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# Effects of Physical Activity and Exercise Training on Cardiovascular Risk in Coronary Artery Disease Patients With and Without Type 2 Diabetes

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## OBJECTIVE

**Leisure-time physical activity (LTPA) and exercise training are essential parts of current guidelines for patients with coronary artery disease (CAD). However, the contributions of LTPA and exercise training to cardiovascular (CV) risk in CAD patients with type 2 diabetes (T2D) are not well established.**

## RESEARCH DESIGN AND METHODS

**We examined the effects of LTPA (*n* = 539 and *n* = 507; with and without T2D, respectively) and 2-year controlled, home-based exercise training (*n* = 63 plus 64 control subjects with T2D and *n* = 72 plus 68 control subjects without T2D) on the CV risk profile and composite end point among CAD patients.**

## RESULTS

**During the 2-year follow-up, patients with reduced LTPA at baseline had an increased risk of CV events (adjusted hazard ratio 2.3 [95% CI 1.1–5.1; *P* = 0.033], 2.1 [1.1–4.2; *P* = 0.027], and 2.0 [1.0–3.9; *P* = 0.044] for no LTPA, LTPA irregularly, and LTPA two to three times weekly, respectively) compared with those with LTPA more than three times weekly. Among patients who completed the 2-year exercise intervention, exercise training resulted in favorable changes in exercise capacity both in CAD patients with T2D (+0.2 ± 0.8 vs. −0.1 ± 0.8 MET, *P* = 0.030) and without T2D (+0.3 ± 0.7 vs. −0.1 ± 0.5 MET, *P* = 0.002) as compared with the control group but did not have any significant effects on major metabolic or autonomic nervous system risk factors in CAD patients with or without T2D.**

## CONCLUSIONS

**There is an inverse association between habitual LTPA and short-term CV outcome, but controlled, home-based exercise training has only minor effects on the CV risk profile in CAD patients with T2D.**


Physical activity and exercise training with well-known health benefits are key elements in the management of coronary artery disease (CAD) (1,2) and type 2 diabetes (T2D) (3). Although current guidelines for patients with CAD or T2D recommend physical activity daily, many patients do not become or remain regularly active (4–6). Almost half of patients with CAD do not attend recommended rehabilitation programs (7), and among attending patients, the dropout rate is even

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40–50% (8,9). After cardiac rehabilitation, maintenance of an increased level of physical activity is difficult, although it would be important for sustaining achieved health benefits. Only ~40% of cardiac patients adhered to physical activity three times or >150 min weekly 1 year after cardiac rehabilitation (10,11).

CAD patients with T2D are less likely to comply with physical activity recommendations and complete cardiac rehabilitation programs than their counterparts without diabetes (6,12). Typically, patients with T2D have many comorbidities that may negatively affect their prognosis. Diabetic patients with a previous myocardial infarction have a higher risk of premature mortality than nondiabetic patients with a myocardial infarction (13–15). It seems that even though an intensive lifestyle intervention produces improvements in cardiovascular (CV) risk factors in adults with T2D (16,17), it does not reduce their long-term CV morbidity and mortality (17).

The goal of the current study was to examine the effects of habitual leisure-time physical activity (LTPA) on short-term CV outcome in CAD patients with and without T2D. A secondary objective was to investigate the effects of a controlled exercise training program on CV risk factors, such as body composition, blood glucose and lipid levels, inflammation markers, cardiac function, exercise capacity, and CV autonomic function among CAD patients with and without T2D.

## RESEARCH DESIGN AND METHODS

### Subjects and Study Protocol

The ARTEMIS study (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection; registered at clinicaltrials.gov, NCT01426685) was initiated to compare traditional and novel CV risk markers between CAD patients with and without T2D and to assess the prognostic value of these markers in predicting CV events. CAD patients with and without T2D (1:1 matched in terms of age, sex, prior myocardial infarction, and revascularization procedure) were recruited from a consecutive series of patients who had undergone coronary angiography at the Division of Cardiology of Oulu University Hospital. CAD was confirmed by coronary angiography, and T2D was defined according to the criteria of the World Health Organization (18).

