Clinical Chemistry

January 2017 Audio Summary

This is the January 2017 issue of *Clinical Chemistry*, Volume 63, Issue 1.

**ON THE COVER** *Cutout, Fall of Icarus, Jazz, Star Details* by Henri Matisse (1869-1954). Each year *Clinical Chemistry* devotes a special issue to a topic of current importance to clinicians and laboratory scientists. This year we revisit the topic of cardiovascular disease, especially the impact of biomarkers, proteomics, and genomics in cardiovascular disease. In addition to the wide variety of review articles and research reports, be sure to read the interview with current FDA Commissioner Robert Califf, in which he discusses not only the FDA but also his own personal experience with heart disease, his groundbreaking work with tissue plasminogen activator, and the people and places that influenced his career. Also be sure to read the five Opinion pieces by experts in the field, where you will find that, regardless of the area of cardiovascular disease discussed, not everyone agrees.

**A Novel Lipid Biomarker Panel for the Detection of Heart Failure with Reduced Ejection Fraction**
By Matthias Mueller-Hennessen, et al.

This study sought to identify novel metabolomic biomarkers suitable for improved diagnosis of heart failure with reduced ejection fraction. In total, 887 individuals consisting of heart failure patients, healthy controls and patients with pulmonary diseases were prospectively recruited. The authors found that NT-proBNP when combined with metabolomic features belonging to several lipid classes exhibited significantly improved diagnostic performance when compared to NT-proBNP alone in heart failure patients, even in the subgroups with mildly reduced left ventricular systolic function and asymptomatic stages. Moreover, they observed that the addition of metabolomic features may overcome well-known diagnostic limitations of NT-proBNP related to age, gender and weight.

**Plasma N-terminal Prosomatostatin and Risk of Incident Cardiovascular Disease and All-Cause Mortality in a Prospective Observational Cohort: the PREVEND Study**
By Ali Abbasi, et al.

This study describes associations of a stable fragment of somatostatin with cardiovascular disease and mortality. Somatostatin plays a key role in neuroendocrine and hemodynamic regulatory pathways that can affect a person's health. No known earlier epidemiological study has investigated a potential link of somatostatin with cardiovascular disease and mortality in the general population. The authors of this study found that increased somatostatin was independently associated with an increased risk of future cardiovascular disease and all-cause mortality, and added predictive value on top of existing risk prediction algorithms. Because somatostatin analogues and antagonists are available as drug treatment, these findings may not only be important for assessing risk, but also for evaluation of treatment effects and reduction of cardiovascular risk by treatment with these drugs.

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**A Novel Protein Glycan–Derived Inflammation Biomarker Independently Predicts Cardiovascular Disease and Modifies the Association of HDL Subclasses with Mortality**
By Robert W McGarrah, et al.

There is evidence to suggest that systemic inflammation may adversely impact HDL function. This study sought to evaluate the independent and incremental predictive performance of GlycA - a novel serum inflammatory biomarker - and HDL subclasses on adverse events in a secondary prevention population. GlycA was found associated with the presence and extent of coronary artery disease as well as all-cause and cause-specific mortality. Moreover, increasing GlycA values attenuated the inverse association of smaller HDL subclasses with mortality. These findings highlight the interaction of systemic inflammation and HDL with clinical outcomes and may increase precision for clinical risk assessment.

**Increased Trimethylamine N-Oxide Portends High Mortality Risk Independent of Glycemic Control in Patients with Type 2 Diabetes Mellitus**
By W.H. Wilson Tang, et al.

The authors of this study analyzed 1,216 sequential stable patients with diabetes undergoing elective, non-urgent, coronary angiographic evaluation, and showed that plasma concentrations of choline, betaine and trimethylamine N-oxide were increased in type 2 diabetes mellitus, and also found to be linked to increased incident cardiovascular risks and mortality rate. Only trimethylamine N-oxide, however, remained predictive of incident risks following multilogistic regression analyses, showing strong prognostic value independent of traditional risk factors, cardiometabolic risks, and glycemic control. The results of this study suggest that microbial production of trimethylamine N-oxide may represent a target for therapeutic efforts for reducing cardiovascular and mortality risks in individuals with diabetes.

