Contents

Preface: Risk Factor Update: Old Wine in a New Bottle? xiii
Valentin Fuster and Jagat Narula

Are Novel Serum Biomarkers Informative? 1
John T. Wilkins and Donald M. Lloyd-Jones
To justify use in routine coronary heart disease (CHD) risk assessment, a novel serum biomarker must be specifically associated with future CHD events and add information beyond techniques currently available. Current risk assessment techniques are probabilistic and imperfect; however, to date, no novel serum biomarker has improved substantially on the current population-based risk stratification approach. Although limited trial-based data are available to assess the utility of biomarkers, insights gained from biomarkers may enhance clinical decision making. Continued basic science and population-based research into CHD biomarkers may help to further the capacity for CHD risk assessment.

LDL Cholesterol: The Lower the Better 13
Seth S. Martin, Roger S. Blumenthal, and Michael Miller
High cholesterol is often a prerequisite for atherosclerotic plaque. Low-density lipoprotein cholesterol (LDL-C) is the focus of the National Cholesterol Education Program Adult Treatment Panel guidelines. LDL-C ranges from 50 to 70 mg/dL in native hunter-gatherers, healthy human neonates, free-living primates, and other wild mammals, who are notably free of atherosclerotic vascular disease. Multiple statin trials and meta-analyses support a treatment target of LDL-C levels less than 70 mg/dL, as this is associated with improved clinical outcomes and atherosclerosis regression. In fact, no threshold has yet been identified below which patients do not benefit from lowering of LDL-C.

HDL-Cholesterol: Perfection is the Enemy of Good? 27
Ragavendra R. Baliga
An inverse relationship between the plasma concentration of high-density lipoprotein (HDL)–cholesterol and the risk of having a cardiovascular event has been shown in several epidemiologic studies. It is likely that this relationship is causal because HDL has several intrinsic properties that can potentially reverse atherosclerosis. However, this has not been conclusively shown in humans, and trying to achieve perfection with pharmacotherapy is possibly the enemy of good (ie, a healthy lifestyle). Patients with low HDL should be advised to change their lifestyle, including smoking cessation, weight reduction, and regular exercise.

Triglycerides: How Much Credit Do They Deserve? 39
Payal Kohli and Christopher P. Cannon
In the modern era of statin therapy, major advances have been made in treating coronary heart disease. However, despite intensive treatment with statin
therapy, residual cardiovascular risk persists and has been attributed to the persistence of atherogenic dyslipidemia and, in part, elevated triglycerides (TGs). In this review, the authors focus on the mechanism of elevated TGs and provide a discussion of the challenges of measuring TGs as a biomarker, its role in the pathogenesis of atherosclerotic heart disease, and results of several recent studies that have elucidated the relationship between TGs and cardiovascular morbidity and mortality.

**Atherosclerosis in Chronic Kidney Disease: Lessons Learned from Glycation in Diabetes**

Dilbahar S. Mohar, Ailin Barseghian, Nezam Haider, Michael Domanski, and Jagat Narula

In diabetes, glycation is a nonenzymatic posttranslational modification resulting from the bonding of a sugar molecule with a protein or lipid followed by oxidation, resulting in the development of advanced glycation end products (AGE). Like glycation, carbamylation is a posttranslational protein modification that is associated with AGE formation. Glycation of extracellular matrix proteins and low-density lipoprotein with subsequent deposition in the vessel wall could contribute to inflammatory response and atheroma formation. It is logical to extrapolate that carbamylation may result in modification of vessel wall proteins similar to glycation, and predispose to atherosclerosis.

**“My Parents Died of Myocardial Infarction: Is that My Destiny?”**

Nupoor Narula, Claudio Rapezzi, Luigi Tavazzi, and Eloisa Arbustini

This article presents an overview of clinical and molecular genetics of myocardial infarction (MI). Discussion includes the partial overlapping of risk factors for myocardial infarction and atherosclerosis, the impact of a positive family history on the risk of MI, the “familial” non-genetic, environmental factors, the inherited risk associated with the low-dose input of many genes, and a simple approach to stratify the individual risk in genetic counseling.

