

EDITORIAL COMMENT

Left Ventricular Hypertrophy Regression and Allopurinol

More Questions Than Answers*

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In this issue of the *Journal*, Szejewski et al. (1), from the University of Dundee, report that administration of allopurinol, 600 mg daily for 9 months, was associated with a reduction in magnetic resonance left ventricular (LV) mass index that was statistically significant compared with placebo in type 2 diabetic patients with echocardiographic left ventricular hypertrophy (LVH). While 90% of subjects had been treated for hypertension, there was no change in blood pressure that might provide an alternative potential mechanism (1). The rationale for the trial was strong basic scientific evidence that: 1) reactive oxygen species are important mediators of myocardial remodeling, myocyte hypertrophy, and myocardial fibrosis; 2) xanthine oxidase produces such superoxides and increases in cardiac remodeling; and 3) xanthine oxidase inhibitors, such as allopurinol, reduce LV remodeling in animal models (2–5). In addition, the Dundee group has previously reported that allopurinol reduces LV mass in patients with chronic kidney disease and in those with ischemic heart disease (6,7). The authors point to the association between LVH regression and reduced adverse outcomes in the LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) study (8) as a basis for anticipation of potential improvements in cardiovascular outcomes with administration of allopurinol in type 2 diabetes.

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Compelling demonstrations of the value of LVH regression in risk reduction, primarily in hypertension, have been a long time coming, although the belief that this would occur has been prevalent for many years. It has been 44 years since Kannel et al. (9) reported from Framingham that electrocardiographic evidence of LVH was associated with very adverse outcomes, 36 years since Devereux and I (10)

demonstrated feasibility of reliable noninvasive quantitation of LV mass, and 34 years since the earliest demonstrations of LVH regression during treatment of hypertension (11). However, it took until 2004 for the echocardiographic substudy of the LIFE study, led by Devereux et al. (8) and Lindholm et al. (12), to demonstrate convincingly the quantitative relationship of LV mass reduction to outcomes. For much of that interval, the belief in the value of LVH regression in hypertension was widespread, and even ubiquitous, but the evidence was weak.

A novel strategy to prevent LVH and adverse remodeling or to promote LVH regression is certainly of great interest and would be highly relevant to large populations with common highly-morbid cardiac disease states, including myocardial infarction. Because diabetic patients have a much higher prevalence of LVH than nondiabetics, with or without hypertension, and diabetics have a much higher prevalence of hypertension than nondiabetics, and LVH reduction resulting from treatment of hypertension is blunted in diabetics, this particular application of the approach is especially attractive (13–15).

Unfortunately, the present study leaves many uncertainties. First, the magnitude of the reduction in LV mass index observed was very small, only 1.3 g/m², and similar small reductions in LV mass were reported in previous studies of chronic renal disease by this group and in patients with prior myocardial infarctions. In contrast, LVH regression in hypertension trials typically ranges from 5 to 10 g/m² or more in the first year and was 14 g/m² in the LIFE study, more than 10-fold greater than that reported in this study. Whether such small changes in LV mass, even if increased in later years, can alter the natural history of disease is certainly unknown.

Second, in recent years there has been rapid growth of understanding that the composition of hypertrophied myocardium varies substantially, both among individuals with the same disease and between disease states, and that differences in composition affect prognosis and outcomes. The consequence is that it is no longer sufficient to evaluate simply the amount of LV myocardium. Rather, one needs to specify the components of the tissue and their change over time. In most disorders, the main issue is myocardial fibrosis. Development of this theme has been driven by CMR, first with the development of methods for accurate quantitation of macroscopic replacement fibrosis in patients with myocardial infarction, hypertrophic cardiomyopathy, nonischemic dilated cardiomyopathy, and aortic stenosis (16–19). More recently, there is convincing evidence that magnetic resonance imaging T1 relaxation mapping of myocardium before and after administration of gadolinium chelate permits quantitation of microscopic interstitial fibrosis, which cannot be seen on images, and that this quantitation, expressed as extracellular volume, correlates with histopathology and impacts prognosis (20,21). Moreover, expansion of extracellular volume in asymptomatic diabetics is predictive of adverse cardiovascular outcomes (22).

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However, in diabetics, myocardial composition may differ significantly from that in other disorders because diabetic patients may have very large amounts of advanced glycosylation end (AGE) products in both intramyocardial vasculature and in the myocardial interstitium, where they may stiffen structural proteins such as collagen by cross-linking and stimulate AGE receptors, leading to further profibrotic and inflammatory responses and altering myocyte function (23). A number of preliminary reports suggest that various blockers of AGE receptors or breakers of glycosylation bonds may be effective in preventing or reversing adverse AGE-related changes in cardiac tissues (24,25). Thus, in diabetic patients, further quantitation of composition of an expanded myocardial interstitium may be needed and, hopefully, new noninvasive tools to assess such composition. Surely it matters whether the small LV mass index reduction is the result of reduction in myocyte size or numbers, collagen content, or reduced AGE. If only myocyte size or numbers were reduced, the effect could actually be adverse. In any event, xanthine oxidase inhibition is not the only potential new strategy for improving cardiovascular outcomes in diabetics.

The final worrisome feature of the data presented in this study is the marked discrepancy between echocardiographic estimates of LV mass at intake and the initial CMR LV mass values. A difference between the two is expected and is attributable to technical issues. On one hand, echo cardiographic (echo) LV mass is calibrated against actual anatomic pathology data, using a regression equation. On the other hand, CMR methods commonly include protuberant trabeculae of myocardium in the cavity volume. The papillary muscles, which tend to increase in size disproportionately in LVH, are also often included in the cavity volume. Thus, it is expected that echocardiographic LV mass will be higher than CMR LV mass in each subject and closer to the true physical weight of the ventricle. However, because CMR LV mass is considerably more reproducible than echo LV mass, it remains the preferred approach because it is both more sensitive and more specific for changes over time. Further improvements in automated segmentation of CMR images may well eliminate this issue. However, in the present paper, the echo LV mass/CMR LV mass ratio is far higher than usual in the literature, resulting in some residual concern about interpretation of the data.

Overall, then, the present study is a small step forward. The results are tantalizing and must be pursued with larger, longer randomized trials, powered to assess outcomes and using all the CMR tools that shed light on myocardial composition. It would also be extremely valuable to develop and apply molecular imaging agents targeted to AGE in the myocardial interstitium, a task probably best done with radionuclide imaging. Whatever the ultimate outcome, one hopes it will not take as long to clarify the role of xanthine oxidase inhibition in cardiac

disease as it has to characterize the benefits of LVH regression in systemic hypertension. In the interim, the most one can conclude is the old Scottish legal verdict, "not proven."

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