**High-Sensitivity Troponin I in Stable Patients with Atherosclerotic Disease in the TRA 2°P - TIMI 50 Trial**
By Alon Eisen, et al.

In this large study from a randomized controlled trial in stable patients with established atherosclerotic disease, there was a strong graded independent relationship between high-sensitivity cardiac troponin I and the incidence of future cardiovascular death or MI. This relationship was demonstrated in patients with prior myocardial infarction, and in patients with symptomatic peripheral artery disease, but to a lesser extent in patients with prior ischemic stroke. High risk patients with prior myocardial infarction identified by increased high-sensitivity cardiac troponin I had a substantial absolute improvement in net clinical outcome with vorapaxar.

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**C-Type Natriuretic Peptides in Coronary Disease**
By Timothy CR Prickett, et al.

Despite evidence that C-type natriuretic peptide (abbreviated CNP) is upregulated in inflamed coronary arteries, plasma CNP products in individuals with coronary disease have not been studied. Here the authors measured CNP and N terminal proCNP or NT-proCNP at baseline in 2129 subjects with Acute Coronary Syndrome and related levels to cardiac and renal function, other natriuretic peptides and outcome (median 4 years follow up). Using a robust multivariate model incorporating established risk factors for predicting outcome, NT-proCNP was a unique and independent predictor of all-cause mortality and cardiac readmission in those with unstable angina. NT-proCNP in acute coronary syndrome without infarction may identify subjects at increased risk of adverse outcome.

**Growth Differentiation Factor 15 Predicts All-Cause Morbidity and Mortality in Stable Coronary Heart Disease**
By Emil Hagström, et al.

This study investigated whether growth differentiation factor 15 (abbreviated GDF-15) predicts both cardiovascular and non-cardiovascular morbidity and mortality in patients with coronary heart disease beyond established risk predictors and biomarkers. Baseline GDF-15 was assessed in models adjusting for conventional risk factors as well as for prognostic biomarkers in 14,577 stable coronary heart disease patients. The study found that GDF-15 was predictive for hospitalization for heart failure, death from cancer, heart failure, as well as sudden death, in addition to cardiovascular death, myocardial infarction, and stroke. Information on GDF-15 therefore might be helpful when assessing the risk of adverse outcomes in patients with stable coronary heart disease.

**Association of Repeatedly Measured High-Sensitivity–Assayed Troponin I with Cardiovascular Disease Events in a General Population from the MORGAM/BiomarCaRE Study**
By Maria Francoise Hughes, et al.

Cardiac troponin is a biomarker of myocardial damage and monitoring changes in troponin may provide early insight into disease processes. The authors of this paper evaluated whether long term changes in troponin are prognostically meaningful for predicting cardiovascular disease. They measured troponin 3 times, 5 years apart in a population cohort initially disease free and aged 30 to 60 years old. They found that three measures were better than one at predicting 10-year risk of cardiovascular disease in models adjusted for cardiovascular risk factors, but the difference between the models was relatively small. A single troponin measure is sufficiently prognostic for primary prevention of cardiovascular disease.

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**Anti–Cardiac Troponin Autoantibodies Are Specific to the Conformational Epitopes Formed by Cardiac Troponin I and Troponin T in the Ternary Troponin Complex**
By Alexandra V Vylegzhanina, et al.

In this study the authors investigated the epitope specificity of autoantibodies to troponins and their influence on cardiac troponin I immunodetection in patients with acute myocardial infarction. Autoantibodies appeared to be specific to the structural epitopes formed by troponin I and troponin T molecules and exhibited their action only on the ternary troponin complex but not on the binary complex. The negative effects of autoantibodies on the measurements of endogenous troponin I in plasma samples of patients with myocardial infarction were less than those on the spiked ternary troponin complex because patients' samples appeared to contain a mixture of binary and ternary troponin complexes.

