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P4.22: THE ROLE OF TESTOSTERONE AND ARTERIAL STIFFNESS IN THE PREDICTION OF RISK FOR CARDIOVASCULAR EVENTS IN HYPERTENSIVE PATIENTS

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index (Alx), aortic-pulse wave velocity (aPWV) and blood samples were obtained at baseline and 8-weeks into the programme. MMP-9 mRNA expression was analysed using real-time PCR, circulating MMP-9 levels assessed via ELISA, and Alx and aPWV were measured via applanation tonometry (SphygmoCor). Participants were split into those who adhered and did not adhere to the exercise programme.

Results: MET-minutes significantly increased; whilst MMP-9 expression, MAP and Alx significantly decreased in the exercise-adherent group compared to the non-adherent group, between baseline and 8-weeks. aPWV did not change significantly between the groups (Table-1). Significant correlations were observed between Δ IPAQ MET-minutes and Δ MMP-9 expression.

Conclusion: Adherence to the exercise programme reduced wave reflection and MAP. These pilot data demonstrate that MMP-9 expression is down-regulated in healthy, sedentary adults after 8-weeks of aerobic, moderate-intensity exercise. Thus suggesting that exercise-induced down-regulation of MMP-9 may result in a reduction in ECM degradation and therefore reduce vascular remodelling. These data provide a biomolecular rationale for how aerobic exercise is effective at delaying age-related increases in aPWV.

Table 1

Parameter	Adherent n=17 (Mean±SE)	Non-Adherent n=19 (Mean±SE)	P Value
Δ IPAQ (MET-minutes)	+2848 ±547	-404 ±267	<0.001
Δ MMP-9 (Ct)	-0.56 ±0.09	+0.42 ±0.44	0.034
Δ Supine MAP (mmHg)	-2.64 ±1.59	+1.45 ±1.16	0.044
Δ Supine Alx@75 (%)	-4.1 ±1.75	+1.9 ±2.23	0.045
Δ CF-PWV (m/s)	+0.3 ±0.2	+0.2 ±0.2	0.854

P4.20

SHORT-TERM EFFECT OF ANTI-VEGF DRUGS ON HEART AND VESSELS

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Objectives: Drugs opposing the effect of vascular endothelial growth factor (anti-VEGF) inhibit angiogenesis slowing down and eventually stopping solid tumors growth. Nevertheless these drugs can cause hypertension (that seems to be correlated with cancer outcome) and cardiac dysfunction. We hypothesize there is a correlation between the early stiffening of cardiovascular system and the drug effectiveness. For this purpose we analyzed the short term changes in cardiovascular structure and function in patients treated with antiVEGF drugs.

Methods: We enrolled 20 patients suffering from metastatic cancer (17 renal, 2 thyroid and 1 GIST), age 64±11 years (mean±SD). We measured blood pressures (BPs), cardiac and vascular parameters at baseline (B) and after two weeks of treatment (T1) (transthoracic echocardiography with 2D strain evaluation, cf-PWV, Aix).

Results: At B our population showed normal BPs (mean±SD:121±17/69±9.5mmHg) and systolic function (EF: 59%). Global longitudinal strain (GLS) was -21±3%, cf PWV was 12.1±3.3m/sec and Aix was 0.24±0.08%. At T1 we observed a significant increase in BPs (137±16/83±10mmHg, p<0.001 vs B), impaired GLS (-19±3%, p<0.005 vs B), and increased cf-PWV (13.5±3m/sec, p=0.01 vs B) while Aix rise didn't reach statistical significance. Adjusting for PAS only strain impairment remained significant and it was not correlated with BP and PWV modifications.

Conclusions: In the short term anti-VEGF drugs causes an increase of BP and of arterial stiffness, while myocardial deformation is impaired. The increase of PWV, without a significant change in Aix, may suggest that anti-VEGF drugs increase arterial stiffness, and, perhaps, have a less apparent effect on wave reflections.

P4.21

MILD UREMIA INDUCES AORTIC DILATATION AND HEART REMODELLING VIA NF-KB ACTIVATION

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Objectives: The aim of this study was to investigate the effects of mild uremia on aortic and heart remodelling in the rat.

Methods: Mild uremia was induced by reduction of renal mass after 5/6 nephrectomy (NE). Rats with proteinuria >300 mg/24h were included in further investigations. Four weeks after NE, an abdominal aortic aneurysm (AAA) was induced via continuous infusion of an isolated aortic segment with elastase. One group of NE animals was additionally treated with hydralazine (15 mg/kg). Sham operated rats served as controls (n=12). Aortic diameter and heart function were measured by ultrasound biomicroscopy. Aortic tissues, renal functional parameters and serum pro-inflammatory cytokines were investigated.

