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2.1. The influence of peripheral vascular resistance on systolic blood pressure

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Isolated systolic hypertension is the most common form of hypertension in young adults. Physiologically, this high pulse pressure (PP) state results from either a high stroke volume (SV), arterial stiffening, or both. However, systolic blood pressure (SBP) can differ substantially between individuals with high PPs. This study examined the haemodynamic mechanisms determining systolic blood pressure (SBP). A subset of data from the ENIGMA study (males aged ≤ 30 years, $n = 667$) were analysed. In all subjects supine blood pressure, pulse wave velocity (PWV, SphygmoCor), SV (InnoCor) and peripheral vascular resistance (PVR) were measured. Subjects

were divided into tertiles of PP. Subjects were further divided in to those with a SBP ≥ 130 and < 130 mmHg. PWV was adjusted for mean arterial pressure. Subjects with a diastolic blood pressure (DBP) > 90 were excluded.

Haemodynamic variables are shown in the Table. Within PP tertiles, SV and PWV did not differ between SBP groups. However, in the highest PP tertile, PVR was greater in subjects with high SBP ($P < 0.01$).

In individuals with raised PP, PVR defines those with SBP elevation, the mechanisms of which remain to be elucidated.

	Low pulse pressure		High pulse pressure	
	Low systolic BP	High systolic BP	Low systolic BP	High systolic BP
Age (years)	20 \pm 3	21 \pm 3	20 \pm 2	21 \pm 3
SBP (mmHg)	115 \pm 8	133 \pm 3	123 \pm 4	139 \pm 9
DBP (mmHg)	68 \pm 6	82 \pm 4	62 \pm 5	72 \pm 8
HR (beats/min)	67 \pm 11	76 \pm 11	62 \pm 9	67 \pm 11
SV (ml)	95 \pm 20	86 \pm 18	113 \pm 22	111 \pm 22
PWV (m/s)	5.74 \pm 0.75	6.09 \pm 0.99	5.81 \pm 0.70	5.88 \pm 0.81
PVR (units)	11.21 \pm 2.35	12.35 \pm 2.63	9.41 \pm 2.73	10.35 \pm 2.62

2.2. A study of the 'obesity paradox' across the spectrum of cardiovascular risk

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Objective: Recent evidence suggests that the impact of obesity outcomes following heart failure and CAD revascularisation is different to that in the general population suggesting an obesity paradox. We investigated the impact of BMI on all-cause mortality across a range of Ischaemic Heart Disease (IHD) in two independent populations.

Methods: The Paisley/Renfrew (PR) population survey comprised 14 722 middle-aged adults with 25 year follow-up, IHD defined as existing IHD or previous MI. The Scottish Coronary Revascularisation Register (SCRR) comprised 5135 patients who underwent elective, first-time PCI with 5 year follow-up. BMI was categorised into ≤ 19 , 19.1–24.9, 25–27.49,

27.5–29.99 and ≥ 30 . Hazard ratios for all-cause mortality were estimated using the Cox proportional hazards model adjusting for age and sex (PR) and age, sex, smoking status, diabetes, left ventricular impairment, previous myocardial infarction, and socioeconomic deprivation (SCRR). Additional analysis was performed stratifying by hypertension status.

Results: Long-term risk of BMI in pre-existing stable IHD or post-elective PCI is U-shaped. BMI of

27.5–29.99 is associated with the lowest long-term risk in the presence of IHD. Hypertension as an additional risk factor does not change the risk profile (Table).

Conclusions: Obese and overweight patients with pre-existing stable IHD or acute ACS requiring PCI do not have an increased long-term risk compared to normal weight patients.

<i>Paisley/Renfrew</i>				
	<i>Referent group—nonsmoker + BMI 19.1–24.9 and no CV risk factors</i>		<i>SCRR</i>	
	<i>Non-smoker + IHD</i>	<i>HTN + IHD</i>	<i>Overall</i>	<i>HTN</i>
≤ 19	4.8 (2.6–8.9)	1.6 (0.2–11.2)	4.2 (1.5–11.7)	11.6 (3.9–34.5)
19.1–24.9	2.0 (1.5–2.8)	3.2 (2.1–5.0)	1	1
25–27.49	1.9 (1.4–2.7)	2.4 (1.7–3.4)	0.7 (0.5–0.98)	0.7 (0.4–1.2)
27.5–29.99	1.6 (1–2.4)	2.2 (1.5–3.3)	0.6 (0.4–0.9)	0.4 (0.2–0.8)
≥ 30	2.2 (1.4–3.5)	2.8 (2–3.9)	0.8 (0.6–1.2)	0.7 (0.4–1.1)

2.3. Radial augmentation index closely approximates the ratio of central to peripheral pulse pressure

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The late systolic shoulder (P2) of the peripheral pulse which defines peripheral augmentation index (pAIx) closely approximates central systolic blood pressure when peripheral waveforms are calibrated assuming equality of central and peripheral mean and diastolic blood pressure (DBP). The purpose of the present study was to determine if peripheral augmentation index ($pAIx = P2 - DBP / (SBP - DBP)$) equates to the ratio of central (cPP) to peripheral pulse pressure (pPP) irrespective of any assumption relating to peripheral DBP. Central systolic aortic pressure (cSBP) was measured with a Millar SPC-454D (Millar instruments Houston, Texas) high fidelity pressure tipped catheter with the tip of the catheter in the proximal aortic root in subjects undergoing cardiac catheterisation. The study was approved by the local research ethics committee and all subjects gave

written informed consent. Peripheral digital pressure (Finometer, Finapres medical systems, Netherlands) was calibrated assuming mean digital pressure to be equal to mean aortic pressure. Simultaneous measurements of digital artery pressure and aortic pressure were obtained at baseline ($n = 32$), after nitroglycerin (NTG, 500 μ g sub-lingual, $n = 22$), hand grip exercise ($n = 10$) and right atrial pacing at 20 beats per minute above resting heart rate ($n = 10$). There was close agreement between the peripheral augmentation index (pAIx) and cPP/pPP with mean differences (standard deviations) of 2.2 (8.2), 0.8 (5.7), 2.6 (7.0) and -2.3 (4.7) % at baseline, after pacing, NTG and handgrip respectively. These results suggest that, regardless of systolic and diastolic calibration, pAIx is a good measure of the ratio of central to peripheral pulse pressure.

2.4. Evidence of augmentation of systolic coronary blood flow by retrograde wave reflection travelling-back from the proximal aorta

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Background: It has been proposed that blood flow in coronary arteries is augmented by waves travelling-

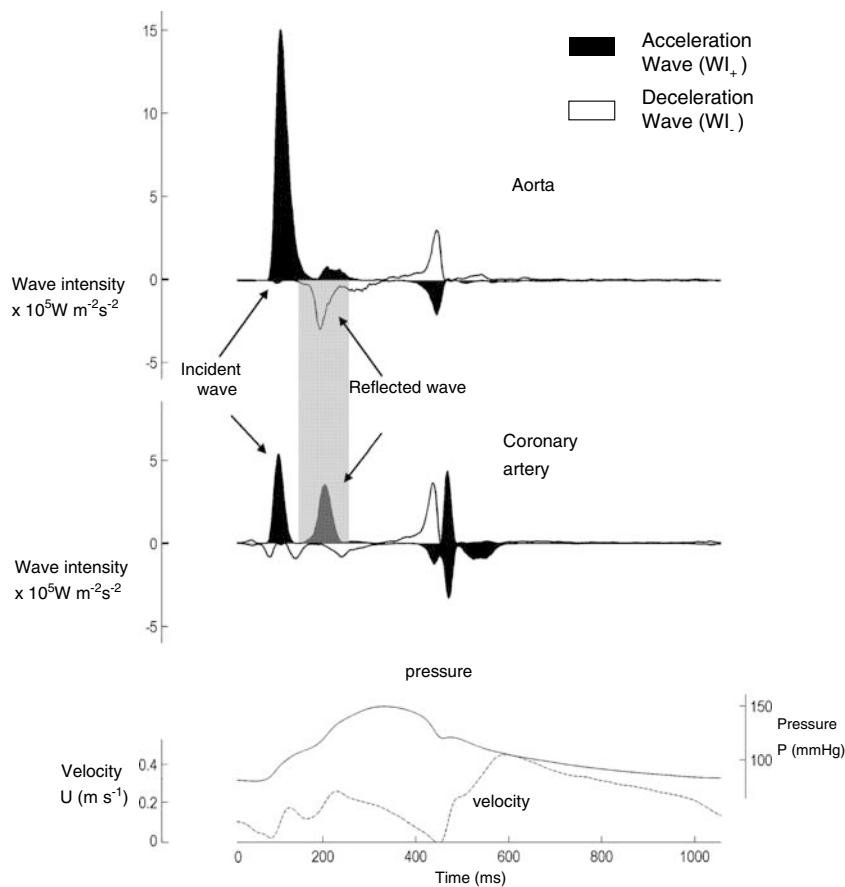
back from the distal aorta. However, these waves have never been identified. We used wave intensity

analysis to time and quantify reflected waves travelling from the proximal aorta into coronary arteries, and assess their contribution to changes in coronary blood flow with ageing and hypertension.

Method and results: In 19 subjects (age 35–73 years) sensor-tipped intra-arterial wires were used to measure pressure and Doppler velocity in the coronary arteries and at proximal aortic root. Separated wave intensity analysis was used to identify and quantify incident and reflected waves. The reflected wave in the proximal aorta occurred in systole in all subjects (159 ± 12 ms after the ECG-R-wave) and could be seen later in the coronary arteries: left main stem (186.8 ± 10.7 ms), circumflex (188.8 ± 7.4 ms) and left anterior descending

(194.4 ± 7.7 ms). In the coronary arteries the mean reflected wave represented $20.3 \pm 2.1\%$ of the incident wave magnitude, and elicited a $38.9 \pm 8.4\%$ instantaneous increase in systolic coronary blood flow velocity (0.2 – 0.28 m/s, $P < 0.002$). This augmentation was seen to increase with increasing age ($r = 0.51$, $P < 0.03$), probably due to an increase in aortic stiffening (pulse wave velocity, $r = 0.77$, $P < 0.001$).

Conclusions: Reflected wave can be followed travelling-back from the proximal aorta into the coronary arteries. These reflected waves augment coronary systolic blood flow. With increasing age the degree of augmentation of systolic coronary blood flow is increased.



2.5. Contribution of wave reflection and arterial stiffness to central pulse pressure in women

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Central pulse pressure (cPP) can be divided into two components: the height of the first systolic

shoulder (P1), thought to be determined by an outgoing pressure wave, and augmentation pressure

(ΔP) determined by the magnitude and timing of reflected pressure waves. We examined the relative contribution of P1 and ΔP to cPP, their relation to arterial stiffness measured by pulse wave velocity (PWV) and heritability in 496 women from St Thomas' TwinsUK registry (112 monozygotic, MZ and 135 dizygotic, DZ pairs) aged 21–81. cPP, P1 and ΔP were estimated using the SphygmoCor system from transformed radial waveforms calibrated from peripheral blood pressure. Carotid-femoral PWV was measured using the same system. Multiple regression analysis was used to examine the relation of P1 and ΔP to PWV, heart rate (HR) and mean arterial blood pressure (MAP). Heritability was estimated from intra-class correla-

tions. In women <60 years, P1 and ΔP accounted for 25 and 73% of cPP variance respectively. P1 was independently associated with PWV and MAP (standardized regression coefficients, $\beta = 0.31$ and 0.25 respectively, $P < 0.001$), whereas ΔP was associated with MAP and HR ($\beta = 0.65$ and -0.52 respectively, $P < 0.001$) but not PWV ($\beta = 0.097$, $P = 0.064$). In women ≥ 60 , the trend remained with ΔP only modestly correlating with PWV ($\beta = 0.11$, $P = 0.02$). Heritability (h^2) of P1, ΔP , cPP and PWV was 0.62, 0.70, 0.70 and 0.34 respectively after adjustment for MAP and HR. These results suggest that ΔP is highly heritable and, independent of PWV, is a major determinant of cPP in women.

2.6. Mechanisms for the greater impact of diabetes on stroke risk in Indian Asians compared to Europeans

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Background: People of Indian Asian descent have a 1.6 fold increased stroke mortality rate compared to Europeans, despite lower resting blood pressure. Diabetes has an enhanced impact on stroke risk in Indian Asians compared with Europeans. Although how is unclear, it may be related to functional responses of the middle cerebral artery (MCA) to chronic dysglycaemia.