The ARTEMIS exercise substudy was a 2-year controlled exercise trial and was performed in the Department of Exercise and Medical Physiology at Verve (Oulu, Finland). There were 507 CAD patients without T2D and 539 CAD patients with T2D in the ARTEMIS database from August 2007 through March 2011. Of those patients, 644 were excluded from the exercise study due to the following criteria: advanced age (>75 years), BMI >40 kg/m$^2$, NYHA class ≥III, left ventricular ejection fraction (LVEF) <40%, scheduled cardiac revascularization therapy, heart failure, unstable angina pectoris, severe peripheral atherosclerosis, diabetic retinopathy or neuropathy, type 1 diabetes, prediabetes, or inability to perform regular home-based exercise, e.g., due to musculoskeletal problems. Altogether 291 patients were willing to participate and were divided into the exercise training and control groups 1:1 matched in terms of sex and presence of T2D. In total, 135 patients in the exercise training group and 132 patients in the control group took part in follow-up measures and were included in the analyses of CV risk factors according to the intention-to-treat principle (Fig. 1). 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 their written informed consent.

### Exercise Training Intervention

The exercise training intervention consisted of home-based endurance exercises and strength exercises. During the first 3 months, the exercise training included three endurance exercises (30 min, 50–60% of the heart rate reserve) and one strength exercise (30 min) weekly. During the last 6 months, it comprised six exercises weekly: one strength and five endurance exercises (40 min). Two of the endurance exercises were at a 50–60% and two at a 60–70% intensity level, and the fifth session was interval training at a 70–80% intensity level. The patients were given a diary in which they entered the realized training mode, duration, and mean heart rate (Polar F1; Polar Electro Oy, Kempele, Finland). The patients in the control group were treated according to usual care, and they did not get any individually tailored exercise prescriptions.

### Measurement of LTPA

At the baseline, the patients filled in a health questionnaire containing a question about the frequency of habitual LTPA. Four physical activity groups were formed by modifying a scale originally developed by Saltin and Grimby (19): *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 two to three times weekly; and *4*) moderate- or high-intensity LTPA more than three times weekly, where "time" means a period of >30 min. The Saltin-Grimby Physical Activity Level Scale has shown good validity (20) and has been shown to be related to both CV risk factors (20,21) and CV outcomes (22).

### Measurement of Exercise Capacity

All the patients performed an incremental symptom-limited maximal exercise test on a bicycle ergometer (Monark Ergomedic 839 E; Monark Exercise AB, Vansbro, Sweden) for assessment of exercise capacity. The test was 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 or ST depression >0.2 mV in electrocardiogram (ECG) (CAM-14; GE Healthcare, Freiburg, Germany). Maximal workload was calculated as the average workload during the last minute of the test, and maximal exercise capacity was then calculated from the maximal workload.

### Measurement of CV Autonomic Function

A 24-h ambulatory ECG was recorded with a digital Holter recorder (Medilog AR12; Huntleigh Healthcare U.K.) and analyzed with HEARTS software (Heart Signal, Kempele, Finland). Ectopic beats and artifacts were removed from R-R intervals based on visual inspection. In the exercise study, 30 patients (11%) from a total of 267 did not undergo the 24-h ECG recording or were excluded from the analysis due to a large amount of technical and biological disturbances. In total, 127 CAD patients and 110 CAD patients with T2D were included in the analyses.

