Results: In sodium-depleted marmosets, aliskiren (0.3–10 mg/kg p.o.) dose-dependently inhibited renin and lowered MAP. After a single oral dose of 3 mg/kg aliskiren, MAP was lowered maximally by 30±3 mmHg (n=6), and significant reductions in MAP persisted for up to 24 h. At equivalent doses, aliskiren lowered MAP as effectively as the ACE inhibitor benazepril and the AT1-receptor blocker valsartan, and more effectively than the previous generation RIs, remikiren and zankiren. In SHR, aliskiren (10–100 mg/kg/day via s.c. osmotic minipumps for 2 weeks) dose-dependently lowered MAP. Administration of submaximally effective doses of aliskiren in combination with either benazeprilat or valsartan strongly potentiated reductions in MAP. In human hypertensive patients, aliskiren (37.5, 75, 150 or 300 mg once daily for 4 weeks) also dose-dependently lowered BP and inhibited renin. Aliskiren treatment was well tolerated at all doses, with BP reductions not being accompanied by changes in heart rate, in marmosets, rats and humans.
Conclusions: Aliskiren provides 24 h blood pressure lowering with good tolerability in sodium-depleted marmosets and human hypertensive patients after once-daily oral dosing. Blockade of the RAS at source with aliskiren may therefore represent an effective, novel approach to antihypertensive treatment both as monotherapy and in combination with other RAS inhibitors.

1085-166 Does Hormone Replacement Therapy in Women Influence Their Benefit of Losartan-Treatment in the LIFE study?

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Background: Effective drug treatment of hypertension has been shown to benefit women, without consideration of concomitant hormone replacement therapy (HRT).This analysis compared the effect of losartan relative to atenolol in women who were and were not taking HRT.
Methods: As part of the LIFE study, in a double-blinded, randomized parallel group trial, a total of 476 hypertensive women were taking HRT (HRT+) at baseline and 4,494 were not taking HRT (HRT-) and followed for an average of 4.8 years.
Results: The composite endpoint of cardiovascular mortality, fatal and non-fatal stroke and fatal and non-fatal myocardial infarction was similarly reduced in HRT- (11.2% with atenolol-based treatment vs. 9.2% with losartan-based treatment, relative risk reduction [RRR]=18.6%, p=0.037) and in HRT+ (7.5% with atenolol vs. 6.2% with losartan-based treatment, RRR=12.6%, p=0.600). Test for interaction between HRT+ and HRT- losartan vs. atenolol treatment was not significant for the composite endpoint (p=0.881). Similarly, there were similar reductions in stroke with losartan compared to atenolol-based treatment (6.9 vs. 4.5% in HRT- RRR=34.9%, p=0.001 and 3.3 vs. 3.8% in HRT+, RRR=-27.2%, p=0.50), test for interaction p=0.105. Non-significant reductions in cardiovascular mortality occurred with losartan-based treatment in both HRT- (3.93 vs. 4.3%, RRR=10.3%, p=0.480) and HRT+ (2.1 vs. 3.5%, RRR=37.9%, p=0.24), Test for interaction p=0.412). Similarly, there were non-significant reductions in fatal and non-fatal myocardial infarction with losartan-based treatment compared to the atenolol treated group (3.3 vs. 3.4% in HRG- RRR=-6.2%, p=0.73) and (2.7 vs. 1.9% in HRG+, RRR=27.6%, p=0.46); test for interaction for myocardial infarction, p =0.461.
Conclusion: Losartan was superior to atenolol for reducing cardiovascular events among women participating in the LIFE study. There is no evidence that this benefit differs according to whether or not the women were taking HRT.

1085-167 Dose-Response Study of the Efficacy and Safety of Fosinopril in Children With Hypertension: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial

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Background: Because the prevalence of childhood hypertension is increasing, there is a growing need for data on using antihypertensive medications in children. This study evaluated the efficacy, safety, and dose-response relationship for fosinopril in children and adolescents 6-16 years of age with hypertension or high-normal blood pressure with an associated medical condition requiring treatment.
Methods: The study was a prospective, double-blind, placebo-controlled, multicenter trial conducted in 78 clinical sites in the US, Russia, and Israel. There were 4 study phases: a screening phase of 10 days maximum, a 4-week dose-response phase, a placebo withdrawal phase of 2 weeks maximum, and a 52-week open-label safety phase. The primary objective of the dose-response phase was to determine whether low (0.1 mg/kg), medium (0.3 mg/kg), or high (0.6 mg/kg) doses of fosinopril, which were based on established adult dosing, affect trough seated systolic blood pressure (SBP). After the dose-response phase, patients entered a double-blind randomized withdrawal and received either fosinopril or placebo. This was followed by the open-label safety phase. Adverse events were recorded throughout the entire study.
Results: During the dose-response phase, all 3 doses were equally effective in lowering SBP. During the placebo withdrawal phase, there was an adjusted mean SBP increase of 5.2 mm Hg for the placebo group and 1.5 mm Hg for the fosinopril group, a net withdrawal effect of 3.7 mm Hg ($P = 0.013$). Fosinopril was generally well-tolerated; serious adverse events occurred infrequently and were generally not attributed to fosinopril.
Conclusion: Children ages 6-16 with hypertension or high-normal blood pressure with concomitant illness or risk factors and treated with 0.1-0.6 mg/kg fosinopril once daily had substantial mean decreases in SBP, yet no dose-response relationship was evident. Withdrawal of fosinopril resulted in a statistically significant increase in SBP. Because children appear to be more sensitive to lower doses of fosinopril than adults, fosinopril starting doses for children should be $\leq$ 0.1 mg/kg.

