

ORAL SESSION

ORAL SESSION 6A:

EPIDEMIOLOGY OF HYPERTENSION AND METABOLIC DISORDERS

LEFT VENTRICULAR DIASTOLIC FUNCTION IN RELATION TO SODIUM DIETARY INTAKE AND RENAL HANDLING

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Objective: Sodium load has been associated with blood pressure (BP) and target organ damage. Sodium sensitivity of BP varies between individuals and may be determined by renal sodium handling.

The present study aimed to investigate ambulatory blood pressure and left ventricular diastolic function in relation to interaction between sodium dietary intake and renal handling.

Design and method: We recruited 303 (mean age, 46.9 years; 55% women) members from randomly selected families. The 24-hour blood pressure monitoring was assessed. Left ventricular mass index, left atrium (LA) diameter, and the ratio of early (E) and late (A) diastolic peak of transmitral flow velocities (E/A) as well as the ratio of E to tissue doppler early diastolic mitral annular velocity (Em) were assessed by echocardiography (VIVID 7). Serum and urinary sodium concentration was measured using an automatic analyzer while lithium concentration by automatic absorption spectrometry. The median value of urinary sodium excretion (uNa) and median value of fractional urinary lithium excretion (FELi) - marker of sodium reabsorption in proximal tubules and as a consequence sodium sensitivity - were calculated.

Results: To evaluate the influence of high sodium diet on parameters of interest we divided participants on two groups: high sodium group (HNa) constituted 86 participants with uNa above the median value (156.6 mmol/day) and FELi below the median value (16.6%), while the low sodium group (LNa) combined 79 persons with uNa below and FELi above the respective median value. 24-hour systolic and diastolic BP, left atrium diameter and E/Em were higher in HNa group in comparison to LNa participants ($p < 0.05$). After adjusting for relatedness, age, gender, and antihypertensive treatment, significant differences between predefined groups in 24-hour systolic BP (120.2 vs 117.0 (mmHg), $p = 0.03$) and E/Em (7.3 vs 6.7(%), $p = 0.016$) ratio persisted.

Conclusions: The study may be the basis for an assumption that in participants with a paradoxical high renal sodium retention in case of sodium overload an impairment of cardiac diastolic function develops sooner, suggesting that a reduction of salt intake may improve cardiac diastolic function.

TREATMENT OF STAGE 1, LOW RISK HYPERTENSION IS ASSOCIATED WITH REDUCTION IN CARDIOVASCULAR MORTALITY: A KOREAN NATIONAL COHORT STUDY

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Objective: There is lack of evidence for the benefit of treatment in uncomplicated, low risk grade I hypertension. As such, some of the major guidelines recommend treatment for grade I hypertensives who have underlying cardiovascular disease, or are at high risk.

Design and method: From National Health Insurance Service (NHIS) Health Examination Database, subjects with grade I hypertension between 2005 and 2006 were selected and followed-up until December, 2015. The subjects had a SBP of 140–159 mmHg and/or DBP of 90–99 mmHg and were not undergoing treatment at baseline. Subjects were grouped into controlled (<140/90 mmHg;

$n = 99,301$) and uncontrolled group ($\geq 140/90$ mmHg; $n = 49,460$) according to mean of the BP recorded during follow-up health examination. All-cause death and cardiovascular outcomes including myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, and end stage renal disease (ESRD) were examined by using Cox proportional hazard models with covariate adjustment method using the propensity scores.

Results: Median follow-up duration was 124 months (IQR: 116–131). Compared to subjects with uncontrolled BP, controlled group had significantly lower risk of all-cause death (HR, 0.50; 95% CI, 0.48–0.52; $p < 0.0001$). For non-fatal events, controlled BP was associated with the lower risk of all stroke (HR, 0.88; 95% CI, 0.82–0.93; $p < 0.0001$), hemorrhagic stroke (HR, 0.75; 95% CI, 0.66–0.85; $p < 0.0001$), ischemic stroke (HR, 0.91; 95% CI, 0.84–0.98; $p = 0.0083$), and ESRD (HR, 0.42; 95% CI, 0.30–0.59; $p < 0.0001$). There was no significant difference between the two groups for non-fatal MI. Importantly, the benefit was evident in young aged hypertensives below the age of 50. The optimal level of BP associated with the lowest risk of all-cause mortality was 120 to < 130 mmHg for SBP and 70 to < 80 mmHg for DBP. However, there was increased risk of MI for subjects with SBP of < 120 mmHg and DBP of 70 to < 80 mmHg.

Conclusions: In a large cohort of treated low risk, grade I hypertensive subjects, BP below 140/90 mmHg was associated with significant reduction in the risk of mortality, stroke and ESRD, with the lowest risk of mortality in the range of 120 to < 130 mmHg and 70 to < 80 mmHg.

EARLY ONSET HYPERTENSION IS ROBUSTLY ASSOCIATED WITH HYPERTENSIVE ORGAN DAMAGE

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Objective: Our prior research has demonstrated that early, and not late, onset hypertension in parents is a strong risk factor for incident hypertension in offspring as well as for cardiovascular death in those with hypertension. Our objective was to study if age of hypertension onset is associated with increased odds of hypertensive organ damage.

Design and method: Our study sample included 2683 participants (50 ± 4 years, 57% women) who attended examination cycle eight of the CARDIA (Coronary Artery Risk Development in Young Adults) study (2010–2011). At examination eight, the participants underwent measurements for echocardiographic left ventricular hypertrophy (increased left ventricular mass index), coronary calcification (Agatston score > 100), albuminuria (elevated urine albumin-to-creatinine ratio), and diastolic dysfunction (abnormal E/A ratio). Assessment of hypertension onset was based on all available blood pressure measurements performed at eight serial examinations from 1985 through 2011. We defined hypertension onset as blood pressure > 140/90 mmHg or use of hypertension medication on two consecutively attended exams. We divided the participants into four groups according to their age of hypertension onset (<35 years, 35–44 years, > 45 years, and no hypertension). We assessed the relation of age at hypertension onset with presence of organ damage with multivariable-adjusted logistic regression models using a case (presence of organ damage) versus control (no organ damage) design, with those who did not develop hypertension as the referent group.

Results: Compared with individuals who did not develop hypertension, hypertension onset at ages < 35, 35–44, and > 45 years was associated with odds ratios (95% confidence interval) of 3.07 (1.85–5.11), 2.24 (1.50–3.33), and 1.61 (0.98–2.66) for left ventricular hypertrophy; odds ratios of 3.20 (1.76–5.82), 1.92 (1.16–3.16), and 1.50 (0.85–2.68) for coronary artery calcification; odds ratios of 1.79 (0.91–3.53), 1.65 (0.97–2.82), and 0.82 (0.38–1.78) for albuminuria; and odds ratios of 2.12 (1.10–4.08), 1.62 (0.95–2.75), and 1.53 (0.80–2.91) for diastolic dysfunction, respectively.

Conclusions: Odds of hypertensive organ damage increase with decreasing age of hypertension onset. Our findings further emphasize the importance of assessing age of hypertension onset in hypertensive patients.

PROGNOSTIC VALUE OF URIC ACID IN RELATION TO DIFFERENT AMBULATORY BLOOD PRESSURE COMPONENTS IN THE ABP-INTERNATIONAL STUDY

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Objective: The intriguing relationship between uric acid (UA) and cardiovascular events (CVE) and mortality is under active scrutiny. Increased UA levels have been associated with elevated BP and adverse prognosis. However, the extent to which UA maintains its prognostic value over and above specific ambulatory BP components is not well defined.

Design and method: We followed 5244 participants of the Ambulatory Blood Pressure International (ABP-I) study with UA determined at entry. We grouped participants by gender-specific UA quartiles (divisions: 4.6, 5.4, and 6.4 mg/dl in men; 3.4, 4.2 and 5.0 mg/dl in women). Cox models were used to estimate the magnitude and changes in UA hazard ratio (HR) for CVE and mortality in relation with different ambulatory BP (ABP) components. The Akaike and Bayes information criteria (AIC, BIC) were used to compare non-nested models.

Results: The 24-hour, daytime and nighttime systolic BPs increased linearly ($p < 0.001$ for all) across the gender-specific UA quartiles. We found no evidence for significant relationships between increasing UA and diastolic ABPs. Participants in the top UA quartile were older ($p < 0.001$), more frequently diabetic ($p < 0.001$), and had decreased renal function ($p < 0.001$), higher cholesterol ($p < 0.001$), and BMI ($p < 0.001$) than the others. During 35,087 person-years of follow-up there were 423 CVE (93 fatal, 330 nonfatal) and 185 deaths. The CVE rate per 100 person-years was 0.99, 0.95, 1.11, and 1.81, and mortality was 1.01, 0.55, 0.93, and 2.01, suggesting a possible non-linear relationship across UA quartiles. In fully adjusted survival models including different ABP components, the HR for CVE and mortality for the top UA quartile always remained significant (all $p < 0.05$ and $p < 0.02$ for CVE and mortality, respectively) with no evidence for HRs heterogeneity ($p = 0.965$ CVE, $p = 0.999$ mortality). Based on AIC and BIC, CVE models including either the average 24-hour or the night systolic BP were equally informative and better than those including daytime BP.

Conclusions: In ABP-I participants, UA was a powerful risk marker for subsequent cardiovascular events and mortality and added prognostic value independently of specific ABP components.

DETERMINANTS OF WHITE MATTER HYPERINTENSITY IN A COMMUNITY-BASED POPULATION STUDY: THE ROLE OF HIGH BLOOD PRESSURE AND LOW CAROTID FLOW

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Objective: High blood pressure and low carotid flow are positively associated with acute cerebrovascular disease risk, such as stroke. However, the determinants of white matter hyper-intensity (WMHI) and its association with blood pressure and carotid flow remains unclear. The present study was conducted to investigate the determinants of WMHI in a general population and its associations with carotid flow and blood pressure.

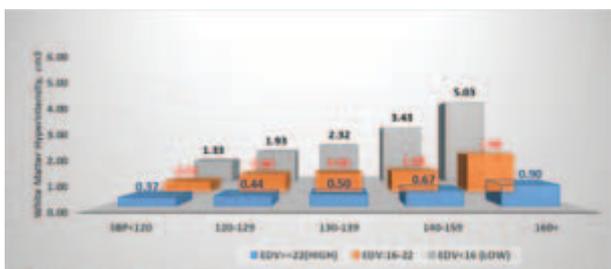


Figure 1. Association of Systolic Blood Pressure (mmHg), Carotid flow (End Diastolic Velocity (cm/sec) at Common carotid Artery) and White Matter Hyperintensity Volume (Median, cm³) in adults aged more than 50 yrs in a community-based study (n = 681).

Design and method: A total 991 adults (≥ 50 yrs) from a community-based study, the I-Lan Longitudinal Aging Study, were evaluated for this study. Flow velocities at common and internal carotid artery (CCA and ICA), including peak

systolic velocity (PSV) and end diastolic velocity (EDV), were measured by Doppler ultrasound. Systolic and diastolic blood pressure (SBP and DBP) were measured by an automatic oscillometric device. WMHI was measured by brain magnetic resonance imaging. General linear regression was used to evaluate the association between carotid flow, blood pressure, and WMHI.

Results: The mean and median of WMHI were 2.20 and 0.857 cm³. SBP ($r = 0.30$), DBP ($r = 0.21$), CCA PSV ($r = -0.21$) and EDV ($r = -0.38$), and ICA PSV ($r = -0.21$) and EDV ($r = -0.32$) were significantly associated with log-WMHI (all p -values < 0.0001). In the multivariable linear regression model, age, SBP, CCA EDV, fasting blood sugar, and homocystein were independent predictors of WMHI. The WMHI in adults with SBP < 120 , 120–129, 130–139, 140–159, and ≥ 160 were 1.30, 2.07, 2.28, 3.18 and 4.04 (cm³), respectively (p -value for trend < 0.001), and in adults with EDV < 16 , 16–21 and ≥ 22 (cm/sec) were 4.58, 2.05, 0.98 (cm³), respectively (p -value for trend < 0.01). The positive association of systolic BP and negative association of EDV with WMHI remained significant in the model with controlling for age, gender, glucose, lipids, inflammatory status, drinking and smoking. The adults with SBP ≥ 160 mmHg plus EDV < 16 cm/sec had higher WMH volume (adjusted mean = 3.21 cm³, p -value < 0.001), compared to those with SBP < 120 plus EDV ≥ 22 cm/sec.

Conclusions: High SBP and low CCA EDV were independently associated with white matter hyperintensity volume. Higher blood pressure and carotid flow may play an important role in the development of white matter hyperintensity volume.

PROGNOSTIC VALUE OF CLINIC, HOME AND AMBULATORY PULSE PRESSURE IN THE GENERAL POPULATION. DATA FROM THE PAMELA STUDY

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Objective: Pulse pressure (PP), is a simple measure of arterial stiffness. Several studies have shown that PP increases the risk of cardiovascular (CV) events but they were limited to clinic measure, mostly performed on individuals with high CV risk. Furthermore few studies reported PP-related risk of morbidity and mortality separately for genders.

Design and method: 3200 subjects, stratified for sex and decades of ages, were randomly selected to be representative of the general population of Monza (Northern Italy). In each subject we performed the following measurements: 1) Clinic (C) Systolic (S) Blood Pressure (BP) and Diastolic (D) BP (sphygmomanometer), 2) Home SBP and DBP (Philips HP 5331), 3) Ambulatory (24 h) SBP and DBP (Spacelabs 90207), 4) Body Mass Index (BMI), 5) Blood Glucose and Serum Cholesterol. Each subject was followed for 12 years, during which all deaths were collected and classified by ICD-X codes as being a CV (ICD-X I-0 to I-99) or non CV death. Non-fatal CV events were identified by hospital diagnosis also using ICD-X codes and validated on the hospital clinical records.