Results: Uremia induced aortic dilatation (2.1±0.04mm vs. 1.8±0.03mm, p<0.001). Histological analysis revealed an outward aortic remodelling, increased elastin fragmentation (p<0.05), cystic medial degradation, calcification of tunica media and inflammatory infiltrates in the adventitia. After aneurysm induction, aortic diameter was further increased in the NE group as compared to AAA rats without NE (2.6±0.05mm vs 2.3±0.03mm, p<0.05). Hydralazine treatment significantly reduced blood pressure (115±4 vs 160±7mmHg, p<0.05) but did not influence aortic diameter. Protein expression of NF-kB was strongly (3-fold) up-regulated in aortic tissues from NE rats. MMP2, MMP9, cathepsin D and TGF-beta1 were significantly (p<0.05) increased after AAA and further up-regulated in the NE/AAA group. Uremia decreased systolic heart function (p<0.05).

Conclusion: Mild uremia induces aortic dilation and heart remodelling independently of blood pressure elevation. Activation of NFkB by uremic toxins may contribute to remodelling via inhibition of elastin- and collagen gene transcription.

P4.22

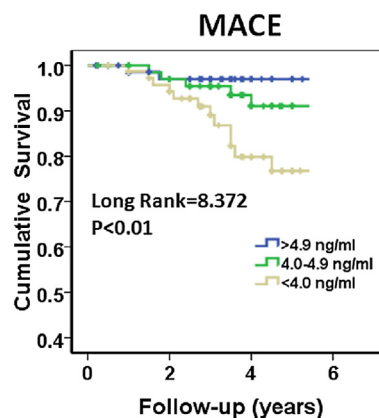
THE ROLE OF TESTOSTERONE AND ARTERIAL STIFFNESS IN THE PREDICTION OF RISK FOR CARDIOVASCULAR EVENTS IN HYPERTENSIVE PATIENTS

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Objectives: Androgen deficiency confers an independent risk for cardiovascular events and total mortality. Hypertension, a major contributory factor to the development of cardiovascular disease (CVD), has been associated with increased prevalence of low testosterone. We investigated whether low androgen concentration predicts major adverse cardiovascular events (MACE) in hypertensive patients without clinical atherosclerosis.

Methods: MACE in relation to total testosterone (TT) were analyzed with proportional hazards models in 228 non-diabetic hypertensive patients without a history of known CVD.

Results: The mean follow-up time was 44 months, during which 19 (8.3%) subjects developed MACE. Compared to patients who did not experience MACE, subjects who developed MACE had lower TT (3.9±0.7 ng/ml vs



4.6±1.5 ng/ml; $P<0.01$) and higher PWV (9.5±1.4 vs 8.4±1.3 m/s; $P<0.001$). Kaplan–Meier survival curves for MACE by TT tertiles at baseline are shown in figure. Subjects in the lowest TT tertile (<4.0 ng/ml) had a statistically significant higher risk of MACE compared to those in the highest tertile (>4.9 ng/ml) in multivariate Cox models adjusted for age, systolic blood pressure and risk factors (all $P<0.05$). Addition of TT to standard risk factors model yielded a net reclassification improvement of 38.8% ($P<0.05$). In regression analysis, PWV was inversely associated with TT ($\beta=-0.207$, $P<0.001$), indicating deterioration of aortic stiffness with decreasing testosterone level.

Conclusions: The principal finding of our study is that androgen deficiency predicts independently MACE in long-term follow-up in hypertensive patients. The association of TT with aortic stiffness may suggest other mechanisms, such as changes in vascular function and structure.

P4.23

CORRECTION OF VITAMIN D DEFICIENCY BY CALCIFEDIOL IN HYPERTENSIVES WITH STAGE 3 CHRONIC KIDNEY DISEASE REDUCES PULSE WAVE VELOCITY BY LOWERING BLOOD PRESSURE

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Objectives: To measure the extent of correction of vitamin D deficiency and hyperparathyroidism after treatment with calcifediol as well as their relationship to blood pressure and arterial stiffness in hypertensive patients with stage 3 chronic kidney disease (CKD).

Methods: Longitudinal study that included 74 treated hypertensives (46 women, 62,2%) with stage 3 CKD (eGFR 47,7 ml/min, SD±10) without previous vitamin D supplementation treatment. Calcifediol 266 µg/2 weeks and calcium 600 mg/d were given if baseline-vitamin D < 30 ng/ml and < 9,5 mmol/l, respectively. A second visit took place after 4 months.

Results: The mean age was 72,9 years (SD±10). The prevalence of vitamin D deficiency decreased from initially 96% to 23% (mean baseline: 18, mean final: 42 ng/ml), and of secondary hyperparathyroidism from 62% to 37% (mean at baseline: 87, mean final: 63 pg/ml). There were no significant changes in eGFR, calcium or phosphor or number of antihypertensive drugs, but pulse wave velocity (measured with MOBILOGRAPH®) and BP decreased significantly from initially 133/76 to 123/72 ($p<0.001$) mmHg and from 10,8 to 10,5 m/sec ($p<0.005$), respectively. In bivariate analysis the difference between baseline and final vitamin D and PTH correlated significantly. The only variable significantly related to the change in PWV was the difference in peripheral SBP. Only one case of asymptomatic hypercalcemia was observed.

