Effect of Changes in Physical Activity on Risk for Cardiac Death in Patients With Coronary Artery Disease

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Leisure-time physical activity (LTPA) is associated with longevity in patients with coronary artery disease (CAD). However, less is known about prognostic significance of longitudinally assessed LTPA in patients with stable CAD. The present study assessed the relationship between changes in LTPA and cardiac mortality in patients with CAD. Patients with angiographically documented CAD (n = 1,746) underwent clinical examination and echocardiography at the baseline. Lifestyle factors, including LTPA (inactive, irregularly active, active, highly active), were surveyed at baseline and after 2 years' follow-up. Thereafter, the patients entered the follow-up (median: 4.5 years; first to third quartile: 3.4 to 5.8 years) during which cardiac deaths were registered (n = 68, 3.9%). The patients who remained inactive (n = 114, 18 events, 16%) and became inactive (n = 228, 18 events, 8%) had 7.6- (95% confidence interval [CI] 4.2 to 13.6) and 3.7-fold (95% CI 2.1 to 6.7) univariate risk for cardiac death compared with those who remained at least irregularly active (n = 1,351, 30 events, 2%), respectively. After adjustment for age, gender, body mass index, diabetes, previous myocardial infarction, left ventricular ejection fraction, angina pectoris grading, cardiovascular event during initial 2-year follow-up, smoking and alcohol consumption, the patients who remained inactive and became inactive still had 4.9- (95% CI 2.4 to 9.8, p <0.001) and 2.4-fold (95% CI 1.3 to 4.5, p <0.01) risk for cardiac death, respectively, compared with patients remaining at least irregularly active. In conclusion, LTPA has important prognostic value for cardiac death in patients with stable CAD. Even minor changes in LTPA over 2 years were related to the subsequent risk for cardiac death. **(Am J Cardiol 2018;121:143–148)**

Physical activity is a core component of primary and secondary prevention of coronary artery disease (CAD) reducing cardiac mortality and improving quality of life in a cost-effective manner.[1–6] However, many studies assessing the association between leisure-time physical activity (LTPA) and health outcome suffer from lack of re-assessment of LTPA during the follow-up that may result in underestimation of the prognostic significance of LTPA.[7] Wannamethee et al suggested that CAD patients who became sedentary or occasionally active during long-term follow-up of 12 to 14 years had greater risk for subsequent cardiovascular death than even those who remained sedentary or occasionally active.[8] Although the current data suggest that even modest LTPA would be beneficial in terms of cardiovascular morbidities,[5,6] Wannamethee et al did not observe significant reduction in the risk for cardiovascular death with increased LTPA. However, it remains unclear whether shorter-term changes in LTPA modify the risk for cardiac death. The aim of the present study was to assess the association of changes in LTPA, observed over 2 years, with cardiac mortality during subsequent follow-up up to 7 years among patients with stable CAD. We hypothesized changes in LTPA over 2 years may modify later risk for cardiac death independently of traditional cardiovascular risk markers in CAD.

Methods

The study population comprised CAD patients from the ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection, ClinicalTrials.gov identifier: NCT01426685) study database (n = 1,946) collected in the Division of Cardiology of the Oulu University Hospital (Oulu, Finland). The ARTEMIS study aims to assess several traditional and novel cardiovascular risk markers as

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determinants of risk for sudden cardiac death during 5 years' follow-up in patients with stable CAD and type 2 diabetes. The patients were recruited from a consecutive series of patients who had undergone coronary angiography 3 to 6 months earlier and had >3 months from possible previous acute coronary syndrome before enrollment. The primary inclusion criterion was angiographically verified CAD with coronary stenosis >50% of ≥1 coronary arteries. Detailed exclusion criteria are described elsewhere in detail.[9] For example, patients who have New York Heart Association class IV, pacemaker or implantable cardioverter defibrillator, planned implantable cardioverter defibrillator implantation, end-stage renal failure needing dialysis, or life expectancy <1 year were excluded. For the present study the patients without 2-year follow-up data about LTPA (n = 200) were excluded. The study was performed according to the Declaration of Helsinki. The local committee of research ethics of the Northern Ostrobothnia Hospital District approved the protocol, and all the subjects gave written informed consent. The study consisted of 3 phases: baseline examinations, initial 2-year follow-up with surveys, and the subsequent main follow-up.

At the baseline, body weight and mass index were measured and subjects without previously diagnosed type 2 diabetes underwent an oral glucose tolerance test to establish their glucose metabolism status. Blood pressure was measured in a supine position after a 10-minute resting period. Left ventricular ejection fraction (LVEF) was measured by the biplane method from 2- and 4-chamber views using the same ultrasound machine for all of the patients (Vivid 7, GE Healthcare, Wauwatosa, WI). An incremental symptom-limited maximal exercise test on a bicycle ergometer started at 30 W, and the work rate was increased by 15 W in men and 10 W in women every minute until voluntary exhaustion. Exercise was calculated as metabolic equivalents from the mean workload during the last minute of the test and normalized according to age and gender.[10] SYNTAX score was analyzed before and after revascularization preceding enrolment (SYNTAX Score website, version 2.11, http://www.syntaxscore.com).

