Three articles in this issue of JASN describe associations among increased risks of cardiovascular disease and lipoprotein(a) levels and particle size (1), disorders of calcium homeostasis (2), and plasma vitamin C concentrations (3). These reports may occasion the reader to question the relevance of continued observational studies of cardiovascular risk factors, given the well-established results of the Framingham Heart Study (4). The Framingham Heart Study identified a set of individual biomarkers, behaviors, and demographic characteristics that are routinely used to predict the risk of cardiovascular disease among individuals without a previous history of coronary heart disease, stroke, or peripheral vascular disease. These risk factors, which include age, gender, history of diabetes, total cholesterol, systolic BP, and smoking status, have been extensively validated in multiple populations (5).

The Framingham validation studies typically examine two characteristics of prediction. First, the difference in rates of cardiovascular disease (i.e., the relative risk) conferred by two or more levels of a single risk factor on individuals in the validation study is compared with that observed in the Framingham population. Second, the number of cardiovascular events predicted for individuals in the population over a fixed period of time based on their risk factor profile is compared with the actual numbers of events observed. Results of the first comparison address the question of whether individual risk factors behave in a similar manner in the different populations, yielding comparable relative risk estimates and implying similar pathophysiology. Multiple validation studies have found relative risks for individual risk factors that were comparable to those reported for Framingham.

In contrast, the predicted risk estimates reported by these validation studies can be quite variable and often either under- or overestimate the risk of cardiovascular disease experienced by members of the validation population. The interpretation of under- or overestimation is that the predicted risk is a function of both the risk conferred by individual risk factors (relative risk) and of the underlying rate of cardiovascular disease in the population, which may differ substantially from that observed in Framingham. The intercept of the multivariable logistic regression model used to calculate the predicted numbers of individuals who will experience cardiovascular disease in the validation population reflects the baseline risk of cardiovascular disease in the Framingham population. Only when adjusting the intercept to reflect the overall rate of cardiovascular disease in the validation population will the new equation yield predicted absolute risks commensurate with those observed (6).

Although this tweaking of the risk logistic allows the absolute, as well as relative, risks predicted by the Framingham model to fit the observed patterns within a validation population, it provides no information about additional factors that might explain the differences between the two populations. This limitation and the recognition that the Framingham risk factors themselves explain only a fraction of the variability of cardiovascular disease risk has led to a search for additional biomarkers and individual characteristics associated with cardiovascular disease in the general population (7). Among these novel risk factors are markers for inflammatory and oxidative stress, homocysteine, obesity, measures of thrombosis, and psychosocial measures of social support and hostility (8,9).

These observations are directly relevant to the study of cardiovascular risk among patients with ESRD. First, ESRD patients have a well-recognized increased risk of cardiovascular disease that begins early in the course of chronic kidney disease (CKD) and results in 10-fold or higher cardiovascular mortality rates after the start of renal replacement therapy (10). Studies that have compared the predicted and observed risks of cardiovascular disease among patients with CKD and ESRD have found the observed risk to be substantially higher than that predicted by the Framingham risk logistic (11–14). While some of the differences among Framingham-predicted and observed risks could be explained by limited severity adjustment (particularly for diabetes and hypertension), several studies have suggested a paradoxical U-shaped relation between mortality and total cholesterol in ESRD, arguably explained by residual confounding by malnutrition (15). Other established, non-Framingham cardiovascular risk factors, including body mass index (BMI) and homocysteine, also appear to generate paradoxical associations with mortality in the ESRD population, because of the dominant adverse effect of malnutrition associated with low BMI and homocysteine concentrations (16,17).

While paradoxical associations have been demonstrated in some epidemiologic studies, unexpected findings have also been generated in clinical trials. For example, a study testing full versus partial correction of anemia in hemodialysis patients with preexisting cardiovascular disease (18) failed to show a benefit of a targeted hematocrit of 42% (with a trend toward...
harm), despite scores of observational studies with findings to the contrary. More recently, preliminary data from the DeutscheDiabetes-Dialyse-Studie (4D) Study (19) suggested no benefit of LDL cholesterol lowering on mortality or cardiovascular events, despite the high overall event rate and numerous studies showing substantial benefits in nonuremic populations.

These observations do not necessarily imply that the basic biology of atherosclerotic cardiovascular disease differs among persons with and without ESRD, although more factors may be operative. Given the complex biology of uremia and the exceptionally high cardiovascular event rates observed in the ESRD population, an aggressive program to identify additional modifiable risk factors for cardiovascular disease among ESRD patients is warranted. The results of the three studies reported in this month’s JASN are instructive in this regard. All three address biologically plausible mechanisms associated with CKD and cardiovascular disease, including risk factors for atheromatous plaque accumulation, increased coagulability, plaque calcification, and oxidative stress. Moreover, these putative risk factors are potentially modifiable and were reported to be prevalent in clinically important proportions of the respective study populations.

These studies, however, must be interpreted with appropriate caution (20). Because they describe relatively new risk factors, each individual study does not fully account for confounding by risk factors identified in the other two studies, and none completely controls for other well-established risk factors for cardiovascular disease. Furthermore, although all studies found a significant “dose-response” between the exposure and risk of cardiovascular disease, the relative risks reported for two of the studies (1,2) were rather modest and the confidence intervals for the third (3) were rather wide. One also must take into account the importance of consistent validation of a risk factor–cardiovascular disease association in diverse populations before strong inferences can be made about the association described. Finally, we must emphasize that appropriately designed clinical trials, based on consistent, biologically plausible, strong, and graded associations with cardiovascular disease, are necessary to establish causality and to legitimately effectuate a change in clinical practice.

References
17. Johansen KL, Young B, Kaysen GA, Chertow GM: Associ-

See related articles, “High Lipoprotein(a) Levels and Small Apolipoprotein(a) Size Prospectively Predict Cardiovascular Events in Dialysis Patients,” on pages 1794–1802; “Calcium, Phosphorus, Parathyroid Hormone, and Cardiovascular Disease in Hemodialysis Patients: The USRDS Waves 1, 3, and 4 Study,” on pages 1788–1793; and “Low Total Vitamin C Plasma Level Is a Risk Factor for Cardiovascular Morbidity and Mortality in Hemodialysis Patients,” on pages 1811–1818.