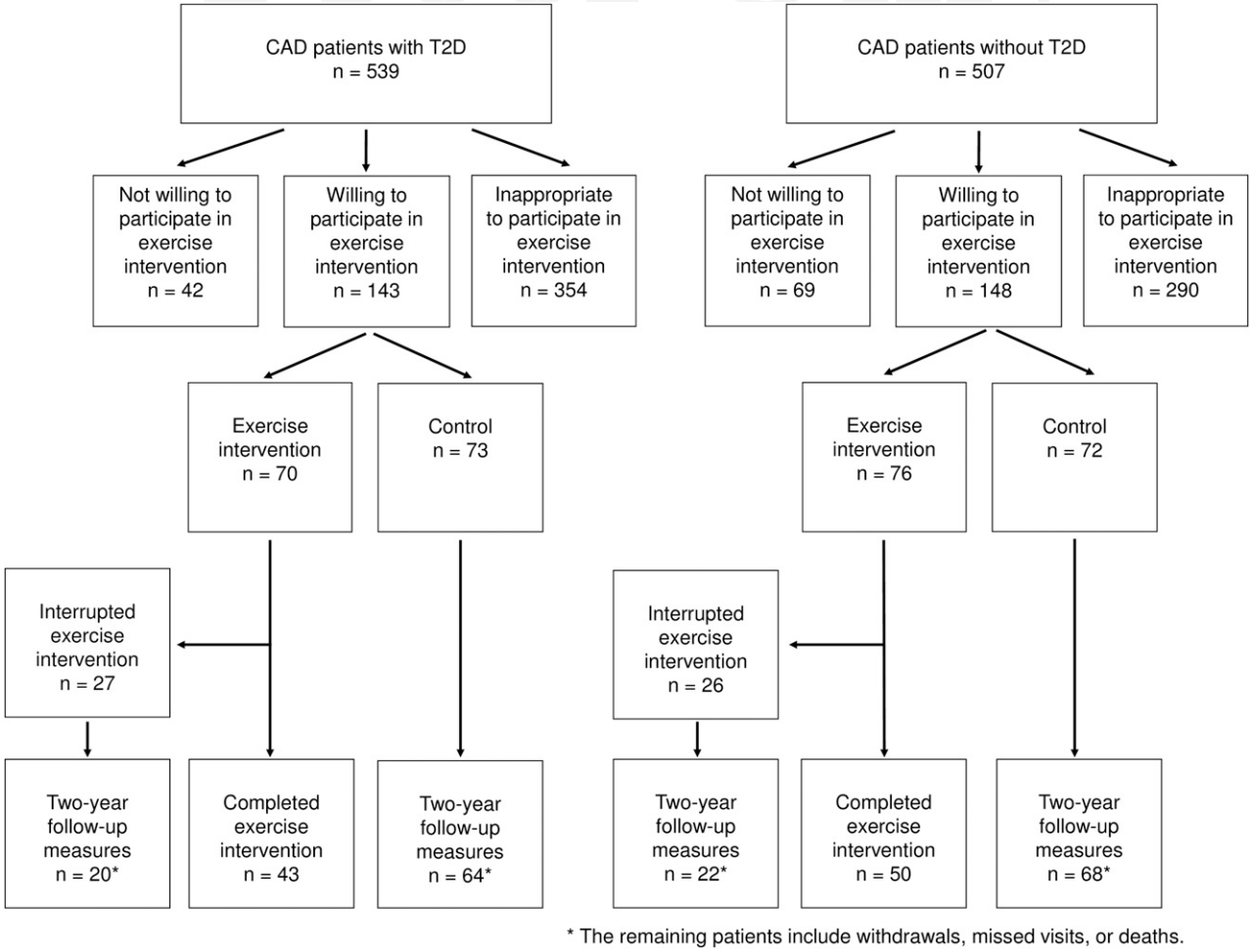


**Figure 1**—Patient selection protocol from the ARTEMIS database.

### Measurements of CV Risk Factors

Body composition was assessed by measurements of weight, waist and hip circumference, and BMI. Blood pressure was measured in a supine position after a 10-min resting period. Left ventricular systolic and diastolic function were assessed by two-dimensional and tissue Doppler echocardiography (Vivid 7; GE Healthcare, Wauwatosa, WI). Left ventricular mass (LVM) was calculated using a previously published corrected equation (23), and the LVM index (LVMI) was calculated by dividing LVM by body surface area. Urine and fasting blood samples were obtained after a 12-h overnight fast for analysis of renal function, plasma glucose and glycated hemoglobin $A_{1c}$ ($HbA_{1c}$) levels, blood lipids, and inflammation markers using standardized methods.

