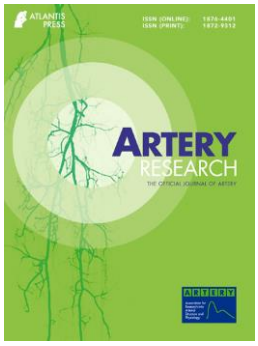

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3.4: EFFECT OF VITAMIN D SUPPLEMENTATION ON AORTIC STIFFNESS AND CENTRAL HAEMODYNAMICS IN OLDER INDIVIDUALS WITH VITAMIN D DEFICIENCY: PROMISING OBSERVATIONAL DATA IS NOT SUPPORTED WHEN TESTED BY DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMISED TRIAL DE

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Conclusions: Significant Bra-Rad-SBP_{Amp} exists during light-moderate exercise. This will result in underestimation of central SBP unless Bra-Rad-SBP_{Amp} is considered and is influenced by variation in peak blood flow velocity magnitude between the brachial and radial arteries.

3.1
QUANTIFICATION OF THREE-DIMENSIONAL VASCULAR SMOOTH MUSCLE ORIENTATION AND ITS DISPERSION IN MURINE CAROTID ARTERIES

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Introduction: Vascular smooth muscle cells (SMCs) play a pivotal role in regulating vascular tone in arteries, and are therefore an essential part of constitutive models of the arterial wall. Since an SMC exerts its contractile force mainly along its longitudinal axis, SMC orientation is a major determinant of arterial biomechanical behaviour. To our knowledge, all current constitutive models assume SMC orientation to be perfectly circumferential. Moreover, the mechanical effect of any dispersion in SMC orientation is neglected. In this study, we developed a method to quantify in 3D the orientation of SMCs in the intact arterial wall.
Methods: SMC nuclei of six excised and mounted murine carotid arteries were imaged using two-photon laser scanning microscopy. 3D image processing was used to identify individual nuclei and their orientations. Subsequently, SMC locations and orientations were converted to cylindrical and spherical coordinate systems, respectively. We found SMCs to be arranged in distinct inner and outer layers. For each layer, SMC orientations were described by a Bingham distribution, a statistical distribution to describe axis orientations in 3D.
Results and Conclusion: Distributions show a statistically significant ($p<0.05$) helical angular component in both layers (inner: $\Theta_h=2.7\pm2.7^\circ$, outer: $\Theta_h=5.1\pm2.7^\circ$, mean±SD), and considerable dispersion. We conclude that vascular SMC orientation 1) can be quantified in 3D, 2) has a distinct helical component, and 3) shows considerable dispersion. The acquired distribution data are essential to improve constitutive modelling of the arterial wall, by quantitatively describing physiological SMC orientation and dispersion.

3.2
INACTIVE MATRIX GLA PROTEIN IS CAUSALLY RELATED TO HEALTH OUTCOMES: A MENDELIAN RANDOMIZATION STUDY IN A FLEMISH POPULATION

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Background: Matrix Gla-protein is a vitamin K-dependent protein that strongly inhibits arterial calcification. Vitamin K deficiency leads to production of inactive nonphosphorylated and uncarboxylated MGP (dp−ucMGP). The risk associated with dp−ucMGP in the population is unknown.
Methods: In a Flemish population study, we measured circulating dp−ucMGP at baseline (1996−2011), genotyped *MGP* and recorded adverse health outcomes until December 31,2012. We assessed the multivariable-adjusted association of adverse health outcomes with dp−ucMGP and we applied a Mendelian randomization analysis based on *MGP* genotypes.
Results: Among 2318 participants, baseline dp−ucMGP averaged 3.61 μg/liter. Over 14.1 years (median), 197 deaths occurred, 58 from cancer and 70 form cardiovascular disease, and 85 participants experienced coronary events. The risk of death and non-cancer mortality curvilinearly increased ($P\leq0.008$) by 15.0% (95% confidence interval, 6.9−25.3) and by 21.5% (11.1−32.9) for a doubling of the nadir: 1.43 and 0.97 μg/liter, respectively. With higher dp−ucMGP, cardiovascular mortality log-linearly increased (hazard ratio for dp−ucMGP doubling, 1.14[1.01−1.28]; $P=0.027$), but coronary events log-linearly decreased (0.93 [0.88−0.99]; $P=0.021$). dp−ucMGP levels were associated ($P\leq0.001$) with *MGP* variants *rs2098435*, *rs4236* and *rs2430692*. For non-cancer mortality and coronary events ($P\leq0.022$), but not for total and cardiovascular mortality ($P\geq0.13$), the Mendelian randomization analysis suggested causality. In a nested case-control study, 64 patients with coronary events had lower dp−ucMGP than 107 matched controls (3.51 *vs.* 4.54 μg/liter; $P=0.012$).
Conclusions: Higher dp−ucMGP predicts total, non-cancer and cardiovascular mortality, but lower coronary risk. For non-cancer mortality and coronary events, these associations are likely causal.

