

The effect of baseline physical activity on cardiovascular outcomes and new-onset diabetes in patients treated for hypertension and left ventricular hypertrophy: the LIFE study

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The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, which enrolled patients with significant cardiovascular pathology, evaluates the relationship between physical activity (PA) at baseline and cardiovascular outcomes and new-onset diabetes.

Physical inactivity increases the relative risk for coronary heart disease (CHD) 1.5-2.4 fold, comparable to hypercholesterolemia, hypertension or smoking. PA is an accepted preventive approach for cardiovascular disease and the management of cardiovascular risk factors. Until now, there is little information on the efficacy of PA for the prevention of cardiovascular outcomes, once cardiovascular disease is already installed.

The LIFE study was a prospective, multi-national, double-blind, randomized trial, which examined the effects of losartan compared to atenolol in 9,193 patients with hypertension and electrocardiographic left ventricular

hypertrophy (LVH). Patients aged 55-80 years, with electrocardiographic LVH, diastolic blood pressure of 95-115 mm Hg and/or systolic blood pressure of 160-200 mm Hg after 2 weeks of placebo treatment were included. 9,193 eligible patients were randomized to losartan or atenolol and matching placebo, with the following titration scheme of the study drug: step 1, study drug 50 mg; step 2, study drug 50 mg plus hydrochlorothiazide (HCTZ) 12.5 mg; step 3, study drug 100 mg plus HCTZ 12.5 mg; step 4, study drug 100 mg plus HCTZ =25 mg or addition of other antihypertensive agents (excluding angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or beta-blockers). Target blood pressure was less than 140/90 mmHg.

The primary endpoint was a composite of cardiovascular death, nonfatal and fatal stroke and nonfatal and fatal myocardial infarction. Patients reported their level of PA at baseline and at the end of the follow up (at 60 months)

as: 1. never exercise; 2. exercise = 30 min twice/week; 3. exercise > 30 min twice per week.

At baseline 51.8 % of the subjects exercised > 30 min twice/week, 26, 2% exercised = 30 minutes twice/week and 22% never exercised. There were significantly higher proportions of women, smokers, obese, diabetic patients and patients with impaired renal function amongst the group with low PA. Patients who didn't exercise had a history of more important cardiovascular disease. There were significant trends to higher quality of life and lower heart rate with higher PA level. The groups had similar values for Framingham risk score. Study drug distribution was similar amongst PA groups.

Blood pressure and heart rate were similarly reduced amongst the PA groups (SBP reduced 29-31 mm Hg, DBP 16-17 mm Hg and heart rate 5 beats per minute). Patients exercising > 30 min twice/week experienced significantly lower rates of the primary composite endpoint and its components (cardiovascular death, stroke and myocardial infarction) compared to those who never exercise. The risk for cardiovascular death and all-cause mortality tended to be intermediate in the = 30 min twice/week group compared to the never exercise group. By subtracting cardiovascular deaths from all-cause deaths, there was only a trend ($P=0.28$) towards fewer non-cardiovascular deaths in the group with higher levels of exercise. A separate gender analysis showed the same lower endpoint rates in the physically active subjects.

The risk of new-onset diabetes was decreased by 36% ($P < 0.001$) in the group with

high PA, compared to patients without PA and was similar after additional adjustments for BMI at baseline, serum creatinine, urinary albumin/creatinine ratio and cardiovascular disease data. The risk reduction was not significantly different between the two treatment groups. The separate gender analysis showed higher absolute event rates amongst males compared to females.

The study has several limitations. The analysis was based on self reported activity level and not objectively measured fitness. Also patients may have been self sorted based on their basal fitness so that higher PA may not have been the cause of the observed benefits, but may have been just a marker of better health. The study didn't assess whether unmeasured behavioral parameters have contributed to the final results.

The data from the presented study suggest that a modest level of PA (>30 min twice/week) in hypertensive patients with LVH can be associated to significant reductions in risks for the primary composite endpoint and its components of cardiovascular death, stroke and myocardial infarction, and also in all-cause mortality and new-onset diabetes. An important finding is the substantial benefit demonstrated with modest PA. The protective effect of exercise was present both in men and in women. We must also underline the fact that the LIFE study is the first study focused on PA conducted in older patients with significant cardiovascular pathology.

Comment on the paper:

Fossum E, Gleim GW, Kjeldsen SE, et al. – The effect of baseline physical activity on cardiovascular outcomes and new-onset diabetes in patients treated for hypertension and left ventricular hypertrophy: the LIFE study. *Journal of Internal Medicine* 2007; 262:439-448