Tuesday, July 31, 2018

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

Cardiac Markers

A-065

Association Of Single Nucleotide Polymorphisms (rs3798220) In The LPA Gene Region With Serum Lp(a) Levels In A Mixed Population

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Over the past several decades, numerous studies have established that increased levels of apolipoprotein(a) [Lp(a)] in plasma are associated with development of coronary heart disease (CHD). Upon discovery of the apo(a) gene (LPA), which was considered one of the most polymorphic transcribed genes in the human genome, researchers reported several polymorphism in LPA gene which associated with CHD and plasma Lp(a) levels. Recently, a single nucleotide polymorphism (SNP) rs3798220, also known as Ile4399Met, encoding an isoleucine to methionine substitution located in the protease-like domain of apo(a) at amino acid 4399 have been shown to be associated with CHD and plasma Lp(a) levels in Caucasians. This study investigated the association of SNP rs3798220 with plasma Lp(a) in a large scale of Berkeley HeartLab samples representing genetically diverse populations. The study showed that the heterozygous carriers of SNP rs3798220 (Ile/Met) had 2.8 fold higher serum Lp(a) levels with a mean of 64.3 mg/dL and 95% CI [63.1, 65.5] ($p = 0.0000$) compare to serum Lp(a) levels of homozygous non-carriers (Ile/Ile) having a mean of 33.4mg/dL and 95% CI [33.0, 33.6]. Interestingly, this study showed that the homozygous carriers (Met/Met) have 2.1 fold lower plasma Lp(a) than non-carriers (Ile/Ile) with a mean of 24.5mg/dL ($p = 0.0034$) and 6 fold lower than heterozygous carries (Ile/Met). This study also investigated the association of the same SNP with other biomarkers and concluded that there was a strong and clinically significant association between carriers of Ile/Met (genotype ag) and Met/Met (genotype gg) with high serum Triglyceride levels.

A-066

Study On Lipid Peroxidation &it Enzymatic Antioxidant Activities In Hypertensive Subjects

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Background
Lipid peroxidation is a degenerative process that affects cell membranes and other lipid containing structures under conditions of oxidative stress which is an essential early event in the pathogenesis of atherosclerosis as a major complication of hypertension. Hypertension is a major public health challenge; a major risk factor for cardiovascular disorder especially essential hypertension characterized by sustained elevation of blood pressure is without any identifiable cause. Hypertension is a major public health challenge; a major risk factor for cardiovascular disorder especially essential hypertension characterized by sustained elevation of blood pressure is without any identifiable cause. This study investigates the generation lipid peroxidation product (malonaldehyde) and its effects on physiological catalase, reduced glutathione and superoxide dismutase activities as enzymatic antioxidants.
Methods
The research subjects were selected from people in Ilesa metropolis of Osun State, Nigeria both male and female with age range of 31-60 years. The research subjects were grouped into two. Group one consist of 100 (male=50, female=50) newly diagnosed, untreated essential hypertensive subjects while group two consist of 100 non hypertensive subjects (male=50, female=50) that were not under any antihypertensive agent as control. Both systolic and diastolic blood pressures were determined using sphygmomanometer while the lipid peroxidation enzymatic antioxidant activities were determined using standard spectrophotometric techniques.
Results
There was a significant increase in serum concentration of MDA in hypertensive subjects ($p<0.05$) when compared with normotensive subjects. Also, serum level of superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) were significantly reduced in hypertensive subjects irrespective of gender ($p< 0.05$) when compared with normotensive subjects.
Conclusion
The significant increase in serum concentration of MDA in hypertensive subjects ($p<0.05$) suggest lipid peroxidative activity involvement in the etiology of hypertension. Serum level of superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) significant reduction in hypertensive subjects irrespective of gender suggest their involvement in the neutralization of free radicals that has been linked with the pathogenesis of hypertension.

A-067

The NT-proBNP level in Subclinical stage of cardiac structural or functional abnormalities among health checkups

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Background: The heart failure stage B is defined as patients with abnormal heart structure/function without symptoms. Circulating concentration of NT-proBNP is raised in symptomatic patients with left ventricular (LV) dysfuction which caused by structural or functional Impairment. This study performed to investigate the association of NT-proBNP level with echo-defined cardiac structural or functional (diastolic) anomalies in asymptomatic subjects with preserved LV function (ejection fraction >50%).
Methods: We retrospectively studied 412 health examinees who underwent echocardiography and NT-proBNP test at a health promotion center in Seoul, between January 2016 and December 2016. Increased left ventricular mass index (LVMI), and left atrial dimension (LAD) were used as markers of structural anomalies, and septal e' velocity and E/e' were used as markers of diastolic dysfunction. NT-proBNP was measured by electrochemiluminescence immunoassay (Siemens Healthcare Diagnostics, DPC Immulite 2000 XPi, Tarrytown, NY, USA).
Results: Multivariate regression analysis indicated that the factors associated with higher NT-proBNP were older age, female sex, lower BMI, lower blood pressure, higher creatinine, and higher LAD. The NT-proBNP levels were higher with increasing age groups, lowest in those aged ≤45 years and highest in those aged >60 years ($P<0.001$). While female in those aged ≤60 years demonstrated higher NT-proBNP levels than males ($P<0.001$), there was no significant difference of NT-proBNP levels in those aged >60 years. The structural anomalies, which were defined increased LVMI or LAD, demonstrated higher NT-proBNP than normal LVMI and LAD ($P<0.05$). However, diastolic dysfunction, which was defined decreased septal e' velocity or increased E/e', was not associated with NT-proBNP level.
Conclusion: The level of NT-proBNP was associated with subclinical cardiac structural anomalies but not associated with diastolic dysfunction in asymptomatic health checkups.

A-068

Diagnostic performance of copeptin for acute myocardial infarction in emergency department

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Background: The aim of this study was to investigate the effectiveness of copeptin in the diagnosis of acute myocardial infarction (AMI), and to compare the diagnostic performance of copeptin with other cardiac markers.**Methods:** We prospectively enrolled 293 patients presenting with chest pain (onset within 12 hours) suggestive of acute coronary syndrome (ACS) to the emergency department. Serum CK-MB, troponin I and copeptin levels were measured in each patient and were compared between ACS groups for statistical differences. The accuracies troponin I, CK-MB and copeptin for AMI diagnosis were assessed by ROC curve analysis. The performance of each marker and combination of three markers is assessed by comparing their AUCs. And diagnostic performance of three markers was analyzed to onset of chest pain. **Results:** Median age was 60 years; 70.0 % were men; 24.6% were ultimately diagnosed with AMI. Patients were consisted of 41 ST segment elevation MI (STEMI), 31 non-ST elevation MI (NSTEMI), 87 unstable angina and 134 other diseases. The combination of three markers (AUC: 0.980, 95% CI: 0.957-0.993) had better diagnostic performance for AMI than troponin I (AUC: 0.801, 95% CI: 0.750-0.840) or CK-MB (AUC: 0.758, 95% CI: 0.705-0.806) or copeptin (AUC: 0.796. 95% CI: 0.745-0.840) alone ($P<0.001$). And the combination of three markers (AUC: 0.902, 95% CI: 0.862-0.934) had better diagnostic accuracy for STEMI than troponin I (AUC: 0.744, 95% CI: 0.690-0.793) or CK-MB (AUC: 0.676, 95% CI: 0.619-0.729) or copeptin (AUC: 0.844, 95% CI: 0.797-0.884) alone ($P<0.001$). The use of three

markers also showed superior performance for NSTEMI than troponin I (AUC: 0.779, 95% CI: 0.727-0.825) or CK-MB (AUC: 0.782, 95% CI: 0.730-0.828) or copeptin (AUC: 0.642, 95% CI: 584-0.697) alone. In patients with onset of chest pain less than 1 hour (1hr group), copeptin was most superior to other markers in diagnosis of AMI (AUC: copetin-0.739, CK-MB-0.620, troponin I-0.595, comparison of AUC: Copeptin vs CK-MB: P=0.028, Copeptin vs troponin I: P=0.003). In group with onset of chest pain less than 2 hours (2hr group), copeptin showed better performance than troponin I for AMI diagnosis (AUC: copetin-0.732, CK-MB-0.642, troponin I-0.609, comparison of AUC: Copeptin vs troponin I: P=0.009). The result of separating group showed that copeptin was best marker for early diagnosis to STEMI (comparison of AUC in 1hr group: Copeptin vs CK-MB: P<0.001, Copeptin vs troponin I: P=0.002/ comparison of AUC in 2hr group: Copeptin vs CK-MB: P<0.001, Copeptin vs troponin I: P<0.001). However, there was no difference in diagnostic performance according to onset of chest pain in NSTEMI group. And copeptin showed higher negative predictive value than other markers in STEMI patients (copeptin-96.71 (95% CI: 92.78-98.54), troponin I- 88.97 (95% CI: 86.85-90.79), CK-MB-89.39 (95% CI: 86.92-91.44).**Conclusion:** In chest pain patients, combination of copeptin in addition to troponin I and CK-MB improves AMI diagnostic performance. And copeptin especially helps in early diagnosis and rule-out of STEMI patients.

A-069

Early detection of doxorubicin-induced cardiotoxicity with high-sensitivity troponin T in chemotherapy-treated patients

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Background: Detection of chemotherapy-induced cardiotoxicity has historically relied on clinical presentation and cardiac imaging measures. Recently, global longitudinal peak systolic strain (GLS) measures with speckle tracking echocardiography (STE) and high-sensitivity troponin T (hs-TnT) have been utilized to evaluate the development of cardiotoxicity. The increased sensitivity of these methods may allow us to detect early development of cardiotoxicity and predict future cardiac dysfunction in chemotherapy-treated patients. We investigated the effectiveness of hs-TnT and GLS in detecting doxorubicin-induced cardiotoxicity. **Methods**: Thirty-six patients with newly diagnosed sarcoma were assigned to receive 72-hours doxorubicin infusion. hs-TnT was monitored before, and at 72 hours of each chemotherapy cycle. All samples were assayed at the same time using hs-TnT (Roche diagnostics). Elevated troponin was defined as hs-TnT > 5 ng/L. STE was performed pretreatment, after cycle 3, and end of chemotherapy. Only patients who received ≥ 150 mg/m^2 of doxorubicin and had at least two STE were included for evaluation of GLS and left ventricular ejection fraction (LVEF). **Results**: Six patients (25%) developed cardiotoxicity as defined as a decline in LVEF >10% by the Cardiac Review and Evaluation Committee. The absolute levels of hs-TnT had significantly peaked from precycle baseline, increased starting at cycle 2, subsequently in each precycle and during the cycle of therapy (p<0.05). Fold changes over baseline hs-TnT level were also significantly increased. In all six patients with cardiotoxicity, GLS increased significantly at the end of chemotherapy, compared with baseline (-21±2 vs -19±2). The increase in GLS by 15% and hs-TnT by 5ng/L were independent predictors of the development of cardiotoxicity at the end of chemotherapy (p<0.05). **Conclusion**: In conclusion, hsTnT and GLS predict the development of cardiotoxicity in patients treated with doxorubicin. These two parameters may be useful in predicting and detecting the development of chemotherapy-induced cardiotoxicity and thus reduction of the incidence of its associated morbidity and mortality.

A-070

Comparison of analytical outlier rates between Roche 4th and 5th generation Troponin T assays using both serum and plasma samples

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Background: Analytical outliers occur with most troponin methods and can adversely affect patient management. Because higher sensitivity troponin reagents result in more troponin values that exceed the 99th percentile value, it may be difficult to identify these analytical outliers. In this study, we compared the analytical outlier rates of the Roche 4th generation Troponin T STAT (cTnT Gen 4) and Roche 5th generation Troponin T STAT (cTnT Gen 5) assays using both serum and plasma samples. **Methods:**

Paired rapid clot serum tubes (RST) and plasma separator tubes (PST) (N=1426 pairs) were collected from hospital patients with orders for clinical cTnT testing. RST and PST samples were centrifuged for 3 minutes at 4000 x g and analyzed on cTnT Gen 4 and cTnT Gen 5 assays on a Roche Cobas e411 immunoassay system. If either of the paired samples displayed measurable cTnT Gen 5 (≥6 ng/L), both samples were stored at 2-8°C within 2 hours of initial measurement (N=1185 pairs). Within 24 hours of initial analysis, paired samples were warmed to room temperature, aliquoted, re-centrifuged at 4000 x g for 3 minutes, and re-analyzed on both Gen 4 and Gen 5 methods. We defined analytical outliers as:

• Initial and repeat results differing on the cTnT Gen 4 assay by >0.03 ng/dL for results <0.20 ng/mL or ≥20% for results ≥0.20 ng/mL

• Initial and repeat results differing on the cTnT Gen 5 assay by >10 ng/L for results <100 ng/L or ≥10% for results ≥100 ng/L

We also calculated the number/percent of repeat values that were on different sides of the 99th percentile upper reference limit (URL) for each assay. **Results:** Using the cTnT Gen 4 assay, 379/1426 (26.6%) RST and 391/1426 (27.4%) PST results were above the 99th percentile of ≥0.01 ng/mL. Using sex-specific 99th percentile cut-offs on the cTnT Gen 5 assay of > 10 ng/L (females) and >15 ng/L (males), 809/1426 (56.7%) RST and 802/1426 (56.2%) PST results were above 99th percentile. For cTnT Gen 4, 6/1185 (0.6%) RST and 8/1185 (0.7%) PST samples analyzed resulted in analytical outliers all of which were all at least 5 times above the 99th % URL. For cTnT Gen 5, we observed analytical outliers in 10/1185 (0.8%) RST and 10/1185 (0.8%) PST samples. However 15% of Gen 5 outliers had repeat values on different sides of the 99th percentile URL. For both Gen 4 and Gen 5 reagents, 50% of outliers had higher TnT results upon repeat testing while 50% had lower results. **Conclusion:** Analytical outliers occur frequently (0.5-1.0% of samples) with both Gen 4 and Gen 5 cTnT assays independent of sample type. No outlier results occurred on different sides of the 99th percentile URL for Gen 4. 5th Gen cTnT had a similar outlier rate but more were relevant to the determination of an elevated value. Compared to 4th Gen cTnT, use of 5th Gen cTnT will increase the percent of patients with elevated (above 99th percentile URL) values without reducing the rate of analytical outliers.

A-071

Comparison of the sensitivity and specificity of the RAMP® Troponin I assay and ADVIA Centaur® TnI-Ultra Assay

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Background: Measurement of cardiac troponin I (TnI) aids in the diagnosis of acute myocardial infarction (AMI) and in the prioritization of patient management. The purpose of this study was to compare the sensitivity and specificity of the RAMP® Troponin I assay on the RAMP 200 instrument and ADVIA Centaur® TnI-Ultra Assay on the ADVIA Centaur CP instrument[1]. The ADVIA Centaur CP System is a mid-volume, high throughput bench top laboratory instrument with chemiluminescent technology; the RAMP system is a lateral flow fluorescent immunoassay platform with a smaller footprint. Testing was performed over two days in the laboratory of a large urban hospital in Portland, OR. **Methods:** Paired lithium heparin plasma and EDTA whole blood waste samples were used for this study. Specimens were selected by medical laboratory staff based on the ADVIA Centaur CP Troponin I result listed in the laboratory information system, de-identified, and provided to study personnel. Lithium heparin plasma samples were retested on the ADVIA Centaur CP concurrently with EDTA blood samples on the RAMP system. Results were compared between instruments, and to the patient diagnosis as determined from the electronic medical record by medical staff. **Results:** EDTA RAMP results were compared to the original lithium heparin Centaur results. Retesting of lithium heparin specimens in the Centaur CP was not reliable due to the presence of fibrin clots in the original specimens. A total of 74 samples were included in this study; 2 samples were excluded due to specimen age (>12 hours elapsed since original testing) and 1 sample was excluded due to an error during sampling. The RAMP Troponin I and ADVIA Centaur TnI-Ultra Assay results showed 97% concordance. Using the 99th percentile as a cutoff, the RAMP Troponin I test (< 0.10 ng/mL) showed comparable sensitivity and specificity, 81% and 91% respectively, to the Advia Centaur TnI-Ultra Assay (< 0.04 ng/mL), 75% and 91% respectively, when compared to the electronic medical record (i.e. ECG result). Also comparable were the positive predictive values (PPV), 84% and 84%, and negative predictive values (NPV), 89% and 85%, for the RAMP and Centaur systems respectively. **Conclusion:** The possibility of using the RAMP Troponin I test at immediate and urgent care facilities is very attractive. Both the RAMP Troponin I test

and the ADVIA Centaur TnI-Ultra Assay showed excellent specificity, when used in conjunction with other clinical findings (e.g. abnormal ECG), in the diagnosis (rule-in) of AMI. The results of the study therefore support the use of the RAMP Troponin I test on the RAMP 200 system as an alternative to the larger laboratory systems, where maintenance and calibration downtime, limited space, or lower volumes would necessitate a smaller, yet effective option. [1] Both devices are available for sale in the US and are CE Marked.

