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Vascular Biomarkers and Surrogates in Cardiovascular Disease

Jean-Claude Tardif, MD; Therese Heinonen, DVM; David Orloff, MD; Peter Libby, MD

Abstract—Cardiovascular biomarker research efforts have resulted in the identification of new risk factors and novel drug targets, as well as the establishment of treatment guidelines. Government agencies, academic research institutions, diagnostic industries, and pharmaceutical companies all recognize the importance of biomarkers in advancing therapies to improve public health. In drug development, biomarkers are used to evaluate early signals of efficacy and safety, to select dose, and to identify the target population. The United States Food and Drug Administration has relied on biomarkers to support clinical applications in many therapeutic fields, including cardiovascular disease. The appropriate application of cardiovascular biomarkers requires an understanding of disease natural history, the mechanism of the intervention, and the characteristics and limitations of the biomarker. Channels of communication among researcher, developer, and regulator must remain open to maximize the success of future biomarker efforts. In 2003, 2004, and 2005, an international panel of cardiovascular biomarker experts convened at the “Cardiovascular Biomarker and Surrogate Endpoints Symposia” held in Bethesda, Md, to discuss the use of biomarkers in the development of improved cardiovascular diagnostics and therapeutics. The information presented in the present report summarizes the authors’ perspective distilled from these proceedings. (*Circulation*. 2006;113:2936-2942.)

Key Words cardiovascular diseases ■ coronary disease ■ diagnosis ■ imaging ■ prevention

An already strained worldwide healthcare system continues to confront a growing prevalence of cardiovascular disease and an expanding population at risk for future events. Traditional biomarkers such as blood pressure and serum cholesterol levels have helped to assess cardiovascular risk and develop effective therapies. Owing to the efficiency of current treatment regimens, the size and duration of clinical end-point trials required to establish an incremental benefit have become daunting. Nevertheless, even our highly effective contemporary treatment regimens do not prevent many cardiovascular events, particularly in high-risk individuals. We urgently require tools to assess potential novel therapies and address the residual burden of cardiovascular risk that represents the major challenge to human health worldwide.¹

Increased biomarker research efforts have been fueled by knowledge and unmet medical need. Drug development programs have used biomarkers to identify and evaluate new risk factors and novel drug targets, establish dose ranges, prioritize research efforts, and establish new treatment guidelines. Channels of communication among researcher, developer, and regulator must remain open to maximize the success of future biomarker efforts. The United States Food and Drug Administration (FDA), the National Institutes of Health (NIH), academic research institutions, and diagnostic and pharmaceutical industries all recognize the important role

of biomarkers in advancing therapies to improve public health. But despite the magnitude of current research efforts, only a few true surrogates of cardiovascular events have undergone rigorous validation.

In 2003, 2004, and 2005, an international panel of cardiovascular biomarker experts convened at the “Cardiovascular Biomarker and Surrogate Endpoints” symposia held in Bethesda, Md, to share knowledge and encourage the collaborative efforts needed to accelerate the development of improved cardiovascular diagnostics and therapeutic strategies. Representatives from US, Canadian, and European regulatory agencies, academic research institutions, the pharmaceutical industry, and diagnostic and biotechnology companies debated the utility of a wide range of soluble biomarkers and imaging technologies. The information presented herein summarizes the authors’ current thoughts about the use of biomarkers in cardiovascular drug development and future research directions, as distilled from these proceedings. The report focuses on biomarkers for vascular disease and atherosclerosis, and there are therefore discussion areas about biomarkers that are beyond the scope of this article.

