The decrease in cardiovascular events over the past 30 years has been clear (1). Such improvements in clinical outcomes have been matched, if not fueled, by advances in understanding basic mechanisms of atherosclerosis and its complications (2).

Despite such progress, major hurdles persist. Cardiovascular complications remain late-stage events; the pathologic process of atherosclerosis is present years if not decades before myocardial infarction (MI) or stroke occurs. As such, many individuals present with cardiovascular disease at the time of a life-threatening cardiovascular event, with a significant percentage not surviving this initial insult or doing so with compromised quality of life and productivity. Among forms of cardiovascular disease, the gains seen in coronary heart disease, like acute MI mortality, have outstripped the trends for stroke (1). Indeed, in some countries, the incidence of stroke has been increasing. Debate has continued around whether various aspects of the lipid profile are predictive of stroke and whether nonstatin cholesterol-lowering therapy decreased cerebrovascular events. Combined, these issues represent distinct vectors: (1) ever-increasing knowledge into mechanisms and specific mediators of atherosclerosis and its complications and (2) the need for earlier, more sensitive detection and prediction of cardiovascular risk, especially as related to stroke.

In this issue, Inoue et al. (3) present data relevant to the prospect that advances in science might be applied to the prediction of cardiovascular disease. A central tenet of atherosclerosis has been the concept that LDL undergoes modification into oxidized LDL (oxLDL) in tissues like the arterial wall. Uptake of oxLDL by macrophages and other vascular cells incites a cascade of events that promote inflammation, atherosclerosis, and eventually plaque rupture. A major advance in this area came with the identification of the lectin-like oxidized LDL receptor 1 (LOX-1) that, upon activation by ox-LDL binding, induces multiple proatherosclerotic responses in endothelial cells (ECs) as well as smooth muscle cells and macrophages, including production of reactive oxygen species, release of matrix-degrading metalloproteinases, recruitment of leukocytes (increasing chemoattractant cytokines and adhesion molecule expression), reduced levels of endothelial nitric oxide synthase, and more apoptosis (4, 5). Mice lacking LOX-1 are protected against atherosclerosis, whereas transgenic LOX-1 overexpression increases atherosclerotic lesion size. A genetic variant in LOX-1 in humans that interferes with ox-LDL binding is associated with decreased atherosclerosis, although the results with genetic LOX-1 variants have been variable. Together, these data raise key clinical issues: does LOX-1 activity predict clinical cardiovascular events? Is LOX-1 signaling a target for therapeutic intervention? In the modern era defined by advances in cardiovascular disease, these basic questions take on added complexity for any biomarker: does the prediction of risk offered by any new target or approach add to existing measures of risk? Does intervening on a new target provide benefit in addition to or beyond proven treatments in current use?

The need for better tools for predicting cardiovascular events has stimulated many strategies as applied to multiple different databases. The Framingham Heart Study, using prospective data in a large cohort of individuals, developed a risk calculator that predicts future cardiovascular events based largely on traditional risk factors such as systolic blood pressure, total cholesterol, and smoking status (www.framinghamheartstudy.org-risk/index.html) (6). Interestingly, the Framingham risk score does not include family history. The Reynolds Risk Score (www.reynoldsriskscore.org), which does include a family history of premature cardiovascular disease, incorporates recent data for increased concentrations of the inflammatory marker high-sensitivity C-reactive protein (hsCRP) as an independent predictor of future cardiovascular events (7). Other risk calculators validated in different cohorts also exist (8). Advanced lipoprotein testing, which
provides more detailed analyses of lipid parameters, has been advocated by some as offering more precise cardiovascular risk prediction (9). A novel approach to harnessing new insight into markers, which may also be drivers of cardiovascular risk, is to combine multiple measures of specific proteins in plasma into a single score (10). Presumably by relying on strength in numbers, testing many markers might improve identification of patients destined for a future cardiovascular event, as has been suggested to be the case for future diabetes (11). With all these approaches, the relevance of the predictive value seen in the original study cohort must be established in a broader population, along with whether the information adds to currently used tools and the practical nature of the test: cost, reproducibility, variability.

