Minimal and Null Predictive Effects for the Most Popular Blood Biomarkers of Cardiovascular Disease

John P.A. Ioannidis, Ioanna Tzoulaki

At least 10 cardiovascular biomarkers that can be measured in blood have accrued more than 6000 published related papers each. A systematic evaluation of the evidence suggests that they have limited or no predictive ability for cardiovascular disease and suggests the need for a paradigm shift in testing and qualifying biomarkers and in the expectations surrounding them.

Hundreds of thousands of papers have addressed cardiovascular biomarkers in the last few decades. Blood biomarkers in particular have been a very attractive topic of research efforts for myriad investigators, given that they require only a blood draw. Emerging biomarkers hold diverse promises.\(^1\),\(^2\) In theory, they may inform about cardiovascular risk; reclassify patients into more appropriate risk categories versus what can be achieved on the basis of traditional risk factors; improve outcomes when used as appropriate guidance for treatment initiation, management, and monitoring; or point to other modifiable factors on which one can act.

In this Perspective, we have reassessed the evidence on the performance of the most popular emerging blood biomarkers for cardiovascular disease. Popularity was defined on the basis of the number of PubMed articles retrieved on each of these biomarkers with a cardiovascular focus using the search string [cardiovascular OR heart OR cardiac OR myocardial OR coronary OR angina OR hypertension OR “blood pressure”] (search performed on January 14, 2012). We screened 36 emerging cardiovascular biomarkers measured in blood, serum, or plasma that are listed in 2 relevant reviews.\(^2\),\(^3\) This does not include traditional risk factors for cardiovascular disease that are already included in the Framingham Risk Score.\(^4\) Of those 36 candidates, we focus here on the 10 biomarkers that had at least 6000 articles each identified with the cardiovascular search string (Table 1). Search terms appear in the Appendix. Of note, not all of these articles directly address with primary data the main promises of biomarkers that are mentioned in the previous paragraph. As in any biomedical research field, approximately half of the articles are nonsystematic reviews, editorials, or news items, and many of the remaining half pertain to other, often tangential questions. Nevertheless, with a literature of anywhere between 6538 and 35 700 papers for each, clearly all of these biomarkers have been highly popular in the scientific literature.

In fact, with 1 exception (brain-type natriuretic peptide), the overall literature for these biomarkers is far broader than the cardiovascular-related papers, which constitute only 10% to 40% of the total scientific output on them. Most of these biomarkers have had a very nonspecific trajectory, with interest attracted for their potential role in very diverse processes, conditions, and diseases. This is most prominent for “transdisciplinary” markers such as myeloperoxidase, serum albumin, and interleukin 6.

How much can these popular markers inform cardiovascular risk prediction? Table 2 summarizes effect sizes from the most recent and largest meta-analyses for associations of these biomarkers with cardiovascular disease, focusing on studies in general populations. Preference was given to meta-analyses of individual-level data whenever available. We standardized the relative risks to correspond to risks per 1 standard deviation (SD) of each biomarker; otherwise, some effects may have appeared to be large simply because extreme exposure contrasts were selected.\(^5\)

Given the potential prevalence of publication and other selective reporting biases in this literature, many of the relative risks derived from these meta-analyses are likely to be inflated.\(^6\) Nevertheless, despite the potential inflation, none of the listed biomarkers had a reported summary relative risk exceeding 1.45 per 1 SD in analyses that adjusted for other known cardiovascular risk factors (Table 2). One should acknowledge that the relative risk may not be an optimal metric to assess the discriminative ability of a biomarker; however, such relative risks are expected to translate to improvements in the range of 0.01 or less in the area under the curve when added to traditional risk factors.\(^7\),\(^8\)