Results: The complete data set was obtained in 2045 subjects. PP was calculated as difference between SBP and DBP. Office, home and 24 h blood pressures were significantly higher in individuals who experienced a CV event or died during follow-up. Clinic, 24 h and Daytime PP were independent predictors of CV events after adjustment for main demographic and clinical parameters in the whole study population (HR 1.24, CI 1.03–1.49; HR 1.17, CI 1.01–1.36; HR 1.2, CI 1.03–1.39, respectively; $p < 0.05$ for all). Nighttime PP was an additional independent predictor in men (HR 1.23, CI 1.03–1.47, $p < 0.05$). None of measured PP (Clinic, Home, 24 h, Day- and Nighttime) was predictor of CV events in women. None of calculated PP was predictor of all-cause mortality in general population and in both genders.

Conclusions: Clinic and 24 h, but not home, PP represent a predictor of CV events in general population and in its male fraction. In females PP does not increase risk of CV events. All-cause death is not predicted by any of the PP measured.

NATIONAL PREVALENCE OF HYPERTENSION, TREATMENT AND CONTROL, IN FRANCE IN 2015 AND TEMPORAL TRENDS SINCE 2006

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Objective: The aims of this public-funded study were to assess prevalence, diagnosis, treatment and control of hypertension in the adult population in France in 2015 and to describe temporal trends between 2006 and 2015.

Design and method: A cross-sectional survey (Esteban) based on a multistage sampling design was conducted in France in 2015–2016. The design was the same as the one of the 2006-survey. Both samples were representative of the French adult population (18–74 years). Blood pressure (BP) was measured in a national sample of non-institutionalized adults during a health examination. Sociodemographic characteristics and risk factors were collected by questionnaires. Reimbursements of pharmacological treatments during the year preceding the survey came from the national health insurance inter-scheme information system. Hypertension was defined by systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or a reimbursement of BP-lowering drugs.

Results: 2,169 adults (men: 42.2%) had a least two BP measurements. Mean age was 46.9 years. Mean BP was 131.2/78.6 mmHg in men and 121.8/74.9 mmHg in women. The BP was > 140 mmHg or > 90 mmHg in 29.5% of men and in 17.7% of women. The prevalence of hypertension was 30.6% [28.1–33.2] (36.5% in men and 25.1% in women) and increased with age. Among hypertensive adults, 47.3% [42.3–52.2] were treated with BP-lowering drugs. Among hypertensive treated adults, 49.6% were controlled (41.4% in men and 60.1% in women). Since 2006, the prevalence of hypertension was stable ($p = 0.90$). The proportion of hypertensive treated adults and of controlled hypertensive treated adults did not differ significantly ($p = 0.11$ and 0.84 , respectively). Considering the threshold of 130/80 mmHg, the prevalence of hypertension would increase up to 48.8% [CI 95%: 46.0–51.7] and control rate would decrease down to 19.2% [CI 95%: 14.1–24.4]. Among hypertensive patients, 38% did not have any other cardiovascular risk factors, 36% had 1 (mostly sedentary and obesity) and 20% had 2 other risk factors

Conclusions: During the past decade, despite production of several guidelines and incentives, the prevalence of hypertension remained high and the treatment and the control of hypertension didn't significantly improve in France.

INTERACTION BETWEEN LDL-CHOLESTEROLEMIA, SERUM URIC LEVEL AND INCIDENT HYPERTENSION: DATA FROM THE BRISIGHELLA HEART STUDY

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Objective: The aim of our study was to evaluate the short-term interaction between SUA, LDL-C and incident hypertension in a sample of overall healthy subjects.

Design and method: We selected from the general database of the Brisighella Heart Study four groups of age- and sex-matched non-hypertensive subjects with different levels of LDL-C and SUA level and examined during the 2008 population survey. Incident hypertension was defined as the increase of systolic blood pressure values over 140 mmHg and/or of diastolic blood pressure over 90 mmHg and/or the beginning of an antihypertensive treatment. The timing of hypertension diagnosis was estimated on the basis of what reported by the patient, the data reported on the general physicians electronic clinical forms and of the beginning of the pharmacological treatment reported by the local pharmacy registries.

Results: In a model adjusted for age, sex and baseline blood pressure Hazard Ratios (HRs) for hypertension development compared to subjects with baseline normal LDL-C and SUA levels were 1.86 (95%CI 0.88–1.58, $p = 0.243$) for subjects with isolated high LDL-C level, 1.53 (95%CI 0.92–2.49, $p = 0.061$) for subjects with isolated high SUA level, and 1.61 (95%CI 1.18–2.11, $p = 0.009$). In a model further adjusted for family history of hypertension, smoking status, Body Mass Index and physical activity intensity, HRs for hypertension development compared to subjects with baseline normal LDL-C and SUA levels were 1.14 (95%CI 0.87–1.55, $p = 0.249$) for subjects with isolated high LDL-C level, 1.55 (95%CI 0.96–2.48, $p = 0.059$) for subjects with isolated high SUA level, and 1.57 (95%CI 1.20–2.15, $p = 0.015$).

Conclusions: In conclusion, in an overall healthy population sample, the contemporary presence of suboptimal LDL-C and SUA values are associated to an increased risk to develop hypertension.

PREVALENCE, TREATMENT AND ASSOCIATED FACTORS OF HYPERTENSION IN URBAN AND RURAL AREAS OF SPAIN

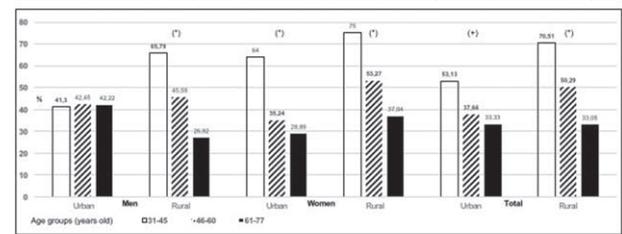
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Objective: To study the prevalence and related factors of hypertensive subjects according to the resident area (rural vs. urban) in two population-based studies from Spain: Variability of Insulin with Visceral Adiposity (VIVA) and Segovia Insulin Resistance Study (SIRS).

Design and method: Cross-sectional survey. 5,941 males and non-pregnant females (54%) aged 35 to 74 years old, from a targeted population of 496,674 subjects from 21 small and middle-sized towns across Spain were invited to participate. Exclusion criteria: (1) Type 1 diabetes mellitus, (2) Heart failure or hepatic insufficiency, (3) Surgery in the previous year, (4) Abdominal wall hernias but for inguinal hernia, (5) Weight loss or gain > 5 kg in the previous six months, (6) Subjects living in nursing homes/hospices/hospitalized/institutionalized, (7) Pregnancy or delivery in the previous year. Medical questionnaires were administered as well as anthropometrics measured, using standardized protocols. Hypertension was diagnosed in pharmacology treated subjects or > 140/90 mmHg of blood pressure (BP). For type 2 diabetes mellitus subjects, hypertension was defined as BP > 140/85 mmHg. Information on educational status, social class, smoking habit and alcohol intake was obtained.

Results: 3,816 subjects were included. Prevalence of diagnosed hypertension was higher in women and showed no differences according to the living area (men: urban 21,88% vs. rural 21,92%, $p = 0,986$; women: urban 28,73% vs. 30,01%, $p = 0,540$). Prevalence of undiagnosed hypertension also increased with age and was higher in urban vs. rural population aged 46–60 years old (19,85% vs 14,18%, $p = 0,018$). Women living in rural areas and men with secondary or tertiary education levels have a lower probability of being BP uncontrolled (OR (95% CI): 0.501 (0.258–0.970)/ $p = 0,040$, 0.245 (0.092–0.654)/ $p = 0,005$ and 0.156 (0.044–0.549)/ $p = 0,004$ respectively). Urban young men (31–45 years) and medium aged women (46–60 years) are worse BP controlled than their rural counterparts (41.30% vs. 65.79%/ $p = 0,025$ and 53.27% vs. 35.24%/ $p = 0,002$ respectively).

Prevalence of controlled blood pressure in hypertensive subjects according to the age group and living area.



(* Overall age categories comparison $p < 0.001$ (+) Overall age categories comparison $p = 0.004$. Comparatives: 31 to 45 years old urban vs. rural men (41.30 vs. 65.79 %, $p = 0.025$), 31 to 45 years old urban vs. rural women (42.22 vs. 33.33 %, $p = 0.263$), 31 to 45 years old urban vs. rural subjects (53.27 vs. 35.24 %, $p = 0.019$), 46 to 60 years old urban vs. rural men (42.45 vs. 45.59 %, $p = 0.684$), 46 to 60 years old urban vs. rural women (53.27 vs. 35.24 %, $p = 0.002$), 46 to 60 years old urban vs. rural subjects (37.66 vs. 50.29 %, $p = 0.002$), 61 to 77 years old urban vs. rural men (42.22 vs. 26.92 %, $p = 0.113$), 61 to 77 years old urban vs. rural women (28.89 vs. 37.04 %, $p = 0.257$), 61 to 77 years old urban vs. rural subjects (33.33 vs. 33.08 %, $p = 0.965$). Statistically significant values are highlighted in bold letters.

Conclusions: Women living in rural areas of Spain and men with secondary or tertiary education levels have a higher probability of being BP controlled. Urban young men (31–45 years) and medium aged women (46–60 years) are worse BP controlled than their rural counterparts. The prevalence of diagnosed hypertension increases with age, with no differences according to areas.

IMPACTS OF THE NEW 2017 ACC/AHA HYPERTENSION GUIDELINE ON THE PREVALENCE OF BRACHIAL HYPERTENSION AND ITS CONCORDANCE WITH CENTRAL HYPERTENSION

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Objective: The new 2017ACC/AHA hypertension guideline lowers the criteria for diagnosing high blood pressure (BP) and will certainly increase the burden of hypertension control. We therefore aimed to investigate how the new guideline influences the prevalence of brachial hypertension and whether the newly defined brachial hypertension improves the prediction of central hypertension in an Asian nationally representative population.

Design and method: A total of 2742 adults older than 19 years participated in the 2013–2016 National Nutrition and Health Survey in Taiwan. Central and brachial BP were simultaneously measured using a cuff-based stand-alone central BP monitor purporting to measure invasive central BP (Type II device). Brachial hypertension was defined by the new criteria of brachial systolic/diastolic

BP \geq 30 or 80 mm Hg or using anti-hypertensive medications, and central hypertension was defined by central systolic/diastolic BP \geq 130 or 90 mmHg or using anti-hypertensive medications.

Results: The national weighted prevalence rates of brachial hypertension with new AHA/ACC guideline were 48.7% in men and 30.4% in women. The prevalence of brachial hypertension increased by 18.8% in men and 9.1% in women, when compared with the prevalence defined by conventional criteria of brachial systolic/diastolic BP \geq 140 or 90 mm Hg or using anti-hypertensive medications. The increased prevalence of brachial hypertension was due to high diastolic BP (\geq 80 mmHg), high systolic BP (\geq 130 mmHg), and both in 47%, 24% and 29% of men, and in 33%, 44% and 23% of women. In comparison with the conventional criteria, the new hypertension criteria had a highersensitivity (93.0% vs. 77.4%), a lower specificity (86.7% vs. 99.6%), and a lower concordance (0.76 vs. 0.82) for detecting the central hypertension.

Conclusions: Almost half of men and one-third of women would be identified as having brachial hypertension by the new AHA/ACC guideline. The increased prevalence of brachial hypertension was mainly attributed to the new diastolic BP criterion in men and the new systolic BP criterion in women. The new hypertension criteria would not improve the concordance between brachial and central hypertension.

GENETIC ANALYSIS OF OVER ONE MILLION PEOPLE IDENTIFIES 535 NOVEL LOCI ASSOCIATED WITH BLOOD PRESSURE AND RISK OF CARDIOVASCULAR DISEASE

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Objective: Hypertension is the leading cause of cardiovascular morbidity. High blood pressure is highly heritable (~30–50%), however all genetic variants identified so far only explain ~3–4% of the trait variance. Hence much of the genetic architecture of blood pressure remains unexplained.

Design and method: We report the largest genome-wide association study to date. Our analyses test for association of ~7 million common genetic variants with systolic & diastolic blood pressure and pulse pressure.

Our discovery meta-analyses combine the UK Biobank cohort (N = 458,577) with the International Consortium for Blood Pressure data (N = 299,024). Our analysis strategy incorporates both a 1-stage design with internal replication and a 2-stage design with independent replication from the VA Million Veteran Program (N = 220,520) and the Estonian Biobank (N = 28,742), totalling over 1 million individuals overall, all of European ancestry.

Results: We identify 535 novel loci, replicate 92 loci for the first time, and confirm all 274 published loci. The total 901 blood pressure associated loci more than triples the number of previously known loci. By comparing the upper and lower quintiles of the genetic risk score, the combination of all blood pressure variants is associated with $>$ 10mmHg higher systolic blood pressure and odds of 2.59 and 1.45 for increased risk of hypertension and cardiovascular outcomes, respectively. Pathway analyses show enrichment of pathways targeted by antihypertensive drugs and highlight a novel pathway: transforming growth factor beta (TGF β), affecting sodium handling in the kidney. Enrichment of blood pressure gene expression is strongest in the vasculature, high in adrenal tissue, and newly observed in adipose tissues. Several novel blood pressure loci (e.g. apolipoprotein-E) are associated with

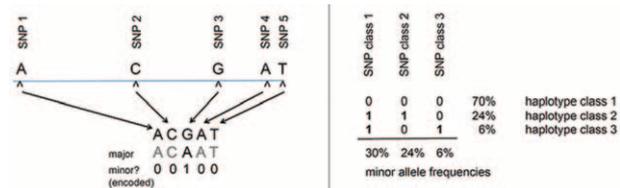
lipids and metabolites, implying pleiotropy across cardio-metabolic traits. We also show genetic overlap between hypertension and lifestyle exposures, with many blood pressure loci also associated with fruit/water/tea/caffeine/alcohol/salt intake, for example.