**Specificity of B-Type Natriuretic Peptide Assays: Cross-Reactivity with Different BNP, NT-proBNP, and proBNP Peptides**
By Amy K. Saenger, et al.

The natriuretic peptides, BNP and NT-proBNP, are globally endorsed in clinical guidelines to aid in the diagnosis of heart failure and monitor disease progression. Immunoassays cross-react variably and differ in immunoreactivity to glycosylated natriuretic peptide fragments, affecting assay clinical performance with implications for patient care. The authors of this study characterized the extent of cross-reactivity of nine B-type natriuretic peptides with five BNP, nine NT-proBNP and six proBNP immunoassays. Their findings demonstrated first, that there was no cross-reactivity between NT-proBNP peptides in BNP assays, second, that NT-proBNP assays did not detect glycosylated proBNP-derived peptides, the major form in heart failure, or BNP peptides, and, third, that proBNP assays were highly specific for various forms of proBNP peptides that may have utility in elucidating the peripheral processing of proBNP 1-108, particularly in individuals with diabetes mellitus whose glycosylation patterns are highly variable.

**Unraveling the Molecular Complexity of O-Glycosylated Endogenous (N-Terminal) pro–B–Type Natriuretic Peptide Forms in Blood Plasma of Patients with Severe Heart Failure**
By Bernhard Halfinger, et al.

The natriuretic B-type peptides BNP and N-terminal proBNP are diagnostic and prognostic biomarkers in heart failure patients. Also the precursor hormone proBNP is found in the circulation of such patients. O-linked glycosylation influences immunoassay response, but the glycosites still have not been characterized in human proBNP or N-terminal-proBNP. The authors of this study established a specific method for the isolation of this low abundance protein and the subsequent identification of glycosites using a high end mass spectrometry method. They describe nine distinct glycosylation sites on circulating proBNP and N-terminal-proBNP in HF patients. This may have an impact on commercial immunoassays, which detect mostly non glycosylated forms.

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**Rapid Rule-Out of Acute Myocardial Injury Using a Single High-Sensitivity Cardiac Troponin I Measurement**
By Yader Sandoval, et al.

In this study the authors first determined whether a single high sensitivity cardiac troponin I measurement at presentation with concentrations below the limit of detection could rule-out acute myocardial injury alone or in combination with a normal electrocardiogram. Second, they examined the safety of this strategy by assessing myocardial injury and cardiac death at 30 days. 27% of patients had troponin I below the limit of detection, with a negative predictive value and diagnostic sensitivity for acute myocardial injury of 99.1% and 99.0% and a negative predictive value for myocardial infarction or cardiac death at 30 days of 99.6%. The authors conclude that a single high sensitivity cardiac troponin I concentration below the limit of detection rules out acute myocardial injury, regardless of etiology, with an excellent negative predictive value and diagnostic sensitivity, and identifies patients at minimal risk of adverse events.

**Glial Fibrillary Acidic Protein Serum Levels Distinguish between Intracerebral Hemorrhage and Cerebral Ischemia in the Early Phase of Stroke**
By Sebastian Luger, et al.

This prospective multicenter trial validated serum concentrations of glial fibrillary acidic protein (abbreviated GFAP) in patients with symptoms of acute stroke and assessed the quantitative relationship between GFAP release, bleeding size and intracerebral hemorrhage localization. GFAP serum concentrations were found significantly increased in patients with intracerebral bleeds compared to patients with ischemic stroke and stroke mimics. GFAP serum concentrations were positively correlated with intracerebral hematoma volume. These results strongly corroborate that a positive GFAP test prior to admission may allow a reliable prehospital diagnosis of intracerebral bleeding in acute stroke patients.

**Soluble CD146 Is a Novel Marker of Systemic Congestion in Heart Failure Patients: An Experimental Mechanistic and Transcardiac Clinical Study**
By Mattia Arrigo, et al.

