ATHEROSCLEROSIS

Atherosclerosis Drug Development in Jeopardy: The Need for Predictive Biomarkers of Treatment Response

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The limited predictability of phase II biomarkers for atherosclerosis outcomes in phase III studies stands in contrast to the number and varied types of biomarkers—soluble, imaging, and functional—that have been used in a diverse array of trials. Although collectively abundant, these biomarker data exist in a fragmented state. Most biomarkers are studied one at a time, only measure a specific aspect of atherosclerosis, are not integrated in a substantive way, and compete with one another for validation; in the end, progress is slow. The proposed solution from the Atherosclerosis Working Group, a committee of experts from academia, the pharmaceutical industry, government, and the nonprofit sector and managed by the Foundation for the National Institutes of Health Biomarkers Consortium, is to integrate these different measures into an in silico model of atherosclerosis. Through integration of diverse biomarker measurements and outcomes in silico, we may be able to improve trial design as well as the predictive power of short-term markers for longer-term outcomes.

INTRODUCTION

The knowledge that a high level of low-density lipoprotein cholesterol (LDL-C) in the blood predicts an increased risk of future atherosclerotic cardiovascular (CV) events enabled the discovery and development of statins—a class of drug used to lower plasma cholesterol level—which subsequently have saved many lives (*1*–*2*). In turn, statin trials have firmly demonstrated that short-term reductions in LDL-C are associated with reduced adverse CV events in the long term. In contrast, for interventions with mechanisms of action that do not alter LDL-C levels, there are no consensus short-term (phase II) biomarkers that predict treatment-induced reduction in clinical atherosclerotic events. Although a plethora of potentially valuable biomarkers have been studied in atherosclerosis, none have yet been proven to be as predictive for treatment outcome as changes in LDL-C.

For three major reasons, the need for better predictive atherosclerosis biomarkers cannot be overstated. First, there are individuals who remain at high risk for CV events but are not identified by the factors included in calculators of risk, such as the Framingham cardiac risk score and the Systematic Coronary Risk Evaluation (known as SCORE) (*3*–*5*). Second, such biomarkers are critical to drug development decision-making, particularly for drugs that work through a mechanism of action that does not alter LDL-C. Given the high cost and risk of atherosclerosis drug development programs, without these markers there has been a decreased investment in the therapeutic area and an exodus of pharmaceutical companies from atherosclerosis as a targeted indication. As CV disease remains the dominant cause of mortality globally (*6*), and high residual CV risk remains even after LDL-C is reduced (*7*), society will bear the burden from the lack of new drugs. Third, the application of these markers is relevant to assessing atherosclerotic risk in the development of drugs for other indications—a need reinforced by the recent guidance from the U.S. Food and Drug Administration (FDA) on the CV risk of diabetes drugs (*8*). This Commentary describes the problem as it relates to drug development and articulates a collaborative, public-private partnership solution overseen by the Foundation for the National Institutes of Health Biomarkers Consortium (FNIH BC).

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BIOMARKERS AND DRUG DEVELOPMENT

The drug discovery and development (DDD) process is a progressive series of expanding and complex investigations (phases) that provide information about whether to continue to advance an investigational drug in the development pipeline. During phases I to III, a series of hypotheses are tested in clinical trials in order to evaluate the safety and efficacy of a promising compound. These progressively complex experiments are necessary to enable quality decisions about further development of the compound.

Overall, DDD is a failure-prone process. From the selection of the molecular target to the regulatory approval of a new drug, the overall probability of success for a new chemical entity (which does not contain any previously approved active moieties) is less than 2% (*9*–*10*). Many of these failures occur in phase II, when the investigational agent is first tested in participants with or at risk for disease. For compounds that act through previously untested molecular mechanisms, however, the specific phase II success rate is only 20% (*11*), with an overall success rate of <1%. These statistics include all therapeutic areas; there are no published data for atherosclerosis drugs, per se.

During each stage of the DDD process, a series of decisions must be made about the performance of the new agent. For the purposes of this Commentary, the most critical of these decisions is whether the new agent is affecting biomarkers in phase II (and often phase I, when agents are usually tested in healthy volunteers) that are believed to reflect a beneficial change in the disease studied. Credible and positive phase II measures provide the warrant to move a project into larger phase III trials. For example, it is widely accepted that decreases in LDL-C predict fewer CV events. In contrast, although epidemiologic data suggest that an increase in high-density lipoprotein cholesterol (HDL-C) should decrease the likelihood of clinical events, an induced and experimental increase in HDL-C is not yet proven to yield a beneficial phase III outcome (*12*). The need for predictive phase II biomarkers is not unique to atherosclerosis; for disease modification in many slowly progressive and chronic diseases, such as Alzheimer's disease or osteoarthritis, the same considerations apply.