A-072

Single Molecule Technology: Equivalence between a research platform and a CE-marked diagnostic platform for the quantification of cardiac troponin I

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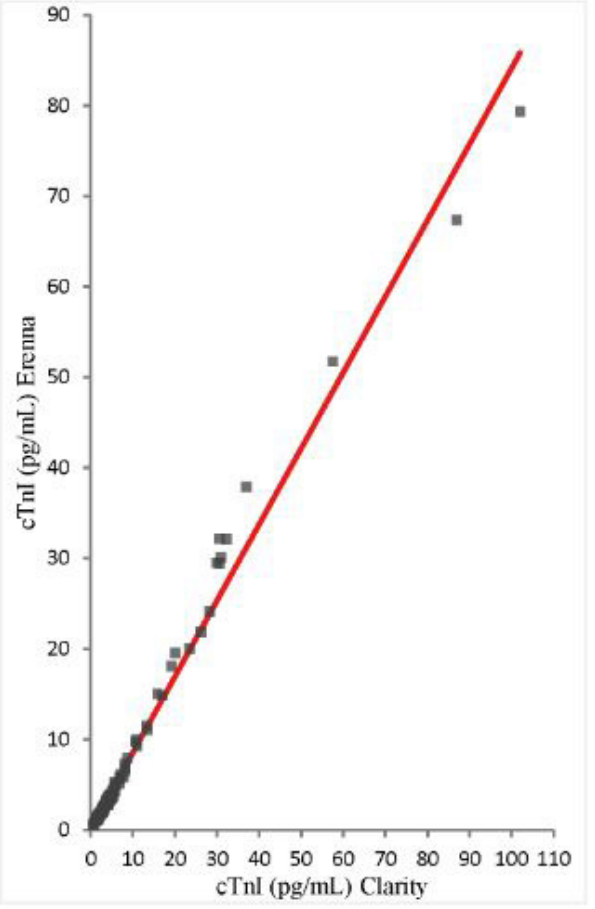
Background: Single Molecule Counting technology has enabled the quantification of intractable low-abundance biomarkers. The Erenna® Instrument (research use only, RUO) and the CE-marked diagnostic Singulex Clarity® system are powered by Single Molecule Technology. Numerous studies have generated clinically important information on RUO-based platforms, but their translatability to clinically useful platforms has not been demonstrated. In this study, the correlation and equivalence of the Singulex Clarity system and the Erenna Instrument for measurements of cardiac troponin I (cTnI) were evaluated. **Methods:** De-identified EDTA-plasma samples (n = 120) were first tested by the Singulex Clarity® cTnI assay on the Singulex Clarity system (limit of quantification 0.14 pg/mL) and subsequently measured on the Erenna Instrument. The study on frozen samples, biobanked from a CLIA-licensed clinical lab, were selected to span a wide range of the assay. Passing-Bablok and Pearson's R correlation analyses were performed to compare and quantify the linear relationship between the assays. **Results:** cTnI was measured in all samples and the concentrations ranged from 0.54 to 102.03 pg/mL, as measured by the Singulex Clarity system. When comparing the Singulex Clarity system and the Erenna Instrument, the Pearson correlation coefficient was 0.99 (95% CI: 0.99-1.00; Figure), indicating nearly all the variance in the Singulex Clarity results could be explained by the Erenna results. The coefficient from the Passing-Bablok regression was 0.85 (95% CI: 0.82-0.89), indicating a slight bias between the two instruments that may be explained by standardization differences. **Conclusion:** The Singulex Clarity cTnI assay on the Singulex Clarity system had good correlation with the Erenna Instrument for cTnI measurements in EDTA plasma, as indicated by a strong linearity relationship between the platforms. The systems provided substantially equivalent results, demonstrating that findings on cTnI measurements using the Erenna Instrument are equivalent to those obtained using the Singulex Clarity system.



A-073

Performance Evaluation of Atellica IM High-Sensitivity Troponin I Assay in a Clinical Chemistry Laboratory

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Background: Cardiac troponins have become the preferred biomarker for diagnosis of MI. As sensitivity of troponin assays has increased, so has the precision at the lower end, shortening time points between serial measurements, and improving the sensitivity for early detection of MI. The Atellica® IM High-Sensitivity Troponin I (TnIH) Assay* is an in vitro diagnostic immunoassay for the quantitative determination of cardiac troponin I in serum or plasma. The objective of this study was to verify the analytical performance (precision and linearity) of the Siemens Healthineers Atellica IM TnIH Assay on the Atellica® IM 1600 Analyzer, and perform method comparison with the ADVIA Centaur® High-Sensitivity Troponin I (TNIH) Assay. (*Not available for sale in the U.S. Future availability cannot be guaranteed.) **Methods:** The Atellica IM TnIH Assay is a dual-capture sandwich immunoassay using magnetic latex particles, a proprietary acridinium ester for chemiluminescence detection, and three monoclonal antibodies. The precision studies were evaluated according to EP05-A3 and EP15-A2 and method comparison to EP09-A3. Precision studies used lithium heparin plasma samples, two sample pools, and three levels of controls. One aliquot of each sample pool and each QC material was tested in replicate in two runs per day on each analyzer for a minimum of ten days with one lot of reagent and calibrator. Each run was separated by approximately a two-hour time interval. A total minimum of 40 replicates were generated per sample. Serial measurements were obtained for lithium heparin samples from >50 chest pain Emergency Department patients. Troponin samples at admission and 1, or 2, or 3, or up to 6 h later were analyzed using the Atellica IM TnIH

Assay, and the ADVIA Centaur TNIH assay. Siemens Healthineers supported the study by providing systems, reagents and protocols and contributed to data analysis. **Results:** Precision studies agreed with the manufacturer's claims: Within day CV%(SD)s were 5.4(0.61), 4.1(1.04), 2.1(0.79), 1.9(67.33), 1.8(325.83) for concentrations of 11.4, 25.4, 37.1, 3497.2, 18056.4 ng/L (pg/mL); within lab (total) CV%(SD)s were 6.9(0.79), 4.4(1.12), 3.4(1.27), 3.0(104.48), 2.4(430.79), respectively. Method comparison between the Atellica IM TnIH Assay and ADVIA Centaur® High-Sensitivity Troponin I (TNIH) assay showed a regression slope of 1.045 (95%CI 1.03 to 1.06), intercept of -2.396 pg/mL(95%CI -2.62 to -2.00) (n=77). Serial measurement results demonstrated 100% total agreement for subjects falling above and below the respective assay 99th percentile value, when comparing Atellica IM TnIH Assay with ADVIA Centaur TNIH assay. **Conclusion:** The Atellica IM TnIH Assay has demonstrated good precision for detecting low cardiac troponin I concentrations, good correlation and agreement with the Siemens ADVIA Centaur TNIH assay.

A-074

assessment of plasma hepcidin concentration as a novel biomarkers of acute coronary syndrome severity

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Background: Hepcidin, produced mainly by liver hepatocytes, is the principal systemic iron regulator. Hepcidin is an acute phase reactant that plays a role in the progression of inflammatory caused diseases including thrombosis formation in coronary artery diseases (CAD). We assessed serum hepcidin level in CAD patients with acute coronary syndrome (ACS). The association of classical atherosclerotic markers such as cardiac troponin I (cTnI), and C reactive protein (CRP) was compared to hepcidin and ferritin serum levels. **Methods:** A total of 80 subjects (60 ACS patients and 20 controls) were enrolled. Sera of ACS patients admitted at the Emergency Department were obtained within 6 hours of chest pain. ACS patients were subdivided into: unstable angina (UA,n=20), non-ST elevation myocardial infarction (NSTEMI, n=20), and ST elevation myocardial infarction (STEMI n=20). Serum hepcidin and ferritin were evaluated using enzyme-linked immunosorbent assay (ELISA). CRP, cTnI, and lipids were measured using spectrophotmetry. The results were statistically compared. **Results:** ACS patients were 68.8% males and 31.3% females. Their overall mean age was 56.00±8.73. Healthy controls mean age was 50.2±9.03 and included 13/65% males and 7/ 35% females. 53.1% of ACS patients were hypertensive and 39.1% were diabetics compared to 15% hypertensive and 10% diabetics in the healthy control group. ACS patients have higher TG, LDL and lower HDL (means114.3±47.6, 127.0±45.2, 35.8±9.3 mg/dl respectively) compared to controls. Mean random blood glucose was 174.4 ±68.2 in ACS and 111.3±30.0 in control subjects. While hepcidin was nearly three folds higher in STEMI patients compared to control, mean 44.5±21.0 and 16.6±17.9 ng/ml respectively (P<0.001), NSTEMI and UA showed near control hepcidin levels. The increased hepcidin in STEMI patients accompanied a significant low level of ferritin compared to healthy control (47.4±41.3 and 118.1±99.9 ng/ml respectively). STEMI, NSTEMI and UA had similar pattern for both Troponin I and CRP plasma levels, the three ACS clinical classification had significant higher Troponin I (9.94±13.19, 5.30±5.75, 0.01±0.02 ng/mL respectively) and CRP (14.1±13.43, 13.2 ±18.9, 6.9±7.3 mg/l respectively) compared to control levels 0.002±0.003ng/ml and 1.4 ±0.3mg/l troponin I and CRP respectively. In the present study, ACS patients had a significant positive correlation between hepcidin and each of troponin I and CRP. The results suggest that hepcidin levels increase with increasing ACS disease severity. Therefore, hepcidin levels may be a useful marker to follow progression of ACS. As the mean iron regulating hormone, in principle, hepcidin is an excellent therapeutic target for strategies to reduce the inflammation associated with the generation of atherosclerosis in ACS. **Conclusion:** We concluded that serum hepcidin is increased in STEMI compared to NSTEMI, UA. The increased hepcidin accompanied a high level of cardiac troponin I and CRP only in STEMI patients but not the NSTEMI. Our findings highlight the association of hepcidin and ACS progression. The present study may provide a preliminary basis for broader scale studies to highlight the interaction of hepcidin with various inflammatory players involved in atheroma formation as well as the underlying activated signaling pathways to explain the mechanisms for hepcidin release in CAD. **Key words: ACS, Hepcidin, Ferritin, STEMI, NSTEMI, UA.**

A-075

Performance of Emergency Testing Functionalities for Atellica® IM TnIH, hCG and BNP Assays on the Atellica® Solution

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Background: The objective of this study was to verify the STAT capabilities of the Atellica Solution, consisting of an Atellica® Sample Handler and two Atellica® IM 1600 Analyzers, with two metrics: (1) turnaround time (TAT) for emergency STAT tests while simultaneously performing routine testing and (2) impact of the STAT capabilities of the system on the TAT of the emergency samples. **Methods:** The study reproduced a typical 3 hour peak period of the day for 650 routine samples with 1561 test requests representative of the lab's workload. To include STAT testing, normally done in a dedicated laboratory, we added to the worklist a representative day's quantity of High-Sensitivity troponin I (TnIH), total hCG (hCG), and B-type natriuretic peptide (BNP) STAT tests corresponding to those same 3 hours, thus creating a single worklist including both routine and STAT. Hence, we were able to load STAT samples into the recreated peak routine testing and observe TAT from tube scanning on the Atellica Solution to result delivery. Routine samples were loaded in 10 minute intervals; STAT tubes were loaded according to the timestamps collected from the original STAT laboratory data. Since hCG was run both as routine and STAT we were able to measure the impact of the system's STAT functionalities on TAT. **Results:** TAT of STAT assays:

	As STAT				As routine			
Assay	**Samples**	**Mean TAT (min)**	**TAT CV (%)**	**TAT range (min)**	**Samples**	**Mean TAT (min)**	**TAT CV (%)**	**TAT range (mins)**
TnIH	13	10.9	6	10.5-12.7	N/A	N/A	N/A	N/A
hCG	6	10.9	4	10.5-11.6	10	11.9	12	10.5-14.8
BNP	7	11.1	6	10.5 – 12.5	N/A	N/A	N/A	N/A

N/A: Not applicable

Conclusion: The Atellica Solution is able to deliver results with a quick and predictable TAT for STAT assays, including TnIH, hCG, and BNP, while simultaneously performing routine testing with minimal impact on throughput. Furthermore, comparing TAT of hCG in STAT vs. routine shows that the Atellica Solution's STAT capability effectively reduces TAT and variability.

* Siemens Healthineers supported the study by providing systems, reagents, protocols and contributed to data analysis

A-076

High-Sensitivity Cardiac Troponin I Whole Blood and Plasma Specimen Comparisons Measured by the ET Healthcare Pylon Point of Care Assay

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Introduction: Cardiac troponin (cTn) testing is the guideline recommended biomarker for ruling in and ruling out acute myocardial infarction (MI) and risk stratification of patients presenting to emergency departments with ischemic symptoms. High sensitivity (hs)- cTnI assays are transitioning to become the optimal methods because of improved analytical performance. The objectives of our study were to compare a) POC hs-cTnI concentrations between matched whole blood and plasma specimens from 40 patients admitted through the emergency department using a novel point of care (POC) assay and b) plasma POC hs-cTnI concentrations with plasma measured on central laboratory hs-cTnI and Gen 5 cTnT assays. Methods: Fresh, waste whole blood EDTA anticoagulated specimens (n=40) were collected in the emergency department. Within 2 hours, the whole blood specimens were analyzed, and then immediately centrifuged to separate the EDTA plasma, which were than immediately analyzed. Whole blood and plasma measurements were performed on the novel Pylon hs-cTnI assay by ET Healthcare; currently only cleared for patient use in China. Further, the POC Pylon plasma results were compared with an investigational hs-cTnI assay by Abbott (ARCHITECT i1000) and the Roche Gen 5 cTnT assay (cobas e601). Specimens were enrolled over a 5-day period. Results: 98% of whole blood and 100% of plasma specimens were measureable

by the Pylon; ranges: whole blood 1.1-61 ng/L; plasma 1.4 to 59, ng/L. The correlation between whole blood and plasma showed the following: WB hs-cTnI = 0.98 plasma hs-cTnI + 1.01. The plasma correlations measured on the Pylon and the a) ARCHITECT and b) cobas e601 showed the following: Pylon hs-cTnI = 0.32 ARCHITECT hs-cTnI + 7.85; Pylon hs-cTnI = 0.10 cobas hs-cTnT + 11.05; respectively. The plasma correlation between the ARCHITECT and cobas e601 showed the following: ARCHITECT hs-cTnI = 0.26 cobas hs-cTnT + 11.56. Conclusions: Preliminary findings of the POC Pylon ET Healthcare hs-cTnI assay showed excellent agreement between whole blood and plasma. Correlation between the Pylon hs-cTnI and ARCHITECT hs-cTnI assays was excellent for 36 of the 40 plasma samples studied; 4 samples showed higher results on the Pylon than the ARCHITECT, resulting in a decrease in the overall correlation. Correlation of cobas hs-cTnT with both the Pylon and the ARCHITECT was poor. Additional studies are underway to evaluate the clinical performance of this POC hs-cTnI assay.

A-077

Method Comparison of 5th Generation "High-Sensitivity" Troponin T with 4th Generation Troponin T

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Background: The Food and Drug Administration cleared Roche Diagnostics Elecsys Troponin T Gen 5 STAT (gen5 cTnT) assay in January 2017, making it the first next generation troponin assay available in the United States. The assay was implemented at our hospital to assist with the rapid rule out of acute myocardial infarction (AMI) and risk stratification of acute coronary syndromes. Analytical relationships were explored between gen5 cTnT and Troponin T STAT (gen4 cTnT; Roche Diagnostics), with emphasis near lower limits of measure. Further, the association between plasma creatinine concentration and gen5 cTnT result was evaluated. **Methods**: Comparisons were made between the gen5 cTnT and gen4 cTnT assays on 4 Cobas 8000 e602 (Roche Diagnostics) instruments. All non-less than gen4 cTnT (>0.09 ng/mL) and gen5 cTnT (>5 ng/L) results were plotted, and Deming regression analysis was performed. Further, additional comparisons were made between plasma creatinine concentration and gen5 cTnT. Gen5 cTnT results >51 ng/L were excluded from analysis and <6 ng/L results were included as 6 ng/L. The comparisons were made between the averaged gen5 cTnT result per group and the grouped plasma creatinine concentration: 0.60-0.79, 0.80-0.99, 1.00-1.19, 1.20-1.39, 1.40-1.59, 1.60-1.79, and 1.80-1.99 mg/dL. Data for all studies was collected from 07/05/17 to 12/03/18. **Results**: The analysis included 614 points from a gen5 cTnT (y axis) range of 6 to 1391 ng/L and a gen4 cTnT (x axis) range of 0.010 to 1.360 ng/mL. The regression analysis displayed a Pearson coefficient (R) of 0.9845, a slope of 901, and intercept of 24. Deming regression analysis was also performed in a smaller sub range, focused on the lower measuring range (i.e. closer to clinically important thresholds). The analysis plotted 373 points from a gen5 cTnT (y axis) range of 6 to 82 ng/L against a gen4 cTnT (x axis) range of 0.010 to 0.050 ng/L. The regression analysis displayed an R of 0.7806, a slope of 1490, and an intercept of 11. The sub range displays a lower correlation compared to the larger range and a proportional bias. To further evaluate differences in the methods, gen4 cTnT results <0.010 ng/mL were compared to the gen5 cTnT results. Of the 3409 samples that were <0.010 ng/mL on the gen4 cTnT assay, 1224 and 1935 results were <6 ng/L or <10 ng/L, respectively, on the gen5 cTnT assay. The remaining 1473 gen5 cTnT results ranged from 10 to 45 ng/L. Linear regression analysis was performed, comparing the averaged gen5 cTnT result to its corresponding creatinine concentration group, displaying an R of 0.987. The lowest plasma creatinine concentration group (0.60-0.79 mg/dL) yielded an average gen5 cTnT of 9 ng/L, and the highest plasma creatinine concentration group (1.80-1.99 mg/dL) gave an average gen5 cTnT of 27 ng/L. **Conclusion**: Overall, gen5 cTnT has a strong linear relationship versus its predecessor assay, gen4 cTnT. However, the correlation decreases towards their respective lower limits. Gen5 cTnT also displays a strong relationship to plasma creatinine concentration.

