sanofi

ESC Congress 2022 Barcelona

Presents

DAILY COVERAGE OF

EUROPEAN SOCIETY OF CARDIOLOGY CONGRESS

August 26 – 29, 2022

TOP 7 SESSIONS
DAILY COVERAGE
DAY-3

TOPIC OF CONTENT

TOPIC OF CONTENT

SESSION-1 :
Heart Failure with Declining, Improved, Preserved and Normal/Supranormal Ejection Fraction – Managing a Changing Landscape

CARDIOPULMONARY RESPONSE TO EXERCISE AND HEART FAILURE WITH PRESERVED EJECTION FRACTION RISK: A COMPARATIVE ANALYSIS OF HFA-PEFF AND H2FPEF SCORES

Barcelona Sunday, August 28th, 2022

A number of new studies were presented at the ESC Congress 2022 on August 28th.

This paper was presented by Dr. Davide Lazzeroni et al., from the IRCCS Don Carlo Gnocchi Foundation - Florence – Italy on 28th August 2022 at the ESC Congress 2022 as a part of the session "Heart Failure with Declining, Improved, Preserved and Normal/Supranormal Ejection Fraction – Managing a Changing Landscape".

Exercise intolerance evaluation in Heart failure with preserved ejection fraction (HFpEF) remains challenging, since several mechanisms (diastolic and systolic reserve abnormalities, low chronotropic reserve (CR), ventricular or vascular stiffening, atrial dysfunction, pulmonary hypertension, endothelial dysfunction, energetic abnormalities and autonomic dysfunction) play different roles. European Society of Cardiology HF guidelines recently suggested a stepwise non-invasive HFpEF diagnostic approach consisting of three steps: clinical, echocardiographic and laboratory data (natriuretic peptides), named HFA-PEEF Score, and finally, in case of inconclusive findings, diastolic stress echocardiography data. Cardiopulmonary exercise testing (CPET) may represent a promising further non-invasive diagnostic tool in HFpEF evaluation since allow to assess the presence of reduced functional capacity as well as to differentiate between cardiovascular, ventilatory or peripheral causes.

The aim of this study is to assess whether increased risk of HFpEF is associated with different and specific cardiopulmonary responses to exercise is still an open issue and this was the aim of our study. 1,156 consecutive subjects with preserved ejection fraction undergoing cardiovascular evaluation at the Cardiovascular Prevention Center of Fondazione Don Gnocchi & University of Parma were enrolled. All subjects underwent cardiovascular evaluation and echocardiography, HFA-PEEF and H2FPEF Score assessment and cardiopulmonary exercise testing. Different cardiopulmonary response to exercise were compared between different groups of HFpEF risk.

According to HFA-PEEF Score, 675 (58%) had 0 or 1 point, 253 (22%) had 2 points and 230 (20%) had 3 or 4 points (moderate-to-high risk). Patients with both higher HFA-PEEF and H2FPEF Score showed lower functional capacity, expressed as low peak V02 ($p<0.001$) associated with lower oxygen pulse (V02/HR) ($p<0.001$), cardiac output (CO) at peak ($p<0.001$), CR ($p<0.001$), ventilatory efficiency (expressed as VE/VC02 slope) ($p<0.001$) and oxygen uptake extraction (OUES) ($p<0.001$). Moreover, higher H2FPEF Score patients showed lower stroke volume (SV) at peak ($p<0.001$), while high HFA-PEEF score was not associated to SV at peak. More specifically, the presence of reduced cardiovascular efficiency (V02/Watt Slope < 7) was associated to a 2.2-fold higher risk of HFpEF ($p=0.003$), impaired ventilator efficiency (VE/VCO2 Slope

> 35) to a 2.4-fold higher risk (p<0.001), reduced CR (<70%) 4.3-fold higher risk (p<0.001). Different degrees HFpEF risk, estimated using both HFA-PEEF and H2FPEF score, are associated with different cardiopulmonary responses to exercise. High HFpEF risk patients show low functional capacity, cardiovascular and ventilator efficiency due to lower cardiac output at peak, despite preserved ejection fraction, associated to lower chrono-tropic response to exercise.

TRENDS IN CAUSE-SPECIFIC READMISSIONS IN HEART FAILURE WITH PRESERVED VERSUS REDUCED AND MID-RANGE EJECTION FRACTION

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Xiaotung Cui et al., from the Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases - Shanghai – China on 28th August 2022 at the ESC Congress 2022 as a part of the session "Heart Failure with Declining, Improved, Preserved and Normal/Supranormal Ejection Fraction – Managing a Changing Landscape".

It remains unclear whether the readmission of heart failure (HF) patients has decreased over time and how it differs among HF with preserved ejection fraction (EF) (HFpEF) versus reduced EF (HFrEF) and mid-range EF (HFmrEF).

We evaluated HF patients index hospitalized from January 2004 to December 2011 in the Swedish Heart Failure Registry with 1-year follow-up. Outcome measures were the first occurring all-cause, cardiovascular (CV) and HF readmissions.

Totally 20,877 HF patients (11,064 HFrEF, 4,215 HFmrEF, 5,562 HFpEF) were included in the study. All-cause readmission was highest in patients with HFpEF, whereas CV and HF readmissions were highest in HFrEF. From 2004 to 2011, HF readmission rates within 6 months (from 22.3% to 17.3%, P=0.003) and 1 year (from 27.7% to 23.4%, P=0.019) in HFpEF declined, and the risk for 1-year HF readmission in HFpEF was reduced by 7% after adjusting for age and sex (P=0.022). Likewise, risk factors for HF readmission in HFpEF changed. However, no significant changes in cause-specific readmissions were observed in HFrEF. Time to the first readmission did not change significantly from 2004 to 2011, regardless of EF subgroup (all P-values>0.05).

Although the burden of all-cause readmission remained highest in HFpEF versus HFrEF and HFmrEF, a declining temporal trend in 6-month and 1-year HF readmission rates was found in patients with HFpEF, suggesting that non-HF-related readmission represents a big challenge for clinical practice.

PROTEOMIC AND PHOSPHOPROTEOMIC PROFILING IN HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) ASSOCIATION BETWEEN PROGNOSIS AND THE USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND/OR ANGIOTENSIN II RECEPTOR BLOCKER IN FRAIL PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

Barcelona **Sunday, August 28th, 2022**

This paper was presented by Dr. Akhioro Sunaga et al., from the Osaka University Graduate School of Medicine - Suita – Japan on 28th August 2022 at the ESC Congress 2022 as a part of the session "Heart Failure with Declining, Improved, Preserved and Normal/Supranormal Ejection Fraction – Managing a Changing Landscape".

The effectiveness of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) has not been demonstrated in patients with heart failure with preserved ejection fraction (HFpEF). We recently reported significant interaction between the use of ACE-I and/or ARB (ACE-I/ARB) and frailty on prognosis in patients with HFpEF.