Methods: 149 Europeans and 151 Indian Asians were recruited. Each group was two-thirds male (aged 35–75 years) and one-third female (aged 55–75 years). All underwent metabolic profiling and measurement of middle cerebral artery flow velocity (V_{MCA}), dynamic autoregulatory index (DCAI) and resistance index (RI: difference between systolic and diastolic V_{MCA} divided by systolic V_{MCA}) using transcranial Doppler ultrasound.

Results: Indian Asians had higher markers of dysglycaemia compared to Europeans, resting

blood pressure however did not differ. Systolic, diastolic and mean V_{MCA} , and RI were higher in Indian Asians than Europeans. DCAI did not differ. Correlation coefficients for the relation between HbA1c and mean V_{MCA} , RI and DCAI were -0.043 , ($P = 0.5$), 0.259 , ($P = < 0.0001$) and -0.024 ($P < 0.7$) respectively. Adjustment in Indian Asians for smaller body surface area accounted for their higher V_{MCA} but not higher RI. Adjustment for HbA1c did not alter the ethnic difference in velocities, but accounted for the difference in RI.

Conclusions: Indian Asians have higher MCA flow velocities, accounted for by smaller body size, and elevated cerebral resistance index, due to greater dysglycaemia, compared with Europeans. Cerebral blood flow control alterations resulting from dysglycaemia may be the mechanism underlying Indian Asian vulnerability to stroke.

3.1. Reduced longitudinal functional reserve on exercise in hypertensive patients with exertional dyspnoea and normal echocardiography at rest

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Background: Many patients with hypertension complain of breathlessness for which there often appears to be no obvious cardiac or pulmonary cause. Despite normal ventricular function at rest, reserve may be impaired on exercise

which may account for the symptoms. Therefore, we have conducted exercise-echocardiography studies in a group of hypertensive patients with normal pulmonary function and normal ejection fraction.

Methods: Hypertensive patients with exertional dyspnoea and normal LV and LA chamber size, LV mass and LVEF > 50%, and age-matched controls were recruited. Supine exercise echocardiography was performed to comparable heart rates and images were analysed off-line (EchoPac). LV systolic and diastolic longitudinal reserve indices (LFRI) were determined from the peak annular velocities by TDI (PW-Doppler) at rest and on exercise (Difference = Δ); longitudinal functional reserve index = Δ Sm(or Em) * (1 - 1/Sm(or Em) at rest). All echocardiograms were read by 2 observers and results averaged.

Results: 28 pts (age 69 ± 7 years, 17 females, LVEF $60 \pm 7\%$) with dyspnoea on exercise and 13 age

matched normal controls (age 66 ± 5 years, 10 females, LVEF $62 \pm 9\%$) with adequate images and heart rate responses on exercise were analysed. The LV mass index (LVMI) and the inter-ventricular septum thickness were similar in both groups (79 ± 17 vs 80 ± 20 g/m² and 1.01 ± 0.30 vs 0.99 ± 0.25 cm). The patients had significantly lower LFRI (systolic LFRI 0.9 ± 1.4 vs 2.2 ± 1.4 ($P = 0.008$); diastolic LFRI 2.2 ± 1.5 vs 3.9 ± 2.9 ($P = 0.023$)).

Conclusions: Exercise echocardiography can reveal abnormal LV function which is not apparent at rest. This may account for the symptoms of exertional dyspnoea in hypertensive patients even in the absence of LV hypertrophy.

3.2. Proteome-wide search for biomarkers in acute ischaemic stroke

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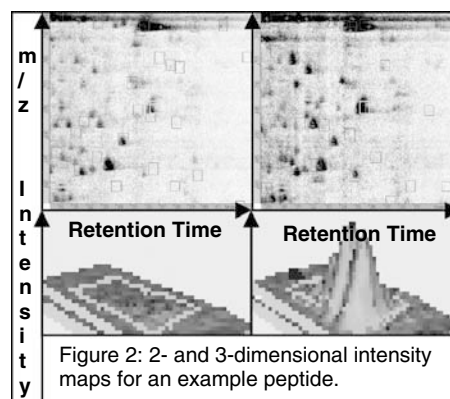
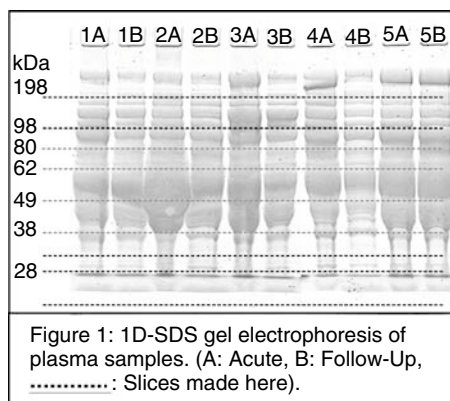
Background: Definitive diagnosis of acute ischaemic stroke requires confirmation of diagnosis by DWI-MRI, an expensive and often-impractical technique. A sensitive, specific blood test might serve as a useful adjunct to the more commonly used CT brain scan. Here we describe the use of novel peptide-detection algorithms with the human proteome database in the identification of candidate ischaemic stroke biomarkers using liquid chromatography and mass spectrometry (LC-MS/MS).

Methods: Plasma was taken from 9 patients with MRI-confirmed ischaemic stroke within 24 h of symptom onset (Acute) and repeated from the same patients at 2–4 months (Follow-Up). The Proteome-Lab Ig-Y Spin column was used to exclude 12 of the most common plasma proteins, and protein separation was achieved by 1-Dimensional sodium dodecyl

sulphate (SDS) gel electrophoresis using 7% tris-acetate gel. Selected protein bands (38–49 kDa, and also 62–80 kDa, see Figure 1) were digested by overnight incubation with 20 μ g trypsin at 37 °C. The peptides were then partitioned by reverse-phase liquid chromatography, and identified by MS/MS. Using DeCyder™ MS Differential Analysis software (Figure 2), and BioWorks™ Browser, the peptides were matched to proteins, the intensities of which were compared between groups by the Wilcoxon signed-ranks test.

Results: Three proteins were identified that differed significantly ($P < 0.05$) between acute and follow-up phases of ischaemic stroke.

Conclusions: We have identified 3 proteins that could potentially be used as biomarkers for ischaemic stroke. Our technique has wide-ranging implications for other diseases.



3.3. Oxidative stress and mitochondrial dysfunction in vessels from patients with coronary artery disease (CAD)

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Objective: Previously we demonstrated increased levels of ROS in the vasculature of patients with CAD relative to controls. The molecular basis for this increase remains to be fully elucidated but recent studies suggest the mitochondria may play a role. We investigated molecular determinants of mitochondrial function in intact vessels and primary endothelial cells from patients with advanced CAD and control subjects.

Methods: Portions of human saphenous vein were obtained from patients undergoing coronary artery bypass grafting (CABG, $n=38$) and varicose vein removal ($n=16$) and endothelial cells (HSVECs) isolated and cultured from selected vessels. Superoxide production was measured using lucigenin-enhanced chemiluminescence in the presence and absence of rotenone, a mitochondrial respiratory chain inhibitor. Gene expression was assessed by qRT-PCR. AMP-activated protein kinase (AMPK) activity was assayed by incorpora-

tion of radioactively labelled ATP in a specific substrate.

Results: On treatment with rotenone, superoxide production was significantly reduced in intact vessels from CABG patients ($P=0.001$, CI: 0.0989, 0.3269) but not in controls ($P=0.563$, CI: -3.91, 6.91), suggesting a greater contribution of the mitochondria to superoxide production in diseased patients. A significant increase in *SOD2* expression ($dCt=4.62 \pm 0.23$ vs 5.66 ± 0.11 , CABG vs control, $P=0.035$) was observed in CABG HSVECs, likely an adaptive response to elevated mitochondrial superoxide production. In addition, basal AMPK activity was increased by 51.8% in CABG cells.

Conclusions: Results indicate that the mitochondria and molecular determinants of cellular bioenergetic function contribute to increased ROS production in CAD patients. Mitochondria-targeted antioxidants could therefore be of therapeutic benefit in the treatment of CAD.

3.4. WNK1—functional analyses of variants associated with blood pressure and essential hypertension

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Gain of expression mutations in *WNK1* cause Gordon's Syndrome, a rare disorder characterised by hypertension and hyperkalemia. We have previously reported association between *WNK1* and BP in the BRIGHT Study and 24-h ambulatory BP in the GRAPHIC study. The associated SNPs map to the promoter and regulatory regions in intron 1, suggesting that changes in *WNK1* expression may contribute to BP and risk for EH in the general population. This study was performed to investigate whether associated variants effect gene expression. Two SNPs were selected for functional analysis, one promoter variant (rs1468326 C/A) and one in intron 1 (rs765250 A/G). Carriers of allele C for rs1468326 have on average lower SBP (-5.05 mm Hg 95% CI (-9.21 , -0.66), $P=0.02$); carriers of allele A for rs765250 have increased SBP (3.14 mm Hg 95% CI (1.26, 4.98), $P=6.77 \times 10^{-4}$) and are at increased risk

for EH (OR 1.34 95% CI (1.05, 1.70), $P=0.015$). For each SNP, multiple copies of each allele were cloned into pGL3 and transfected into HEK293 cells, followed by luciferase assay.

Reporter assays demonstrated that rs1468326C had lower activity than rs1468326A, ~ 3.36 fold decrease in luciferase activity 95% CI (-3.93 , -2.80), $P=3.6 \times 10^{-10}$. The intronic SNP, rs765250A showed a ~ 1.50 fold increase compared to rs765250G, 95% CI (1.10, 1.90), $P=1.14 \times 10^{-4}$.

These results correlate well with the reported genetic associations. The SNPs associated with increased (decreased) BP also demonstrate increased (decreased) reporter activity, suggesting that these are functional variants that could alter *WNK1* expression. These new data lend further support to the hypothesis that variation in *WNK1* expression contributes to BP and EH.

3.5. Human WNK3 splice variants differentially affect NCCT expression: further evidence that NCCT expression and activity can be independently regulated

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Renal sodium transport by NCCT, the target for thiazide diuretics, is crucial for salt homeostasis and blood pressure regulation. It is now clear that NCCT transporter trafficking and membrane expression is orchestrated by a protein scaffold that includes WNK3, a kinase closely related to WNK1 and WNK4 that are mutated in Gordon syndrome (PHAII). WNK3 has 2 isoforms: a *renal* isoform (RWNK3) that increases NCCT expression, and a *brain* isoform (BWNK3) of unknown function. NCCT activity can also be altered independently from trafficking through phosphorylation of conserved N terminal residues especially threonine 58.

Site mutation was used to produce plasmids expressing ECFP-NCCT T58D or T58A and a kinase-dead WNK3. *Xenopus* oocytes were injected with cRNA for these plasmids or wild-type cRNAs. NCCT function was assessed by $^{22}\text{Na}^+$ flux and

confocal microscopy of the blue fluorescent ECFP-NCCT protein.

RWNK3 increased NCCT flux 242% by increasing surface membrane expression whereas kinase-dead RWNK3 produced the opposite effect. BWNK3 inhibited NCCT by 50% whereas the kinase-dead mutant was non-functional. The NCCT T58D mutant increased $^{22}\text{Na}^+$ flux 220% and the T58A mutant decreased flux by 46% without altering membrane expression. Nevertheless, co-expressing WNK3 or WNK4 affected mutant expression in the same manner as wild-type NCCT.

Thus Brain and Renal isoforms of WNK3 affect NCCT trafficking differently. They both act in a kinase dependent manner, but the T58 mutants show that phosphorylation of this key residue is not necessary for WNK3/4 action. The WNK3 c-terminal and NCCT phosphorylation motifs may be interesting targets for future antihypertensive therapy.

