Tuesday, August 1, 2017

Poster Session: 9:30 AM - 5:00 PM

Cardiac Markers

A-064

The Effect of Heparin on Measurement of High Sensitivity Cardiac Troponin I: Influence on Diagnostic Misclassification at Decision Thresholds.

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BACKGROUND: The combined influence of anticoagulant bias and imprecision on hs-cTnI measurement on test interpretation is unknown. OBJECTIVES: 1) Determine the effect of heparin on the measurement of hs-cTnI. 2) Audit concentration of heparin in hs-cTni specimens. 3) Simulate the effect of heparin-bias on misclassification error at hs-cTnI thresholds. METHODS: Serum pools (9, 35, 77 ng/L) were prepared with patient specimens. Aliquots were dispensed into BD PST Lithium Heparin (n=5) and hs-cTnI was measured using the Abbott ARCHITECT i2000. Heparin concentrations were determined gravimetrically. Monte Carlo error simulation models were used to assess the misclassification rate at hs-cTnI thresholds with heparin-biases observed clinically and imprecision (0-20%). RESULTS: Heparin concentration demonstrated a negative troponin-dependent bias on measurement of hs-cTnI: (9ng/L cTnI, y= -0.006x + 9.32; 35 ng/L cTnI, y=-0.012x + 35.56; 77ng/L cTnI, y=-0.041x + 76.99). Whole blood heparin concentrations in hs-cTni specimens (n=167) ranged from 14.4 IU/ml to 96.6 IU/ml due to incomplete tube filling. Simulations predicted the combined influence of assay imprecision and heparin-bias on misclassification would be greatest at the 52 ng/L threshold: At CV=6%, a false-negative misclassification of 0.5% with 95 IU/mL heparin, and false-negative misclassification of 0.2% in the absence of heparin. CONCLUSION: Heparin potencies observed in clinical practice have a negative bias on hs-cTnI measurements. The influence of heparin is dependent upon troponin concentration and the predicted effect of heparin on hs-cTni misclassification is slight and unlikely to influence clinical decisions.

A-065

Measurement of intact fibroblast growth factor 23 in patients with heart failure with reduced ejection fraction

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Background: Biomarkers can contribute to the prognostication of patients with heart failure (HF) and to implementation of more tailored based approach. Fibroblast growth factor 23 (FGF-23) is the most potent phosphaturic hormone and also regulates bone and mineral metabolism. FGF-23 is a strong and independent factor of adverse cardiovascular events and death in HF patients. However, most of the studies were based on the measurement of C-terminal FGF23 and only few have investigated the concentrations of intact FGF-23 (iFGF-23) in HF. We determined the circulating levels of iFGF-23 in patients with HF with reduced ejection fraction (HFrEF) as well as its relation with cardiac biomarkers and adverse cardiovascular events. **Methods:** One hundred thirty three chronic HF patients (females n=31; males n=102; NYHA II-IV; mean age: 67 years; etiology: ischemic n=92, dilated cardiomyopathy n=41; mean EF: 23 %) were enrolled in the study. The primary outcome was CV death. Levels of iFGF-23 were measured at baseline with a recently released fully automated and sensitive immunoassay. The 95th percentile of the reference interval of this assay is 81 pg/mL. Levels of 25-hydroxyvitamin D (25OHD), 1,25-dihydroxyvitamin D (1,25(OH)2D), PTH(1-84), B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), soluble ST2 (sST2) and Galectin-3 (Gal-3) were also determined. **Results:** The median plasma level of iFGF-23 was 73 pg/mL and 56 patients (42%) had values higher than the 95th of the reference interval. HF patients NYHA III-IV have significantly higher iFGF23 (81 pg/mL) than NYHA II (57 pg/mL). Concentrations of iFGF23 were not significantly different between dilated and ischemic cardiomyopathies (67 vs. 77 pg/mL). Intact FGF23 correlated with left ventricular ejection fraction (r = -0.18; P = .04), estimated glomerular filtration rate (eGFR; r = -0.43; P < .001), PTH(1-84) (r = 0.41; P < .001), (1,25(OH)2D) (r = -0.46; P < .001), Gal-3 (r = -0.39; P < .001) but not with age, (25OHD), BNP, NT-proBNP or sST2. After 8 years of follow-up, 106 patients reached the primary endpoint. Concentration of iFGF23 was significantly higher in HF patients who died in comparison to survivors (87 vs 57 pg/mL). In patients with eGFR >60 mL/min levels of iFGF23 remain associated to adverse cardiovascular events. **Conclusions:** Intact FGF23 is a strong and independent predictor of cardiovascular mortality in chronic HF.

A-066

Shorter Telomeres are Associated With Low Levels of Human Telomerase Reverse Transcriptase and Fetuin-A In Patients With Acute Myocardial Infarction

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Background: Telomeres, which are tandem repeats of DNA sequences at the end of eukaryotic chromosomes, have been linked to age related conditions and diseases including cardiovascular diseases (CVDs), Telomere lengths are maintained by telomerase and leukocyte telomere length (LTL) has been shown to be a marker of cell senescence and CVDs risk. Leukocyte telomerase activity has been associated with the presence and progression of calcified atherosclerotic coronary plaque in patients with short LTL. Fetuin-A, an anti-inflammatory glycoprotein synthesized in the liver, inhibits apoptosis of vascular smooth muscle cells and prevents heterotropic calcification. Low Fetuin-A concentration has been shown to be associated with overproduction of inflammatory cytokines, mitral and aortic calcification and cardiac fibrosis. As short LTL and low telomerase have been implicated in the development of atherosclerotic processes, this study explores potential associations between LTL, human Telomerase Reverse Transcriptase (hTERT) and Fetuin A as potential disease markers in patients with Acute Myocardial Infarction (AMI). **Materials and Methods:** LTL, hTERT, Fetuin A, Troponin I, and lipid profile were measured in 144 consecutive patients with increased Troponin I and symptoms suggestive of AMI and 192 age, gender and ethnicity matched healthy control subjects. AMI was diagnosed according to National Academy of Clinical Biochemistry (NACB) guidelines **Results:** AMI patients had significantly shorter (mean ± SD) LTL and lower (mean ± SD) hTERT levels compared to controls - [0.9±1.1 vs 4.5±3.9, p<0.0001] and [23.0±5.5 ng/ml vs 32.9±8.9 ng/ml, p<0.0001] respectively. Serum levels of Fetuin A were significantly (p<0.0001) lower in patients with AMI compared to control subjects - [31.9±9.5 ng/ml vs 38.5±12.9 ng/ml]. LTL correlated negatively with Troponin I and Fetuin -A levels (r = -0.13, p=0.02, r = -0.36, p=0.002). hTERT levels correlated negatively with Troponin I (r = -0.19, p=0.003) and Fetuin -A (r = -0.28, p=0.004). Binary logistic regression analysis showed that the odds ratio (OR) of having shorter LTL and lower hTERT were 2.1 (95%CI 1.5-6.2) and 1.6 (95%CI 1.2-8.8) respectively in patients with AMI compared to apparently healthy control subjects. **Conclusions:** We postulate that lower levels of hTERT and Fetuin A could predispose to heterotropic calcification in coronary-arteries. Short LTL and lower levels of hTERT and Fetuin A are risk factors that may play significant roles in the pathogenesis of AMI. Estimation of LTL, hTERT and Fetuin A could be useful adjuncts for the identification of patients with high risk of CVDs. .

A-067

Diagnosis based on admission or rapid serial measurements using the high sensitivity Abbott cardiac troponin I assay.

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Objectives: To examine diagnostic and prognostic efficiency of admission and rapid serial measurements of a high sensitivity cardiac troponin I (cTnI) assay.

Methods: Samples analysed were from the point of care arm of the RATPAC trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers), set in the emergency departments of six hospitals. Prospective admissions with chest pain and a non-diagnostic electrocardiogram were randomised to point of care assessment or conventional management. Blood samples were taken on admission and 90 minutes from admission.. Samples were initially analysed using the Stratus CS (CS) (Siemens Healthcare Diagnostics), range 30-50,000 ng/L 10% CV 60ng/L 99th percentile 70 ng/L. An additional blood sample was taken at admission and 90 minutes from admission, separated and the serum stored frozen until subsequent analysis for cTnI by using the Architect hsTnI (Abbott Diagnostics), range 1.1-50,000 ng/L 10% CV 4.7ng/L.

The universal definition of myocardial infarction (MI) utilising laboratory measurements of cardiac troponin performed at the participating sites together with

measurements performed in a core laboratory was used for diagnosis. Myocardial infarction was diagnosed by the combination of a delta troponin plus a value exceeding the 99th percentile. All patients were followed up to 30 days for major adverse cardiac events (MACE).The following diagnostic strategies were examined: the admission sample only using discriminants of 3 and 5 ng/L and the 99th percentile (26 ng/L); serial measurements using the peak value and the same discriminants plus additional use of an absolute delta value corresponding to a clinically significant change within the reference interval at 10% imprecision (8.7 ng/L).

Results: 290 patient samples were available (175 male, median age 54.3 years, range 23.7-90.6) with 180 serial samples. The incidence of MI was 26/290 (9%) and MACE 7/290 (2.4%). For admission measurement MI was excluded as follows: 3 ng/L 220/290 (75.9%); 5 ng/L 233/290 (80.3%) with no missed MI at either discriminants; 26 ng/L 261/290 (93.1%) with 9 missed MI. For patients below the diagnostic discriminant, there was no MACE at the 3 ng/L and 5 ng/L cut-offs and 3 MACE at the 26 ng/L cut-off. Serial sampling did not improve diagnostic sensitivity for rule out compared to admission sampling alone. Serial sampling detected 6 additional cases where the initial sample had a value between 3 and 26 ng/L. In patients with troponin above the low-level discriminants (3 ng/L or 5 ng/L) a positive delta value was seen in 4/6 patients with MI and 4/45 (>3ng/L) and 4/27 (>5ng/L) patients without MI. A delta value improved diagnostic specificity only when combined with use of the 99th percentile as discriminant. 2 cases with MI had a delta which failed to exceed the discriminant.

Conclusion: Rule out of MI using low-level discriminants with or without a delta change was reliable. Rule in requires the use of the 99th percentile plus judicious interpretation of a delta value. Delta values alone are unreliable to confirm or exclude MI.

A-068

Evaluation of the European Society of Cardiology recommended rapid diagnostic algorithms in a challenging low risk cohort.

P. O. Collinson[1], D. Gaze[2], S. Goodacre[3]. *[1]St George's Hospital, London, United Kingdom, [2]Westminster University, London, United Kingdom, [3]University of Sheffield, Sheffield, United Kingdom*

Objectives: To examine diagnostic efficiency of the proposed European Society of Cardiology rapid diagnostic algorithms in a challenging low risk cohort.

Methods: Samples analysed were from the point of care arm of the RATPAC trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers), set in the emergency departments of six hospitals. Prospective admissions with chest pain and a non-diagnostic electrocardiogram were randomised to point of care assessment or conventional management. Blood samples were taken on admission and 90 minutes from admission. Patients were admitted if the initial of 90 minute sample exceeded the 99th percentile for cardiac troponin I (cTnI) analysed using the Stratus CS (CS) (Siemens Healthcare Diagnostics), range 30-50,000 ng/L 10% CV 60ng/L 99th percentile 70 ng/L. An additional blood sample was taken at admission and 90 minutes from admission, separated and the serum stored frozen until subsequent analysis for cTnI by using the Architect hs cTnI (Abbott Diagnostics), range 1.1-50,000 ng/L 10% CV 4.7ng/L and high sensitivity cardiac troponin T (hs cTnT) by the Roche high sensitivity cardiac troponin T assay hs-cTnT (Elecsys 2010, Roche diagnostics), range 3 - 10,000ng/L, 10% CV 13ng/L, 99th percentile 14 ng/L.