"In the present study, we examined the association between ACE-I/ARB and prognosis in patients with HFpEF stratified by the presence or absence of frailty." Said Dr. Sunaga.

We examined the association between the use of ACE-I/ARB and prognosis according to the presence (Clinical Frailty Scale (CFS) $\geq$ 5) or absence (CFS $\leq$ 4) of frailty in patients with HFpEF in a post-hoc analysis of registry data. Primary endpoint was the composite of all-cause mortality and heart failure admission. Secondary endpoints were all-cause mortality and heart failure admission.

Of 1059 patients, median age was 83 years and 45% were male. Kaplan-Meier analysis showed that the risk of composite endpoint (log-rank P = 0.001) and all-cause death (log-rank P = 0.005) in patients with ACE-I/ARB was lower in those with CFS $\geq$ 5, but similar between patients with and without ACE-I/ARB in patients with CFS $\leq$ 4 (composite endpoint: log-rank P = 0.830; all-cause death: log-rank P = 0.192). In a multivariable Cox proportional hazards model, use of ACE-I/ARB was significantly associated with lower risk of the composite endpoint (hazard ratio = 0.52, 95%CI = 0.33-0.83, P = 0.005) and heart failure admission (hazard ratio = 0.45, 95%CI = 0.25-0.83, P = 0.010) in patients with CFS $\geq$ 5, but not in patients with CFS $\leq$ 4 (composite endpoint: hazard ratio = 1.41, 95%CI = 0.99-2.02, P = 0.059; heart failure admission: hazard ratio = 1.43, 95%CI = 0.94-2.18, P = 0.091). The association between ACE-I or ARB and prognosis did not significantly differ by CFS (CFS $\leq$ 4: log-rank P = 0.562; CFS $\geq$ 5: log-rank P = 0.100, for with ACE-I vs. ARB, respectively). Adjusted HRs for CFS 1 - 4 were higher than 1.0, but were less than 1.0 at CFS 5.

In patients with HFpEF, use of ACE-I/ARB was associated with better prognosis in patients with frailty as assessed with the CFS, but not in those without frailty.

SESSION-2 :
Heart Failure: Prevention Is Better Than Cure!

ASSOCIATION OF BASELINE AND LONGITUDINAL CHANGES IN CARDIOMETABOLIC HEALTH WITH RISK OF HEART FAILURE AMONG ADULTS WITH TYPE 2 DIABETES: AN ANALYSIS FROM THE LOOK AHEAD TRIAL

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Ambarish Pandey et al., from the University of Texas, Southwestern Medical Center on 28th August 2022 at the ESC Congress 2022 as a part of the session "Heart Failure: Prevention Is Better Than Cure!".

Type 2 diabetes (T2D) is characterized by co-morbid cardiometabolic abnormalities and elevated heart failure (HF) risk. The purpose of this study was to evaluate the associations of baseline and longitudinal changes in cardio-metabolic health with risk of HF among adults with T2D.

Adults with T2D enrolled in the Look AHEAD (Action for Health in Diabetes) trial without prevalent HF were included. Adjusted Cox models were used to create a cardiometabolic health score incorporating target levels of parameters weighted based on relative risk for HF. The associations of baseline, 1- and 4-year changes in the cardiometabolic health score with risk of overall HF, HF with preserved ejection fraction (HFpEF; EF>=50%), and HF with reduced EF (HFrEF; EF<50%) were assessed using adjusted Cox models.

Of the 5,080 participants included, there were 257 incident HF events during 12.4-year follow-up. The cardiometabolic health score included 2-points each for target levels of waist circumference, glomerular filtration rate, urine albumin-to-creatinine ratio and 1-point each for blood pressure and hemoglobin A1c at target. Higher baseline cardiometabolic health score was significantly associated with lower risk of overall HF (adjusted hazard ratio [aHR] per 1-unit higher score, 0.72 [95% CI, 0.66-0.79]) with similar associations observed for HFpEF and HFrEF. Improvement in cardiometabolic health over 1- and 4-years was significantly associated with lower risk of overall HF (aHR per 1-unit increase in score at 1- and 4-years, 0.82 [95% CI, 0.73-0.92] and 0.80 [95% CI, 0.70-0.91], respectively). Among adults with T2D, achieving target levels of more cardiometabolic health parameters at baseline and sustained improvements were associated with lower HF risk.

CLINICAL OUTCOME AND MORTALITY IN PATIENTS WITH ICD FOR PRIMARY PREVENTION

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Anil Ahmet Baskurt et al., from the Dokuz Eylul University - Izmir – Turkey on 28th August 2022 at the ESC Congress 2022 as a part of the session "Heart Failure: Prevention Is Better Than Cure!".

ICD (Implantable Cardiac Defibrilator) for primary prevention is indicated in patients with EF ≤35% and NYHA class II-III heart failure despite at least 3 months of optimal medical therapy. However, the studies that form the basis of this recommendation belong to more than 20 years ago. These studies may not reflect the characteristics and treatment of current heart failure patients. Therefore, the effect of ICD for primary prevention on prognosis may have been changed. Recent studies have called into question the effectiveness of the ICD in primary prevention. The aim of our study is to evaluate the patients who had ICD for primary prevention implanted retrospectively.

The primary outcomes of all-cause death and sudden death were compared in patients who underwent ICD for primary prevention at our clinic between 01.01.2015 and 01.03.2020 and patients with ICD indication but who did not accept this treatment.

Of the 228 patients who had ICD for primary prevention implanted, 175 (76.8%) were male. The mean age of the patients was 65.63±11.94 years. The mean follow-up period of the patients was 39.45±18.89 months. The mean left ventricular ejection fraction of the patients was found to be 24.30±6.19%. Procedural complications developed in 36 (15.8%) of 228 patients. When these complications were analyzed according to the gender of the patients, complications developed in 21 (12%) of 175 male patients and 15 (28.3%) of 53 female patients (p = 0.004). When the ICD implanted group and the control group were compared in terms of all-cause mortality, 67 (29.4%) of 228 patients in the ICD arm and 39 (26%) of 150 patients in the control group died due to all causes mortality (p=0.473). When the ICD implanted group and the control group were compared in terms of sudden death, 2 patients in the ICD arm and 8 patients in the control group had sudden death (p=0.017). Age, left ventricular ejection fraction, BNP value, and previous hospitalization due to decompensation heart failure were found to be independent predictors of all-cause mortality by multiple logistic regression method. Mortality was 3.4 times higher in patients who were hospitalized with decompensated heart failure before the procedure. In the ICD implanted group, the all-cause mortality of patients with a BNP value above 508.5, LVEF value below 24.5%, and age greater than 68.5 was 25 times higher than in other patients (Wald: 9.938 OR (95% Cl) 0.039 (0.005-0.293) p = 0.002). It was found that the presence of coronary artery disease was not an independent risk factor.