Given the connections between LOX-1 pathways and atherosclerosis, Inoue et al. (3) reasoned that more focused measurements of LOX-1 and its activity might predict future cardiovascular events. They tested this hypothesis using a cohort of 2437 patients (30–79 years of age) living in Suita, Japan, who were followed for 11 years and at baseline had no history of cardiovascular disease. LOX-1 can be released from the endothelial cell surface, generating soluble LOX-1 (sLOX-1). A plausible assumption is that sLOX-1 levels correlate with endothelial LOX-1 levels. This may not necessarily be the case, however, as sLOX-1 levels may be influenced by other factors such as levels and control of LOX-1–regulating enzymes, forces that release LOX-1 from the cell surface, and sLOX-1 clearance. To get at a measure of LOX-1 activity, these authors added another component to their assessment by measuring concentrations of apolipoprotein B–containing lipoproteins, molecules that can bind to and presumably activate LOX-1, referred to as ligand-containing apoB (LAB). Of note, this LAB measure circumvents an intriguing aspect of LOX-1, namely its ability to bind many molecules that may promote atherosclerosis, including platelets, apoptotic cells, and CRP itself. As such, LAB might not fully represent LOX-1 activation. Nevertheless, by multiplying the level of sLOX-1 by LAB, a LOX index is derived that might better reflect LOX-1 activity and hence its subsequent consequences. Over the course of the 11 years that Suita patients were followed in this study, 68 coronary heart disease and 91 stroke cases occurred. After adjusting for many (but not all) known cardiovascular risk factors such as sex, age, smoking, hypertension, diabetes, non–high-density lipoproteins, and lipid-lowering drug use, the highest quartile of the LOX index was still associated with a significant increase in risk for coronary heart disease and stroke.

Perhaps most striking about the data for the LOX index in this study is the predictive value for stroke. Although many studies have demonstrated that statin therapy reduces the incidence of stroke, the relationship between cholesterol concentrations and stroke, and whether nonstatin cholesterol-lowering therapies also decrease stroke risk, have remained controversial issues (12, 13). One issue in the stroke arena may derive from the various kinds of stroke patients can experience, some of which may be less related to LDL cholesterol lowering (embolic stroke from atrial fibrillation or hemorrhagic stroke from hypertension) than others (atherothrombotic stroke from atherosclerotic carotid plaque). A recent large metaanalysis of the relationship between cholesterol and stroke confirmed the impact of statin use on reducing nonfatal stroke but also suggested it was linked to lowering total and LDL cholesterol, with nonstatin therapy also having effects, although not as effectively owing to lesser LDL cholesterol lowering (13). Perhaps drilling down to LOX-1 pathways and its activation by oxLDL will provide a better connection between stroke and factors directly connected to stroke pathogenesis. The data presented by Inoue et al. provide initial if limited evidence that such a possibility might be worth considering further.

Inevitably a study like this one generates additional questions and hurdles before its potential clinical use. Is the LOX index valid in populations outside of Suita, Japan? No relationship was seen between the LOX index and the presence of diabetes, despite other lines of evidence that strongly implicate LOX-1 in the pathogenesis of diabetes, including its cardiovascular complications. Perhaps this is a function of the nature of diabetes in Japan, different patterns of obesity, or the relatively low incidence of diabetes in this cohort. Obesity itself, which has also been implicated in stroke risk, was not controlled for in this study. In addition, hsCRP was not measured. Does the predictive value of the LOX index, especially in terms of stroke, persist even after controlling for hsCRP concentrations? A recent metaanalysis of individual records of 106309 people with no history of cardiovascular disease found an increased relative risk (1.27) for ischemic stroke among those with increased hsCRP values (14). In a Swedish cohort of 5067 subjects followed for 12.8 years, hsCRP correctly and significantly predicted risk for the subsequent 418 cardiovascular events, including strokes, that occurred in the study, although the numbers reclassified were modest (8% for cardiovascular events) and most often involved a downclassification of risk (15).

Questions remain about LOX-1 and how its activation by various molecules, including ox-LDL, contributes to atherosclerosis, and whether this information might be harnessed to better predict future cardiovascular events or reveal new therapeutic targets. That such issues are increasingly at hand reflects the extensive study and progress by many groups in the
LOX-1 area. The study provided here by Inoue et al. extends these issues, raising the prospect that perhaps surrogate measures of LOX-1 signaling might help predict cardiovascular events, especially as they relate to stroke. These data also serve as a model to think about where advances in science and the need for better predictive tools might take us. No doubt additional players that either protect against or promote atherosclerosis, including that which occurs in distinct vascular beds, will continue to be identified—the vector of basic biomedical research. Those leads that hold up under further study will be pursued for their predictive value or therapeutic utility—the vector of clinical science. It is at the intersection of these two powerful vectors that new opportunities for understanding, predicting, and treating atherosclerosis and its complications will be found.

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