3.6. Development of a gene transfer vector expressing angiotensin 1-7 and assessment of its effects on cardiac hypertrophy

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Although the systemic actions of the renin-angiotensin system (RAS) are well documented, evidence suggests the presence of local tissue-specific RAS. For example, angiotensin converting enzyme 2 (ACE2) an ACE homologue is selectively expressed in heart, kidney and testis. In heart, ACE2 produces the novel peptide Angiotensin1-7 (Ang1-7) which counteracts AngiotensinII (AngII). Presently, only systemic actions of Ang1-7 can be studied through osmotic minipump implantation. We have engineered an adenoviral vector overexpressing Ang1-7 (RAdAng1-7) to study its tissue-specific actions. RAdAng1-7 expresses a fusion protein resulting in secretion of Ang1-7 from adenovirus-transduced cells. Efficient expression of Ang1-7 fusion protein in transduced cells was confirmed by western immunoblotting. Next, we used an *in vitro* hypertrophy model. H9c2 rat cardiomyocytes were stimulated with 100 nM AngII for 4 days. Unstimulated cells were 112.31 ± 13.53 nm whereas

AngII-stimulated cells were significantly longer (149.69 ± 15.63 nm) ($n = 50$, $P < 0.05$). Transduction of AngII-stimulated H9c2 cells with RAdAng1-7 at 500 and 1000 plaque forming units (pfu)/cell inhibited hypertrophy (RAdAng1-7 500pfu = 109.8 ± 11.5 nm; RAdAng1-7 1000pfu = 117.7 ± 13.7 nm; AngII = 144.6 ± 15.5 nm; Control = 109 ± 10.4 nm; $P < 0.05$). A conditioned media assay was used to confirm peptide secretion from RAdAng1-7 transduced cells. HeLa cells were transduced with RAdAng1-7. Cells were incubated for 48 hours to allow Ang1-7 to accumulate in the media. Conditioned transferred to AngII-stimulated H9c2 cells was able to inhibit AngII-induced hypertrophy (RAdAng1-7 = 125.5 ± 14.6 nm; AngII = 178 ± 21.7 nm; Control = 135.2 ± 15 nm; $P < 0.05$). In conclusion gene transfer can be used to overexpress Ang1-7. RAdAng1-7 will be useful for probing Ang1-7's tissue-specific effects *in vivo* following delivery to individual tissues.

4.1. Gene-centric association of 98 candidate genes and blood pressure in the pamela study—heterogeneity in blood pressure subphenotypes

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It is increasingly clear that phenotyping accuracy is the key to a successful genetic association study. Blood pressure measurements show heterogeneity depending on the method and time of measurement, sexual dimorphism and measurement errors. All these makes the results of gene association studies difficult to interpret. Our strategy is to perform a gene centric experiment with dense tagging SNP coverage including the promoter and untranslated regions of major cardiovascular genes in a large population (PAMELA) with office, home and ambulatory blood pressure measurement for every individual.

Methods: The PAMELA study consists of 2000 adults aged 25–74 years, resident in Monza, Italy. We genotyped 1536 Tag SNPs in 98 candidate genes selected based on known pathways involved in sympathetic nervous system, oxidative-stress, renin-angiotensin-system and sodium balance. Geno-

typing performed on the Illumina BeadChip platform. Quality checking included DNA quality, call rate and Hardy Weinberg equilibrium. Association analysis was performed using Plink on home, clinic and ambulatory blood pressure measurements (24 h, day and night) as quantitative traits.

Results: The Table summarises the top association signals for different BP measures in the overall population and stratified by sex.

Conclusions: For systolic blood pressure, polymorphisms in LEPR, DRD1, ADIPOQ, IGF1 and SOD2 in females and for diastolic BP ICAM1, LEPR and NPPA in males showed consistent associations for home and ambulatory BP values. The significance of an association signal is not consistent by sex or across different BP subphenotypes and this will have major implications on the interpretation of association studies.

	Gene	SNP	All					Males					Females					
			CLINIC	HOME	24H	DAY	NIGHT	CLINIC	HOME	24H	DAY	NIGHT	CLINIC	HOME	24H	DAY	NIGHT	
SYSTOLIC	NOS1	rs4766836	7.E-01	7.E-01	5.E-01	6.E-01	3.E-01	4.E-02	6.E-04	4.E-03	6.E-03	1.E-02		3.E-01				
	LEPR	rs9436739	2.E-01	8.E-01	1.E+00	1.E+00	8.E-01	3.E-01	5.E-01	4.E-01	2.E-01	1.E+00	9.E-04	1.E-03	8.E-05	8.E-04	3.E-03	
	LEPR	rs1938484	2.E-01	3.E-01	5.E-02	4.E-02	1.E-01	4.E-02	5.E-02	7.E-04	7.E-04	3.E-03	2.E-01	5.E-02	2.E-01	9.E-02	8.E-01	
	DRD1	rs265976	8.E-01	1.E-01	7.E-01	8.E-01	9.E-01	1.E+00	6.E-01	1.E+00	9.E-01	6.E-01	8.E-02	4.E-05	2.E-03	3.E-03	4.E-02	
	ADIPOQ	rs822396	2.E-01	2.E-01	4.E-01	4.E-01	2.E-01	8.E-01	5.E-01	7.E-01	7.E-01	8.E-01	7.E-03	4.E-03	8.E-03	5.E-02	2.E-04	
	IGF1	rs12821878	4.E-01	5.E-01	6.E-01	6.E-01	8.E-01	4.E-01	4.E-01	1.E-01	2.E-01	8.E-02	6.E-02	3.E-04	4.E-03	6.E-03	1.E-02	
	AGTR1	rs13095522	3.E-02	5.E-01	1.E+00	1.E+00	9.E-01	4.E-04	4.E-02	7.E-02	1.E-01	3.E-02	2.E-01	6.E-01	9.E-01	9.E-01	9.E-01	
	SOD2	rs7855	4.E-01	6.E-03	2.E-01	1.E-01	3.E-01	9.E-01	9.E-01	1.E+00	8.E-01	8.E-01	4.E-02	3.E-03	5.E-04	4.E-04	4.E-03	
DIASTOLIC	SERPINE1	rs2227672	5.E-01	2.E-01	8.E-01	9.E-01	8.E-02	3.E-06	1.E-01	3.E-01	2.E-01	6.E-01	1.E+00	9.E-01	7.E-01	7.E-01	7.E-01	
	HNF4A	rs3212197	7.E-01	1.E-01	5.E-01	4.E-01	3.E-01	4.E-01		7.E-02	2.E-01	5.E-06	6.E-01	1.E+00	5.E-01	5.E-01	6.E-01	
	ICAM1	rs281440	9.E-01	2.E-01	8.E-02	2.E-01	2.E-01	2.E-01	1.E-02	4.E-04	3.E-03	1.E-04	6.E-04	2.E-01	2.E-01	1.E-01	6.E-01	
	NOS1	rs4766836	8.E-01	6.E-01	5.E-01	5.E-01	3.E-01	3.E-02	1.E-04	8.E-03	9.E-03	4.E-02		6.E-01				
	LEPR	rs1938484	2.E-01	1.E-01	2.E-02	1.E-02	1.E-01	3.E-02	1.E-01	3.E-04	5.E-04	1.E-03	8.E-01	4.E-02	2.E-01	2.E-01	5.E-01	
	ADRA1D	rs3810568	1.E-02	2.E-01	7.E-02	5.E-02	2.E-01	4.E-01	4.E-01	7.E-01	4.E-01	6.E-01	5.E-04	3.E-04	6.E-03	5.E-03	5.E-02	
	NPPA	rs5063	7.E-01	4.E-02	9.E-02	3.E-01	2.E-01	1.E-02	7.E-03	5.E-04	8.E-04	7.E-03						

4.3. Neuroprotective effect of the AT₂ receptor in an endothelin-1 model of stroke in spontaneously hypertensive rats

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On the basis of AT₂ receptor knockout studies, the AT₂ receptor is implicated to be neuroprotective although this premise has not been directly tested. Therefore, we have examined the potential neuroprotective role of the AT₂ receptor following intracerebroventricular (icv) administration of AT₂ receptor agonist CGP42112 in a conscious rat model of stroke.

Spontaneously hypertensive rats (SHR) were treated with either CGP42112 (0.1–10 ng/kg/min icv) alone or in combination with the AT₂ receptor antagonist PD123319 (36 ng/kg/min icv), commencing 5 days prior to stroke induction. A focal reperfusion model of stroke was induced in conscious rats by administering endothelin-1 adjacent to the middle cerebral

artery through a surgically implanted cannula. Behavioural tests were used to assess the severity of neurological deficit as a result of the ischemic event. Cortical and striatal infarct volumes were measured 72 h post stroke. Blood pressure was unaffected by treatments. CGP42112 dose-dependently reduced cortical infarct volume post stroke ($P < 0.05$). When administered in combination with PD123319, CGP42112 (1 ng/kg/min) had no effect on infarct volume. PD123319 had no effect on infarct volume

alone. These results were consistent with the behavioural findings, indicating that CGP 42112 reduced motor deficit on the lateral beam test at 72 h post stroke ($P < 0.05$). These results indicate that centrally administered CGP42112 exhibits a neuro-protective effect, based on infarct and behavioural data, which appears to be independent of blood pressure. Thus, this study has shown for the first time that central AT₂ receptor stimulation is neuro-protective in a conscious rat model of stroke.

5.1. Assessment of hyperacute blood pressure and outcome after ischaemic stroke: data from the VISTA collaboration

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Introduction: Hypertension is independently associated with poor outcome after acute ischaemic stroke. However, most studies enrolled patients up to 48 h after onset, so that 'baseline' blood pressure (BP) was taken on average 24 h post ictus. We sought to examine the effect of the timing of measurement on the relationship between BP and outcome.

Methods: Data from 1722 patients in hyperacute trials from the VISTA collaboration were analysed. BP at enrolment and after 1, 2, 16, 24, 48 and 72 h were related to early (NIH, divided at the median score) and late (modified Rankin scale, poor 3–6)) outcome. Logistic regression models, with adjustment for confounding variables, were used to calculate odds ratios (OR) and 95% confidence intervals (CI) per 10 mm Hg change in BP.

Results: Mean time to enrolment was 3.7 hours (range 1.0–7.9). Poor early and late outcome were significantly associated with high SBP at all the measured time-points. Point estimates were highest at 16 h or after. Change in SBP over the first 16 h was significantly associated with poor early and late outcome (poor early outcome, 1.08, 95% CI 1.01–1.16; poor late outcome OR 1.10, 95% CI 1.03–1.18, $P = 0.005$), i.e. larger falls in SBP were associated with a better outcome.

Conclusions: Hyperacute high BP is associated with poor outcome after stroke. Sustained hypertension one day post onset is most predictive of poor early and late outcome, reflecting patients in whom high BP fails to fall in the first hours after stroke.

5.2. Assessment of telmisartan in secondary prevention in 20 333 patients with recent ischaemic stroke: the PROFESS trial

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Background: Individuals with ischaemic stroke have a high risk of recurrence and death. Lowering BP with diuretics and/or angiotensin converting enzyme inhibitors (ACE-I, but not β -receptor antagonists) reduces the risk of recurrence after stroke. The PROFESS ('Prevention Regimen for Effectively Avoiding Second Strokes') trial compared telmisartan (ARA) with placebo (and combined aspirin and extended-release dipyridamole with clopidogrel, factorial design) in the reduction of recurrent stroke.

Methods: PROFESS was a multicentre, randomised, double-blind trial involving 695 sites from 35 countries. Patients ≥ 50 years presenting with an

ischaemic stroke < 120 days who were stable were randomised. The primary outcome for the trial was recurrent stroke (time-to-event/superiority analysis). Key secondary outcomes included the composite of stroke, myocardial infarction or vascular death, new congestive heart failure, new diabetes, and death. Safety was evaluated as the risk of major hemorrhagic events.

Results: 20 333 patients were randomised with mean age 66 (9) years, 36% female. The median time from qualifying event to randomisation was 15 days with 40% of patients randomised within 10 days. Index strokes included: large-vessel disease

28.5%; small-vessel disease 52.1%; cardioembolism 1.8%; other aetiology 2.0%; undetermined etiology 15.5% (TOAST criteria). The mean baseline BP was 144/84 mm Hg. Baseline treatment included: ACE-I 36.8%; CCB 24.2%; β -RA 20.7%; statin 47.2%.

Conclusions: PROFESS is the largest secondary stroke prevention trial to date and has assessed the safety and efficacy of telmisartan (as well as two antiplatelet regimens) in the secondary prevention of stroke. Key results will be presented.