Defining Biomarkers and Surrogate End Points

To foster effective communication about biomarkers and surrogate end points, the NIH Definition Working Group

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established the following working definitions²: (1) biomarker—a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention; (2) clinical end point—a characteristic or variable that reflects how a patient feels, functions, or survives; and (3) surrogate end point—a biomarker intended to substitute for a clinical end point. A surrogate end point should predict clinical benefit (or harm, or lack of benefit or harm) on the basis of epidemiological, therapeutic, pathophysiological, or other scientific evidence. Changes in the biomarker that result from therapy are expected to reflect changes in clinically meaningful end points. Previously proposed criteria for the validation of surrogate end points in phase III trials include correlation with the true clinical outcome and the ability to capture the full effect of intervention on clinical outcome.³ Although many potential surrogates correlate with clinical outcome, very few are able to reflect the full therapeutic effect on the clinical outcome.⁴

Low-density lipoprotein cholesterol (LDL-C) is a widely used cardiovascular biomarker. Several decades ago, biological plausibility was established and significant correlation between LDL-C and coronary artery disease (CAD) was demonstrated.^{5–7} Numerous large clinical trials have now shown that reducing LDL-C clearly decreases the incidence of CAD-related clinical events.^{8–10} Confidence in LDL-C as a surrogate end point remains high because it captures reasonably well the clinical impact of intervention by this mechanism.

Many other biomarkers have failed as surrogates of cardiovascular disease. Factors that may explain their failure include the following: (1) The surrogate does not cause the disease; (2) the surrogate is involved in only 1 pathway in a multiple-pathway disease; (3) the surrogate is insensitive or not affected by the intervention's effect; and (4) the surrogate measures an effect independent from the disease process.^{4,11}

The Cardiac Arrhythmia Suppression Trial (CAST) illustrates the potential of biomarkers to generate incorrect assumptions in the absence of outcome data.¹² Ventricular premature beats correlate with an increased risk for cardiovascular death.¹³ Encainide and flecainide, approved by the FDA for patients with life-threatening and symptomatic ventricular arrhythmias, effectively suppress ventricular premature beats. The NIH sponsored the CAST study to determine whether reduction of ventricular premature beats with these approved agents in patients with recent myocardial infarction would decrease mortality. The results showed that the risk of death for the treated patients was higher (2.5 fold) than for patients receiving placebo. The CAST study cast doubt on the validity of the biomarker concept and increased skepticism about the use of surrogate end points to substitute for clinical end points in phase III trials.

In heart failure, several drugs have improved ventricular function but either had a negative or neutral effect on mortality and morbidity.¹⁴ Although left ventricular function has a strong prognostic value in patients with CAD,¹⁵ increases in ejection fraction induced by some pharmacological agents may not improve clinical outcomes. Thus, correlation between a single cross-sectional biomarker measure-

ment and clinical outcomes is not sufficient for it to become a validated surrogate end point. These examples highlight the importance of rigorous validation and may explain the reluctance of regulatory agencies to readily embrace many potential surrogate end points as evidence of cardiovascular drug efficacy and safety. Greater success has been obtained with left ventricular remodeling changes than with ejection fraction, but this is beyond the scope of the present report.

Soluble Biomarkers and Imaging Technologies

Specific soluble biomarkers and imaging technologies have inherent advantages and limitations. Choice of efficacy measures should consider a drug's target within the multistep pathological process and the expected perturbations of disease natural history. Given the complex pathophysiology of cardiovascular disease, no single biomarker will likely prove able to provide a universal surrogate whereby change observed independently predicts benefit, increased risk, or no effect across all drugs and mechanistic targets. In general, imaging technologies can assess disease in animal models and human clinical trials with a high degree of sensitivity and specificity but may be limited by technical difficulty, availability, and cost. Soluble biomarkers may offer the advantage of availability, relative ease of collection and storage, and lower cost, but they may not prove as sensitive as imaging modalities in the detection or assessment of disease.

Cardiovascular Imaging: Current Utility and Future Direction

Cardiovascular imaging currently serves clinically to screen individuals at risk, determine disease severity in symptomatic patients, and direct the course of therapy. Noninvasive imaging has great clinical potential to stratify patients at intermediate risk and determine whether early intervention is warranted. New technologies enable exploration of the artery wall where the lesion itself resides. With increased reliability and availability and decreased costs, the clinical applications will likely expand. Additionally, imaging is used extensively in clinical trials to speed drug development by providing functional and anatomic information with smaller sample sizes and shorter trial durations than possible with cardiovascular morbidity and mortality trials. This advance has particular importance given the need for better therapeutic agents in an era in which effective treatments exist, thereby rendering placebo control groups unethical in many circumstances.

