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3.6: GENE EXPRESSION ANALYSIS IDENTIFY GENES ASSOCIATED WITH ARTERIAL STIFFNESS AND CAROTID DIAMETER IN THE TWINS UK COHORT

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(0.16 ± 1.9 vs -0.12 ± 2.2 m/s; $P=0.4$), or any other haemodynamic variable relative to control at six or 12 months (all $P > 0.05$).

Conclusions: Despite many observational studies to suggest that vitamin D supplementation could be a useful therapy for improving aortic stiffness and associated haemodynamic indices, 12-months intervention yielded no improvement in older people with vitamin D deficiency. These results do not support use of vitamin D supplementation to improve cardiovascular health in this patient population.

3.5

EFFECTS OF BETA-BLOCKERS WITH OR WITHOUT VASODILATING PROPERTIES ON CENTRAL BLOOD PRESSURE: A META-ANALYSIS OF RANDOMIZED TRIALS IN HYPERTENSION

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Beta-blockers are effective in reducing peripheral blood pressure (pBP), but less effective than other drugs in reducing central blood pressure (cBP). It is controversial whether vasodilating (VB) beta-blockers may be more effective in reducing cBP compared to non-vasodilating (NVB) beta-blockers.

Methods: a meta-analysis was conducted by selecting randomized trials exploring the effect of beta-blockers on cBP. Twenty-two studies were selected. Comparisons were made between 33 trial arms (NVB=22, VB=11). In a random-effect meta-regression model, the following covariates were introduced: treatment (0=baseline, 1=treatment), drug class (VB vs NVB), interaction term: (treatment x drug class), mean age, study duration, study design, treatment-induced heart rate changes.

Results: 1225 subjects (NVB=908, VB=317) were included in the analysis. Mean pSBP was 147 mmHg for NVB and 148 mmHg for VB at baseline, and 133 mmHg for NVB and 134 mmHg for VB after treatment. The difference between pSBP and cSBP at baseline (pSBP - cSBP) was 12.9 mmHg for NVB and 13.4 mmHg for VB. Treatment with either VB or NVB determined a reduction of the above difference to 8.6 mmHg for NVB and 11.3 mmHg for VB (both $p < 0.01$). In the final model, the effect of drug class on the difference between pSBP and cSBP (after treatment - baseline) was not significantly smaller for VB (-2.1 mmHg) than for NVB (-4.3 mmHg; $p=0.09$).

Conclusions: VB have a marginally, although not significantly, less unfavourable effects on cSBP than NVB. The blood pressure-lowering effect of beta-blockers is more pronounced for pSBP than for cSBP.

3.6

GENE EXPRESSION ANALYSIS IDENTIFY GENES ASSOCIATED WITH ARTERIAL STIFFNESS AND CAROTID DIAMETER IN THE TWINS UK COHORT

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Background: Previous studies have identified several genetic variants associated with arterial stiffness. The aim of this study was to investigate whether expression profiles of these genes associate with measures of aortic stiffness and diameter.

Method and Results: In a cross-sectional study of 2092 women aged 21-84 years from the TwinsUK cohort, measures of aortic stiffness (carotid-femoral pulse wave velocity [PWV], carotid distensibility), carotid diameter and heritability were made. In a subsample ($n=470$), gene expression levels of 62 genes previously associated with PWV were measured in leukocytes with Affymetrix microarrays. PWV and carotid diameter increased by 75% and 18%, respectively, from the second to seventh decade. Carotid distensibility decreased by 73%. Pleiotropic genetic effects accounted for 53% of the phenotypic correlation between carotid distensibility and diameter. Leukocyte-derived transcript ENPP1 significantly correlated with PWV. In 121 women that had repeat vascular measures over a follow-up period of 4.3 ± 1.4 years, leukocyte-derived ENPP1 expression and COL4A1 strongly related to PWV progression in multivariable regression ($\beta=0.19$, $p < 0.01$ and $\beta=0.32$, $p < 0.0001$; respectively). For carotid distensibility, leukocyte-derived transcript for angiotensin converting enzyme (ACE) most strongly associated with a reduction in carotid distensibility ($\beta=-0.20$, $p < 0.001$). Expression levels of ACE gene also associated with progression in carotid diameter ($\beta=0.21$, $p < 0.05$).

