food; average intake 103 ± 4 mg/kg/day). Half of the rats in each group was studied after 12 weeks of treatment, at the age of 34 weeks; the other half at the age of 54 weeks.At the end of treatment, indexes of systemic and regional hemodynamics were measured in conscious instrumented rats. Radiomicrospheres were used for flow measurements.
Results: E decreased mean arterial pressure after 12 and 32 weeks of treatment; it did not affect left ventricular (LV) mass; and E decreased LV hydroxyproline concentration (an estimate of collagen) after 32 weeks of therapy. E did not affect coronary blood flow and resistance under basal conditions, but decreased minimal coronary vascular resistance (MCVR) and increased coronary flow reserve, measured after dipyridamole infusion.

Cardiovascular Effects of Eplerenone

	Control (34w)	E (34w)	Control (54w)	E (54w)
Mean Arterial Pressure (mmHg)	178±4	157±3*	179±6	165±3*
LV Mass (mg/g)	2.89±0.04	2.83±0.05	3.16±0.07	3.05±0.05
LV Hydroxyproline (mg/g)	4.62±0.21	4.47±0.24	6.23±0.24	5.41±0.18
Coronary Blood Flow (ml/min/g)	5.86±0.33	5.40±0.20	4.89±0.32	4.25±0.20
Coronary Vascular Resistance (U/g)	30.94±1.31	29.53±1.38	38.68±3.82	39.51+1.74
MCVR (U/g)	14.65+1.01	11.74+0.51*	20.18+1.45	15.69±0.92*
Coronary Flow Reserve (ml/min/g)	4.50±0.40	5.94±0.36*	3.12±0.47	5.32±0.57*

Conclusions: Extended therapy with E improved coronary hemodynamics and reduced myocardial collagen suggesting that aldosterone may be involved in mediating age- and hypertension-related cardiac fibrosis.

1085-195 The Renin Inhibitor Aliskiren Is a Potent and Long-Acting Antihypertensive in Double Transgenic Rats Expressing Human Renin and Angiotensinogen Genes

Dean F. Rigel, Fumin Fu, Shaoyong Li, Wieslawa Maniara, Dominik N. Muller, Friedrich C. Luft, Novartis Institutes for BioMedical Research, East Hanover, NJ, Franz Volhard Clinic, Berlin, Germany

Background: Aliskiren is a potent and selective renin inhibitor currently in clinical development. The purpose of this study was to compare the antihypertensive responses of i.v. and p.o. aliskiren to those of enalapril(at) and valsartan in double transgenic rats (dTGR) expressing the human angiotensinogen and renin genes.
Methods: Studies were conducted on 5.5- to 10.7-week-old male dTGR [(h-REN)L10J x (h-AOGEN)L1623] instrumented with chronically indwelling femoral arterial and venous catheters (exteriorized through a tether system). Aliskiren (hemifumarate salt) was administered i.v. (0.003-3 mgEq/kg) or p.o. (0.3-30 mgEq/kg) as single or escalating cumulative doses on a given day followed by at least 3 days of recovery before the next experiment. Enalapril(at) (0.003-1 mgEq/kg i.v.; 0.01-1 mgEq/kg p.o.) and valsartan (0.003-1 mg/kg i.v.; 0.1-10 mg/kg p.o.) were given in a like manner. Mean arterial pressure (MAP) was monitored before ("baseline") and for up to 72 hours after dosing. In separate experiments, arterial blood samples were collected for pharmacokinetic analyses of aliskiren.
Results: Each agent dose-dependently (i.v. and p.o.) lowered MAP (baselines ~203 mmHg; range, 146-272 mmHg; maximal decreases ~60-70 mmHg) . Aliskiren, enalaprilat, and valsartan were equipotent as i.v. antihypertensives, whereas p.o. aliskiren tended to be less potent than p.o. enalapril and valsartan due to its lower functional and pharmacokinetic oral bioavailabilities. Aliskiren (p.o.) rapidly lowered MAP (15-30 minutes post-dosing) reflecting the short time (15 minutes) to peak plasma concentration (14.8 nM @30 mgEq/kg). In spite of its relatively rapid plasma clearance (elimination half-life: 2.8 hours; clearance: ~10 L/hour/kg), aliskiren exhibited a prolonged duration of action (MAP recovery required up to 72 hours).
Conclusion: Aliskiren is a rapidly absorbed, potent, and long-acting antihypertensive in dTGR. Our results extend previous observations in other preclinical models and support the continued development of aliskiren as the first agent in a novel class of renin inhibitors with the potential for treatment of hypertension.