A-078

NT-proBNP assays that are based on antibodies which are specific to nonglycosylated regions of NT-proBNP display a similar diagnostic accuracy in distinguishing heart failure patients compared to the Roche NT-proBNP assay

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Background: N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) is a useful blood biomarker for the diagnosis of heart failure (HF). NT-proBNP is O-glycosylated within the central part and present in the circulation as a pool of molecules with different glycosylation levels. An automated NT-proBNP immunoassay manufactured by Roche is widely used for NT-proBNP measurements. This assay employs monoclonal antibodies (mAbs) that are specific to the epitopes 27-31 and 42-46 in the central region of NTproBNP. One of the mAbs is specific to the partially glycosylated region of NT-proBNP as the epitope 42-46 comprises Ser_{44}, which is modified by glycosidic residues. The presence of O-glycans at this site makes NT-proBNP undetectable by the Roche NT-proBNP assay due to the steric hindrance. In light of this, the assay is able to detect only the NT-proBNP fraction that is nonglycosylated at the 42-46 region and not the "total" NT-proBNP, i.e. both glycosylated and nonglycosylated subfractions. Since O-glycosylation tends to be heterogeneous, its pattern and extent might vary significantly among individuals and this could in turn impact the clinical value of NT-proBNP measurements by glycosylation-sensitive NT-proBNP assays. We have developed an alternative type of NT-proBNP immunoassays that are not affected by analyte glycosylation and are able to measure the concentration of the "total" NT-proBNP. The aim of this study was to compare the diagnostic accuracy of measurements of the "total" NT-proBNP (by two prototype immunoassays) with measurements of NT-proBNP that is nonglycosylated at Ser_{44} subfraction of NT-proBNP (by the Roche NT-proBNP assay) in distinguishing HF from non-HF patients. **Methods:** NT-proBNP levels were measured by two HyTest's prototype NT-proBNP assays (capture mAb - detection mAb: $29D12_{5-12}$ - $NT34_{25-32}$ and $15C4_{67-73}$ - $13G12_{15-20}$) and the Roche NT-proBNP assay (automated Roche Cobas e 411 analyzer) in EDTA-plasma samples that were obtained from 51 patients who had been diagnosed with HF and 53 healthy individuals (age-matched). HyTest's prototype NT-proBNP assays were linear in the range of 20 to 80,000 ng/L and the detection limits were 5-10 ng/L. Recombinant nonglycosylated NT-proBNP 1-76 (HyTest, produced in *E. coli*) was used as a calibrator in the prototype NT-proBNP assays. The diagnostic accuracy of the assays was analyzed by the comparison of the ROC curves. **Results:** ROC-AUC for the prototype assays $29D12_{5-12}$ - $NT34_{25-32}$/$15C4_{67-73}$ - $13G12_{15-20}$ were 0.951/0.946 (sensitivity 0.86/0.84 and specificity 0.93/0.98 respectively) compared to 0.965 (sensitivity 0.86 and specificity 0.98) for the Roche NT-proBNP assay. Differences were statistically insignificant (p-value = 0.365/0.369). **Conclusion:** NT-proBNP immunoassays that are based on antibodies which are specific to nonglycosylated regions of the NT-proBNP molecule are expected to have at least a similar clinical value for HF diagnosis as the Roche NT-proBNP assay that detects only a subfraction of endogenous NT-proBNP. Taking into account the known high variability in levels and site occupancy of O-glycosylated proteins, we suggest that immunoassays which measure "total" NT-proBNP levels might be advantageous for HF diagnostics and/or therapy monitoring in certain groups of patients and disease states due to their ability to detect endogenous NT-proBNP independently of its glycosylation status.

A-079

Do High-Sensitivity Cardiac Troponin I Clinical Performance Data in Package Inserts Reflect Realistic Clinical Expectations?

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Background: Cardiac troponin (cTn) is a cornerstone for diagnosis and management of myocardial infarction (MI). High-sensitivity troponin (hs-Tn) provides earlier MI rule-in/rule-out. The 2015 European Society of Cardiology guidelines proposed hs-Tn algorithms for NSTEMI-management. However, estimates of hs-cTn performance may vary based on the anchor-time used for analysis. Typically cTn data have been organized relative to the "first study sample" (1stSS) collection time, including in

manufacturers' package inserts. Alternatively data can be organized based on time of presentation (TOP). We investigated diagnostic performance of the ADVIA Centaur® hs-TnI (TNIH) up to 3.5 hours using TOP or 1stSS anchor-time.**Method:** Samples from >2,300 'all-comer' suspected MI patients were collected at 29 IRB-approved sites; 310 (13%) patients were adjudicated MI positive. The TNIH assay was validated as hs-TnI: total CV was 2.9% at the female 99th percentile (37 ng/L); using the AACC Universal Sample bank, 58.9% and 85.8% of values from healthy women and men, respectively, exceeded LoD (1.6ng/L).**Results:** Median delay between local standard-of-care first blood draw and 1stSS was 49 min. Table-Section A shows TNIH sex-specific performance based on TOP analysis (n=4,502 observations). Table-Section B displays sex-specific performance using 1stSS (n=6,346 observations). At 3.5-hours, TOP sensitivity was 95.8% & 89.7% and Negative Predictive Value (NPV) was 99.5% & 98.1% for women and men, respectively. For 1stSS at 3.5-hours, sensitivity was 95.0% & 89.2% and NPV was 99.3% & 97.6% for women and men, respectively. Although at 3.5-hours, TOP (n=198) had more adjudicated MIs than 1stSS (n=114) (p<0.001), sensitivity/NPV was not significantly different than anchoring at 1stSS (p-value=0.44).**Conclusion:** Reporting performance relative to TOP or the 1stSS does not yield different values for sensitivity/NPV or other MI diagnostic parameters at 3.5 hours. We advocate reporting data anchored to clinical presentation time to facilitate harmonizing with clinical guidelines.

		Sensitivity		Specificity		PPV		NPV	
Sex	Time-point	N		N		N		N	
SECTION A- Anchored To Time Of Presentation (TOP)									
Females (cutoff=37 ng/L)	0 to 1.5 hr*	41	82.9%	396	93.9%	58	58.6%	379	98.2%
	1.5 to 2.5 hr*	76	89.5%	710	91.8%	126	54.0%	660	98.8%
	2.5 to 3.5 hr*	72	95.8%	605	91.9%	118	58.5%	559	99.5%
Males (cutoff=57 ng/L)	0 to 1.5 hr*	100	74.0%	561	92.0%	119	62.2%	542	95.2%
	1.5 to 2.5 hr*	162	87.7%	913	90.7%	227	62.6%	848	97.6%
	2.5 to 3.5 hr*	126	89.7%	740	90.1%	186	60.8%	680	98.1%
*from time of presentation									
SECTION B-Anchored To Time Of First Study Sample (1stSS)									
Females (cutoff=37 ng/L)	Baseline‡	102	87.3%	887	91.4%	165	53.9%	824	98.4%
	0.75 - 1.5 hr†	89	89.9%	820	91.6%	149	53.7%	760	98.8%
	1.5 - 2.5 hr†	44	97.7%	427	92.3%	76	56.6%	395	99.7%
	2.5 - 3.5 hr†	40	95.0%	317	87.4%	78	48.7%	279	99.3%
Males (cutoff=57 ng/L)	Baseline	194	81.4%	1088	90.9%	257	61.5%	1025	96.5%
	0.75 - 1.5 hr†	166	86.7%	1038	90.9%	238	60.5%	966	97.7%
	1.5 - 2.5 hr†	93	86.0%	605	90.6%	137	58.4%	561	97.7%
	2.5 - 3.5 hr†	74	89.2%	362	91.4%	97	68.0%	339	97.6%

‡baseline defined as study samples collected within +/-90 minutes from the time of the first local standard-of-care blood draw
†from the time of the 1st study sample

A-080

Macrotroponin T causing a false positive troponin elevation

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Presentation: A 54 year old Asian British male was admitted with a 4 day history of chest pain for 7 days. Past medical history: Chronic hepatitis B (e-Antigen negative), non-alcoholic steatohepatitis, hypertension and type-2 diabetes. Previous admissions for chest pain 4 and 2 years prior to this episode. Family history: Type 2 diabetes, hypertension and hypercholesterolaemia. Clinical course: Troponin T (cTnT) Roche Diagnostics Cobas 8000 (10% CV = 13ng/L, 99th percentile URL = 14ng/L) was elevated on admission and noted to remain consistently elevated. Investigations: Imaging by thoracic CT (aortic imaging, no abnormality detected), coronary angiography (no obstructive epicardial disease) and cardiac MRI (no evidence of injury or wall motion abnormality) did not support acute myocardial injury as a cause for the raised troponin. An analytical interference was suspected and serial dilution and polyethylene glycol (PEG) precipitation of the sample was performed and the sample was analysed for cardiac troponin I (Abbott diagnostics hs cTnI, 10% CV = 4.7 ng/L, 99th percentile URL = 26.2 ng/L). Results: cTnI was < 2ng/L. Serial dilution showed comparable recovery with a known native high troponin sample (y = 0.9856x - 60.759, R^2 = 0.9986). PEG precipitation showed a large disparity in recovery between original measurements and against known native troponin samples (Day 4 = 1.13% and Day 5= 1.36% recovery, control samples = 94.46% and 85.09% recovery). Conclusion: The results were consistent with macrotroponin and not acute cardiac injury. Macrotroponin T has not been widely reported.

Date	Day 1	Day 1	Day 2	Day 2	Day 3	Day 3	Day 4	Day 5	Day 6
Troponin T (ng/L)	1588	1842	1690	1789	1684	1718	1745	1697	1674

A-081

First High-Sensitivity Cardiac Troponin I Assay Cleared by the United States Food and Drug Administration

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Background: High-Sensitivity (hs) cardiac troponin (Tn) assays must meet two criteria according to 2018 AACC Academy and IFCC TFCACB Expert Opinion Recommendations: (i) cTn values above the limit of detection (LoD) for >50% of male and female healthy cohorts of ≥300 individuals each; (ii) imprecision ≤10% total CV for sex-specific 99th-percentile clinical decision values (CDVs). No current FDA-cleared assay has evidence of hs-Tn criteria to date. The LoD, percent healthy females and males exceeding LoD, and total %CV at sex-specific CDVs were determined to examine hs-TnI status of the PATHFAST cTnI-II (TnI-II) assay. **Methods:** CLSI EP17 was used to determine the TnI-II's Limit of Blank (LoB) by LoB=mean+1.645xSD and the LoD by LoD=LoB+[1.645xSD]. CLSI EP15 was used for verifying TnI-II's total %CV at the 99th percentile CDV of the female, male and overall healthy populations. Lithium-heparin samples from the AACC Universal Sample Bank (USB), comprised of 847 healthy women (49.4%) and men (50.6%) was used to determine sex-specific 99th-percentile CDVs with Non-parametric, Harrell-Davis and Robust modeling. USB subjects with evidence of underlying health conditions from Health/Medication questionnaires, and amino-terminal proBNP (NT-proBNP), Hemoglobin A_{1c} and creatinine for calculating estimated Glomerular Filtration Rate (eGFR) surrogate biomarkers were excluded. **Results:** The LoB was -0.00092ng/L; LoD was 2.3 ng/L, which is 46% lower than the 5.0 ng/L LoD reported in TnI-II's FDA-submission. The total %CV was validated as <8% at 30 ng/L and 20 ng/L. After excluding 113(13.3%) USB-volunteers by surrogate biomarkers, the final healthy population had 734-members (See figure). 52.8% of females and 78.8% of males exceeded LoD. **Conclusions:** The cTnI-II system, FDA-cleared in 2011, fulfilled criteria as an hs-TnI assay. At the 99th-percentile CDVs, the total %CV for healthy female and male cohorts were ≤10%, and Greater than 50% of both healthy females and males exceeded the LoD.

Healthy Population Data after exclusion for eGFR<60 mL/min/1.73 m² OR HbA1c ≥ 6.5% OR NT-proBNP >125 ng/L if <75 years or >450 ng/L if ≥75 years.			
Description	**Overall**	**Females**	**Males**
Healthy populations, number of subjects	734	352	382
Number of cohort with TnI-II values > Limit of Detection (% of cohort > Limit of Detection)	487 (66.3%)	186 (52.8%)	301 (78.8%)
Non-parametric percentile method (CLSI C28-A3)			
99th percentile Clinical Decision Value	27.9 ng/L	20.3 ng/L	29.7 ng/L
90% Confidence Interval	90% CI: 20.1 – 29.7	90% CI: 12.8 – 29.7	90% CI: 21.2 – 36.9
Robust method (CLSI C28-A3)			
99th percentile Clinical Decision Value	14.0 ng/L	10.5 ng/L*	16.4 ng/L*
90% Confidence Interval	90% CI: 12.7 - 15.3	90% CI: 8.6 - 12.3	90% CI: 14.5 - 18.2
Harrell-Davis method			
99th percentile Clinical Decision Value	26.1 ng/L	21.0 ng/L	28.6 ng/L
90% Confidence Interval	90% CI: 20.7–31.5	90% CI: 13.9 - 28.0	90% CI: 23.9 – 33.3

*Differences for the 99th percentile cutoffs between the male and female cohorts achieved statistical significance.

A-082

Natriuretic Peptide NT-proBNP: Method comparison of two analysers.

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Background: Here we summarize the outcome of a comparison study to evaluate NT-proBNP assay. It has been performed at two analysers, AQT90 Flex from Radiometer®, a point of care technology, and cobas e801 from Roche Diagnostics®, the gold standard.Natriuretic peptides are secreted by the heart into the bloodstream as a result of an increase of intracardiac volumes and pressures. NT-proBNP has become an important biomarker of heart failure. The aim of the study is to compare the results and their interchangeability in order to determine the concordance between both immunoassays. **Methods:** The measurements were performed in serum samples from random real patients. The samples were processed in both analysers at the same day, in parallel. Statistical analysis was carried out with the MedCalc software, where the

correlation was calculated by the Pearson´s coefficient, the Passing-bablok regression and Bland Altman plots. **Results:** Below, there is a summary data table of the regression results.

Test	Instrument	Study Unit	N	Correlation coefficient Pearson r	Passing-Bablok		
NT-proBNP Serum	**x = AQT90 Flex; y = Cobas e801**	**pg/mL**	**124**	**0,9974** CI 95% = 0,9963 - 0,9982	**Slope= 0,93** CI 95% = 0,91 - 0,95**1 not included**	**Intercept= 0,79** CI 95% = (-5,52) - 5,40**0 included**	**Deviation from linearity P = 0,52 No significant deviation from linearity**

Results show a high degree of correlation coefficient and adjustment to linearity; however, there exists a **proportional bias**. It would be necessary to check the clinical concordance of the results, checking if this bias could be ignored under our working standard conditions.Concordance according to cut-off for heart failure was 96% (119/124). These five different results were in grey zone, very close to cut-off.**Conclusion:** Results from both analysers show a good correlation between the two methods. Due to the high clinical concordance, the proportional bias we found in the method comparison could be ignored and the interchangeability of methods is possible. Point of care technology offers a short response time what added to a good correlation results with the gold standard open an option to further accelerate the diagnosis of heart failure and thereby the initiation of adequate therapy.