Conclusion: This study demonstrates that expression levels of ENPP1, which associated with arterial calcification, and COL4A1, associated with collagen

formation, relate to progression in PWV. In addition, our findings suggest that ACE gene expression may exert pleiotropic effects on reduced carotid distensibility and dilation.

4.1

NORMAL VALUES AND DETERMINANTS OF FEMORAL ARTERY STIFFNESS

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Aims: Carotid-femoral pulse wave velocity (PWV) is considered the gold standard measure of arterial stiffness, representing mainly aortic stiffness. As compared to the elastic carotid and aorta, the more muscular femoral artery may be differently associated with cardiovascular risk factors (CV-RFs), or provide additional predictive information beyond carotid-femoral PWV. Still, clinical application is hampered by the absence of reference values. Therefore, our aim was (1) to establish age- and sex-specific reference values for femoral artery stiffness in healthy subjects and (2) investigate the associations with CV-RFs.

Methods: femoral artery distensibility coefficient (DC), the inverse of stiffness, was calculated as the ratio of relative diastolic-systolic distension (obtained from ultrasound echo-tracking) and pulse pressure among 5,069 individuals (49.5% men, age range: 15-87 year). Individuals without cardiovascular disease (CVD), CV-RFs and medication use ($n=1,489$; 43% men) constituted a healthy sub-population used to establish sex-specific equations for percentiles of femoral artery DC across age.

Results: In the total population, femoral artery DC Z-scores were independently associated with body mass index (BMI), mean arterial pressure (MAP), and total-to-HDL cholesterol ratio. Standardized β s, in men and women respectively, were -0.18 (95% CI: -0.23;-0.13) and -0.19 (-0.23; -0.14) for BMI; -0.13 (-0.18; -0.08) and -0.05 (-0.10; -0.01) for MAP; and -0.07 (-0.11; -0.02) and -0.16 (-0.20; -0.11) for total-to-HDL cholesterol ratio.

Conclusion: In young and middle-aged men and women, normal femoral artery stiffness does not change substantially with age up to the 6th decade. CV-RFs related to metabolic disease are associated with increased femoral artery stiffness.

4.2

GENETIC VARIATIONS ON CHROMOSOME 14 INFLUENCE BCL11B GENE EXPRESSION LEVELS AND AORTIC STIFFNESS

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Background: Genetic variants in the 3'-BCL11B gene desert on 14q32.3 were recently shown to associate with aortic pulse wave velocity in the AortaGen Consortium GWAS meta-analysis. This region is believed to harbour a gene enhancer targeting BCL11B. We investigated the influence of 5 polymorphisms from this study (rs1381289C>T, rs6485690G>A, rs10782490C>T, rs1461587G>T and rs17773233G>T) on BCL11B mRNA levels and stiffness measured as Young's Elastic Modulus (EM) in 167 donor aortic tissue samples.

Methods: Demographic and other data were obtained, and EM was measured using Instron. SNP genotyping and BCL11B gene expression levels were determined using ABI assays.

Results: Mean age of sample was 57 ± 15 years. As expected, EM correlated significantly with age ($r=0.47$, $P < 0.001$). BCL11B gene expression levels were higher in subjects carrying rs1381289 T and rs10782490 C alleles ($P < 0.05$). rs1461587G>T and rs17773233G>T polymorphisms showed genotype specific higher EM values ($P < 0.05$); subjects homozygous for the risk allele had stiffer arteries compared to those who were heterozygous or those who did not carry the allele. Multiple regression adjusted for confounders showed rs1461587G>T and rs17773233G>T associated with increased EM ($\beta=-0.15$, $P < 0.05$) and ($\beta=0.17$, $P < 0.05$) respectively.

Conclusions: We have demonstrated for the first time that rs1381289 and rs10782490 have an effect on BCL11B transcription, resulting in different