The universal definition of myocardial infarction (MI) utilising laboratory measurements of cardiac troponin performed at the participating sites together with measurements performed in a core laboratory was used for diagnosis. Myocardial infarction was diagnosed by the combination of a delta troponin plus a value exceeding the 99th percentile. The two proposed algorithms for ruling out and ruling in MI were then applied to the admission and serial samples to directly compare diagnostic efficiency of the two analytes.

Results: 276 patient samples were available (169 male, median age 54.5 years, range 23.7-90.6) with 165 serial samples. The incidence of MI was 276 (9.4%). A single measurement on admission excluded MI in 174/276 (63%) for hs cTnI with no missed cases, negative predictive value (NPV) 100% and in 219/276 (79.3%) for hs cTnT with 2 missed cases, NPV 99.1%. Serial sampling excluded 128/165 (77.6%) for hs cTnT with no missed cases, NPV 100% and 149/165 (90.3%) for hs cTnT with 1 missed case, NPV 99.3%. 27/165 (16.4%) were classed as indeterminate for hs cTnI and 8/165 (4.8%) for hs cTnT. Rule in sensitivity for hs cTnI was 100% (5/5) at 96.9% specificity with no indeterminate cases. For hs cTnT rule in sensitivity was 40% (2/5) at 96.3% specificity with 2 intermediate cases.

Conclusion: Both single measurement and serial measurement algorithms proved excellent rule out tools but the rule in algorithm was less reliable in this patient group. This probably reflects the difficulty of diagnoses in low risk patients with relatively small troponin changes.

A-069

Performance of body mass index and percentage of body fat to identify risk factors for cardiometabolic disease in Thai adults

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Background: Body mass index (BMI) and percentage of body fat (PBF) are commonly accepted measures of obesity, with specified cut-offs for age, gender and race/ethnicities. Generally, Asian women have higher PBF and lower BMI than to men and other ethnic populations. We aim to compare the performance of BMI and PBF associate with obesity-related metabolic risks in the adult Thai population.

Methods: A total of 222 (64 men and 158 women), aged 21-79 years, outpatients were recruited. To define obesity, we used the criteria $\geqslant$25.0 and $\geqslant$27.0 kg/m^2 for BMI and $\geqslant$35% and $\geqslant$25.0% for PBF, for women and men, respectively. Blood samples were analyzed for total cholesterol, triglycerides, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, lipoprotein subclasses, apolipoprotein A-I, apolipoprotein B, glucose, HbA1c, insulin, adiponectin, leptin, high sensitive C-reactive protein and 25-hydroxyvitamin D.

Results: Among participants 42.3% were obese by PBF and 27.4% by BMI. Among those subjects normal by BMI, 25% were obese by PBF and among those normal by PBF, 7% were obese by BMI. Prevalence of metabolic syndrome was higher in subjects obese by PBF only (51.2%) than those obese by BMI only (33.3%). Obese by PBF showed greater association with the estimate of 10-year risk for coronary heart disease (Framingham risk score and The American College of Cardiology/American Heart Association guideline) than those obese by BMI. Using multivariable linear regression analysis adjusted for age and smoking, PBF showed significant associations with the lipid markers and adiponectin, while BMI associated with glucose metabolic markers in men (all $p < 0.005$). BMI was demonstrated a significant variable for lipid and glucose metabolic markers as well as adiponectin levels in women (all $p < 0.05$). There was no association between high sensitive C-reactive protein with BMI or PBF in men but there was with PBF in women. Both obesity indexes were significantly related with leptin concentration independent of gender. Cardiometabolic risk markers showed stronger association when both obesity indices were positive.

Conclusion: Obesity, in our Thai population, by PBF was more strongly associated with cardiometabolic risk markers than obesity by BMI; however, obese by BMI included those missed by PBF alone, thus both obesity indices provide information associated with risk factors. Because of the differences between PBF and BMI association with cardiometabolic risk markers and potentially cardiovascular disease, obesity by PBF should be included with that of BMI when screening populations for potential cardiovascular risk.

A-070

Characteristics of the new Beckman Coulter Access hsTnI Assay.

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BACKGROUND: In order to meet new IFCC guidance new Troponin I assays should exhibit increased sensitivity (LoB, LoD and LoQ), precise measurement of cTnI concentrations in the range seen in healthy individuals and the capability to accurately detect changes in cTnI concentration within this range.

METHODS: The verification and clinical validation of the new Access hsTnI assay was performed in accordance with CLSI guidelines.

RESULTS: Beckman Coulter's new high sensitivity Access hsTnI assay exhibits superior sensitivity in comparison to other currently marketed devices with an estimated LoB of < 0.0005 ng/mL (0.5 pg/mL), LoD < 0.002 ng/mL (2 pg/mL) and 10% CV LoQ < 0.020 ng/mL (20 pg/mL). The estimated 99th percentile URL of a random healthy population is 0.032 ng/mL (32 pg/mL) determined with < 3% intra-assay and 8% Total imprecision. In addition, this new Access hsTnI assay is capable of accurately measuring 0.010 ng/mL (10 pg/mL) changes in cTnI concentrations. This

Access hsTnI assay accurately measures cTnI in comparison to a currently validated device (correlation between Access AccuTnI+3 and hsTnI within 5%) and exhibits < 5% bias between sample types (serum, plasma). The assay does not exhibit cross reactivity to cardiac TnT, cardiac TnC, skeletal TnI or skeletal TnT and is robust against common interferences (400 mg/dL hemoglobin, 40 mg/dL bilirubin, 3000 mg/dL triglyceride 60 mg/mL albumin, 1000 mg/dL fibrinogen, 28.8 U/mL heparin).

CONCLUSIONS: Beckman Coulter's new high sensitivity Access hsTnI assay is highly sensitive and sufficiently accurate to precisely measure cTnI in > 90% of the normal population and meets new IFCC guidance to accurately detect changes in cTnI concentration within healthy subjects. This new assay is currently is in development, pending achievement of CE compliance and is not available for *in vitro* diagnostic use.

A-071

Combined troponin and CK-MB in early diagnosis of acute myocardial infarction

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Background: Despite the great advances in early diagnostics and rapid treatment, acute myocardial infarction (AMI) is the leading cause of death in the United States. Diagnostic work-up for ruling out AMI includes electrocardiogram (ECG) and serum biomarkers of cardiac injury testing. Two cardiac biomarkers of myocardial damage commonly employed are the MB isozyme of creatine kinase (CK-MB) and the inhibitory subunit of myocardial troponin (cTnI). When myocardial cells are infarcted, CK-MB and cTnI are released into the circulation at relatively high concentrations, which can be detected and quantified in patient's serum using immunoassays. Although both markers have been found to rise within the first six hours after the onset of AMI symptoms, there is some evidence that CK-MB may serve as a more reliable marker in the acute period. Our aim is to investigate the combined use of serum cTnI and CM-MB for the early diagnosis of AMI.

Methods: This is a retrospective, cross-sectional study looking at CK-MB and cTnI serum levels for all patients entering our emergency department (ED) for the month of January 2015 who presented for rule out AMI. We extracted CK-MB and cTnI data from our laboratory information system for which both tests were ordered and analyzed simultaneously. The records of these patients were also followed to determine the final diagnoses. We will determine the sensitivity and specificity of both tests.

Results: We've identified 148 patients (age range: 30 - 98 years; mean age: 64.5 ± 14.6 years; M/F: 1.3/1) who presented to our ED to rule out AMI where both CK-MB and cTnI were analyzed simultaneously. Twelve of the 148 patient cohort were found to have AMI. Of these either or both serum markers were found to be positive for eleven patients, giving a combined sensitivity of 91%. Significantly, three of the patients with negative troponins were found to be have positive CK-MB, and five other patients were found to be positive for troponin and negative for CK-MB. The remaining three patients were found to be positive for both markers. The specificity for troponin was 90% and that for CK-MB was 70%. The lower specificity for CK-MB derives from the occurrence of positive CK-MB values for patients with end-stage renal disease and/or acute exacerbations of congestive heart failure in patients who were subsequently found to be negative for AMI, findings which we are exploring further.

Conclusion: Our preliminary results suggest both tests should be performed on patients with rule out AMI. A positive result from either test increases the diagnostic accuracy and allows early diagnosis of this condition.

A-072

Red Cell Distribution Width and Cardiovascular Risk: Insights from de Longitudinal Study of Adult Health (ELSA-Brasil)

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Background: Red Cell Distribution Width (RDW) is a quantitative laboratory test that measure the variability in the size of circulating erythrocytes. RDW is easily obtained with automated hematology analyzers, as part of complete blood count (CBC), and is generally used as an indicator of the differential diagnosis of microcytic anemia. Recent studies have shown that RDW is a predictive, diagnostic, and prognostic marker of mortality and cardiovascular events in general population as well as in patients with cardiovascular diseases (CVD). Although pathophysiological mechanisms are still unclear, the evidence obtained so far encourages further research on the RDW in different populations and clinical settings. The aim of this study was to investigate the relationship of the RDW with CVD risk factors included on the Framingham Risk Score (FRS), and the score itself, in participants of the Longitudinal Study of Adult Health (ELSA-Brasil). **Methods**: We used the baseline data (2008-2010) of 5136 civil servants (aged 35-74 year) enrolled in the ELSA-Brasil study. RDW were quantified by coefficient of variation of red blood cells volume (RDW-CV%) using XE 2100 D hematologic analyzers (Sysmex, Kobe, Japan), that use impedance technology to estimate particle count and volume. The population was distributed according to their exposure to different risk factors, and stratified for cardiovascular risk, based on FRS. The association of RDW with CVD risk factors was performed using the Spearman test. Multiple regression analysis was used to estimate the association of RDW measures with the FRS, after adjusting for variables that can increase the variation in the volume of red blood cells, and for variables that are not part of the FRS, but can increase CVD risk.

Results: RDW (adjusted r^2=0.517; $p<0.001$) was independently associated with the FRS after adjustment for age, education, skin color, body mass index, abdominal obesity, metabolic syndrom, bariatric surgery, hemoglobin concentration, mean corpuscular volume, platelets, C-reactive protein, estimated glomerular filtration rate, vitamin supplement use, dietary folate, iron and vitamin B12 intake, . It was observed that a one unit increase in RDW increases the FRS by 1.15%.

Conclusion: In this large cohort of free living Brazilians, ours results showed that increased RDW is independently associated with higher CVD risk based on the FRS. The investigation of inexpensive, easily obtained, and widely used markers, such as RDW, should be strongly encouraged in order to confirm its potential in predicting of adverse cardiovascular events. The prospective follow up of the participants will may help to clarify if RDW can add accuracy to the CVD risk stratification in this population.

A-073

Prognostic significance of Cystatin C in Acute coronary syndrome

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Back ground: Coronary artery disease(CAD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium. The clinical spectrum of CAD is stable angina (SA), unstable angina (UA) and myocardial infarction (MI. ACS includes UA and MI. The frequency of ACS is extremely high among Indians; India has the highest burden of ACS in the world. The rising incidence of ACS in Indians may be associated with changes in the lifestyle, the westernization of the food practices, the growing prevalence of diabetes mellitus and probably genetic factors. In recent years cystatin C has emerged as a potential marker for cardiovascular risk and predicts the cardiovascular events. Cystatin C is a naturally occurring protease inhibitor that protects the host tissue from cysteine proteases, which is a proatherogenic factor. **Materials and Methods**:Study group comprised of 114 patients diagnosed as having ACS based on clinical and bio-chemical criteria. Control group included 66 age and sex matched subjects (non ACS cases) using the above mentioned criteria. **Results**:In this study, significant increase of mean serum cystatin C levels was observed in ACS cases than controls. Highest mean cystatin C values were observed in MI than UA.Highest mean cystatin C values were observed in ACS cases with risk factors. **Conclusion:** Cystatin C plays an important role in the development of ACS and serum cystatin C is a might have a role as a prognostic marker in patients with ACS.