A-083

Development and Evaluation of Analytical Performance of Immunoassay for the High Sensitive Measurement of Cardiac Troponin I for LUMIPULSE® L2400 Analyzer

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Background: Cardiac Troponin I (cTnI) and T (cTnT) are being used internationally as the standard biomarkers for the detection of myocardial injury, risk stratification in patients suspected of acute coronary syndrome (ACS) and for the diagnosis of myocardial infarction. In the recent international guidelines, algorithms are presented for rule-in and rule-out of non-ST-elevation myocardial infarction with the use of high-sensitivity (hs) cTnI or cTnT. We have developed new high sensitivity cTnI IVD kit, Lumipulse Presto hs Troponin I which is a fully automated chemiluminescence enzyme immunoassay (CLEIA) for LUMIPULSE L2400 analyzer. The higher throughput (240 tests/h) and STAT mode (approx. 15 minutes measurement time) of LUMIPULSE L2400 allows for quicker diagnosis. The analytical performance of the Lumipulse Presto hs Troponin I assay was evaluated, and compared with other hs cTn assays. **Methods:** Lumipulse Presto hs Troponin I is a two-step sandwich CLEIA. The resulting reaction signals are proportional to the amount of cTnI in the serum or plasma sample allowing quantitative determination of cTnI. Analytical performance of the assay was evaluated on LUMIPULSE L2400 analyzer (with STAT mode) according CLSI guidelines. **Results:** Limit of blank (LoB), detection (LoD) and quantitation (LoQ) were 0.5 pg/mL, 0.9 pg/mL and 2.7 pg/mL or less, respectively. The 99th percentile URL, imprecision at 99th percentile and detectable healthy population were estimated to be 21.0 pg/mL, 1.7%CV and 93%. Linearity was demonstrated over the range 2.5 to 46151.5 pg/mL. The coefficient of variation (CV) of total imprecision was 1.3 - 2.2%CV with 8 levels of samples. Results of method comparisons were correlation coefficient = 1.00, regression slope = 1.07 against Lumipulse G hs Troponin I, correlation coefficient = 1.00, regression slope = 0.98 against Architect high sensitivity Troponin I. While correlation with Roche hs Troponin T was correlation coefficient = 0.93, regression slope = 10.13. The measurement value variations by various interferences (bilirubin, hemoglobin, triglycerides, chyle, total protein, rheumatoid factor and HAMA) were ≤ 10% at the clinically high enough concentration. Unlike cTnT assay, no significant interference by hemoglobin was observed. **Conclusion:** Lumipulse Presto hs Troponin I assay met the latest criteria for "high-sensitivity" proposed by IFCC. The assay showed high assay precision, high robustness and high correlation with current hs-cTnI assays, Lumipulse G hs Troponin I and Architect high sensitivity Troponin I assays. It is expected that the new assay is useful as an aid in the diagnostics and risk management of ACS patients.

A-084

Human Epididymis protein 4 levels in acute cardiac failure

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Introduction:
Cardiac failure is a major health problem worldwide that concerns the health systems of developing countries. Cardiac failure is a clinical diagnosis based in specifics signs and symptoms but several laboratory markers had been proposed for its diagnosis. NT-proBNP is the only biomarker used for the diagnostic and prognostic of cardiac failure and it had been included in specific guidelines. There are a few studies that have seen association between HE4 (human epididymis protein 4)and acute heart failure severity in patients without tumoral pathology and normal renal function.
Objective:
We evaluated the level of human epididymis protein 4 (HE4)in selected patients with normal renal function, without gynecological pathology and non tumoral pathology described in the clinical histories
Methods:
22 patients that consulted the Emergency Department, with myocardial infarction were selected. Determination of NT-proBNP was made in the first 24 hours seeking for a laboratory diagnostic of hearth failure. The determination of NT-pro BNP and HE4 was made using an immunologic assay. To analyze the data we have used SPSS 16. Patients were divided in two groups using the NT-proBNP diagnostic value as recommended by the European Society of Cardiology with 88% positive predicting value: 1. Heart failure group (HFG). 13 patients (6 men and 7 women). 2. non Heart failure group (nHFG). 9 patients (4 men and 5 women) We calculated the medians and the IQR of both groups and the area under the curve (AUC), sensitivity and specificity were estimated
Results:
The mean age of HFG group was 62.22 and for the nHFG group was 70.25. No sex or age differences were observed. The HE4 median and IQR of HFG group and nHFG group was 185.44 (98.96) pmol/L and 59.50 (7.84) pmol/L respectively. We found statistically significant differences between both group (p=0.002). The AUC was 0.88 [IC95% = (0,71-1,00)] with 75% sensitivity and 100% specificity with a cutoff point of 97.1 pmol/L
Conclusions
The present study suggests a positive association between increased HE4 levels in acute cardiac failure. Further studies are needed to investigate the value of HE4 as a biomarker in acute hearth failure.

A-085

Analytical performance of the Elecsys® Troponin T Gen 5 STAT assay

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Background: The Elecsys® Troponin T Gen 5 Short Turn Around Time (TnT Gen 5 STAT; Roche Diagnostics) assay received FDA clearance in January 2017 and provides a high negative predictive value for ruling out acute myocardial infarction. We report analytical performance of this assay, including specificity versus diverse troponin isoforms. **Methods:** Precision was evaluated using human Li-heparin plasma and PreciControl Troponin samples per Clinical and Laboratory Standards Institute EP05-A2; two runs per day in duplicate for 21 days (n=84). Samples were measured using the Elecsys TnT Gen 5 STAT assay on the **cobas e** 411 and **cobas e** 601 analyzers (three reagents lots). Specificity for cardiac troponin T (at concentrations of 14ng/L, 4,000ng/L and 7,000ng/L) was tested versus skeletal muscle troponin T and I, cardiac troponin I, and human troponin C. Cross-reactivity with endogenous substances (including biotin) and commonly used/cardiac-specific drugs was tested at cardiac troponin T concentrations of 15ng/L and 9,000ng/L. Analytical specificity criteria were: recovery within ±1.4ng/L for cardiac troponin T concentrations <14ng/L; recovery within ±10% for cardiac troponin T concentrations ≥14ng/L. **Results:** On the **cobas e 601** analyzer, coefficient of variation (CV) ranges for repeatability and intermediate precision were 0.7-3.0% and 1.5-6.4%, respec-

tively (human Li-heparin plasma: 7.42-9,455ng/L; **Table**). On the **cobas e 411** analyzer, CV ranges for repeatability and intermediate precision were 0.7-5.6% and 1.4-10.3%, respectively. No interference was observed with skeletal muscle troponin T (up to 10,000ng/L) or I (up to 100,000ng/L), cardiac troponin I (up to 10,000ng/L), or human troponin C (up to 80,000ng/L). No interference was observed when biotin was tested up to 82nmol/L (20ng/mL) or with each of 16 commonly used/18 cardiac-specific drugs at the concentrations tested. **Conclusion:** The Elecsys TnT Gen 5 STAT assay demonstrated good analytical performance on **cobas e** 411 and **cobas e** 601 analyzers.

Intermediate precision and repeatability of the Elecsys TnT Gen 5 STAT on the Cobas e 601 analyzer

		Repeatability		Intermediate precision	
Sample	Mean, ng/L	SD, ng/L	CV, %	SD, ng/L	CV, %
PreciControl cTnT 1	24.2	0.27	1.1	0.77	3.2
PreciControl cTnT 2	1971	13.3	0.7	45.0	2.3
Human Plasma 1	7.42	0.22	3.0	0.47	6.4
Human Plasma 2	13.5	0.25	1.9	0.56	4.1
Human Plasma 3	154	1.23	0.8	2.24	1.5
Human Plasma 4	4831	38.0	0.8	124	2.6
Human Plasma 5	9455	62.7	0.7	256	2.7

Legend: SD, standard deviation; CV, coefficient of variation

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Heart-type fatty acid-binding protein measurements to aid in interpreting abnormal and non-changing cardiac troponin concentrations

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Background: Stable or non-changing abnormal high-sensitivity cardiac troponin (hs-cTn) concentrations may indicate the presence of cardiac diseases other than acute coronary syndrome, or might even identify an analytical interference resulting in this high concentration. There are heterophile antibodies, autoimmune antibodies to cardiac troponin, and even macrocomplexes that may result in an abnormal hs-cTn concentration. When evaluating possible interferences affecting hs-cTn assays it may be useful to measure another cardiac biomarker using another type of methodology. In this regard, heart-type fatty acid binding protein (H-FABP), a biomarker that is released early after cardiac injury, and can be measured turbidimetrically on chemistry analyzers with open-channel capabilities might prove to be useful when investigating a possible analytical reason for abnormally high and non-changing hs-cTn concentrations. Our objective was to validate the Randox H-FABP on the Abbott ARCHITECT c8000 and to assess if measuring H-FABP in patients' samples with elevated and non-changing hs-cTn concentrations could identify analytical interferences. Methods: The Randox H-FABP assay, a latex particle-enhanced turbidimetric assay, was loaded on the Abbott ARICHTECT c8000 platform, with total imprecision at two concentrations assessed over 2 months, linearity evaluated (5 different concentrations), stability (freeze [- 80^{0}C]/thaw cycles and room temperature with EDTA plasma) assessed, with matrix comparison (lithium heparin versus EDTA plasma) and correlation with Abbott hs-cTnI concentrations in EDTA plasma. Also, EDTA plasma samples from patients with persistently elevated and stable cTnI concentrations (Abbott hs-cTnI≥52ng/L which equates to ≥2xULN/99th=26ng/L with change between results <20%) from patients with a primary discharge diagnosis not related to a cardiac etiology were collected and frozen (-20^{o}C). These samples were tested with the H-FABP assay (ULN/99th=6.3ng/L) and with polyethylene glycol (PEG) precipitation to identify macrocomplexes. Results: The imprecision (%CV) with Randox QC level 1 = 5.39 ug/L was 14.8% (n=40) and QC level 2 = 31.16 ug/L was 3.6% (n=37). The assay was linear from 3.8 ug/L to 95 ug/L. H-FABP was stable after 4 freeze/thaw cycles and, at room temperature, up to 150 hours in EDTA plasma as differences from baseline measurements (i.e., room temperature sample H-FABP = 12.50 ug/L and freeze/thaw sample H-FABP = 15.11 ug/L) were <20%. Comparison between lithium heparin and EDTA plasma samples for H-FABP was acceptable (mean bias=0.05ug/L, n=20 paired samples, with H-FABP range from 4.94 to 25.78 ug/L). The correlation between H-FABP and hs-cTnI results from 100 EDTA plasma samples was weak to moderate (Spearman's rho = 0.383 (95%CI: 0.201 to 0.539); p<0.001. During the validation, there were 4 patients with a non-cardiac discharge diagnosis with elevated and stable hs-cTnI concentrations ≥2xULN, all 4 had H-FABP concentrations <2xULN with 3 patients also having macrocomplexes that resulted in the high hs-cTnI concentration. Conclusion: The Randox H-FABP assay on the Abbott ARCHITECT c8000 analyzer yielded acceptable imprecision, linearity, and comparability between different matrices and under different storage conditions. H-FABP measurement might be useful when investigating patients with persistently high hs-cTn concentrations who do not have a clear cardiac etiology for this elevation; as the presence of macrocomplexes might be the cause for the elevation.

A-087

Characterisation of microparticles in patients with acute coronary syndrome - a pilot study

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Background: Extracellular vesicles (EVs) in human blood can be subdivided into microparticles (MPs), 0.1-1µm in size, and exosomes below 0.1µm in size. MPs consist of a phospholipid bilayer and a substantial number expose procoagulant phosphatidylserine. They derive from different cell types upon proliferation, activation or apoptosis. It was shown that the number of MPs increases in thrombotic, inflammatory and hypoxic situations and it is suggested that they play an important pathophysiological role. We evaluated the amount and subtypes of MPs in patients with acute coronary syndrome (ACS) compared to a control group of patients presenting with chest pain, but without ACS. The characterization of MPs in ACS may give a better insight into the pathophysiology of the disease and add prognostic relevant information for the risk stratification. **Methods:** This is an ongoing study that recruited patients with thoracic pain suggestive for ACS from the emergency unit of the Kantonsspital Aarau/Switzerland and from the University Hospital in Vienna/Austria. Patients with recent myocardial infarction, malignancy, pulmonal embolism, pneumonia, sepsis or acute infection, severe heart or renal failure were excluded as in these patients increased MPs are suspected. Preliminary results derive from the first center, where patients have been divided into ACS-positive (n=26) and ACS-negative (n=36) groups are presented here. Citrate blood was immediately drawn upon presentation (t1), and for ACS-patients also approx. 4 hours later (t2) and on the next day (t3). Blood tubes were transported to the laboratory on foot without agitation and immediately centrifuged two times to receive platelet free plasma (PFP). PFP was stored at -80°C until batch analysis using a 4 laser flow cytometer (CytoFLEX, Beckman Coulter). The gate for MPs was set with silica beads and triggering was done on Annexin-V Cy5. Different MPs were investigated using calcein and Annexin-V combined with fluorescence labeled antibodies against erythrocyte (EMPs), platelet (PMPs), monocyte (MMPs) and endothelium (EnMPs) derived MPs. Additionally, CRP and N-terminal pro B-type natriuretic peptide (NT-proBNP; both on a Dimension Vista from Siemens Healthineers) and high-sensitivity cardiac troponin I (hs-cTnI; Architect analyser from Abbott Diagnostics) were measured. Mann-Whitney U test for between group comparison, Wilcoxon test for within group comparison and Spearman rank correlations were performed by SPSS 24. **Results:** These preliminary results show that Annexin-V positiv MP levels were significantly increased in ACS-patients at t2 and t3 compared to controls (p=0.008 and p=0.038, respectively) and between ACS patients at t1 and t2 (p=0.039). EnMP concentrations (CD31+CD54+CD146+CD42-) were significantly higher in ACS-patients than in controls upon presentation (p=0.03) and significantly higher at t2 in ACS compared to controls (p=0.016). Similar results were found for the subgroup of NSTEMI patients. There was a significant correlation between EnMPs and CRP (r=0.388, p=0.002), hs-cTnI (r=0.408, p=0.002) and NT-proBNP (r=0.486, p<0.001). **Conclusion:** Annexin-V positive MPs and EnMPs were significantly increased in ACS patients compared to controls. Further, EnMP concentrations correlated significantly with established cardiac markers, suggesting Annexin-V and EnMP as prospec-

tive candidates for the evaluation of their prognostic value in a follow-up of ACS patients.

A-088

Performance Evaluation of Atellica IM High-Sensitivity Troponin I Assay in a CORE Laboratory

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Background: The objective of this study was to verify the analytical performance (precision) of the Siemens Healthineers Atellica IM High-Sensitivity Troponin I (TnIH) Assay on the Atellica® IM Analyzer, and perform method comparison vs. ADVIA Centaur® High-Sensitivity Troponin I (TNIH) assay, and Dimension EXL® High Sensitivity Troponin I (TNIH) assay. In addition, the effects of hemolysis and biotin were assessed. **Methods**: The assay is a dual-capture sandwich immunoassay using magnetic latex particles, a proprietary acridinium ester for chemiluminescence detection, and three monoclonal antibodies. Precision studies were performed according to CLSI protocols EP05-A3 and EP15-A3 using lithium heparin plasma samples - two sample pools (SP), and three levels of controls. One aliquot of each sample pool and each QC material was tested in replicate in two runs per day on each analyzer for a minimum of ten days with one lot of reagent and calibrator. Each run was separated by at least a two hour time interval. A total minimum of 40 replicates were generated per sample. Hemolyzed samples (150 mg/dL and 500 mg/dL) and samples spiked with biotin (30 and 1500 ng/mL) were run in duplicate on the Atellica IM TnIH Assay. **Results:** Precision studies agreed with the manufacturer's claims: Within day (repeatability) CV%(SD)s were 3.1(0.36), 2.7(0.69), 1.7(1.66), 2.2(5.60), and 1.5(84.62) for concentrations of 11.43(SP), 25.57(SP), 98.48, 259.22, and 5805.88 ng/L; within lab (total) CV%(SD)s were 5.8(0.66), 4.5(1.15), 2.6(2.60), 2.8(7.20), and 1.5(85.29) respectively. Method comparison of Atellica IM TnIH Assay vs. ADVIA Centaur TNIH assay showed a regression slope of 0.88 (95%CI 0.862 to 0.902), intercept of 0.77 (95%CI 0.33 to 2.61), and correlation coefficient r=0.997 (n=39); and, Atellica IM TnIH Assay vs. Dimension EXL TNIH assay showed a regression slope of 0.97 (95%CI 0.933 to 1.01), intercept of -0.24 (95%CI -6.13 to 9.48) and correlation coefficient r=0.998 (n=0.998). All hemolysis (up to 500 mg/dL) and biotin (up to 1500 ng/mL) samples tested with the Atellica IM TnIH Assay demonstrated ≤10% change in results. **Conclusion:** The Atellica IM TnIH Assay has demonstrated good precision for detecting low cardiac troponin I concentrations and good correlation with the Dimension EXL TNIH assay and a slight negative bias with the ADVIA Centaur TNIH Assay. At levels of biotin up to 1500 ng/mL and hemolysis up to 500 mg/dL, there was ≤10% change in results.