Conclusions: Our novel loci offer new biological insights into blood pressure regulation. The combined effect of all associated variants shows a large aggregated risk, warranting further investigation of a potential precision medicine strategy to prevent future cardiovascular disease amongst patients at high genetic risk.

GENOMIC LOCI THAT INFLUENCE BLOOD PRESSURE: USING HAPLOTYPE ANALYSIS AND 1000 GENOMES PROJECT DATA TO INTEGRATE ASSOCIATION FINDINGS FROM LOCAL POPULATION STUDIES

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Objective: Studies and metastudies of the past decade have found human genes or loci reproducibly associated with elevated blood pressure (BP) levels and/or risk of cardiovascular disease. Confirmed associations of systolic (S) and diastolic (D) BP levels with genetic variation at individual SNPs have also been repeatedly reported, but with modest effect sizes ($<$ 2 mmHg/allele). We explored the use of population haplotype analysis methods in order to better understand association findings focusing on BP levels.



Design and method: We used available and originally derived methods for analyzing association evidence and haplotype data in a cohort of individuals from Medellín, Colombia (n = 357), which we integrated with public data from 1000 Genomes (n = 2,504). Genotyping at different loci previously reported to be associated with BP levels or cardiovascular disease, including 67 SNPs from 9p21.3, was performed. Conventional SBP and DBP levels were measured and defined by the average of four conventional sitting BP measurements made at five min intervals by two trained physicians. Ambulatory BP monitoring (ABPM, Mobil-O-Graph NG, IEM, Stolberg, Germany) was performed and mean SBP and DBP were averaged for the day, night and 24-hour periods.

Results: The loci we analyzed showed a marked tendency: haplotypes at a given locus (from one of the two homologous chromosomes) consisted mainly of few (5 or less) distinct, easily distinguishable multi-SNP motifs (see Figure, or Gallo et al., 2017, JACC 70:1539–1540) that mostly recur across the world's populations. Consistent associations were found either for conventional or ambulatory BP levels in several loci, in particular in 9p21.3.

Conclusions: Although marked haplotype-block structures have been noted before, association studies have only very rarely incorporated them into their methods. The variation at the SNPs observed in our study consists largely of variation among haplotype classes, modulated by local point mutations within classes. For instance, the results for 9p21.3 show how haplotype methods can help understanding and interpreting SNP-by-SNP variation and associations. These results would be compatible with the hypothesis that elevated BP levels could be one of the mechanisms by which genetic variation in 9p21.3 increases risk of cardiovascular disease.

ORAL SESSION

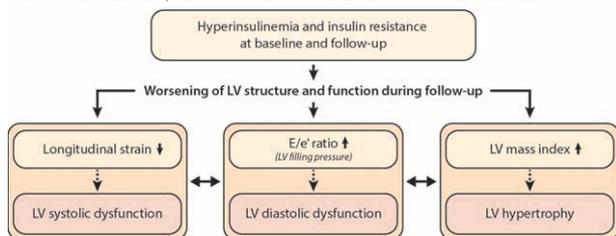
ORAL SESSION 6B: HEART AND HAEMODYNAMICS

THE RELATION BETWEEN INSULIN RESISTANCE AND LONGITUDINAL CHANGES IN LEFT VENTRICULAR STRUCTURE AND FUNCTION IN A GENERAL POPULATION

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Objective: Population data on the longitudinal changes of left ventricular (LV) structure and function in relation to insulin resistance are sparse. Therefore, we assessed in a general population whether hyperinsulinemia predicts longitudinal changes in LV and arterial characteristics.

CENTRAL ILLUSTRATION. Impact of Insulin Resistance on Left Ventricular Structure and Function



In this longitudinal population study, progression of insulin resistance status during follow-up was associated with a decline in LV systolic performance (by longitudinal strain), a worsening in diastolic function (by E/e') and increased LV hypertrophy (by LV mass index).
[IR = insulin resistance; LS, longitudinal strain; LV = left ventricular; PE = parameter estimate]

Design and method: In 627 participants (mean age 50.7 years, 51.4% women), we assessed echocardiographic indexes of LV structure and function and carotid-femoral pulse wave velocity (PWV) by applanation tonometry at baseline and after 4.7 years. We regressed longitudinal changes in these indexes on baseline fasting insulin and its change during follow-up, and reported standardized effect sizes as a percentage of the standard deviation of LV changes associated with a doubling of insulin.

Results: After full adjustment, higher baseline insulin predicted a greater longitudinal increase in LV mass index (LVMI) (effect size: +15.1%) and E/e' ratio (+22.1%), and greater decrease in e' peak and global and basal-mid longitudinal strain (-11.2 to -17.1%). Furthermore, a greater increase in insulin during follow-up was related to a greater increase in LVMI (+10.7%) and stronger decline in ejection fraction and global and basal-mid longitudinal strain (-11.4 to -15.7%). Participants who became or remained insulin resistant during follow-up experienced worse changes in global and basal-mid LS, E/e' and LVMI as compared to participants who didn't develop or even improved insulin resistance over time ($P < 0.033$). Moreover, the multivariable-adjusted increase in PWV was higher in subjects with diabetes than in non-diabetic participants (+1.46 m/s vs +0.71 m/s; $P = 0.039$).

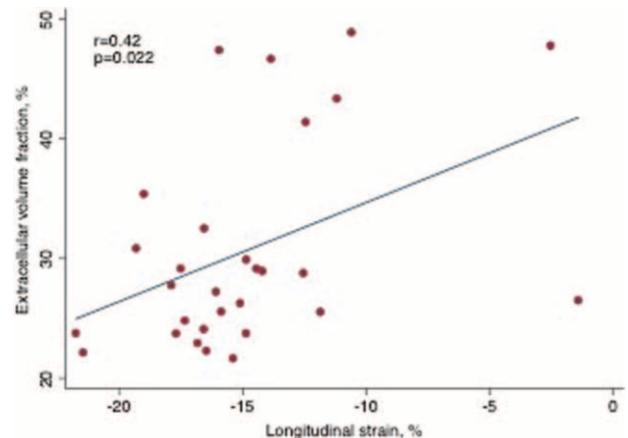
Conclusions: Hyperinsulinemia at baseline and during follow-up predicted worsening of cardiac function and remodeling over time. Our findings underline the importance of management of insulin resistance in subjects at risk for heart failure.

RELATIONSHIP OF CARDIAC MAGNETIC RESONANCE-DERIVED MYOCARDIAL FIBROSIS WITH CARDIAC GEOMETRY AND STRAIN IN HYPERTENSIVE HEART DISEASE

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Objective: Novel cardiac magnetic resonance (CMR) imaging techniques have shown potential in quantification of diffuse cardiac fibrosis, with T1 mapping, and estimating preclinical cardiac dysfunction, with strain analysis. The aim was to investigate the relationship of CMR-assessed fibrosis with cardiac geometry and strain in hypertensives with left ventricular hypertrophy (LVH).



Design and method: CMR was performed in hypertensives with positive ECG-derived criteria for LVH free of cardiomyopathy other than LVH. Extracellular volume fraction (ECV) and the partition coefficient as measures of cardiac fibrosis were assessed using the T1 mapping technique shMOLLI. Longitudinal, circumferential and radial strain were assessed using CMR-feature tracking. Pearson's correlation and multiple linear regression analysis controlling for gender, age, height, weight, heart rate and 24-h systolic BP were performed in order to assess the relationship between available variables.

Results: 36 hypertensives (83% males, mean age 50.6 ± 4.3) underwent CMR imaging, and T1 mapping was performed in 29 (79% males, mean age 50.1 ± 4.3) participants. Correlation models showed a significant relationship of ECV and the partition coefficient with left atrial (LA) diameter, LV mass, LV posterior wall thickness, LV end-diastolic volume and longitudinal strain. In fully adjusted regression models, ECV was associated with LA diameter ($\beta = 0.75$, $p = 0.005$, $R^2 = 0.47$) and longitudinal strain ($\beta = 0.43$, $p = 0.030$, $R^2 = 0.38$) (figure 1); the partition coefficient was associated with LV posterior wall thickness ($\beta = 0.53$, $p = 0.046$, $R^2 = 0.49$).

Conclusions: CMR-assessed fibrosis showed significant associations with cardiac geometry and myocardial strain: A greater extension of cardiac fibrosis was related to an increase in cardiac dimensions and a reduction (i.e., "less negative" values) in longitudinal strain. Cardiac fibrosis was a relevant component of changes in LV posterior wall thickness, LA diameter and myocardial strain.

CARDIOVASCULAR REMODELING IN MILD HYPERTENSION: ROLE OF SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS

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Objective: To assess the correlation between soluble receptor for advanced glycation end products (sRAGE) and office, 24 hours and central blood pressure (BP) and heart morpho-functional parameters in untreated mild hypertensive patients.

Design and method: We enrolled 74 patients, 35–55 years-old, with mild untreated hypertension, free from cardiovascular diseases or diabetes, not smokers. 52 normotensives age, sex and anthropometric parameters-matched were enrolled in the control group. Each subject underwent office and 24 hours BP measure-

ment, arterial tonometry (central BP, Pulse Wave Velocity-PWV), echocardiography (left ventricular mass-LVM, atrial size), carotid ultrasonography (intima media thickness-IMT) and blood tests, with sRAGE dosage too.

Results: sRAGE dosage was similar in hypertensives and normotensives (891 ± 697.9 pg/ml vs. 900 ± 560.4 pg/ml). There was no difference also between patients with normal glucose and with impaired fasting glucose, as well as between subjects with and without metabolic syndrome. In hypertensives, we found a negative correlation between sRAGE and LVM ($r: -0.24, p: 0.04$), also confirmed by multivariate analysis ($b: -0.223, p: 0.04$). A negative correlation was also observed between sRAGE and left atrial (LA) antero-posterior diameter ($r: -0.37, p: 0.002$), LA volume ($r: -0.34, p: 0.004$, confirmed by multivariate analysis $b: -0.214, p: 0.03$) and BSA-indexed LA volume ($r: -0.30, p: 0.01$). sRAGE correlated also with right atrial (RA) area ($r: -0.38, p: 0.001$), but not with RA volume ($r: -0.24, p: 0.08$). There was no correlation between sRAGE and office, 24 hours and central BP, PVW, carotid-IMT, glycemia, HOMA-index and uricaemia.

Conclusions: Correlations between sRAGE and LVM, LA and RA dimensions suggest how advanced glycation end products could play a role in cardiovascular remodeling. Mild hypertension and young age of our population may explain lack of differences between sRAGE dosage in hypertensives and normotensives. Importantly, all the observed correlations were found in absence of drugs interference.

THE ASSOCIATION OF EXAGGERATED EXERCISE AND 24H BLOOD PRESSURE WITH LEFT VENTRICULAR HYPERTROPHY IN NORMOTENSIVE MEN AND WOMEN ADJUSTED FOR CARDIORESPIRATORY FITNESS

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Objective: Left ventricular hypertrophy (LVH) increases the risk of cardiac events. Exercise blood pressure (BP) and ambulatory BP (ABPM) are associated with LVH, while cardiorespiratory fitness (CRF) is associated with lower BP at absolute workloads. This suggests that abnormally elevated BP during daily activities may be the stimulus for LVH. Thus, we assessed the association between exercise BP, ABPM and LVH in normotensive individuals based on office BP.

Design and method: We assessed cardiac structure and function, ABPM, and CRF in 1,022 normotensive men ($n = 697$; age: 51 ± 10) and women ($n = 325$; age: 54 ± 10), not treated by any medications.

Results: LVH was present in 24.7% with women having approximately 3 times higher prevalence (14.9% vs 45.5%). The strongest predictors of LVH were the increase in SBP from resting to exercise at Bruce I (5 METs), (OR = 1.17; $p < 0.001$); the difference between resting and SBP at 3 min of exercise (OR = 1.17; $p < 0.001$, and daytime ABPM (OR = 1.16; $p < 0.001$). There was also a 44% reduction in the risk for LVH for every 1 MET increase in the workload (OR: 0.56; $P < 0.001$). Cut-off analysis revealed a threshold for LVH > 150 mmHg for SBP at 5 METs and 15 mm Hg increase beyond resting BP at Stage I and 140 mm Hg for daytime SBP. The LVH risk increased by approximately 5-fold for every 10 mm Hg increases beyond these thresholds. To account for the impact of CRF on LVH, we stratified the cohort into age-specific fitness quartiles and compared cardiac parameters (Table).

	Least-Fit	Mode-Fit	Fit	High-Fit
PW (mm) ²	10.3±1.2	9.8±0.96	9.8±0.87	9.7±0.87
IVS (mm)	10.7±1.2	10.1±0.95	10.1±0.95	10.1±0.87
LVEDD (mm)	49.4±3.0	47.7±3.0	47.9±3.1	48.3±3.1
LVM (g/m ²) [*]	105.6±22	92.3±20	89.8±18	89.8±19
Systolic BP @ 5 METs [*]	157±17	147±12	146±11	143±11
Exercise BP-Rest BP [*]	25±12	16±8	15±7	14±6
Daytime Systolic ABPM [*]	147±12	139±11	139±10	140±11
% LVH [*]	50.4	23.6	15.5	13.8
% Concentric LVH (RWT≥0.43) [*]	40.4	27.2	25.8	13.8

Conclusions: Systolic BP response during workloads of approximately 5 METs provides the stimulus for increased left ventricular mass and LVH. CRF attenuates the BP response and the development of LVH.