The patients completed a health questionnaire containing a question about the frequency of habitual LTPA, smoking status (yes/no), and alcohol consumption (yes/no) at the baseline and after 2 years' initial follow-up; body weight was also surveyed after 2 years. Four LTPA groups were formed by modifying a scale originally developed by Saltin and Grimby[11]: (1) no LTPA (hardly any physical activity or only light housework; (2) LTPA irregularly (some light physical activity randomly, e.g., walking or cycling); (3) moderate-intensity LTPA regularly 2 to 3 times weekly; and (4) moderate- or high-intensity LTPA >3 times weekly, where "time" means a period of 30 minutes. The Saltin-Grimby Physical Activity Level Scale has shown good validity[12] and has been shown to be related to both cardiovascular risk factors[12,13] and outcomes.[5] Longitudinal analysis of LTPA was based on our previous report,[14] where the optimal cut-off value for LTPA in prediction of total mortality by Youden's index was *less than irregular*. Based on this cut-off value, the patients were categorized as (1) Active-Active (LTPA ≥ irregular at both time points), (2) Inactive-Active (No LTPA at the baseline, LTPA ≥ irregular at 2 years), (3) Active-Inactive (LTPA ≥ irregular at baseline, No LTPA at 2 years), and (4) Inactive-Inactive (No LTPA at both time points).

During the initial 2-year follow-up, new (1) acute coronary syndrome (myocardial infarction or unstable angina pectoris), (2) cardiac procedure (angiography, revascularization, pacemaker, or defibrillator implantation), (3) stroke or transient ischemic attack, (4) arteriosclerosis obliterans (carotid or femoral artery), (5) hospitalization due to heart failure, and (6) cardiac arrhythmia (ventricular fibrillation/tachycardia, supraventricular tachycardia, or atrial fibrillation/flutter) were registered by mailed inquiry or phone calls or from hospital records. A composite end point of all events during initial follow-up, described above, was used as covariate in the analysis of the main follow-up data. Risk score for cardiovascular death based on the Reduction of Atherothrombosis for Continued Health-project (REACH score)[15] were also calculated at the baseline and at 2 years.

The main follow-up started after the initial 2 years' follow-up. The deaths were registered during the main follow-up and defined as cardiac or noncardiac. The primary end point of this ARTEMIS substudy was cardiac death. The follow-up information was collected from the national death registries (Statistics Finland, Helsinki, Finland), from patients by mailed inquiry, telephone calls to the closest relatives of the victims of death, and from the electronic patient records.

The between-group differences were assessed by one-way analysis of variance, Kruskal-Wallis, or chi-square followed by post hoc analyses by Bonferroni, Mann-Whitney *U* test, or chi-square adjusted for multiple comparisons. The predictive power of LTPA variables was assessed by univariate Cox regression followed by adjustment for age, gender, baseline body mass index, diabetes, history of myocardial infarction, LVEF, Canadian Cardiovascular Society grading for angina pectoris (CCS class), cardiovascular event during initial 2-year follow-up, smoking status at 2 years, and alcohol consumption at 2 years. Complementarily, Cox regression analyses were further adjusted for exercise capacity. Incremental prognostic value of changes in LTPA to REACH score at the baseline and at 2 years was also established. Interactions of dichotomized LTPA variables ($LTPA_{Baseline}$ = Inactive, $LTPA_{2years}$ = Inactive; $LTPA_{Baseline\text{-}2years}$ = Inactive-Inactive; yes/no) with gender and diabetes were also studied by Cox regression (model: gender/diabetes, LTPA, gender/diabetes*LTPA). Kaplan-Meier analysis was used to illustrate survival curves of different groups of risk. The data were analyzed using SPSS software (IBM SPSS Statistics 21, IBM Corp., Armonk, New York). A p value <0.05 was considered statistically significant.

Results

During the median follow-up of 54 months (in survivors; first to third quartile 41 to 69 months), there were 68 cardiac deaths (3.9%) (Table 1). Among covariates, age (hazard ratio [HR] 1.10, 95% confidence interval [CI] 1.05 to 1.14, p <0.001), diabetes (HR 2.13, 95% CI 1.24 to 3.66, p = 0.006), LVEF (HR 0.95, 95% CI 0.93 to 0.97, p <0.001), and CCS class ≥2 (HR 2.62, 95% CI 1.47 to 4.67, p = 0.001) were significantly associated with cardiac death in multivariate analysis without LTPA variables. The baseline REACH score alone was also a significant predictor of cardiac death (HR 1.54, 95% CI 1.39 to 1.71, p <0.001).

Baseline LTPA was significantly associated with cardiac death in univariate and multivariate analyses (Tables 2 and