"Our patient population and our findings are compatible with current life data. We think that the recommendations for ICD for primary prevention implantation in the guidelines may be downgraded in the future with current treatment options. It will be important to determine which patient population will most benefit from the ICD treatment for primary prevention."

SEX-RELATED DIFFERENCES IN LONG-TERM OUTCOME OF HEART FAILURE IN LOW-RISK PATIENTS WITH ATRIAL FIBRILLATION: A SWEDISH REGISTRY CASE-CONTROL STUDY

Barcelona **Sunday, August 28th, 2022**

This paper was presented by Dr. Carmen Basic et al., from the Institute of Medicine - Sahlgrenska Academy – Sweden on 28th August 2022 at the ESC Congress 2022 as a part of the session "Heart Failure: Prevention Is Better Than Cure!".

Knowledge about sex-related differences regarding long-term risk of heart failure (HF) among patients with atrial fibrillation (AF) is limited.

The aim of the study is to evaluate the impact of sex on risks for new onset HF in patients with AF.

All patients from the Swedish National Patient Register, with a first-time diagnosis of AF between 1987 and 2018 were identified and compared with two matched controls without AF from the Total Population Register. Patients < 18 years, or any previous cardiovascular disease, diabetes mellitus and renal failure at the baseline were excluded.

In total 227 811 patients and 452 712 controls were included; 44.5% were women. The mean age (SD) for men was 65.5 (15) vs. 72.7 (13) in women ($p<0.0001$). The incidence rate for HF onset per 1000 person-years within one and five years after AF diagnosis was 77.3 (75.5-79.1) and 45.0 (44.3-45.7) in women vs. 66.5 (65.0-68.0) and 35.3 (34.8-35.9) in men, respectively. The incidence rate for HF onset increased with age in both patients with AF and controls, but was generally more pronounced in women. Women had 26% and 34% higher risk for HF onset, within five and thirty years, respectively. The highest risk for HF onset was found in women 18-34 years and 35-49 years of age, HR 24.64 (95%, confidence interval (CI) 7.59-80.0) and 8.09 (95%, CI 6.34-10.33) vs. 9.86 (95%, CI 6.81-14.27) and 6.52 (95%, CI 5.87-7.25) in equally old men. The mortality rate after HF was 42.3% and 33.1% in women and men with AF ($p<0.0001$).

In this nationwide, register-based cohort study, when compared to matched controls we found that the risk for HF onset was higher in women with AF, particularly in reproductive age, highlighting great importance of further research for prevention of HF in young women with AF but without any other cardiovascular risk factors.

SESSION-3 :
Cardiovascular Risk Assessment - Scores 2

PREDICTION OF LIFETIME CARDIOVASCULAR RISK AND INDIVIDUAL LIFETIME TREATMENT BENEFIT IN FOUR EUROPEAN RISK REGIONS: GEOGRAPHIC RECALIBRATION OF THE LIFE-CVD MODEL

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Stefan Hageman et al., from the University of Utrecht Medical Center – Netherlands on 28th August 2022 at the ESC Congress 2022 as a part of the session "Cardiovascular Risk Assessment - Scores 2".

The life expectancy free of cardiovascular disease (CVD) in individuals without previous CVD can be estimated with the LIFEtime-perspective CardioVascular Disease (LIFE-CVD) model, as recommended by the 2021 ESC CVD prevention guidelines. Our aim was to systematically recalibrate the LIFE-CVD model to four European risk regions using contemporary and representative registry data. The LIFE-CVD model was systematically recalibrated to four distinct risk regions within Europe, using representative aggregate data on age- and sex-specific expected CVD and non-CVD mortality incidences and risk factor distributions. For external validation, 1,451,077 individuals without previous CVD were included from seven European cohorts, with 53,721 CVD events and 62,902 non-CVD deaths during follow up. After applying the recalibrated risk prediction models to external validation cohorts, C-indices ranged from 0.670 (95%CI 0.650-0.690) to 0.787 (95%CI 0.785-0.789). Predicted risks matched the observed risks in the CPRD data. With the recalibrated LIFE-CVD model, the estimated gain in CVD-free life expectancy from preventive therapy differed per region, for example 50-year-old smoking women with a systolic blood pressure of 140mmHg was estimated to gain 0.4 years of CVD-free life from 10 mmHg SBP reduction in the low-risk region, whereas this would be 1.5 years in the very high-risk region. By taking into account geographical differences in CVD incidence, the recalibrated LIFE-CVD model provides a more accurate tool for the prediction of lifetime risk and CVD-free life expectancy for individuals without previous CVD, facilitating shared decision-making in cardiovascular prevention options as recommended by the 2021 European Prevention Guidelines.

COMBINING EUROPEAN SOCIETY OF CARDIOLOGY AND AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION RISK PREDICTION MODEL WITH POLYGENIC RISK SCORES TO REFINE CARDIOVASCULAR PREVENTION

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Roxane de La Harpe et al., from the University Hospital Centre

Vaudois (CHUV), Department of Medicine, Division of Internal Medicine - Lausanne – Switzerland on 28th August 2022 at the ESC Congress 2022 as a part of the session "Cardiovascular Risk Assessment - Scores 2".

Polygenic risk scores (PRS) predict the risk of developing atherosclerotic cardiovascular disease (ASCVD). However, their utility in combination with existing clinical risk scores remains uncertain. We first validated four different PRS in a Swiss population-based cohort. Second, using the PRS with the best predictive capacity, we assessed its benefit when combined with two clinical risk scores: the Systematic COronary Risk Evaluation 2 (SCORE2) and the Pooled Cohort Equation (PCE).

"We used data from a prospective cohort involving 6733 European participants at baseline (2003-2006). The predictive accuracy of the PRS was assessed with discrimination and calibration metrics. For the second aim, subjects with prevalent ASCVD or statin therapy at baseline were excluded. We tested associations between risk prediction models (PRS alone and combined clinical and PRS) and incident ASCVD, using Cox proportional hazard regressions. Net reclassification index (NRI) detected any improvement of ASCVD risk categorisation following the addition of the PRS to clinical risk scores in overall sample and in subgroups (e.g., sex, age, clinical intermediate-risk category)".

For the first aim, 4215 subjects (53% women; mean age 53.7±10.7), with 357 prevalent ASCVD, were analysed. The PRS developed by Inouye et al., comprising >6 million variants, presented the best predictive capacity (area under the receiver operating characteristic of 0.77) and was used in the following analyses. For the second aim, 3390 subjects (mean follow-up of 12.0±3.3 years), with 188 incident ASCVD, were analysed. Individuals in the top 20% of the PRS distribution had the same magnitude of association with ASCVD as current smokers or diabetic subjects. Combining the PRS with SCORE2 led to a reclassification of 17.1% (95% CI, 4.7-29.5) of subjects in the intermediate-risk category. Likewise, adding the PRS to PCE translated into an NRI of 19.2% (95% CI, 4.8-22.4) in the intermediate-risk category (not shown).