PRE-HYPERTENSION AND SUBCLINICAL CARDIAC DAMAGE: A META-ANALYSIS OF ECHOCARDIOGRAPHIC STUDIES

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Objective: The association between pre-hypertension (pre-HTN) and subclinical cardiac organ damage is not well defined. We performed a systematic meta-analysis of echocardiographic studies in order to provide a comprehensive information on cardiac structural and functional changes in untreated pre-HTN subjects.

Design and method: Studies were identified by crossing the following search terms: pre-hypertension, high normal blood pressure, heart, left ventricular hypertrophy, left ventricular function, diastolic function, left atrial size, aortic root size, echocardiography.

Results: A total 73,556 subjects (44,170 normotensive, 17,314 pre-HTN, and 12,072 HTN individuals) of both genders were included in 20 studies. Left ventricular (LV) mass index was greater in pre-HTN than in normotensives (standard means difference SMD: 0.32 ± 0.07 , $p < 0.001$). Mitral E/A ratio was lower (SMD: -0.34 ± 0.05 , $p < 0.001$), E/e' ratio (SMD: 0.26 ± 0.02 , $p < 0.001$) and left atrium (LA) diameter higher (SMD: 0.55 ± 0.02 , $p < 0.001$) in pre-HTN than in normotensive counterparts. HTN subjects showed a greater LV mass index (SMD: 0.27 ± 0.03 , $p < 0.001$), reduced E/A (SMD: -0.38 ± 0.08 , $p < 0.001$), increased E/e' ratio (SMD: 0.38 ± 0.09 , $p < 0.001$), and LA diameter (SMD: 0.31 ± 0.12 , $p < 0.001$) than pre-HTN subjects

Conclusions: Our meta-analysis shows that alterations in cardiac structure and function in pre-HTN subjects are intermediate between normotensive and HTN individuals. These findings reinforce the view that pre-HTN should not be longer considered a benign entity.

PULSE PRESSURE AMPLIFICATION AND AUGMENTATION INDEX IN ASSOCIATION WITH CARDIAC STRUCTURAL AND FUNCTIONAL DAMAGE: THE NORTHERN SHANGHAI STUDY

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Objective: To investigate and compare the associations of pulse pressure amplification (PPA) and augmentation index (Aix) with asymptomatic cardiac structural and functional damage in an elderly Chinese population.

Design and method: 1940 participants (mean age of 71.6 years) were included in the present study. Central blood pressure (BP) parameters were measured by SphygmoCor device. PPA and Aix were calculated as the ratio of central and brachial pulse pressures and the ratio of augmentation pressure and aortic pulse pressure, respectively. Cardiac structural and functional parameters including left ventricular mass index (LVMI), the ratio of peak early diastolic transmitral flow velocity and early diastolic lateral mitral annular velocity (E/Ea), were evaluated using standardized methods.

Results: In correlation analysis, both PPA and Aix significantly correlated with LVMI and E/Ea ratio. When PPA and Aix separately put into same multivariate full-mode linear regression models, both PPA and Aix significantly associated with LVMI (regression coefficient [b] = 4.664, per 10% increase of PPA, $P < 0.001$; $b = 1.998$, per 10% increase of Aix, $P = 0.02$) and E/Ea ratio ($b = 0.499$, per 10% increase of PPA, $P < 0.01$; $b = 0.152$, per 10% increase of Aix, $P = 0.18$). When PPA and Aix both put into same multivariate stepwise linear regression models, only PPA were stayed in the model. When PPA and Aix separately put into same multivariate full-mode logistic regression models, only PPA was significantly associated with left ventricular hypertrophy (Odds ratio[OR]: 1.242, 95% confidence interval[CI]: 1.026–1.505, per 10% increase of PPA) and dysfunction (OR: 1.407, 95%CI: 1.087–1.820, per 10% increase of PPA). When PPA and Aix both put into same multivariate stepwise logistic regression models, only PPA were stayed in the model. In all multivariate models, brachial systolic BP was included and significantly associated with cardiac damage.

Conclusions: PPA showed stronger BP-independent association with cardiac structural and functional damage than Aix.

Table 5. Association of cardiac structural and functional alterations with PPA and Aix analyzed by multivariate regression analysis when both PPA and Aix both put into the same model

	LVMI		E/Ea	
	β	P	β	P
Age, year	0.440	0.0024
Gender (male=1, female=0)	3.974	0.0279	-0.785	0.0011
Current smoking (yes=1, no=0)
Body mass index, kg/m ²	1.370	<0.0001	0.086	0.0136
Total Cholesterol, mmol/L
HDL, mmol/L
Diabetes (yes=1, no=0)
Brachial SBP, + 5mmHg	0.835	0.0010	0.094	0.0047
PPA, +10%	4.691	<0.0001	0.463	0.0033
Aix, +10%

Multivariate stepwise linear regression was conducted to investigate the association of each TOD with PPA and Aix. Variables staying in the final model were represented in the table. ... designates no statistical significance. PPA, pulse pressure amplification; Aix, aortic augmentation index; LVMI, left ventricular mass index; E/Ea, ratio of peak early diastolic transmitral flow velocity (E) and early diastolic lateral mitral annular velocity (Ea).

Table 7. Association of cardiac damage with PPA and Aix analyzed by multivariate regression analysis when both PPA and Aix put into the same model

	LVH		LVDD	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age, year	1.026(1.004, 1.049)	1.040(1.013, 1.069)
Gender (male=1, female=0)	0.354(0.266, 0.471)	0.444(0.303, 0.651)
Current smoking (yes=1, no=0)
Body mass index, kg/m ²	1.074(1.032, 1.119)	1.096(1.043, 1.153)
Total Cholesterol, mmol/L
HDL, mmol/L
Diabetes (yes=1, no=0)
Brachial SBP, + 5mmHg	1.048(1.008, 1.090)	1.048(0.998, 1.100)
PPA, +10%	1.255(1.038, 1.517)	1.376(1.068, 1.773)
Aix, +10%

Multivariate stepwise logistic regression was conducted to investigate the association of each TOD with PPA and Aix. Variables staying in the final model were represented in the table. ... designates no significance. PPA, pulse pressure amplification; Aix, aortic augmentation index; LVH, left ventricular hypertrophy; LVDD, left ventricular diastolic dysfunction.

THE INFLUENCE OF GENDER ON LEFT VENTRICULAR MECHANICS IN HYPERTENSIVE PATIENTS

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Objective: The aim of this study was to evaluate the influence of gender on left ventricular (LV) mechanics in hypertensive individuals.

Design and method: This cross-sectional study included 198 untreated hypertensive subjects and 107 normotensive controls who underwent 24-hour ambulatory blood pressure monitoring and comprehensive two-dimensional echocardiographic examination including strain assessment.

Results: There was no difference in 24-h blood pressure between hypertensive men and women. LV mass index was significantly higher men than in women in hypertensive and normotensive group. Hypertensive men and women had significantly lower 2D LV global longitudinal, circumferential and radial strains than their normotensive counterparts. LV global longitudinal strain was lower in hypertensive men than in women (-20.2 ± 2.3 vs. -18.8 ± 2.0, p < 0.01). LV global circumferential strain was also worse in hypertensive men than in men (-21.4 ± 2.9 vs. -19.5 ± 2.5, p < 0.01). The difference in LV radial strain was not discovered between hypertensive women and men. Assessment of layer-specific LV strain showed that endocardial and mid-myocardial longitudinal and circumferential strains were significantly lower in hypertensive population and especially in hypertensive men comparing with hypertensive women. Furthermore, LV twist was significantly higher in hypertensive women than in hypertensive men (20.6 ± 6.8 degree vs. 21.6 ± 7.3 degree, p = 0.02). Female gender and arterial hypertension, as well as their interaction, were associated with LV hypertrophy, reduced LV global longitudinal strain and increased LV twist.

Conclusions: LV longitudinal and circumferential strains were significantly reduced in hypertensive patients. Endo- and mid-myocardial LV layers were particularly influenced by arterial hypertension. However, hypertensive women suffered more significant changes in LV longitudinal strain and LV twist than hypertensive men.

ASSESSMENT OF MYOCARDIAL MECHANOENERGETIC EFFICIENCY IN PATIENTS WITH PRIMARY ALDOSTERONISM

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Objective: Available data indicate that patients with primary aldosteronism (PA) have an increased risk of cardiovascular (CV) events; furthermore, CV risk seems to be, at least in part, independent of blood pressure (BP) elevation. Previous studies have shown that patients with PA have a greater prevalence of left ventricular (LV) hypertrophy, which might contribute to the increase in CV risk. Recently, a non-invasive approach for the estimation of LV mechanical efficiency through the calculation of the ratio between stroke work (SW) and heart rate (HR)-pressure product has been proposed by de Simone and coworkers. This index, which expresses the amount of blood pumped in a single beat in 1 second by the heart, may be easily obtained by echocardiography.

Design and method: The aim of our study was to evaluate the determinants of myocardial mechanoenergetic efficiency index (MEEi), calculated as SV/HR and indexed to LV mass (MEEi = MEE/LVM) in a large group of patients with primary aldosteronism and in a control group of essential hypertensives (EH). PA was diagnosed in the presence of a positive aldosterone to renin ratio (>30) and post saline aldosterone > 100ng/ml). Ninety-nine patients with PA were compared with 99 EH patients matched for age and BP values.

Results: No differences between groups were observed for age, gender, BMI, BP values, glucose, lipid profile and renal function. LV mass index was greater in PA vs EH (101 ± 34 vs 84 ± 20, gr/m², p < 0,05); also relative wall thickness was greater in PA vs EH (0.36 ± 0.1 vs 0.32 ± 0.4, p < 0,05). Ejection fraction was not different between groups, while endocardial and midwall fractional shortening were lower in PA vs EH (40 ± 7 vs 43 ± 6, and 18 ± 3 vs 21 ± 2 both p < 0,05). MEEi was lower in PA vs EH (0.44 ± 0.14 vs 0.52 ± 0.10, p < 0,05). A negative correlation was observed between MEEi and aldosterone levels (r = -0.20, p < 0.05).

Conclusions: In patients with primary aldosteronism MEEi is lower as compared to EH. These findings may contribute to explain the increased risk of CV events in patients with PA.

INTRACARDIAC AND PERIPHERAL CIRCULATING ENDOTHELIAL MICROPARTICLES ARE ASSOCIATED WITH CENTRAL SYSTOLIC BLOOD PRESSURE IN PATIENTS WITH CORONARY ARTERY DISEASE

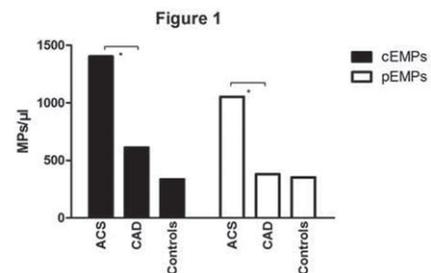
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Objective: Circulating endothelial microparticles (EMPs) are expected to reflect underlying endothelial damage observed in coronary artery disease (CAD). However, it is not clear if and in what extent, EMPs increase in acute coronary syndromes (ACS) compared to stable CAD and whether they reflect local or systemic cardiovascular damage.

Table 1. Summary of baseline characteristics

Baseline characteristics	ACS (n=38)	Stable (n=17)	Controls (n=6)	p-value
Age (years)	65±11	65±7	67±8	0.920
Female Gender (%)	23.7	23.5	31.2	0.211
Hypertension (%)	82	83	89	0.538
Dyslipidemia (%)	73	65	66	0.432
Diabetes (%)	26	25	32	0.811
Smoking (%)	55.1	58.2	34.5	0.269
Family History CAD (%)	61.2	54.1	56.7	0.311
Obesity (%)	23.5	25	29	0.397
GFR (ml/min/1.73m ²)	99±30	94±21	102±17	0.370
Framingham risk score (%)	19.3±8.8	18.6±7.4	17.1±8.1	0.770
Red blood cells (x10 ⁹ /μl)	4.9±1.3	4.7±0.6	4.8±0.6	0.991
Platelets (x10 ⁹ /μl)	252±77	284±138	214±73	0.569

Values as mean±SD or median±interquartile range for continuous or number (percentage) for categorical variables. Abbreviations: ACEI/ARB, ace inhibitor/angiotensin receptor blocker; CAD, coronary artery disease



Design and method: We enrolled consecutive adult patients with a clinical indication for coronary angiography in our Cardiology Department during a 1-year period. Central blood pressure (cBP) measured during angiography and patients'

history were recorded. Coronary sinus and peripheral blood samples were collected. Flow cytometry protocol was standardized based on previous studies. Double-positive events for Annexin and CD144 in the microparticles region were measured and quantified using Flow Count Fluorospheres.

Results: We have studied 38 patients with ACS (22 STEMI and 16 NSTEMI), 17 patients with stable CAD and 6 control patients (Table 1). We found significantly increased EMPs in patients with CAD compared to controls, both in peripheral ($p = 0.001$) and coronary circulation ($p = 0.003$). This confirmed the validity of our method and the absence of artificial or ex vivo activation. Then, we analyzed EMPs in ACS versus stable CAD. ACS patients had significantly increased EMPs both in peripheral ($p = 0.008$) and coronary circulation ($p = 0.045$), compared to stable CAD (Figure 1). No difference was found in patients with STEMI versus NSTEMI. Furthermore, coronary EMPs were significantly increased compared to peripheral ($p = 0.021$). Although no association was found with traditional cardiovascular risk factors, both peripheral ($r = 0.489$, $p = 0.003$) and coronary ($r = 0.312$, $p = 0.048$) EMPs were associated with cSBP.