A-089

Atellica IM High-Sensitivity Troponin I Assay: Analytical Evaluation Among University Hospitals

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Siemens Healthineers supported the study by providing systems, reagents, and protocols, and contributed to data analysis. **Background:** Cardiac troponin is the favorite biomarker for aiding in the diagnosis of myocardial infarction (MI). By definition, high sensitivity troponin assays must demonstrate increased analytical sensitivities and gain of precision at the lower concentrations, allowing the time point shortening of serial measurements, and improving their diagnostic sensitivity for early MI detection. The Atellica® IM High-Sensitivity Troponin I (TnIH) Assay is an *in vitro* diagnostic immunoassay for the quantitative determination of cardiac troponin I (cTnI) in serum or plasma (lithium heparin). The goal of this study was to check TnIH Assay analytical precision run on Atellica® IM 1600 Analyzer, and to compare TnIH Assay to Abbott ARCHITECT STAT High Sensitive Troponin-I (ARCHITECT TnIhs) and ADVIA Centaur High-Sensitivity Troponin I (TNIH) assays. **Methods:** The Atellica IM TnIH Assay is a dual-capture sandwich immunoassay using three monoclonal antibodies, magnetic latex particles and an unique proprietary acridinium ester for chemiluminescence detection. Precision studies were performed according to CLSI protocols EP05-A3 and EP15-A2 using lithium heparin plasma samples (two sample pools), and three levels of quality controls (QC). One aliquot from each pool and each QC material was tested in duplicate using one lot of reagent and calibrator (two runs per day on each analyzer) during at least ten days. Each run was kept apart by at least a two hour time interval. At least 40 replicates were generated for each of the two sample pools and the three levels of QC. Method comparison was performed according to EP09-A3. cTnI samples (lithium heparin) were obtained from acute chest pain patients selected in three university Emergency Departments (Bichat, Beaujon and Tenon). Serial samples were collected on two times, one at admission and one within 1, 2, 3, or up to 6 h later and were tested using the three cTnI assays. Assay comparisons were made using Deming correlation. **Results:** Within run repeatability for cTnI concentrations of 10.7, 25.0, 95.0, 252.8, 5717.0 ng/L (CV%(SD) were 3.6 (0.38), 2.9 (0.73), 1.6 (1.50), 1.7 (4.35), and 1.2 (67.03). Within lab (total) CV%(SD)s were 6.8 (0.72), 3.4 (0.85), 4.0 (3.78), 4.3 (10.93), 2.7 (154.90), respectively. Atellica IM TnIH Assay comparison with Abbott ARCHITECT TnIhs assay (range 0.28 ng/L to 15,989 ng/L for Atellica IM TnIH Assay and range 0.2 ng to 30,602 ng/L for Abbott ARCHITECT assay; n=99) showed a slope of 1.01 (95%CI 0.885 to 1.152) and intercept of 0.77 (95%CI -0.195 to 1.898), r=0.964, and with ADVIA Centaur TNIH assay (range 0.28 ng to15,988 ng/L for Atellica IM TnIH assay and range 0.36 ng to 16,473 ng/L for ADVIA Centaur TNIH assay; n=97) a slope of 1.02 (95%CI 1.004 to 1.039) and intercept of 0.68 (95%CI 0.437 to 1.065), r=0.999. **Conclusion:** The Atellica IM TnIH Assay demonstrated acceptable precision for detecting low cTnI concentrations and confirmed the manufacturer's claims. Furthermore, no significant analytical bias was found when compared to two commercially available high sensitivity cTnI assays.

A-090

Will different clinical cut-offs impact the diagnostic accuracy of hs-cTnI assays in suspected ACS patients?

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Background: BACKGROUND: Chest pain is a common cause of hospital admission world widely and is a major burden on healthcare resources. Cardiac troponin assays have substantially improved the accuracy of diagnosis and prognostic assessment of patients with suspected acute coronary syndrome (ACS). We aim to investigate the influence of different choices of cut-offs for high sensitivity cardiac troponin I (hs-cTnI) assays in patient admission or discharge (according to assigned color code and pain during triage), in order to identify the best senario in terms of diagnostic accuracy and the need of hospitalization. **Methods:** METHODS: A retrospective analysis was conducted on 586 Emergency Department (ED) patient records within a month who had chest pain complaints in 2017. Only patients who were diagnosed with ACS were included in the analysis. Patients with non-cardiac diagnosis such as thoracic trauma were excluded. All eligible patient samples were measured using Beckman Coulter Access hsTnI and Abbott ARCHITECT hsTnI assays. We investigated three different scenarios using established hs-cTnI cut-off values for ruling in chest pain patients in our population: Beckman Coulter Access hsTnI's manufacture insert (male 19.8 ng/L and female 11.6 ng/L), gender specific 99th percentile cut-offs from Abbott hsTnI's manufacture insert (male 34 ng/L and female 15 ng/L) and 12 ng/L recommended by Dr. Shah's group for Abbott hsTnI (NCT01852123). Factors that could impact the need of hospitalization were further analyzed. **Results:** RESULTS: We included 338 patients (178 men and 160 women) with ACS diagnosis in our final analysis. The need of hospitalization was associated with troponin values above the hs-cTnI cut-offs adopted in each scenario with statistical significance (Abbott, p-value < 0.001; Beckman Coulter, p-value < 0.001; Shah, p-value < 0.001). No statistically significant difference was found among the three scenarios using various hs-cTnI cut-offs in identifying hospitalized patients. Moreover, the higher hsTnI cut-off is associated with an increased probability of admission, corrected for age, gender and color code (Abbott odds ratio (OR) 7.74, 95% CI 2.89-20.75, p<0.001; Beckman 3.93, 95%CI 1.89-8.18, p < 0.001; Shah 5.06, 95% CI 2.51-10.22, p < 0.001). The hospitalization is highly associated with the color code (p<0.001) given during the triage. **Conclusion:** CONCLUSION: In our patient population, there is no statistically significant difference among the three scenarios adopting different hs-cTnI cut-offs in identifying hospitalized patients. There is a statistically significant association observed between the color code given during the triage, the hs-cTnI level and the hospitalization. Therefore, the appropriate use of hs-cTnI assays is the key to the correct diagnosis.

A-091

High-sensitivity cardiac troponin T assay has increased susceptibility to biotin interference

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Background: Biotin, vitamin B7, can interfere in assays that have streptavidin-biotin interaction as a part of their assay reaction. The high-sensitivity cardiac troponin T generation 5 assay (hs-cTnT) now available in the US is one of the assays vulnerable to biotin interference because of its assay design. Given the importance of the hs-cTnT assay in rapidly ruling-in and ruling-out acute myocardial infarction (AMI) in patients presenting with chest pain in the emergency department (ED)[2], we sought to evaluate the extent of biotin interference in the new assay in comparison to the contemporary 4th generation troponin T assay (cTnT). Further we sought to estimate the impact of biotin interference in hs-cTnT in ruling out AMI through simulations based pharmacokinetic studies. **Methods:** This was a University hospital, laboratory based study of discarded blood samples received from patients presenting to the ED and referred for troponin measurement. 23 cTnT-positive patient samples were tested by hs-cTnT and cTnT assays after adding known plasma concentrations of biotin achievable from a 5-day course of biotin, 10 mg daily. Maximum plasma biotin concentrations of 140, 100 and 50 ng/ml achievable at 1, 2 and 4 h after the last dose taken on the 5th day were simulated. Next, biotin spiking experiment with a wide range of plasma biotin concentrations (10-2000 ng/ml), as required by the FDA was undertaken in cTnT positive patient samples. In the presence of biotin, false decreases >10% or suppression of cTnT values below the 99th percentile of upper reference limit and/or our institution's threshold for abnormal (hs-cTnT≥52 ng/L; cTnT≥0.01 ng/ml) were considered significant. **Results:** A simulation of daily biotin use in 23 cTnT-positive patient samples resulted in significant interference in hs-cTnT values compared with the cTnT assay. 78% and 33% of hs-cTnT results were falsely decreased below the upper reference limit of 19 ng/L at 140 and 100 ng/ml concentration of plasma biotin, respectively. Among 12 samples that were significantly abnormal (hs-cTnT≥52 ng/L), 83%, 70%, and 29% had values <52 ng/L at 1, 2, and 4 h post-dose biotin simulations, respectively. In contrast, cTnT results remained unaffected at these plasma biotin concentrations. In dose-dependent biotin testing, the hs-cTnT assay was susceptible to biotin interference at plasma biotin >31 ng/ml compared with a threshold >315 ng/ml for the cTnT assay. **Conclusions:** Our data suggest a significant risk of false rule-out or delayed rule-in of AMI in the presence of biotin with hs-cTnT, far more than with the prior cTnT assay, at plasma biotin concentrations reflecting those contained in commonly used over-the-counter supplements. We suggest careful history taking for OTC supplements in patients presenting for rule out of AMI using the hs-cTnT assay. We also suggest the manufacturer work to increase the biotin tolerance levels of the assay or convert it to a non-biotinylated assay. Finally, we advise health care systems using this assay to make ordering providers aware of the potential for biotin interference in hs-cTnT levels.

A-092

Performance Evaluation of the VITROS® hs Troponin I Assay* on the VITROS® 5600 Integrated and VITROS® 3600 and ECi/ECiQ Immunodiagnostic Systems

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Background: The Joint European Society of Cardiology/American College of Cardiology guidelines state that cardiac troponins are the preferred biomarkers for the detection of myocardial injury, for risk stratification in patients diagnosed with acute coronary syndrome, and for the diagnosis of myocardial infarction. Because of the demand for accurate and precise measurement of low troponin levels, there is an increased need for assays with improved analytical performance. **Methods:** We are developing a rapid, fully automated high sensitivity assay for the measurement of cardiac Troponin I (cTnI) in human serum and plasma (heparin) for use on the VITROS® Systems. The VITROS® hs Troponin I (hsTnI) assay uses an immunometric technique in which the cTnI present in the sample reacts simultaneously with one streptavidin-conjugated antibody, bound by biotin-BSA on the wells, and a dual antibody-horseradish peroxidase conjugate. The antigen-antibody complex is captured by the antibody coated on the wells. Unbound materials are removed by washing, and the bound HRP conjugate is measured by a luminescent reaction. A reagent containing luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The amount of HRP conjugate bound is directly proportional to the concentration of cTnI present in the sample. The time to first result in the system is 15 minutes. **Results:** Preliminary data show an assay range of 1.70 - 30,000 ng/L. The Limit of Blank, Limit of Detection, and Limit of Quantitation (LoQ) of 0.29 ng/L, 1.04 ng/L, and 1.70ng/L (20% CV) respectively were established according to CLSI-EP-17-A2. The LoQ concentration at 10%CV was 4.34 ng/L. In a CLSI-EP05-A3 precision study, five precision pools with mean cTnI concentrations of 2.19, 21.45, 131.0, 523.1 and 17,778 ng/L had within-run percent coefficient of variation (%CV) of 12.71%, 1.53%, 1.45%, 1.26%, and 1.67% respectively and within-laboratory %CV of 19.33%, 5.54%, 3.16%, 3.46%, and 3.42% respectively. Correlation between the VITROS hsTnI assay and the contemporary VITROS Troponin I ES (TropIES) assay was obtained using 123 patient samples spanning the common measuring range of the two assays. The regression statistics, using Passing and Bablock, were as follows: VITROS hsTnI = 1.02*TropIES - 4.51; Pearson Correlation Coefficient (r) = 1.00. **Conclusion:** In summary, the VITROS® hs Troponin I assay demonstrates reliable and acceptable performance on the VITROS® 5600 Integrated and VITROS® 3600 and ECi/ECiQ Immunodiagnostic Systems. *Under Development

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Human cardiac TnI degradation and antibody selection for the assay development

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Background: The measurement of cardiac troponin I (cTnI) in blood is one of the most trusted methods of acute myocardial infarction (AMI) diagnosis. However, in spite of a long history of this biomarker in clinical practice, the selection of antibodies for new generations of cTnI assays remains a complex task. Over the last decade it was shown that the samples of some patients contain autoantibodies that negatively interfere with most of the immunoassay mAbs which are specific to the central (~40-130 amino acid residues, aar) fragment of cTnI (which is considered to be the most stable part of the cTnI molecule). In the current study we aimed: a) to analyze the dynamics of cTnI degradation after AMI, and b) to border cTnI proteolytic fragments that are presented in the circulation of AMI patients in order to determine the epitopes of antibodies that are not significantly influenced by the proteolytic degradation. **Methods:** Serial blood samples were collected from 66 patients over a period of 1-36 hours following the onset of AMI, both before and after stenting. cTnI and its fragments were studied by Western blotting and fluoroimmunoassay analysis. **Results:** In the blood of all AMI patients, cTnI was presented by an intact molecule and 11 major fragments with relative molecular masses of 14-24 kDa. Stenting neither affected the repertoire nor the ratio of different cTnI fragments. The ratio of full sized cTnI and its fragments did not change considerably within the first 36 hours after the onset of AMI. mAbs with the epitopes located between ~23-196 aar recognized more than 80% of all detected cTnI. **Conclusion:** The composition of cTnI fragments in the circulation is mainly constant within the first 36 hours following AMI. More than 80% of all detected fragments comprise 23-196 aar of cTnI which enables the utilization in immunoassays antibodies that are specific to the regions 23-40 and/or 140-196 that are only mildly affected by autoantibody interference.

A-094

Serum Gamma-Glutamyltransferase Levels are Associated with Cardiovascular Risk Factors in China:A Nationwide Population-Based Study

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Background: Serum Gamma-Glutamyltransferase (GGT), which is mainly derived from the liver, is a sensitive marker of liver cell damage and oxidative stress. More recently, it has been found that the increased plasma activity of GGT is also associated with cardiovascular disease (CVD). However, data on the relationship between GGT and cardiovascular risk factors (CRFs) are lacking in nationally representative samples of the Chinese population. Here, we aim to investigate both the association between GGT and CRFs and CRFs clustering. Methods: A cross-sectional survey was conducted in a nationally representative sample of 22897 adults aged 18 years and older from 2007 to 2011, including a plurality of ethnic minorities. Questionnaires and physical examinations were performed, and laboratory measurements were collected. The participants were then divided into quartiles of sex-specific serum GGT. Results: People in Northern and Rural areas tended to have a greater chance of belonging to the upper quartiles of GGT, and for ethnic groups, Mongolians had the highest serum level of GGT. From the low to the high GGT quartile, the incidence of each CRF and clustered risk factors increased after adjusting for age, uric acid (UA), drinking, ethnicity and all other risk factors. Subjects in the upper stratum (>75th percentile) had higher prevalence rates of CRFs than did those in the lower stratum. Furthermore, the individuals with clustering of 1, 2 or ≥3 CRFs were still more likely to belong to the upper GGT quartiles (75th percentiles) than were those without risk factors in both genders. Conclusion: Our data highlight the association between higher serum GGT levels and CRFs in Chinese adults. We found that people with higher serum GGT levels tend to have a greater chance of CRFs and that there was a dose-response association between the number of CRFs and higher serum GGT, especially in men, suggesting that serum GGT may serve as a valuable clinical marker of cardiovascular disease in China. Further studies are needed to elucidate the causality between serum GGT and CRFs and to evaluate the effects of serum GGT lowering therapies on CVD prevention and outcome.

A-095

Sex-specific versus universal clinical decision limits for troponin I and T for the diagnosis of acute myocardial infarction -a systematic review

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Background: The universal clinical decision limits of high-sensitivity cardiac troponin I (hs-cTnI, 26 ng/L) and T (hs-cTnT, 14 ng/L) may contribute to underdiagnosis of acute myocardial infarction in women. We performed a systematic review to investigate sex-specific and universal 99th percentiles of hs-cTnI and hs-cTnT derived from healthy reference populations. **Methods:** We searched in PubMed and EMBASE for original studies, and by screening reference lists. Reference populations designed to establish 99th percentiles of hs-cTnI(Abbott) and/or hs-cTnT(Roche), published between January 2009 and October 2017, were included. Sex-specific and universal 99th percentile values of hs-cTnI and hs-cTnT were compared with universal clinical decision ranges (hs-cTnI: 23.3-29.7 ng/L, hs-cTnT: 12.7-24.9 ng/L). **Results:** A total of 28 studies were included in the systematic review. Of 16 hs-cTnI and 18 hs-cTnT studies, 14 (87.5%) and 11 (61.1%) studies reported lower female-specific hs-cTn cut-offs than universal clinical decision ranges, respectively. Contrary, men-specific thresholds of both hs-cTnI and hs-cTnT were in line with currently used universal thresholds, particularly hs-cTnT (90% concordance). The variation of estimated universal 99th percentiles was much higher for hs-cTnI than hs-cTnT (29.4% versus 80.0% of hs-cTnI and hs-cTnT studies reported values within the current universal clinical decision range, respectively). **Conclusion:** Our data show substantially lower female-specific upper reference limits of hs-cTnI and hs-cTnT than universal clinical decision limits of 26 ng/L and 14 ng/L, respectively. The statistical approach strongly affects for the hs-cTnI threshold. Downwards adjustment of hs-cTn thresholds in women may be warranted, to reduce underdiagnosis of acute myocardial infarction in women.