Carotid artery intima-media thickness (IMT) measured by ultrasound correlates with existing CAD and predicts CAD-related clinical events in subjects without clinically evident disease. The correlation between IMT measurements and risk of cardiovascular events has been firmly established in large studies.^{16–18} Additional clinical trials have established a link between the reduction in IMT progression and CAD risk reduction with several antiatherosclerotic strategies.^{19,20} As a result, the authors now consider carotid IMT a surrogate end point for the effect of therapy on atherosclerotic disease.

In contrast, the utility of electron beam computed tomography (EBCT) remains incompletely established. Although correlation between calcium score as measured by EBCT and extent of coronary atherosclerosis has been demonstrated,²¹

Atherosclerosis Imaging Technologies: Application in Clinical Drug Trials

Technique (End Point)	Advantages	Disadvantages	Validation
Coronary angiography (coronary change score, change in maximal percent stenosis)	<ul style="list-style-type: none"> ● Common clinical procedure ● Clinical trial experience 	<ul style="list-style-type: none"> ● Invasive ● Provides dimensions of lumen only ● Compares to (diseased) reference segment for extent of stenosis ● Lumen changes are relatively slow to occur (years of therapy) ● Radiation exposure 	<ul style="list-style-type: none"> ● Associated with cardiovascular events^{18,28,29} ● Accepted surrogate for expanded indications
Carotid IMT (change in mean IMT)	<ul style="list-style-type: none"> ● Noninvasive ● Availability ● Clinical trial experience ● Cost 	<ul style="list-style-type: none"> ● Changes are slow to occur, requiring relatively long (≥ 2 years) study periods ● Technically demanding ● Noncoronary assessment ● May not specifically measure atherosclerotic plaque 	<ul style="list-style-type: none"> ● Associated with CAD risk factors, CAD, and cardiovascular events^{16,17,30}
EBCT (change in Agatston score)	<ul style="list-style-type: none"> ● Noninvasive ● Ease of use 	<ul style="list-style-type: none"> ● Limited reproducibility ● Equipment not widely available ● Has not been commonly used in multicenter drug trials 	<ul style="list-style-type: none"> ● Unclear relationship between EBCT changes and change in risk
Brachial artery ultrasound (change in flow-mediated dilatation of the brachial artery)	<ul style="list-style-type: none"> ● Noninvasive ● Shows rapid response to physiological change (days to weeks of therapy) ● Clinical trial experience ● Cost 	<ul style="list-style-type: none"> ● Need for standardized protocols across trials ● Impacted by environmental factors (smoking, eating) ● Noncoronary assessment ● Need to restrict to small number of sites (1 to 4) to reduce variability 	<ul style="list-style-type: none"> ● May be associated with cardiovascular events³¹ ● Fidelity to outcome studies inconsistent (estrogen)
Coronary IVUS (absolute change in plaque volume, percent change in plaque volume, change in percent atheroma volume)	<ul style="list-style-type: none"> ● Direct imaging of the disease ● Standardized protocols ● Clinical trial experience ● May show rapid response to therapies 	<ul style="list-style-type: none"> ● Invasive ● Plaque composition difficult to assess ● Assesses anatomy, not function 	<ul style="list-style-type: none"> ● Associated with cardiovascular events^{26,32} in limited evaluations
Carotid magnetic resonance imaging (change in mean vessel wall area)	<ul style="list-style-type: none"> ● Noninvasive ● Plaque characterization possible 	<ul style="list-style-type: none"> ● Need for standardized protocols ● Noncoronary assessment ● Experience in image analysis 	<ul style="list-style-type: none"> ● No validation with clinical events
Computed tomography coronary angiography (change in maximal percent stenosis in each segment)	<ul style="list-style-type: none"> ● Noninvasive ● Rapid acquisition 	<ul style="list-style-type: none"> ● Equipment not widely available ● Limited experience in clinical trials ● Radiation exposure 	<ul style="list-style-type: none"> ● No validation with clinical events

support for EBCT as a surrogate of clinical outcomes with therapeutic intervention all but disappeared after the results of the Beyond Endorsed Lipid Lowering with EBCT Scanning (BELLES) trial.²² BELLES did not demonstrate any differences in coronary calcium score changes between moderate and aggressive lipid-lowering strategies despite differences in clinical outcomes demonstrated with the same treatments.¹⁰ Because of design limitations (lack of placebo group, short follow-up period, and limited patient population), the BELLES study may represent the failure of a clinical trial to validate a good potential surrogate or may highlight the shortcoming of the imaging technology and potential surrogate itself.

