METHODS Studies on conventional treatment of CHD plus sertraline versus conventional treatment alone in treating CHD patients with depression were retrieved from MEDLINE, EMBASE, Cochrane Library, CNKI, and WANFANG DATA from 1970 to 2015. Primary outcomes were Hamilton Depression Scale (HAMD) scores, Hamilton Anxiety Scale (HAMA) scores and cardiovascular death; secondary outcomes were Self-Rating Depression scale (SDS) scores, Self-Rating Anxiety Scale (SAS) scores and major adverse cardiovascular events (MACE).

RESULTS We identified 13 RCTs enrolling 1981 patients who fulfilled our inclusion criteria. When compared with conventional treatment alone, conventional treatment plus sertraline was associated with significant improvement in HAMD scores (mean difference, −7.98; 95% confidence intervals [CI], −13.24-−2.73), HAMA scores (mean difference, −13.03; 95% CI, −19.52-−6.54), cardiovascular death (risk ratio [RR], 0.19; 95% CI, 0.05-0.73), SDS scores (mean difference, −11.39; 95% CI, −14.94-−7.84), SAS scores (mean difference, −11.59; 95% CI, −15.62-−7.55) and MACE (RR, 0.20; 95% CI, 0.11-0.37). Adverse events observed in the studies were not severe and resolved without special treatment.

CONCLUSIONS Sertraline reduce depression and anxiety symptoms and cardiovascular events of Chinese patients with CHD and depression. However, further studies with more subjects, long-term follow-up, systemic adverse events evaluation are still required to verify the efficacy and safety of sertraline in CHD patients with depression in China.

GW27-e0386

Pravastatin attenuate Ets-like protein 1 action to prevent atherosclerosis in apolipoprotein E knockout mice

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OBJECTIVES In this study, we investigated into the role and mechanism of pravastatin preventing atherosclerosis. Our objection is to provide evidence to the conclusion that pravastatin prevent atherosclerosis induced by high cholesterol.

METHODS Mice were bred at a temperature of 22±2°C and in a relative humidity of 55±15%-controlled room environment with a 12-hr light and dark cycles and fed on a diet of food and tap water ad libitum. Evaluation of atherosclerotic lesions by morphology and morphometry. The aortic roots were embedded in paraffin and sequential 5-um sections were sliced through the aortic roots. Paraffin sections were stained with Hematoxylin and Eosin. The whole lumen referred to the area that the residual cavity plus the atherosclerotic lesion. In order to estimate the relative size of the lesions, we measured the ratio of the lesion area compared with that of the whole lumen area and expressed as a ratio in terms as a percentage. Detecting of aortic protein expression by Western Blotting analysis SDS-PAGE and Western blot analysis were performed as previously described on the extracted thoracoabdominal aortas. The serum and thoracoabdominal aorta concentrations of ox-LDL was measured by ELISA. Quantitative data is expressed as mean ± SD.

RESULTS We determined the size of the atherosclerotic lesion in each group of the mice. The aortic intima of the C57BL/6J mice on a non-cholesterol diet was morphologically normal, however mice in the atherosclerosis group showed advanced atherosclerotic lesions in the aortic root. By contrast, mice in the pravastatin group showed a marked reduction in the size of the aortic lesions.

A high cholesterol diet increased the levels of serum LDL-C and TC, which was not significantly alleviated by pravastatin. Serum levels of LDL-C and TC in the atherosclerotic mice was significantly higher in contrast to that of LDL-C and TC in control mice. But, those concentrations of LDL-C and TC were not significantly different in those mice administered with pravastatin in contrast to atherosclerotic ones.

Pravastatin suppresses ox-LDL concentrations in serum and aorta

The concentrations of ox-LDL in serum and aorta were measured by ELISA. The concentrations of ox-LDL in serum and aorta of apoE-/- mice fed on a diet containing 1.25% cholesterol were significantly increased, compared with the concentrations in C57BL/6J mice fed on a normal diet.

CONCLUSIONS The findings of the present study provide a new mechanism through Which pravastatin can prevent atherosclerosis in apolipoprotein E knockout mice. This provides us with a new therapeutic approach and a clearer insight into the clinical benefits of pravastatin.