5.3. Comparison of effectiveness and safety of fixed-dose combinations of antihypertensive agents with the free-drug combination of its components when given separately in hypertensive patients: a meta-analysis of 32 134 patients

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Combination of 2 or more antihypertensive agents is required to achieve blood pressure (BP) control in the majority of patients, thus its increasing use in routine clinical practice. However, it is not clear whether the use of fixed-dose combinations (FDC) of 2 or more agents in a single tablet will provide benefits beyond that of the free-drug combination of its components when given separately.

Objectives: To assess compliance, adherence, BP control and safety associated with the use of a FDC of antihypertensive agents in comparison to use of its free components when given separately in the treatment of hypertension.

Methods: We searched Pub med, Web of Science and the Cochrane Controlled Trial Registry using keywords such as FDC, combination therapy, hypertension, antihypertensive agents, clinical trial etc. Reference lists of the identified articles, reviews and commentaries were hand searched for further relevant articles. Studies, published in the English language, were included if they compared the use of FDC of antihypertensive agents with free drug regimens as 2 separate agents, and reported extractable data pertaining to 1 or more outcomes of interest: compliance/adherence, blood

pressure efficacy, adverse effects and cost effectiveness.

Results: Out of the 478 articles, only 15 studies ($n = 32\,134$) met with our inclusion criteria. Use of a FDC, in comparison to its free-drug combination, was associated with a significant improvement in compliance by 18% (odds ratio [OR] 0.82; 95% CI 0.70–0.97, $n = 17\,910$), systolic and/or diastolic BP normalisation rates by 34% (OR 0.66; 95% CI 0.43–0.99, $n = 566$), and adverse events by 22% (OR 0.78, 95% CI 0.63–0.96, $n = 1648$). There was no evidence of heterogeneity in any of these analyses. The evidence regarding lowering of BP levels on FDC regimen was equivocal, with an insignificant reduction of 2.6 (95% CI –8.5–3.3) and 1.3 (95% CI –5.4–2.7) mm Hg in SBP and DBP respectively, associated with use of FDC as compared to its free-drug combination ($n = 1441$). There was some evidence of heterogeneity in this analysis.

Conclusions: Use of FDC's in the hypertensive patients is associated with a significant improvement in compliance and BP control, and a reduction in reported adverse effects. However, whether these benefits subsequently translate to reduction in cardiovascular outcomes is unknown, but, a likely consequence.

5.4. Ethnic differences in blood pressure response to atenolol and amlodipine monotherapy and to add on diuretic and ACE inhibitor dual therapy in hypertensive patients from UK in ASCOT-BPLA

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Background: Some studies suggest that BP-lowering effects of commonly-used antihypertensive drugs differ among ethnic groups. However, differences in the response to 2nd-line therapy have not been studied.

Methods: Valid BP recordings in patients of European ($n = 4368$), African (203) and South-Asian (132) origin on uninterrupted unchanged monotherapy (atenolol or amlodipine) and/or on second-line therapy

(added thiazide or perindopril) were analysed. Interaction between ethnicity and both first and second line therapies was assessed in a regression model (Table).

Results: Ethnic groups responded differentially to monotherapy and to subsequent addition of thiazide and perindopril (Table).

Among those who received atenolol monotherapy, patients of African origin were significantly less responsive. In contrast, on amlodipine monotherapy BP response among the three ethnic groups did not differ significantly.

On adding a diuretic to atenolol, BP lowering was similar among the three ethnic groups. However, on addition of perindopril to amlodipine, BP response differed significantly ($P=0.004$): compared to Europeans, patients of African origin had a lesser, albeit insignificant, response to perindopril and south Asians had a significantly greater BP lowering response (-6.2 mmHg).

Conclusion: Significant differences in BP response among ethnic groups exist on both first- and second-line therapy. These findings should inform guidelines and practice.

SBP difference (95% CI) on mono and dual therapy

	Europeans	Africans	South-Asians	Log likelihood ratio test for interaction between treatment and ethnicity
<i>Monotherapy*</i> (N = 4683)	N = 4348	N = 203	N = 132	P-value
Atenolol (N = 2257)	Referent	+1.7 (-1.1, 4.6)	3.3 (-7.1, 0.5)	0.05
Amlodipine (N = 2426)	-8.9 (-9.7, -8.0)	-11.7 (-14.6, -8.8)	-9.8 (-13.2, -6.5)	
<i>Dual-therapy*</i> (N = 2794)	N = 2583	N = 129	N = 82	P-value
Diuretic added to atenolol (N = 1424)	Referent	-1.7 (-4.7, 1.2)	+2.8 (-1.1, 6.8)	0.004
Perindopril added to amlodipine (N = 1370)	-1.7 (-2.8, -0.7)	+0.8 (-2.5, 4.2)	-6.2 (-10.2, -2.2)	

*Adjusted for SBP at onset of mono/dual therapy, BMI, age, sex, socio-economic status, duration of therapy, number of risk factors, previous antihypertensive drugs, H/O diabetes etc.

5.5. Central blood pressure: variability within categories of brachial pressure and the impact of cardiovascular risk factors: the Anglo-Cardiff collaborative trial

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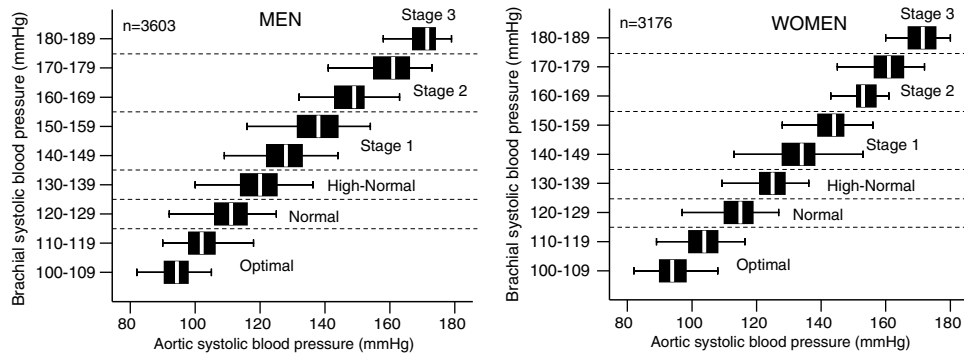
Pulse pressure varies throughout the arterial tree due to pressure amplification, meaning that peripheral pressure does not accurately represent central pressure. However, the degree of variation in central pressure for given levels of brachial pressure and the impact of cardiovascular risk factors on pressure amplification is unclear.

Seated peripheral (brachial) and central (aortic) blood pressures were assessed and pressure amplification (brachial PP:Central PP) calculated in 11 340 individuals, aged between 18–101 years. The analyses included healthy individuals (no cardiovascular risk factors, medication or disease), diabetics, patients with cardiovascular disease, and in individuals with only one of the following—hypertension, hypercholesterolaemia, or smoking ($n=10\,613$).

Stratifying individuals by brachial pressure revealed considerable overlap in aortic pressure, such that over 70% of individuals with high-normal brachial

pressure had similar aortic pressures to those with Stage 1 hypertension (Figure). In addition, although ageing was associated with a smaller difference between brachial and aortic blood pressure, there was still an average (\pm s.d.) difference between brachial and aortic systolic pressure of 11 ± 4 and 8 ± 3 mmHg, for males and females aged over 80 years, respectively. Finally, compared with healthy individuals, pressure amplification was significantly reduced (i.e. central systolic pressure was relatively higher) in individuals with risk factors or disease ($P<0.01$ for all comparisons).

These data demonstrate that for a given brachial pressure, central pressure varies considerably and central pressure cannot be reliably inferred from measurements of peripheral pressure. Cardiovascular risk factors also affect pressure amplification. Assessment of central pressure may improve risk management.



5.6. Blood pressure analyses from 25 595 patients (from 25 620 randomised) during the ONTARGET trial: reflections on current guidelines

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ONTARGET randomized 25 620 patients (mean age 66 years) who were at high risk of cardiovascular events, between Telmisartan, Ramipril, or both. Outcomes were similar in all 3 arms, so we related outcomes, in 25 595 patients with available data to in trial SBP partitioned by baseline SBP quartiles (Q) It can be seen from the Table that cerebrovascular outcomes were better related to baseline BP than were other outcomes such as MI or CHF or CV mortality (all adjusted for several covariates). During follow up (median 56 months) there were 1145 strokes (not including TIA), and 1290

myocardial infarctions (MI)—fatal + non-fatal first events.

These data from high risk but generally well treated pts suggest that in this elderly population the benefits from lower SBP in high normal or stage 1 hypertension (as recommended in current guidelines) are mainly from reduction of stroke or TIA. For many other outcomes there seems little further benefit. Future trials in subjects with SBP 140–160 mmHg should aim to clarify the benefits for major events of BP lowering in this range.

Quartiles of baseline SBP	Overall (N = 25595*)				Q2 vs Q1: HR (95% CI)	Q2 vs Q1: P-value	Q3 vs Q2: HR (95% CI)	Q3 vs Q2: P-value	Q4 vs Q3: HR (95% CI)	Q4 vs Q3: P-value
	Q1: ≤130	Q2: >130 and ≤142	Q3: >142 and ≤154	Q4: >154						
Number randomized	6867	6320	6200	6208						
Mean (s.d.)	120.38 (8.47)	137.06 (3.35)	148.50 (3.32)	163.71 (9.64)						
SBP, mmHg										
Baseline % probability (95% CI) of primary outcome over 4.5 year	13.97 (13.5, 14.4)	14.34 (13.9, 14.8)	14.98 (14.5, 15.4)	15.92 (15.5, 16.4)		0.2535		0.0503		0.0046
CV death/MI/stroke/CHF Hosp	1070 (15.58%)	944 (14.94%)	1025 (16.53%)	1175 (18.93%)	0.92 (0.84–1.01)	0.0663	1.07 (0.98–1.17)	0.1261	1.09 (1.00–1.18)	0.0500
CV death	468 (6.82%)	430 (6.80%)	426 (6.87%)	492 (7.93%)	0.97 (0.85–1.11)	0.6891	0.95 (0.83–1.09)	0.4473	1.06 (0.93–1.20)	0.4118
MI	361 (5.26%)	286 (4.53%)	289 (4.66%)	354 (5.70%)	0.87 (0.74–1.01)	0.0702	1.01 (0.86–1.19)	0.9198	1.19 (1.01–1.39)	0.0321
Stroke	223 (3.25%)	245 (3.88%)	303 (4.89%)	374 (6.02%)	1.10 (0.92–1.32)	0.2952	1.19 (1.01–1.41)	0.0388	1.16 (1.00–1.35)	0.0537
TIA	164 (2.39%)	141 (2.23%)	150 (2.42%)	196 (3.16%)	0.86 (0.69–1.08)	0.2044	1.01 (0.80–1.27)	0.9497	1.20 (0.97–1.48)	0.0979
Stroke or TIA	363 (5.29%)	365 (5.78%)	425 (6.85%)	530 (8.54%)	1.00 (0.87–1.16)	0.9777	1.11 (0.97–1.28)	0.1382	1.16 (1.02–1.32)	0.0197
CHF Hosp	302 (4.40%)	240 (3.80%)	260 (4.19%)	277 (4.46%)	0.84 (0.71–1.00)	0.0525	1.04 (0.87–1.24)	0.6776	0.97 (0.82–1.15)	0.7192
Renal	132 (1.92%)	138 (2.18%)	152 (2.45%)	203 (3.27%)	1.05 (0.83–1.34)	0.6658	1.06 (0.84–1.34)	0.6000	1.22 (0.98–1.50)	0.0697
NON-CV death	290 (4.22%)	283 (4.48%)	330 (5.32%)	343 (5.53%)	1.01 (0.85–1.19)	0.9277	1.15 (0.98–1.35)	0.0905	0.94 (0.81–1.10)	0.4475
All death	758 (11.04%)	713 (11.28%)	756 (12.19%)	835 (13.45%)	0.99 (0.89–1.10)	0.8461	1.02 (0.92–1.13)	0.6586	1.01 (0.91–1.11)	0.9183

*Excluded 25 patients missing baseline SBP.

**Adjusted by covariates with P≤0.1.

Poster abstracts

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PA.01. Effect of modest salt reduction on blood pressure in white, black and Asian individuals with untreated mildly raised blood pressure—a randomised double-blind placebo-controlled crossover trial

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Background: Randomised trials have shown that salt reduction lowers blood pressure (BP). However, most previous trials were in whites, fewer in blacks and none in Asians.