Plaque volume as measured with intravascular ultrasound (IVUS) is a potential surrogate marker still under evaluation. A number of dose-ranging multicenter clinical trials have used coronary plaque imaging with IVUS to evaluate short-term efficacy of new agents and determine whether more

definitive phase III trials should be initiated.^{23–25} Additionally, IVUS end points in phase IV clinical trials have evaluated the potential for expanded clinical indications and have furnished mechanistic insights into the natural history of CAD.^{26,27} Many drug development programs incorporate invasive, noninvasive, anatomic, and functional cardiovascular imaging measures, because each modality has its own inherent strengths and weaknesses (Table).^{16–18,26,28–32} These trials will provide additional insight into disease pathophysiology and help determine the best future application of these imaging technologies.

Pathophysiology of Atherosclerosis and Relevance for Biomarkers

A dynamic inflammation model has supplanted the previously held view of atherosclerosis as a passive deposition of debris in the arterial wall.^{33,34} Lesion initiation involves the expression of adhesion molecules on the surface of the

endothelial cells and the recruitment and directed migration of blood-borne inflammatory cells into the artery wall. Numerous mediators contribute to atherogenesis, including chemokines, cytokines, growth factors, proteases, adhesion molecules, hemostasis regulators, and receptors, and their interactions may regulate plaque progression and instability. Understanding this pathophysiology may lead to more rigorous evaluation of some of these mediators as biomarkers. Because these processes act both globally and locally, decreasing risk and prolonging life require modification of the underlying biology of the disease.³⁵ Statins appear to reduce atherosclerotic risk because they modify this biology. However, because the majority of CAD-related clinical events are still not being prevented, we must seek new strategies to guide the development of novel antiatherosclerotic therapies beyond LDL-C reduction.³⁶

The current state of risk prevention has emerged from more than 50 years of epidemiological studies.^{37,38} Biomarkers of cardiovascular disease have emerged from these efforts, but new risk markers could improve our predictive capabilities. Recent data have renewed interest in C-reactive protein (CRP) as a clinically useful marker of inflammation in the context of atherosclerosis. Numerous studies have now demonstrated the ability of CRP to identify risk of atherosclerotic complications,³⁹ and recently completed evaluations comparing patients with low CRP levels to those with higher CRP levels after statin therapy raise the provocative possibility that CRP may serve as a goal of therapy and as a risk marker.⁴⁰ Current guidelines now support a limited role for CRP as part of the risk-assessment arsenal. Other promising soluble biomarkers include non-LDL-C lipids and apolipoproteins and additional markers of inflammation and oxidative stress. With the completion of the sequencing of the human genome, genetic tools currently in development and under evaluation also may enhance identification of high-risk patients and individualization of treatment. Proteomic and metabolomic technologies may also yield development of novel biomarkers. Molecular imaging is another area of research that may help strengthen the link between basic science and clinical utility.

Use of Biomarkers for Drug Approval in the United States

The FDA has relied on biomarkers to support clinical applications in many therapeutic fields, including cardiovascular disease. The initial approvals of statins, fibrates, niacin, resins, and ezetimibe relied on soluble biomarkers, supported by epidemiology, animal data, and natural history studies. Subsequent to these initial approvals, clinical trials generated corroborative imaging evidence utilizing quantitative coronary angiography and carotid ultrasound. Final confirmation of efficacy came from cardiovascular “outcome” studies. In an era in which research efforts extend beyond LDL-C lowering, soluble biomarkers and vascular imaging may provide more efficient methods for correct identification of drugs that safely and effectively reduce cardiovascular risk. The current landscape justifies some optimism due to (1) a better understanding of the underlying pathophysiology, (2)

identification of numerous rational targets for intervention, and (3) drugs that target specific etiologic mechanisms.