Conclusions: In hypertensive patients with stage 3 CKD, correction of vitamin D deficiency by oral calcifediol leads to a substantial reduction of incipient hyperparathyroidism and a significant decrease of arterial stiffness.

P4.24

DIETARY INORGANIC NITRATE LOWERS CENTRAL BLOOD PRESSURE

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Background: Dietary inorganic nitrate is reduced to (nitric oxide) NO in the body. Beetroot is a rich source of dietary inorganic nitrate and has been shown to lower brachial blood pressure (BP) by this mechanism. The effect on aortic (central) BP, which may be a better predictor of cardiovascular disease, has not been studied.

Objectives: To measure the effect of dietary nitrate in beetroot juice on central BP at both 30 minutes and over a 6 hour period post-beetroot juice consumption.

Method: A double-blind, randomised, placebo-controlled crossover trial was performed in nine healthy, normotensive men and women aged between 22 and 45 years. Participants were randomised to receive beetroot juice (6.5-7.3 mmol nitrate) or placebo juice (0.04-0.06 mmol nitrate). Brachial and central BP were measured at baseline, 30 and 60 minutes post-ingestion, and at least hourly for the following 24 hours. Following a washout period, the procedure was repeated within seven days with

crossover to the opposite arm of the trial. There were no dietary restrictions during the study.

Results: Compared with placebo, beetroot juice lowered central systolic BP at 30 minutes (change in beetroot juice: -2.6±3.4 mmHg vs. change in placebo: 1.8±5.9 mmHg, $P=0.045$). Beetroot juice also lowered central systolic BP averaged over 6 hours post-ingestion (beetroot: 106±8 mmHg vs. placebo: 111±11 mmHg, $P=0.029$).

Conclusion: Consumption of beetroot juice lowered central BP. Beetroot juice could have a role in CV risk management in the general population, but further research is required to establish its long-term benefits, safety and tolerability.

P4.25

COMPARISON BETWEEN EFFECTS OF BEZAFIBRATE AND EICOSAPENTAENOIC ACID ON ARTERIAL STIFFNESS MONITORING WITH CARDIO-ANKLE VASCULAR INDEX

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Background: Bezafibrate and Eicosapentanoic acid (EPA) were known to decrease serum triglyceride. And, EPA administration for 5 years was reported to improve cardiovascular events by JLIT study. Cardio-ankle vascular index (CAVI) was a new index reflecting arterial stiffness from the origin of the aorta to the ankle, and is reported to be a predictor of cardiac events or death rate of cardiovascular events. But, the effects of both agents on arterial stiffness were not fully clarified.

Object: The purpose of this paper is to clarify the effect of bezafibrate and EPA on the arterial stiffness monitored with CAVI in the type 2 diabetic patients with hypertriglyceridemia.

Subjects and methods: Eighty type 2 diabetic outpatients with hypertriglyceridemia were randomly divided into two groups: bezafibrate (BEZA; 400mg/day) and EPA (1800mg/day) groups and took each treatment for 6 months. Glucose and lipid metabolism, d-ROMs; an oxidative stress marker were also studied. CAVI was measured using Vasela1500 (Fukuda Denshi. Co.LTD).

Results: After 6 month treatment, blood pressure, LDL-cholesterol (LDL-C), CK were not significantly changed comparing with before values, in both groups. Triglyceride (TG) and remnant-like particle cholesterol decreased significantly in both groups, and there were no significant differences between groups. HDL-C, Apo A-1 increased and HbA1C, d-ROMs decreased significantly only in BEZA group. CAVI decreased by 0.1 in EPA group (not significant) and by 0.5 in BEZA group ($p<0.005$). There was a significant difference in the changes of CAVI between both groups ($p<0.05$). In BEZA group, there were no significant correlations between changes of CAVI and the changes of the other parameters.

Conclusion: Bezafibrate administration improved arterial stiffness monitored with CAVI significantly, whereas EPA administration did not change CAVI, in type 2 diabetic patients with hypertriglyceridemia.

P4.26

ASSOCIATIONS BETWEEN FGF23-LEVEL AND ARTERIAL DISTENSIBILITY IN CHRONIC KIDNEY DISEASE

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Vascular calcification and hemodynamical abnormalities lead to reduced arterial elasticity in end stage renal disease. Fibroblast growth factor-23 (FGF23) predicts cardiovascular mortality in advance stages of renal failure possibly indicating more advanced vascular calcification. The relation of FGF23 to arterial stiffness in chronic kidney disease is currently under investigations.

The aim of our cross sectional study was to assess the potential associations between FGF23 and arterial distensibility.

FGF23 (ELISA), pulse wave velocity (PWV), augmentation index (AI) and central pulse pressure (CPP) (PulsePen), were measured in patients with