A-096

Decision limits, delta troponin or both for the confirmation and exclusion of myocardial infarction using contemporary and high sensitive assays

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Objective: To examine the impact of a combination of a delta troponin with different decision limits for the rapid confirmation or exclusion of myocardial infarction (MI). Methods: The study was a sub study of 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 for measurement of a panel of cardiac markers. An additional blood sample was taken at admission and 90 minutes from admission, separated and the serum stored frozen until subsequent analysis. All patients were followed up to 30 days for major adverse cardiac events (MACE). Samples were analysed for cardiac troponin I (cTnI) by the Stratus CS (CS) (Siemens Healthcare Diagnostics), range 30-50,000 ng/L 10% CV 60ng/L 99th percentile 70 ng/L; the Beckman AccuTnI enhanced (B) (Access 2 , Beckman-Coulter) range 1 - 100,000 ng/L, 10% CV 30 ng/L, 99th percentile 40 ng/L, the Siemens Ultra (S) (ADVIA Centaur, Siemens Healthcare Diagnostics), range 6 - 50,000 ng/L, 10% CV 30 ng/L 99th percentile 50 ng/L. and cardiac troponin T (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 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 a value exceeding the 99th percentile and/or the combination of a delta troponin. Myocardial infarction was excluded when either the admission or all values fell below the limit of detection of the assay and there was no delta troponin. All other patients were classed as non-diagnostic. Results: Samples were available from 813 and serial samples in 617 /1132 patients enrolled in the study, 60% male, age 23.7-92.8 years median 53.8 years. The admission sample below the limit of detection (LOD) missed 0.6-1.2% of patients. Both samples remaining below the LOD of the assay with no delta change excluded myocardial infarction in 99.8% of cases and was associated with a MACE rate of 0.2-0.3%, all of which were readmissions with acute coronary syndrome. Use of a delta change did not improve detection of MI but increased the number of false positive diagnoses by 0.1-1.5%. Conclusion: Serial measurements are required for reliable rule out of MI. Troponin below the limit of detection measured with a sensitive or contemporary sensitive assay without a delta change identified a very low risk group who can be considered for immediate further investigation or discharge. The 99th percentile alone on serial sampling was the most effective. Rule in with a delta in addition generated false positive results.

A-097

Study of the association between bone mineral disorders <and> intradialytic hypertension in patients on maintenance hemodialysis

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Background:
Intradialytic hypertension (ID-HTN) affects up to 15% of hemodialysis (HD) patients and is associated with significant risk of hospitalization and death. Abdominal aortic calcification affects 81% of MHD patients with its severity increases with age, duration of dialysis and history of cardiovascular disease (CVD). Mineral Bone Disease (CKD-MBD) related factors such as serum calcium, phosphorus, and parathyroid hormone are strong-

ly associated with severity of Aortic calcification (AC) in HD patients. FGF-23 level increases progressively in CKD patients, beginning in its early stages achieving the highest values in end-stage renal disease (ESRD) patients, to maintain normal serum phosphate levels. Elevated FGF-23 has been linked with hypertension, left ventricular hypertrophy and increased cardiac mortality in CKD patients, but its role in pathogenesis of ID-HTN via inducing vascular calcification and stiffness remains to be explored.
Methods:
This study included sixty ESRD patients on regular HD for more than 6 months, that were classified into two groups; Group *(1):* forty five ID-HTN prone HD patients who developed episodes of ID-HTN in more than 2/3 of HD sessions done during last 3 consecutive weeks, and *Group (2):* fifteen hemodynamically stable (S) HD patients, without history of ID-HTN as a control group. To all subjects, laboratory investigations were performed including pre- dialysis serum urea, creatinine, electrolytes, minerals, iPTH and FGF-23. Abdominal aortic calcification score (AACS) was assessed in lateral abdominal radiographs by Kauppila method. Atherosclerosis score (AS) was calculated based on measurement of carotid intima media thickness (CIMT), detection of carotid plaques with or without significant stenosis and measurement of ankle brachial BP index.
Results:
Hypertension prone (HP) patients had significantly longer duration of dialysis and higher AACS compared with hemodynamically stable (S) patients. Serum phosphorus, calcium phosphorus product (CaPhP), iPTH and FGF23 were higher in HP than S patients, but the difference was not statistically significant. There was a statistically significant positive correlation between FGF23 and each of duration of dialysis (P = 0.003) and CIMT (P = 0.043). Moreover, AS had a statistically significant positive correlation with serum calcium (P = 0.009).
Conclusion:
The occurrence of ID-HTN is associated with significantly more advanced vascular calcification and fairly increased levels of humoral MBD mediators involved in this process like FGF23, iPTH and CaPhP. FGF23 significantly correlates with CIMT, possibly indicating its involvement in the atherosclerotic process from the early beginning. It remains to be elucidated whether interventions to control FGF23 rise and other MBD parameters would reduce ID-HTN episodes.

A-098

Analytical Evaluation of a New Ultra-Sensitivity Troponin I Assay using Human Serum

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Background: The universal definition of acute myocardial infarction (AMI) puts cardiac troponin at the forefront of diagnosis. With the advent of high-sensitivity assays for cardiac troponins the diagnosis of AMI can be made sooner with a higher degree of confidence. The objective of this study was to provide an analytical evaluation of a newly developed ultra-sensitivity cardiac troponin I assay (us-cTnI), using serum samples.
Methods: Us-cTnI was measured using the Sgx Clarity™ cTnI Assay (us-$TnI_{(Singulex)}$) on the Singulex Clarity System, with a reported limit of detection (LoD) of 0.08 ng/L and a 99th percentile upper reference limit (URL) of 8.67 ng/L in EDTA plasma. The us-$TnI_{(Singulex)}$ limit of blank (LoB) and LoD were calculated in this study after measuring the zero calibrator 22 times. Imprecision profile, linearity and sample stability were determined using pooled human serum samples. A sample type comparison was performed with paired serum and EDTA plasma. The 99th percentile URL was calculated with serum from 638 apparently healthy individuals (318 females and 320 males) using the Harrell-Davis quantile bootstrap statistical method. Receiver operating characteristic (ROC) curves were used to compare the clinical performance of the us-$TnI_{(Singulex)}$ with the hs-$cTnI_{(Abbott)}$ and hs-$cTnT_{(Roche)}$ assays in a limited study using serum; the hs-$cTnI_{(Abbott)}$ and hs-$cTnT_{(Roche)}$ 99th percentile URLs of 26.2 ng/L and 14 ng/L, respectively, were used as the diagnostic cut-offs. The hs-$cTnI_{(Abbott)}$ assay has a LoD of 1.1-1.9 ng/L and a 10% CV of 4.7 ng/L; the hs-$cTnT_{(Roche)}$ has a LoD of 5 ng/L and a 10% CV of 13 ng/L.
Results: The LoB was 0.01 ng/L and the LoD 0.04 ng/L. The 10% CV from the imprecision profile was 0.49 ng/L and the assay was linear from 0.5-20,000 ng/L. Serum samples with a cTnI concentration ranging from 0.59-18,148 ng/L had an overall positive bias of 36% when compared to EDTA plasma. Serum samples were stable for five days and for five freeze-thaw cycles at -20^{o}C, four days at 4^{o}C and for two days at room temperature. The overall 99th percentile URL was 4.33 ng/L (95% CI 2.83-5.72 ng/L) with 99.8% of individuals having a cTnI concentration above the LoD. The female 99th percentile URL was 2.53 ng/L (95% CI 1.66-3.99 ng/L) and the male 5.53 ng/L (95% CI 3.73-7.25 ng/L). Area under the ROC curves for the us-$TnI_{(Singulex)}$ when compared to the hs-$cTnI_{(Abbott)}$ and hs-$cTnT_{(Roche)}$ assays were 0.900 (95% CI 0.805-0.995) and 0.927 (95% CI 0.860-0.993), respectively.
Conclusion: The us-$TnI_{(Singulex)}$ assay had a LoB, LoD and 10% CV lower than any other assay currently on the market, making it the most sensitive cardiac troponin assay available. Sample stability was acceptable enough to allow both clinical and research applications. There was a matrix effect in serum when compared to EDTA plasma. The 99th percentile URL in serum was lower than that reported in EDTA plasma, which likely reflects differences in the underlying reference populations. There was an expected male/female difference in serum 99th percentile URL. Clinical diagnostic performance of the us-$TnI_{(Singulex)}$ assay appeared better than the predicate assays tested.

A-099

Simultaneous Assessment of N-terminal pro-B-type Natriuretic Peptide and Presepsin Improves Risk Prediction of Acute Kidney Injury and Mortality after Cardiac Surgery

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Background
Acute kidney injury (AKI) is common after cardiac surgery. Also sepsis has shown to contribute to the development of AKI in intensive care patients. Presepsin (PSEP) has proven as a marker with high diagnostic and prognostic validity in assessment of disease severity and association to kidney function in septic patients. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels reflect cardiac filling pressures. Therefore NT-proBNP is a surrogate marker for hemodynamic status. It has been shown association of NT-proBNP with AKI and cardiac events after cardiac surgery.
Objective
The aim of the present study was to evaluate the diagnostic validity of NT-proBNP and PSEP to predict the risk of cardiac surgery-associated AKI (CSA-AKI) and postoperative mortality in comparison with the inflammatory markers C-reactive Protein (CRP) and procalcitonin (PCT) and creatinine.
Methods
The marker concentrations were measured in plasma samples which were drawn in the early morning after surgery from 856 patients undergoing elective cardiac surgery. Outcome measures were postsurgical AKI during hospitalization and mortality. PSEP and NT-proBNP were determined by using PATHFAST Presepsin (LSI Medience corporation, Tokyo) and Elecsys NT-proBNP (Roche Diagnostics). CRP, PCT and creatinine were measured using routine clinical chemistry methods in the central laboratory.
Results
Patients who developed AKI (n=221, *25.8%*) had higher PSEP and NT-proBNP levels than patients without AKI (PSEP: 632 ng/L (IQR 378-1069) *versus* 304 ng/L (228-434), Difference 328 ng/L, p<0.0001; NT-proBNP: 1594 ng/L (IQR 667-3838) *versus* 352 ng/L (IQR 122-1084), Difference 1242 ng/L, p<0.0001. The results for 6-month death (n=49, *5.8%*) were PSEP: 337 ng/L (IQR 246-512) *versus* 1081 (511-1962), Difference 744 ng/L, p<0.0001 and NT-proBNP: 499 ng/L (IQR 161-1475) *versus* 2632 ng/L (IQR 1308-3874), Difference 2133 ng/L, p<0.0001 for survivors *versus* non-survivors, respectively. AKI has been assessed according to AKIN classification: stages 1 (n=122), 2 (n=54), 3 (n=45). The marker concentrations increased significantly from AKIN 1 to 3. Receiver operator curve (ROC) analysis for prediction of 6-month death revealed AUC values of 0.792 and 0.847 for NT-proBNP and PSEP compared to AUC values of 0.670, 0.778 and 0.639 for creatinine, PCT and CRP, respectively. Similar results were obtained for prediction of postsurgical AKI by ROC analysis. AUC values were 0.758 and 0.783 for NT-proBNP and PSEP, compared to AUC values of 0.671, 0.671 and 0.512 for creatinine, PCT and CRP, respectively. Examination of the predictive value of marker combinations by logistic regression revealed an AUC value of 0.796 for the combination PSEP and NT-proBNP. This finding demonstrated superiority of the simultaneous assessment by using the combination NT-proBNP and PSEP for the risk of developing postsurgical AKI compared to the markers alone and to all other possible marker combinations.
Conclusion
PSEP and NT-proBNP demonstrated comparable predictive power for risk of 6-month mortality after cardiac surgery and to identify patients who were at risk of developing CSA-AKI. Moreover, the combination of both markers was found to improve the prognostic performance. The simultaneous assessment of NT-proBNP and PSEP allows early risk prediction of AKI already at the first day after surgery and may enable individual risk stratification with appropriate individualized patient care.

A-100

The implementation of the high sensitivity Troponin T (hs-TnT) generation five assay at a large teaching county hospital. A multi-speciality effort

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Background
A highly sensitive Troponin T assay (hs-TnT) was recently approved by the FDA for clinical use. In addition to the assay's much improved sensitivity, the reporting units, reference intervals and critical limits for notification are markedly different. Furthermore, current acute myocardial infarction (AMI) rule out protocol requires serial samples and monitoring for up to 6 hours and it is not known if adopting hs-TnT will impact the protocol. This report describes the implementation of the hs-TnT assay at a large teaching county hospital.
Methods:
A multi-speciality team from Clinical Chemistry, Laboratory Administration and Information Technology support services, Nursing, Cardiology, Hospitalists, Performance Improvement and Emergency departments was set up. The hs-TnT assay was validated as per protocol on the Cobas® 6000 system, e601 immunoanalyzer (Roche Diagnostics) for analytical performance. Samples received into the laboratory from patients being investigated for acute coronary syndrome were analysed using the conventional 4th generation TnT assay and results reported in the usual manner. The Fifth generation hs-TnT was also measured but results not reported to the electronic medical record. The imprecision of the assay was assessed at recommended decision levels. A new test code was set up in the Laboratory Information System, for the hs-TnT with test specific parameters for measurements limits and critical value. At three months of data and clinical correlation, educational materials were prepared and training sessions conducted for pathology residents and staff, nursing staff, and medical staff, by the clinical chemist, nursing education, and cardiologists respectively.
Results:
969 samples from 541 patients (56% men, 44% women) being investigated for acute coronary syndrome were analysed for both conventional and fifth generation hs-TnT. There was no numerical correlation between the two assays on admission (P=0.39). Laboratory results of both assays correlated well when using clinical assessment of patients. A two step one hour and 3 hours rule-out protocol was developed. The imprecision of the hs-TnT assay ranged from 0% at 12.0 ng/L, 3.3 % at 16.4 ng/L, 2.2% at 24.4, 2.1% at 42.6 ng/L, and 0.9% at 60 ng/L. Training sessions were completed on time and educational material circulated through the hospital units and made available through the electronic laboratory handbook. The implementation was done in 2 steps: first phase targeted the Rapid Response Lab performing over 5,000 Troponin tests a month serving the critical care areas. A second phase, 6 weeks later, added the Core Lab supporting the inpatient non-critical units and the outpatient clinics.
Conclusion:
Manufacturer's claim for assay performance was successfully verified. The imprecision of the assay was acceptable at the established decision limits rule out (<6 ng/L) and a delta of 3 ng/L on serial samples. A real-world pre-implementation scenario was conducted where samples were assayed for both conventional and 5th generation hs-TnT to assess potential impact on patients, and on current and new protocols. This provided the basis for educational material needed to support the implementation.

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Performance Evaluation and Method Comparison of Atellica IM High Sensitivity Troponin I Assay

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Background: The objective of this study was to verify the analytical performance of the Siemens Healthineers Atellica® IM TnIH Assay* on the Atellica® IM 1600 Analyzer, and perform method comparison vs. Roche Cobas® e411 HS-TnT assay, ADVIA Centaur® High-Sensitivity Troponin I (TNIH) Assay, and Dimension Vista® High Sensitivity Troponin I (TNIH) assay. The effects of hemolysis and biotin were assessed.
Methods: Precision studies were performed per EP05-A3 and EP15-A3 using three levels of controls. A total minimum of 40 replicates were generated per sample. Limit of Blank (LoB) and Limit of Detection (LoD) were evaluated per EP17-A2. Linearity verification was performed (EP06-A). Method comparison was performed (EP09-A3). Serial measurements were obtained for lithium heparin samples from >50 chest pain ED patients. Troponin at admission and up to 6 h later were measured using the Atellica IM TnIH Assay, Roche Cobas e411 HS-TnT assay, ADVIA Centaur TNIH assay, and Dimension Vista TNIH assay. Hemolyzed samples (150 mg/dL and 500 mg/dL) and samples spiked with biotin (30 and 1500 ng/mL) were run in duplicate on the Atellica IM TnIH Assay.
Results: Precision results agreed with the manufacturer's claims: Within run repeatability CV%(SD)s for concentrations of 92, 242, and 5390 ng/L were 4,3(3.99), 3.5(8.49), and 3.6(195.2); within lab (total) CV%SDs were 5.4(4.97) 5.3(12.78), 5.1(272.38), respectively. LoB and LoD agreed with the manufacturer's claims of 0.58 ng/L and 1.27 ng/L, respectively. Method comparison of Atellica IM TnIH Assay vs. Cobas® e411 HS-TnT assay showed a Deming regression slope of 1.67 (95%CI 1.39 to 1.95) and intercept of -4.67 (95%CI -6.20 to -3.13) (n=118); Atellica IM TnIH Assay vs. ADVIA Centaur TNIH assay had a slope of 1.07 (95%CI 1.03 to 1.11) and intercept of 0.81 (95%CI 0.51 to 1.10) (n=127); and, Atellica IM TnIH Assay vs. Dimension Vista TNIH assay had a slope of 1.03 (95%CI 0.98 to 1.07) and intercept of -1.14 (95%CI -1.54 to -0.75) (n=122). All hemolysis (up to 500 mg/dL) and biotin (up to 1500 ng/mL) samples tested with the Atellica IM TnIH Assay demonstrated ≤10% change in results. Serial sample testing demonstrated good agreement among troponin assays in terms of trend between time points in patients where troponin was greater than the lower limits of the assay range. Discrepant results among high sensitivity assays involved patients where the difference between serial samples was <5 pg/mL.
Conclusion: The Atellica IM TnIH Assay has demonstrated good precision for detecting low cardiac troponin I concentrations and good correlation with the ADVIA Centaur and Dimension Vista TNIH assays. At levels of biotin up to 1500 ng/mL and hemolysis up to 500 mg/dL, there was ≤10% change in results.
* Siemens Healthineers supported the study by providing systems, reagents and protocols and contributed to data analysis.

