmentation index (AIx), ankle-brachial pressure index, stiffness beta and intima-media thickness) as well as vascular smooth muscle function using reactivity testing with nitrate administration (strain-gauge plethysmography and vascular ultrasound evaluation) requires an understanding of the vasculature as its target [4]. The vascular system consists of the vasculature and the lymphatic system. It has become clear that the vasculature is not only a conduit for oxygen, nutrients, and waste products, but also performs many functions necessary to sustain life. Normally, blood vessels have a three-layered structure. The lumen of blood vessels, both arterial and venous, is covered by a single layer of endothelial cells that form the inner layer, a tunica media composed of smooth muscle cells that surrounds the endothelial cells, and an outer membrane that lies outside the tunica media. Connective tissue and extracellular matrix provide a rigid vascular structure. The three-layered structure of blood vessels not only supports the structure of the vessels themselves but also plays an important role in the development, maintenance, and progression of atherosclerosis. Classically, the venous system of the vasculature is considered as capacitance vessels (blood storage vessels), but in recent years, it has been shown that the veins themselves may also have a variety of functions. Ideally, it is essential to evaluate the function of all of the vessels that make up the vascular system.

Measurement of chemical biomarkers in blood or urine is the most convenient and noninvasive method for assessing cardiovascular risks and cardiovascular events. Traditional cardiovascular risk factors are established as predictors for cardiovascular events. However, unfortunately, there is little information on a biomarker that defines the progression of individual diseases and the events that correspond to them. Even when it comes to vascular function, there are various problems such as the possibility that measurements do not directly reflect nitric oxide production and the accuracy of measurements. These measurements should be considered as adjuncts to physiological endothelial function assessment methods. If a biomarker is highly specific as an

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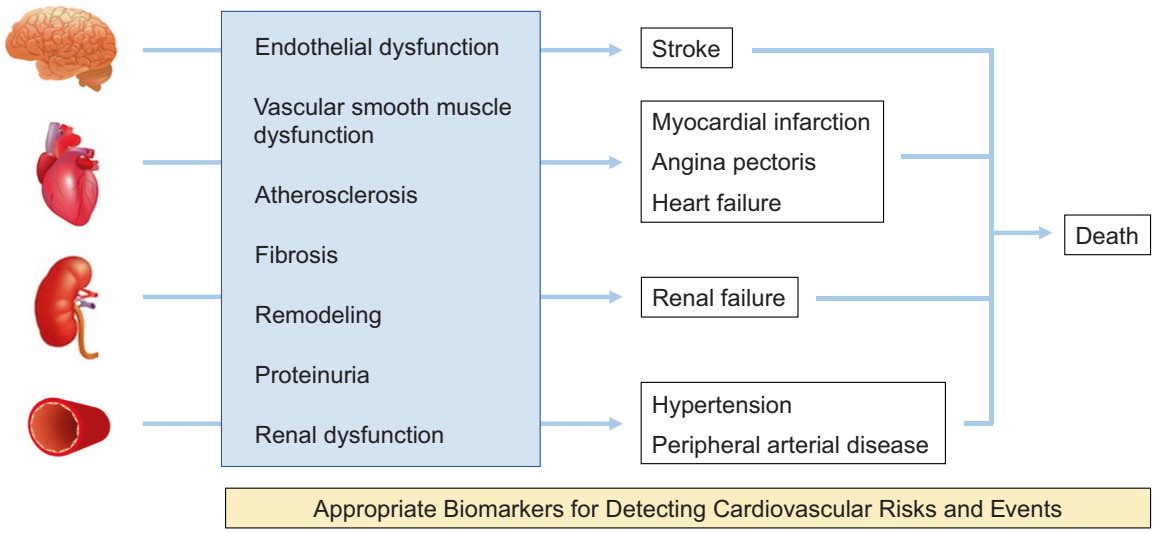

Fig. 1 The era of biomarker-based disease risk management. What is an appropriate biomarker for detecting cardiovascular risks and events? Cascade from cardiovascular risks to cardiovascular events in each target organ

indicator of vascular endothelial function or atherosclerosis, it can be evaluated by measuring its concentration in blood or urine, and measurements can thus be performed easily and can be used in large-scale clinical trials or cohort studies. The Framingham risk score (FRS), published in 1998, is known to predict ischemic heart disease within 10 years based on the sum of age, gender, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diabetes, and smoking [7]. FRS is used not only to predict the development of ischemic heart disease but also to predict cardiovascular events in various diseases. Vascular endothelial progenitor cells, endogenous nitric oxide synthesis inhibitor, endothelial microparticles, and Rho-associated kinase activity in monocytes are expected to be candidate biomarkers that reflect vascular function.

In this issue, Li et al. [8]. reported that FRS but not RHI or AIx was a predictor for the decline of estimated glomerular filtration rate (eGFR) as an index of renal function in patients with chronic kidney disease. It is well known that components of FRS are independent predictors for RHI and AIx and that RHI or AIx per se also is associated with eGFR in chronic kidney disease [9, 10]. It is therefore somewhat curious that only FRS, and not RHI or AIx, is a predictor of lower eGFR in these patients. Anyhow, it is likely that FRS is a useful biomarker for the decline in renal function in chronic kidney disease. Long-term observations are needed to determine whether the use of these markers can further define the decline in renal function and the onset of cardiovascular events. The use of a chemical marker alone, as well as the combination of the chemical marker with physiological testing, is highly promising in its potential to help predict target organ damage and further cardiovascular events. The era of biomarker-based disease risk management is upon us.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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