**Age As a Risk Factor**

Ravi Dhingra and Ramachandran S. Vasan

The risk of developing cardiovascular disease (CVD) is generally dependent on the presence or absence of traditional risk factors. Age is a well-known traditional risk factor, generally considered non-modifiable. This review discusses the common use of individual age in prediction of CVD incidence using different risk scores, whether or not age as a risk factor can be modified, the methods used to evaluate long-term and short-term CVD risk, appropriate communication of individual risk based on age group and CVD risk, and the influence of age on cardiac and vascular risk factors.

**Coronary Artery Disease in Aging Women: A Menopause of Endothelial Progenitor Cells?**

Randolph Hutter, Juan Jose Badimon, Valentin Fuster, and Jagat Narula

The cardiovascular protection provided to women during the reproductive age and the unique angiogenic properties of the female reproductive
system provide insights into the complex regulatory network of female sex hormones, angiogenic growth factors, and stem cell regulatory molecules. The intricate and interwoven endometrial physiology of the female menstrual cycle shows that in order to harness the physiologic cardioprotection provided by nature to women of reproductive age, for better cardiovascular therapies in postmenopausal women and the population in general, a coherent and systematic approach is needed.

Imaging for Prevention
Leslee J. Shaw

Cardiovascular disease deaths have declined considerably, with more than 35% reductions during the past two decades, yet a sizable detection gap remains. Cardiovascular disease remains the leading cause of morbidity and mortality in the United States and across the world, including in developing and developed nations. Recent statistics reveal that approximately 840,000 deaths were attributed to cardiovascular disease, approximately 300,000 more deaths than reported for cancer; three-quarters were reported in previously asymptomatic individuals, raising the question as to whether screening for cardiovascular disease is warranted in detecting potentially high-risk patients.

Genomics: Is It Ready for Primetime?
Sonny Dandona, Alexandre F.R. Stewart, and Robert Roberts

The next decade will focus on identifying the missing heritability of coronary artery disease (CAD). This process will involve a more comprehensive interrogation of common single nucleotide polymorphisms (SNPs) that impart modest biologic effect and an interrogation of rare SNPs that impart profound biologic effect. In parallel, an investigation of the underlying biology of the described association will likely yield novel pathways that provide therapeutic targets. Once we obtain a more complete inventory of sequence variation that predisposes to CAD, a more realistic assessment of the role of genetic risk scoring allied with standard risk algorithms will be possible.

Statins Personalized
H. Robert Superko, Kathryn M. Momary, and Yonghong Li

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor medications, commonly referred to as statins, are among the most widely prescribed medications. Variation in individual response to statins concerning low-density lipoprotein cholesterol reduction, clinical event benefit, and side effects has been observed. Some of this variability is attributed to demographic and environmental issues, chief of which is compliance. A large portion of the individual response to statin therapy is attributed to single nucleotide polymorphisms that have recently been elucidated, several of which seem to have clinical utility.

Childhood Cholesterol Disorders: The Iceberg Base or Nondisease?
Sarah D. de Ferranti

Pediatric cholesterol disorders are common, affecting 1 in 5 adolescents, although most are mild or moderate abnormalities. Because cholesterol
values during childhood are moderately predictive of adult cholesterol levels, and are associated with atherosclerosis by pathology and by vascular testing, and because familial hyperlipidemias are associated with early cardiovascular events, cholesterol screening is recommended during childhood. Identified lipid abnormalities are an indication for lifestyle improvement and, in rare cases, pharmacotherapy. However, many gaps in the pediatric knowledge base remain about the benefits and risk, the optimal method for lipid screening, and about appropriate indications for pharmacotherapy.