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LC-MS quantification of BNP in plasma without immuno-enrichment

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Background:
B-type natriuretic peptide (BNP) is a cardiac hormone routinely measured in clinical laboratories to rule-out acute heart failure, and for screening or prognosis of heart failure. However, interpretation of BNP levels is not useful as a "rule-in" marker due to poor positive predictive value. The primary analytical technique used for BNP quantification in the clinic is the immunoassay, which is reported to show significant discrepancies among platforms due to several factors, including non-specificity of antibodies, heterogeneity of patient proteoforms, and patient phenotype. As yet, no attempts have been made to harmonize or standardize these clinical immunoassays through use of reference standards and the development of higher order approaches such as isotope dilution mass spectrometry (ID MS). BNP is found at exceedingly low serum concentrations, justifying an immuno-enrichment step prior to detection. One recent report detailing an antibody-free approach to quantifying plasma-spiked synthetic BNP allows for the possibility of achieving absolute quantification of BNP from matrix. In addition to abundance, stability is also a major concern for BNP quantification as the active form BNP_{1-32} is known to metabolize through numerous biochemical and enzymatic routes. At least 15 metabolites of BNP_{1-32} are known in blood of various chain lengths. This heterogeneity constitutes a major contribution of immunoassay variability. Here, isotope-labeled standards and LC-MS techniques have been used to measure BNP_{1-32} and its metabolites and estimate their stabilities in plasma. Further efforts have been made detect pre-spiked BNP at clinically-defined "healthy" levels using mass spectrometry in both intact and *in vitro* digested BNP, as well as native BNP_{1-32} in "diseased" patient samples.
Methods:
Isotopically-labeled and non-labeled synthetic, intact BNP standards were used for relative quantification of BNP metabolites using a targeted LC-MS/MS (MRM) approach. Isotopically-labeled and non-labeled synthetic tryptic peptides of BNP_{1-32} were used for estimating "total" BNP through a bottom-up technique, also based on LC-MRM-MS. An organic extraction pre-enrichment method and cleanup was optimized to measure BNP_{1-32} in clinically-obtained patient sera. This antibody-free approach permits use of an appropriate calibration system for the higher-order quantification of BNP.
Results:
An LC-MS/MS MRM method was optimized for quantification of BNP_{1-32} and 14 metabolites. BNP_{1-32} was shown to degrade rapidly in plasma (< 1% remaining after 2 hours). Other metabolites exhibited interesting kinetics, growing-in and degrading at various rates. Interestingly, "shared" tryptic peptides summed from all BNP metabolites were demonstrated to decrease slowly in abundance over time, suggesting possible unknown routes of BNP degradation. Synthetic BNP pre-spiked and extracted from plasma was detected down to <100 attamoles by LC-MS techniques, adequate for quantification at clinical levels. Native BNP

from patient sera was subsequently tested using the optimized LC-MS approach.
Conclusion:
Extending an antibody-free ID MS approach to the quantification of native BNP in plasma is necessary for development of the appropriate calibration system and measurement standards required to harmonize clinical immunoassays.

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Susceptibility of High Sensitivity Cardiac Troponin I and Gen 5 cTnT Assays to Biotin Interference

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Background: The FDA has alerted clinicians, laboratory personnel, and manufacturers of immunoassays that patient ingestion of high levels of biotin in dietary supplements can cause clinically significant incorrect lab test results. Depending on a test assay's configuration, increased biotin in patient samples can cause falsely high or low results. Our objective was to examine the susceptibility of two cardiac high-sensitivity troponin (hs-cTn) assays used globally in clinical practice to biotin supplementation. Methods: Four experiments were performed using excess, discarded lithium heparin plasma from patients with a positive cTnT (Roche 4th Gen) concentration. Overall, 133 specimens were analyzed by both the Abbott (investigational in US) hs-cTnI, Architect i2000), and Roche Gen 5 cTnT (cobas e601; FDA version of hs-cTnT used globally) assays. First, positive cTnT specimens (n=16) were titrated against a range of biotin levels (0-140 ng/mL) by simulating 1, 2, and 4-hour post-dose plasma biotin levels achievable for daily dose of 10 mg taken for 5 days. Second, the effect of mega doses of biotin (500 and 1000 ng/mL) was tested (n=10). Third, biotin levels were titrated against a range of biotin levels between 0 and 2000 ng/mL (n=12). Fourth, the effectiveness of streptavidin beads in blocking biotin that had been spiked into patient samples (n=3) was tested. Spiked samples with known levels of biotin (100 and 500 ng/mL) followed by blocking with 50 µL of streptavidin beads. The samples were then incubated at room temperature for 1 hour with intermittent shaking, centrifuged, and the supernatant was taken for cTn testing. False decreases at >10% or suppression of values below the 99th percentile URL (Gen 5 cTnT 16 ng/L, hs-cTnI 18 ng/L) in the presence of biotin were considered significant. Results: hs-cTnT concentration suppression crossed the 10% threshold at a 35 ng/mL biotin level. hs-cTnT concentrations were suppressed 24%, 50%, 78% and >90% at 50, 100, 140 and 500 ng/mL biotin levels, while hs-cTnI concentrations were <8% suppressed at all levels. 4%, 25%, 43% and 62% of hs-cTnT levels, respectively, were suppressed from increased to below the 99th percentile URL. Blocking with streptavidin beads eliminated hs-cTnT concentration suppression from 59% at 100 ng/L biotin and 95% at 500 ng/mL biotin levels to <7%. Conclusions. The Gen 5 cTnT assay that uses a sandwich immunoassay with biotinylated antibodies experienced significant negative interference with biotin concentrations at >35 ng/mL, that could result in false negative concentrations. The hs-cTnI assay was free from biotin interference at all concentrations tested.

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Highly Sensitive Cardiac Troponin Assay: Experience at a US Academic Medical Center

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Background: About 6 million patients present to the Emergency Department (ED) each year with complaints of chest pain. Of those, about 1.5 million rule in as having an acute myocardial infarction (MI). A key component of diagnosis is the rise and fall (>20%) of cardiac troponin (cTn), a highly sensitive and specific biomarker. A highly sensitive generation 5 (gen5) cTn assay has been in use in Europe and parts of Asia for over 10 years, but this was not clinically available in the United States. Recently, the FDA approved the gen5 assay for use within the U.S. In this study, the performance of a generation 4 (gen4) cardiac troponin T (cTnT) assay was compared to the highly sensitive gen5 cTnT assay for the first time within a U.S. healthcare system. **Methods:** Over a two-month period, all patients within University of California, San Diego (UCSD) Health in whom cTnT was ordered had both gen4 and gen5 measured. A total of 4,809 troponin orders from 2,516 patients (1,185 female and 1,221 male) were analyzed, giving an average of 1.9 troponin orders per patient. **Results:** The correlation between gen4 and gen5 (R^2) was 0.99 and 0.98 for male and female patients, respectively. The gen4 cTnT assay detected cTnT levels down to 0.01 ng/mL whereas the highly sensitive gen5 assay detected levels down to 0.006 ng/mL (6 ng/L). This increased sensitivity allowed for the detection of cTnT in 81% of samples (3879/4809) analyzed by the gen5 assay, whereas gen4 only detected cTnT in 33% of samples (1572/4809). Any detectable level of cTnT (> 0.01 ng/mL) using the gen4 assay was considered elevated. When using the gen5 sex-specific 99th percentile cutoffs of 14 ng/L for females and 22 ng/L for males, a total of 871 samples from 565 patients were positive by the gen5 assay but had undetectable levels by gen4. Many of these patients (302) had only a single troponin order, while 167 had at least a second cTnT ordered within 8 hours of the initial measurement. Of these 167 patients, 119 exhibited a stable elevation of cTnT by gen5 and 35 were detected by both gen4 and gen5 in the serial measurement. A total of 13 patients, however, exhibited >20% change in gen5 while remaining undetectable in gen4. Of these cases, 3 patients were diagnosed with a non ST-elevation MI (NSTEMI) and 2 with an ST-segment elevation MI. Two of the NSTEMI patients demonstrated a >20% elevation in cTnT using the gen5 assay before it was detected by gen4. **Conclusions:** The initial experience at UCSD Health was that gen5 cTnT detected elevations of cTnT in significantly more patients than the gen4 assay. The majority of these patients had stable elevations of cTnT. During this two month evaluation, gen5 cTnT detected a >20% changes in cTnT prior to detection by gen4 in several patients. These results confirm the importance of monitoring serial changes in time when implementing highly sensitive troponin assays and suggest that gen5 cTnT will allow for a faster rule-out protocol.

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Quantifying the prevalence of elevated biotin in a cohort with suspected acute coronary syndrome

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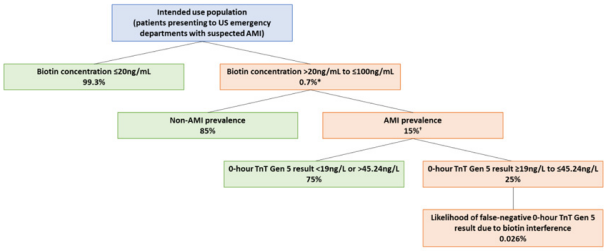
Background: Biotin can reduce recovery of the Elecsys® Troponin T Gen 5 (TnT Gen 5) assay at concentrations >20ng/mL (90% recovery), potentially leading to false-negative prediction of acute myocardial infarction (AMI). We aimed to determine the prevalence of biotin concentrations >20ng/mL and the 99th percentile biotin concentration in the intended use population. **Methods:** Biotin was quantified using an in-house assay (lower limit of detection: 0.1ng/mL) in residual 0-hour and 3-hour blood samples from 850 patients presenting to 15 US emergency departments with suspected AMI from July 2014 to October 2015. Potential impact of biotin on the negative predictive value (NPV) of the TnT Gen 5 assay and likelihood of false-negative AMI prediction was estimated at biotin concentrations 3 times the highest observed concentration (per Clinical and Laboratory Standards Institute [CLSI] EP07). **Results:** The 99th percentile biotin concentration for 0-hour samples was 2.62ng/mL and for 3-hour samples was 2.38ng/mL. These values are >7 times lower than the TnT Gen 5 assay interference threshold (conforming with CLSI EP07 criteria). Biotin was >20ng/mL in 1/797 (0.13%; 95% confidence interval [CI] 0-0.70%) 0-hour and 1/646 (0.15%; 95% CI 0-0.86%) 3-hour samples (30.23ng/mL and 24.48ng/mL, respectively); both samples were from the same patient. Based on extreme biotin assumptions derived from the study population (0.7% prevalence of 0-hour biotin up to 100ng/mL; maximal reduction in troponin recovery of 42% at 100ng/mL; 15% prevalence of AMI), 0-hour TnT Gen 5 results between 19ng/L and 45.24ng/L could potentially lead to false-negative AMI prediction. As 25% of patients with AMI had 0-hour results within this range, the likelihood of false-negative results due to biotin interference was estimated as 0.026% (**Figure**). **Conclusion:** Our results suggest biotin interference has a minimal effect on the NPV of the TnT Gen 5 assay and should not change current clinical practice.

Figure. Estimating the probability of false-negative AMI prediction, based on 0-hour TnT Gen 5 result, due to biotin interference



*Interference model assumed 0-hour biotin concentrations of 100ng/mL, approximately 3 times the highest observed concentration (30.23ng/mL); prevalence of 0-hour samples with biotin >20ng/mL was based on the upper confidence limit of the observed prevalence (0.13% [95% CI 0–0.70%]). †In the primary TnT Gen 5 study (Peacock et al. JAMA Cardiol 2017), 10.3% of patients were diagnosed with AMI; a more conservative estimate for AMI prevalence of 15% was used for this analysis.

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Baseline High-Sensitivity Cardiac Troponin I Aids in Risk Assessment in Patients with Diabetes, Hypertension, and Dyslipidemia without Myocardial Infarction

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Background: Cardiac troponin has been shown to be a powerful prognostic biomarker for patients both with and without acute coronary syndromes. The objective of our study was to determine use of baseline high-sensitivity cardiac troponin I (hs-cTnI) concentrations for the risk stratification of patients with diabetes, hypertension, and dyslipidemia among emergency department patients without acute myocardial infarction. Methods: Prospective, observational cohort study (UTROPIA) including patients presenting to a United States emergency department in whom high sensitivity hs-cTnI concentrations were measured on clinical indication using an investigational assay (Abbott, 99th percentile URLs: males 34 ng/L and females 16 ng/L). Patients with myocardial infarction (n=168) were excluded. We assessed the impact of comorbidities across the entire cohort for each hs-cTnI tertile. Outcomes examined were 180-day mortality and major adverse cardiac events (MACE). Results: Among 1,463 patients, 436 (30%) had diabetes, 947 (65%) had hypertension, and 612 (42%) had dyslipidemia. Tertile analysis of baseline hs-cTnI concentrations showed a higher risk for 180-day mortality and MACE, with increasing risk by tertile (T) for each comorbidity examined; diabetes (mortality: T1: 2.8%, T2: 3.3%, T3: 10.6% and MACE: T1: 4.2%, T2: 5.3%, T3: 21.8%); hypertension (mortality: T1: 2.9%, T2: 5.2%, T3: 9.7% and MACE: T1: 4.9%, T2: 6.4%, T3: 21.5%); dyslipidemia (mortality: T1: 2.0%, T2: 6.0%, T3: 10.5% and MACE: T1: 3.5%, T2: 8.9%, T3: 23.5%). Cumulative comorbidities increased the risk for 180-day mortality and MACE in the entire cohort (mortality: no comorbidities: 3.7%, 1 comorbidity, 5.0%, 2 comorbidities: 6.4%, 3 comorbidities: 6.4% and MACE: no comorbidities: 4.5%, 1 comorbidity 8.8%, 2 comorbidities 11.1%, 3 comorbidities 13.9%). In patients with very low concentrations (T1: hs-cTnI <3ng/L), mortality and MACE rates were 0.5% when no comorbidities were present compared to 1.6% and 3.2%, respectively, when at least one comorbidity was present. Conclusions: Baseline hs-cTnI concentrations aid in the risk assessment of patients with diabetes, hypertension, and dyslipidemia, even without myocardial infarction; patients with higher hs-cTnI concentrations are at higher risk than those with lower concentrations. The cumulative presence of comorbidities increased the risk of adverse events and the presence of ≥1 comorbidity increased the risk for adverse events even in those with very low hs-cTnI concentrations.