Methods: 71 whites, 69 blacks and 29 Asians with untreated mildly raised BP completed a randomised double-blind crossover trial of salt restriction with Slow-Sodium (Slow-Na) or placebo, each for 6 weeks.

Results: Mean \pm s.d.

in 24-h urinary sodium) of 3.5, 2.7 and 4.0 gram/day in whites, blacks and Asians respectively.

Conclusions: Our study demonstrates that a reduction in salt intake from an average of 9.7 to 6.5 gram/day, which is almost identical to the current public health recommendations in the UK, causes significant and important falls in BP in white, black and Asian individuals with mildly raised BP. The results in Asian participants are of particular interest, as this is the first well-controlled modest salt reduction

	Whites		Blacks		Asians	
Age (years)	52 \pm 12		50 \pm 9		47 \pm 10	
Baseline BP (mm Hg)	146 \pm 12/90 \pm 8		149 \pm 13/90 \pm 8		142 \pm 13/92 \pm 10	
<i>Randomised crossover</i>	<i>Slow-Na</i>	<i>Placebo</i>	<i>Slow-Na</i>	<i>Placebo</i>	<i>Slow-Na</i>	<i>Placebo</i>
Salt intake (gram/day)	9.6 \pm 3.2	6.1 \pm 3.2***	9.5 \pm 3.5	6.8 \pm 2.6***	10.4 \pm 3.8	6.4 \pm 2.9***
Systolic BP (mm Hg)	145 \pm 12	141 \pm 12**	149 \pm 13	144 \pm 12***	140 \pm 12	134 \pm 13**
Diastolic BP (mm Hg)	90 \pm 7	88 \pm 8**	91 \pm 9	89 \pm 9**	91 \pm 8	89 \pm 9*

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, Slow-Na vs Placebo.

From Slow-Na to placebo, there was a significant fall in BP of 4.6/2.2, 4.8/2.2, and 5.4/2.2 mm Hg with a reduction in salt intake (calculated from the change

trial in this group and demonstrates a clear benefit of salt reduction.

PA.02. Early metabolic changes with thiazide or beta blocker therapy for essential hypertension

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A minority of patients on long term treatment with thiazides or beta blockers develop diabetes, and guidelines suggest the risk from such drugs is additive. Our aims were to estimate [i] whether an

increase in 2-h glucose in the oral glucose tolerance test (OGTT) is detectable after 4 weeks of high-dose treatment, and [ii] whether any change is amplified by combining the classes.

42 patients with essential hypertension, aged 35–74 (median 59), 30 male, 12 female, participated in a

(4 vs 0 weeks), 0.013 (BFZ vs placebo). There was no change in 30-min insulin.

Weeks	Placebo		BFZ		Atenolol		Combination	
	0	4	0	4	0	4	0	4
Glucose	5.34	5.36	5.34	5.59	5.23	5.38	5.38	5.60
Fasting	(0.67)	(0.66)	(0.51)	(0.78)	(1.14)	(0.77)	(0.55)	(0.61)
2-h	7.65	7.87	7.49	8.31**	7.74	7.44	7.61	7.81
	(2.58)	(2.66)	(2.20)	(2.43)	(2.54)	(2.17)	(2.25)	(2.20)
BP	139.3	137.8	138.4	129.3	139.4	128.1	140.6	120.3
	(13.33)/86.1	(12.94)/85.1	(11.25)/86.4	(10.38)/81.0	(13.10)/85.6	(16.19)/77.2	(12.5)/86.7	(10.28)/74.3
	(10.54)	(9.24)	(9.77)	(6.52)	(8.86)	(8.13)	(9.83)	(8.68)
K ⁺	4.13	4.08	4.15	3.59	4.12	4.20	4.13	3.85
	(0.30)	(0.30)	(0.27)	(0.38)	(0.24)	(0.31)	(0.29)	(0.38)

double-blind, cross-over study. They received, in random order, 4 weeks of once-daily treatment with each of bendroflumethiazide (BFZ) 5–10 mg, atenolol 50–100 mg, combination (BFZ 2.5–5 mg + atenolol 25–50 mg) and placebo. Each active treatment was force-titrated at 2 weeks and separated by a 4-week placebo washout. At each visit, we measured BP and plasma electrolytes, and a 75 g OGTT was performed. Data (shown as mean (s.d.)) was analysed by repeated measures, within and between drugs. Only BFZ increased the 2-h glucose, by 11%, $P=0.006$

Short-term dosing with high-dose thiazide allows significant impairment of glucose tolerance to be detected after just 4 weeks. This should help investigation of the pathogenesis of thiazide-induced diabetes. Unlike the clearly synergistic effect of combination on BP, there was no change in the OGTT, due perhaps to the protective effect of better BP control. The interesting question now is whether, using this methodology, we can show K-sparing diuretics to be superior to thiazides in their influence on glucose tolerance.

PA.03. Gender differences in the cross-sectional relationships between sleep duration, interleukin-6 and high-sensitivity C-reactive protein: the Whitehall II study

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Background: Emerging evidence suggests that sleep disturbances play a role in the morbidity of chronic conditions, including the development of hypertension and cardiovascular disease for which an underlying inflammatory component has been proposed.

Methods and results: The relationships between sleep duration and two markers of inflammation, interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) were examined in white-collar British civil servants (all white individuals) from the Whitehall II study ($n=4642$ for IL-6; $n=4677$ for hs-CRP).

Following multiple adjustments for demographic characteristics and cardiovascular risk factors including blood pressure there were no overall linear or non-linear trends between sleep duration and IL-6. However, in women but not men (interaction

$P<0.05$), levels of IL-6 were consistently lower in individuals who slept 8 h (11% [95% CI 4–17]) as compared to 7 h ($P=0.05$). With hs-CRP there was no association between hs-CRP and sleep duration in men. However, there was a significant non-linear U-shaped association in women, the level of hs-CRP being significantly higher in short sleepers after multiple adjustments ($P=0.04$) (interaction $P<0.05$).

Conclusions: No significant variation in inflammatory markers with sleep duration was observed in men. By contrast, both IL-6 and hs-CRP levels vary with sleep duration in women. The observed pattern of variation was different according to the inflammatory marker observed. Further longitudinal studies are required to see if there is a temporal relationship between short sleep and markers of inflammation to support causality.

PB.01. Effects of essential hypertension on short latency somatosensory evoked potentials: evidence for peripheral neuropathy in hypertension

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Reduced tactile sensibility in hypertension may be explained by subclinical axonal neuropathy of sensory afferents. The present study investigated the association between hypertension and function of the ascending somatosensory pathway. N9 and N20 short latency somatosensory evoked potentials (sSEPs) were assessed in 14 unmedicated essential hypertensives and 22 normotensives. The sSEPs were elicited by 100 μ s supramaximal electrocutaneous stimulation of the median nerve at the wrist for 2000 trials.

Mean daytime ambulatory blood pressures were higher ($P < 0.001$) in hypertensives (148/98 mm Hg) compared to normotensives (119/78 mm Hg). N9 amplitudes were significantly reduced ($P < 0.01$) in hypertensives ($M = 3.6 \mu$ V) compared to normotensives ($M = 5.7 \mu$ V). These effects survived adjustment for age and stimulation-to-recording distance. N9 amplitudes were inversely associated with ambulatory systolic ($P < 0.01$) and diastolic

($P < 0.05$) blood pressure. In contrast, N20 amplitudes were not different between hypertensives ($M = 4.4 \mu$ V) and normotensives ($M = 3.9 \mu$ V). Further, sSEP latencies were unaffected by blood pressure status.

As N9 amplitudes, generated by peripheral sensory nerve fibres at the brachial plexus, were 37% smaller in hypertensives than normotensives these data suggest that hypertension affects the peripheral nervous system by reducing the number of active sensory nerve fibres without affecting myelination. N20 amplitudes, generated in primary somatosensory cortex, were unaffected by blood pressure levels suggesting that hypertension does not affect the afferent somatosensory pathway within the central nervous system. These data provide further evidence that hypertensives may suffer from mild subclinical peripheral neuropathy in sensory afferents.

Research supported by the British Heart Foundation (FS/03/128).

PB.02. Left ventricular hypertrophy in 'normotensive' individuals: would further reduction in blood pressure enhance regression of LVH?

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Background: Patients with normal blood pressure (normotensives) and left ventricular hypertrophy (LVH) are common. It is unknown whether extra BP reduction in them would regress their LVH.

Objective: The aim of the study was to assess whether lowering systolic blood pressure already in the normal range by approximately 10 mm Hg would lead to a reduction in LVH.

Methodology: Fifty-one normotensive subjects with echocardiographic LVH were randomly assigned to an active treatment arm (extra antihypertensive medication); or placebo in a ratio of 2:1. Cardiac magnetic resonance imaging (CMR) was used to establish changes in left ventricular mass index (LVMI) over the 12 months' study period. Thirty-five subjects completed the study (active 23; placebo 12).

Results: Average baseline systolic blood pressure was 122.10 mm Hg in the active group and 123.83 mm Hg in the placebo group ($P = 0.646$). The mean baseline CMR LVMI was 59.16 g/m² in the placebo group and 65.88 g/m² in the active group ($P = 0.114$).

The mean difference between baseline and end of study blood pressure was -9.33 mm Hg in the active group and -0.08 mm Hg in the placebo group ($P = 0.007$). This is a much greater BP fall than, for example, the HOT study.

The mean change in CMR LVMI was -4.68 g/m² in the active group and +1.97 g/m² in the placebo group ($P = 0.014$).

Conclusion: It is possible to cause LVH regression if BP is reduced further, even when baseline BP begins below target BP. This may translate into a reduction in cardiovascular events in those with normotensive LVH.

PB.03. Dose-response relationship between alcohol consumption, arterial and myocardial stiffening and left ventricular hypertrophy

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While moderate alcohol consumption is associated with reduced coronary artery disease, high intake may have adverse cardiovascular effects.

We examined the relationship between chronic alcohol intake, arterial stiffness and cardiac structure and function, in a cross-sectional design, in untreated subjects referred for assessment of hypertension.

Two hundred consecutive subjects [aged 46 ± 2 , mean \pm s.e.m.; 50% male] M-Mode and 2-D Echocardiography to assess left ventricular (LV) size and systolic function and Tissue Doppler Imaging (TDI) to measure E'/A' , an index of Left ventricular (LV) diastolic function. Arterial parameters included brachial blood pressure (BP), pulse wave velocity (PWV, Complior) and augmentation index (Aix, SphygmoCor). Subjects were categorised into non-drinkers, moderate drinkers (males; ≤ 21 units/week, females; ≤ 14 units/week) and heavy drinkers (males; ≥ 21 units/week, females; ≥ 14 units/week).

There was a dose response relationship between alcohol intake and aortic systolic ($P=0.02$) and diastolic BP ($P=0.003$), Aix ($P=0.01$), PWV ($P=0.03$) and indices of LV diastolic function; E'/A' ($P=0.002$) in males only. In females, alcohol intake was related in a dose-response fashion with LV septal ($P=0.03$) and posterior wall thickness ($P=0.05$), LV relative wall thickness ($P=0.05$) and LV mass index ($P=0.04$) with no relationship with LV diastolic function or arterial stiffness. Alcohol intake was significantly associated with LV mass index ($r=0.23$, $P<0.01$), midwall fractional shortening ($r=-0.22$, $P<0.001$), left atrial size ($r=0.17$, $P<0.05$), aortic root size ($r=0.23$, $P<0.001$), $E'(r=-0.16$, $P<0.05$) and ejection fraction ($r=-0.17$, $P<0.01$).

High alcohol intake causes significant arterial and ventricular stiffening and an enlarged heart; all three factors associated with poor cardiovascular outcome in hypertensive populations.

PB.04. Aspirin resistance in patients with acute ischaemic stroke

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Introduction: Aspirin is the most commonly used anti-platelet drug in the secondary prevention of ischaemic stroke. Biochemical aspirin resistance may be defined as failure of aspirin to inhibit platelet thromboxane A_2 production, whereas clinical aspirin resistance is diagnosed following the occurrence of an atherothrombotic event in patients receiving a therapeutic dose of aspirin. We determined the prevalence and nature of aspirin resistance in 44 adults admitted with a diagnosis of suspected ischaemic stroke.

