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On the cover this month: *Stephen's Broken Leg* by Larry Rivers. Osteoporosis is common among postmenopausal women. But it can also affect men in advanced age. In fact, one-third of osteoporotic fractures have been reported to occur in men. Older men who have lower concentrations of testosterone tend to have a higher risk for bone fracture. But there is more than one analytical technique for quantifying testosterone, the 2 most widely used techniques being immunoassay and liquid chromatography-mass spectrometry. But how do these techniques compare analytically, and how does each technique perform clinically in the prediction of fracture? This issue of *Clinical Chemistry* contains the results of a study designed to determine whether the fracture–testosterone relationship was affected by the method of measurement at the population and individual levels.

Identifying an Optimal Cut Point for the Diagnosis of Hypertriglyceridemia in the Nonfasting State
By Khendi T. White, et al.

Hypertriglyceridemia is clinically diagnosed from fasting lipids although nonfasting triglycerides are similar or superior to fasting triglycerides in assessing cardiovascular risk. Obtaining nonfasting concentrations also provides practical advantage. The authors of this study set out to systematically determine an optimal cutpoint for hypertriglyceridemia in relation to cardiovascular disease through the use of robust statistical measures of calibration. Suggested cutpoints were chosen arbitrarily with European and U.S. guidelines proposing 3 different values. A nonfasting triglyceride concentration of 175 mg/dL provided the most optimum assessment of risk which corresponds to that proposed by the European Atherosclerosis Society. This study provides the first validated evidence for an optimal cutpoint for nonfasting hypertriglyceridemia.

Longitudinal Changes in Multiple Biomarkers Are Associated with Cardiotoxicity in Breast Cancer Patients Treated with Doxorubicin, Taxanes, and Trastuzumab
By Mary Putt, et al.

Anthracyclines and trastuzumab (or Herceptin®) have led to improvements in breast cancer survival but are also associated with an increased risk of cardiotoxicity. Biomarker strategies may play an important role in identifying patients at risk of developing cardiomyopathy. The results of this study indicate that increases in myeloperoxidase are associated with doxorubicin and trastuzumab cardiotoxicity, and combined assessment with placental growth factor and growth differentiation factor 15 may be of value. Additional cohort studies are needed to validate the role of these biomarkers for cardiotoxicity diagnosis and risk stratification with doxorubicin and trastuzumab.

γ-Glutamyl Transferase Is Associated with Mortality Outcomes Independently of Fatty Liver

By Ki Chul Sung, et al.

No single cohort study has evaluated the relationships between all commonly measured liver function tests and mortality outcomes. Additionally no large cohort study has investigated the relationship between liver function tests and mortality outcomes after adjusting for the presence of alcoholic or nonalcoholic fatty liver disease. The authors of this study sought to evaluate these factors in a large occupational cohort. Causes of deaths were recorded over 7 years. Liver enzyme activities and liver fat were assessed at baseline. Increased serum activities of γ-glutamyl transferase were strongly associated with increased risk of death from all causes, cancer and cardiovascular disease. High circulating γ-glutamyl transferase activities may be a biomarker for increased risk of death.

Relationship between Serum Testosterone and Fracture Risk in Men: A Comparison of RIA and LC-MS/MS

By Thach S. Tran, et al.

Different methods of measurement can yield different measured values of testosterone. This study sought to address whether the testosterone-fracture relationship is distorted by measurement methods. Total testosterone was measured by liquid chromatography-tandem mass spectrometry and radioimmunoassay methods from 602 elderly men whose incident fracture had been continuously ascertained from 1989 to 2010. The authors found that the concordance between these two methods was moderate with a concordance correlation coefficient of 0.71. However, the predicted risk of fracture based on mass spectrometry was highly correlated with that based on radioimmunoassay method with a correlation coefficient of 0.96. The moderate concordance in testosterone measurements does not distort the testosterone-fracture relationship.

Diagnostic Accuracy of Noninvasive Genotyping of *EGFR* in Lung Cancer Patients by Deep Sequencing of Plasma Cell-Free DNA

By Junji Uchida, et al.

The genotyping of epidermal growth factor mutations is indispensable for therapeutic decision making regarding whether to use epidermal growth factor tyrosine kinase inhibitors for lung cancer. Noninvasive genotyping of epidermal growth factor in circulating tumor DNA would be beneficial for cases difficult for biopsy. The authors of this paper developed a detection system for epidermal growth factor mutations in circulating tumor DNA using deep sequencing of plasma DNA. The sensitivity of the system was 72.7% for advanced lung cancer. The specificity was 98.0% and 94.1% for the 2 major mutations, respectively. The high specificity of the system may enable a direct recommendation for epidermal growth factor tyrosine kinase inhibitors based on positive results with plasma DNA.

Estimation of Values below the Limit of Detection of a Contemporary Sensitive Troponin I Assay Improves Diagnosis of Acute Myocardial Infarction

By Jes-Niels Boeckel, et al.

Using contemporary troponin assays, many patients have concentrations below the limit of detection. The values below the limit of detection are not reported. In this study the authors' aim was to test whether improved estimation of troponin I values below the limit of detection had an impact on the diagnostic information. Troponin I was measured using a contemporary assay in a cohort of 1549 patients with suspected acute myocardial infarction. As a comparator, to test whether estimation of those very low troponin I concentrations was able to regain diagnostic information, the high-sensitivity version of the same assay was used. Use of the high-sensitivity assay improved the diagnostic information of troponin I over data measured with a contemporary assay.