GW27-e0479

Unexpected Effect of Evacetrapib on Simvastatin Pharmacokinetics in Healthy Chinese Subjects

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OBJECTIVES To evaluate the reciprocal pharmacokinetic (PK) effects of selected statins and evacetrapib at steady state.

METHODS Selected statins + evacetrapib were evaluated in a Phase 1, open-label, 2-part, single- and multiple-dose study in healthy native Chinese subjects. Part 1 evaluated evacetrapib PK after a single 130-mg evacetrapib dose and after once-daily (QD) dosing for 14 days. In Part 2, subjects received simvastatin (simva) 40 mg or atorvastatin (atorva) 20 mg QD for 4 days (Days 1 to 4); 130 mg evacetrapib QD for 10 days (Days 5 to 14); then statin + evacetrapib for 8 days (Days 15 to 22). Blood samples were collected predose through 24 hours postdose on Days 4, 14, and 22 to assess evacetrapib and statin concentrations. PK parameters were estimated using non-compartmental methods. Blood samples were also analyzed for high-density lipoprotein cholesterol (HDL C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, and triglyceride (TG). Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory evaluations, and 12-lead electrocardiograms (ECGs).

RESULTS Sixty-two subjects aged 19 to 48 years entered the study, and 60 completed (16 in Part 1; 44 in Part 2). Two subjects discontinued in Part 2: 1 withdrew consent and 1 discontinued due to an AE of abdominal pain with unknown relationship to study treatment after 4 days of evacetrapib + simva.

In Part 1, mean estimates of evacetrapib area under the concentration-time curve (AUC) from time zero to the last time point with a measurable concentration (AUC[0-tlast]) and maximum observed drug concentration (Cmax) were, respectively, 7300 ng?h/mL and 418 ng/mL after a single 130-mg evacetrapib dose and 21900 ng?h/mL and 954 ng/mL after QD dosing for 14 days. Evacetrapib median time of Cmax (tmax) and mean half-life were comparable for both treatments.

In Part 2, simva AUC from zero to 24 hours (AUC[0-24]) and Cmax increased, respectively, by 123% and 58%, and simva acid AUC(0-24) and Cmax increased by 108% and 79%, with evacetrapib. Evacetrapib did not affect simva tmax. Atorva AUC(0-24) and Cmax were 16% and 20% higher, respectively, and median tmax increased by 0.26 hours with evacetrapib.

After evacetrapib + simva, mean HDL-C increased 91%, mean LDL-C decreased 72%, and mean total cholesterol decreased 17% from baseline. Mean TG was within 10.5% of baseline. After evacetrapib + atorva, mean HDL-C increased 96%, mean LDL-C decreased 78%, and mean total cholesterol decreased 19% from baseline. Mean TG was within 11.5% of baseline.

Oral 130-mg evacetrapib single or QD doses were well-tolerated alone or with a statin. There were no safety concerns noted in clinical laboratory test, vital sign, and ECG data.

CONCLUSIONS When coadministered with evacetrapib, simva exposure increased more than that of atorva. Simva and atorva are CYP3A4 substrates, while simva is also a substrate of CYP3A5, which is polymorphically expressed in Chinese. Evacetrapib weakly inhibited CYP3A4 in other clinical studies not conducted in China and it inhibited CYP3A5 in vitro. One hypothesis for the effect on simva exposure is that evacetrapib may inhibit CYP3A5 in vivo. CYP3A5 pharmacogenetic (PGx) expression could have elucidated these unexpected drug-drug interactions, but the samples were not collected for this study. The clinical interpretation of drug-drug interaction studies can be best informed in the context of data from in vitro, in vivo, and PGx sources.

GW27-e0498

Rosuvastatin dose-dependently improves flow-mediated dilation, but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients

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OBJECTIVES Increased risk of type 2 diabetes noted with statins is at least partially explained by HMG-coenzyme A reductase inhibition. We investigated vascular and metabolic phenotypes of different dosages of rosuvastatin in hypercholesterolemic patients.