Methods: On admission to the stroke unit, platelet function was measured by optical aggregometry in platelet-rich plasma, after stimulation with arachidonic acid (AA), ADP and collagen. Urinary 11-dehydro-thromboxane B2 metabolite was measured by immunoassay. Platelet function was tested again 24 h after administration of 150 mg aspirin on the ward.

Results: Residual AA-stimulated platelet aggregation ($\geq 10\%$ aggregation) indicating a poor response to aspirin was found in 18 patients (41%). Of these, 10 remained poorly responsive after aspirin dosing in hospital, suggesting causes other than poor compliance in 23% of patients. *In vitro*, platelet aggregation could be inhibited further by addition of acetylsalicylic acid in only 3 of these subjects, indicating true biochemical aspirin resistance in 16%. Urinary 11-dehydro-TxB2 was not significantly different between good and poor responders to aspirin (median (iqr) 77.0 (38.9–156.8) vs 86.2 (50.0–261.2) ng/mmol of creatinine) and therefore may not be a good marker of impaired platelet response to aspirin.

Conclusions: These data suggest that biochemical aspirin resistance and poor compliance with therapy contribute to failure of aspirin in a significant proportion of patients with acute stroke.

PB.05. Superoxide release by whole blood and mononuclear cells as markers of oxidative stress in patients with coronary artery disease

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Reactive oxygen species are a key factor in the development of coronary artery disease (CAD). Superoxide anion (SO) release by mononuclear cells (MC) and whole blood (WB) contributes significantly to vascular and systemic oxidative stress in CAD.

We analysed SO levels in WB and MC in 50 patients undergoing elective coronary artery bypass graft (CABG) surgery (aged 68 ± 2 years) and 14 controls (aged 69 ± 2 years). Furthermore, we analysed 24 patients post-CABG surgery, before and after a 3-month cardiac rehabilitation programme. SO was detected by electron paramagnetic resonance spectroscopy. MC were analysed in basal conditions and after stimulation with PMA to evaluate maximum SO release.

Both basal SO release (48 ± 4 vs 31 ± 5 AU/min, $P=0.012$) and maximum SO release (505 ± 4 vs

187 ± 3 AU/min, $P<0.001$) by MC were higher in patients than in controls. There was a correlation between SO release from WB and MC [$R^2=0.833$, $P<0.001$]. The cardiac rehabilitation programme did not modify blood pressure, body mass index or white cell count but reduced MC maximum SO release (752 ± 0 vs 526 ± 7 AU/min, $P=0.029$) and whole blood SO generation (44 ± 5 vs $31 \pm 4 \times 10^3$ AU/min, $P=0.003$), not modifying MC basal SO generation.

We identified, for the first time, the correlation between systemic SO levels and MC SO release. Our results indicate that the cardiac rehabilitation programme after CABG surgery improves the oxidative stress status. We propose that SO determination in MC and WB may be a tool for assessing oxidative stress in patients with CAD.

PC.01. What do GPs do with the results of ambulatory blood pressure monitoring?

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Methods: We retrospectively identified 400 untreated, newly diagnosed, hypertensive patients (awake average $\geq 145/95$ mm Hg) from our direct access ABPM database, divided equally pre and post GMS contract implementation (contract target $\leq 150/90$ mm Hg) and recorded subsequent management in primary care.

Results: After 12 months 75% of patients only were on antihypertensive therapy with no difference pre and post contract. Of those treated 60% achieved a BP $\leq 150/90$ mm Hg pre contract (66% post contract) with only 17% reaching a 'guideline' target of $<140/90$ mm Hg pre contract (39% post contract)— $P<0.001$. Most treated patients (56% pre and 60% post contract) remained on a single antihypertensive agent. Office BP fall at one year was greater post contract— $6/4$ vs $12/6$ mm Hg, $P<0.001$.

QOF data for the practices involved in the study quote BP $\leq 150/90$ mm Hg in 78% of patients i.e., a 12% discrepancy.

Conclusion: Despite confirmation of hypertension by ABPM 25% of patients were left untreated. The rate of blood pressure control in those commenced on therapy was substantially less than the average GP population with little evidence of treatment escalation and only a minor impact of incentivisation. It seems likely that patients for whom GPs request an ABPM are atypical of their general hypertensive population and may be less inclined to accept therapy. It is arguable however whether GPs use ABPM appropriately given their apparent rejection of the results.

PC.02. A novel method to derive central aortic systolic pressure (CASP) from the radial artery pressure waveform: validation with data from the CAFE study

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Objective: Central systolic pressure (C_SP) may be estimated directly from the radial artery pressure waveform (RAPWF) by identifying an inflection

point on the systolic down-stroke. Identification of this inflection point can however, be problematic. This study describes and evaluates a novel method

for identifying C_SP from RAPWFs which is independent of the need to identify an inflection point or the use of a generalised transfer function (GTF).

Methods: We used an n -point forward moving average method ($n=1/4$ tonometer sampling rate) to derive the maximum pressure value from RAPWF data arrays, which we hypothesised would equate to C_SP and have termed CASP. We used 5366 RAPWFs obtained using applanation tonometry from the Leicester cohort of the CAFE study to compare calculated values of CASP with values for C_SP derived by conventional RAPWF GTF transformation (SphygmoCor[®]).

Results: CASP showed an excellent correlation with C_SP ($r^2=0.993$). Bland Altman analysis showed close agreement with minimal scatter (mean difference [CASP—C_SP] -0.3 , s.d. 1.0 mm Hg). This tight agreement was maintained even after stratifying data by treatment and modulation of heart rate: Amlodipine-based treatment: C_SP: 121.0 ± 0.3 mm Hg vs CASP: 121.5 ± 0.3 mm Hg; Atenolol-based treatment: C_SP: 125.1 ± 0.4 mm Hg vs CASP: 125.2 ± 0.4 mm Hg, $P=NS$.

Conclusions: We describe a novel, robust and accurate method for deriving C_SP from the RAPWF which does not use a GTF or the identification of an inflection point on the RAPWF.

PC.03. Evidence of a ‘common’ reservoir pressure transmitted along the length of the aorta which is the predominate determinate of arterial pressure in humans

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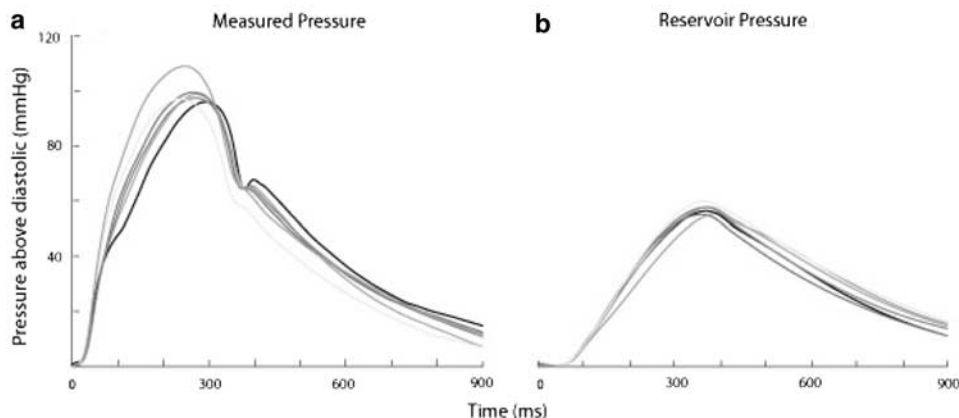
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Background: Despite the large variation in pulse pressure waveform throughout the aorta, the diastolic decay of the pressure waveform is almost identical. We hypothesise that this is because there is a common reservoir pressure along the entire aorta, principally determined by the highly elastic proximal aortic root. We apply a new technique to calculate this reservoir pressure along the aorta to test this hypothesis.

Method and Results: Using intra-arterial wires, pressure and Doppler velocity were measured at 10 cm intervals along the aorta in 16 patients (aged 55 ± 11 years). Pressure was separated into reservoir and wave components using the new wave-reservoir technique. In all patients, the intra-subject reservoir pressure waveforms were almost identical (mean correlation coefficient 0.99 ± 0.01) regardless

of the marked changes in the measured pressure waveform (systolic pressure $P=0.020$ and pulse pressure $P=0.001$). Significant variation in reservoir pressure was seen between subjects (peak reservoir = $63.4-21.4$ mm Hg). The reservoir pressure was the predominate determinant of the pressure waveform and accounted for $67.0 \pm 8.8\%$ of the total integrated pulse pressure across all aortic sites.

Conclusions: The aortic pressure waveform is predominately determined by the reservoir pressure. This reservoir pressure is similar along the length of the aorta despite marked changes in the shape of the measured pressure waveform. Manipulation of the arterial reservoir, rather than wave-reflection sites may be more important in regulation of blood pressure control.



PC.04. Calibration and evaluation of self-measurement BP devices following extensive hospital use

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Objective: The majority of automated BP devices recommended for clinical use according to a recognised protocol are designed for home use. Robust hospital use of these devices is thought to be restricted by a limited sensor lifespan. This is the first study to assess the influence of extensive/robust hospital use on the accuracy and calibration of home use devices.

Methods: Two Microlife devices (ProM and 3AC1-1) with inflation and error counters were distributed equally with two 'AND' devices (UA-774 and UA-767+) to clinical areas at three large teaching hospitals in London (UK). Leak and calibration tests were performed regularly over one year, on the 103 devices using the Druck DPI800 as reference standard. One device with >10 000 inflations was revalidated according to the BHS protocol.

Results: All devices remained within the calibration requirement i.e., ≤ 3 mm Hg from the reference standard, although there was a significant increase in calibration error ($P < 0.05$). There was also a significant increase in leak rate, although insufficient to affect device accuracy. Up to a third of inflations in some devices resulted in error readings. On re-evaluation, the Microlife 3AC1-1 achieved an A/A grade even after 10 000 inflations.

Conclusion: Self measurement devices provide an extensive choice of accurate and far cheaper devices for hospital based practice. An increased leak rate and calibration error over time may warrant frequent accuracy and calibration checks, but this does not preclude them from being used extensively and accuracy is retained after 10 000 inflations.

PC.05. Doppler waveform analysis using wavelet transform detects ocular microvascular abnormalities in impaired glucose tolerance

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Impaired glucose tolerance (IGT) precedes diabetes and is associated with increased cardiovascular risk. Structural and functional abnormalities in the microvasculature often predate the earliest stages of the cardiovascular disease process. The ocular microcirculation in particular represents a preferential target for many disease processes. We aim to identify abnormalities in ocular blood flow using a novel technique, which may represent microvascular dysfunction in impaired glucose tolerance.

Methods: Doppler ultrasound flow velocity recordings of the central retinal artery (CRA) and ophthalmic artery (OA) were carried out in 40 IGT patients and compared with 25 controls. The wavelet transform technique (1) was employed to analyse the waveforms in the frequency domain and the resistive index (RI) was calculated from peak systolic and end-diastolic velocities.

Results: In the CRA there was a significantly different mean spectral amplitude content between the two groups in frequency band 4 (IGT mean 6.94 ± 1.23 versus control mean 6.10 ± 1.37 ; $P < 0.05$). This difference was also apparent in frequency band 4 of the OA (IGT mean 6.44 ± 1.39 versus control mean 5.71 ± 1.21 ; $P < 0.05$). RI was not significantly different between the two groups in either artery.

Conclusions: In patients who have not yet developed diabetes, there are characteristic abnormalities in ocular blood flow which are detected using wavelet transform, but not identified using the more traditional RI. This may be a useful way to predict cardiovascular disease in this patient group.

1. Ubeyli ED, Guler I. Wavelet-based neural network analysis of internal carotid arterial Doppler signals. *J Med Syst* 2006; **30**: 221–229

PC.06. Systolic blood pressure and age and not the anti-hypertensive agent determine improvement in diastolic function in early hypertension

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Diastolic dysfunction is common in early hypertension but there remains uncertainty as to whether the

choice of antihypertensive therapy, particularly angiotensin blockade confers a therapeutic advantage.