Using a Swiss population-based cohort, PRS presented good predictive capacities for ASCVD. Combining a PRS with clinical risk scores improved reclassification of risk for ASCVD, especially for subjects in the intermediate-risk category. Introducing PRS in clinical practice may refine cardiovascular prevention for subgroups of patients in whom prevention strategies are uncertain.

DEVELOPMENT AND VALIDATION OF THE HARMS2-AF LIFESTYLE RISK SCORE TO PREDICT INCIDENT AF

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Peter Kistler et al., from the The Alfred Hospital - Melbourne – Australia on 28th August 2022 at the ESC Congress 2022 as a part of the session "Cardiovascular Risk Assessment - Scores 2".

Lifestyle risk factors (RFs) are a modifiable target in atrial fibrillation (AF) management. However, the relative contribution of individual lifestyle RFs to AF incidence has not been described. The purpose of this study is to look at the development and validation of a novel AF-lifestyle risk score to determine AF risk in the general population.

The UK Biobank (UKB) is a large prospective cohort with outcomes measured >10 years. In the UKB, we performed regression analysis of AF lifestyle RFs which were then evaluated in a multivariable model and a weighted score was

developed. Next, the risk score was externally validated in the Framingham Heart Study (FHS) population. Kaplan-Meier estimates ascertained the 10-year risk of AF development.

In the UKB, AF incidence was 5.3% among 302,926 participants, with a median time to AF 7.3 years (IQR 4.3-9.8). Hypertension, sleep apnoea, male sex, age, obesity (BMI >30 kg/m^2), alcohol and smoking were predictive variables (all p<0.001); physical inactivity (OR 1.02, 95%CI 0.97-1.10, p=0.3), diabetes (OR 0.98, 95%CI 0.91-1.06, p=0.2) and BMI 27-30 kg/m^2 (OR 1.02, 95%CI 0.97-1.07, p=0.424) were not significant. The HARMS2-AF score had similar predictive performance (AUC=0.782, LogLoss 0.178, Brier Score 0.046) to the unweighted regression model (AUC 0.808) in the UKB. Validation in the FHS (AF incidence 6.7% of 7206 participants) maintained excellent predictive performance with an AUC of 0.747 (95% CI 0.724-0.769). A higher HARMS2-AF score (>5 points) was associated with a heightened 10-year AF risk (score 5-9: OR 9.35, score 10-14: OR 33.34).

The HARMS2-AF score is a novel lifestyle risk score which may help identify individuals at risk of AF and assists in general population screening.

SESSION-4 :
Clinical Challenges in Atrial Fibrillation

WATCHMAN DEVICE MIGRATION AND EMBOLIZATION: A REPORT FROM THE NCDR LAAO REGISTRY

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Daniel Friedman et al., from the Duke University, Durham on 28th August 2022 at the ESC Congress 2022 as a part of the session "Clinical Challenges in Atrial Fibrillation".

Incomplete anchoring of the Watchman left atrial appendage closure (LAAO) device can result in substantial device migration or device embolization requiring percutaneous or surgical retrieval. The purpose of this study is to report rates and characteristics of in-hospital and post-discharge Watchman device migration and embolization events in the United States.

We performed a retrospective analysis of Watchman procedures (January 2016 through March 2021) reported to the National Cardiovascular Data Registry LAAO Registry. We excluded patients with prior LAAO interventions, no device released, and missing device information. In-hospital events were assessed among all patients and post-discharge events were assessed among patients with 45-day follow-up.

Of 120,278 Watchman procedures, device migration or embolization occurred in 0.07% of patients (n=84) during the index hospitalization and surgery was performed in 39 patients. The in-hospital mortality rate was 14% among patients with device migration or embolization and 20.5% among patients who underwent surgery. In-hospital migration or embolization was more common: at hospitals with a lower median annual procedure volume (24 vs. 41 procedures, $p<0.0001$), with first-generation Watchman versus next-generation Watchman FLX devices (0.08% vs. 0.04%, $p=0.0048$), with larger LAA ostia (median 23mm vs. 21mm, $p=0.004$), and with a smaller difference between device and LAA ostial size (median difference 4mm vs. 5mm, $p=0.04$). There were no differences by age, sex, hospital type, hospital size, or teaching versus non-teaching status. Of 98,147 patients with 45-day follow-up, device migration or embolization after discharge occurred in 0.06% (n=54) patients and cardiac surgery was performed in 7.4% (n=4) of cases. The 45-day mortality rate was 3.7% (n=2) among patients with post-discharge device migration or embolization. Post-discharge migration or embolization was more common among men (79.7% of events but 58.9% of all procedures, $p=0.0019$), taller patients (177.9 cm vs. 172 cm, $p=0.0005$), and those with greater body mass (99.9 kg vs. 85.5 kg, $p=0.0055$); in contrast to in-hospital events, there were no differences in hospital volume, device characteristics, or LAA characteristics.

Watchman device migration or embolization is rare but associated with high mortality and frequently requires surgical retrieval. A substantial proportion of all device migration or embolization cases occur after discharge and different patient and procedure characteristics are associated with in-hospital versus post-discharge cases. Given the morbidity and mortality associated with device migration or embolization, risk mitigation strategies and on-site cardiac surgical back-up are of paramount importance.

COMPARISON OF EMBOLISM AND BLEEDING RISK PROFILE IN PATIENTS WITH ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. J A Parada Barcia et al., from the Hospital Universitario Alvaro Cunqueiro - Vigo - Spain on 28th August 2022 at the ESC Congress 2022 as a part of the session "Clinical Challenges in Atrial Fibrillation".

Clinical decision-making on anticoagulation in chronic kidney disease (CKD) patients with atrial fibrillation (AF) is challenging. Current strategies are based on small observational studies with conflicting results. A better comprehension of patients' risk profiles is therefore needed. The present study explores the impact of glomerular filtration rate (GFR) in the embolic – haemorrhagic balance among a large cohort of AF patients.

The study cohort included all patients from the health area of Vigo (Galicia, Spain) diagnosed with AF between January 2014 and April 2020. Subjects without data regarding to glomerular filtration rate were excluded. The final population of the study consisted of 15,457 patients. The risk of ischaemic stroke and major bleeding was determined by competing risk regression using the Fine and Gray model, considering death as a competing risk.

During a mean follow-up of 4.29±1.82 years, 3,678 patients died (23.80%), 850 had an ischaemic stroke (5.50%) and 961 had a major bleeding (6.22%). The incidence of stroke and bleeding increased as baseline GFR declined. GFR <30 mL/min/1.73 m^2 was associated with increased stroke and major bleeding. Interestingly, below GFR <30 mL/min/1.73 m^2, bleeding risk was clearly higher than the embolic risk.