3.3
ASSOCIATIONS BETWEEN PLASMA INCRETIN HORMONE RELEASE AND AORTIC STIFFNESS AND BLOOD PRESSURE IN INDIVIDUALS WITHOUT KNOWN DIABETES: THE ADDITION-PRO STUDY

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The role of incretin hormone release on vascular structure and function remains unclear. Hence, in 836 Danish individuals without know diabetes and without antihypertensive treatment, we examined the associations of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) release during a 3-point 75 g oral glucose tolerance test (0, 30, 120 minutes) with carotid-femoral pulse wave velocity (PWV), and brachial and central blood pressure. For GLP-1 and GIP, total area under the curve (AUC) reflecting circulating incretin levels, and incremental AUC (iAUC) reflecting the incretin response were calculated and transformed by the base 2 logarithm. Associations were analysed by linear regression adjusting for age and sex, and for heart rate and mean blood pressure in the PWV analyses. Mean age was 55.1 (SD: 7.4) years, and 52% were men. A doubling in $iAUC_{GLP\text{-}1}$ was associated with a PWV (95% CI) of -0.04 (-0.12;0.04) m/s, and a central systolic and diastolic blood pressure and pulse pressure (95% CI) of -1.2 (-2.1;-0.3), -0.8 (-1.3;-0.2), and -0.4 (-1.0;0.2) mmHg, respectively. Associations with brachial blood pressure were of similar magnitude as central blood pressure. For $AUC_{GLP\text{-}1}$, only brachial diastolic blood pressure showed a statistically significant association (-1.0 (95% CI: -1.9;-0.2) mmHg for an $AUC_{GLP\text{-}1}$ doubling). Besides a positive association between $iAUC_{GIP}$ and brachial pulse pressure, GIP was not associated with PWV or blood pressure. Although cross-sectional, these results indicate that a high GLP-1 response has a beneficial impact on the vascular function but not on vascular structure, whereas GIP does not affect the vasculature.

3.4
EFFECT OF VITAMIN D SUPPLEMENTATION ON AORTIC STIFFNESS AND CENTRAL HAEMODYNAMICS IN OLDER INDIVIDUALS WITH VITAMIN D DEFICIENCY: PROMISING OBSERVATIONAL DATA IS NOT SUPPORTED WHEN TESTED BY DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMISED TRIAL DESIGN

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Background: Observational studies report a relationship between increased aortic stiffness and low vitamin D levels. This suggests that aortic stiffness may be improved with vitamin D supplementation, but there is limited intervention data to support this hypothesis. This study aimed to determine the effect of vitamin D supplementation on aortic stiffness and associated central haemodynamic indices.
Methods: In a double-blind, placebo-controlled trial, 265 individuals (63±7, female 50%) with vitamin D deficiency were randomized to 12-months intervention (vitamin D 50,000 IU/month; n=132) or matching placebo (n=133). Aortic stiffness (carotid-femoral pulse wave velocity; aPWV), central haemodynamic indices (augmentation index, augmented pressure, central pulse pressure) and brachial blood pressure were measured at baseline, six and 12 months.
Results: At baseline there were no significant differences between the groups in aPWV (9.0±0.3 vs 9.1±0.2 m/s; P=0.6), nor any other central hemodynamic indices or brachial blood pressure (all $P > 0.05$). Intervention failed to make any clinical or statistically significant changes to aPWV

(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 βs, 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