We studied 40 untreated hypertensive subjects [age 52 ± 1.4 years, mean \pm s.e.m.] diastolic dysfunction based on Canadian Consensus Guidelines. The patients received in random fashion either bendroflumethiazide 1.25 mg for first month then 2.5 mg for following two months or candesartan 8 mg for one and 16 mg for following two months, in a single-blind parallel group study. LV structure and function was assessed by 2D, M Mode, conventional echocardiography and tissue Doppler imaging [TDI]. Treatment reduced BP significantly at three months (systolic 168 ± 2 to 143 ± 2 mm Hg and diastolic 97 ± 1 to 86 ± 1 mm Hg, $P < 0.0001$) with no difference between drugs. TDI E' increased significantly at one and three months (7.5 ± 0.14 to 10 ± 0.35 cm/s,

$P < 0.001$) with no difference observed between drugs. The improvement in TDI E' was independent of left ventricular mass index (LVMI) regression but was significantly related to the fall in systolic BP [$r = 0.051$, $P < 0.001$]. Regression in LVMI over time ($P < 0.0001$) was independent of change in BP and type of antihypertensive drug used. In stepwise multivariate regression analysis reduction in systolic BP and age were the only significant and independent determinants of improvement in TDI E' ($R^2 = 0.42$, $P < 0.0001$).

In patients with early hypertension and diastolic dysfunction, systolic BP reduction and age, but not type of antihypertensive, are the independent determinants of improvement in diastolic function.

PD.01. Double congenic strain confirms interaction between blood pressure loci in the stroke-prone spontaneously hypertensive rat

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Objective: We previously identified blood pressure quantitative trait loci (QTL) mapping to rat chromosomes 2 and 3 in an F2 cross derived from SHRSP and WKY strains. We also identified significant interaction between loci on chromosomes 2 and 3 using Pseudomarker (v0.9) statistical framework. The aim of this study was to generate a double congenic strain to confirm chromosome 3 QTL and investigate the interaction between loci on the implicated chromosomes.

Methods: A marker-assisted breeding strategy was used to generate SP.WKYGla2a/3a double congenic strain (D2Rat13-D2Rat157, D3Mgh16-D3Wox28), using SHRSP as recipient and WKY as the donor strain. Haemodynamic measurements were carried out using radiotelemetry during baseline and salt-loaded periods. Microarray expression profiles comparing salt-loaded SHRSP and WKY kidneys were analysed by Ingenuity Pathway Analysis (IPA).

Results: Systolic blood pressure was significantly reduced in the SP.WKYGa2a/3a strain ($166.8 \pm$

4.6 mm Hg, $n = 7$) compared to SHRSP (258.1 ± 6.1 mm Hg, $n = 13$) ($P = 0.0001$, $F = 97.77$, repeated measures ANOVA). Pulse pressure was also significantly reduced compared to SHRSP (49.4 ± 1.6 vs 69.1 ± 3.1 mm Hg, $P = 0.0001$, $F = 34.17$) and achieved levels comparable to WKY (45.3 ± 1.9 mm Hg, $n = 10$). Pulse pressure diurnal variation observed in SHRSP during salt-loading was abolished in the double congenic strain (AUC; $P = 0.0001$, $F = 13.56$). IPA identified a cluster of transcription factors (PHTF1, FUBP3, PBX3, CEBPD, DNAJB6) located within the implicated congenic intervals, underlying inflammation, cellular growth, proliferation and cell death functional networks.

Conclusions: Almost complete reversal of SHRSP hypertensive haemodynamic profiles has been achieved in the SP.WKYGla2a/3a congenic strain. This strain will allow interrogation of complex gene-gene, gene-environment interactions contributing to salt-sensitive hypertension in the SHRSP.

PD.02. Metabolic phenotypes in SHRSP and chromosome 2 congenic strains

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Background: We have previously shown that 60% fructose feeding (FF) alters adiposity, lipid profiles and glucose tolerance in the stroke-prone spontaneously hypertensive rat (SHRSP), relative to the Wistar-Kyoto (WKY) strain. Rat chromosome 2 (chr2) harbours genetic loci responsible for a

number of metabolic and cardiovascular phenotypes. The aim of this study was to phenotype chr2 congenic substrains to further define these loci.

Methods: SHRSP, WKY and seven chr2 congenic strains ($n = 4-15$) received FF diet for 14 days. Fasted intraperitoneal glucose tolerance tests

(IPGTT), biochemical and histological analyses were performed.

Results: IPGTT AUC significantly increased in SHRSP versus WKY (1242 ± 45.8 vs 1059 ± 35.7 ; $P = 0.0049$). The SP.WKYGla2a 'large' congenic strain had improved IPGTT ($P = 0.091$ vs SHRSP, $N = 6-15$). Conversely, the reciprocal WKY.SPGLa2a strain had significantly increased AUC, ($P = 0.00191$ vs WKY, $N = 5-13$). Of the smaller congenics only the SP.WKYGla2f strain exhibited reduced AUC ($P = 0.043$, $N = 4-15$). Adiposity was significantly greater in FF SHRSP than WKY (24 ± 0.9 vs 19 ± 1.1 mg/g; $P = 0.0036$, $N = 13-15$). The SP.WKY-Gla2a and WKY.SPGLa2a strains had adiposity inter-

mediate to parental strains. FF SHRSP livers exhibited marked lipid deposition, consistent with fatty liver disease. Increased left ventricular mass index in SHRSPvWKY was preserved on FF diet (2.86 ± 0.04 vs 2.48 ± 0.06 mg/g; $P < 0.0001$, $N = 11-13$). In three chr2 sub-congenic strains LVMI was significantly greater than the SHRSP parental strain.

Conclusions: Specific chr2 regions may determine development of phenotypic changes occurring in FF-SHRSP. Integration of biochemical, expression profiling and congenic techniques will yield candidate genes and pathways potentially translatable into human metabolic syndrome studies.

PD.03. Disruption of glutathione and oxidative stress pathways during development of hypertension in the SHRSP

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Objective: To utilise congenic strains and microarray gene expression profiling during the development of hypertension to identify candidate genes and pathophysiological pathways underlying oxidative stress and hypertension in young SHRSP.

Methods: Renal microarray profiles were compared with Affymetrix RGU34 genome chips from 5 week old SHRSP, WKY and the SP.WKYGla2c* (2c*) congenic strain containing *Gstm1*, a previously identified positional candidate gene for hypertension. Significant differential expression was determined by Rank Products (false discovery rate (FDR) of 5%) and analysed with Ingenuity Pathway Analysis. Superoxide was measured in whole kidney homogenates and glutathione (GSH) levels measured and analysed with ANOVA or *T*-test.

Results: Renal SHRSP, 2c* and WKY expression profiles were compared identifying significantly differentially expressed genes involved in glutathione metabolism including *Gstm1* (2c* vs SHRSP,

FDR = 0.0, FC = 9.4, WKY vs SHRSP FDR = 0.0, FC = 7.5) and solute carrier 7, member12-like (*Slc7a12-like*) (2c* vs SHRSP, FDR = 0.0, FC = -2.9, WKY vs SHRSP, FDR = 0.0, FC = -2.3). Differential expression was confirmed by qRT-PCR and sequence analysis identified single nucleotide polymorphisms in the promoters. There was a significant increase in NADH stimulated superoxide levels in the SHRSP compared to 2c* and WKY (SHRSP 10.8 ± 1.3 , 2c* 8.5 ± 1.1 , WKY 8.3 ± 0.9 $\mu\text{moles}/\text{min}/\mu\text{g}$ protein $F = 6.5$, $P = 0.016$) and GSH levels were significantly increased in WKY (SHRSP 18.3 ± 3.4 , 2c* 15.4 ± 2.7 , WKY 29.1 ± 5.0 $\mu\text{moles}/\text{mg}$ protein $F = 20.9$, $P < 0.001$). At 16 week of age there was a significant increase in GSH levels only in the 2c* strain (5 week 15.4 ± 2.7 vs 16 week 20.5 ± 1.6 $P = 0.006$).

Conclusion: These findings identify significantly regulated genes and disrupted pathways affecting oxidative stress and glutathione metabolism in the SHRSP during the development of hypertension.

PD.04. Evaluation of a targeted delivery platform for *in vivo* modulation of *Gstm1* expression

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Background: Glutathione s-transferase mu-type 1 (*Gstm1*) has previously been identified as a positional and functional candidate gene for hypertension in the stroke prone spontaneously hypertensive rat (SHRSP). At present, there are no selective pharmacological inhibitors of *Gstm1*, making further investigation of its function difficult. To overcome

this, an approach involving both RNA interference via short interfering RNA (siRNA) and vector driven expression of *Gstm1* has been used.

Methods: Specific siRNA sequences against *Gstm1* were tested in a rat kidney tubular epithelial cell line (NRK52E). Cells were transfected with 30–100 nM siRNA. After 48 h, knock-down of *Gstm1*

protein and mRNA was determined by western blot and qRT-PCR. In addition to this, adenovirus vectors were generated to over-express *Gstm1*. *LacZ* expressing adenoviral vectors (Ad19pHTT) specifically designed to target renal tubular cells were generated and tested in the SHRSP. *LacZ* expression was determined by immunohistochemistry.

Results: *Gstm1* mRNA expression was significantly reduced, up to 85% ($n=6$, $P<0.01$). *Gstm1* protein levels were also reduced compared to controls. Over-expression of *Gstm1* resulted in a 2-fold

increase in total glutathione transferase activity ($n=3$, $P<0.01$). Ad19pHTT infusion of SHRSP resulted in localised expression of *LacZ* within the tubular epithelium of the kidney.

Conclusions: The techniques used in this study have resulted in successful modulation of *Gstm1* expression *in vitro*. The integration of targeted vectors and modulation of *Gstm1* expression will allow the role of *Gstm1* to be investigated more fully *in vivo*. This system can also be applied to evaluate other candidate genes in hypertension.

PD.05. The anorexigenic peptides, neuromedin U-25 and neuromedin S, are present in the human cardiovascular system and function as potent vasoconstrictors

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Neuromedin U (NMU), shown to elicit a pressor response in rats (Minamino *et al.*, 1985), was paired with the 'orphan' G-protein-coupled receptors, NMU1 and NMU2 (Howard *et al.*, 2000). This peptide has an important role in energy regulation; *NMU*^{-/-} mice developed obesity (Hanada *et al.*, 2004) and *NMU* Arg165Trp variant co-segregated with childhood obesity (Hainerova *et al.*, 2006). Recently, neuromedin S (NMS) was paired with the same receptors and also has pressor (Mori *et al.*, 2005) and anorexigenic actions (Ida *et al.*, 2005) in rats. However, little is known about direct effects of these peptides on vascular beds and on their vascular effects in humans. Using a novel RIA, NMU-25-LI was detected in human plasma, left ventricle (LV), coronary artery (CA), saphenous vein (SV) and adipose tissue. HPLC established both NMU-25 and NMS were present in

LV. Receptor autoradiography, using [¹²⁵I]-NMU-25, demonstrated binding to myocardium of LV and medial smooth muscle layer of small and large diameter blood vessels. [¹²⁵I]-NMU-25 showed saturable, specific and high affinity binding. In accordance with binding distribution, we have shown NMU-25 to be a potent vasoconstrictor of artery and vein *in vitro*. In CA, NMU-25 caused vasoconstriction with potency and maximum contractile response similar to angiotensin II. NMS constricted SV with similar potency to NMU-25 but a significantly lower maximum response, whereas NMU-25 (Arg165Trp) was without effect. Identification of specific binding sites, presence of endogenous peptide and discovery of function fulfil criteria for NMU-25 as an emerging transmitter in the human cardiovascular system.

PD.06. Improved left ventricular function in a hypertensive congenic strain

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Objective: We previously identified a QTL for left ventricular mass index (LVMI) on rat chromosome 14 in an F2 cross between SHRSP and WKY, which was confirmed by generation of the SP.WKYGla14a congenic strain. This study aimed to identify candidate genes and evaluate left ventricular (LV) function in SP.WKYGla14a.

Methods: 16-week old male SHRSP ($n=7$) and SP.WKYGla14a ($n=6$) were imaged by echocardiography; LVMI (mg/g), relative wall thickness (RWT), ejection fraction (EF%), fractional shortening (FS%) were calculated from m-mode images. LV diastolic function was assessed using pulse wave Doppler. Vector velocity imaging (VVI) determined end

systole (SR_s), end diastole (SR_d) strain rate and time to peak (TPk). Positional genes were identified by comparative mapping and analysed qRT-PCR in SHRSP and WKY whole heart.