Conclusions: EMPs are increased in patients with ACS versus stable CAD and exhibit a profound increase in the coronary circulation compared to periphery, indicative of ongoing endothelial damage during acute myocardial ischemia. The extent of this damage may have implications regarding treatment and prognosis in these patients. The association between EMPs and cSBP possibly reflects an effect of endothelial dysfunction on central hemodynamics and aortic stiffness. Further prospective studies are needed to better clarify the role of microparticles as prognostic and possibly therapeutic targets.

NT-PROBNP COMBINED WITH R WAVE IN AVL LEAD PREDICTS MORTALITY BETTER THAN ECHOCARDIOGRAPHIC LEFT VENTRICULAR MASS IN HYPERTENSION

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Objective: Plasma NT-proBNP and R wave in aVL lead (RaVL) have been associated with mortality in hypertensive patients. The aim of the present study was to test the prognostic value of their combination, in comparison to left ventricular mass index assessed by echocardiography (LVMI).

Design and method: 1104 hypertensive patients having at baseline an assessment of plasma NT-proBNP, a resting 12-lead ECG and an echocardiography were included. LVMI was assessable in 921 patients. After a median follow-up of 8.5 [5.4–13.3] years, 110 deaths occurred, 62 of which were from cardiovascular cause.

Results: Optimal thresholds of RaVL and plasma NT-proBNP to predict mortality were 0.7 mV and 150 pg.mL⁻¹, respectively. A 3-modality variable based on RaVL and NT-proBNP, was built: 0 when none were above the threshold, 1 or 2 when only one or both were above the threshold, respectively. After adjustment for cardiovascular risk factors, previous cardiovascular event and LVMI in Cox regression analysis, we observed a gradual increase risk for patients having 1 marker above the threshold (hazard ratio (HR) 1.76; 95% confidence interval (CI) (1.08–2.86) for all-cause mortality, HR 2.18; 95 %CI (1.06–4.46) for cardiovascular mortality) or 2 markers above the threshold (HR 2.76; 95 %CI (1.51–5.03) for all-cause mortality, HR 3.90; 95 %CI (1.69–9.00) for cardiovascular mortality); the prognostic value of the combination of RaVL and NT-proBNP was greater than that of LVMI, which did not reach statistical significance while included in the same model. Similarly, the combination demonstrated the best accuracy to predict outcome in comparison to LVMI (C-index, ROC curves and likelihood ratio test).

Conclusions: Risk stratification in hypertension with the combination of NT-proBNP and RaVL is a simple method that appears more powerful and accurate than LVMI. This approach should be considered as a game changer in hypertension.

ORAL SESSION

ORAL SESSION 6C: LARGE ARTERIES

ARTERIAL STIFFNESS INDEPENDENTLY PREDICTS STROKE IN PATIENTS WITH ESSENTIAL HYPERTENSION: DATA FROM A GREEK 8-YEAR-FOLLOW-UP STUDY

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Objective: Although arterial stiffening is related to atherosclerosis progression, its prognostic role in cerebrovascular events in hypertension is not fully elucidated. The aim of the present study was to assess the predictive role of arterial stiffness for the incidence of stroke in a cohort of essential hypertensive patients.

Design and method: We followed up 1079 essential hypertensives (mean age 55.8 years, 572 males, office blood pressure (BP) = 144/91 mmHg) for a mean period of 8 years. All subjects had at least one annual visit and at baseline underwent blood sampling for assessment of metabolic profile and arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method. The distribution of PWV was split by the median (8.1 m/sec) and accordingly subjects were classified into those with high (n = 546) and low values (n = 533). Stroke was defined as rapid onset of a new neurological deficit persisting at least 24 hours unless death supervened confirmed by computed tomography and magnetic resonance angiography and/or cerebrovascular angiography findings.

Results: The incidence of stroke over the follow-up period was 2.03%. Hypertensives who had stroke (n = 25) compared to those without stroke at follow-up (n = 1054) were older at baseline (63 ± 8 vs 55 ± 10 years, p = 0.012), had higher office BP levels (155 ± 13 vs 144 ± 16 mmHg, p = 0.022) and prevalence of high PWV levels (68% vs 42%, p = 0.019). No difference was observed between hypertensives with stroke and those without stroke with respect to baseline renal function and lipid levels (p = NS for all). In multivariate Cox regression model, baseline age (hazard ratio = 1.098, p = 0.04) and PWV (hazard ratio = 1.105, p = 0.015) but not baseline office BP levels turned out to be independent predictors of stroke.

Conclusions: In essential hypertensive patients, PWV predicts future development of stroke, independently of established confounders, including BP. These findings support that PWV constitutes a potent prognosticator of cerebrovascular events and its estimation is essential in order to improve risk stratification in hypertension.

DETERMINANTS OF ARTERIAL STIFFNESS IN A YOUNG URBAN POPULATION FROM SWEDEN: THE ROLE OF LIFESTYLE AND SOCIAL FACTORS

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Objective: An indicator of arterial aging is arteriosclerosis, meaning age-dependent relatively less elastin as well as more collagen content of the arterial media. This leads to stiffer elastic arteries, i.e. of the aorta, contributing to higher blood pressure and measured as increased pulse wave velocity (PWV). An individual's lifestyle is supposed to play a considerable role for arterial stiffness.

We aimed to use carotid-femoral (c-f) PWV as a measure of vascular ageing (arterial stiffness) in order to analyze c-f PWV in a younger (<45 years) population in Malmö, Sweden, and also to identify lifestyle and risk factors associated with healthy vascular ageing (HVA).

Design and method: c-f PWV was measured by Sphygmocor® in a total of 1156 subjects from the Malmö Offspring Study (MOS). Cardiovascular risk factors, including systolic blood pressure (SBP), were measured and a questionnaire filled by participants. We first statistically compared sub-groups with the 10% lowest c-f PWV (HVA) and the 10% highest c-f PWV (Early Vascular Aging, EVA) from the distribution. Secondly, we also used a multiple linear regression of all subjects to identify cardiovascular risk factors and lifestyle factors significantly associated with c-f PWV, stratified for gender.

Results: c-f PWV and hypertension status differed (p = 0.03) when we compared HVA and EVA subjects. There was a significant relationship between PWV and systolic and diastolic blood pressure in both genders (p < 0.001), whereas hypertension status was significant only in men. For the total sample, we found significance for men regarding the positive association between c-f PWV and age (p < 0.001) as well as SBP (p = 0.006) as well as increasing alcohol intake (p = 0.002), but also significant inverse relationships with self-reported chronic stress (p = 0.015) and educational level (p = 0.016). For women, c-f PWV was significantly associated only with age and SBP (both p < 0.001).

Conclusions: Besides increasing chronological age and elevated blood pressure, also social and lifestyle-related factors seems to play an important role in the process of vascular ageing (arterial stiffness). Further research should aim to identify targets for preventive actions which could contribute to healthier vascular ageing.

DIFFERENTIAL CHARACTERISTICS OF AORTIC BLOOD PRESSURE AND CAROTID BLOOD FLOW AUGMENTATION: ASSOCIATIONS WITH AORTIC STIFFNESS AND IMPLICATIONS FOR MICROVASCULAR BRAIN DAMAGE

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Objective: Aortic stiffness and pressure wave reflection have been associated with age-related cerebrovascular disease, but the underlying mechanism remains obscure. Recent evidence suggests that aortic reflected pressure waves augment carotid artery flow in late systole, affecting cerebral hemodynamics. We comparatively investigated aortic pressure augmentation index (PAIx) and carotid flow augmentation index (FAIx) in terms of 1) age-related changes, 2) cross-sectional associations with aortic stiffness and 3) potential involvements in microcerebrovascular lesions.

Design and method: In 286 patients with hypertension (mean age, 54 ± 13 years), carotid flow velocity waveforms were recorded with duplex ultrasound to measure the early-systolic (F1) and late-systolic (F2) flow amplitudes and calculate FAIx as F2/F1. Tonometric waveforms were recorded to estimate aortic incident wave height (P1), augmented pressure (AugP) and PAIx from radial waveforms, compute aortic compliance, and to determine carotid-femoral (aortic) and carotid-radial (peripheral) pulse wave velocities (PWVs). Additionally, in a subset of subjects (n = 168), periventricular and subcortical white matter hyperintensities (WMH) on brain MRI were evaluated using the Fazekas scale.

Results: With increasing age, F2 significantly (P < 0.001) increased whereas F1 decreased, although AugP increased parallel to P1. According to a quadratic function, both FAIx (mean, 65 ± 26%) and PAIx (27 ± 12%) increased with age (r = 0.54 and r = 0.42, P < 0.001), but the age-dependent curves were concave and convex upward, respectively. FAIx increased exponentially with increasing PAIx (r = 0.64). Compared to PAIx, FAIx was more closely (P < 0.002) correlated with aortic PWV (r = 0.19 versus r = 0.35), aortic compliance (r = -0.26 versus r = -0.45) and aortic/peripheral PWV ratio (r = 0.19 versus r = 0.39). FAIx was associated with WMH scores independently of various confounders including age, gender, diabetes, hypercholesterolemia and aortic PWV (P = 0.02), and was more predictive of WMH presence than PAIx (adjusted OR [95% CI] per 1SD increase: 2.6 [1.3–5.1] versus 1.6 [0.8–3.4]).

Conclusions: Carotid FAIx had closer associations with age, aortic stiffness and cerebral WMH than did aortic PAIx. The present results indicate that late-systolic carotid flow augmentation (as enhanced with aortic stiffening and pressure wave reflection from the lower body) increases cerebral flow pulsations and thereby causes microcerebrovascular injury, but such detrimental effect of flow augmentation is even greater than predicted by PAIx.

PCSK9 LEVELS ARE ASSOCIATED WITH CENTRAL HEMODYNAMICS AND SUBCLINICAL ATHEROSCLEROSIS

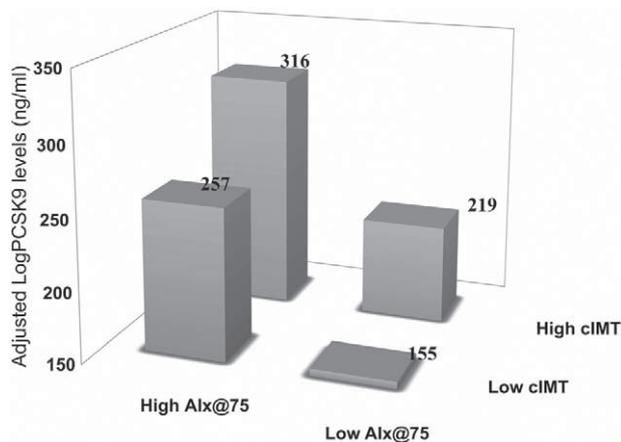
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Objective: Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels are related with cardiovascular risk. The aim of the present study was to determine the

correlation of PCSK9 levels with predictors of cardiovascular risk, such as central hemodynamics and carotid intima-media thickness (cIMT) in subjects with familial dyslipidaemias.

Design and method: Thirty three asymptomatic subjects (mean age = 45.4 ± 12.3 , 21 men) with either familial combined hyperlipidemia or heterozygous familial hypercholesterolemia, free of hypolipidemic therapy, underwent evaluation of aortic augmentation index (AIx@75) and augmented pressure, and cIMT. PCSK9 levels were measured by ELISA.

Results: In the univariate model, circulating PCSK9 levels were related to age ($r = 0.351$, $P = 0.045$), AIx@75 ($r = 0.463$, $P = 0.007$), augmented pressure ($r = 0.442$, $P = 0.011$) and cIMT ($r = 0.559$, $P = 0.001$). In multivariable analysis, a significant positive association of AIx@75, augmented pressure and cIMT with PCSK9 levels was observed after adjusting for relevant confounders ($P < 0.05$ for all). Patients with both high cIMT (>0.81 mm) and high AIx@75 ($>20\%$) had significantly increased PCSK9 levels compared with subjects presented with both low cIMT and low AIx@75 (316 ng/ml vs 155 ng/ml, $p = 0.037$). (Figure)



Conclusions: In patients with familial dyslipidemia PCSK9 levels were positively associated with central hemodynamics and cIMT. These relationships may imply that part of the effect of PCSK9 in cardiovascular risk is mediated by abnormal central hemodynamics and cIMT in patients with familial dyslipidemias, and may permit identification of a high risk subgroup of patients within these entities.