As glomerular filtration rate decreased, anticoagulation was associated with an increased bleeding risk (sHR 1.72, 95% CI 1.15-2.56; P = 0.01 for patients with GFR 30-59 mL/min/1.73 m^2 and 2.05, 95% CI 0.80-5.28; P = 0.13 for subjects with < 30 mL/min/1.73 m^2 in comparison with those with GFR > 60 mL/min/1.73 m^2, respectively), but it was not associated with a reduction in embolic risk in patients with GFR < 30 mL/min/1.73 m^2 (sHR 1.91, 95% CI 0.73-5.04; P = 0.19).

In advanced chronic kidney disease (GFR <30 mL/min/1.73 m^2), the increase of major bleeding risk was higher than the increase of ischaemic stroke risk, with a negative anticoagulation balance (greater increase in bleeding than reduction in embolism).

In this setting, left atrial appendage occlusion appears to be an alternative to consider.

IMPACT OF METABOLIC SYNDROME ON THE RISK OF ISCHEMIC STROKE IN NON-ANTICOAGULATED ATRIAL FIBRILLATION PATIENTS HAVING LOW CHA_2DS_2-VASc SCORES

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Hyojeong Ahn et al., from the Seoul National University on 28th August 2022 at the ESC Congress 2022 as a part of the session "Clinical Challenges in Atrial Fibrillation".

Metabolic syndrome (MetS) predisposes to a thromboembolic state. However, conflicting results have been reported on whether MetS confers an increased risk of ischemic stroke in atrial fibrillation (AF), especially in patients with low CHA_2DS_2-VASc score who are not indicated for oral anticoagulant therapy.

"We investigated the risk of ischemic stroke according to the presence of MetS, the number of MetS components (metabolic burden), and the individual metabolic components in non-anticoagulated AF patients with low CHA_2DS_2-VASc score."

A total of 76,015 oral anticoagulant-naïve AF patients with low CHA_2DS_2-VASc score (0.1 in male and 1 in female) were included from the Korean National Health Insurance Service database. The status of MetS and individual metabolic components were evaluated based on health examination data within two years of AF diagnosis. We estimated the risk of ischemic stroke according to MetS, metabolic burden, and an individual component of MetS using Cox proportional-hazards models.

The mean age was 49.8 ± 11.1 years and 52,388 (68.9%) were male. The average CHA_2DS_2-VASc score was 0.7 ± 0.5 and MetS was prevalent among 21,570 (28.4%) of the study population. During a mean follow-up of 5.1 years, ischemic stroke was developed in 1,395 (1.84%) patients. MetS was associated with a higher risk of ischemic stroke after adjustment for age, sex, lifestyle behaviors, low income, and cardiovascular comorbidities: adjusted hazard ratio (aHR) 1.19, 95% confidence interval (CI) 1.06-1.33, p=0.002. A positive linear correlation was observed between metabolic burden and ischemic stroke risk. Patients with five MetS components showed the highest aHR of 1.55 (95% CI 1.14-2.11, whereas those with a single MetS component had a marginal risk of ischemic stroke (aHR 1.18, 95% CI 0.99 – 1.41). Among individual metabolic components, elevated blood pressure and increased waist circumference was significantly associated with an increased risk of ischemic stroke: aHR (95% CI), 1.45 (1.30-1.62), p<0.001, and 1.15 (1.03-1.30), p=0.016, respectively.

Among AF patients initially with CHA_2DS_2-VASc score 0 and 1 with no anticoagulation, the presence of MetS is associated with an increased risk of ischemic stroke. Given the linear incremental correlation between metabolic burden and ischemic stroke, special attention to the care of metabolic derangements is required in AF patients who are not indicated for anticoagulation.

SESSION-5 :
Advances in Cardiac Arrest Mechanisms and Treatment

TREATMENT WITH IMPELLA AND VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION DURING CARDIAC ARREST ON SURVIVAL IN A MULTICENTER COHORT

Barcelona **Sunday, August 28th, 2022**

This paper was presented by Dr. Tharusan Thevathasan et al., from the Charite University Hospital, Department of Cardiology - Berlin – Germany on 28th August 2022 at the ESC Congress 2022 as a part of the session "Advances in Cardiac Arrest Mechanisms and Treatment".

International organisations advocate the use of extracorporeal cardio-pulmonary resuscitation (ECPR) with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in selected patients with therapy-refractory cardiac arrest. Although VA-ECMO allows for full circulatory support, it is inherent to increased left ventricular (LV) pressure due to retrograde aortic perfusion, which may hamper myocardial recovery and aggravate pulmonary oedema. In order to mitigate these negative sequelae, adjunct LV unloading with an Impella microaxial flow pump may be considered. The effects of concomitant treatment with VA-ECMO and Impella (ECMELLA) in patients with therapy-refractory cardiac arrest due to acute myocardial infarction (AMI) remains unclear. To the best of our knowledge this is the first study to investigate whether treatment with ECMELLA is associated with improved 30-day mortality rate in patients with therapy-refractory cardiac arrest caused by AMI, compared to treatment with VA-ECMO alone.

Patients treated with ECMELLA were propensity score (PS)-matched to patients receiving VA-ECMO based on age, electrocardiogram (ECG) rhythm, cardiac arrest location (out-of-hospital or in-hospital) and Survival After Veno-Arterial ECMO (SAVE) score. Cox proportional-hazard and Poisson regression models were used to analyse 30-day mortality rate (primary outcome), hospital and intensive care unit (ICU) length of stay (LOS) (secondary outcomes). Multiple sensitivity analyses on patient demographics and cardiac arrest parameters were performed.

95 adult patients from three tertiary care centers were included, out of whom 34 pairs were PS-matched. ECMELLA treatment was associated with 47% decreased 30-day mortality risk [95% Confidence Interval (CI) 0.31-0.91, P=0.021], 71% prolonged hospital [95% CI 1.50-1.95, P<0.001] and 81% prolonged ICU LOS [95% CI 1.57-2.08, P<0.001]. Kaplan-Meier analyses and multiple sub-group analyses (age, sex, initial ECG rhythm, Charlson comorbidity index, body mass index, SAVE score, cardiac arrest location, lactate and pH levels) confirmed survival benefits in the ECMELLA group. Especially patients with prolonged low-flow time and high initial lactate benefited from ECMELLA therapy. Moreover, LV ejection fraction strongly improved in the ECMELLA group between ICU admission and ICU discharge from 15% to 40%, compared 15% and 20% in the VA-ECMO group.

In this multicenter propensity score-matched cohort of patients with ECPR during therapy-refractory cardiac arrest caused by AMI, treatment with ECMELLA was associated with improved survival compared to treatment with

VA-ECMO alone. These findings support current guideline recommendations on early evaluation of ECPR in well selected patients with therapy-refractory cardiac arrest. A clinical trial is urgently needed to further evaluate the role of LV unloading in patients with therapy-refractory cardiac arrest.