Preliminary validation of a biomarker should include demonstration that the marker tracks with a “validated” surrogate; reproducibility and standardization; acceptable sensitivity and specificity as measured against the current reference standard or clinical outcome; additivity to established biomarkers; and evidence that multiple mechanistic approaches of known clinical benefit impact the putative surrogate similarly. Novel biomarkers shown to track with a surrogate previously validated on the basis of clinical endpoint trials may be more readily accepted when applied in studies of therapeutics directed at novel pathological targets. For example, the demonstrated effects of LDL-C-lowering agents on carotid IMT or coronary IVUS plaque volume suggest that similar changes due to high-density lipoprotein (HDL) cholesterol-raising agents may indicate effectiveness in reducing risk for clinical atherosclerosis events. On the other hand, effects of a novel therapeutic, first-in-mechanistic class on biomarkers not previously studied may be insufficient for drug approval; rather, clinical end points may be necessary to validate the therapeutic approach. Definitive validation includes demonstration that the change due to intervention independently predicts benefit and that a clear “correlation” exists between change in surrogate and change in risk. By necessity, validation of an imaging method requires multiple stages and caution to avoid a mismatch between the pathophysiological mechanism targeted by the drug and the imaging marker. The study design to test a novel therapeutic agent should involve control or background therapy with a known clinically effective drug and with a documented or plausible effect on the chosen biomarker. A demonstrable effect on the biomarker greater than that which occurs with clinically effective agents indicates a potential salutary health effect. Definition of a clinically meaningful effect size has considerable importance, and the statistical analysis plan should specify this effect size a priori on the basis of historical reference, epidemiological evidence, or clinical trial data. The clinically meaningful effect size may be based on the minimum magnitude change associated with a clinically meaningful alteration in LDL-C (reduction $\geq 15\%$) or other validated biomarker. Alternatively, effect size may be based on the change demonstrated with a proven clinically effective dose of statin or another antiatherosclerotic agent, regardless of the effects on the soluble biomarker. Ultimately, biomarker changes should be correlated with changes in clinical risk. Results must always be considered in a context that recognizes that the effect may be limited to the particular drug, drug mechanism, disease stage, or subpopulation.⁴¹

Cardiovascular imaging and biomarkers may merit regulatory consideration in several situations: (1) for the initial approval of a new molecular entity or first approval for a population at risk for cardiovascular disease; (2) for broadening a claim for approved cardiovascular risk-modifying agents; and (3) for approval of marketed drugs for a new indication. The authors’ view based on the symposium proceedings is that the initial approval model would require at least 2 imaging modalities, 2 vascular beds, and 2 studies;

plausible or formally valid soluble biomarker effects; large safety experience with no unresolved concerns from animals, drug metabolism, or the clinical safety database; and phase IV "hard" end points. For example, an HDL-raising drug development plan might include an evaluation of the agent in combination with statin versus statin alone; 2 imaging studies (one targeting the coronary arteries and the other the carotid artery, with evaluations of change from baseline to end point); demonstrated statistical difference between monotherapy and combination therapy; favorable soluble biomarker effects; and detailed preclinical demonstration of HDL functionality in reverse cholesterol transport and possibly antiinflammatory assays. To broaden a claim for approved cardiovascular risk-modifying agents, the FDA historically accepted a single imaging modality, relying on overall plausibility and consistent biomarker effects. After approval, the labeling for lovastatin, pravastatin, and fluvastatin was modified and information added on the basis of a single imaging modality (quantitative coronary angiography or carotid B-mode ultrasound). To obtain a new claim based on another expected benefit for a drug approved earlier (eg, antidiabetic drugs), the expectation is for 1 or 2 modalities evaluated in at least 2 trials; plausible biomarker effects; evaluation of unique safety issues in new target population; evaluation of potential countervailing cardiovascular effects that might invalidate reliance on biomarker; and phase IV hard end points. The rationale for phase IV hard end-point trials is that in some instances (the statins being a prime example), products have been approved for chronic, preventive therapy on the basis of biomarkers, with final confirmation of clinical utility coming in phase IV. Under the contingent-approval regulations, the FDA has the option, under certain circumstances, to grant approval on the basis of a surrogate, fully contingent on the conduct of the confirmatory study, such that failure to conduct the study or failure of clinical outcome data to support safety and efficacy for the proposed use could lead to withdrawal of the approval.

