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### **P4.6: GREATER CAROTID CIRCUMFERENTIAL WALL STRESS IS ASSOCIATED WITH INCIDENT CARDIOVASCULAR DISEASE IN INDIVIDUALS WITH TYPE 2 DIABETES – THE HOORN STUDY**

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We examined cross-sectional associations of self-reported PA intensities with arterial stiffness in elderly Caucasians of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA). Mixed central and peripheral arterial stiffness was measured oscillometrically by the cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV). The self-reported International Physical Activity Questionnaire (IPAQ) long version was administered to classify each subject's PA level. We used univariable and multivariable mixed linear and logistic regression models for analyses in 1908 persons aged 50 years and older. After adjustment for several confounders moderate, vigorous and total PA were inversely associated with CAVI ( $p=0.02-0.03$ ). BaPWV showed negative and marginally significant associations with vigorous and moderate PA (each  $p=0.06$ ), but not with total PA ( $p=0.28$ ). Increased arterial stiffness (CAVI $\geq 9$ , upper tertile) was inversely and significantly associated with vigorous PA (Odds Ratio (OR)=0.65, 95% Confidence Interval (CI): 0.48-0.88), and marginally significantly with total PA (OR=0.76, 95% CI: 0.57-1.02) and moderate PA (OR=0.75, 95% CI: 0.56-1.01). The odds ratio for baPWV $\geq 14.4$  was 0.67 (95% CI: 0.48-0.93) across the vigorous PA levels, and was non-significant across the total (OR=0.91, 95% CI: 0.66-1.23) and moderate PA levels (OR=0.94, 95% CI: 0.69-1.28). In this general Caucasian population of older adults higher levels especially of vigorous PA were associated with lower arterial stiffness. These data support the importance of PA for improving cardiovascular health in elderly people.

#### P4.4

##### INHIBITION OF ARTERIAL CALCIFICATION BY MATRIX GLA PROTEIN AS DETERMINANT OF RENAL FUNCTION IN THE GENERAL POPULATION

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**Background:** Carboxylation of matrix Gla protein (MGP), a vitamin K dependent process, activates the protein to a powerful inhibitor of arterial calcification. Circulating dephosphorylated and uncarboxylated MGP (dp-ucMGP) and total uncarboxylated MGP (t-ucMGP) are associated with macrovascular disease. The association with microcirculatory disease remains unknown.

**Methods:** In 1174 randomly recruited Flemish (51.4% women; mean age, 38.2 years), we studied the estimated glomerular filtration rate (eGFR) and microalbuminuria, as prototypes of microcirculatory traits, in relation to dp-ucMGP and t-ucMGP. In multivariable linear and logistic regressions, we expressed effect sizes for a doubling of the biomarkers, while accounted for anthropometric characteristics, lifestyle, risk factors and use of medications.

**Results:** Among all participants, geometric means of dp-ucMGP and t-ucMGP were 3.68 mg/L and 45.2 mg/L, respectively. In relation to dp-ucMGP (figure), eGFR decreased by 1.57 mL/min/1.73 m<sup>2</sup> ( $p=0.015$ ), while the risk of renal dysfunction (eGFR <60 mL/min/1.73 m<sup>2</sup>) increased by 19% ( $p=0.022$ ) with a 43% trend in the same direction ( $p=0.069$ ) for microalbuminuria (albumin-to-creatinine ratio  $\geq 3.5$  mg/mmol in women and  $\geq 2.5$  mg/mmol in men). In relation to t-ucMGP (figure), eGFR increased by 1.89 mL/min/1.73 m<sup>2</sup> ( $p=0.041$ ) with no changes in the risks of renal dysfunction or microalbuminuria ( $p\geq 0.12$ ).

**Conclusion:** In the general population, eGFR is inversely correlated with dp-ucMGP, a marker of vitamin K deficiency, whereas the opposite is the case for t-ucMGP, a marker of prevalent arterial calcification.

#### P4.5

##### VASCULAR HEALTH ASSESSMENT OF THE HYPERTENSIVE PATIENTS (VASOTENS) REGISTRY: RATIONALE, DESIGN AND METHODS OF AN INTERNATIONAL REGISTRY FOR AMBULATORY BLOOD PRESSURE AND ARTERIAL STIFFNESS TELEMONITORING

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**Background:** Ambulatory (A) blood pressure (BP), central BP and pulse wave velocity (PWV) are parameters recommended by hypertension guidelines for estimating BP control and vascular impairment. Recent advances in technology made available devices allowing combined non-invasive estimation of these parameters over the 24-h during ABPM. However, at present, there is limited evidence on the usefulness of such an approach for routine hypertension management.

**Objective:** We recently launched an investigator-initiated, international, multicenter, observational, prospective study aiming at: i) evaluating non-invasive 24-h ABP and arterial stiffness estimates (through 24-h pulse wave analysis, PWA) in hypertensive subjects; ii) assessing the changes in estimates following treatment; iii) weighing the impact of 24-h PWA on target organ damage and cardiovascular prognosis; iv) assessing the relationship between arterial stiffness, BP absolute level and variability, and prognosis.