Without more effective biomarkers of clinical efficacy in phase II, sponsors must make a difficult choice regarding investing in phase III: to answer the efficacy question in morbidity and mortality studies or to abandon the project. The decision to proceed represents two very large risks. First, it is not acceptable to put ~15,000 people at risk for four to five years if the confidence

is not high that the participants in the study would benefit. Second, a drug development program in atherosclerosis requires a large financial investment (>$400 million) (Table 1) and therefore is an opportunity cost—another initiative is not undertaken because the sponsor is not able to invest in it. Because of the low probability of success and long duration of dosing, it is understandable that investment in investigational therapies for atherosclerosis has declined (*13*). If this issue is not addressed, fewer new therapies for atherosclerosis will emerge.

The above discussion of atherosclerosis drug development success rates and finances is not an argument to justify the cost of medicines. Rather, it is meant to explain the necessary considerations given that atherosclerosis programs are both high risk and high cost. Whether in academia, government, or industry, few would take on very expensive projects that would likely fail, place participants at risk, and jeopardize other new projects.

THE WEALTH OF BIOMARKERS IN ATHEROSCLEROTIC CV DISEASE

Although there are no consensus phase II biomarkers that predict beneficial clinical outcomes in phase III for mechanisms of action that do not alter LDL-C levels, a trove of biomarker data from a variety of well-designed and -executed studies exists (*14*–*19*). These biomarkers include more than 80 soluble (blood and urine) markers and 10 imaging and/or functional assessments (*20*–*26*), many of which have been used to study the effects of multiple interventions in different populations. In addition to markers of disease progression, these biomarkers are valuable indicators of pathophysiology. However, they have often been studied in a univariate manner by various researchers who often use nonstandardized methodology. Although there are careful analyses combining multiple biomarkers (*27*) or meta-analyses of a single variable (*28*) for identification of high-risk individuals, most data largely exist in relative isolation.

This fragmentation of knowledge prevents effective use of data to reach consensus about the utility of biomarkers for predicting clinical outcomes. When studied separately, the biomarkers compete with each other for validation and acceptance. Therefore, it becomes difficult for the intended users of these biomarkers to choose among them. Ultimately, few biomarkers undergo sufficient validation to achieve wide acceptance.

Table 1. Summary of participant numbers, cost per participant, and cost per phase for atherosclerosis drug development programs. Data are derived from recent drug development programs (*17*–*19*) or publicly available data (*37*). The cost per phase was derived by multiplying subject number per phase and the corresponding cost per subject per phase. In order to show a reduction in clinical events (such as myocardial infarction), a large number of participants must be recruited, which also demands a large financial investment. Phase II biomarkers, therefore, must provide a high-quality and decisive assessment of whether to commit to phase III. Additional cost may be incurred depending on technologies used and other issues.

Variable	Preclinical	Phase I	Phase II	Phase III	Regulatory	Total
Subject number	N/A	100	500 to 1000	15,000	N/A	~16,000
Cost/subject	N/A	$15K	$19K	$23K	N/A	
Cost/phase	$3M	$15M	$19M	$345M	$20M	$402M

THE COMPLEXITY OF APPLYING BIOMARKER DATA TO DECISION-MAKING IN ATHEROSCLEROSIS DRUG DEVELOPMENT

At each stage of drug development, sponsors must make informed decisions to advance a project. These decision nodes require the selection of biomarkers and respective criteria regarding the magnitude of change in subjects participating in these trials. This complexity is illustrated in a hypothetical program with an anti-inflammatory investigational drug (Fig. 1).

Because lipid metabolism, inflammation, thrombosis, anatomy, and vascular function all contribute to atherosclerosis, it is likely that more than one biomarker may be needed to predict the efficacy of an intervention. In addition, these elements change over different time frames, and their differential contributions to CV events vary among individuals. Therefore, it is unlikely that a single biomarker will suffice to characterize risk or fully reflect the impact of an intervention for everyone; multiple biomarkers will be needed that differ in type (imaging, soluble, or functional) as well as timing of their measurement. A panel of markers will probably be needed to adequately characterize atherosclerotic disease risk as well as response to treatment in subpopulations of patients.