ABNORMAL FLOW PATTERN AND GEOMETRY ARE INTERRELATED AND CONTRIBUTE TO PROXIMAL DESCENDING AORTA DILATION IN MARFAN PATIENTS: A 4D FLOW MRI STUDY

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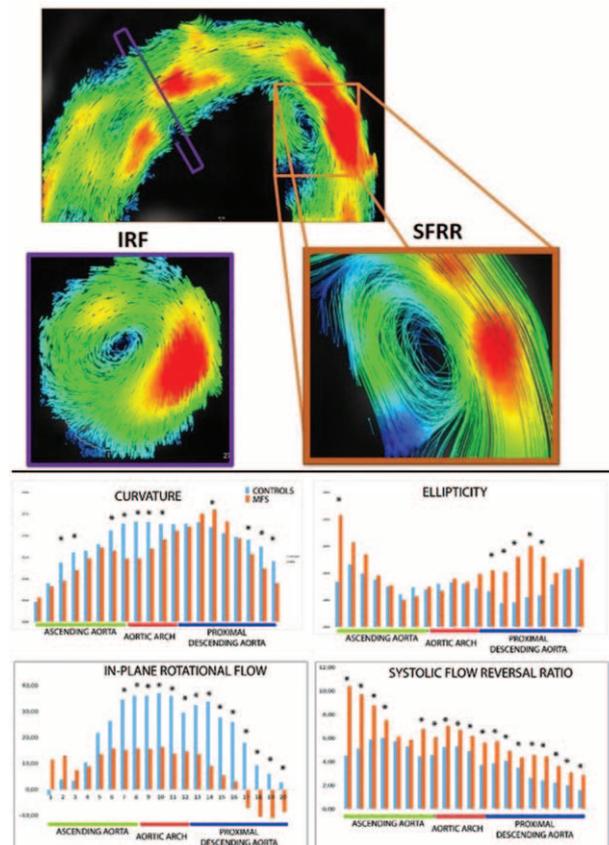
Objective: Marfan syndrome (MFS) is a hereditary connective tissue disorder caused by mutation in the FBN1 gene. Diseases of the ascending aorta (AAo), like dilation or type A dissection, are very prevalent. However, after improvements in the surgical AAo management, diseases of the descending aorta (DAo) emerged as a clinical issue. Recent qualitative studies in MFS have revealed the existence of abnormal vortex in the proximal DAo which were related to local dilation. However, any study has investigated the origin of these vortices. The aim of the present investigation was to investigate the relationship between aortic geometry and abnormal flow characteristics in the thoracic aorta of MFS

Design and method: Fifty-three confirmed MFS patients without congenital heart diseases or aortic valve disease were prospectively included from our Aortic unit. Also, 40 age-matched healthy volunteers (HV) were recruited. All participants underwent non-contrast-enhanced 4D flow-MRI, obtaining flow field and angiography. Geometric parameters (diameter, ellipticity and curvature) and rotational flow characteristics (in-plane rotational flow IRF, systolic flow reversal ratio SFRR) were evaluated (see figure 1) at 20 planes through the thoracic aorta.

Results: Aortic diameters were significantly-larger in MFS in the proximal AAo ($p < 0.001$) and in the proximal DAo ($p = 0.028$) compared to HV, while no differences were found in the remaining region. Ellipticity was increased and peak of aortic curvature was larger and more distal in MFS compared to controls (figure 2) Rotational flow (IRF, related to helicity) was reduced in MFS patients in the majority of the thoracic aorta, while SFRR (backward systolic flow) was increased

in the proximal AAo and DAo. Bivariate correlation showed inverse relation between arch ellipticity ($R = -0.34$, $p = 0.016$) as well as proximal DAo peak curvature ($R = -0.35$, $p = 0.015$) and arch IRF. Maximum proximal DAo diameter was negatively correlated with local IRF ($R = -0.3$, $p = 0.038$) and positively correlated with local SFRR ($R = 0.605$, $p < 0.001$).

Conclusions: Abnormal aortic ellipticity and curvature were evident in MFS patients and related to a reduction of flow helicity and increase of vorticity in the DAo. Longitudinal studies are needed to investigate eventual prognostic value of aortic geometry and flow in MFS patients.



PREDICTION OF TOTAL AND CAUSE-SPECIFIC MORTALITY, AS WELL AS CARDIOVASCULAR MORBIDITY, IN THE ELDERLY BY CAROTID-FEMORAL PULSE WAVE VELOCITY: THE MALMO DIET CANCER STUDY

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Objective: Arterial stiffness (AS) increases with age and predicts total mortality and total cardiovascular (CV) events. It has also been shown that a positive family history (FH+) of cardiometabolic disease influences AS. We aimed to: (a) examine if AS predicts total-, CV- and non-CV mortality among elderly subjects, as well as total and non-fatal CV events; and (b) to assess if FH+ influences the prediction of AS for events.

Design and method: Participants from the Malmö Diet Cancer CV cohort (MDC-CV; $n = 3,056$, mean age 71 years, 40% men) in Sweden were examined during 2007–2012. AS was measured by carotid-femoral pulse wave velocity (c-f PWV; Sphygmocor®). Follow-up started from date of measurement and ended at death, emigration, or on 31/DEC/2014 (to be updated until 31/DEC/2016 during spring 2018). Endpoints for mortality and morbidity were assessed by linkage to National and regional registers, based on personal identification. Hazard ratios (HRs) with 95% confidence intervals (CI) were computed using multivariable Cox and competing risks regression (sub-hazard ratio, SHR) adjusting for age, sex, cardiovascular risk factors, prevalent cardiometabolic diseases, and FH+.

Results: c-f PWV (per log-unit) significantly predicted total mortality, HR 2.57 (95%CI: 1.28–5.16, $p = 0.008$), after full adjustment for risk factors, and HR 3.01 (95%CI: 1.41–6.42) after adjusting for FH. The prediction of total CV events was

of borderline significance, HR 1.85 (95%CI: 0.91–3.78, $p = 0.09$). After adjustment for FH+, c-f PWV had a borderline significant relationship with non-CV mortality, SHR 2.30 (95%CI: 0.89–5.95, $p = 0.085$).

Conclusions: Arterial stiffness (c-f PWV) predicts total mortality in the elderly, even adjusted for family history of cardiometabolic disease. Thus c-f PWV is a promising risk marker for total mortality, reflecting vascular ageing (arterial stiffness), beyond the prediction offered by conventional risk factors. Updated endpoints will be included during spring 2018.

PULSE WAVE VELOCITY PROGRESSION OVER A 3.7 YEARS FOLLOW-UP: FOCUS ON METABOLIC SYNDROME

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Objective: The role of classic cardiovascular risk factors on the progression of arterial stiffness has not yet been extensively evaluated particularly regarding Metabolic Syndrome (MS). The aim of the current longitudinal study was to evaluate the determinants of the Pulse Wave Velocity (PWV) progression over a 3.7 years follow-up period in hypertensive subjects focusing on metabolic syndrome.

Design and method: We enrolled 448 consecutive hypertensive outpatients 18–80 aged, followed by the Hypertension Unit of St. Gerardo Hospital (Monza, Italy). At baseline anamnestic, Blood Pressure (BP) and laboratory data as well as c-f-PWV were assessed. We performed PWV again at a follow-up examination with a median time amounting to 3.7 ± 0.5 years. NCPET-ATPIII criteria were used to define MS as the presence of three or more items. Data are reported as mean \pm SE.

Results: At T0 the mean age was 53.7 ± 1.1 years, SBP and DBP were 141.3 ± 1.7 and 86.4 ± 1.2 mmHg and PWV was 8.5 ± 0.15 m/s. 125 patients (27.9%) meet the criteria for MS. Those patients were older (56.3 ± 1.0 vs 52.7 ± 0.7 , $p = 0.007$) with superimposable baseline SBP and DBP values ($141.4 \pm 1/87.2 \pm 0.6$ vs $142.4 \pm 1.6/86 \pm 1$, $p > 0.05$ for both comparison) as well as PWV values (8.7 ± 0.18 vs 8.58 ± 0.1 , $p = 0.43$). At follow-up examination MS subjects showed a lower decrease in SBP/DBP (SBP: -4.7 ± 1.7 vs -10.2 ± 1.1 ; DBP: -5.1 ± 1.1 vs -8.3 ± 0.7 , $p < 0.01$ for both comparison) with a higher increase in PWV values (1.1 ± 0.2 vs 0.39 ± 0.1 , $p = 0.03$). This difference remains significant also in a multivariate model with age, sex, smoking, baseline PWV and delta MBP as covariates.

Conclusions: arterial aging and BP values in treated hypertensive subjects during a 3.7 years follow-up seems to be influenced by the presence of MS. In fact subjects with MS showed a worse BP control and an increase in PWV values during the follow-up. PWV changes over time would probably give important information that need further future research studies.

CHILDHOOD-ONSET TAKAYASU ARTERITIS IN COMPARISON WITH ADULT-ONSET TAKAYASU ARTERITIS

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Objective: The study aims to investigate clinical, diagnostic and therapeutic algorithm of childhood-onset Takayasu arteritis (c-TA) compared with TA in adults.

Design and method: Records were analyzed of patients with TA onset at age lower than 18 and over 18, hospitalized in Fuwai Hospital from 2001 to 2014. TA was diagnosed according to the diagnostic criteria recommended by ACR (1990) and the EULAR/PRINTO/PRES (2010). Data collected were clinical, laboratory, imaging features, treatments and outcomes.

Results: A total of 136 c-TA patients (female to male, 3.1 to 1; mean age, 14.7 ± 3.2 years) and 468 adult-onset TA patients (F/M, 3.8 to 1) were enrolled with a delay to diagnosis of 6.2 ± 9.2 and 5.6 ± 8.0 years, respectively ($p > 0.05$). The most common presentations among c-TA were hypertension (HTN, 78.5%), dizziness (40.3%) and claudication (33.3%). HTN was more popular with higher DBP compared with adults (HTN, 78.5% and 60.5%; secondary HTN, 75% and 56.8%; highest DBP, 111.3 ± 29.0 mmHg and 99.5 ± 33.9 mmHg; baseline DBP, 88.8 ± 27.1 mmHg and 77.8 ± 27.3 mmHg; $p < 0.05$). The superior causes of hypertension were renal artery and aortic involvement (55.9% and 32.4%). Bruits and decreased pulse presented in 68.4% and 45.9% cases. Active disease according to NIH criteria was found in 28.7%. Higher level of neutrophils, anti streptolysin, NTpro-BNP and lower level of glucose, triglyceride, albumin among c-TA were significantly measured ($p < 0.05$). DSA, CTA and MRA were performed in 66.2%, 20.6% and 5.1%. Right or left renal artery (50.4%; 48.8%), left subclavian artery (46.5%), left common carotid artery (37.2%), thoracic aorta (35.7%) and abdominal aorta (35.7%) were commonly involved. Renal artery and right coro-

nary artery involvement were more frequent than in adults ($p < 0.05$). Glucocorticoids, anti-hypertensive (particularly CCB and beta-blockers) and antiplatelet drugs were prescribed in 59.8%, 76.5% and 68.2% patients. During a follow-up of 5.1 ± 3.4 years, 4 patients died, including 2 heart failure, one intracerebral hemorrhage and one pulmonary involvement.

Conclusions: This is the largest cohort of c-TA patients. Hypertension is the major clinical feature of c-TA generally with renal artery or descending aorta involvement. Steroids, anti-hypertensive and antiplatelet medications are common prescriptions. The remarkable delayed diagnosis should not be ignored.

INFLUENCE OF HIV INFECTION AND ANTIRETROVIRAL THERAPY ON AORTIC STIFFNESS: A META-ANALYSIS

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Objective: A growing body of evidence indicates that risk of CV events is higher in HIV-infected patients (HIV+) when compared to HIV-uninfected persons (HIV-). This enhanced risk may in part be mediated through preclinical CV damage. Large artery stiffness, a well-documented marker of arterial damage and predictor of adverse CV prognosis, is usually assessed by measuring aortic pulse wave velocity (PWV). Several studies examined arterial stiffness in HIV+ with inconsistent results. In a previous meta-analysis, showing increased arterial stiffness in HIV+ than in HIV- subjects, studies assessing aortic and peripheral PWV were pooled together. This may be misleading, because only the former has a demonstrated prognostic significance.

We performed a new meta-analysis with the aim to evaluate the influence of HIV-infection and its therapy only on aortic PWV (aPWV).

Design and method: A literature search was performed in PubMed, Google Scholar, Web of Science and Medline for articles, also in abstract form, concerning the effect of HIV infection and ART on aortic stiffness. The standardized mean difference (SMD) and corresponding 95% confidence intervals were calculated for aortic PWV in different comparison groups, which contained naive HIV+ versus HIV-, HIV+ receiving ART versus HIV- and HIV+ receiving ART versus naive HIV+. Statistical heterogeneity, assessed by Q test and I² statistic, was observed in all these comparisons. Therefore, both the fixed and random effect models were implemented, even if only the results of the latter were presented.

Results: In a total of 11 studies, naive HIV+ ($n = 566$) showed increased aPWV compared to HIV- ($n = 816$): SMD = 0.386 (0.197–0.575), $p < 0.001$. Nine studies were identified comparing HIV+ treated with ART ($n = 631$) to HIV- ($n = 637$) showing higher values of aPWV in the former than in latter: SMD = 0.681 (0.396–0.967), $p < 0.001$. In 8 studies HIV+ treated with ART ($n = 599$) exhibited greater aPWV values than those of naive HIV+ ($n = 325$): SMD = 0.259 (0.006–0.512), $p < 0.04$.

Conclusions: Our meta-analysis seems to suggest that HIV infection per se and even more ART may impair aortic distensibility.

FREQUENCY OF CERVICAL AND INTRACRANIAL ARTERIES LESIONS AND ASSOCIATED CLINICAL SYMPTOMS IN PATIENTS WITH CONFIRMED RENAL FIBROMUSCULAR DYSPLASIA - ARCADIA-POL STUDY

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Objective: To assess the frequency of cervical and intracranial arteries involvement and associated clinical symptoms in consecutive patients with renal fibromuscular dysplasia (FMD) enrolled into ARCADIA-POL study.

Design and method: From 183 patients with FMD enrolled into ARCADIA-POL study since 2015 (Polish-French collaboration) all consecutive 157 patients

(132F, 25 M, mean age: 45.1 ± 15.1 years) with renal FMD were analyzed. All patients underwent clinical evaluation: ABPM, biochemical evaluation, biobanking, duplex Doppler of cervical and abdominal arteries and whole body angio-CT including cervical and intracranial arteries.

