

# Adducin- and Ouabain-Related Gene Variants Predict the Antihypertensive Activity of Rostafuroxin.

## Part 2: Clinical Studies

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(Published 24 November 2010; Volume 2 Issue 59 59ra87)

Twenty years of genetic studies have not contributed to improvement in the clinical management of primary arterial hypertension. Genetic heterogeneity, epistatic-environmental-biological interactions, and the pathophysiological complexity of hypertension have hampered the clinical application of genetic findings. In the companion article, we furnished data from rodents and human cells demonstrating two hypertension-triggering mechanisms—variants of adducin and elevated concentrations of endogenous ouabain (within a particular range)—and their selective inhibition by the drug rostafuroxin. Here, we have investigated the relationship between variants of genes encoding enzymes for ouabain synthesis [LSS (lanosterol synthase) and HSD3B1 (hydroxy-d-5-steroid dehydrogenase, 3 $\beta$ - and steroid d-isomerase 1)], ouabain transport {MDR1/ABCB1 [ATP-binding cassette, sub-family B (MDR/TAP), member 1]}, and adducin activity [ADD1 (adducin 1) and ADD3], and the responses to antihypertensive medications. We determined the presence of these variants in newly recruited, never-treated patients. The genetic profile defined by these variants predicted the antihypertensive effect of rostafuroxin (a mean placebo-corrected systolic blood pressure fall of 14 millimeters of mercury) but not that of losartan or hydrochlorothiazide. The magnitude of the rostafuroxin antihypertensive effect was twice that of antihypertensive drugs recently tested in phase 2 clinical trials. One-quarter of patients with primary hypertension display these variants of adducin or concentrations of endogenous ouabain and would be expected to respond to therapy with rostafuroxin. Because the mechanisms that are inhibited by rostafuroxin also underlie hypertension related organ damage, this drug may also reduce the cardiovascular risk in these patients beyond that expected by the reduction in systolic blood pressure alone.