



LETTER TO THE EDITOR

Reduced heat shock proteins—a mechanism to explain higher cardiovascular events associated with doxazosin

I share the surprise expressed by Beevers and Lip in their recent commentary in the *Journal of Human Hypertension* concerning the result of the ALLHAT trial.¹ ALLHAT demonstrated that doxazosin administration was associated with an increased risk of major cardiovascular events.² This result was unanticipated because doxazosin has been associated with a beneficial metabolic profile—raising HDL, lowering triglycerides, increasing insulin sensitivity, and improving fibrinolysis,³ while also reducing left ventricular after-load.⁴ A biological mechanism to explain doxazosin's role in increasing cardiovascular disease has not been apparent.

Reduced heat shock proteins in the heart and vascular system may offer an explanation of why doxazosin was associated with a negative cardiovascular outcome. Heat shock proteins or stress proteins protect cells from the deleterious effects of acute or chronic stress. They act as cellular chaperones to proteins, lipids and nucleic acids by reducing oxidation, preventing apoptosis, suppressing proinflammatory cytokines, repairing ion channels, and aiding in protein folding.⁵ While known to molecular biologists for the past three decades, heat shock proteins have received little clinical attention.

Prazosin, a drug in the same class of alpha-adrenergic blockers as doxazosin, blocks heat shock

protein expression in the myocardium in response to noradrenaline stimulation and abolishes noradrenaline-induced cardioprotection, thus, leaving the heart vulnerable to injury.⁶ Heat shock proteins are normally expressed in response to cardiac strain and ischaemia which aids the cells to survive and recover from the insult. In addition, overexpression of heat shock proteins in transgenic mice reduces infarct size in heart and brain ischaemic models.⁷ Reduced heat shock proteins from an alpha-blocker like doxazosin or prazosin would result in unprotected cells and put the patient at a higher cardiovascular risk than otherwise might be anticipated, explaining the adverse outcome of doxazosin on the heart in the ALLHAT trial. Importantly, as pointed out by Beevers and Lip, prazosin has been associated with a higher mortality compared to other after-load reducers in the Vasodilator-Heart Failure Trial-1,⁸ suggesting that poorer cardiovascular outcome with alpha-adrenergic blockade may be a class effect.

The recent demand in the medical literature for studies with outcome data is further validated by the results of the ALLHAT trial. Improvement in cardiovascular risk factors by doxazosin would have predicted a reduced number of cardiovascular events. However, this trial proved that not to be the case, leading to an early

termination of the doxazosin arm of the study.

Philip L Hooper
University of Colorado Health
Care Sciences Center
Denver Colorado, 80262
2915 Ruth Ct.
Loveland, CO 80537, USA
E-mail: hooper@oneimage.com

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