Title	Urotensin II in hypertension
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CVS-11 Randomised trial of candesartan and enalapril (RACE) in the treatment of hypertension – final results

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Introduction: The renin-angiotensin system plays an important part in the pathophysiology of hypertension. We compared two ways of blocking the system, using an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker.

Method: 22 hypertensive patients (16 men, 6 women; age 47±10 yrs) were randomised to either candesartan 8 mg or enalapril 10 mg daily for 3 months. The dose could be doubled after 6 weeks for blood pressure control. Ambulatory blood pressure monitoring was performed before randomisation and before the final visit. Echocardiography was performed at randomization, 2 and 12 weeks. Flow-mediated dilatation was measured at the brachial artery to assess endothelial function. Exhaled nitric oxide was measured using an integrated chemiluminescent system. The coefficient of variation of left ventricular mass index (LVMI), flow-mediated dilatation (FMD) and nitric oxide measurement were 7%, 5% and 3% respectively.

Results: Candesartan and enalapril both significantly lowered systolic and diastolic blood pressure. This was confirmed by ambulatory blood pressure monitoring.

There were no significant differences between the treatments in their effect on LVMI and exhaled nitric oxide. Changes in LVMI correlated strongly with changes in the ambulatory systolic blood pressure ($r=0.62$, $p=0.02$) and diastolic blood pressure ($r=0.61$, $p=0.02$). FMD increased with enalapril but not candesartan treatment ($p=0.04$). Neither treatment significantly altered plasma potassium, creatinine, renin and aldosterone. Fasting blood glucose decreased significantly from 5.6±0.4 to 5.1±0.3 mmol/L in the enalapril group ($p=0.01$) only.

Conclusions: Both drugs are efficacious in lowering blood pressure. Candesartan tended to lower blood pressure more than enalapril, which might be the result of the dosages used. Enalapril appears to have a favourable effect on blood glucose and endothelial function. We conclude that candesartan may be used as an alternative to enalapril in the treatment of hypertension, particularly in those who are intolerant of the latter.

	Baseline SBP	Final SBP	Baseline DBP	Final DBP	Baseline LVMI	Final LVMI
candesartan	158.2±5.7	134.5±4.3*	100.3±3.9	85.3±3.2*	139.8±12.5	134.9±11.1
enalapril	159.8±4.0	145.3±6.1**	97.4±3.0	87.0±3.4*	127.3±6.4	134.5±8.0

*$p<0.05$ vs. baseline; ** $p<0.05$ vs. baseline and $p=0.05$ vs. candesartan

CVS-12 Urotensin II in hypertension

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Introduction: Urotensin II (UII) is an 11 amino acid cyclic peptide and is the most potent vasoconstrictor known. UII receptors are found in the heart and arterial vessels, including atherosclerotic plaques, suggesting that urotensin II has a role in cardiovascular diseases. UII circulates in human plasma and its plasma concentration is raised in cardiac and renal failure. The role of UII in hypertension has not been investigated.

Method: We studied the plasma level of UII levels in 22 hypertensive subjects (68% male, age 51±10 yrs) and 37 normal controls (49% male, age 51±12 yrs) with consent from the subjects and approval from the Ethics Committee. Plasma UII was measured using a radioimmunoassay.

Results: Plasma UII was 10.6±1.4 pg/ml in normotensive controls and 21.0±3.6 pg/ml in hypertensive subjects ($p=0.003$). UII in men and women were not significantly different. UII did not vary significantly with age in normal healthy subjects ($r=0.09$, NS) but was inversely related to age in hypertensive subjects ($r=-0.35$, $p=0.025$). In hypertensive subjects but not in control subjects, UII was related to diastolic blood pressure ($r=0.31$, $p<0.05$). UII is not related to plasma creatinine or creatinine clearance ($p>0.05$).

Conclusions: Our results raise the possibility that this novel and potent vasoconstrictor may have an aetiological role in hypertension or may be involved in the complications of hypertension. Antagonists to urotensin II might be antihypertensive agents with a novel mechanism of action.