In fact, some of these markers have nonstatistically significant predictive effects that cannot be differentiated from the null, as in the case of triglycerides and intercellular adhesion molecule 1. In other cases (interleukin 6, serum albumin, homocysteine, and uric acid), the effects are very small, and the 95% confidence intervals exclude the possibility of even...
modest predictive effects (such as a relative risk of 1.35 per 1 SD). For such small effects, it is difficult to be certain that they are not simply the result of residual confounding or selection biases in the literature. For example, for uric acid, the more recent meta-analysis had clear evidence for funnel plot asymmetry, which is indicative, if not conclusive, of publication bias. The summary effect was drawn away from the null by some very small studies with implausibly large negative results. Similarly, mendelian randomization studies of genotypes associated with lifelong variation in popular markers, such as CRP, are often negative for the most common genetic variants, partly because even then, the reported risk estimates were not substantially biased. For all 3 of these biomarkers, the predictive effects shown in data sets from randomized trials are smaller than those shown in data sets from observational studies. Only CRP and fibrinogen have reached on the rules of engagement (for conduct and reporting) the more recent meta-analysis had clear evidence for publication bias. The summary effect was drawn away from the null by some very small studies with implausibly large effects. An earlier meta-analysis had concluded that uric acid has no independent predictive ability for coronary heart disease. Finally, some of the effects are of modest magnitude, as in the case of brain-type natriuretic peptide, C-reactive protein (CRP), and fibrinogen (relative risks of approximately 1.4 per 1 SD); however, these estimates are probably substantially biased. For all 3 of these biomarkers, the predictive effects shown in data sets from randomized trials are smaller than those shown in data sets from observational studies. Only CRP and fibrinogen have been examined in individual participant meta-analyses; however, even then, the reported risk estimates were not explicitly adjusted for the full Framingham Risk Score or all the Framingham Risk Score variables (Table 2). Predictive models that incorporate CRP in addition to traditional risk factors (Reynolds Risk Score) have shown only modest improvement in discrimination over the Framingham Risk Score in men and women and require further validation by independent investigators.

Despite the very limited predictive ability, there would be some stronger reassurance and renewed interest about these markers if they could be shown to have causative links to cardiovascular disease; however, proof of causality is difficult, and most attempts have been negative for the most popular markers. For example, CRP has been tested in a large number of mendelian randomization studies with consistently negative results. Similarly, mendelian randomization studies of genotypes associated with lifelong variation in fibrinogen concentrations have not shown associations with cardiovascular risk to date.

Despite these disappointing results, measurement of CRP is currently recommended by several guidelines to guide treatment in individuals at moderate risk of developing coronary heart disease. This is a paradox, because hardly any other cardiovascular markers have such an extensively negative documentation as CRP.

Given that the majority of the predictive effects for these popular biomarkers are either null or small, their ability to improve reclassification of patients into more appropriate categories of risk is also expected to be infinitesimal. Detailed discussion of this accumulating literature is beyond the scope of this Perspectives article. Despite the large number of articles published, they are susceptible to selective reporting, with selective choices of thresholds of risk used to define reclassification (even when these thresholds have been generally agreed upon) and with straw man downward-adjusted performance of the standard risk factors. Unless this literature is standardized and an agreement reached on the rules of engagement (for conduct and report-
ing of research), it is likely that spurious claims of markedly improved reclassification performance will multiply, further confusing the field.

Importantly, there are no randomized trials to date that have tested whether use versus nonuse of any of these popular biomarkers can improve hard clinical outcomes by improving decisions about treatment initiation, management, and monitoring in the general population. Such trials should be feasible to perform and would be most informative on whether it is worth using these markers. An example that can be followed in trials involving the general population is offered by a randomized trial that successfully examined the use of brain-type natriuretic peptide in the diagnosis of patients with acute dyspnea.25 The JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) on patients without hyperlipidemia but with elevated CRP levels reported significant reduction of cardiovascular disease in the treatment (rosuvastatin) arm versus placebo, but patients with low CRP or without CRP measurements were not studied, and therefore, the clinical impact of a CRP measurement cannot be examined.26

Finally, several of these biomarkers have pointed to other modifiable factors that one can potentially act on and thus use to reduce cardiovascular risk; however, to date, this avenue has also met with almost ubiquitous failures. A great deal of effort has been invested in decreasing risk by correcting homocysteine, eg, through administration of folate and B vitamins. Results from many observational studies have shown associations between homocysteine intake and incident cardiovascular disease, but the evidence from large randomized controlled trials does not support a protective effect of folic acid supplementation (rectifying homocysteine levels) in cardiovascular disease. Many hypotheses have been proposed to explain these discrepancies.27–29 One can debate endlessly about potential effect modifications and subgroup effects (eg, that the folate intervention may work only with certain background folate levels, or only in patients not taking other cointerventions such as aspirin), but it is quite likely that simply correcting homocysteine levels does not work. Similarly, several trials have tried to treat coronary heart disease as an inflammatory, if not infectious, process, given that many of the most popular biomarkers are inflammatory markers.30,31 Despite promising results with antibiotics in early small studies, the current results are again largely null.32