The Critical Path Initiative

The FDA has an interest in addressing drug development efficiencies. Biomarkers have a recognized utility in evaluating early signals of efficacy and safety, as well as in dose and patient selection. With the advent of basic science tools such as genomics, proteomics, metabolomics, system biology, molecular imaging, and nanotechnology, along with increased research and development funding by industry and government, one might expect the number of new drug applications to rise. The reality has proven contrary to this. Rather, advances in basic medical sciences appear to have surpassed clinical development. There is a need to learn how to design better clinical trials and to think innovatively about developing new agents. The FDA outlined its concerns in a document issued in March 2004 ("Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products"), which discusses the need to modernize techniques used to evaluate safety and efficacy and to question old assumptions about how to develop drugs most efficiently.

Current FDA efforts in this regard include the evaluation of pooled internal databases to utilize better markers of toxicity and provide guidance to sponsors. Opportunities exist to develop therapies for a limited, severely diseased population, thereby decreasing risk while creating a platform for further biomarker development. The use of biomarkers in drug development programs may serve to identify high-risk patients for targeted efficacy evaluations. Focus on a high-risk patient population may permit detection of a treatment effect with a smaller sample size. Such a targeted population approach might miss a potential effect in a different population, a risk that requires due consideration. Alternatively, one could conduct a study in a broad population and then predefine high-risk subsets with biomarkers. Eventually, the use of genetic markers may permit refinement of this approach and help determine populations expected to have the greatest or least response to treatment (ie, application of pharmacogenomics).

The European Perspective

For validation of biomarkers, the European Medicines Agency (EMA) relies on 3 basic principles, including the demonstration of (1) biological plausibility, (2) correlation with epidemiological studies, and (3) treatment effects on the surrogate that predict treatment effect on outcome. Currently acceptable surrogates for EMA drug approval include LDL-C, blood pressure, and glycosylated hemoglobin. The EMA does not presently consider other biomarkers, including carotid ultrasound or IVUS, to be surrogates for clinical end points. The use of biomarkers or potential surrogate end points to expedite drug approval by the EMA may depend on medical need and the risk/benefit in a particular population. Currently acceptable uses of biomarkers for European approval include dose selection and early phase I/II feasibility decisions.

Other Important Issues

There are a number of other issues that warrant discussion. In the conduct of studies involving surrogate markers, there are usually patient dropouts, which may be disproportionate in treatment groups. This is a major issue in pivotal trial design with nonmorbid/nonmortal primary end points. The usual approach to the use of biomarkers and surrogates as end points for assessments of drug efficacy is to use the intention-to-treat principle, with the last observation carried forward as the primary analysis. This will usually bias against an effective drug. For example, in trials of new agents for diabetes mellitus, dropouts for lack of glycemic control will usually occur more frequently among placebo-treated patients. Carrying their last glycosylated hemoglobin values forward will result in an underestimation of difference between placebo and an effective drug. This constitutes a conservative approach to address this important issue.

Also, composite end points in clinical trials generally comprise either surrogate markers or clinically meaningful outcomes, but not the combination of the two. Nevertheless, it is critically important to study biomarkers (for example, IVUS) and clinical end points in the same study to evaluate their correlation in pharmacological intervention trials.⁴² This

approach represents indeed the best strategy to validate a biomarker. There may be instances where clinical events influence the analysis of the surrogate. One example is the NIH-funded WAVE (Women's Angiographic Vitamin and Estrogen) trial of hormone replacement therapy and vitamins. In this trial, patients who died or experienced myocardial infarction before measurement of the surrogate marker (coronary angiography) at follow-up were imputed the worst rank of angiographic outcome.⁴³

The use of a biomarker will never permit an accurate estimate (ie, risk reduction) of the actual clinical benefit associated with a treatment, whether it is on myocardial infarction or stroke risk for a lipid-altering agent or on risk for diabetic sequelae with a glucose-lowering agent. Additionally, regardless of the study size, it is difficult if not impossible to balance serious clinical safety findings against surrogate measures of benefit. From the standpoint of elucidation of safety of new agents, clinical trial size should, in the end, be considered with regard to capacity to exclude events occurring at any particular frequency. By the "rule of 3," a trial of 1000 patients treated with a drug in which no events of a particular nature are observed is only sufficient to exclude, with 95% confidence, that such an event actually might occur more frequently than 3 times per 1000 patients treated.⁴⁴ It is crucial to take this issue into account when clinical event trials are designed.