A-074

Performance Evaluation of the Atellica® IM High Sensitivity Troponin I Assay

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Introduction: The 2015 European Society of Cardiology guidelines propose algorithms for faster rule-in or rule-out of AMI in patients and for the management of NSTEMI. High-sensitivity cardiac troponin I (cTnI) assays will more accurately and precisely measure changes in cTnI concentrations in serial draws providing useful data to assist in identifying acute versus chronic cTnI elevations, and acceptable rule-in and rule-out performance within 1 to 3 -hours of presentation. This study evaluated the performance of Siemens High Sensitivity Troponin I (TNIH) assay[1] developed for use on the Atellica Immunoassay Analyzer[2] is presented. The assay is a dual-capture sandwich immunoassay using preformed magnetic latex particles, a proprietary acridinium ester for chemiluminescence detection, and three monoclonal antibodies.

Methods: The limit of blank (LoB) and limit of detection (LoD) assessments used three reagent lots on two Atellica immunoassay systems with both lithium heparin and serum matrixes and run according to CLSI EP-17A2. LoD studies collected 60 replicate measurements for each of 10 serum and 10 lithium heparin samples per lot and per system. CLSI protocol EP12-A2 was followed to compare the Atellica TNIH assay to the ADVIA Centaur TNIH assay with n = 144 AMI patient samples spanning the range of reportable results. The 99th percentile cutoff values were established using a well-characterized population of apparently healthy subjects (n=2007) in both lithium and serum matrixes. Clinical correlation of cTnI levels above the 99th percentile to adjudicated AMI diagnosis is assessed in all-comer emergency department (ED) subjects in both sample matrixes.

Results: The LoB was 0.58 ng/L across two Atellica Immunoassay analyzers and three reagent lots. LoD was determined to be 1.27 ng/mL. The cTnI concentration at 20% CV_{Total} (LoQ) had a pooled value of 2.51 ng/L. 75% of the normal health population was above the LoD. The observed assay repeatability on the Atellica Immunoassay analyzer ranged from 4.0 to 5.4% CV, and within-lab precision ranged from 5.2 to 7.0% CV between 9 and 20 ng/L. Above 20 ng/L repeatability on the Atellica Immunoassay analyzer ranged from 0.9 to 3.2% CV, and within-lab precision ranged from 1.9 to 5.2% CV. The repeatability and within-lab precision at the pooled (female and male) 99th percentile (45.2 ng/L) were 2.8% CV and 3.7% CV, respectively. The 99th percentile observed for females is 34.11 ng//L and for males 53.48 ng/L. Method comparison between the Atellica IM TNIH and ADVIA Centaur TNIH assays yielded slopes of 104 to 109% across the three reagent lots. Clinical sensitivity and clinical specificity in pooled-genders at 1, 2, 3, and 6-9 hours post ED presentation ranged from 88 to 94% and 87 to 91% respectively.

Conclusion: The Siemens Atellica IM TNIH assay has a 10% Total CV at a cTnI concentration 10-fold lower than the 99th percentile. This new TNIH assay allows the establishment of gender specific 99th percentile cutoffs, and shows acceptable clinical utility in an all-comer ED population.

[1] Under development. Not available for sale in US. Not CE marked. The performance characteristics of this device have not been established. .

A-075

Diagnostic Performance of High Sensitivity Cardiac Troponin I for the Diagnosis of Myocardial Infarction

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Background: The purpose of the present study was to compare the diagnostic performance of high sensitivity cardiac troponin I (hs-cTnI) vs. contemporary cTnI assays using the 99th percentile, alone or in combination with normal electrocardiogram (ECG), to rule-in and rule-out acute myocardial infarction (MI), including the integration of serial changes (delta) to improve the rule-in for acute MI. **Methods**: Our prospective, observational cohort enrolled consecutive patients presenting to the emergency department in whom serial cTnI measurements, using both a contemporary cTnI assay (clinically used; 99th percentile 30 ug/L) and a hs-cTnI (investigational; sex-specific 99th percentiles: male 34 ng/L, female 16 ng/L) assay (Abbott Diagnostics), were obtained on clinical indication at Hennepin County Medical Center (Minneapolis, MN, USA) (Use of TROPonin In Acute coronary syndromes [UTROPIA]; NCT02060760). Diagnostic performance for acute MI, including analyses by MI subtypes (types 1 and 2 MI), and 30-day risk stratification safety outcome of acute MI or cardiac death, were examined. **Results:** Among 1,631 patients, acute MI occurred in 12.9% using the contemporary cTnI assay and 10.4% using the hs-cTnI assay. For ruling-out acute MI, serial contemporary cTnI measurements at 0/3/6h with concentrations ≤99th percentile and a normal ECG had a NPV 99.5% (95% CI: 98.6-100) and sensitivity of 99.1% (95% CI: 97.4-100) for both the diagnostic and safety outcome. Conversely, serial hs-cTnI measurements at 0/3h with concentrations ≤99th percentile and a normal ECG had a NPV and sensitivity of 100% (95% CI: 100, 100) for both the diagnostic and safety outcome. For ruling-in acute MI, the contemporary cTnI assay had specificities of 84.4% (95% CI: 82.5-86.3) at presentation and 78.7% (95% CI: 75.4-82.0) with serial testing at 0/3/6h, improving to 89.2% (95% CI: 87.1-91.3) using a relative delta cTnI value >150%. In contrast the hs-cTnI assay had specificities of 86.9% (95% CI: 85.1-88.6) at presentation and 85.7% (95% CI: 83.5-87.9) with serial testing at 0/3h, improving to 89.3% (95% CI: 87.3-91.2) using an absolute delta hs-cTnI >5 ng/L. In early presenters (≤ 2h), using the hs-cTnI assay the sensitivity and NPV were 100% (95% CI: 100-100) at 0/3h, alone or in combination with a normal ECG for the diagnostic outcome of acute MI. **Conclusion**: Both the hs-cTnI and contemporary cTnI assays are excellent in ruling-out acute MI following consensus recommendations predicated on the use of a) serial testing and b) the 99th percentile upper reference limit, when used in combination with a normal ECG. Delta values improve the specificity for acute MI and varied according to whether the initial sample was normal or increased.

A-076

Dietary Biotin Causes a Negative Interference for Troponin in the Advia Centaur Assay

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Introduction: Biotin, a common over-the-counter supplement, is involved as a coenzyme in several carboxylation reactions and its effects in strengthening hair and nails, controlling blood glucose levels, and easing peripheral neuropathy are well known. The recommended daily dose of biotin is 30 µg for adults. Biotin levels in the general population range from 0.3 to 1 ng/mL (1.2 to 4.3 nmol/L). Levels have been reported to reach 494.9 ± 161.0 ng/ml to 823.8 ± 303.1 ng/ml (Cmax) in 1.25 h to 1.5 h (tmax) after administration of a single dose of 100 to 300 mg in patients on high dose biotin supplementation respectively. Sufficient biotin concentrations in serum can lead to falsely increased (competitive assay) or falsely decreased (sandwich assay) results in immunoassays utilizing the biotin-streptavidin interaction.

Objectives: The aim of our study was to characterize the extent of biotin-mediated interference in ADVIA Centaur XP immunoassays. We studied the potential biotin interference in both competitive (free T4) and non-competitive immunoassays (troponin I and intact parathyroid hormone).

Methods: Biotin interference studies were performed by spiking increasing concentrations of biotin from 3-100 ng/mL (8 concentrations) into remnant serum patient pools. For troponin, 5 pools were evaluated at the following concentrations: 0.04, 0.09, 0.13, 6, and 8.5 ng/mL (99th percentile < 0.04 ng/mL). In addition, 18 individual remnant samples ranging from 0.05-0.27 ng/mL were evaluated after spiking in 100 ng/mL biotin. For iPTH and free T4, three and five serum pools, respectively, were evaluated as described for troponin. All measurements were performed on the ADVIA Centaur XP. A concentration differing by >10% was considered significant interference. MagnaBind™ streptavidin beads, which can be used for affinity purification of biotin labeled molecules, were evaluated in three serum pools in attempts to reverse the interferences observed. To remove the MagnaBind Beads from the suspension, an external magnetic field is used. The beads were washed three times with PBS and 70 µl of MagnaBind™ Streptavidin beads were added to serum samples and incubated on a shaker at room temperature for 1 hour. Four conditions were evaluated and compared, original sample with or without biotin and with or without Streptavidin bead treatment.

Results: No significant difference was observed for free T4 or iPTH after biotin treatment at all concentrations. However, significant differences (>10%) were observed for troponin with concentrations greater than 50 ng/mL in all 5 serum pools. At 100 ng/mL biotin, concentrations were decreased up to 90%. In the 18 individual patient samples with troponin levels right above the 99th percentile (0.05-27 ng/mL), 14 samples dropped to below the 99th percentile after addition of 100 ng/ml biotin. The MagnaBind™ streptavidin beads successfully reversed the biotin interference.

Conclusions: This study verified that the TRPI assay is sensitive to biotin interference. The magnitude of interference could have a potential clinical impact on patients taking biotin supplements. It highlights the importance of laboratory, physician, and patient awareness of potential biotin interference in immunoassays.

A-077

Plasma kynurenine predicts severity of heart failure and associates with established biochemical and clinical markers of disease

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Background: Kynurenine (KYN) is a metabolite of tryptophan (TRP) produced by the enzyme indoleamine 2,3-dioxygenase. Apart from exerting effects on neuro-regulation and cancer immunology, KYN and its metabolites impact on vascular inflammation, endothelial integrity, and oxidative stress. KYN or the KYN-TRP ratio have recently been suggested to predict cardiovascular prognosis, particularly in coronary artery disease (CAD). Data on chronic heart failure (CHF) are scarce. **Methods:** In 114 patients with diastolic or systolic CHF, we investigated a possible relation between KYN and CHF severity. KYN was determined using an ELISA (Neuroimmun GmbH and Immundiagnostik).

Results: Baseline KYN increased with NYHA class ($p < 0.001$) and was significantly higher in deceased versus survivors ($p = 0.01$). The discrimination between dead and alive by KYN (ROC AUC 0.70) was at least comparable to that afforded by NT-proBNP (AUC 0.66). In bivariate logistic regression, KYN was a significant predictor of death (OR 1.44 [1.03 - 2.00]) as opposed to NT-proBNP (OR 1.00). In univariate analyses, KYN associated negatively with left ventricular ejection fraction (Pearson's $r = -0.33$, $p < 0.001$), estimated GFR (Pearson's $r = -0.61$, $p < 0.001$), as well as peak oxygen uptake during exercise (subgroup of patients only) (Pearson's $r = -0.64$, $p = 0.004$); and positively with NT-proBNP (Pearson's $r = 0.52$, $p < 0.001$).**Conclusion:** This is one of the first reports to show that KYN reflects the severity of CHF and has predictive power therein. KYN furthermore associates with established markers of clinical severity, such as renal function, exercise capacity, NT-proBNP, and systolic function.