1085-170 Benefits of Losartan on Preventing Stroke in Patients With Isolated Systolic Hypertension: A LIFE Substudy

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Stroke is now more common than myocardial infarction in hypertension. In a substudy of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study we tested the hypothesis that a losartan-based regimen was more effective than an atenolol-based regimen beyond blood pressure control in reducing cardiovascular (CV) morbidity and mortality (composite CV death, stroke or myocardial infarction) in patients with ISH and left ventricular hypertrophy (LVH) on electrocardiogram (ECG). Men and women (60%) aged 55-80 (average 70) years with ISH (sitting blood pressure 160-200/<90 mmHg, average 174/83 mmHg) and ECG-LVH were followed for a mean of 4.7 years. Blood pressure was similarly reduced by 28.4/8.5 and 28.2/8.8 mmHg in the losartan (n=660) and atenolol (n=666) arms, respectively. The primary composite endpoint was reduced by 26% in the losartan group (25.1 per 1000 patient years) compared to the atenolol group (35.8 per 1000 patient years; relative risk [RR] adjusted for Framingham risk score and degree of ECG-LVH 0.74 [95% CI 0.55 – 1.00], p=0.051, unadjusted RR 0.70 [95% CI 0.52 –0.94], p=0.019). Stroke data in this ISH group follow. (Three atenolol patients had multiple stokes of different types. These patients are counted only once in the patients with any stroke category.)

	Losartan n=660	Atenolol n=666	Adjusted RR (95% CI)	p-value
Patients with any stroke	32 (4.8%)	56 (8.4%)	0.60 (0.38-0.92)	0.020
Fatal stroke	4 (0.6%)	14 (2.1%)	0.30 (0.10-0.92)	0.035
Atherothrombotic stroke	22 (3.3%)	42 (6.3%)	0.55 (0.32-0.92)	0.022
Embolic stroke	8 (1.2%)	13 (2.0%)	0.64 (0.26-1.56)	0.33
Hemorrhagic or other stroke	2 (0.3%)	4 (0.6%)	Too few events	

Consistent with LIFE primary results, these data suggest losartan-based treatment to be superior to atenolol-based treatment for patients with isolated systolic hypertension and high CV risk, especially for stroke.

1085-193 The Effect of Losartan Versus Atenolol on Hemostasis and Fibrinolysis in Hypertensive Patients With Left Ventricular Hypertrophy: A LIFE Substudy

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Background: In some studies treatment with angiotensin converting enzyme (ACE) inhibitors seem to improve fibrinolysis. Our aim was to investigate the long-term effects of an angiotensin II receptor blocker, losartan, on mass-concentrations of tissue plasminogen activator (tPA), its inhibitor, PAI-1, tPA/PAI-1-complex, trombomodulin and von Willebrand factor (vWF) in patients with hypertension and left ventricular hypertrophy.
Methods: In 44 patients recruited for the LIFE Study with stage II-III hypertension and ECG left ventricular hypertrophy we measured tPA, PAI-1, tPA/PAI complex, trombomodulin, and von Willebrand factor (vWf) at baseline, after one and five years of anti-hypertensive treatment with either an atenolol- or a losartan-based regime.
Results: Plasma levels of tPA (10.5 vs. 8.8µg/l, p=0.01), PAI-1 (31,6 vs. 8,4 µg/l, p=0.002 tPA/PAI-1 complex (7.6 vs. 4.8µg/l, p=0.03) and trombomodulin (10.6 vs. 8.4µg/l, p=0.06) were reduced during five years of losartan-based antihypertensive treatment, whereas PAI-1 (24,4 vs. 11,4µg/l, p=0.036) and vWF (175 vs. 174%, p=0.05) was reduced in patients treated with atenolol-based antihypertensive treatment. Comparing the two treatments, there were no significant differences in plasma tPA, PAI-1, and vWF at baseline, after one and five years of antihypertensive treatment. However, after five years of treatment, plasma levels of tPA/PAI-1 complex (4.8 vs. 6.8µg/l, p=0.02) and trombomodulin (8.4 vs. 11.8µg/l, p=0.01) were significantly lower in patients treated with losartan.
Conclusion: In hypertensive patients with left ventricular hypertrophy losartan seemed to have a beneficial time-dependent effect on the fibrinolytic system and the plasma level of trombomodulin compared to treatment with atenolol.

1085-194 Eplerenone Improves Coronary Hemodynamics and Reduces Cardiac Fibrosis in Aging Spontaneously Hypertensive Rats

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Background: Aldosterone is considered to be involved in development of age- and hypertension-related cardiac fibrosis and its consequences such as impaired coronary hemodynamics. Thus, the effects of an aldosterone antagonist, eplerenone (E), on cardiovascular mass, myocardial collagen, and coronary circulation were examined in spontanously hypertensive rats.
Methods. Male, 22-week old rats were randomly divided into two groups (30 rats in each). The control group did not receive any treatment, the second group was given E (mixed in