TARGETED METABOLOMICS IN OUT-OF-HOSPITAL CARDIAC ARREST (OHCA)

Barcelona **Sunday, August 28th, 2022**

This paper was presented by Dr. Rasmus Paulin Beske et al., from the Rigshospitalet - Copenhagen University Hospital - Copenhagen – Denmark on 28th August 2022 at the ESC Congress 2022 as a part of the session "Advances in Cardiac Arrest Mechanisms and Treatment".

Out-of-hospital cardiac arrest is a leading cause of death. Even if successfully resuscitated, mortality and morbidity remain high due to ischemic and reperfusion injury (I/R). The oxygen deprivation leads to a metabolic derangement amplified upon reperfusion resulting in an uncontrolled generation of reactive oxygen species, triggering cell death mechanisms and organ damage. Understanding the I/R damage in humans following OHCA remains sparse, with no existing treatment to attenuate the reperfusion injury. The aim of this study is to describe metabolic derangement in patients following OHCA. Blood samples from consecutive resuscitated unconscious OHCA patients drawn at hospital admission were analyzed using ultra-perfor-mance liquid mass-spectrometry. Sixty-one metabolites of the ~3000 compounds detected were prespecified for quantification and analyzed in the current study. We used hierarchical cluster data analysis to identify metabolic clusters/phenotypes.

In total, 163 patients were included, of which 143 (88%) were men, and the median age was 62 years (53 – 68). All measured metabolites from the tricarboxylic (TCA) cycle were significantly higher in non-survivors vs. survivors (180-days survival). Hierarchical clustering identified four (A-D) phenotypes of patients with distinct metabolic profiles. The mortality was significantly different in two phenotypes; A and B (A: 62% and B: 59% vs. C: 21% and D: 24%, $p<0.001$). There were no significant differences in age between the four phenotypes ($p=0.35$). Phenotype A and B had longer time to ROSC (A: 33 min (21 – 43), B: 27 min (24 – 35), C: 18 min (13 – 28), and D: 18 min (12 – 25), $p<0.001$). Phenotype A and D, who both had higher levels of free fatty acids, also a higher prevalence of ST-elevation or acute left bundle branch block in first ECG as compared to phenotype B and C (A: 76%, B: 55 %, C: 36% and D: 75%, $p<0.001$.

Circulating levels of metabolites from the TCA cycle best described the variance between survivors and non-survivors. Four different metabolic phenotypes were identified. These phenotypes had significantly different mortality.

GLOBAL LONGITUDINAL STRAIN TO PREDICT MYOCARDIAL FIBROSIS IN PATIENTS IN CARBON MONOXIDE POISONING

Barcelona **Sunday, August 28th, 2022**

This paper was presented by Dr. Young In Kim et al., from the Wonju Severance Christian Hospital - Wonju - Korea on 28th August 2022 at the ESC Congress 2022 as a part of the session "Advances in Cardiac Arrest Mechanisms and Treatment".

Carbon monoxide (CO) inhibits oxygen delivery and subsequently causes ischemic changes that

can lead to myocardial damage. Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) reflects myocardial fibrosis and detects subclinical myocardial damage in patients with acute CO poisoning. However, CMR is expensive and hard to perform in patients with neurologic deficit. Therefore, this study aims to investigate which echocardiographic parameters could predict the presence of myocardial fibrosis represented by LGE in CO intoxication patients.

This prospective observational study included 128 consecutive patients (Mean age: 52.2±16.2) with acute CO poisoning and elevated troponin I (defined as > 0.045 ng/mL) at the emergency department of a tertiary university hospital. All participants underwent hyperbaric oxygen therapy (HBOT). CMR and conventional echocardiography with 2D speckle-tracking were performed within 7 days. Subjects were categorized into late gadolinium enhancement (LGE) and no LGE group according to the CMR findings.

Mean left ventricular (LV) ejection fraction (EF) and global longitudinal strain (GLS) were 57.0±10.0% and -16.3±3.7% respectively. LGE was observed in 89 (69.5%) patients and the most common pattern was mid-wall involvement. Clinical characteristics such as age, sex, shock, time elapsed from rescue to HBOT, and the level of troponin I were not different between groups with LGE and without LGE. Among echocardiographic parameters, LV EF was not significantly different between groups (LGE: 56.0± 10.5% vs 59.3±8.1%, p = 0.089). LV GLS was more impaired in patients with LGE compared to those without LGE (-15.7±3.8% vs -17.9±3.0%, p = 0.003). In multivariate logistic analysis, LV GLS was independently associated with the presence of LGE [Odds ratio (OR) 1.279, 95% confidence interval (CI) (1.047-1.563), p=0.016], but not LV EF.

In patients with acute CO poisoning and elevated troponin I, LV GLS predicted the presence of LGE in CMR. These finding suggest that subclinical myocardial dysfunction represented by LV GLS may reflect the burden of CO induced myocardial fibrosis.

SESSION-6 :
Novel Insights into Vascular Inflammation

LEPTIN MEDIATES PROTECTIVE EFFECTS ON THE VASCULATURE

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Vanina Filipova et al., from the University Hospital Leipzig - Leipzig - Germany on 28th August 2022 at the ESC Congress 2022 as a part of the session "Novel Insights into Vascular Inflammation".

Lipodystrophy (LD) syndromes are characterized by the loss of adipose tissue resulting in metabolic complications and accelerated atherosclerosis. The systemic concentration of the adipokine leptin is reduced in LD as a result of adipose tissue deficiency. A therapeutical option to treat LD is the substitution of leptin, which improves metabolic complications and reduces mortality. However, the vascular effects of leptin remain largely unknown. Here we analyze the direct effects of leptin on the vascular system and the development of atherosclerosis. Treatment of human endothelial cells (ECs) with leptin reduced endothelial inflammation and the process of endothelial-to-mesenchymal transition (EndMT) (CNN1, -41.4%, $p<0.05$, n=4). In addition, leptin administration prevented the EndMT-induced increase of endothelial permeability. The protective effect of leptin on EndMT was confirmed in vivo in a combined lipodystrophic and atherosclerosis-prone mouse model (LDLR-/-;aP2-nSrebp1c). Treatment of the mice with leptin (3.0 mg/kg body weight daily for 8 weeks) decreased EndMT. Leptin showed no effect on plaques size but reduced the protrusion of plaques in atherosclerotic areas of the aortic roots (-31%, $p<0.05$, n=4-6).