A-078

Development of immunoassay for the high sensitive measurement of cardiac Troponin I for LUMIPULSE® *G* systems

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Background: Troponin I is a subunit of the troponin (Tn) complex, which is a heteromeric protein bound to the skeletal and cardiac muscle thin filaments. The cardiac troponin I (cTnI) is expressed exclusively in heart. Normal cTnI levels in blood are very low and increase substantially with heart muscle damage. They start to rise within an hour after the onset of acute myocardial infarction (AMI), peak at approximately 24 hours and return to baseline over 7 to 10 days. Current high sensitive cTnI assays are able to detect elevated levels of cTnI within 1 to 3 hours after the onset of chest pain. Given the improved sensitivity, the longer diagnostic window and tissue-specificity, cTnI is the preferred biomarker for the detection of myocardial necrosis compared to other available biomarkers. We have developed a fully automated chemiluminescence enzyme immunoassay (CLEIA) for LUMIPULSE G systems (LUMIPULSE G1200 and LUMIPULSE G600II) for the quantitative and high sensitive measurement of cTnI. In this study, the analytical characteristics of the new Lumipulse G hs Troponin I assay were evaluated.

Methods: High-sensitivity cTnI assay for LUMIPULSE is a two-step sandwich CLEIA as a principal. The resulting reaction signals are derived within 30 minutes/test, and are proportional to the amount of cTnI in the serum or plasma sample allowing quantitative determination of cTnI. Analytical performances of the assay were evaluated on LUMIPULSE G1200 according CLSI guidelines.

Results: The detection limit (LoD) of the assay was 1.9 pg/mL, and the cTnI concentration corresponding to a total CV of 10% was 7.3 pg/mL (LoQ). Linearity was demonstrated over the range 1.0 to 43,098.1 pg/mL. The assay did not exhibit cross reactivity to cardiac TnT, cardiac TnC, skeletal TnI or skeletal TnT, and was not affected by various interferences in blood (bilirubin, hemoglobin, triglycerides, chyle, total protein, rheumatoid factor or HAMA). The assay's total imprecision was ≤ 7.2% CV. The correlation coefficient and the regression slope between serum and plasma (Li heparin, K2 EDTA or Na citrate) samples were 1.00 and ≥ 0.90 (0.96, 0.90 or 0.98), respectively. The estimated 99th percentile URL in serum for a healthy population were overall 26.9 pg/mL and, 29.4 pg/mL and 21.4 pg/mL in male and female, respectively. The imprecision estimated at the 99th percentile was ≤ 4.6%CV (calculated from the precision profile). The percentage of measurable cTnI values below the 99th percentile and above the LoD (= 2.1 pg/mL used) was 68.1%. The correlation coefficient and the regression slope of Lumipulse G hs Troponin I and ARCHITECT STAT High Sensitive Troponin I (Abbott) were 1.00 and 1.05, respectively (N=63).

Conclusion: The Lumipulse G hs Troponin I assay showed to be sensitive, specific and precise. The performance of the assay met current requirements for a high sensitive assay to be used as an aid in the diagnostics and risk management of acute coronary syndrome patients.

A-079

Hyperuricemia and clustering of cardiovascular risk factors in the Chinese adult population

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Background: Hyperuricemia is common in China and the relevance of hyperuricemia and cardiovascular disease (CVD) risk has been highlighted, but to date there has been no large-scale study for China adults covering different racial populations. The aim of this study was to estimate the current prevalence of hyperuricemia and evaluate the associations between hyperuricemia and cardiovascular risk factors (CRFs) clustering in a large sample of China adults including a plurality of ethnic minorities.

Methods: A cross-sectional survey in a nationally representative sample of 22983 adults aged 18 years and older was conducted from 2007 to 2011. Questionnaire data and information on anthropometric characteristics, and laboratory measurements were collected. Hyperuricemia was defined as SUA ≥ 416 mmol/L for men or SUA ≥ 357 mmol/L for women. Major CRFs including dyslipidemia, hypertension, diabetes, current smoking, and overweight were estimated and clustering of CRFs were analyzed.

Results: The prevalence of hyperuricemia was 13.0% (18.5% in men and 8.0% in women) among adults in China. Overall, hyperuricemic subjects had higher prevalence rates of ≥ 1, ≥ 2 and ≥ 3 CRFs clustering than non-hyperuricemic subjects (80.6%, 49.4% and 21.8% vs. 81.1%, 54.8% and 24.8% in men; 80.6%, 49.4% and 21.8% vs. 58.1%, 27.2% and 8.6% in women). Hyperuricemia is positively associated with dyslipidemia, hypertension and overweight in both men and women. Furthermore, the odd ratio and 95%CI of hyperuricemia with 1, 2 and ≥ 3 CRFs were 1.22(1.03-1.45), 2.03(1.72-2.40) and 3.04(2.57-3.59) for men, and 1.49(1.22-1.83), 2.49(2.01-3.07) and 4.06(3.23-5.11) for women, respectively.

Conclusion: A high prevalence of hyperuricemia and CVD risk factors clustering are common among Chinese adults. Coexistence of more CVD risk factors was associated with significantly increased risk of hyperuricemia and a stronger association of hyperuricemia with CVD risk factors clustering was found in females than in males. Guidance and effective lifestyle intervention are required to prevent hyperuricemia and reduce the cardiovascular disease risk in China.

A-080

Cardiac Troponin I Measured with the Singulex Sgx Clarity™ cTnI Assay: A Step Forward on High Analytical Sensitivity

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Background: High-sensitivity cardiac troponin (hs-cTn) assays measure the 99th reference percentile (p99) value with an appropriate low imprecision. The improved analytical sensitivity of hs-cTn assays permits to observe cTn kinetics in shorter periods than with previous assays. The Sgx cTnI Assay (Singulex Inc., Alameda, CA),

currently for investigational use only, uses the Single Molecule Counting technology for cTnI detection at concentrations otherwise undetectable with previous assays. Aim: We calculated the p99 and evaluated the clinical performance of the Sgx cTnI Assay in chest pain (CP) patients. Methods: The hs-cTnI assay was run on the Sgx Clarity™ System. The limits of blank (LoB) and detection (LoD) were preliminary assessed by the manufacturer to be 0.02 and 0.08 pg/mL, respectively. The limit of quantitation (LoQ) was 0.53 pg/mL at 10% CV and 0.14 pg/mL at 20% CV.The percent hs-cTnI healthy-subject detection was analyzed in 359 self-declared healthy blood donors; those with antecedents of cardiovascular risk factors or diseases were excluded. The p99 was calculated with a non-parametric method. Hs-cTn was measured in 144 CP patients prospectively admitted to our emergency room; patients with ST-elevation myocardial infarction were excluded. Sgx cTnI and hs-cTnT (Roche Diagnostics) were measured at admission (0h) and 1h later. Sgx cTnI concentrations were evaluated using the p99 values obtained in the healthy population. Hs-cTnT concentrations were evaluated using the cutoff values proposed in the 0-1h algorithm of the 2016 European Society of Cardiology (ESC) guidelines. Final diagnoses were adjudicated by two independent physicians. Results: Median age of healthy donors was 47 years (range 18-65 years), 49.9% were female and Sgx cTnI ranged between 0.06 and 10.9 pg/mL. Based on the observed preliminary LoD, Sgx cTnI was detectable in 99.5% of healthy subjects. The p99 of the overall population was 6.74 pg/mL (obtained at 1.8% CV), but sex differences existed: the p99 was 3.35 pg/mL in females (3.1% CV) and 9.24 pg/mL in males (1.34% CV). Median age of CP patients was 70 years (range 26-100) and 63.8% were males. Smoking, hypertension, diabetes, dyslipidemia, and renal dysfunction existed in 17%, 60%, 33%, 58%, and 12% of the patients, respectively. NSTEMI was diagnosed in 10.6% and unstable angina in 4.9% of the cases. Coronary angiography was performed in 14.9% of the patients. At 0-1h, 68% of patients showed Sgx cTnI values below the respective p99, whereas only 54% showed hs-cTnT below the limits proposed in the ESC guideline (p<0.001). Only one patient, ruled out by both assays, was diagnosed with NSTEMI, resulting in a negative predictive value (NPV) of 98.95% for both assays. Conclusions: The Singulex assay measured the cTnI p99 with an extremely low imprecision, was detectable in nearly 100% of healthy donors, although sex differences existed in the p99 values. In patients with CP NSTEMI, the Sgx cTnI Assay increases significantly the proportion of patients showing values below the limits of clinical decision at admission and 1h later, allowing the use of rapid rule-out strategies. Although more clinical studies are required, the Sgx cTnI Assay showed promising features for the evaluation of myocardial injury.

A-081

Carboxy-terminal Fragment of Insulin-like Growth Factor Binding Protein-4 (CT-IGFBP-4). A New Biomarker for Assessing Future Risk in ST-elevation Myocardial Infarction (STEMI)?

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BACKGROUND One of the more life-threatening presentations of acute coronary syndromes (ACS) is the ST-segment elevation myocardial infarction (STEMI). Patients that survive are still at high risk of future cardiovascular events and could take advantage of more refined risk stratification. Pregnancy associated plasma protein-A (PAPP-A) is a matrix-metalloproteinase found in vulnerable atherosclerotic plaques where degrades extracellular matrix and cleaves IGFBP-4 into its amino- and carboxy-terminal fragments. PAPP-A was originally proposed as a prognostic biomarker of major adverse cardiac events (MACE) in STEMI, but its measurement is affected by several physiological and methodological factors and its usefulness as a biomarker of ACS has been questioned. Recently, it has been proposed that circulating IGFBP-4 fragments concentration could reflect the atherosclerotic plaque destabilization caused by PAPP-A. **AIM** To investigate whether CT-IGFBP-4 values measured at admission in STEMI patients could add value to or complement the prognostic role of the currently used variables. **METHODS** We evaluated 236 STEMI patients admitted in our hospital. CT-IGFBP-4 concentrations were measured with a research-use-only enzyme-linked immunosorbent assay (Mercodia, Uppsala, SW) in EDTA-plasma aliquots obtained at admission and stored at -80 ºC. Future risk of MACE was clinically calculated at admission with GRACE 2.0 (Global Registry of Acute Coronary Events) Risk Score. New non-fatal myocardial infarction (MI), need of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) after discharge and cardiovascular death during hospital stay or follow-up were registered as MACE up to 6-months after discharge. **RESULTS** Mean age was 65 years and 25.3% of cases were female, 51.7% were Killip > 1 and 68 patients (25.7%) were Killip IV. In-hospital all-cause mortality was 12.5 % (33 patients), increasing to 15.8% (42 patients) at 6 months. 52 MACE [27 cardiovascular death (23 in-hospital), 10 MI, 14 PCI, 1 CABG] were registered after 6-months follow-up. Age, gender, antecedents of diabetes and renal disease, Killip class, GRACE risk score, high sensitivity troponin T, NT-proBNP and LDL cholesterol differed between patients with and without MACE (p<0.05) meanwhile antecedents of hypertension, dyslipidemia, smoking habit or IMC did not differed. The ability of CT-IGFBP-4 to predict MACE was investigated by area under ROC curves (AUC) analysis. CT-IGFBP-4 was a predictor of MACE [AUC 0.666 (95% CI 0.576-0.755; p=0.001)]. CT-IGFBP-4 cutoff that best discriminated patients with and without MACE was ≥62 µg/L. Kaplan-Meier survival curves for MACE showed that patients above the cutoff had higher event rate (log rank 16.683; p=0.001). CT-IGFBP-4 concentrations ≥62 µg/L were associated with an increased risk of future MACE [Hazard ratio (HR) = 3.03 (95% CI, 1.73-5.31), p=0.001]. After adjusting the model for the GRACE Risk Score 2.0, CT-IGFBP-4 concentrations were still associated with increased risk of MACE [HR= 1.96 (95% CI. 1.09-3.54); p=0.02]. **CONCLUSIONS** In STEMI patients, CT-IGFBP-4 concentrations ≥62 µg/L were associated with a 3 times higher risk of MACE during hospital stay or 6-months follow-up and added value to the risk stratification provided by the GRACE 2.0 score. If confirmed in other studies, CT-IGFBP-4 at admission could help to further stratify the future risk of STEMI patients.