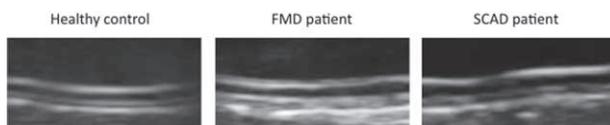
Results: Among 157 patients with renal FMD, 38 (24.2%) had coexisting FMD lesions in cervical and/or intracranial arteries and/or intracranial aneurysms: 17(10.8%) patients in carotid, 7(4.5%) patients in vertebral and 24(15.3%) patients had lesions in intracranial arteries. Dissections of carotid arteries were present in 3(1.9%) patients and vertebral artery dissections in 3(1.9%) patients. In 10(6.4%) pts internal carotid artery aneurysm and in 2(1.3%) patients vertebral artery aneurysm were found. 18(11.5%) patients had intracranial aneurysms: 15 (9.6%) patients had one aneurysm, 2(1.3%) pts 2 aneurysms and 1(0.6%) patient had 3 aneurysms. Patients with and without cervical and/or intracranial FMD lesions didn't differ in terms of age, gender, clinical and ambulatory blood pressure levels, hypertension prevalence and number of antihypertensive medications. There were no significant differences in the prevalence of symptoms such as headaches, tinnitus, dizziness and cervical bruits between the patients with and without cervical and/or intracranial FMD. There was only a significant difference in the presence of Horner's syndrome between patients with and without cervical and/or intracranial FMD (16.7% vs.1.9%; $p = 0.001$, respectively). There was no difference in the prevalence of stroke, transient ischemic attack or intracranial bleeding between the groups.

Conclusions: There were no specific clinical features suggesting the presence of FMD lesions and vascular complications in cervical and/or intracranial arteries in patients with confirmed renal FMD included into ARCADIA-POL STUDY. Our study showed that systematic evaluation of cervical and intracranial arteries in patients with renal FMD results in revealing relatively high prevalence of FMD lesions and vascular complications in cervical and/or intracranial arteries.

IDENTIFICATION OF RADIAL VASCULAR WALL ABNORMALITIES BY VERY-HIGH FREQUENCY ULTRASOUND IN FIBROMUSCULAR DYSPLASIA AND SPONTANEOUS CORONARY ARTERY DISSECTION: THE FUCHSIA STUDY

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Objective: Fibromuscular dysplasia (FMD) is an idiopathic disease of small-and medium-sized arteries. Subclinical alterations have been found also in non-affected segments, suggesting that FMD is a systemic disease. Spontaneous coronary dissection (SCAD) may represent a manifestation of FMD too. This case-control study is aimed at identifying vascular wall abnormalities in the radial arteries in patients with FMD and SCAD by means of a novel ultrasound technique.



Design and method: Two 5¢-clips from the left radial artery were obtained by Vevo MD (70 MHz probe, FUJIFILM, VisualSonics). Radial wall showed two echogenic interfaces: the 1st (lumen-media) and the 2nd (media-adventitia). Intima-media (IMT), adventitia (AT), and global thickness (IMAT) and wall cross-sectional area (WCSA) Measured. Vascular wall disarray was assessed calculating the root mean square error (RMSE) between 20 gray-level profiles crossing the

two interfaces and the profile obtained averaging them, normalized for the maximum value of the corresponding mean profile (RMSE/mean).

Results: 12 SCAD patients, 21 FMD patients and 12 healthy controls (C), matched for age (51 ± 12 , 47 ± 7 , 43 ± 12 , $p = 0.12$) and sex (2 M, 1 M, 2 M), were enrolled. IMT (0.182 ± 0.056 , 0.170 ± 0.033 , 0.133 ± 0.020 mm, $p = 0.01$), AT (0.108 ± 0.027 , 0.116 ± 0.029 , 0.076 ± 0.014 mm, $p = 0.001$) and IMAT (0.290 ± 0.076 , 0.286 ± 0.045 , 0.209 ± 0.029 mm, $p = 0.001$), were significantly higher in SCAD and FMD compared to C. WCSA, but not M/L, was increased too in SCAD and FMD. RMSE/mean was significantly increased in SCAD and FMD compared to controls either in the 1st (1.48 ± 0.84 , 1.28 ± 0.52 , 0.74 ± 0.26 , $p = 0.01$) or in the 2nd interface (2.44 ± 1.38 , 1.56 ± 0.58 , 1.19 ± 0.93 $p = 0.01$).

Conclusions: The radial artery walls of FMD and SCAD patients present similar subclinical abnormalities, namely increased thickness and inhomogeneity, in comparison to controls.

CAN MEASURES OF VASCULAR COMPLIANCE BE USED TO PREDICT SARCOPENIA IN THE ELDERLY?

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Objective: Sarcopenia, the loss of lean mass and increase in fat mass with age, is associated with increased cardiovascular risk. Sarcopenic muscle atrophy has been correlated with arterial stiffness (measured via brachial-ankle pulse wave velocity) in large-scale studies of predominately Asian patients. Our study investigated the correlation between sarcopenia and arterial stiffness in Caucasians, centring on the relationship between skeletal mass index (SMI) and the cardio-ankle vascular index (CAVI), to assess the use of CAVI in predicting sarcopenia.

Design and method: 366 UK participants (177 male, 189 female, age 70.8 ± 7.9) had measurements of body composition and vascular compliance. Bioimpedance analysis (TANITA BC-418) was used to derive SMI, according to Janssen et al¹. CAVI was measured using VaSera VS-1500N[®] (Fukuda Denshi, Japan). Handgrip strength was measured with a dynamometer.

Results: CAVI was significantly correlated with SMI ($r = -0.285$, $p < 0.001$), higher in females ($r = -0.416$, $p < 0.001$) than males ($r = -0.214$, $p = 0.01$). CAVI had the highest correlation with SMI from appendicular muscle mass (fat free mass in males $-r = -0.253$, $p = 0.002$, and predicted muscle mass in females $-r = -0.436$, $p < 0.001$). Using muscle mass, CAVI was significantly higher in sarcopenic (9.80) than non-sarcopenic individuals (8.98, $p < 0.001$). Using handgrip strength, sarcopenic individuals had significantly higher CAVI (9.53) than non-sarcopenic (9.10, $p = 0.018$).

After adjustment for age, CAVI was a significant predictor of SMI in females (Beta = -0.332 , $p < 0.001$) but not males. On nominal regression, CAVI was a significant predictor of the presence of moderate sarcopenia (odds ratio OR 1.49, 95% CI 1.04–2.14, $p = 0.03$) and, especially, severe sarcopenia (OR 1.87, 95% CI 1.26–2.76, $p = 0.002$) according to Janssen's criteria¹. In females, CAVI predicted moderate sarcopenia with OR 1.74 (95% CI 1.08–2.78, $p = 0.02$) and severe sarcopenia with OR 2.74 (95% CI 1.52–4.92, $p = 0.001$). In males, CAVI became non-significant as a predictor of sarcopenia after adjustment for age.

Conclusions: Indices of sarcopenia are independently associated with increased arterial stiffness, with higher correlation in females than males. Average CAVI assesses overall vascular compliance and may be a useful tool by which we can measure sarcopenia and its cardiovascular implications in older patients.

¹ Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc.* 2002;50(5):889-96.

ORAL SESSION

LATE-BREAKERS:
SESSION 3

INITIAL ANTIHYPERTENSIVE TREATMENT STRATEGIES AND THERAPEUTIC INERTIA: EVIDENCE FROM A LARGE POPULATION-BASED COHORT

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Objective: In several hypertensive patients, treatment is not upgraded despite lack of blood pressure control, due to therapeutic inertia. Information is limited, however, on the extent of this phenomenon in real-life medicine. The aim of this study was to assess whether two-drug combination as first treatment step results into a reduced role of therapeutic inertia compared to initial monotherapy.

Design and method: 125,635 residents in the Italian Lombardy Region who were aged 40 to 85 years and were newly treated with one antihypertensive drug (n = 100,982) or two-drug combination therapy (free or fixed dose, n = 24,653) during 2008 were included in the cohort and followed for 3 years after treatment initiation. The proportion of patients under combination treatment (2 or more drugs) at various time-points during follow-up (6 months, 1, 2 and 3 years) were compared between groups. A log-binomial regression model was used to estimate the prevalence ratio, and its 95% confidence interval (CI), of combination therapy in relation to the initial treatment strategy.

Results: In the initial monotherapy group, single drug prescription always remained by far the most common treatment, those prescribed drug combinations being 22%, 27%, 32% and 36% at 6 months, 1, 2 and 3 years, respectively. This was in striking contrast with the initial combination treatment group, in which the corresponding percentage of subsequent combination treatment prescriptions were 85%, 82%, 79% and 78%. After adjusting for several covariates, compared to patients under initial monotherapy, those on initial combination therapy showed a markedly greater propensity of being on combination treatment throughout the entire observation period: 3.92 (95% CI, 3.84–4.00) at 6 months, 3.18 (3.12–3.25), 2.56 (2.51–2.60) and 2.23 (2.19–2.27) at 1, 2 and 3 years, respectively (P < 0.001 for all).

Conclusions: In our real-life cohort, most patients prescribed initial antihypertensive monotherapy failed to move to combination treatment over the following three years, despite guidelines recommendations. This was largely avoided by the initial prescription of a two-drug combination. Thus, therapeutic inertia plays a major adverse role in up-titration to effective treatment in medical practice.

ESH-ENDORSED EUROPEAN/INTERNATIONAL FIBROMUSCULAR DYSPLASIA REGISTRY: RESULTS OF THE FIRST 609 PATIENTS

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Objective: The pioneering works of French and United States research teams have changed our conception of Fibromuscular Dysplasia (FMD) from a rare cause of renal artery stenosis in young women to a more frequent, often systemic vascular disease, which can be diagnosed at all ages, both in men and women. We report here the main characteristics of the first 609 patients enrolled in the European/International FMD registry endorsed by the ESH.

Design and method: The current analysis was performed in 609 patients enrolled from November 2015 to January 2018 in 30 centres from 17 countries also including 3 extra-European countries (Argentina, Japan and Tunisia).

Results: Enrolled patients were predominantly women (83%) and Caucasians (88%). Age at diagnosis was 45.8 ± 15.8 years, 74% of patients were hypertensive, 72% had a multifocal FMD and 31% multivessel FMD. Family history of FMD was reported in 2.7% of cases. Compared to patients with multifocal FMD, patients with focal FMD were younger (39.2 ± 15.9 vs. 48.4 ± 14.9 years, p = 0.003), more often male (26% vs. 13%, p = 0.0002), had less often multivessel FMD (12% vs. 39%, p = 0.0001) and more frequent revascularization interventions (70% vs. 50%, p = 0.01). Compared to patients with single-vessel FMD, patients with multivessel FMD were older (49.5 ± 14.2 vs. 44.1 ± 16.1 years, p = 0.03), had lower eGFR (84.2 ± 28.1 vs. 94.4 ± 40.6 mL/min, p = 0.0005) and were more frequently of the multifocal subtype (89% vs. 64%, p = 0.00001). Notably, the proportion of arterial dissections was higher in men than in women (12% vs. 2%, p = 0.01).

Conclusions: The main findings of the European/International FMD registry are in line with those of the French-Belgian ARCADIA study and the United States registry, with the exception of a lower proportion of multivessel FMD, which probably reflects a lack of systematic vascular exploration in some centres. In the near future, the European/International FMD registry will make possible further comparisons between old and young, incident and prevalent patients, and/or patients from different ethnicities or regions of the world. Accumulation of follow-up data may also provide insights on predictive factors of progression/complication.

RADIANCE-HTN SOLO: A MULTICENTER, RANDOMIZED, SHAM-CONTROLLED STUDY OF RENAL DENERVATION IN PATIENTS WITH UNCONTROLLED HYPERTENSION IN THE ABSENCE OF ANTIHYPERTENSIVE MEDICATIONS

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Objective: The RADIANCE-HTN SOLO trial is the first randomized, double-blind (for endpoint assessors), sham-controlled study of intravascular ultrasound-based renal denervation (RDN) to treat hypertension in an off-medication population that was prospectively powered for efficacy.

Design and method: Between March 2016 to December 2017, 804 patients were screened at 44 centers in Europe and the USA. A total of 146 subjects treated with 0–2 antihypertensive medications at screening who had a daytime ambulatory BP > = 135/85 mmHg and < 170/105 mmHg after a 4-week medication washout or run-in period, a suitable renal artery anatomy and eGFR > = 40 mL/min were randomized in a 1:1 ratio to treatment with the Paradise RDN catheter or a sham procedure. The primary endpoint was the between-group difference from baseline to 2 months in daytime ambulatory SBP. Secondary endpoints were difference in changes from baseline to 2 months in daytime ambulatory DBP, 24-hr ambulatory SBP/DBP, and night-time ambulatory SBP/DBP. Patients and clinicians assessing outcomes were blinded to treatment allocation through 6 months.

Results: The 146 randomized subjects (42% women; age, 54 ± 10 years) were enrolled in Europe (53%) and in the US (47%). Prior to wash-out, 21%, 41% and 38% of patients were on 0, 1 and 2 medications, respectively. Procedural success rates and 2-month BP results will have been presented prior to this presentation. Predictors of BP response will be presented for this abstract.