### CV End Point

The end point was defined as a combination of CV death, an acute coronary event, a stroke, or hospitalization for heart failure. The follow-up data were collected from the patient records of Oulu University Hospital and the mortality statistics of Statistics Finland and the Causes of Death Register.

### Statistical Analyses

A Kolmogorov-Smirnov *z* test was used to examine the Gaussian distribution of the data. At the baseline, comparisons between groups were obtained by using one-way ANOVA with a Bonferroni post hoc test, the Kruskal-Wallis H test followed by post hoc analyses by Mann-Whitney *U* test, or a $\chi$ test, accordingly. After the follow-up, univariate Cox regression was used to estimate hazard ratios (HRs) with 95% CIs for the association between levels of LTPA and CV outcome. Thereafter, multivariate Cox regression analysis was performed, including age, sex, presence of T2D, smoking, BMI, systolic blood pressure, HDL and LDL cholesterol, hs-CRP, LVEF, history of acute myocardial infarction, and revascularization procedure as covariates. The Kaplan-Meier survival curves were plotted to illustrate one minus cumulative proportional probabilities of the end point across categories of habitual LTPA, and the log-rank test was used to assess the statistical significances of the differences between the curves.

The effects of the exercise training on CV risk factors were analyzed by two-factor ANOVA with time and interventions. Variables with non-Gaussian distribution were transformed into natural logarithms before parametric statistical testing. First, the analyses by two-factor ANOVA were performed according to the intention-to-treat principle. Second, the same analyses were done only among patients who completed the whole 2-year intervention, regardless of their realized training. When significant time $\times$ intervention interaction was observed, a post hoc analysis was performed using a paired Student *t* test

between pre- and postintervention values within each group and a Student *t* test for independent samples for between-group comparison at pre- and postintervention conditions. Statistical analyses of the data were performed with SPSS software (SPSS 22; SPSS Inc., Chicago, IL), and statistical significance was defined as a *P* value $<0.05$ for all tests.

## RESULTS

### LTPA and CV End Point

The baseline characteristics of the ARTEMIS study population, categorized according to levels of LTPA, are described in Table 1. During the 2-year follow-up, a total of 131 patients (13%) reached a composite CV end point, including 80 patients (8%) with T2D and 51 patients (5%) without T2D (*P* = 0.035). Patients with reduced levels of LTPA at baseline had an increased risk of a CV end point (no LTPA, HR 3.41 [95% CI 1.67–6.96], *P* = 0.001; LTPA irregularly, 2.28 [1.18–4.36], *P* = 0.014; LTPA two to three times weekly, 2.04 [1.06–3.95], *P* = 0.033) compared with those who reported LTPA more than three times weekly (Fig. 2). Further adjustment for CV risk factors changed the HRs only slightly (no LTPA, 2.33 [1.07–5.06], *P* = 0.033; LTPA irregularly, 2.13 [1.09–4.17], *P* = 0.027; LTPA two to three times weekly, 1.98 [1.02–3.86], *P* = 0.044). When patients who participated in the exercise intervention were excluded from the Cox regression analysis, the adjusted HRs remained unchanged (no LTPA, 2.26 [1.01–5.08], *P* = 0.048; LTPA irregularly, 2.08 [1.03–4.23], *P* = 0.043; LTPA two to three times weekly, 1.97 [0.98–3.98], *P* = 0.058).