A-082

Analytical performance characteristics of the Sgx Clarity™ cTnI Assay from Singulex for the detection of cardiac troponin I

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Background: More precise tools for early detection and rule-out of coronary artery disease (CAD) and acute myocardial infarction (AMI) would avoid unnecessary diagnostics, reduce healthcare costs, and improve patient care. Cardiac troponins I (cTnI) and T (cTnT) are used in the management of suspected AMI and have been associated with risk of future CVD. The Sgx Clarity™ cTnI Assay (Singulex Inc., Alameda, CA) is a novel high-sensitivity Single Molecule Counting immunoassay currently for investigational use only. It is a fully-automated, quantitative, fluorescent, one-step sandwich immunoassay, currently in development for the Sgx Clarity system. Here, we report analytical performance characteristics of the assay for the detection of cTnI in plasma.

Objective: To evaluate the limit of blank (LoB), detection (LoD), and quantification (LoQ/ functional sensitivity), and precision of the Sgx Clarity cTnI Assay using EDTA plasma in a multisite study.

Methods: LoB and LoD was estimated by testing four blank samples and four samples with low cTnI values, respectively, in replicates of five on each day of testing over three days for each of two reagent lots. LoQ was estimated by testing ten samples with low cTnI values in replicates of four over three days on one instrument and two reagents lots, following CLSI guidelines. LoB, LoD, and LoQ were measured at Singulex.

Test panels in various cTnI concentrations were generated to perform and compare testing for functional sensitivity and precision across multiple external sites. Functional sensitivity was measured by testing ten samples near the LoQ in replicates of four in two runs. Precision was estimated by analysing ten samples across the dynamic range in triplicates in two runs by different operators over five days. Precision and functional sensitivity were evaluated on two external sites (St Pau Hospital Barcelona and St Georges Hospital London). All testing was performed in EDTA plasma.

Results: LoB and LoD for the Sgx Clarity cTnI Assay was preliminary assessed to be 0.02 and 0.08 pg/mL, respectively. LoQ was estimated to be 0.14 pg/mL at 20% CV and 0.53 pg/mL at 10% CV. Observed precision was 4.0% - 9.6% and 2.7% - 10.7%, respectively. Functional sensitivity was 0.36 and 0.31 pg/mL at 20% CV and 0.82 and 0.71 pg/mL at 10% CV, respectively.

Conclusions: The Sgx Clarity cTnI Assay has high and reproducible analytical sensitivity and precision for the detection of cTnI in plasma, and the assay allows for reliable measurements of very low analyte concentrations. The Sgx Clarity cTnI Assay also provides high-sensitivity cTnI detection that has the potential to provide a paradigm change in the diagnosis and risk stratification of AMI and CAD.

A-083

Sex Specific Versus Overall 99th Percentile Upper Reference Limits For The Diagnosis Of Acute Myocardial Infarction Using A High Sensitivity Cardiac Troponin I Assay

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Background: Analytical differences in cardiac troponin (cTn) concentrations exist between sexes when measured by high sensitivity assays, with men having higher 99th percentiles than women. However, while analytical differences exist, whether the use of sex-specific vs. overall 99th percentile translates to different clinical outcomes remains uncertain. Our goal was to compare the diagnostic performance of a high-sensitivity (hs) cTnI assay using sex-specific vs. overall 99th percentiles for the diagnosis of acute myocardial infarction (MI). **Methods:** Consecutive patients presenting to the emergency department with serial cTnI measurements (0/3/6/9h) on clinical indication (UTROPIA, NCT02060760) using an investigational hs-cTnI assay (Abbott, 99th percentiles upper reference limits (URL): overall 26 ng/L; female 16 ng/L; male 34 ng/L) were enrolled. Diagnostic accuracy statistics were compared using sex-specific vs. overall 99th percentiles for diagnosing acute MI. **Results:** Acute MI occurred in 170 (10.4%) patients. Using the overall 26 ng/L URL for both genders (n=1631), diagnostic indictors at 0, 3, 6, and 9 h were as follows: sensitivities - 64.1%, 89.9%, 90.5%, and 89.8%, respectively; specificities - 88.0%, 87.7%, 84.8%, 84.6%, respectively. Conversely, using sex-specific URLs diagnostic indictors at 0, 3, 6, and 9 h were as follows: males (34 ng/L) only (n=911, sensitivities - 62.3%, 94.4%, 95.3%, and 95.6%, respectively; specificities - 89.2%,88.7%, 85.5%, 86.0%, respectively; females (16 ng/L) only (n=720), sensitivities - 70.5%, 92.7%, 92.0%, and 93.2%, respectively; specificities - 83.7%,82.0%, 81.3%, 81.4 %, respectively; **Conclusions:** The use of sex-specific 99th percentiles for high sensitivity cTnI improved the diagnostic sensitivity for acute MI compared to the overall 99th percentile.

A-085

Comparison of two POC cTnI Assays with High-Senstivity cTnI and cTnT Assays in a 0, 1 and 3 Hour Algorithm in the Diagnosis of Myocardial Infarction

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Background

There is a clinical need to rapid rule out or rule in AMI in patients admitted with chest pain to the ED or CPU. LSIM Corporation, Tokyo offers two POC cTnI assays which are identical except the standardization by using different concentrations of the NIST standard SRM 2921. Measurement ranges, reference intervals and 99th percentile upper reference limits (URLs) are different between both assays. First evaluation studies demonstrated that the assays might meet the criteria for high-sensitivity cardiac troponin assays (imprecision at the 99th percentile URL CV < 10%, quantifiable values below the URL > 50%, 99th percentile cutoffs in males higher than in females).

Objective

We thought to determine the analytical criteria of both POC assays and to examine the diagnostic validity in a 0, 1 and 3 hour algorithm in the diagnosis of myocardial infarction (MI) in comparison with established high-sensitivity cTn assays.

Methods

cTn values were measured by using the POC cTnI assys in plasma samples obtained from selected patients admitted with chest pain (n = 95, age 22-94 years, males 67%) at 0, 1 and 3 hours. Additionally, hs-cTnT (Roche Diagnostics) and hs-cTnI (Architect STAT, Abbott Laboratories) were measured for comparison. To examine the diagnostic validity of the POC cTnI methods the dichotomized cTn values were compared by cross table evaluation. The discriminative power between myocardial infarction rule-out and rule-in diagnosis was examined by ROC analysis at 0, 1 and 3 hours. The 99th percentile URLs of the POC cTnI methods were established using the cTnI values obtained in a normal healthy population of 474 individuals.

Results

According to CLSI C28-A3 the 99th percentiles URLs of 15.5 (males 16.9, females 11.5) and 27.5 (males 31.3, females 24.9) ng/L (females n=236, males n=238) were obtained for the POC cTnI assays A and B, respectively. Additionally, the limits of detection (LoD) of the POC cTnI assays A and B were estimated with 1.0 ng/L and 1.75 ng/L. The cross table comparison of the POC cTnI assays A and B with the hs-cTn assays revealed proportions of individuals getting the same classification for both POC cTnI assays of 95, 94% at 0 h, 92, 94% at 1 h and 93, 96 % at 3 h. ROC analysis for discrimination between patients with rule-out and rule-in diagnosis of MI revealed AUC values of 0.879, 0.908 for the POC cTnI asssays and 0.826, 0.842 for hs-cTnI and hs-cTnT at 0h compared to 0.914, 0.927 and 0.916, 0.885 at 1h and 0.951, 0.952 and 0.945, 0.913 at 3 h, respectively.

Conclusion

The results demonstrated comparable diagnostic validity of the POC cTnI assays in comparison with the high-sensitivity assays Abbott cTnI and Roche cTnT. Thus, both POC cTnI-II assays can be used in the chest pain unit in parallel with the hs-cTnI and hs-cTnT assays in the central laboratory without the risk of misinterpretation of the results. The different standardization of the POC cTnI assays resulted in different analytical criteria. Further investigation should identify the most advantageous standardization method.

A-086

Evaluation of POC Troponin I Assays on Alere Triage and Abbott iSTAT and Their Comparison to Abbott Architect High Sensitivity Troponin I Assay

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Objectives: To evaluate the precision of Point of Care (POC) Troponin I (TnI) assay on the Alere Triage and the Abbott iSTAT as well as the accuracy of each of these platforms compared to the Architect High Sensitivity Troponin I (hs-TnI) as the reference assay.

Methods: Venous whole blood (WB) was collected in Lithium Heparinized (LH) tubes. A patient sample pool was used to establish within run imprecision (20 replicates). Day-to- day precision was examined using the vendor's control materials (N=10). The Architect hs-TnI was used as the reference assay, against which the two POC devices were compared "head to head" using fresh LH patient samples (N=40). Both EDTA and LH WB samples were also run in parallel for comparison of TnI results on the Triage.

Results: A Coefficient of Variation (CV) of 20.3% at a mean value of 18 ng/L (one outlier <10 ng/L, the detection limit of the device) was obtained with the Triage and a CV of 19.7 % at a mean value of 35 ng/L with the iSTAT using the same patient pool. A mean value of 28.4ng/L was obtained for this patient pool using the Architect hs-TnI assay. As shown in the Table below, the iSTAT yielded a closer agreement with the reference method with a much lower positive bias at the proposed 99th percentile of the latter while the Triage gave a much higher negative bias. TnI results from the Triage with LH WB were more comparable to the reference assay than those obtained with EDTA samples.

Conclusions: The two POC devices overall have comparable precision. The iSTAT showed a better agreement with Architect hs-TnI assay at the clinical decision cutoff value. Additionally, LH WB is suitable, if not superior to EDTA, for Triage TnI analysis.