This study assessed the sources and effects of vascular stress on release of soluble CD146, an endothelial biomarker of heart failure. The source of soluble CD146 was confirmed to be extra-cardiac by the finding of a negative transcardiac gradient with lower concentrations in the coronary sinus than in peripheral vein. Plasma soluble CD146 was measured at baseline and after 90 minutes of unilateral forearm venous congestion. The induction of venous stress was associated with pronounced increase of soluble CD146 in the congested arm compared to the control arm. Soluble CD146 is rapidly released from the peripheral vasculature in response to venous stretch and may reflect systemic congestion in heart failure.

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**Immediate Rule-out of Acute Myocardial Infarction Using Electrocardiogram and Baseline High-Sensitivity Troponin I**
By Johannes Neumann and Nils Sörensen, et al.

The early rule-out of acute myocardial infarction is important and based on serial measurements of high-sensitivity troponin. The authors of this study set out to challenge this approach using a single baseline troponin I measurement in combination with a non-ischemic electrocardiogram. High-sensitivity troponin I was measured in 4,606 individuals with suspected acute myocardial infarction and showed a high negative predictive value of 100%, when a low troponin I cutoff concentration of 3 ng/L was used in combination with a non-ischemic electrocardiogram. The study findings suggest, that a rapid baseline approach is safe and feasible in acute cardiac care of low risk patients, when low cutoff concentrations are used.

**Rule-In and Rule-Out of Myocardial Infarction Using Cardiac Troponin and Glycemic Biomarkers in Patients with Symptoms Suggestive of Acute Coronary Syndrome**
By Colleen Shortt, et al.

This is a study designed to investigate possible algorithms using various cardiac troponin assays and glycemic markers such as glucose and hemoglobin A1c for the early rule-in/rule-out of myocardial infarction. The authors examined a variety of different cut-offs aimed specifically at maximizing those ruled-out and ruled-in. They found that combining troponin with glucose (dual negative) criteria and a high-risk troponin cut-off achieved this, while adding hemoglobin A1c to this strategy identified previously unknown diabetes without significantly affecting rule-out capabilities. Using these findings a patient's disposition vis-à-vis myocardial infarction may be determined using only presentation samples, and previously unknown cases of diabetes identified.

**Discordance between ICD-Coded Myocardial Infarction and Diagnosis according to the Universal Definition of Myocardial Infarction**
By Jorge Díaz-Garzón, et al.

The International Classification of Diseases (abbreviated ICD) coding is the standard diagnostic tool for healthcare management. At present, type 2 MI classification by the Universal Definition of Myocardial Infarction remains ignored in the ICD system. This study determined the concordance for the diagnosis of MI using ICD-9 coding versus the Universal Definition. Cardiac troponin I was measured by both contemporary cardiac troponin I and high sensitivity cardiac troponin I assays in 1927 consecutive emergency department patients (UTROPIA cohort) who had cardiac troponin I ordered on clinical indication, and concordance assessed between ICD-9 code 410 and type 1 MI and type 2 MI. ICD-9 coded MIs captured only a small proportion of adjudicated MIs, primarily due to type 2 MI not being coded. These findings emphasize the need for an ICD code for type 2 MI.

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**Trimethylamine N-oxide and Risk Stratification after Acute Myocardial Infarction**
By Toru Suzuki, et al.

Trimethylamine N-oxide, abbreviated TMAO, has been shown to promote atherosclerosis, associate with atherosclerotic burden, induce platelet hyperreactivity and increase thrombotic risk. However, it is not currently understood how TMAO affects prognosis post-ischemia. This report analyzes a substantial cohort of acute myocardial infarction patients and is the first to show that TMAO is associated with adverse outcome in this population. The authors report that TMAO is prognostic for all-cause mortality or reinfarction at 2 years, superior to multiple advanced contemporary biomarkers and aids in risk stratification when combined with the GRACE clinical scoring system for risk at 6 months.

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