In CAD patients with T2D, HRs for a CV end point were 2.68 (95% CI 1.06–6.75; *P* = 0.037), 2.12 (0.89–5.06; *P* = 0.089), and 1.88 (0.76–4.63; *P* = 0.171) for no

**Table 1—Characteristics and composite CV end point in the ARTEMIS study population categorized according to levels of LTPA**

| | | Levels of physical activity | | | | |
|---|---|---|---|---|---|---|
| | ARTEMIS study population, *n* = 1,046 | No LTPA, *n* = 122 (12%) | LTPA irregularly, *n* = 371 (35%) | LTPA 2–3 times weekly, *n* = 374 (36%) | LTPA >3 times weekly, *n* = 175 (17%) | *P* value for main effect |
| Men, *n* | 716 (69%) | 82 (67%) | 252 (68%) | 244 (65%) | 135 (77%)‡ | 0.045 |
| Patients with T2D, *n* | 539 (52%) | 92 (75%) | 214 (58%)* | 154 (41%)*,† | 75 (42%)*,† | <0.001 |
| Age, year | 67 ± 8 | 69 ± 9 | 67 ± 8* | 67 ± 8* | 67 ± 7 | 0.017 |
| Weight, kg | 81.3 ± 15.7 | 93.1 ± 20.2 | 83.1 ± 15.5* | 78.0 ± 13.7*,† | 76.8 ± 12.5*,† | <0.001 |
| BMI, kg/m$^2$ | 28.4 ± 4.7 | 32.7 ± 6.2 | 29.0 ± 4.4* | 27.3 ± 4.0*,† | 26.5 ± 3.4*,† | <0.001 |
| Systolic BP, mmHg | 147 ± 23 | 150 ± 25 | 145 ± 23 | 147 ± 22 | 149 ± 22 | 0.055 |
| Diastolic BP, mmHg | 78 ± 11 | 80 ± 12 | 78 ± 10 | 78 ± 11 | 78 ± 10 | 0.295 |
| LVEF, % | 65 ± 9 | 62 ± 11 | 65 ± 9 | 65 ± 9 | 65 ± 9 | 0.058 |
| Exercise capacity, MET | 6.0 ± 1.8 | 4.3 ± 1.4 | 5.8 ± 1.6* | 6.3 ± 1.7*,† | 7.1 ± 1.8*,†,‡ | <0.001 |
| Current smokers, *n* | 529 (51%) | 70 (57%) | 199 (54%) | 182 (49%) | 77 (44%)*,† | 0.065 |
| History of AMI | | | | | | |
| NSTEMI, *n* | 307 (29%) | 51 (42%) | 121 (33%) | 91 (24%)*,† | 43 (25%)* | 0.001 |
| STEMI, *n* | 159 (15%) | 23 (19%) | 57 (15%) | 54 (14%) | 23 (13%) | 0.415 |
| Revascularization | | | | | | |
| PCI, *n* | 596 (57%) | 76 (62%) | 205 (55%) | 210 (56%) | 102 (58%) | 0.517 |
| CABG, *n* | 253 (24%) | 31 (25%) | 82 (22%) | 97 (26%) | 43 (25%) | 0.663 |
| Laboratory analyses | | | | | | |
| $HbA_{1c}$, % | 6.5 ± 1.1 | 7.0 ± 1.4 | 6.5 ± 1.1* | 6.3 ± 1.1* | 6.3 ± 1.0* | <0.001 |
| $HbA_{1c}$, mmol/mol | 48 ± 12 | 53 ± 15 | 48 ± 12* | 45 ± 12* | 45 ± 11* | <0.001 |
| Fasting plasma glucose, mmol/L | 6.5 ± 2.0 | 7.7 ± 2.8 | 6.5 ± 1.7* | 6.3 ± 1.9*,† | 6.3 ± 1.9* | <0.001 |
| Total cholesterol, mmol/L | 4.0 ± 0.9 | 4.1 ± 0.9 | 4.0 ± 0.9 | 4.0 ± 0.8 | 3.9 ± 0.8 | 0.739 |
| HDL cholesterol, mmol/L | 1.3 ± 0.3 | 1.2 ± 0.3 | 1.2 ± 0.3 | 1.3 ± 0.3*,† | 1.3 ± 0.4*,† | <0.001 |
| LDL cholesterol, mmol/L | 2.3 ± 0.8 | 2.4 ± 0.8 | 2.3 ± 0.8* | 2.3 ± 0.7 | 2.2 ± 0.8† | 0.048 |
| Triglycerides, mmol/L | 1.4 ± 0.8 | 1.8 ± 0.9 | 1.4 ± 0.8* | 1.3 ± 0.8*,† | 1.2 ± 0.7*,† | <0.001 |
| hs-CRP, mg/L | 2.3 ± 4.7 | 4.1 ± 7.9 | 2.4 ± 4.4* | 1.9 ± 3.5*,† | 1.6 ± 4.1*,† | <0.001 |
| Composite end point | 131 (13%) | 24 (20%) | 50 (14%) | 46 (12%) | 11 (6%)* | 0.015 |
| Death, *n* | 21 (2%) | 7 (6%) | 7 (2%) | 7 (2%) | 0 (0%)* | 0.016 |
| ACS, *n* | 81 (8%) | 5 (4%) | 34 (9%) | 32 (9%) | 10 (6%) | 0.261 |
| Heart failure, *n* | 25 (2%) | 10 (8%) | 7 (2%)* | 7 (2%)* | 1 (1%)* | <0.001 |
| Stroke, *n* | 13 (1%) | 4 (3%) | 4 (1%) | 5 (1%) | 0 (0%)* | 0.144 |