Sample	Method	Passing & Bablok fit	% bias at 99th tile (26.2 ng/L)	N	Mean ± SD (ng/L)	Mean Bias	% Bias at the Mean	Data Range (ng/L) and N of samples <10 ng/L
Plasma (LH)	Reference method (Architect i1000)	na	na	40	485 ± 1344	na	na	0.1-7020 (7)
WB (EDTA)	Triage	y= 0.67 x - 0.53	-35.0%	27	473 ± 945	-12	-2.5%	10-3820 (13)
WB (LH)	Triage	y= 0.82 x - 1.87	-25.1%	31	499 ± 1026	14	2.9%	10-4330 (9)
WB (LH)	iStat	y= 0.90 + 1.38	4.7%	34	500 ± 1131	15	3.1%	10- 3520 (6)

A-087

Evaluation of Diagnostic Accuracy of Abbott Architect High Sensitivity Troponin I Assay

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Objectives: To evaluate the diagnostic accuracy of the Abbott high sensitivity troponin I (hs-TnI) assay by comparing it against the Roche high sensitivity troponin T (hs-TnT) assay for acute myocardial infarction (AMI) in patients presenting to the emergency department (ED) with chest pain. **Methods:** Patients presenting to ED with symptoms of potential acute coronary syndrome were studied. Blood was drawn at baseline, 3h, and 6h or more, following presentation. The diagnosis of AMI was adjudicated by cardiologists using clinical information and investigations, including the baseline and follow-up hs-TnT results (e411, Roche). Comparison between the diagnostic accuracies of the hs-TnI (ARCHITECT i1000, Abbott) and the hs-TnT was done using the 99th percentile cutoffs of 26.2 ng/L and 14 ng/L, respectively. The 50 ng/L value for hs-TnT is considered as the 'rule-in' value, above which patients may be considered for triage. Hence a Passing-Bablok comparison was employed for hs-TnT values of between 25- 75 ng/L (N=75) against their corresponding hs-TnI values to establish the equivalent 'rule-in' value for hs-TnI. The diagnostic efficiency of each of the assays at their defined 'rule-in' cutoff values was then compared. **Results:** 200 pairs of hs-TnI vs. hs-TnT results were obtained; 68 (34%) from females and 132 (66%) from Males. Comparison between hs-TnT at the cutoff 14ng/L and hs- TnI at 26.2 ng/L showed a diagnostic agreement of 68.5%. None of the results that showed an hs-TnI above the relevant cut-off demonstrated an hs-TnT value below its cutoff. However, in the 63 pairs of discrepant results with an elevated hs-TnT but an hs-TnI below the cut-off, there was no evidence of new onset of AMI for these patients based on the assessment by cardiologists. This indicates a higher diagnostic specificity for hs-TnI at the cutoff of 26.2 ng/L to rule out AMI. The Passing-Bablok comparison revealed an AMI 'rule-in' cutoff of 140 ng/L for hs-TnI, as being equivalent to the cutoff of 50 ng/L for hs-TnT. Correlation between the two cutoffs revealed a diagnostic agreement of 83.5% between the two assays. Clinical assessment of the 7 patients who were positive for hs-TnI but negative for hs-TnT demonstrated no evidence of new onset of AMI. Analysis of the 26 pairs of discrepant results that were positive for hs-TnT but negative for hs-TnI revealed only one diagnosis of AMI. Hence using these 'rule-in' cutoffs, hs-TnI showed a12% higher specificity and 2% lower sensitivity for the diagnosis of AMI in the discrepant group compared to hs-TnT. **Conclusions:** hs-TnI assay using the 99th percentile cutoff of 26.2 ng/L showed a better diagnostic specificity than the hs-TnT at 14 ng/L, which improves the AMI rule-out efficiency. AMI 'rule-in' cutoff at 140 ng/L for the hs-TnI also showed a better specificity than that for hs-TnT at 50 ng/L, while it has a comparable diagnostic sensitivity for AMI.

A-088

Elevated CA-125 levels are associated with increased immune activation in coronary sinus blood samples of patients with chronic heart failure

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Background: Heart failure is considered to be a complex syndrome associated with the neurohormonal and cytokine activation, that contribute to its progression. Interestingly, there are evidences which showed that, carbohydrate antigen 125 (CA-125), a tumor marker widely used for ovarian cancer therapy monitoring, was significantly elevated in chronic heart failure (CHF) patients. Previous studies have found that CA-125 could be produced by mesothelial cells as a consequence of fluid overload/serosal effusions and/or inflammation, but the precise mechanisms leading to CA-125 elevation in CHF are still unknown. We hypothesized that increased chronic left ventricular filling pressure, inflammation and cytokine stimulation may be responsible for CA-125 production and release. The aim of the study was to investigate the serum levels of CA-125, N-terminal pro-brain natriuretic peptide (NT-proBNP), interleukins IL-1β, IL-6, IL-8, IL-4 and tumor necrosis factor-alpha (TNF-α) from peripheral venous blood (PVB) and coronary sinus blood (CSB) samples in patients with CHF during cardiac resynchronization therapy (CRT).

Methods: Twenty-seven patients (15M/12F) with CHF (III-IV NYHA functional class) implanted with a biventricular pacemaker/defibrillator and 40 healthy controls (23 M/17 F) were investigated. PVB samples were collected at baseline and 1 week, 3 months after CRT device implantation and CSB samples during CRT. Cardiac function was assessed echocardiographically.

Results: Median serum concentrations of NT-proBNP, CA-125, IL-1β and IL-6 have been found to be significantly higher in the CS than in periphery (1392 pmol/L vs. 1156 pmol/L; 82.4 IU/mL vs. 48.6 IU/mL; 21.4 pg/mL vs. 7 pg/mL and 112 pg/mL vs. 51 pg/mL, all P<0.001). In the CS, CA-125 inversely correlated with left ventricular ejection fraction (LVEF) (r= - 0.49, P<0.001) and positively with NT-proBNP (r=0.60, P=0.001), IL-6 (r=0.36, P=0.003), IL-1β (r=0.40, P=0.001). CRT induced significant improvement in the NYHA class (baseline 3.2±0.5 vs. 1.4±0.6 at 3 months, P=0.002), NT-proBNP (baseline PVB: 1160 pmol/L vs. 353 pmol/L at 3 months, P<0.001) and CA-125 (baseline PVB: 48.6 IU/mL vs. 14.2 IU/mL at 3 months, P=0.001). Throught the monitoring period, CA-125 was inversely correlated with LVEF increase (r= -0.67, P<0.001) and positively, with left ventricular end-systolic volume (LVESV) and NT-proBNP reduction (r=0.40 and r=0.47, P<0.001).

Conclusion: More localized interactions within the heart may be better studied from sinus coronary blood samples. Our findings indicate that the heart secretes CA-125, which is also present in peripheral venous serum in patients with CHF. Higher CA-125 concentrations in the CS than in periphery demonstrate that inflammation and cytokine stimulation, especially increased IL-6 and IL-1β, are responsible for CA-125 production and release. More than that, because CA-125 serum levels are associated with severity of HF, it can be used as a biomarker for monitoring and guiding therapy in these subjects.

A-089

Sex-Specific 99th Percentile Cardiac Troponin Normal Limits with the Medience PATHFAST Point-of-Care Cardiac Biomarker Analyzer

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Objectives: Primary: To determine sex-specific 99th percentile normal cutoffs for cardiac troponin (cTn) I and the proportion of normal samples detectable with the PATHFAST Point of Care (POC) analyzer using a sufficiently powered normal healthy population. Secondary: Evaluate the assay's classification as contemporary or high-sensitivity.

Relevance: cTn is the cornerstone for diagnosis of myocardial infarction (MI) and detection of cardiac injury. Use of POC cTnI measurements can result in earlier rule-out/rule-in decisions for acute MI. However the diagnostic sensitivity and analytic parameters among POC systems vary substantially so each must be characterized near the 99th percentile cutoff.

Methods: The PATHFAST cTnI-II system (LSI Medience) was used for all cTnI measurements. The system's limit of detection (LoD) was 2.3 ng/L and the concentrations above 19 ng/L have CVs< 10%. EDTA specimens from the AACC Sample Bank were used for determining sex-specific 99th percentile cutoffs. Exclusion criteria were subjects without sample, race, sex or birthdate information, and subjects having NTproBNP>300ng/L, eGFR<60 ml/min and HbA1c≥6.5%.

Results: Data are displayed in the table below.

	Overall	Female	Male	No Sample/ Age/ Sex/ Race
Total AACC Sample Bank	897	428	450	19
Number excluded from Sample Bank	73	19	35	19
Normal Healthy Population	824	409 (49.7%)	415 (50.3%)	
# of normal healthy population > LoD	418	155	263	
99th percentile Cutoff	24.8 ng/L	20.7 ng/L	26.4 ng/L	
% of normal healthy population > LOD	50.7%	37.9%	63.4%	

The PATHFAST cTnI-II system yielded detectable results for 50.7% of a sex-balanced normal healthy population. Of the 897 total subjects from the AACC Sample Bank 19 had no sample/age/sex/race available; 35 males and 19 females did not meet NT-proBNP/creatinine/HbA1C criteria. The final normal healthy population consisted of 415 males and 409 females.

Conclusion: The sex-specific 99th percentile cutoffs for females was 20.7ng/L and for males was 26.4ng/L for the PATHFAST TnI-II POC system. Consistent with the current IFCC TF-CB definition of high-sensitivity cTn assays, the PATHFAST detected >50% of the normal healthy population above the assay's LoD, and the CV is <10% at the 99th percentile cutoff.

A-090

Circulating VCAM-1 as potential biomarker of atherosclerosis

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Background: Adhesion molecules such a vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and selectins play an important role in the development of atherosclerosis, which is the primary origin of most common cardiovascular disorders. ICAM-1 facilitates monocyte/macrophage emigration and adherence to endothelial cells, whereas VCAM-1 facilitates macrophage uptake into the subintimal space. E-selectin is involved in the tethering, rolling, and activation of leukocytes. Together, these molecules form an integrated and overlapping system for the transport of leukocytes and recruitment of additional cytokines, growth factors and matrix metalloproteinases into the vascular wall. Matrix metalloproteinases provokes disruption of atherosclerotic plaques and participates in the degradation of the extracellular matrix, which may lead to acute cardiovascular events. In a search for molecules that complement invasive atherosclerotic disease diagnostic techniques, the present study aimed to investigate the relationships among VCAM-1, ICAM-1, E-selectin and matrix metalloproteinase 9 (MMP9) serum concentrations and the extent of coronary lesion. **Methods:** Seventy-four male and female individuals aged between 30 to 74 years who were undergoing coronary angiography for diagnostic purposes were enrolled in this study. Morning fasting blood samples were obtained for analysis of biochemical parameters (glucose, total cholesterol and fractions, urea, creatinine K, uric acid, alanine aminotransferase and aspartate aminotransferase) and for the determination of VCAM-1, ICAM-1, E-selectin and MMP9 serum concentrations. Biochemical tests were performed using colorimetric and colorimetric-enzymatic methods on a semi-automatic biochemical analyzer, and serum concentrations of the adhesion molecules and MMP9 were quantified using The Millipex® MAP Human CVD Panel 1 Immunoassay Kit, according to the manufacturer's instructions. The extent of the coronary lesion was assessed using the Friesinger Index and subjects were classified in four groups: no lesion, minor lesion, intermediate lesion and major lesion. **Results:** Significant differences in the clinical and biochemical data were not found among the groups. The VCAM-1 serum concentration was higher than 876 ng/mL in individuals with intermediate and major lesions ($p < 0.001$ and $p = 0.020$, respectively). Moreover, logistic regression analysis showed that these patients had an increased risk of having an intermediate lesion (odds ratio (OR): 9.818, 95% confidence interval (CI): 1.840-52.384, $p = 0.007$). Interestingly, all individuals with major lesions had VCAM-1 concentrations higher than 876 ng/mL. No association was found between the serum concentrations of the other proteins and the Friesinger Index. **Conclusion:** Therefore, circulating VCAM-1 may be strongly associated with the presence and extent of coronary lesions. Further investigation is needed to consider whether monitoring the VCAM-1 serum level would be valuable for the assessment of cardiovascular risk.

