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Biomarkers in cardiovascular disease: Statistical assessment and section on key novel heart failure biomarkers

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A B S T R A C T

Cardiovascular disease (CVD) is a leading cause of death worldwide and continues to increase in prevalence compared to previous decades, in part because of the aging of the world population. Atherosclerotic CVD starts at a very young age and progresses over time allowing sufficient time for screening and early detection of the condition. Advances in biomarker research and developments related to CVD over the past 30 years have led to more sensitive screening methods, a greater emphasis on its early detection and diagnosis, and improved treatments resulting in more favorable clinical outcomes in the community. However, the use of biomarkers for different purposes in CVD remains an important area of research that has been explored by scientists over the years and many new developments are still underway. Therefore, a detailed description of all CVD biomarkers that are currently been used or investigated for future use in the field of cardiovascular medicine is out of scope for any review article. In the present review, we do not intend to replicate the information from previous exhaustive review on biomarkers, but highlight key statistical and clinical issues with an emphasis on methods to evaluate the incremental yield of biomarkers, including their clinical utility, a prerequisite before any putative novel biomarker is utilized in clinical practice. In addition, we will summarize information regarding recent novel heart failure biomarkers in current practice, which are undergoing scrutiny before they can be available for clinical use, and their impact on clinical outcomes.

Key words: Biomarkers, Cardiovascular disease, Heart failure.

"Prediction is difficult, especially about the future."—Anonymous

Cardiovascular disease (CVD) is a leading cause of death worldwide and continues to increase in prevalence compared to previous decades, in part because of the aging of the world population [1]. Atherosclerotic CVD starts at a very young age and progresses over time allowing sufficient time for screening and early detection of the condition [2]. Advances in biomarker research and developments related to CVD over the past 30 years have led to more sensitive screening methods, a greater emphasis on its early detection and diagnosis, and improved treatments resulting in more favorable clinical outcomes in the community [3,4]. However, the use of biomarkers for different purposes in CVD remains an important area of research that has been explored by scientists over the years and many new developments are still underway. Therefore, a detailed description of all CVD

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biomarkers that are currently being used or investigated for future use in the field of cardiovascular medicine is out of scope for any review article. In the present review, we do not intend to replicate the information from previous exhaustive reviews on biomarkers [5], but highlight key statistical and clinical issues with an emphasis on methods to evaluate the incremental yield of biomarkers, including their clinical utility, a prerequisite before any putative novel biomarker is utilized in clinical practice. In addition, we will summarize information regarding recent novel heart failure biomarkers in current practice, which are undergoing scrutiny before they can be available for clinical use, and their impact on clinical outcomes.

Biomarker definition

The National Institute of Health Consortium in 2001 defined a biomarker as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [6]. Subsequently, in 2009 the American Heart Association outlined the extensive criteria for how newer biomarkers should be evaluated in a standardized fashion before their clinical use can be recommended [7]. The characteristics of an ideal biomarker to be used for a given purpose in any disease condition with a special emphasis on CVD are detailed in previous reviews [5,8].

Biomarker types

Biomarkers play an important role in the evaluation of disease as well as in the development of drug treatments for disease conditions. In the late phases of drug development, biomarkers can even be helpful in determining the accurate doses for any given drug. In more recent times, biomarkers are being considered as surrogate end points for clinical trials as well. Biomarkers are traditionally classified on the basis of their intended use as screening, diagnostic, or prognostic. Desired characteristics of a novel biomarker according to their intended use are also displayed in Fig. 1. More recently, there has been a national shift toward development of precision medicine, especially with a focus on development of new cancer drugs. On January 30th 2015, US President Barack Obama introduced in his State of Union address the Precision Medicine Initiative [9] that takes into account individual differences in genes, environment and lifestyle factors, emphasizing more effective, and targeted treatment goals [10].

From a precision medicine perspective, biomarkers can be classified as prognostic, pharmacodynamic, or predictive biomarkers. A prognostic biomarker is one that provides information on the likely course of a disease condition in an untreated individual or in an individual treated with conventional therapies. In contrast, a predictive biomarker is one that can be used to identify individuals who are most likely to respond to a given therapy or that distinguishes candidates who can be considered for specific targeted therapies [11,12]. Thus, predictive biomarkers help to tailor

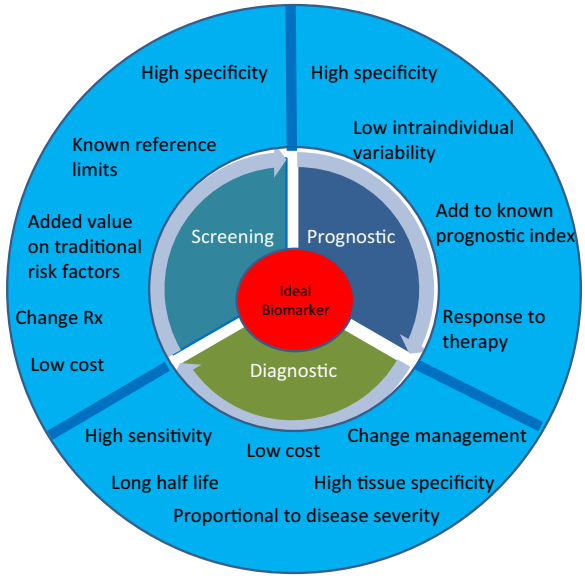

Fig. 1 – Ideal characteristics of a biomarker according to their intended use.

therapy according to the patient's needs. So far these clinical trial designs based on evaluating a biomarker for prognostic or predictive utility have been limited to the field of oncology; however, other fields of medicine including cardiovascular medicine and infectious diseases have now started adopting these designs as well [13]. Lastly, pharmacodynamic biomarkers measure the effect of a drug on the disease state itself. In other words, they represent the change in a target organism in response to the disease and its treatment. For example, changes in circulating natriuretic peptide levels are reflective of heart failure severity and, therefore, blood natriuretic peptide levels are now being proposed as a surrogate end point to test the efficacy of drug treatment [14]. Similarly, use of statins to reduce serum cholesterol levels is another example where changes in concentration of a biomarker [low-density lipoprotein (LDL) cholesterol] is used to guide therapy to reduce the risk of CVD in future. But first, it is imperative to confirm that biomarker levels (natriuretic peptide or LDL cholesterol as examples above) should correlate well with a clinical outcome at individual and population levels.

Biomarker characteristics—general principles

Accuracy, precision, high sensitivity, and specificity are important characteristics of an ideal biomarker. Before clinical utilization, if a biomarker is to be used for screening or for prognostic purposes, a high specificity [which is expressed as likelihood ratio (LR)] is required ("rule in") [15]. The desirable likelihood ratio for a screening test is typically >10. Whereas, if a biomarker is evaluated for diagnostic purposes, a high sensitivity ($LR<0.10$) is recommended. Second, it is important to establish reference limits [16] with the understanding that reference limits are influenced by the characteristic of an assay in the group analyzed to derive those limits [17]. For instance, blood troponin assays made by several manufacturers are different and have varying reference limits for detection of clinically important vascular events such as an