Cytokine screening revealed an increase of the growth differentiation factor 15 (GDF15) in serum of LD patients (+26.2%, $p<0.05$, n=53-58) and in ECs after EndMT (+138%, $p<0.05$, n=6743-10920). This increase was reversed using leptin treatment in ECs undergoing EndMT, in the LD mice model, and in LD patients after 4 weeks of leptin administration. Indeed, treatment of endothelial cells with GDF15 induced EndMT (CNN1, +7.7-fold-control, $p<0.05$, n=3), and impaired EC barrier function. Neutralizing antibodies targeting GDF15 inhibited EndMT-mediated expression of mesenchymal genes (CNN1, -54%, $p<0.05$, n=4). The treatment of ECs with serum from LD patients induced EndMT and the increase of mesenchymal marker expression was inhibited with additional administration with neutralizing antibodies targeting GDF15 (CNN1, -28%, $p<0.05$, n=3). Our findings indicate that EndMT is part of the cardiovascular disease progression in lipodystrophy syndromes. Leptin treatment has direct protective vascular effects by preventing inflammation, EndMT, and maintaining endothelial integrity.

THE ROLE OF P2Y12 IN CARDIOVASCULAR DISEASE BEYOND ATHEROTHROMBOSIS: P2Y12 SIGNALLING PROMOTES EMERGENCY HEMATOPOIESIS AFTER MYOCARDIAL INFARCTION

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Hana Seung et al., from the University Heart Center Freiburg,

Cardiology and Angiology I - Freiburg – Germany on 28th August 2022 at the ESC Congress 2022 as a part of the session "Novel Insights into Vascular Inflammation".

Adenosine diphosphate (ADP) plays a pivotal role in platelet activation. The purinergic ADP-receptor P2Y12 has therefore been targeted in the treatment of cardiovascular disease (CVD) to prevent atherothrombosis. Beyond P2Y12 expression on platelets, purinergic receptors have also been described on hematopoietic stem and progenitor cells (LSK). After myocardial infarction (MI), accelerated LSK proliferation launches emergency hematopoiesis as the driving force behind the inflammatory response to MI, increasing inflammatory cell production in the bone marrow (BM) and providing leukocyte resupply for local cell recruitment to the infarct. The inflammatory cascade after MI covers intricates multilayered interactions between the injured myocardium and the hematopoietic BM that still remain to be fully elucidated and may unearth novel therapeutic strategies. Whereas P2X receptors have recently been found to be involved in cell trafficking, the role of P2Y receptors in the hematopoietic BM have not yet been characterized. This study aims to characterize the influence of P2Y12 signaling on emergency hematopoiesis and cardiac remodeling after MI.

Permanent coronary ligation was performed for MI to assess BM activation, inflammatory cell composition, cardiac remodeling and function in murine global and platelet-specific P2Y12 knockout models and under pharmacological P2Y12 inhibition with prasugrel using flow cytometry, qPCR, immunohistochemistry and echocardiography. In vitro studies including colony forming unit (CFU) assays and flow cytometry allowed for investigation of ADP-dependent effects on LSK cells and intracellular pathway analysis.

We identified ADP as a danger signal for the hematopoietic BM, fueling emergency hematopoiesis by promoting Akt phosphorylation and cell cycle progression. Detection of P2Y12 expression in LSK implicated a direct effect of ADP on LSK via P2Y12 signaling. P2Y12 deficiency and P2Y12 inhibition with prasugrel decelerated emergency hematopoiesis and consecutively reduced the excessive inflammatory response to MI, translating to lower numbers of hematopoietic progenitors and inflammatory cells in the blood and infarct. Ultimately, P2Y12 inhibition ameliorated chronic adverse cardiac remodeling and preserved cardiac function after MI.

ADP-dependent P2Y12-mediated activation of hematopoietic stem and progenitor cells in the BM promotes emergency hematopoiesis after MI and fuels post-ischemic inflammation, proposing a novel role of P2Y12 antagonists in CVD beyond atherothrombosis.

SOTAGLIFLOZIN, A DUAL SGLT1/2 INHIBITOR, REDUCED EXPRESSION OF NEUTROPHIL DEGRANULATION PROTEINS DURING ENDOTHELIAL DYSFUNCTION COMPARED WITH A SELECTIVE SGLT2 INHIBITOR

Barcelona **Sunday, August 28th, 2022**

This paper was presented by Dr. Preston Mason et al., from the Brigham and Women's Hospital, Harvard Medical School on 28th August 2022 at the ESC Congress 2022 as a part of the session "Novel Insights into Vascular Inflammation".

Angiotensin II (Ang II) is a potent vasoconstrictor released during endothelial cell (EC) dysfunction that contributes to inflammation and atherothrombotic risk. Results from randomized clinical trials (SCORED, SOLOIST) indicate that dual SGLT1/2 inhibition with sotagliflozin in patients with diabetes produced large reductions in a composite of death from cardiovascular causes and hospitalization for heart failure (HF), with greater reductions in ischemic events, including stroke, than seen with prior SGLT2 inhibitors. We compared the effects of sotagliflozin and empagliflozin (a highly selective SGLT2 inhibitor) on neutrophil degranulation signaling protein in human vein ECs (HUVECs) subjected to Ang II.

HUVECs were treated with sotagliflozin or empagliflozin (100 nM) for 30 minutes and then challenged with Ang II (100 nM) for 24 hours. Global proteomic analysis was performed using LC/MS to measure relative expression levels of >1,000 proteins, simultaneously. Only significant ($p<0.05$) changes in expression between treatment groups (>1-fold) were analyzed using differential enrichment analysis of proteomics data (DEP). Biological pathways were analyzed using proteins that survived the cutoff criteria via gene set enrichment analysis (GSEA).

Sotagliflozin and empagliflozin treatment modulated the expression of 493 and 68 proteins, respectively, in HUVECs challenged with Ang II. GSEA revealed sotagliflozin, not empagliflozin, significantly modulated the neutrophil degranulation pathway (GO:0043312) with a pathway adjusted - p value of 9.47×10^{-7}. Within this pathway, sotagliflozin significantly affected expression of 35 proteins while empagliflozin only significantly affected expression of 6 proteins (pathway adjusted - $p = 0.09$). Among the proteins modulated by sotagliflozin but not empagliflozin in this pathway were heat shock 70 kDa protein 8 (1.1-fold decrease relative to Ang II alone, $p = 0.001$), heat shock 86 kDa (1.1-fold decrease relative to Ang II alone, $p = 0.009$), and the pro-inflammatory cytokine cyclophilin A (1.2-fold decrease relative to Ang II alone, $p = 0.026$).

The dual SGLT1/2 inhibitor sotagliflozin significantly modulated expression of neutrophil degranulation proteins in human ECs during inflammation compared with a selective SGLT2 inhibitor. These favorable effects of dual SGLT1/2 inhibition on mechanisms of inflammation have implications for ischemic disease, including myocardial infarction and stoke, as demonstrated in outcome trials.