A-091

Genetic Diagnosis of Monogenic or Polygenic Familial Hypercholesterolemia in Northern Ireland: Evaluation of the Randox FH Arrays in Combination with the Randox 6SNP Polygenic Hypercholesterolemia Array

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Background Familial Hypercholesterolemia (FH) is a common genetic disorder characterised by elevated LDL-C and early onset coronary heart disease. The condition is primarily monogenic caused by a single mutation in 1 of 3 genes (LDLR, APOB or PCSK9) with a prevalence of 0.2-0.5%. Despite its commonality, FH is highly underdiagnosed in most countries (<10%). With a clinical diagnosis of 'possible FH', 60% of patients are mutation-negative and may have polygenic hypercholesterolemia, most likely due to an accumulation of common small-effect LDL-C raising alleles. The aim of this study was to determine the effectiveness of the Randox FH Arrays for monogenic mutation detection and the 6SNP Polygenic Hypercholesterolemia Array (Randox Laboratories Ltd. Crumlin, UK) to identify possible polygenic hypercholesterolemia. **Methods** A total of 414 cases of 'possible FH' based on Simon Broome criteria, were selected for analysis. Mutation analysis for monogenic FH was carried out by Sanger sequencing or with the FH Arrays which permit detection of the 40 most common monogenic mutations associated with FH in the UK and Ireland. 6SNP genotyping was conducted by Sanger sequencing and the results used to validate the 6SNP Polygenic Hypercholesterolemia Array. This panel permits genotyping of six SNPS associated with raised LDL-C values that occur across five genes (APOE: rs7412, rs429358, APOB: rs1367117, ABCG8: rs6544713, CELSR2: rs629301 and LDLR: rs6511720). A weighted LDL-C Genetic Risk Score (GRS) was calculated for all 414 possible FH cases. **Results** A definite monogenic FH diagnosis (mutation positive) was confirmed in 196 cases, the FH Array panel detects 72% of the point mutations identified, and the remaining 218 clinically 'possible FH' cases were mutation negative. The mean LDL-C GRS for the mutation positive group was 0.705 but this value was significantly higher in the mutation negative group with a mean LDL-C GRS of 0.777 [p<0.001]. Mutation negative patients had 2.3 times the odds of having a LDL-C GRS exceeding 0.81 than mutation positive patients, thus increasing the chance of polygenic hypercholesterolemia. **Conclusion** The FH Arrays and 6SNP Polygenic Hypercholesterolemia Array successfully genotyped a subset of the Northern Irish population deemed clinically to have 'possible FH'. Recent literature concludes that the LDL-C GRS consistently distinguishes mutation negative patients from healthy individuals and that a high proportion of mutation negative patients are likely to have a polygenic basis to their condition (Futema *et al*, 2015). This combined approach of using the Randox FH Arrays and the 6SNP Polygenic Hypercholesterolemia Array can be used to define patients affected with monogenic FH and likely polygenic hypercholesterolemia and assist with clinical management decisions. The approach may reduce the need for further comprehensive DNA sequencing in many patients and negate the use of family cascade screening. This combined method has the potential to improve the management and treatment of patients with hypercholesterolemia.

A-092

Prognostic value of copeptin on adverse clinical outcomes after successful percutaneous coronary intervention in patients with acute myocardial infarction

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Background: Copeptin has been demonstrated to be of utility in early risk stratification and prognostication of acute myocardial infarction (AMI) patients. However, it is uncertain about the prognostic role of copeptin measured right after successful percutaneous coronary intervention (PCI) in patients with AMI. We aimed to evaluate the association between blood copeptin levels immediately after successful PCI and major adverse cardiac events (MACE) in patients with AMI.

Methods: We enrolled 149 patients with AMI who successfully received PCI with or without coronary stenting in the Chonnam National University Hospital between February 2013 and December 2014. Serum copeptin levels were analyzed using a time-resolved amplified cryptate emission immunoassay (Thermo Fisher Scientific Clinical Diagnositics BRAHMS GmbH, Germany) from blood samples taken from enrolled patients immediately after successful PCI. We examined the associations of serum copeptin levels with incidence of major adverse cardiac events (MACE; composite of death, repeat PCI, recurrent MI or coronary artery bypass grafting) during follow-up period.

Results: The serum copeptin was analyzed in total 149 patients (ST-segment elevation myocardial infarction [STEMI] 40 and NSTEMI 109 patients). Of 149 patients, MACE occurred in 34 patients (22.8%) during a median follow-up of 30.1 months (IQR, 22.9-36.8 months). Although the area under the receiver operating curve for copeptin (0.631) was not large for the prediction of MACE, the copeptin levels (mean ± SD) were higher in patients with MACE than those without MACE (40.7 ± 95.4 pmol/L versus 180.6 ± 396.6 pmol/L, P=0.049). Because copeptin level exhibited a right skewed distribution, the data were subjected to a natural log transformation. In a multiple logistic regression model, a e-fold (approximately 2.71828) increase in copeptin level was associated with an odds ratio for MACE of 1.6 (95% CI, 1.15-2.20, P=0.005) after adjusting confounding variables (age,

diabetes mellitus, previous PCI history, low density lipoprotein-cholesterol and high sensitivity CRP). The MACE-free survival of patients with high copeptin levels was significantly shorter than that of patients with low copeptin level (P=0.045).

Conclusions: High concentration of copeptin measured immediately after successful PCI was associated with MACE in patients with AMI during long-term clinical

follow-up. It suggests that copeptin can be served as a prognostic marker for risk stratification improvement in patients with AMI after successful PCI.

Key Words: Copeptin, Major adverse cardiac events, Percutaneous coronary intervention

A-093

miRNAs as potential biomarkers for new-onset fibrillation: *in silico* and *in vivo* analysis.

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Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. The AF diagnostic methods are given by electrocardiogram (ECG) and Holter for 24hrs, and considering this limitation, some non-coding RNAs (miRNAs) have been involved in regulatory activity in arrhythmogenesis, targeting genes that contribute to the development of AF. However, the role of these non-coding RNAs (miRNAs) as a circulating biomarker for diagnosis of atrial fibrillation is not well reported. Therefore, the objective of this study was to evaluate the expression of miRNAs of patients with AF, new-onset AF and its application as biomarkers, as well as to search for interactions of target miRNAs with mRNAs and cardiovascular processes that may involve AF.

Methods: In the *In Vivo* study, Six miRNAs miR-21, miR-133a, miR-133b, miR-150, miR-328 and miR-499 were selected as targets in this study. They were isolated from plasma of individuals aged from 20 to 85 years old with AF (n = 17), new-onset AF (n = 5) and without AF (n = 15). The results were analyzed by Real-Time PCR (RT-PCR) with *miScript SYBR Green PCR*. An *In Silico* study was carried out to search for potential miRNA targets differentially expressed in the *In Vivo* study, correlating with the top 30 mRNAs targets of these miRNAs by the *Target Scan 7.1* tool, and then integrative analysis through the *Ingenuity Pathway Analyses* 6 (IPA) software, seeking interactions miRNA-mRNA-cardiovascular process.

Results: *In vivo* data, we observed that miR-21, miR-133b, miR-328 and miR-499 had a different level of expression between the three groups ($p < 0.05$). There was increase expression of miR-21 (0.6-fold), miR-133b (1.4-fold), miR-328 (2.0-fold) and miR-499 (2.3-fold) in patients with new-onset AF, when compared to AF and control subjects. The miR-133a and miR-150 expression did not differ among the groups. In silico data, the miRNA-mRNA interactions showed 14 mRNAs regulated by the miRNAs miR-21, miR-133 and miR-499 and observed the association of these miRNAs in different pathophysiological processes that may trigger or be a consequence of AF. We also observed that of the 14 mRNAs, 10 were related to cardiac pathophysiological processes and of these, 3 (SMAD7, FASLG and TIMP3) are directly related to the pathophysiology of AF, acting in the processes of atrial apoptosis and atrial fibrosis.

Conclusion: Our data suggest that miR-21, miR-133b, miR-328 and miR-499 may be potential biomarkers for AF as well as for new-onset AF, for monitoring and for the diagnosis. These miRNAs have also demonstrated important association with several cardiovascular pathophysiological processes, regulating different mRNAs that are expressed in these conditions and these findings may contribute to the understanding of the process that triggers AF outcome, encouraging the development of new studies to evaluate the application of these molecules as future clinical markers for this disease.

A-094

TREML4 polymorphisms and mRNA expression in blood leukocytes are associated with the extension of the atherosclerotic lesions in patients with coronary artery disease

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Cardiovascular disease (CVD) is the leading cause of death and morbidity in developed and developing countries. The discovery of novel circulating biomarkers involved in the pathophysiology of the atherosclerosis may contribute to evaluate the cardiovascular risk. In a microarray based gene expression study, we observed that the expression of the receptor *Trem-like transcript 4* (*TREML4*) in blood leukocytes mRNA was increased in patients with acute coronary syndrome (ACS). It is likely that TREML4 is involved in the atherosclerosis process, and it may have an innovative potential as a biomarker of cardiovascular risk. We investigated the association of *TREML4* polymorphisms and mRNA expression in blood leukocytes with the extension of the atherosclerotic lesions in CAD patients without ACS.

One hundred and fifty one CAD patients aged 30 to 74 years old, submitted to the first coronary angiography were enrolled in this study. The extension of coronary artery lesion was assessed by the Friesinger index. Subjects were stratified in fuor group. Peripheral blood samples were obtained before coronary angiography. Blood samples were used for biochemical analysis, DNA extraction and isolation of leukocyte. Total RNA was extracted from leukocytes using RiboPureTM Blood kit. DNA synthesis was performed using High Capacity cDNA Reverse Transcription Kit. *TREML4* mRNA expression was analyzed by real time PCR (qPCR). The reference gene selected was *ACTB*. Genomic DNA was isolated using the QIAamp DNA Blood Mini Kit. *TREML4* polymorphisms rs2803495 (A>G) and rs2803496 (C>T) were genotyped by real time PCR using the TaqMan SNP Genotyping Assays and the 7500 Fast Real-Time PCR System.

Patients with intermediate and major artery lesions had greater age when compared to those without lesion ($p=0.002$ and $p=0.001$, respectively). Subjects with intermediate lesions had higher systolic pressure than those without lesion ($p=0.01$) and low lesion patients presented higher body mass index than those without lesion ($p=0.02$). Other clinical variables and the biochemical parameters did not differ among the groups ($p>0.05$). Subjects carrying rs2803495 G allele (AG+GG genotypes) are more likely to be *TREML4* expressors than AA genotype carriers (OR= 2.4, 95%CI= 1.0-5.7, $p<0.05$). However rs2803495 variant was not associated with the degree of *TREML4* mRNA expression ($p>0.05$). Analysis of the *TREML4* rs2803496 variant showed that carriers of C allele (CT+CC genotypes) have high likelihood of being in Expressor group than subjects carrying TT genotype (OR=7.8, 95%CI= 2.9-20.9, $p<0.01$). Moreover C allele was associated with high mRNA expression levels (O.R.=5.1, 95%CI= 1.5-15.6, $p<0.01$). CAD patients with major artery lesions had higher *TREML4* mRNA levels than those with intermediate (1.4-fold) or low (1.2-fold) artery lesions ($p<0.05$). Patients with major artery lesions also expressed 1.4-fold higher the *TREML4* than those without lesion ($p<0.01$). The results of this study suggests that mRNA expression of *TREML4* in leukocytes is influenced by the extension of coronary artery lesion and gene polymorphisms in CAD patients, and therefore the measurement of mRNA levels may be a potential biomarker to evaluate the progression of CAD. However, further investigations are necessary to confirm these results in larger population samples of CAD patients.

A-095

Evaluation of free and complex cardiac troponin I in serial samples of MI patients

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Background: Cardiac troponin (cTn), part of the myofiber complex, is the preferred biomarker for detection of myocardial infarction (MI). It is predominantly present as a complex of three subunits (troponin I, T and C), while ~6-8% is unbound ('free') and presumably located in the cytosol. It has been hypothesized that free troponin can be released by ischemia without cell death. Furthermore, it is thought that during an MI free troponin is released first, after which the structurally bound complex troponin leaks out slowly. If proven, an assay that is able to distinguish between free and complex troponin may become a valuable clinical assay to evaluate timing and severity of cardiac damage, and to distinguish between type 2 MI (ischemia due to a supply/demand imbalance) and type 1 MI (spontaneous event related to the rupture of an atherosclerotic plaque).