All the biomarkers that we evaluated in this Perspectives article were proteins, lipids, or metabolites. Many other blood biomarkers are proposed currently that are based on newer technologies that allow a wide diversity of biological measurements. Genomic biomarkers have been particularly popular in the last decade. Almost all of the candidate-gene–era genetic biomarkers of cardiovascular disease failed to be validated,33,34 and we suspect that a similar fate awaits the other popular biomarkers that we have discussed above. Conversely, the use of massive testing with agnostic approaches has yielded an impressive number of robustly validated genetic risk factors for cardiovascular disease or cardiovascular risk factors in the last few years.35–37 A key lesson from these validated markers is that single genetic variants ubiquitously confer extremely small risks, rarely corresponding to risks more than 1.25 per allele and typically corresponding to risks of 1.15 or less. Given power considerations, it is likely that the discovered markers are actually among the strongest in effect sizes, and what remain yet to be uncovered are primarily markers with relative risks of 1.10 or less, or even well below 1.05. Sequencing efforts may also, in theory, discover rare variants with much larger relative risks, but given their extremely low frequency, their contribution to prediction would be even more minimal.

Overall, the composite picture on popular biomarkers offers some useful lessons and potential suggestions about what pathway to follow in the future. First, the quest for single biomarkers with large effects may need to be tempered, if not totally abandoned. Continued massive investment of thousands of studies focused on a handful of popular biomarkers that are evaluated 1 or a few at a time may be a poor investment. It is possible that there are thousands of noncausal biomarkers that would have similar predictive effects as CRP, fibrinogen, or homocysteine (if these markers have any non-null predictive effect at all). Furthermore, fragmented efforts in single studies are highly susceptible to selective outcome and analysis reporting biases and may create spurious claims that cause herding and bandwagon effects38 and loss of valuable research resources. The field is already highly sensitized to the need for large-scale, consortium-level work, as exemplified by excellent initiatives by the Emerging Risk Factors Collaboration consortium and genomic consortia for cardiovascular outcomes.40–42 It is likely that approaches that take for granted the small magnitude of effects for single biomarkers and that test composites of a large number of biomarkers may be more informative. These may combine blood protein, lipid, metabolite, and genetic markers, as well as markers based on imaging and other measurement methods. The composite predictive ability and reclassification potential can be evaluated in large consortia with standardized definitions and analyses and minimization of selection biases. Once progress has been demonstrated unequivocally on these fronts, incorporation of biomarkers into clinical care will then require rigorous randomized trials to test whether their availability improves hard patient outcomes. Eventually, pricing of these markers for clinical use can be adjusted accordingly, and pricing should also be juxtaposed and titrated against the outcomes of these trials.

Until a paradigm shift is adopted, cardiovascular biomarker research may remain fascinating but probably unhelpful to medical practice and public health, if not also a potential major, unjustified waste of effort and a sizeable threat to healthcare budgets. At a price of “only” $18.22 for a test of CRP and $23.74 for a test of homocysteine (as per Medicare clinical laboratory fee schedule prices), the annual cost to test all the adult US population for these 2 markers alone exceeds $10 billion.43 Government, insurance, private, and/or other research or healthcare agencies could well spend a tiny fraction of that amount to support rigorous, standardized research efforts that would give us informative answers on large consortia and thousands of putative biomarkers to select not the most popular ones, but the very best.
B-type natriuretic peptide BNP or BTNP or "brain-type natriuretic peptide"
Interleukin 6 IL-6 or interleukin-6
Fibrinogen
Serum albumin "Serum albumin"
Myeloperoxidase Myeloperoxidase
ICAM-1 ICAM-1 or sICAM-1
Homocysteine Homocysteine
Uric acid "Uric acid" OR urate

IL indicates interleukin; BNP, brain-type natriuretic peptide; BTNP, brain-type natriuretic peptide; and sICAM-1, soluble intercellular adhesion molecule 1.

Other markers screened included the following (No. of papers/papers with cardiovascular focus retrieved in PubMed): troponin T (5033/4309), troponin I (6295/5532), tissue plasminogen activator antigen (520/340), postload glucose (137/68), apolipoprotein A isoforms (658/260), fasting insulin (4539/2075), apolipoprotein A (12 367/4520), apolipoprotein B (13 666/5538), apolipoprotein B:A ratio (21/17), D-dimer (5660/1784), Chlamydia (22 083/1615), leukocyte count (51 572/5018), serum amyloid A (5242/8090), lipoprotein-associated phospholipase A2 (276/226), lipoprotein(a) (6286/8350), non–high-density lipoprotein cholesterol (1555/1053), selenium (23 234/2006), interleukin-18 (3469/1384), cystatin C (3898/826), asymmetric dimethylarginine (1631/1136), matrix metalloproteinase-9 (14 383/2966), tissue inhibitor of metalloproteinase-1 (6469/1196), and von Willebrand factor (17 052/5324).

Disclosures

References


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