The Stratification of Short-Term and Long-Term CVD Risks: The Impact of Conventional Risks and Biomarkers

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Assessing cardiovascular risk in systematic ways that allows directed prevention and treatment strategies to be implemented rationally and systematically at a population level is a cornerstone of improving population cardiovascular health. A number of conventional risk factors and biomarkers to assist clinicians in assessing cardiovascular risk have been developed and validated through intensive research efforts. This talk will review the recently updated risk assessment guidelines from the American Heart Association, which have attempted to incorporate the state of the evidence into a practical and useful algorithm for both the public and clinicians. The development of risk stratification tools such as this, has both strengths and limitations, and these guidelines have raised interesting discussion about both the benefits and potential pitfalls of using such an algorithmic approach to guide treatment. For example, rarely are the databases for modeling broadly representative enough to include the spectrum of diversity in race and ethnicity that are represented in the US population, and this same limitation potentially affects translation of the risk models to other countries and regions of the world. In addition, the features included in any algorithm that is developed depend on the data elements available in the databases from which the risk models are developed. For example, if creatinine or other measure of renal function is not included in the databases used for modeling, regardless of how strong a cardiovascular risk indicator it is, it will not be represented in the risk algorithms that result. In addition, while age is an important indicator of risk, at some point, it begins to dominate the risk equations. It is less clear what actions would be appropriate solely on the basis of age-driven risk, particularly when many effective therapies in clinical trials populations have been less well studied among older groups. Finally, as a recent study pointed out, what endpoints should be considered in assessing risk is unclear and may vary by sex and age. This talk with address the state-of-the-art in conventional risk assessment, including clinical factors and biomarkers that are available today, and will discuss the strengths and limitations of current risk models and algorithms. The focus will be on cardiovascular prevention.

Novel Biomarkers Associated with Future CVD Events

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Hundreds of reports of protein biomarker associations with cardiovascular outcomes appear in the peer reviewed literature each year, but often in isolation of other putative biomarkers and with limited consideration of clinical predictors of outcome. As a first step to understanding the relative importance of the biomarkers in published observations, we assayed 53 of these putative protein biomarkers that had at least modest literature-reported association with outcomes (HR $\geq$1.50) in 550 individuals with suspected coronary disease in the MURDOCK Horizon 1 Cardiovascular Disease Study. Using a modern statistical approach (penalized regression using the Elastic Net) to perform coefficient estimation and variable selection simultaneously across potentially collinear variables (proteins sharing the same biological "pathway") as well as unrelated biomarkers and detailed clinical characterization, we generated smaller panels of biomarkers that were independently associated with outcomes. For example, this method identified a set of 6 biomarkers (ICAM-1, MMP-3, NT-proBNP, IL-6, sCD40L, and IGFBP2) and 5 clinical variables (age, red-cell distribution width, diabetes mellitus, hemoglobin, and New York Heart Association class) that were strongly associated with death or myocardial infarction during a median 2.5 years of follow up. While this reflects an important step forward, these methods and results only scratch the surface of what is needed and soon may be possible to bring the promise of "stratified medicine" to fruition. Although genetic, protein, metabolite, and transcriptomic biomarkers have been associated with cardiovascular risk, their contributions that may reflect multiple intersecting pathways or read outs on the same pathway may not be considered in the context of systems biology, and most frequently assessment of disease state and risk is static, failing to incorporate the influence of temporal changes in biology or the interactions of the macro- and micro-environment or individual behavior with biology over time. Longitudinal population registries and biorepositories, advances in molecular platform technology, and access to electronic health records combined with evolution in computing, informatics, and statistical capabilities promise to enable temporal characterization of health and disease not only by gross phenotypic observation but according to underlying molecular mechanism and influence of social determinants, and in turn enable development of targeted therapeutic interventions and disease prevention strategies at the individual and population levels.