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A proteomic surrogate for cardiovascular outcomes that is sensitive to multiple mechanisms of change in risk.

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A reliable, individualized, and dynamic surrogate of cardiovascular risk, synoptic for key biologic mechanisms, could shorten the path for drug development, enhance drug cost-effectiveness and improve patient outcomes. We used highly multiplexed proteomics to address these objectives, measuring about 5000 proteins in each of 32,130 archived plasma samples from 22,849 participants in nine clinical studies. We used machine learning to derive a 27-protein model predicting 4-year likelihood of myocardial infarction, stroke, heart failure, or death. The 27 proteins encompassed 10 biologic systems, and 12 were associated with relevant causal genetic traits. We independently validated results in 11,609 participants. Compared to a clinical model, the ratio of observed events in quintile 5 to quintile 1 was 6.7 for proteins versus 2.9 for the clinical model, AUCs (95% CI) were 0.73 (0.72 to 0.74) versus 0.64 (0.62 to 0.65),; c; -statistics were 0.71 (0.69 to 0.72) versus 0.62 (0.60 to 0.63), and the net reclassification index was +0.43. Adding the clinical model to the proteins only improved discrimination metrics by 0.01 to 0.02. Event rates in four predefined protein risk categories were 5.6, 11.2, 20.0, and 43.4% within 4 years; median time to event was 1.71 years. Protein predictions were directionally concordant with changed outcomes. Adverse risks were predicted for aging, approaching an event, anthracycline chemotherapy, diabetes, smoking, rheumatoid arthritis, cancer history, cardiovascular disease, high systolic blood pressure, and lipids. Reduced risks were predicted for weight loss and exenatide. The 27-protein model has potential as a ”universal” surrogate end point for cardiovascular risk.

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