**Methods:** Approximately 2000 subjects, referred to 20 hypertension clinics for routine diagnostic evaluation and follow-up of hypertension, will be recruited. Data collection will include ABPM, performed with a device allowing simultaneous non-invasive assessment of BP and arterial stiffness (BPLab), and clinical data (including cardiovascular outcomes). A web-based telemedicine platform will be used for data collection. Subjects will visit the centers at 6-12 month intervals. First follow-up results are expected to be available in the next 2-years.

**Conclusions:** The results of the VASOTENS Registry will help defining the normalcy thresholds for current and future indices derived from 24-h PWA, according to outcome data. They will also provide supporting evidence for the inclusion of such evaluation in recommendations on hypertension management.

#### P4.6

##### GREATER CAROTID CIRCUMFERENTIAL WALL STRESS IS ASSOCIATED WITH INCIDENT CARDIOVASCULAR DISEASE IN INDIVIDUALS WITH TYPE 2 DIABETES – THE HOORN STUDY

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**Introduction:** Arterial remodeling is an adaptive phenomenon aimed at maintaining circumferential wall stress (CWS) within operating limits. It is characterized by widening of the inter-adventitial diameter (IAD) and increases in intima-media thickness (IMT). This process is maladaptive when CWS increases despite remodeling. Type 2 Diabetes (T2D) is associated with increased carotid CWS, but its association with cardiovascular disease (CVD) is unknown.

**Methods:** The cohort consisted of 277 individuals with normal glucose metabolism (NGM), 162 with impaired glucose metabolism (IGM) and 131 with T2D (age 69.6  $\pm$  6.4, 51.0% women, systolic pressure 141.9  $\pm$  20.6 mmHg, bmi 26.9  $\pm$  3.5 kg/m<sup>2</sup>, prior CVD 50.1%). Carotid arterial properties (IAD, IMT, lumen diameter (LD)) were quantified by ultrasonography. CWS was calculated as PP-LD/(2IMT), where PP is the brachial pulse pressure. A morbidity and mortality register was kept on all individuals.

**Results:** After a median of 7.7 [IQR 7.0-8.1] years of follow up, 130 CVD events and 93 deaths were recorded. CWS was 31.7, 31.5 and 34.4 kPa in NGM, IGM and T2D, respectively (Ptrend= 0.06). Greater CWS was associated with incident CVD in T2D only (hazard ratio(95%CI) per SD increase in CWS for NGM: 0.92 (0.70-1.21); IGM: 1.02 (0.66-1.58) and T2D 1.52 (1.09-2.14), after adjustment for age, sex, height and other CVD risk factors.. No associations were observed between CWS and all-cause mortality.

**Conclusion:** T2D is associated with greater CWS compared to NGM and IGM. Greater carotid CWS is associated with incident CVD in T2D but not in NGM or IGM.

#### P4.7

##### PLASMA COPPER AND CERULOPLASMIN IN RELATION TO CAROTID-FEMORAL PULSE WAVE VELOCITY

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Copper participates in the redox mechanisms and is a cofactor of enzymes responsible for appropriate structure of elastic fibres. The aim of the study was to assess the relationship between plasma copper as well as ceruloplasmin concentrations and carotid-femoral pulse wave velocity (cfPWV). The study group, recruited from the population-based family study, included 138 parents (age 61.5±7.9 years, 57M/81F, 80.4% hypertensives) and 165 offspring (mean age 34.8±8.4 years, 79M/86F, 32.7% hypertensives). Information about each participant's clinical data were collected with the use of standardized questionnaires. The cfPWV was measured by Micro-Tip pressure transducer (Model SPT-301, Millar Instruments, Houston, Texas, USA) and the SphygmoCor system (ver. 6.31 AtCor Medical Pty., Ltd., Australia). The plasma copper concentration was determined by ICP-MS (Inductively Coupled Plasma Mass Spectrometry) and plasma ceruloplasmin concentration by ELISA test. Database management and multivariate analyses were performed with SAS software (SAS Institute, Cary, NC, version 9.3).

The average values of plasma levels were: copper (male 620.4±229.7µg/l, female 740.9±339.3µg/l); ceruloplasmin (male 612.6±221.6µg/ml, female 766.7±337.0µg/ml).

With adjustments applied for age, sex, cholesterol level, fasting glucose, body height, use of antihypertensive drugs, smoking and alcohol intake, we observed a positive correlation between the cfPWV and plasma copper concentration (0.00074±0.0003, p=0.011) as well as plasma ceruloplasmin concentration (0.0007±0.0003; p=0.0095).

In our study group, higher plasma copper and ceruloplasmin concentrations were related to higher cfPWV. The excess body copper might contribute to the lower antioxidant status and arterial stiffening.