Values are means ± SD or the number of subjects (proportion). ACS, acute coronary syndrome; AMI, acute myocardial infarction; BP, blood pressure; CABG, coronary artery bypass grafting; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction. **P* value $<0.05$ compared with group of no LTPA. †*P* value $<0.05$ compared with group of LTPA irregularly. ‡*P* value $<0.05$ compared with group of LTPA two to three times weekly.

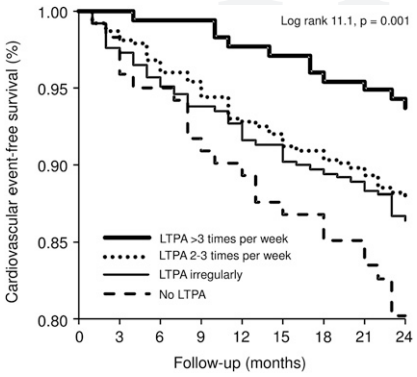


**Figure 2**—LTPA levels as predictors of a composite end point of CV death, acute coronary event, stroke, or hospitalization for heart failure in Kaplan-Meier survival analysis.

LTPA, LTPA irregularly, and LTPA two to three times weekly, respectively, when compared with those who reported LTPA more than three times weekly. Similarly, HRs adjusted for CV risk factors were 2.02 (0.75–5.47; $P$ = 0.166), 2.17 (0.89–5.27; $P$ = 0.087), and 1.69 (0.68–4.24; $P$ = 0.260) for no LTPA, LTPA irregularly, and LTPA two to three times weekly, respectively.

In CAD patients without T2D, HRs for a CV end point were 4.26 (95% CI 1.29–13.85; $P$ = 0.017), 2.12 (0.78–5.77; $P$ = 0.144), and 2.27 (0.86–5.94; $P$ = 0.096) for no LTPA, LTPA irregularly, and LTPA two to three times weekly, respectively. Adjusted HRs were 3.11 (0.87–11.09; $P$ = 0.080), 1.82 (0.64–5.14; $P$ = 0.261), and 2.25 (0.85–5.98; $P$ = 0.105) for no LTPA, LTPA irregularly, and LTPA two to three times weekly, respectively.