The use of biomarkers, as proposed in this Commentary, is distinct from the use of a biomarker as a surrogate for a clinical effect when regulatory approval of a drug is being sought. Acceptance of a surrogate rather than a clinical outcome by a regulatory agency requires a very large body of evidence to support the use of the biomarker in such a manner (*29*). Rather, the focus here is on biomarkers that enable decision-making at the end of phase II trials and facilitate investments in large phase III outcome trials. If we can gain confidence in these markers, similar to the confidence we have in LDL-C, then regulatory agencies might use them as surrogates (*30*).

THE FNIH BC

Just as no single biomarker will likely provide a solution, no single organization can solve this problem. To address this complex challenge, the Metabolic Disorders Steering Committee (MDSC) of the FNIH BC chartered the Atherosclerosis Working Group (AWG). The BC (*31*) is a public-private partnership with representatives from government (FDA, NIH, and the Centers for Medicare and Medicaid Services), industry (pharmaceutical and biotechnology companies), academia, and the nonprofit sector. Its goals are to facilitate the development, validation, and qualification of biomarkers for specific applications in diagnosing disease, predicting a therapeutic response, or improving clinical practice.

Selected representatives from multiple sectors with expertise in atherosclerosis imaging, drug development, soluble biomarkers, clinical trials, and genetics were recruited to participate on the AWG and established two goals: (i) identification of a clinically meaningful change in the atherosclerotic process or disease burden within 6 months (or less) of treatment through the use of one or more biomarkers and (ii) identification of individuals at higher risk of a major adverse cardiac event beyond the estimate provided by current risk calculators.