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Sex-Specific 99th Percentiles Derived from the AACC Universal Sample Bank for 8 High-Sensitivity Cardiac Troponin Assays

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Introduction: Defining the 99th percentile upper-reference limit (URL) of cardiac troponin (cTn), the concentration threshold used to support the diagnosis of acute myocardial infarction (Universal Definition of Myocardial Infarction), is critically important. An added challenge is defining normality of subjects used to derive the 99th percentile URL. With increasing implementation of high sensitivity (hs)-cTnI and hs-cTnT assays in global clinical practice, clear guidance is needed to define normal (healthy) subjects used to determine 99th percentiles. Our objective was to determine overall and sex-specific 99th percentiles in 8 hs-cTn assays using a universal sample bank. Methods: Plasma specimens from apparently healthy subjects were obtained from the American Association of Clinical Chemistry (AACC) Universal Sample Bank (USB). These subjects included 423 men and 415 women who were screened using a health questionnaire. hs-cTnI (7 assays) concentrations were determined on: Abbott Architect i2000, Singulex Clarity, Beckman Coulter Access 2 Immunoassay System, Siemens Healthineers Dimension Vista 1500, Siemens Healthineers ADVIA Centaur XP, Ortho-Clinical Diagnostics VITROS 3600 Immunodiagnostic System, and ET Healthcare Pylon analyzers. hs-cTnT measurements were determined on 1 Roche Diagnostics Cobas analyzer (e602 using Gen 5 reagents). Hemoglobin A1c (URL 6.5%), NT-proBNP (URL 125 ng/L <75 y, 450 ng/L ≥75y) and eGFR (60 mL/min), along with statin use assisted in verifying subject normality, and used as surrogate biomarker health exclusions. 99th percentiles were determined by the non-parametric, Harrell-Davis Bootstrap, and Robust methods. Results: Demographics: ages 19 to 91y; Caucasian 58%, African American 27%, Pacific Islander/Asian 11%, other 4%; Hispanic 8%, non-Hispanic 92%. 99th percentiles for all assays, before and after exclusion (decreased using surrogate excluders), were influenced by the statistical method use, both for the overall and sex-specific 99th percentiles, with substantially different 99th percentiles between assays. For all assays, men had higher 99th percentiles (ng/L) than women. For women, the Roche (21%) and Beckman (48%) assays did not measure cTn ≥LoD in >50% of subjects. Conclusions: Our study has important clinical practice implications, in that a) sex-specific 99th percentiles vary according to the hs-assay and the statistical method used, b) not all hs-cTn assays provide measurable concentrations ≥ LoD in >50% for women, and c) surrogate exclusion criteria used to define normality tends to lower 99th percentiles.

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Poor correlation and concordance between NT-proBNP and BNP in patients with suspected heart failure

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B type natriuretic peptide (BNP) and N-terminal- pro B type natriuretic peptide (NT-proBNP) are viewed as comparable in their ability to diagnose and monitor heart failure in clinical guidelines. However, no large-scale study has directly established a correlation between BNP and NT-proBNP. This is particularly relevant in the context of chronic kidney disease (CKD), as NT-proBNP is elevated in CKD relative to BNP. Importantly, a large number of patients with CKD have concomitant heart failure. Our laboratory recently switched from BNP to NT-proBNP as the primary marker of ventricular strain. Prior to this change, we performed simultaneous BNP (Abbott BNP, Chicago USA) and NT-proBNP (Roche Corporation proBNP II, Basel Switzerland) testing for our clinicians for two months. We then compared plasma concentrations of BNP and NT-proBNP in different patient populations including those with and without CKD as determined by the CKD-EPI equation. Patient location, age, sex and creatinine along with BNP and NT-proBNP concentrations were available for 2,729 patient samples. The primary analyses were correlation and diagnostic concordance between BNP and NT-proBNP in the presence or absence of CKD in the acute (i.e. patients seen in the Emergency Department) vs. non-acute settings (all other settings) and at different ages. Common cutoffs for BNP and NT-proBNP to rule out or rule in acute and non-acute heart failure were used. In the acute ED setting, overall concordance between BNP and NT-proBNP was 72.0% with a weighted kappa of 0.695. In non-acute patients, the overall concordance was 92.5% with a kappa of 0.642. Concordance was not statistically different between different age groups. Patients

with an eGFR <60 ml/min had significantly lower concordance (70%, kappa 0.636) than those with eGFR >60 ml/min (77%, kappa 0.731). Moreover, the mean ratio of NT-proBNP to BNP was significantly higher in patients with CKD (10.7:1) than in non-CKD patients (5.7:1). Consequently, there was significantly greater correlation between NT-proBNP and BNP concentrations in patients with eGFR >60 (r^2 = .717) than patients with eGFR <60 (r^2 = .581) in the acute setting. Finally, for patients with multiple measurements of natriuretic peptides, there was variability between changes in BNP relative to changes in NT-proBNP concentrations over time. Overall, 20% of paired temporal measurements had an inverse relationship (increase in one peptide and a decrease in the other). Together these data showed surprising differences in diagnostic concordance and monitoring values between BNP and NT-proBNP, particularly among patients with CKD. We conclude that using the current cutoffs for heart failure, concentrations of NT-proBNP and BNP have surprisingly poor diagnostic concordance. Further studies are required to examine the diagnostic concentrations of natriuretic peptides, modes of clearance, and assay specificity for the multiple circulating forms of natriuretic peptides.

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Analytical Comparison of High Sensitivity Cardiac Troponin I and T Assays in Patients Presenting to the Emergency Department - the CONTRAST Study

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Background: This study compared the frequency of increases in high-sensitivity cardiac troponin (hs-cTn) I, hs-cTnT, and contemporary cTnI assay performances in patients being evaluated in a US emergency department undergoing cTnI measurements on clinical indication. Objectives were to determine the concordance of positive and negative results based on sex-specific 99th percentile upper reference limits (URLs) and correlations between hs-cTn assays and a contemporary assay. Methods: This analytical sub-study examined plasma (EDTA) specimens (n=1,000) randomly selected from >9,000 specimens from patients enrolled in the 'COmparisoN of High-sensitivity Cardiac TRoponin I and T Assays' (CONTRAST) study (clinicaltrials.gov NCT03214029). Patient clinical information was not included nor was available to determine whether single or multiple serial specimens from the same patient were included. Fresh specimens were measured by the hs-cTnI Abbott Architect assay and the Gen5 cTnT Roche cobas e601 assay directly upon completion of clinical testing with the contemporary cTnI (Abbott). Two sex-specific 99th percentiles were used to evaluate each hs-assay: manufacturer's package inserts (PI) and 99th percentile URLs derived from the AACC's Universal Sample Bank (USB), were: Abbott, PI - M 34 ng/L, W 16 ng/L; USB - M 19 ng/L, W 10 ng/L; Roche PI - M 22 ng/L, W 14 ng/L; USB M 16 ng/L, W 10 ng/L. The 99th percentile URL of the contemporary assay was 0.03 µg/L. The values of all assays were plotted and described using Pearson's correlation coefficients (r value) with Fisher's 95% confidence intervals (CI). Proportions of increased results were cross-tabulated to determine agreement with the Kappa statistic. Results: Using PI URLs, the percentage of specimens above the 99th percentile was 30% for hs-cTnI and 47.4% for Gen 5 cTnT. For comparison, using the lower USB URLs increased the percentage of increased results to 40.6% for hs-cTnI and 55.5% for Gen 5 cTnT. Using the PI URLs, 94.3% of Gen 5 cTnT results were greater than the 99th percentile in specimens with increased hs-cTnI results. In comparison, only 59.5% of hs-cTnI results were increased in specimens that had increased Gen 5 cTnT results; kappa of 0.575 (95%CI, 0.507,0.623). A similar difference in cross-assay increased rate was also observed using the USB URLs. Compared to a rate of increased contemporary cTnI results of 31.1%, using the PI hs-assays URLs, there was a 3.6% decrease in hs-cTnI increases compared to a 52.4% increase in Gen 5 cTnT increases. The Pearson correlation coefficient between the hs-cTnI and hs-cTnT assays was 0.298 (CI 0.241,0.354). Conclusions: Our findings demonstrate substantial differences between the hs-cTnI and Gen 5 cTnT assays in the proportion of values above the sex-specific 99th percentiles, regardless of the URL used. There were greater numbers of increased values for both assays using the lower USB 99th percentile URLs, and for Gen 5 cTnT for both URLs compared to the hs-cTnI assay. Furthermore, there was a substantial increase in the proportion of increased values found between the contemporary cTnI assay and the Gen 5 cTnT assay; with a small decrease found for the hs-cTnI assay.

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Race- and Sex- Dependent Association of BNP and Galectin-3 Levels with 6-Month All-Cause Mortality in Patients with Elevated BNP

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Background: B-type natriuretic peptide (BNP) and galectin-3 (Gal-3) are recognized as outcome-predicting factors for heart failure patients, with increased risks of death in the presence of low hemoglobin (Hb) or high creatinine. This study aims to evaluate the association of serum BNP and Gal-3 levels with 6-month prognosis of patients with elevated BNP. **Methods:** A total of 710 patients (ages 18 or older) from two medical centers with BNP>100 pg/mL at admission were enrolled in this study. A reflex testing of Gal-3 was then performed via the Abbott Architect immunoassay. Hb and serum creatinine concentrations at admission, the occurrences of re-admissions and death within 6 months from the first discharge were retrieved via patient chart review. The biomarker levels, all-cause death rates, days to re-admissions, and re-admission frequencies were compared among different races (white/black), sexes (male/female), and quartiles groups based on BNP and/or Gal-3 levels. The relationship between biomarkers and mortality was assessed via correlation and multivariate regression analysis (MRV). **Results:** Black patients had significantly higher levels of Gal-3, creatinine, and Hb than white patients. Male patients had greater levels of Gal-3 and Hb than female patients. However, similar BNP levels, death rates, days to re-admissions, and re-admission frequencies were observed in patients with different races or sexes. When patients were divided into 4 subgroups according to the quartiles of their BNP levels, significantly higher death rates (2-5 times) were only observed in white or male patients in the highest BNP quartile (Q4:>936.6-21375.1 pg/mL vs. Q1: 101.2-196.4 pg/mL). Additionally, the 30-day and 6-month re-admission frequencies were 2 times higher in BNP Q4 than Q1 in white and black patients, respectively. On the contrary, death rates of patients in higher Gal-3 quartiles (Q3: > 26.0-38.3 ng/mL and Q4: >38.3-180.1 ng/mL) were 2-10 times greater than those in Q1: (8.4-19.0 ng/mL) irrespective of race and sex. Patients with higher Gal-3 (Q3 or Q4: vs. Q1) also had a higher 30-day readmission frequency, with no difference between different races or sexes. No additional increase in mortality or re-admission rates was observed when BNP and Gal-3 quartiles were combined. Correlation analysis revealed positive association between death and creatinine in white females (R = 0.254), but negative correlation with Hb in black males (R = -0.264). Moreover, Gal-3 showed strong positive correlation with creatinine (R = 0.571), weak positive association with BNP (R = 0.275), but negative association with Hb (R = -0.302) in all patients. MRV analysis showed that Gal-3 was the only significant variable in the all-cause mortality of all patients, which together with creatinine and Hb formulate a linear regression to predict the death in black male patients (Mortality = 0.005XGal-3 - 0.023XHb - 0.033XCreatinine, $p<0.05$). In contrast, BNP was only associated with the mortality in white patients ($p = 0.018$). **Conclusion:** Our data suggest the race- and sex- dependent association between BNP and Gal-3 with 6-month all-cause mortality in patients with elevated BNP. In addition to BNP, Hb and creatinine, Gal-3 measurement may provide extra value for predicting all-cause mortality, especially in black male patients.

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A Single High Sensitivity Cardiac Troponin I Measurement From Siemens Healthineers Can Be Used to Rule Out Acute Myocardial Infarction at Low Risk in Patients Presenting to the Emergency Department

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Background: High sensitivity cardiac troponin (hs-cTn) assays are able to quantitate low concentrations of cTn and provide an opportunity to rule out acute myocardial infarction (MI) at an early stage following a patient's presentation to an emergency department. The objectives of the current study were to examine the performance of single hs-cTnI measurement strategy to rule out acute MI and predict 30-day safety outcomes at presentation in these patients. Methods: This was a prospective, observational study of patients (n = 2333). Acute MI occurred in 299 patients (12.8%). Patients presented to US emergency departments with suspected acute coronary syndrome. Cardiac troponin measurements

were obtained using the investigational ADVIA Centaur XPT TNIH (hs-cTnI) Assay (Siemens Healthcare Diagnostics Inc.). Clinical data and hs-cTnI results were analyzed to determine: 1) clinical sensitivity and negative predictive value (NPV) for ruling out acute MI and 2) safety outcomes of acute MI and death at 30 days, using the hs-cTnI limit of detection (LoD) 1.6 ng/L concentration. Results: In patients with a hs-cTnI <LoD (n=376, 16.1%), the clinical sensitivity and negative predictive value (NPV) for acute MI were 100% (95% CI 98.8,100) and 100% (CI 99.0,100), respectively. Further, the sensitivity and NPV for the safety outcome of acute MI or death within 30 days for hs-cTnI <LoD were 99.7% (CI 99.1,100) and 99.7% (CI 99.2,100), respectively. One patient out of 376 (0.26%) had an event within 30 days. Conclusion: A strategy of using a single hs-cTnI <LoD at presentation allowed the immediate identification of 16.1% of patients highly unlikely to have acute MI and who were at very low risk for events at 30 days. Additional study to understand the clinical utility and cost-savings of this strategy is needed.

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Red Cell Distribution Width and Cardiovascular Risk: four-year follow up of 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 at the baseline of the study with the risk of CVD risk at four years of follow-up in participants of the Longitudinal Study of Adult Health (ELSA-Brasil).**Methods**: We used baseline (2008-2010) and second visit (2012- 2014) data of 4471 civil servants enrolled in the ELSA-Brasil cohort. Mixed linear regression model for longitudinal data was used to determine association between RDW and increased cardiovascular risk based on Framingham Risk Score (FRS). 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.**Results**: RDW (adjusted r^2=0.921; $p<0.001$) was independently associated with the FRS after adjustment for education, skin color, body mass index, abdominal waist circumference, bariatric surgery, hemoglobin concentration, mean corpuscular volume, platelets, C-reactive protein, alcohol consumption. It was observed that a one-unit increase in RDW increases the FRS by 14%, in average. **Conclusion**: In this large cohort of free living Brazilians, ours results showed that RDW is independently associated with increased CVD risk based on the FRS at four-year follow up. The RDW, an inexpensive, easily obtained, and widely used test, holds potential evidence to be a novel biomarker in predicting CVD risk in asymptomatic individual. Prospective follow-up of ELSA-Brasil cohort is necessary to confirm the association between RDW and CVD.

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Assay Development And Evaluation Of Serum Aggrecan And Versican As Novel Biomarkers For Thoracic Aortic Aneurysm And Dissection

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Objectives: Thoracic aortic aneurysm and dissection (TAAD) is a progressive vasculopathy with a high rate of mortality due to an increased risk of vessel wall rupture. Aorta diameter is currently the gold standard for dictating surgical intervention, however the majority of dissections occur below surgical decision limits, illustrating a pressing need for new biomarkers for aneurysm detection and dissection risk stratification. Proteoglycan accumulation in medial degeneration lesions is a histologic hallmark of TAAD. We hypothesize that the proteoglycan constituents of medial degeneration lesions will enter the circulation in aneurysm and/or dissection and can be used as diagnostic and prognostic biomarkers. The objectives of this study were to develop assays for the detection of proteoglycans and evaluate their presence in the peripheral circulation of TAAD patients. **Methods**: We identified the proteoglycan constituents of the ascending aorta by tandem mass spectrometry (MS/MS) analysis of affinity-isolated proteoglycans. Ascending aorta tissue was collected from patients undergoing elective (aneurysm) or emergent (dissection) surgical intervention. Aortas from heart donors were used as normal controls. Total protein was extracted from tissue and proteoglycans isolated by anion exchange chromatography. Shotgun MS/MS was performed on isolated proteoglycans using a Thermo Scientific Orbitrap Elite hybrid analyzer. Shotgun analysis was repeated on isolated proteoglycans as well as on total aorta protein extracts using a Thermo Scientific Orbitrap Fusion Lumos tribrid analyzer to identify peptide candidates for selected reaction monitoring (SRM) assay development. Targeted analysis was performed on TAAD and control serum samples to verify candidate peptides could be identified in the peripheral circulation. Additionally, proteoglycan concentration in TAAD patient serum was determined in triplicate by a commercially available sandwich ELISA (research use only; R&D Systems). Blood from TAAD patients (n = 25) was collected pre-operatively in 3.5 mL SST BD vacutainer tubes. **Results**: The proteoglycans aggrecan and versican were identified as major constituents of medial degeneration lesions. Due to the large number of post-translational modifications in the central glycosaminoglycan domains, peptides were limited to the N- and C-terminal globular domains and included 11 and 18 unique peptides for aggrecan and versican, respectively. Two peptides for each proteoglycan were chosen for further SRM development. Targeted MS/MS analysis of TAAD serum identified peptides, but at low intensities, suggesting further pre-analytic processing, such as albumin/Ig depletion, may be required. An aggrecan ELISA was optimized for serum with a sensitivity of 100 pg/mL and an intra-assay imprecision of <5.0 %CV (range: 0.0-16.5%). 11 of 25 TAAD patients had detectable aggrecan levels (>100 pg/mL), including 3 of 5 dissection patients, with concentrations ranging from 279-17979 pg/mL. **Conclusions**: Aggrecan and versican accumulate in TAAD and are detectable in the peripheral circulation by MS/MS and immunoassay. Despite consistent detection by MS/MS, serum aggrecan levels were detectable by ELISA in some, but not all cases of TAAD indicating that differences in circulating fragments may be influenced by disease progression, primary etiology, and other unknown factors. Aggrecan and versican are potential serum biomarkers for TAAD and warrant further investigation.