Results: LVMI and RWT were reduced in SP.WKY-Gla14a (2.7×10^{-3} , $P<0.006$; 0.48 ± 0.03 , $P<0.0002$, respectively) versus SHRSP (3.0×10^{-3} , 0.61 ± 0.04 respectively). E/A ratio was significantly reduced in SHRSP (1.19 ± 0.02 m/s, $P<0.001$) versus SP.WKY-Gla14a (1.47 ± 0.01 m/s). LV SR_s, SR_d and TPk were significantly decreased in SHRSP (-1.8 ± 0.1 s⁻¹, 0.8 ± 0.2 s⁻¹; $P<0.001$; 46.83 ± 10.7 ms, $P<0.01$ respectively) versus SP.WKYGla14a (-3.4 ± 0.2 s⁻¹, 4.20 ± 0.5 s⁻¹, 98.2 ± 14.88 ms respectively). There

was no significant difference in EF% and FS%. Expression of vitamin D binding protein (DBP) was increased 6-fold in SHRSP ($P < 0.0004$) versus WKY. **Conclusions:** We have confirmed LVMI QTL on rat chromosome 14 and demonstrated improved LV

function in the SP.WKYGla14 congenic strain. The positional candidate DBP may contribute to hypertrophic and functional cardiac phenotypes in the SHRSP.

PE.01. Adipokines and their influence on blood pressure in young women

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Introduction: Adiposity influences blood pressure (BP) but how remains uncertain. Adipose tissue secretes peptide adipokines, including pro-inflammatory TNF- α and Interleukin (IL)-6, and adiponectin and leptin which influence vascular function. Their role on BP is not yet clear. Our hypothesis was that each adipokine independently influences systolic (S) and diastolic (D) BP.

Patients and methods: In our ongoing investigation of early development of vascular dysfunction, 193 women (mean Age, 95% CI: 35.3, 34.6–36, years; BMI: 27.3, 26.5–28.2 kg/m²) had standardised measures of anthropometry, BP, fasting blood glucose, lipid profile, and serum hs-C reactive protein, TNF- α , IL-6, adiponectin and leptin.

Results: Correlations between BP and serum adipokines were:

	TNF- α	IL-6	Adiponectin	Leptin
SBP				
<i>r</i>	0.26	0.27	-0.10	0.10
<i>P</i>	<0.001	<0.001	0.17	0.20
DBP				
<i>r</i>	0.27	0.31	-0.19	0.29
<i>P</i>	<0.001	<0.001	0.01	<0.001

Adjusting for age, weight, Townsend's index (measure of social deprivation), ethnicity, smoking history, alcohol consumption, fasting glucose, serum cholesterol, triglycerides and serum C-reactive protein, the independent influence of the adipokines on blood pressure were as follows:

	β , 95% CI	SBP	DBP
TNF- α	0.31, 0.16–0.46***		0.23, 0.12–0.33***
IL-6	1.41, 0.7–2.1***		1.04, 0.56–1.52***
Adiponectin	0.16, -1.28 to 1.59, <i>P</i> =0.83		-0.07, -1.04 to 0.09, <i>P</i> =0.9
Leptin	-0.27, -0.47 to -0.06**		-0.09, -0.23 to 0.06, <i>P</i> =0.23

*** = $P < 0.001$; ** $P = 0.01$.

Conclusion: Three adipokines were independently associated with SBP and DBP at this age. The pro-inflammatory adipokines had more influence on both BP measures independent of the women's body weight, other risk factors and inflammatory state measured by C-reactive protein.

PE.02. The influence of dietary salt on postprandial plasma sodium concentration

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The mechanisms whereby dietary salt intake regulates blood pressure (BP) are not clear. Physiological increases in sodium in plasma or tissue culture are known to stimulate thirst and thereby fluid retention but also activate the local hypothalamic RAS, cellular changes in arterial smooth muscle and cardiac myocytes as well as endothelial stiffness. Large changes in salt intake alter plasma sodium but the effects of smaller changes are not known. We

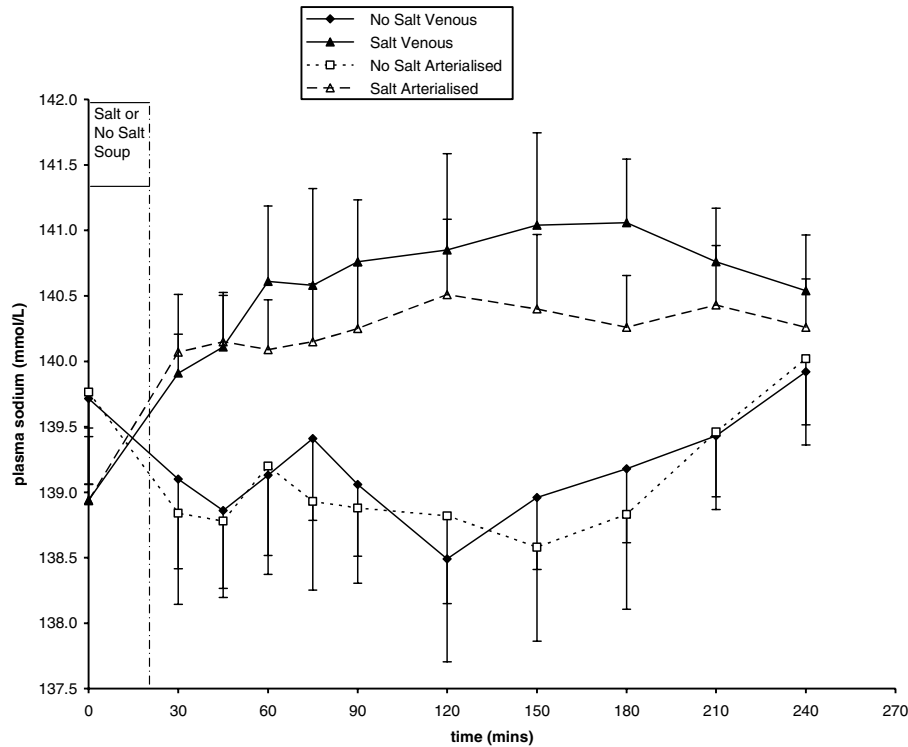
therefore studied the effect in 10 normotensive subjects in a randomised crossover study of 400 mls of soup with either 6 gms of salt or no added salt.

Venous and arterialised blood samples and systolic and diastolic blood pressure were taken at baseline and at 30 min intervals for 4 h.

Results: Salt soup increases, at its maximum, venous sodium by 3.13 ± 0.75 mmol/l, osmolality

by 6.975 ± 1.145 mosmol/l and chloride by 3.74 ± 0.91 mmol/l compared to control ($P < 0.05$). This trend was also seen in arterialised samples.

comparison to control. These changes could be sufficient to directly alter endothelial stiffness as well as cellular changes in myocytes and smooth



Conclusions: Physiological increases in salt intake raise plasma sodium, chloride and osmolality by relatively large amounts from initial values and in

muscle and thereby affect blood pressure both acutely and chronically.

PE.03. An acute elevation of non-esterified fatty acids increases oxidative stress, impairs NO availability and increases exercise blood pressure

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We examined effects of an acute elevation in non-esterified fatty acids (NEFA) on oxidative stress, basal release of nitric oxide (NO) and systemic haemodynamics. Healthy normotensive men ($n = 30$), aged 18–40 years took part in a randomised, 2-phase cross-over study, each phase separated by 7 days receiving intravenous saline and intralipid (150 mg min^{-1} of soybean oil) with heparin ($0.2 \text{ unit kg}^{-1} \text{ min}^{-1}$) in each phase over 4 h. Gas chromatography was used to measure plasma concentrations of 8-epi-prostaglandin- $F_{2\alpha}$, a marker of oxidative stress ($n = 10$). Cardiac output (CO) and systemic vascular resistance (SVR) were measured by re-breathing of soluble and inert gas tracers (Innocor, Innovision). The forearm blood flow response to brachial artery infusions of the NO synthase inhibitor N^G -monomethyl-L-arginine (L-NMMA, 2, 4 and $8 \mu\text{mol min}^{-1}$, $n = 10$) was used to assess basal

NO availability. Exercise blood pressure was measured during low work load bicycle ergometry (50–100 Watts, $n = 10$). Plasma isoprostanes increased after intralipid compared to the change after saline (26.8 ± 25.0 vs -29.3 ± 39.0 pg/ml, $P < 0.05$). SVR increased after intralipid compared to the change after saline (0.6 ± 3.1 vs -2.7 ± 2.5 mm Hg.l.min $^{-1}$, $P < 0.01$). L-NMMA reduced forearm blood flow less after intralipid compared to saline (mean reduction: 0.61 ± 0.13 vs 1.10 ± 0.28 ml min $^{-1}$ 100 ml $^{-1}$, $P < 0.05$). Exercise diastolic blood pressure was higher after intralipid compared to after saline (68.0 ± 4.6 vs 63.3 ± 4.7 mm Hg, $P < 0.05$). These results are consistent with an acute elevation of NEFA causing an increase in oxidative stress, decrease in availability of basal NO and increase in SVR at rest and during exercise.

PE.04. Is the relationship between pulse wave velocity or blood pressure and mortality modulated by serum fatty acid composition?

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Aims/hypothesis: Aortic stiffness predicts all-cause and cardiovascular mortality in high blood pressure (BP) and/or diabetes. Whether arterial stiffness indices such as aortic pulse wave velocity (PWV) are related to fatty acid (FA) composition is unknown.

Methods: Participants were randomly sampled from primary care population registers, with non-diabetics administered a 75 g glucose challenge (GTT). Serum FA composition was determined by HPLC. Brachial BPs and Doppler-derived aortic PWV were measured ($n=174$). Mortality data over 18 years' follow-up were obtained via ONS.

Results: Palmitic acid (PA, 16:0), and linoleic acid (LA, 18:2 $n=6$) were the most abundant FAs. Docosahexaenoic (DHA; $r=-0.22$) and Arachidonic acid (AA; $r=-0.25$) were inversely related to PWV. Principal component analyses including ethnicity,

age, sex and FAs identified five components. Spearman correlations showed direct relationships between PWV, systolic BP (sysBP), smoking or central adiposity and Component 1 (higher saturated FAs myristic and PA, but lower levels of polyunsaturated FAs—LA, Dihomo-gamma-linoleic and AA), but inverse relationships with Component 4, a pattern with higher levels of AA, DHA eicosapentaenoic and lower oleic, PA and LA levels. In Cox models, Component 1 was associated with increased mortality (Hazard Ratio = 1.13, 1.01–1.27) while Component 4 was associated with decreased mortality risk (Hazard Ratio = 0.49 (0.39, 0.62) independent of PWV ($P=0.03$) or sysBP ($P=0.03$)). **Conclusion:** Patterns of serum fatty acids, in part reflecting diet, are associated with mortality and may modulate PWV and sysBP through actions on micro and macro-vascular function.

PE.05. Visceral rather than generalised obesity reduces the blood pressure lowering effect of antihypertensive mono-therapy

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Although obesity is reported to reduce the blood pressure response to antihypertensive drugs, the influence of visceral obesity remains unclear.

We compared the role of abdominal adiposity (waist circumference) to generalized obesity (BMI) on the antihypertensive response to mono-therapy.

306 consecutive newly diagnosed untreated hypertensive individuals received the following drugs at standard doses in random fashion: diuretics ($n=89$), beta blockers ($n=59$), calcium channel blockers ($n=52$) alpha blockers ($n=12$) angiotensin converting enzyme inhibitors ($n=51$) or angiotensin II receptor blockers ($n=55$). Response was evaluated after 4 weeks of therapy using Omron 705 by an independent blinded observer. Results were analysed using JMP Version 7 statistical software.

The cohort (56% males), had a mean (\pm s.d.) age 52 ± 11 years, BP $161 \pm 17/95 \pm 9$ mm Hg, waist 94 ± 13 cms, waist: hip ratio 0.9 ± 0.1 , BMI (kg/m^2) 28 ± 4.7 . The fall in systolic BP (16 ± 14 mm Hg) was related inversely to waist circumference ($P<0.01$). Males, but not females in the lowest tertile of waist (≤ 90 cms) had 7 mm greater fall in SBP ($P<0.01$) compared to those with waist > 90 cm. There was no relationship with BMI. In a stepwise regression analysis only the drug group and waist were related to BP response with no contribution from fasting cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, BMI or metabolic syndrome.

Conclusion: Our study suggests that abdominal obesity, rather than generalized obesity, significantly reduces the BP response to antihypertensive mono-therapy.