INTEGRATING BIOMARKER AND OUTCOME DATA INTO AN IN SILICO MODEL OF ATHEROSCLEROSIS

After assessing the state of atherosclerosis biomarkers, the members of AWG con-

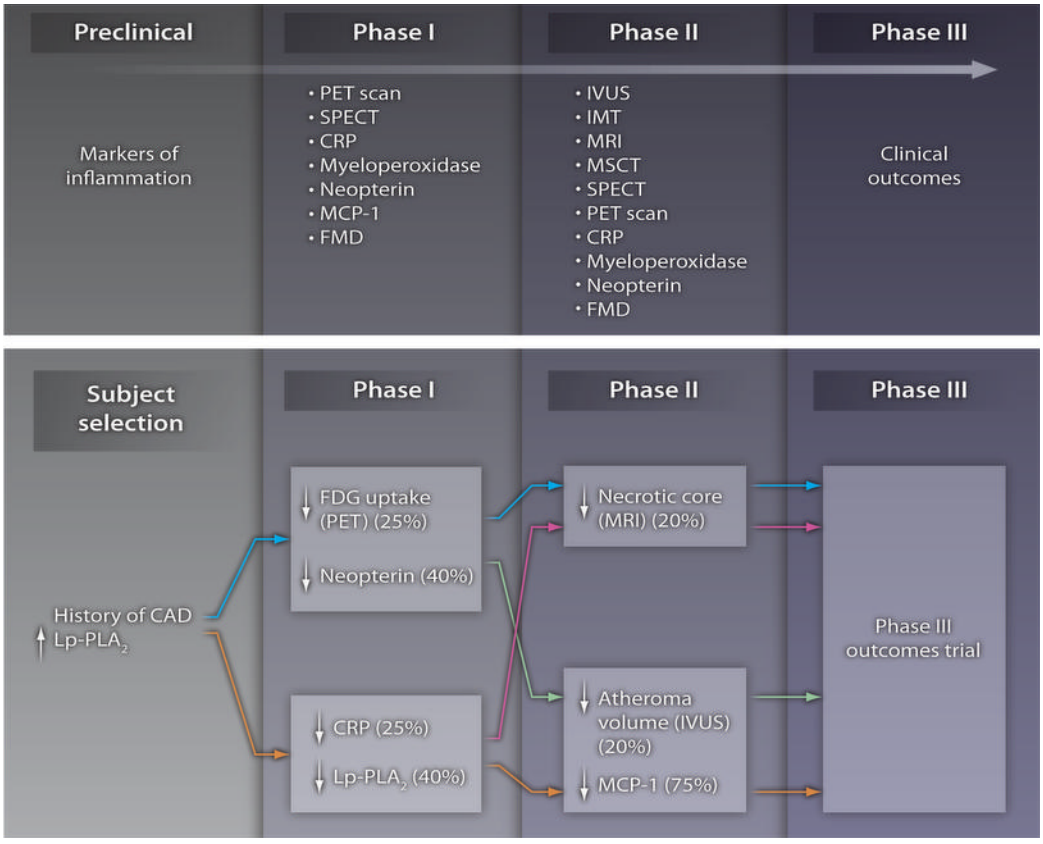

Fig. 1. Many options in biomarker selection. An illustration of the complexity of biomarker selection for testing the effects of a hypothetical, anti-inflammatory, investigational agent. (**Top**) An incomplete, noncomprehensive, and nonprioritized list of some biomarkers (and relevant imaging techniques) and their time-dependent application. The intent is to illustrate some of the possible choices that sponsors of atherosclerosis programs must decide among. Some measures could be deployed in either phase I or II. (**Bottom**) The augmented complexity of decision-making when clinically meaningful changes are included. In addition, it is possible that more than one biomarker could be assessed in phase I or II, further increasing complexity. Illustrated are a few different investigational paths, as symbolized by the differentially colored arrows. For example, in phase I with participants with a history of coronary artery disease (CAD) and increased Lp-PLA_2, an investigator/sponsor could choose to measure a change in the uptake of labeled glucose [fluorodeoxyglucose (FDG)] by atherosclerotic plaques using positron emission tomography (PET) scanning as well as urinary (or plasma) levels of the inflammatory marker neopterin. In phase II, measurements of the necrotic core component of plaques by means of magnetic resonance imaging (MRI) or analysis of plaque volume through intravascular ultrasound (IVUS) and levels of monocyte chemoattractant protein-1 (MCP-1, a marker of inflammation) could be chosen. Associated with these variables are the degrees of change that would be considered meaningful. Taken together, there may be several paths that lead to a decision to initiate a phase III program. For any of these paths, however, the investigator/sponsor must have reason to believe that the markers will be predictive of a positive phase III outcome. If that is not achieved, the development of the new agent would be stopped. SPECT, single-photon-emission computed tomography; FMD, flow-mediated dilatation (a measure of endothelial cell function in blood vessels); IMT, intima-media thickness (in reference to the thickness of the carotid artery wall); MSCT, multislice computed tomography of the coronary circulation.

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cluded that the trove of existing biological marker data represented a unique opportunity. Instead of proposing the identification of new biomarkers, we chose to integrate extant biomarker and outcome data—not because we felt that all useful biomarkers have already been identified, but as an attempt to gain further value and insight from the wealth of data that has already been collected. Atherosclerosis is a complex disorder with differential contributions from lipid metabolism, inflammation, anatomic alterations, platelet dysfunction, vascular reactivity, and other factors, yet comparatively little is known about the relative contributions of these individual components to risk and response. Second, many of the existing biomarkers reflect the same or related pathways [for example, inflammation is indexed by C-reactive protein (CRP), interleukin-1 (IL-1), IL-6, tumor necrosis factor, and lipoprotein-associated phospholipase A_2 (Lp-PLA_2)]. Therefore, one of our main goals is to help determine the relative importance of each of these biomarkers in a pathophysiologic category and select the most impactful, as emphasized by Wang *et al.* (*27*).

Given the volume and complexity of the data sets, AWG proposes integrating this array of selected biomarker and clinical outcomes data into an in silico model of atherosclerosis. In silico models provide a distinct way to integrate data at various levels (biological, physiological, and clinical) in a quantitative manner and to investigate how different patient populations will respond to various therapies by using what-if scenarios. Thus, the goal is to create a model that links pathobiology to clinical outcomes (such as myocardial infarction, stroke, and death) and that has the following characteristics: (i) incorporation of relevant pathobiology (such as inflammation, lipid metabolism, or platelet function), (ii) incorporation of relevant functional and/or mechanical aspects of the circulation (such as blood pressure or vascular responsiveness), (iii) the ability to identify higher-risk individuals (including those with genetic risks), and (iv) the capacity to include biomarkers that vary both with absolute time and with different time scales relative to each other (for example, anatomical changes will be much slower than biochemical changes). This effort is consistent with the strategic plan of the National Heart, Lung, and Blood Institute.