#### P4.8

##### ASSOCIATIONS OF MID-LIFE CARDIOVASCULAR RISK FACTORS WITH LATER LIFE COGNITIVE FUNCTION

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**Background:** Mid-life cardiovascular risk factors may be detrimental to cognitive function in later life; however results are inconsistent. We investigated the impact of mid-life blood pressure, glucose, cholesterol and obesity on cognitive function.

**Methods:** In a community based sample aged 49.6±6years: waist-to-hip ratio (WHR), fasting blood glucose, HDL cholesterol and blood pressure were measured. 20 years later 1284 of these individuals underwent cognitive function testing to assess global function, executive function, memory and attention. Data are β±SE, \*p<0.05, \*\*p<0.01.

**Results:** After adjusting for age, sex, ethnicity, years of education and smoking no associations were found between cognitive function and mid-life glucose or blood pressure measures. Lower mid-life WHR and higher HDL cholesterol levels were significantly associated with better scores in all cognitive domains. Per unit increase in WHR: Global function -1.45±0.3\*\*; Executive function -1.82±0.3\*\*; Memory -1.27±0.3\*\* and Attention

-1.23±0.03\*\*. Per mmol/L increase in HDL: Global function 0.19±0.06\*\*; Executive function 0.13±0.06\*\*; Memory 0.14±0.06\*\* and Attention 0.17±0.05\*. These associations remained after further adjustment for current concomitant risk factors: diabetes, hypertension, previous stroke, coronary artery disease and current WHR/ HDL (WHR: Global function -1.05±0.4\*\*; Executive function -2.2±0.4\*\*; Memory -1.1±0.4\*\* and Attention -1.15±0.4\*\*. HDL: Global function 0.20±0.07\*\*; Executive function 0.15±0.07\*\*; Memory 0.19±0.07\*\* and Attention 0.15±0.07\*\*).

**Discussion:** Elevated WHR and lower HDL cholesterol in mid-life are significant risk factors for cognitive decline 20 years later. These mid-life risk factors have effects independent of current risk factors and may be important targets for prevention of cognitive decline in later life.

#### P4.9

##### ENDOTHELIN-1 IS LINKED WITH ARTERIAL STIFFNESS AND INTERLEUKIN-6 IN BLACK SOUTH AFRICAN WOMEN: THE SABPA STUDY

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Up-regulation of ET-1 activates inflammatory cells such as macrophages that release pro-inflammatory mediators such interleukin-6 which promote vascular inflammation and endothelial dysfunction, leading to arterial stiffness.

Included in this study were 194 black and 197 white South-Africans. Cardiovascular variables were recorded using the Finometer and the Compliar. ET-1 and interleukin-6 were determined by recognized biochemical methods.

The participants were divided into black and white men and women due to significant interactions of ethnicity (F(391) = 6.78; p < 0.001) and gender (F(391) = 2.39; p < 0.05) on the association of ET-1 with systolic blood pressure.

No significant difference in ET-1 levels between black and white groups emerged. Black men and women had higher blood pressure and pulse wave velocity in comparison to white men and women (p < 0.05). C-reactive protein and interleukin-6 were higher in the black groups compared to the white group (all p < 0.05). A positive correlation (single) existed between ET-1 and interleukin-6 (r = 0.27; p = 0.007), systolic blood pressure (r = 0.27; p = 0.008), pulse pressure (r = 0.25; p = 0.014) and pulse wave velocity (r = 0.23; p = 0.026) in black women. After partial adjustments for BMI and GGT the correlation remains. With forward stepwise multiple regression ET-1 associated with interleukin-6 (adj.R<sup>2</sup> = 0.13, β=0.278, P=0.005) and measures of arterial stiffness.

ET-1 independently associated with systolic blood pressure, pulse pressure and interleukin-6 in black women. Our results suggest that adverse endothelial function is potentially driven by pro-inflammation.

#### P4.10

##### ASSOCIATION OF ARTERIAL STIFFNESS WITH BLOOD PRESSURE VARIABILITY

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Increase of arterial stiffness is an independent predictor of cardiovascular morbidity and mortality. Short term blood pressure (BP) variability is recognised as a marker and a risk factor for cardiovascular complications. The study aims to determine the relation between arterial stiffness and short -term variability in general population.

**Methods:** We recruited 303 subjects (55.12% Female). Short-term BP variability was calculated as the standard deviation (SD) of 24-hour, daytime, or nighttime BP, and as weighted SD of 24-hour BP defined as the mean of daytime and nighttime BP SD weighted by the duration of each time period. Carotid – femoral pulse wave velocity (PWV) were evaluated by means of pulse wave analysis.

**Results:** In the study group the SD of day- and nighttime Systolic BP (SBP), SD of 24-hour SBP and weighted SD of 24-hour SBP showed a significant association with PWV (P<0.003). Above-mentioned SBP variability indices except SD of night SBP independently predicted PWV along with age, gender, 24-hour SBP and antihypertensive treatment. None of the examined measures of diastolic BP variability had a relation with carotid-femoral PWV.