SESSION-7 :
Myocarditis: Still Many Open Questions

IMPACT OF MYOCARDIAL INJURY ON MORTALITY AND ADVERSE EVENTS IN HOSPITALIZED PATIENTS WITH INFLUENZA: A PROSPECTIVE COHORT STUDY

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Amabile Valotta et al., from the Cardiocentro Ticino - Lugano – Switzerland on 28th August 2022 at the ESC Congress 2022 as a part of the session "Myocarditis: Still Many Open Questions".

Myocardial injury (MINJ) defined as elevated high-sensitivity cardiac troponin level (hs-cTnT) above normal values is a well-recognized prognostic marker in different clinical conditions, nonetheless, its relevance in Influenza remains poorly defined. We aimed to analyse incidence, predictors, short and mid-term prognostic role of MINJ in hospitalized patients (pts) with Influenza.

During 2018-2019 Influenza epidemic, a prospective multicentre observational cohort study was conducted enrolling all hospitalized adult patients with laboratory confirmed Influenza infection. MINJ was prospectively assessed at admission and defined as hs-cTnT>14 ng/L. Primary endpoint was all-cause death at 28-days. Secondary endpoints were all-cause death at 28-days or intensive care unit (ICU) admission/mechanical ventilation and all-cause death at follow up.

145 consecutive pts were enrolled. MINJ was evident in 94 (65.5%) pts. At a 28-days follow up, 7 deaths (4.8%) occurred, all in patients with MINJ at admission (log rank p=0.048). MINJ showed a strong association with the occurrence of death, ICU admission or mechanical ventilation (OR 5.74, 95% CI 1.28-53.29; p=0.015). At a median follow-up of 32.7 months, 15 (10.3%) deaths occurred, all among patients with MINJ at index hospitalization leading to a significantly high mortality rate at follow-up among patients with MINJ (log-rank p=0.003).

Influenza related MINJ is common and identifies patients at higher likelihood of short-term adverse events and midterm mortality.

PROGNOSTIC IMPLICATION OF NEUTROPHIL-LYMPHOCYTE RATIO (NLR) IN MYOCARDITIS: RESULTS FROM A MULTICENTRE, MULTINATIONAL STUDY

Barcelona Sunday, August 28th, 2022

This paper was presented by Dr. Matthew Sadler et al., from the King's College London - London on 28th August 2022 at the ESC Congress 2022 as a part of the session "Myocarditis: Still Many Open Questions".

Neutrophil–lymphocyte ratio (NLR) is an accessible inflammatory biomarker. Recently, baseline NLR has been shown to be independently associ-

ated with incident cardiovascular (CV) events and all-cause mortality. However, whether this applies to acute myocarditis (AM) has not been evaluated. The aim of the present study was to investigate the prognostic value of NLR in patients with AM.

All consecutive patients with a diagnosis of AM admitted to three tertiary referral cardiac centres in two countries between October 2006 and June 2020 were included in the study. Diagnosis was confirmed by either cardiac magnetic resonance or endomyocardial biopsy. The outcome measure was all-cause mortality. Patients were divided into two groups according to NLR value defined in previous studies (i.e., 2.5).

A total of 287 patients with AM were included in the study. Baseline characteristics were comparable in both groups. Approximately two thirds of patients were males (n=194, 68%) with a mean age of 39±16 years. The main clinical presentation was predominantly infarct-like (n=215, 75%), followed by heart failure (HF) (n=46, 16%) and arrhythmic (n=26, 9%). Patients admitted with a HF presentation were more prevalent in the group with elevated NLR, while no difference was found in the other clinical presentations. For all patients, ECG features were comparable between groups. However, patients with elevated NLR presented with slightly higher LVEF (55±11% vs 50±13% respectively, p=0.003). Over a median follow-up of 54 months, higher NLR was associated with worse prognosis, p=0.02). Patients with high NLR have a 7-fold higher risk of adverse events during follow-up (Hazard Ratio 7.83, 95% confidence interval 1.02 – 59.89, p=0.047).

NLR is a promising and accessible inflammatory biomarker. In patients with AM, elevated NLR is associated with worse prognosis. Further research is advocated to confirm these data in larger populations.

GENETIC CHARACTERIZATION OF BIOPSY-PROVEN MYOCARDITIS: A PILOT STUDY

Barcelona **Sunday, August 28th, 2022**

This paper was presented by Dr. Maria Beuno Marinas et al., from the University of Padova on 28th August 2022 at the ESC Congress 2022 as a part of the session "Myocarditis: Still Many Open Questions".

Myocarditis is characterized by the presence of an inflammatory infiltrate in the myocardium with degenerative/necrotic changes of cardiomyocytes, not-related to ischemic damage. Its clinical presentation is extremely heterogenous. Endomyocardial Biopsy (EMB) is the diagnostic gold standard and provides etiopathogenetic diagnosis. Biopsy-proven myocarditis may be infectious, mainly viral, toxic o non-infectious immune-mediated/autoimmune. A complex interplay between genetic factors, environmental triggers (i.e., viral infection) and the immune response of the host is postulated at the basis of different disease evolution.

The purpose of this study was to determine the prevalence of pathogenic/likely pathogenic (P/LP) variants in cardiomyopathy-related genes in a well-characterized cohort of biopsy-proven myocarditis.

Sixty-six biopsy-proven myocarditis-affected patients (mean age 51±9, 41 males) underwent screening of 200 genes related to inherited cardiomyopathies. Definite/moderate gene association with Dilated Cardiomyopathy (DCM) and Arrhythmogenic Cardiomyopathy was based on the ClinGen framework. Variant prioritization was carried out using American College of Medical Genetics and Genomics rules. Correlation with presence of virus on endomyo-

cardial biopsy by polymerase chain reaction, family history and serum anti-heart autoantibodies (AHA) and/or anti-intercalated-disk autoantibodies (AIDA) was appraised.

Nineteen of the 66 biopsy-proven myocarditis patients (28%) carried a P/LP variant in cardiac-related genes. Titin (TTN) was the most over-represented gene accounting for 11% of cases (7/66), followed by Myosin Heavy Chain 7 (MYH7) and Myosin Binding Protein C3 (MYBPC3) each accounting for 3% of cases (2/66), respectively. Of note, 29 of the 66 of index cases (44%) referred family history for cardiomyopathy and/or sudden cardiac death. However only 13/29 patients with family history were genotype-positive (45%), indicating that other immunogenetic factors might contribute to triggering myocarditis. Circulating AHA and/or AIDA were detected in 31% of our genotype-positive cohort (6 of 19); a virus positive diagnosis was obtained in 15% of cases.

The prevalence of clinically actionable P/LP variants in cardiomyopathy-related genes is nearly one third of biopsy-proven viral or autoimmune myocarditis patients, most of them associated with DCM. On the other hand, positive family history (44%) in the absence of known cardiomyopathy-related genes indicates that additional immunogenetic factors might contribute to disease pathogenesis.

An Educational Initiative By

sanofi

MAT-IN-2202246-1.0-08/2022