CVS-23 The Heart Protection Study findings with simvastatin reanalysed by number needed to treat

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Introduction: *Number Needed toTreat* (NNT) is superior to *Relative Risk Reduction* (RRR) as a means of assessing clinical trial results. We therefore opted to compare relevant RRRs and NNTs in the *MRC/BHF Heart Protection Study(HPS) with Simvastatin* the largest randomized trial of coronary heart disease (CHD) prevention to date, which recruited patients with prior CHD, diabetes or hypertension [HPS Collaborative Group 2002 Lancet 360:7-22].
Methods: Using an Excel spreadsheet to enter event rates, NNTs and respective 95% CIs were calculated and compared with corresponding published (or derived) RRRs.
Results: Respective event rates, 5 year NNTs & CIs are shown in the table.
Conclusions: NNTs are more discriminating than RRRs. They confirm that the benefits of statins: are clinically significant in terms of all-cause mortality and stroke, and that for major vascular events they are similar in persons with CHD only or diabetes only and in all cholesterol level and age categories.

Outcome of Interest		Event Rate (%)		%RRR	NNT
		Simvastatin	Placebo	(95% CIs)	(95% CIs)
All Cause Mortality		12.9	14.7	12 (5 to 18.)	57 (37 to 128)
Vascular Mortality		7.6	9.1	17 (8 to 24)	66 (44 to 134)
Non-vascular Mortality		5.3	5.6	4 (* to 15)	444 (* to 117)
1st Major CHD Event		8.7	11.8	26 (19 to 32)	32.7 (26 to 45)
1st Stroke		4.3	5.7	24 (14 to 33)	73 (50 to 131)
Revascularisaton		9.1	11.7	22 (15 to 29)	39 (29 to 58)
1st Major Vascular Event					
Total Cholesterol (mmol/L)	<5.0	17.7	23.1	23 (12 to 33)	19 (13 to 35)
	≥5.0 <6.0	16.9	24.5	23 (15 to 30)	18 (13 to 27)
	≥6.0	21.6	26.8	19 (12 to 26)	19 (14 to 30)
Age (years)	<65	16.9	22.1	23 (16 to 30)	19 (15 to 28)
	≥65 <70	20.9	27.2	23 (14 to 32)	16 (11 to 26)
	≥70	23.6	28.7	18 (9 to 26)	20 (14 to 36)
Prior CHD only		16.8	22.5	25 (17 to 33)	18 (13 to 26)
Prior Diabetes only		13.8	18.6	26 (13 to 37)	21 (14 to 40)
Prior CHD + Diabetes		33.4	37.8	11 (* to 24)	23 (12 to *)

* Denotes a negative value indicating an increased event rate in the treated group, renderng further analysis inappropriate; 1st major coronary event = non-fatal MI or CHD death; Revascularisation = coronary and non-coronary bypass and angioplasty; 1st major vascular event = 1st major coronary event, stroke or revascularisation

CVS-24 Endotoxin increases adrenomedullin expression in heart, lung and mesenteric artery

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Introduction: Previous studies have shown that the circulating levels of adrenomedullin (AM) are elevated during inflammation. The levels of AM and its messenger RNA (mRNA) in various tissues during the time course of inflammation remain to be determined.
Method: Inflammation was induced in rats by intraperitoneal injection of lipopolysaccharide (LPS, 10mg/kg). The tissues were harvested at 0, 1, 3 and 6 hours after LPS administration. Tissue levels of AM were determined by radioimmunoassay. The gene expression levels of AM were determined by solution hybridization-RNase protection assay of preproAM mRNA levels.
Results: PreproAM mRNA levels were increased in mesenteric artery and right atrium at 1 hour, in the left ventricle and the lung at 3 and 6 hours and in the right ventricle at 6 hours, after LPS injection. AM levels in the mesenteric artery were increased at 1, 3 and 6 hours and at 3 and 6 hours in the lung after LPS injection.
Conclusions: There is an increase in AM release in the lung, so it may be an important organ for AM secretion in the septic state. However, the response of the lung and the mesenteric artery to LPS in terms of AM secretion appears to be different.