Primary hypertension contributes to more than 50% of all the worldwide cardiovascular deaths. Its therapy is still targeting the physiological mechanisms regulating blood pressure, but not the genetic "causal" ones, therefore still important unmet medical needs remain. More than 30 years of genetic studies have been unable to prove causation in human for any of the 1,000 gene variants detected with GWAS. This PEARL-HT study was aimed at assessing "gene causation" in humans by testing whether rostafuroxin is more effective than losartan in lowering blood pressure in Caucasian and Chinese carriers of pre-specified variants, defined as genetic profiles, modulating the adducin (*ADD1* and *ADD3*) and endogenous ouabain (*LSS*, *MDR1* and *HSD3B1*) effects, that are selectively inhibited by rostafuroxin.

Methods and findings

This was a multicentre phase 2b trial conducted in Italy and Taiwan enrolling newly discovered and never treated patients with primary hypertension. Of 902 screened patients, 172 were enrolled in Italy and 107 in Taiwan. After stratification for country and genetic background, patients were randomized to rostafuroxin or losartan. Office Systolic Blood Pressure (OSBP) change two months after randomization was the primary variable. In Caucasians, the between-group differences (rostafuroxin 50 μg minus losartan 50 mg in OSBP (mmHg, (95% CI)) were statistically significant both in the genetic profile P2a and *LSS rs2254524 AA* mutant carriers (9.8 (0.6-19.0) with p=0.038 and 13.4 (25.4-2.5) with p=0.031, respectively). While in the *LSS CC* wild, losartan tended to be more effective than rostafuroxin, being the interaction between *LSS* genotypes with rostafuroxin response significant (p=0.023). Chinese had similar OSBP fall to that of Caucasians with losartan but no OSBP change with rostafuroxin. The lack of the BP responses to rostafuroxin in Chinese patients with the related power reduction is the major limitation of this study.

Conclusions

The selective blockade of mutant adducin and endogenous ouabain pressor mechanisms by rostafuroxin improves the therapy of primary hypertension in carriers of the related gene variants.