The feasibility of this undertaking is enabled by the existence of in silico models of atherosclerosis (systems biology models) (*32*–*35*), among others. However, current models are often restricted by one or more of four major limitations: (i) their focus on either basic biology or clinical outcomes data, (ii) the use of group means and re-

spective distributions from published work rather than data from individual participants, (iii) the application of limited numbers and types of biomarkers (for example, those derived from imaging were not included), and (iv) limited access to negative trial results (including biomarker responses).

To build as robust and predictive an in silico model as possible, AWG will do the following:

(i) Define the specific questions and focus area to begin construction of the model.

(ii) To address these questions, acquire and integrate carefully selected and relevant subject-level data from a variety of trials and observational studies in both private (for example, pharmaceutical companies) and public (for example, NIH) domains.

(iii) Incorporate a broad range of biomarker and outcome data across multiple mechanisms and types of interventions, including, as indicated, statins, fibrates [peroxisome proliferator–activated receptor (PPAR) agonists that improve HDL-C levels], HDL-C modulators, niacin, antihypertensive agents, diet, and hormones. In addition, therapies (drug and nondrug) that are not directed at atherosclerosis but that could have CV effects (such as PPARγ agonists) will also be sought for inclusion.

Data from individual participants are critical to increase the degrees of freedom and gain greater insight from the extreme biomarker responses and their relationship to outcomes beyond published means and distributions. Because current computer models do not include many relevant atherosclerosis biomarkers, in particular those from imaging, these markers need to be incorporated into the BC model. Biomarker responses from studies with negative results (such as those involving acyl-coenzyme A cholesterol acyltransferase inhibitors) are especially important in determining predictive power.

By strategically expanding the breadth, depth, and volume of data, a robust and useful model could be developed. The model will have multiple uses, including the selection of (i) the highest-risk participants, especially for the investigational agent's mechanism of action; (ii) phase II biomarker end points and their respective changes that predict positive clinical outcomes; (iii) optimal drug doses for phase III studies based on biomarkers in phase II studies; (iv) the development of diagnostics; and (v) stratification of patient subtypes.

BEYOND EFFICACY: APPLICATIONS OF THE MODEL TO ATHEROSCLEROSIS SAFETY

Measures that predict efficacy will probably be applicable to the prediction of safety outcomes beyond standard measures of, for example, lipids or blood pressure. The need for a predictor of atherosclerosis safety is exemplified by the FDA guidance on evaluating CV risk for new drugs for diabetes mellitus. With the new regulation, investigational agents under development for lowering blood glucose levels must have an acceptable cardiac risk assessment before approval. This recent requirement will probably add one or more years and many participants to the development path for diabetes drugs (*36*). An ability to project phase III clinical outcomes before enrolling a large number of higher-risk participants would be highly desirable. If the proposed model predicts unfavorable outcomes, then a sponsor would consider stopping development or conducting more-focused studies before phase III. Conversely, signals suggesting a benefit could enable phase III designs that address this requirement more quickly than a boilerplate design. Moreover, estimates of safety could apply to other drugs beyond those used to treat diabetes, such as nonsteroidal anti-inflammatory drugs.

BUILDING THE MODEL

To make the proposed atherosclerosis model as robust as possible, it is important to have many partners contributing data, intellectual prowess, and funding. Presently, several companies have agreed in principle to share data, but more are needed to launch this initiative. Combining the efforts of our scientific communities should accelerate our ability to reach a consensus about atherosclerosis biomarkers. Once developed, and according to standard BC principles, the model will be made accessible to the broad scientific community, creating an important research resource for the future.

Without a doubt the undertaking of this initiative will have multiple challenges, including those associated with data management, the use of different assays, variable conduct of imaging procedures, and complex multivariate analyses. Informed consent issues will also need to be addressed. The development of this model is a complex undertaking, but if successful it will pave the way as a template for similar initiatives in the future, including those outside of the field of atherosclerosis.

LOOKING TOWARD THE FUTURE

The in silico atherosclerosis model should continue to evolve, raising new hypotheses and generating new experiments. As new data are added, the model will be progressively tested, refined, and validated, eventually serving as a source for potential new diagnostics, monitoring of therapy, and guidance for molecular targets. Furthermore, the model should provide concrete steps toward personalized medicine in the diagnosis and treatment of atherosclerosis.

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