Safety Markers

Because no clinical trial will ensure absolute certainty of drug safety in broader postmarketing exposure, biomarkers of safety and toxicity are of great interest. Safety markers such as transaminases and bilirubin to evaluate potential liver toxicity and ECGs to evaluate potential cardiac toxicity have had long and extensive use. Biomarkers might serve to identify patients with the highest likelihood of developing drug toxicity. Clinical trials that target this selected patient population could then monitor safety signals. If no safety concern arises with a new drug in such an enriched trial, it may indicate a lesser risk of adverse effects when that agent is then used in a broad population. Application of genomics may aid in the identification of such susceptible populations.

Conclusions

Data resulting from the clinical evaluation of current biomarkers should guide their future applications. Research designed to better understand the underlying pathology of atherosclerosis has already yielded information that has expanded our focus to encompass inflammation among other biological processes. Continued efforts may result in further challenges to some long-held notions and contribute to improved diagnostic and treatment tools. By using biomarkers in combination, better risk profiles may emerge to provide prognostic information, direct therapy, gauge efficacy of interventions, and develop new medications. The challenge remains to determine the best way to combine information in a multi-marker strategy, facilitate measurement, and establish clinically useful algorithms.

Additionally, the research community has not yet achieved consensus on the best methods for clinical assessment of

vascular disease risk. Efficient development of biomarkers may benefit from pooling of data and resources among regulators, academicians, and sponsors. We view open communication about specific biomarkers, with identification of both the advantages and the limitations, as essential to maximize progress in this field. Collectively, organizations must identify gaps in the data needed to validate a biomarker for surrogate use and undertake to complete the data set. New initiatives for sharing information and building on it to create better processes should enhance efficiencies in the development of improved therapeutics.

Disclosures

Dr Tardif holds the Pfizer and Canadian Institutes of Health Research chair in atherosclerosis. The other authors report no conflicts.

References

- Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*. 1997; 349:1498–1504.
- Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69:89–95.
- Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med*. 1989;8:431–440.
- Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996;125:605–613.
- Watanabe Y, Ito T, Shiomi M. The effect of selective breeding on the development of coronary atherosclerosis in WHHL rabbits: an animal model for familial hypercholesterolemia. *Atherosclerosis*. 1985;56: 71–79.
- Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease: lipid levels in 500 survivors of myocardial infarction. *J Clin Invest*. 1973;52:1533–1543.
- Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. *JAMA*. 1986;256:2835–2838.
- Lipid Research Clinics Program. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984; 251:365–374.
- 4S Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet*. 1994;344:1383–1389.
- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
- DeMets DL, Califf RM. Lessons learned from recent cardiovascular clinical trials. *Circulation*. 2002;106:746–751.
- The CAST Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med*. 1989;321:406–412.
- Bigger JT Jr, Fleiss JL, Kleiger J, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation*. 1984; 69:250–258.
- Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML; the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med*. 1991;325:1468–1475.
- Halkin A, Stone GW, Dixon SR, Grines CL, Tcheng JE, Mehran R, Lansky AJ. Impact and determinants of left ventricular function in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction. *Am J Cardiol*. 2005;96:325–331.
- Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol*. 1997; 146:483–494.
- O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for

- myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22.
18. Azen SP, Mack WJ, Cashin-Hemphill L, LaBree L, Shircore AM, Selzer RH, Blankenhorn DH, Hodis HN. Progression of coronary artery disease predicts clinical coronary events: long-term follow-up from the Cholesterol Lowering Atherosclerosis Study. *Circulation*. 1996;93:34–41.
 19. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet*. 2001;357:577–581.
 20. Wiklund O, Hulthe J, Wikstrand J, Schmidt C, Olofsson SO, Bondjers G. Effect of controlled release/extended release metoprolol on carotid intima-media thickness in patients with hypercholesterolemia: a 3-year randomized study. *Stroke*. 2002;33:572–577.
 21. Agatston AS, Janowitz WR, Kaplan G, Gasso J, Hildner F, Viamonte M Jr. Ultrafast computed tomography-detected coronary calcium reflects the angiographic extent of coronary arterial atherosclerosis. *Am J Cardiol*. 1994;74:1272–1274.
 22. Raggi P, Davidson M, Callister TQ, Welty FK, Bachmann GA, Hecht H, Rumberger JA. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation*. 2005;112:563–571.
 23. Tardif JC, Gregoire J, Schwartz L, Title L, Laramee L, Reeves F, Lesperance J, Bourassa MG, L'Allier PL, Glass M, Lambert J, Guertin MC. Effects of AGI-1067 and probucol after percutaneous coronary interventions. *Circulation*. 2003;107:552–558.
 24. Tardif JC, Gregoire J, L'Allier PL, Anderson TJ, Bertrand O, Reeves F, Title LM, Alfonso F, Schampaert E, Hassan A, McLain R, Pressler ML, Ibrahim R, Lesperance J, Blue J, Heinson T, Rodes-Cabau J; Avasimibe and Progression of Lesions on UltraSound (A-PLUS) Investigators. Effects of the acyl coenzyme A:cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. *Circulation*. 2004;110:3372–3377.
 25. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:2292–2300.
 26. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071–1080.
 27. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292:2217–2225.
 28. Buchwald H, Matts JP, Fitch LL, Campos CT, Sanmarco ME, Amplatz K, Castaneda Zuniga WR, Hunter DW, Pearce MB, Bissett JK. Changes in sequential coronary arteriograms and subsequent coronary events: Surgical Control of the Hyperlipidemias (POSCH) Group. *JAMA*. 1992;268:1429–1433.
 29. Waters D, Craven TE, Lesperance J. Prognostic significance of progression of coronary atherosclerosis. *Circulation*. 1993;87:1067–1075.
 30. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid artery intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation*. 1997;96:1432–1437.
 31. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation*. 2000;101:948–954.
 32. von Birgelen C, Hartmann M, Mintz GS, van Houwelingen KG, Depermann N, Schmermund A, Bose D, Eggebrecht H, Neumann T, Gossel M, Wieneke H, Erbel R. Relationship between cardiovascular risk as predicted by established risk scores versus plaque progression as measured by serial intravascular ultrasound in left main coronary arteries. *Circulation*. 2004;110:1579–1585.
 33. Libby P. Lesion versus lumen. *Nat Med*. 1995;1:17–18.
 34. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868–874.
 35. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation*. 2005;111:3481–3488.
 36. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol*. 2005;46:1225–1228.
 37. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes JJ. Factors of risk in the development of coronary heart disease: six year follow-up experience. *Ann Intern Med*. 1961;55:33–50.
 38. Menotti A, Jacobs DR Jr, Blackburn H, Kromhout D, Nissinen A, Nedeljkovic S, Buzina R, Mohacek I, Seccareccia F, Giampaoli S, Dontas A, Aravanis C, Toshima H. Twenty-five-year prediction of stroke deaths in the Seven Countries Study. *Stroke*. 1996;27:381–387.
 39. Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. *Curr Probl Cardiol*. 2004;29:439–493.
 40. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E; Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005;352:20–28.
 41. Temple R. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, eds. *Clinical Measurement in Drug Evaluation*. New York, NY: Wiley; 1995:3–22.
 42. Capizzi T, Zhang J. Testing the hypothesis that matters for multiple primary endpoints. *Drug Inform J*. 1996;30:949–956.
 43. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, Ouyang P, Thompson P, Tardif JC, Higginson L, Bittner V, Steffes M, Gordon DJ, Proschan M, Younes N, Verter JI. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA*. 2002;288:2432–2440.
 44. Lewis JA. Post-marketing surveillance: how many patients? *Trends Pharmacol Sci*. 1981;2:93–94.