1085-196 The Effects of Aspirin on Blood Pressure in Untreated Hypertensive Patients Are Dependent on the Time of Drug Administration

Ramon C. Hermida, Diana E. Ayala, Carlos Calvo, Maria J. Dominguez, Manuel Covelo, Jose R. Fernandez, Artemio Mojon, Jose E. Lopez, University of Vigo, Vigo, Spain, Hospital Clinico Universitario, Santiago, Spain

Background: An administration time-dependent effect of low-dose aspirin (ASA) on blood pressure (BP) has been previously documented in normotensive volunteers, patients with mild hypertension, and pregnant women at high risk for preeclampsia [Hermida et al. Hypertension. 2003;41:651-656 and 2003;41:1259-1267]. We have extended these results by investigating the influence of ASA on BP in previously untreated hypertensive patients who received ASA at different times of the day according to their rest-activity cycle.
Methods: We studied 264 untreated patients with mild hypertension (101 men), 43.6±12.6 (mean±SD) years of age, randomly divided in 3 groups: non-pharmacological hygienic-dietary recommendations (HDR); the same HDR and ASA (100 mg/day) on awakening; or HDR and ASA (100 mg/day) before bedtime. BP was measured every 20 min from 07:00 to 23:00 hours and every 30 min at night for 48 consecutive hours before and after 3 months of intervention. The circadian pattern of BP in each group was established by population multiple-component analysis.
Results: After 3 months of non-pharmacological intervention, there was a small and non-significant reduction of BP (0.4 and 0.5 mm Hg for systolic and diastolic BP; P>0.584). BP was slightly elevated after ASA on awakening, mainly during nocturnal resting hours (increase of 2.7 and 1.5 mm Hg in the 24-hour mean of systolic and diastolic BP; P<0.020). A highly significant BP reduction was, however, observed in the patients who received ASA before bedtime (decrease of 7.1 and 4.6 mm Hg in systolic and diastolic BP, respectively; P<0.001).
Conclusion: This trial corroborates the highly significant administration-time dependent effect of low-dose ASA on BP in untreated patients with mild hypertension. Results indicate that the timed administration of low-dose ASA with respect to the rest-activity cycle of each patient could provide a valuable approach not just for the secondary prevention of cardiovascular disease, but also in the added BP control of patients with mild essential hypertension and poor compliance with HDR.

1085-197 Blood Pressure Control, Angina Episodes, and Cardiovascular Outcomes in Patients With Ischemia: The International Verapamil/Trandolapril Study

Rhonda M. Cooper-DeHoff, Rainer Kolloch, Franz H. Messerli, Eileen M. Handberg, Carl J. Pepine, University of Florida, Gainesville, FL

INTRODUCTION: More than 60% of patients with ischemia also have hypertension (HTN) and are at high risk for CV events. This analysis evaluates BP control, angina frequency and episodes and CV events in CAD patients with HTN and ischemia (classic angina pectoris or concordant abnormalities on 2 different types of stress tests [e.g. ST segment or wall motion and perfusion]) and without prior MI. METHODS: In the prospective INternational VErapamil SR/trandolapril STudy (INVEST), patients with HTN and CAD were randomized to either a verapamil-SR based (Ve) or atenolol based (At) treatment strategy and followed 2.7 years (mean). Trandolapril and HCTZ were available in both strategies to achieve JNC VI BP goals (<140/<90 or <130/<85 in diabetes or renal dysfunction). The primary outcome (PO) was time to first occurrence of death (all-cause), nonfatal MI or nonfatal stroke. This analysis includes 10,617 patients with ischemia at baseline. RESULTS: See table. BP reduction, control and outcomes were similar comparing strategies. At 24 months, presence of angina was also similar and reduced from baseline. Heart rate (HR) and systolic BP-HR product were significantly lower in the At strategy, however episodes of angina / month was significantly lower in the Ve strategy. CONCLUSIONS: Despite decreased indices of cardiac oxygen demand in the At strategy, patients in the Ve strategy had a greater reduction of anginal episodes, suggesting an alternate mechanism of action for reduced anginal symptoms from verapamil-SR .

AT ENTRY	Verapamil-SR Strategy(n=5,335)	Atenolol Strategy(n=5,282)	p value
Mean Age (yr) (SD)	65 (10)	65 (10)	1.00
Mean BMI (kg/m^2) (SD)	29 (6)	30 (6)	0.12
% w/ Angina	95	95	0.84
Mean # Angina Episodes / Mo (SD)	5.2 (8.4)	5.2 (7.2)	0.66
OUTCOME DATA			Unadjusted HR (95% CI)
Primary Outcome n (%)	361 (7)	332 (6)	1.08 (0.93-1.26)
Death n (%)	285 (5)	279 (5)	1.02 (0.86-1.20)
Fatal and nonfatal MI n (%)	135 (3)	129 (2)	1.04 (0.82-1.33)
Fatal and nonfatal Stroke n (%)	62 (1)	60 (1)	1.03 (0.72-1.47)
AT 24 MONTHS	Verapamil-SR Strategy(n=3,788)	Atenolol Strategy(n=3,803)	p value
Mean Systolic BP (mmHg) (SD)	132 (15)	132 (16)	0.99
Mean Diastolic BP (mmHg) (SD)	78 (9)	78 (8)	0.95
BP Control (JNC VI) %	64	63	0.51
Mean HR (bpm) (SD)	73 (8)	70 (9)	<0.001
Mean SBP-HR Product (SD)	9647 (1638)	9269 (1654)	<0.001
% w/ Angina	42	42	0.88
Mean # Angina Episodes / Mo (SD)	2.4 (4.36)	2.8 (4.92)	0.05