Methods: To distinguish free from complex cTnI, we coupled antibody 20C6 (Hytest, Finland), which recognizes complex troponin (IC/TIC) and not the individual subunits, to Dynabeads® magnetic beads. Patients samples or controls, diluted 1:2 with PBS/4% BSA/0.5% Tween-20, were incubated with or without the 20C6-coupled beads. After removal of the beads using a magnet, the samples were measured on a Siemens ADVIA Centaur® analyzer using the TnI-Ultra™ assay. The percentage reduction after bead incubation was then calculated. Up to now we have selected serial troponin samples, which displayed a rise and fall, from three type 1 and twenty-six type 2 MI patients and we are selecting more type 1 MI samples.

Results: Using standards of free and complex (TIC) cTnI, we determined the percentage reduction after incubation with 20C6-coupled beads at multiple cTnI concentrations. When complex or free cTnI was spiked in TnI-free serum at 30, 7.5, 1.88, and 0.47 ng/mL, we observed a reduction in complex cTnI of 95, 94, 95, and 100%, respectively. At low concentrations, however, a significant amount of free cTnI was removed as well (13, 24, 33, and 39%, respectively). So far, we have analyzed

serial samples of 5 patients with a type 2 MI, and one patient with a type 1 MI. With the exception of one sample set, all samples showed a reduction >75%. In one type 2 MI sample, values were reduced between 6.7 and 12.1%. We compared the reduction percentage of the first rising cTnI with the last falling cTnI. The reduction was 75.4±29.8% (average±SD) for the first rising cTnI and 73.5±29.7% for the last falling cTnI (paired *t*-test; p=0.34, n=6). Corresponding cTnI values were 1.25±0.4 and 1.71±1.0 (paired *t*-test; p=0.41, n=6).

Conclusions: In 5 out of 6 samples, the majority of released cTnI was present as complex cTnI. When comparing early vs. late serial samples, there was no significant difference in the percentage of cTnI reduction using 20C6-coupled beads, suggesting the proportion of complex cTnI was similar at both time points. We are currently testing more patient samples and we are working on new methods to directly measure free and complex cTnI.

A-096

Performance Evaluation of the ADVIA Centaur® High Sensitivity Troponin I Assay

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Background: The 2015 European Society of Cardiology guidelines propose algorithms for faster rule-in or rule-out of AMI in patients admitted in the acute care setting and for the management of NSTEMI. High-sensitivity cardiac troponin I assays will more accurately and precisely measure changes in cTnI concentrations in serial draws providing useful data to assist in identifying acute versus chronic cTnI elevations, and acceptable rule-in and rule-out performance within 1 to 3-hours of presentation. This study evaluated the performance of the ADVIA Centaur High Sensitivity Troponin I (TNIH) assay developed for use on the ADVIA Centaur family of immunoassay analyzers.[1] The ADVIA Centaur TNIH assay is a dual-capture sandwich immunoassay using preformed magnetic latex particles, a proprietary acridinium ester for chemiluminescence detection, and three monoclonal antibodies. **Method:** The limit of blank (LoB) and limit of detection (LoD) assessments used three reagent lots on two ADVIA Centaur XP and two ADVIA Centaur XPT Immunoassay Systems for both Lithium Heparin and Serum matrixes following CLSI EP-17A. The 99th percentile cutoff values were established non-parametrically using a well-characterized population of healthy subjects. Clinical correlation of cTnI levels above the 99th percentile to AMI diagnosis as adjudicated by three cardiologists was assessed in all-comer emergency department (ED) subjects in both sample matrixes. **Results:** LoB results ranged from 0.11 to 0.90 ng/L with a typical value of 0.5 ng/L, and LoD results ranged from 1.10 ng/L to 2.21 ng/L (95% confidence interval 1.05 to 2.54 ng/L). The cTnI concentration at 20% CV_{Total} (LoQ) had a pooled value of 2.50 ng/L. The 99th percentile estimated for 2026 apparently healthy volunteers with an equal number of males and females was a gender-combined 48 ng/L. The 99th percentile observed on the Centaur XP and Centaur XPT for females is 37ng/L to 39 ng/L, respectively, for males 57 to 62 ng/L. The percentage of the normal population above 1.10 ng/L ranged from 66% to 80% on the Centaur XP and XPT, respectively. Identical 99th percentiles were obtained with Lithium Heparin plasma and Serum samples. The with-in Lab CV at the 99th percentile at 37 ng/mL was less than 3%. Clinical sensitivity and clinical specificity in pooled-genders at 1, 2, and 3-hours post-ED presentation ranged from 87.6 to 93.2% and 90.0 to 91.5% respectively. **Conclusion:** The ADVIA Centaur TNIH assay under development has a 10% total CV at a cTnI concentration 10-fold lower than the 99th percentile. This new assay allows the establishment of gender-specific 99th percentile cutoffs and shows acceptable clinical utility in an all-comer ED population. [1] Under development. Not available for sale. The performance characteristics of this device have not been established. Product availability will vary from country to country and will be subject to varying regulatory requirements.

A-097

DIAGNOSTIC PERFORMANCE OF A HIGH SENSITIVITY TROPONIN I ASSAY IN PATIENTS WITH CHEST PAIN

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Background: There are many methodologies available in the market, which use different targets and formats to assembly an assay, and depending on the type of assay and type of antigen used, different results and interpretations could be made. Due to the higher sensitivity and diagnostic accuracy for the detection of Acute Coronary Syndrome (ACS) at presentation and after 1 hour, the time interval to the second cardiac troponin assessment can be shortened with the use of high-sensitivity assays. Hospital Procardiaco is a reference in cardiology in Rio de Janeiro and has well-structured protocols for evaluation of chest pain.

Methods: 137 consecutive samples collected from patients of different ages admitted to the Emergency Department (ED) with chest pain and suspected ACS. The determination of Troponin I in serum samples were initially analyzed with method of high-sensitivity LOCI Cardiac Troponin I using a homogeneous sandwich chemiluminescent immunoassay in the *Dimension EXL 200* (*Siemens*) ® (HS).

Results: Excellent diagnostic accuracy was obtained in patients with a higher probability of pre-testing for ACS and with a shorter time onset of pain with a sensitivity of 71.4%, specificity of 96.8%, positive Likelihood ratio of 22 , 3%, AUROC 0.81 and CI of (0.571-1). For the Rule out of these patients at 1 hour post admission, an excellent result was obtained with sensitivity of 93.8% specificity of 100%, AUROC 0.98 and CI of (0.968-1).

Conclusion: In the present study the population evaluated with the Troponin I HS methodology presented accurate results for the diagnosis of AMI (Rule in) and for the release of the patients from ED (Rapid 1-hour Rule out).

A-098

High-sensitivity cardiac troponin I (hs-cTnI) detects postoperative myocardial damage after elective knee or hip replacement

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Background: More than 200 million patients worldwide undergo non-cardiac surgery every year. Despite the benefits of treating disease and improving quality of life, non-cardiac surgery is associated with a risk of vascular complications including myocardial injury (JAMA. 2012; 307:2295). The VINO trial showed that preoperative high sensitivity troponin T (hs-cTnT) levels predicted both postoperative myocardial infarction (MI) and long-term mortality (Am Heart J. 2013;166:325).

Objective: The aim of this study was to examine the change from pre- to post-operative day 2 (POD 2) plasma concentrations of cardiac troponin I (hs-cTnI) among elderly patients undergoing elective knee or hip replacement.

Method: This was an ancillary study to a randomized controlled trial, the Genetics-InFormatics Trial (GIFT) (Pharmacogenomics J. 2012;12:417.). We measured hs-cTnI using the Abbott Architect assay on pre-operative and POD 2 plasma samples from 791 subjects that underwent elective hip or knee replacement. At 26 pg/mL (the overall 99th percentile for this method) the coefficient of variation was 4%. We quantified how many patients had a delta hs-cTnI $\geq$ 10 pg/mL, a common (but conservative) delta for ruling in/out MI at 3 hours in an emergency setting. We also examined whether in patients with a delta hs-cTnI $\geq$ 10 pg/mL, the delta exceeded the short-term biological variability of hs-cTnI (Reference change value = 50 – 60%).

Result: Before surgery, 10/791 patients had hs-cTnI values $\geq$ 26 pg/ml (range 27-217) but only one of these patients exhibited $\geq$ 10 pg/mL delta at POD 2. Ninety-nine patients (12.5%) had a delta $\geq$ 10 pg/ml (range 10 –8901 pg/mL, median 29 pg/mL) rise in hs-cTnI levels at POD 2. Of these, only one had a pre-operative hs-cTnI > 26 pg/mL (99th%). Of the 99 patients with a > 10 pg/dL delta, 60 also had a POD 2 above 26 pg/mL (range 27- 8906 pg/mL, median 62 pg/mL). All but two of the patients with a > 10 pg/mL rise had a percent delta change > 100% (median 992%). Six patients had a clinical diagnosis of MI during this trial.

Conclusion: In this study of elderly patients undergoing elective arthroplasty, 12.5% of patients showed a biologically significant (> 10 pg/mL) rise in hs-cTnI at POD 2. In contrast, <1% of patients had a clinical diagnosis of MI. The clinical significance of the rise in hs-cTnI after elective non-cardiac surgery requires further study.

A-099

Sex-Specific 99th Percentiles Derived from the AACC Universal Sample Bank for the Roche Gen 5 cTnT Assay

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Background: The recent FDA clearance of the Roche Elecsys Troponin T Gen 5 Stat Immunoassay provides 99th percentile upper reference limits (URL) for 1301 apparently healthy adults. The concentrations were: overall 19 ng/L, women 14 ng/L, men 22 ng/L. These concentrations represent a substantial shift from their overall 14 ng/L (no sex-specific URLs) used internationally. The purpose of our study was to determine the overall and sex-specific 99th percentile URLs based on the AACC Universal Sample Bank. **Methods**: Lithium heparin plasma from 838 normal subjects, enrolled following informed consent and completion of a health questionnaire, were purchased from the AACC. Blood was collected from 423 men and 415 women recruited from both the 2015 annual AACC meeting in Atlanta and at the University of Maryland. The e602 instrument was used to measure cTnT by the Gen 5 assay, with a limit of detection (LoD) of 3 ng/L. Hemoglobin A1c (URL 6.5%), NT-proBNP (URL 250 ng/L) and eGFR (60 ml/min) were measured, along with identification of statin use, to help define a normal status. 99th percentile URLs were determined by the non-parametric (NP) and Harrell-Davis Bootstrap (HDB) methods. **Results**: 83 of 838 subjects were excluded based on abnormal surrogate biomarkers or based on statin use. Ages ranged from 19 to 91y; race: Caucasian 58%, African American 27%, Pacific Islander/Asian 11%, other 4%; ethnicity: Hispanic 8%, non-Hispanic 92%. Overall <50% of subjects had measureable concentrations >LoD (46% no exclusion, 44% after exclusion); males: 68% no exclusion, 66% post exclusion); females: 22% (both). Excluding subjects decreased the 99th percentiles by both statistical methods as follows: overall, 17 to 16 ng/L for both NP and HDB methods; males 18 to 16 ng/L for NP method, and 21 to 18 ng/L for HDB method. For females, there were no differences before and after exclusion, but there were differences by statistical method: 13 ng/L NP and 14 ng/L HDB. **Conclusions**: Our findings are consistent with the majority of the literature in that a) the Gen 5 cTnT assay does not meet the IFCC guideline for high-sensitivity assays which requires >50% of measureable concentrations above the LoD, b) using surrogate biomarker criteria lowers 99th percentiles, and c) the statistical method used impacts 99th percentiles. Our data suggest lower sex-specific cTnT 99th percentile concentrations than FDA approved should be used in clinical practice for the Gen 5 assay. Our study highlights the importance of detailing the criteria used to include and exclude subjects for defining a healthy population to determine cTn 99th percentiles and the statistical method used to calculate 99th percentiles.