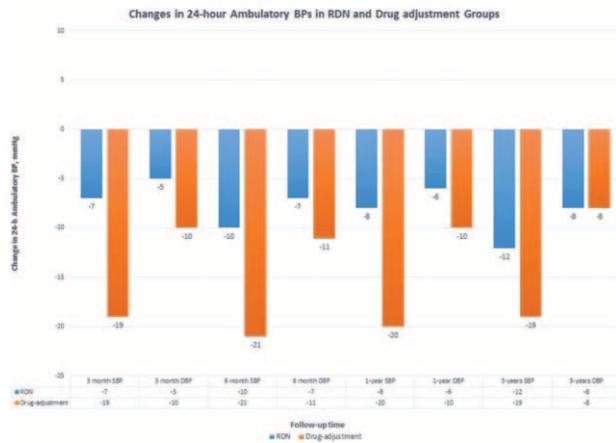
Conclusions: This is the first prospectively powered randomized, sham-controlled, study of ultrasound-based RDN in hypertensive patients in whom background antihypertensive medications have been withdrawn.

LONG-TERM OUTCOME OF THE RANDOMIZED OSLO-RDN STUDY

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Objective: The blood pressure (BP) lowering effect of renal sympathetic denervation (RDN) in treatment resistant hypertension (TRH) shows variation among the few randomized studies. The duration of antihypertensive effect and long-term effect and safety of RDN requires further follow-up. We aimed to report the office, ambulatory blood pressure changes as well as long-term safety at 3 years follow-up in our Oslo-RDN study.



Design and method: Patients with apparent TRH (n = 65) were referred specifically for RDN and those with secondary and spurious hypertension (n = 26) were excluded. TRH was defined as office systolic BP > 140 mmHg despite maximally tolerated doses of at least 3 antihypertensive drugs including a diuretic. Furthermore, ambulatory daytime systolic BP > 135 mmHg following witnessed intake of antihypertensive drugs was required. This procedure revealed that 20 patients had normalized BP, indicating poor adherence, and these patients were excluded. Patients with true TRH were randomized and underwent RDN with Symplicity catheter (n = 9) versus adjusted drug treatment (n = 10). Patients came for follow-up 3–4 years after baseline.

Results: 24-hour ambulatory systolic and diastolic BPs in the drug adjustment group changed from $151 \pm 13/84 \pm 7$ mmHg at baseline to $132 \pm 15/77 \pm 6$ mmHg at 3-years, and in the RDN group from $149 \pm 9/89 \pm 7$ mmHg at baseline to $137 \pm 13/81 \pm 10$ mmHg at 3-years follow-up. Office, daytime and nighttime ambulatory BPs changed in parallel to the 24-hour ambulatory BPs. The absolute differences in systolic or diastolic BPs between the groups were consistent with earlier follow up points with a tendency toward a smaller difference between the groups. The difference in systolic BP at long-term follow up was not significant (p = 0.34). There were no significant changes in renal arteries assessed by MRI or CT scans at long-term follow-up. No deterioration of renal function was observed.

Conclusions: The results at the three-year follow-up are consistent with earlier time points, with a tendency toward a smaller difference in BPs between the TRH and RDN groups. Our data support that RDN is a safe procedure on long-term follow-up and this allows further research to identify characteristics of patients who might respond to RDN.

A DOUBLE BLIND PHASE III STUDY OF ESAXERENONE (CS-3150) COMPARED TO EPLERENONE IN PATIENTS WITH ESSENTIAL HYPERTENSION (ESAX-HTN STUDY)

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Objective: ESAX-HTN study is a randomized, double-blind phase III study of esaxerenone (CS-3150), a novel non-steroidal mineralocorticoid receptor blocker, compared to eplerenone in patients with essential hypertension. The primary objective is to confirm non-inferiority of antihypertensive effect of esaxerenone 2.5 mg once daily compared to eplerenone 50 mg once daily. The secondary objective is to confirm superiority of antihypertensive effect of esaxerenone 5 mg/day as compared to 2.5 mg/day.

Design and method: 1001 subjects with essential hypertension (sitting systolic blood pressure (sSBP): 140–< 180mmHg, diastolic blood pressure (sDBP):

90–< 110mmHg, 24-h blood pressure (BP) by ABPM: > 130/80mmHg) from 42 sites in Japan were enrolled in the study. Subjects were assigned to one of 3 groups (n = 330/group), and received 2.5 mg/day, 5 mg/day of esaxerenone, or 50 mg/day of eplerenone. Treatment period lasted 12weeks following 4-week washout period. Efficacy was assessed by monitoring trough sSBP/sDBP, and 24-h BP. Safety was assessed by monitoring serum potassium changes from baseline, and the occurrence of adverse events. Primary efficacy endpoint was changes of trough sSBP/sDBP from the baseline at the end of treatment.

Results: Changes of sSBP/sDBP from the baseline were -13.7/-6.8mmHg in 2.5 mg of esaxerenone, -16.9/-8.4mmHg in 5 mg of esaxerenone and -12.1/-6.1mmHg in 50 mg of eplerenone. Non-inferiority of 2.5 mg esaxerenone to 50 mg eplerenone was confirmed in antihypertensive effect in the analysis with per protocol set. Superiority of 5 mg esaxerenone in sSBP/sDBP to 2.5 mg esaxerenone was confirmed in analysis with full analysis set (all p < 0.001). Similarly, mean 24-h SBP/DBP changes showed non-inferiority of 2.5 mg esaxerenone to 50 mg eplerenone, and 5 mg esaxerenone lowered mean 24-h SBP/DBP to a significantly greater extent as compared with 2.5 mg esaxerenone (p < 0.0001). Compared with 50 mg eplerenone, both doses of esaxerenone were well tolerated. No-dose dependent hyperkalemia (> = 5.5mEq/L) was observed in esaxerenone groups, and most were transient and recovered without any treatment.

Conclusions: A novel non-steroidal mineralocorticoid receptor blocker esaxerenone showed good efficacy profiles on antihypertensive effect without significant safety concerns in essential hypertensive patients.

ALLOPURINOL AND FEBUXOSTAT EFFECT ON TOTAL MORTALITY IN HYPERURICEMIC PATIENTS AFFECTED BY MILD-TO-MODERATE HEART FAILURE

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Objective: Hyperuricemia is an emerging risk factor for heart failure (HF) development and negative prognosis. Some data suggest that reducing serum uric acid by inhibiting xanthine oxidase (XO) could reverse the negative impact of uric acid on HF patient prognosis. Our aim is to evaluate if treatment with different XO inhibitors could have a different impact on the HF prognosis in a setting of clinical care.

Design and method: We prospectively considered a cohort of 255 outpatients affected by chronic HF and pharmacologically treated with SUA lowering drugs, currently attending the HF clinic of the Internal Medicine Dept. at the S. Orsola-Malpighi University Hospital (Bologna, Italy). The sample included only non-previously hospitalized outpatients with mild-to-moderate HF secondary to chronic arterial hypertension or coronary artery disease, after exclusion of patients with HF related to congenital heart diseases, valvulopathies, or cardiomyopathies. We also excluded those patients with a diagnosis of gout, with severe kidney disease or malignancy in order to exclude SUA outliers. Subjects were treated with allopurinol or, if intolerant to allopurinol, with febuxostat.

Results: Febuxostat (N. 120) and allopurinol (N. 135) patient groups were balanced for a large number of categorical and continuous variables. No statistically significant difference has been observed as it regards the distribution of CVD risk factors, echocardiographic parameters and cardiopreventive drug used. As it regards NYHA class, at the beginning of the observation febuxostat treated patients were respectively 19.2%, 46.7% and 34.2% in class I, II and III, while allopurinol treated patients 13.3%, 54.8% and 31.9% in class I, II and III, without significant difference between groups. This distribution did not significantly change over the observation period. After a mean follow-up period of 6.2 years, the cumulative survival of febuxostat treated patients was 0.96 (95%CI 0.93 to 0.99), while the one of allopurinol treated patients was 0.89 (95%CI 0.84 to 0.93). The between group difference was statistically significant (p = 0.04).

Conclusions: In conclusion, from our data it appears that the use of febuxostat, a more selective XO inhibitor than allopurinol, is associated to a reduced risk of all cause death in HF patients.

URINARY PROTEOMIC SIGNATURES ASSOCIATED WITH BETA-BLOCKADE AND HEART RATE IN HEART TRANSPLANT RECIPIENTS

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Objective: Heart transplant (HTx) recipients have a high heart rate (HR), because of graft denervation and are frequently started on beta-blockade (BB). We assessed

whether BB and HR post HTx are associated with a specific urinary proteomic signature.

Design and method: In 336 HTx patients (mean age, 56.8 years; 22.3% women), we analyzed cross-sectional data obtained 7.3 years (median) after HTx. We recorded medication use, measured HR during right heart catheterization, and applied capillary electrophoresis coupled with mass spectrometry to determine the multidimensional urinary classifiers HF1 and HF2 (known to be associated with left ventricular dysfunction), ACSP75 (acute coronary syndrome) and CKD273 (renal dysfunction) and 48 sequenced urinary peptides revealing the parental proteins.

Results: In adjusted analyses, HF1, HF2 and CKD273 ($p < = 0.024$) were higher in BB users than non-users with a similar trend for ACSP75 ($p = 0.06$). Patients started on BB within 1 year after HTx and non-users had similar HF1 and HF2 levels ($p > = 0.098$), whereas starting BB later was associated with higher HF1 and HF2 compared with non-users ($p < = 0.014$). There were no differences in the urinary biomarkers ($p > = 0.27$) according to HR. BB use was associated with higher urinary levels of collagen II and III fragments and non-use with higher levels of collagen I fragments.

Conclusions: BB use, but not HR, is associated with a urinary proteomic signature that is usually associated with worse outcome, because unhealthier conditions probably lead to initiation of BB. Starting BB early after HTx surgery might be beneficial.

SEX-SPECIFIC REGULATION OF URINARY PEPTIDES IN EARLY DIABETIC NEPHROPATHY

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Objective: There are differences in the development of diabetic nephropathy (DN) between men and women but the molecular mechanisms underlying these are incompletely understood. The urinary proteome may contain sex-specific biomarkers and thereby highlight differentially regulated mechanisms leading to DN in men and women.

Design and method: Urine samples were obtained from 157 patients with type 2 diabetes (age, 61 [29–71] years; 120 men and 37 women), preserved renal function (eGFR, 88 ± 17 mL/min) and confirmed microalbuminuria (UAER, 85 [34;194] mg/d). Peptidomic analysis was undertaken using capillary electrophoresis coupled to mass spectrometry. We compared individual urinary peptides between men and women.

Results: We detected a total of 4914 individual peptides in at least one participant. Sex-specific differences were seen in expression of 343 peptides (Chi squared, $P < 0.05$) with 86 and 257 peptides being more common in men and women, respectively. We then performed quantitative analysis of the abundance of 196 peptides that were found in at least 25% of male or female subjects and were more frequent compared to the other sex. Of these, 165 peptides were significantly (Mann-Whitney U-test, $P < 0.05$) differently expressed in urine. Sex remained the strongest determinant of these peptides' abundance after adjustment for age, eGFR and urinary albumin excretion. In men, presence of Peptide 186095 was associated with lower levels of UAER ($P < 0.001$), and in women this was the case for Peptide 187114 ($P = 0.024$). Of the 196 peptides with significant sex-specific

regulation, 25 are also components of the CKD273 peptidomic panel for prediction of DN.

Conclusions: Out of 4914 urinary peptides 196 exhibit sex-specific regulation in a cohort of patients at early stage of DN. Biological activity and predictive value of these peptides are currently unknown. The majority of peptides within the CKD273 classifier are not sex-specific. CKD273 is therefore a robust biomarker in both men and women but probably less ideally suited to dissect sex differences in the initiation and progression of DN. Larger datasets will have to be explored to confirm these results and to investigate whether sex-specific regulation of urinary peptides explains differences in DN progression between men and women.

MICROBIOTA CO-METABOLISM MODULATION AND EARLY DEVELOPMENT OF CARDIOMETABOLIC DISEASE ON HOST ORGANISM ANALYZED BASED ON METABOLOMICS AND PYROSEQUENCING

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Objective: Cardiometabolic disease (CMD) is a clustering of cardiometabolic risk factors of obesity, hypertension, fatty liver disease, type 2 diabetes and cardiovascular disease. This disorder that involve Host-microbiota co-metabolism and Western diets, with high-fat content is one of the main causes of mortality with fast increment nowadays. The study of metabolism involved and a development of specific biomarkers for early detection of cardiometabolic disease seems essential in patient management.

The objective is to identify potential CMD biomarkers through analysis of changes involved in serum metabolism by NMR-metabolomics and microbiota modulation by DGGE and Pyrosequencing.

Design and method: Male Wistar rats, 16 weeks old, were fed with a high-fat and sucrose diet (HFD) for 12 weeks to induce MS. Blood serum from high-fat fed rats was analyzed by Metabolomic analysis. This analysis was performed by Nuclear magnetic resonance (1H NMR) and microbiota diversity was observed in fecal samples by Denaturant gradient gel electrophoresis (DGGE) and Pyrosequencing.

Results: HFD induced an increase in body weight, changes in glycemic levels and higher levels of arterial blood pressure and triglycerides and lower HDL levels in comparison with control rats. Liver histology revealed higher intra-hepatocytic lipid content, suggesting an early hepatic damage. The metabolomic profile of blood serum, demonstrated metabolism differences in HFD group that affected metabolites involved in different metabolic pathways. Moreover, host-microbiota co-metabolites were also altered. This analysis seems indicate a correlation between some microbial metabolites with cardiometabolic parameters. In addition, Pyrosequencing and DGGE studies revealed changes in the microbiota composition that this revealed lower microbiota diversity in the HFD group.

Conclusions: Microbiota co-metabolism seems modulate the early development of CMD on host organism and the 1H NMR-based metabolomics can provide a non-invasive mean for MS early detection.