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A Randomized Study of the Beneficial Effects of Aldosterone Antagonism on LV Function, Structure, and Fibrosis Markers in Metabolic Syndrome

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OBJECTIVES The purpose of this study was to identify the effects of spironolactone on left ventricular (LV) structure and function, and serological fibrosis markers in patients with metabolic syndrome (MS) taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

BACKGROUND Myocardial fibrosis may be an important contributor to myocardial impairment in MS, and aldosterone antagonism may reduce fibrosis.

METHODS Eighty patients (age 59 ± 11 years) with MS, already being treated with angiotensin II inhibition, were randomized to spironolactone 25 mg/day or placebo for 6 months. Each patient underwent baseline and follow-up conventional echocardiography and color tissue Doppler imaging. Raw data files were used to measure calibrated integrated backscatter and to calculate radial and longitudinal strain. Blood was obtained at baseline and follow-up to measure fibrosis markers (procollagen type III amino-terminal propeptide and procollagen type I carboxy-terminal propeptide [PICP]).

RESULTS The spironolactone group showed significant improvement of LV function, myocardial reflectivity, and LV hypertrophy, with a parallel decrease in levels of PICP and procollagen type III amino-terminal propeptide. No analogous changes were seen in the placebo group. Baseline strain ($\beta = 0.47$, $p < 0.0001$), spironolactone therapy ($\beta = -0.38$, $p < 0.0001$), and change in PICP level ($\beta = -0.19$, $p < 0.03$) were independently associated with LV systolic function improvement (increase in strain). Correlates of LV diastolic function improvement (increase in early diastolic mitral annular velocity) were baseline early diastolic mitral annular velocity ($\beta = 0.47$, $p < 0.0001$), spironolactone therapy ($\beta = -0.21$, $p < 0.03$), change in PICP level ($\beta = -0.23$, $p < 0.02$), and age ($\beta = 0.22$, $p < 0.04$). Favorable effects of spironolactone on cardiac function were not demonstrated in patients with less fibrosis (the lower baseline PICP tertile) or preserved function (the upper baseline strain tertile).

CONCLUSIONS Addition of spironolactone to standard angiotensin II inhibition improved myocardial abnormalities and decreased fibrotic markers in MS. The magnitude of benefit on cardiac performance is determined mainly by baseline LV dysfunction and collagen turnover as well its response to intervention. (J Am Coll Cardiol Img 2011;4:1239–49) © 2011 by the American College of Cardiology Foundation

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The constellation of cardiovascular risk factors represented by metabolic syndrome (MS) is associated with increased cardiovascular morbidity and mortality. Cardiac complications of MS include abnormal left ventricular (LV) structure and function, leading progressively to congestive heart failure (1–5). As the prevalence of this condition rises to nearly a quarter of the adult population, exceeding 40% in those older than 50 years (6), these cardiac ramifications are likely to become a major public health concern.

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ABBREVIATIONS AND ACRONYMS

A = peak late diastolic flow velocity

AA = aldosterone antagonist

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

E = peak early diastolic flow velocity

e′ = peak early diastolic mitral annular velocity

Em = peak early diastolic myocardial velocity

IB = integrated backscatter

LV = left ventricular

MS = metabolic syndrome

PICP = procollagen type I carboxy-terminal propeptide

PIIINP = procollagen type III amino-terminal propeptide

RAA = renin-angiotensin-aldosterone

SR = peak systolic strain rate

TGF = transforming growth factor

The mechanisms behind cardiac derangements in MS are multifactorial, but one of the pivotal contributors is thought to be myocardial fibrosis (7). Accordingly, measures targeting this pathophysiology might improve outcomes by reducing the pathological substrate accounting for myocardial impairment. The renin-angiotensin-aldosterone (RAA) system has been incriminated in the process of cardiac fibroblast proliferation and collagen synthesis. However, although angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used for the treatment of hypertension in MS, suboptimal aldosterone suppression due to "aldosterone escape" (8–10) may limit the potential suppression of myocardial fibrosis by these drugs.

Aldosterone antagonists (AAs) may improve LV systolic and diastolic function as well as reduce cardiac fibrosis in various heart diseases (11–17), although the combination of AAs and ACEIs/ARBs is less well explored (18,19). The effect on the extracellular matrix was a contributor to the improved outcomes in 2 large randomized trials that demonstrated that the addition of AAs to standard therapy (including ACEIs or ARBs) diminished the risk of mortality and morbidity in heart failure (20,21). Given the role of enhanced fibrosis in the pathophysiology of metabolic disorders, as well as growing evidence on the beneficial effect of AAs extending beyond patients with moderate to severe heart failure (17,22), we hypothesized that implementation of spironolactone in addition to drugs opposing angiotensin II would improve cardiac abnormalities in the population with MS regardless of the symptoms of heart decompensation. Circulating markers of collagen type I and type III turnover—procollagen type I carboxy-terminal propeptide (PICP) and procollagen type III amino-terminal propeptide (PIIINP)—may reflect the intensity of myocardial fibrosis and thus may provide insight into fibrous tissue accumulation in the heart muscle (23–25). In this randomized controlled trial, we sought to determine the effects of adding spironolactone to ACEIs or ARBs on LV structure and function and serological fibrosis markers in patients with MS.

METHODS

Study design. The present study was designed as a prospective, blinded, parallel-group, placebo-controlled trial evaluating the potential of 6 months of treatment with spironolactone 25 mg/day to improve cardiac function and morphology and reduce fibrosis intensity in patients with MS. The primary endpoints were alterations in LV function as assessed by systolic echocardiographic parameters (strain and peak systolic strain rate [SR]) and diastolic parameters (peak early diastolic velocity [Em] and the ratio of mitral inflow early diastolic velocity to peak early diastolic mitral annular velocity [E/e′]). Secondary endpoints included changes in collagen metabolism as reflected by serum levels of PICP and PIIINP, myocardial echodensity as estimated by integrated backscatter (IB), LV wall thicknesses, and LV mass. This report follows the recommendations of the 2010 Consolidated Standards of Reporting Trials Statement (26).

Sample size was calculated on the basis of previous data from patients with MS (1). Assuming a significant difference in peak strain of 10% between spironolactone and placebo and applying the variance seen in our patients, the predicted sample size was 37 per group at 95% power and 2-sided alpha level of 0.05. To allow for possible dropouts, we increased the number of patients in each group to 40.

Randomization to spironolactone or matching placebo was done in blocks of 10 with an allocation ratio of 1:1 using sequentially numbered, opaque, sealed envelopes. The randomization list and the study drugs were prepared by the assigned person coordinating the study, who was not involved in the procedures. Patients' selection and randomization were carried out by the designated investigators. The study participants and the investigators assessing the outcomes were blinded to group assignment.

Study medication was withheld in the presence of significant hyperkalemia (>5.5 mmol/l), renal impair-