### Adherence to Exercise Training

During the intervention, 26 CAD patients (34%) and 27 CAD patients with T2D (39%) interrupted the exercise training, mainly due to a lack of motivation or musculoskeletal problems. The dropout rate did not differ between CAD patients with and without T2D ($P$ = 0.584). Patients who dropped out had a lower exercise capacity at baseline condition compared with those who completed the 2-year exercise training (6.6 ± 1.7 vs. 7.5 ± 1.9 MET, $P$ = 0.002).

During the first 3 months, the realized training was 164 ± 96 min/week in CAD patients without T2D and 141 ± 50 min/week in CAD patients with T2D ($P$ = 0.295), corresponding to 148 ± 87 and 128 ± 46% of targeted exercise time. During the last 6 months, the realized training was 179 ± 91 min/week in CAD patients without T2D and 146 ± 69 min/week in CAD patients with T2D ($P$ = 0.093), corresponding to 99 ± 50 and 81 ± 38% of targeted exercise time.

### Exercise Training, CV Risk Factors, and End Point

The baseline characteristics and the training responses of the ARTEMIS exercise study groups, according to the intention-to-treat analyses, are presented in Table 2. In CAD patients without T2D, the change in maximal exercise capacity was greater in the exercise training group than in the control group (time × group interaction, $P$ = 0.045). In CAD patients with T2D, the changes in waist circumference and LVMI were significantly greater in the exercise training group than in the control group (time × group interaction, $P < 0.05$ for both).

Additionally, the effects of exercise training were analyzed separately in the patients who completed the 2-year exercise intervention (Fig. 1). In CAD patients with T2D, exercise training resulted in changes in exercise capacity (from 6.7 ± 1.7 to 6.9 ± 1.6 MET), waist (from 103 ± 10 to 101 ± 10 cm) and hip circumference (from 104 ± 8 to 103 ± 8 cm), LVM (from 201 ± 56 to 227 ± 55 g) and LVMI (from 101 ± 24 to 116 ± 25 g/m$^2$), and 24-h mean heart rate (from 65 ± 8 to 68 ± 7 bpm) compared with control group (time × group interaction, $P < 0.05$ for all). In CAD patients without T2D, exercise training positively affected only exercise capacity (from 8.2 ± 1.9 to 8.5 ± 1.7 MET, time × group interaction, $P$ = 0.002).

The number of patients who reached a CV end point did not differ between the exercise training and control groups. In CAD patients without T2D, five patients reached an end point in the exercise training and control groups ($P$ = 0.929). In CAD patients with T2D, eight patients (11%) reached an end point in the exercise training group and seven patients (10%) in the control group ($P$ = 0.741).

## CONCLUSIONS

The current study demonstrated that habitual LTPA is associated with reduced CV morbidity and mortality among CAD patients with and without T2D. However, 2-year controlled exercise training resulted in only minor improvements in exercise capacity and waist circumference and did not have any effects on major metabolic risk factors or trends in CV events.

### LTPA, Exercise Training, and CV Outcome

The role of regular LTPA in the prevention of CV events and mortality in CAD patients has been well established (22,24,25). Most recently, Mons et al. (24) demonstrated that the least active CAD patients who rarely or never engaged in LTPA had a roughly twofold risk for major CV events and a fourfold risk for mortality compared with patients with LTPA at least two times weekly. The positive effects of LTPA on risk of CV diseases and mortality have been established also among patients with T2D (26,27). However, to our knowledge, the current study was the first to investigate the effects of LTPA on CV events in patients with both stable CAD and T2D. Our study showed that patients with no or reduced levels of LTPA had an over twofold increased risk of a composite CV end point compared with those who engaged in LTPA over three times weekly, despite of the relatively short follow-up of 2 years.

The new finding in the current study was that controlled exercise training did not produce any decreasing trends in the incidence of CV events. Meta-analysis has concluded that exercise-based cardiac rehabilitation is effective in reducing total and CV mortality (28). In our study, the incidence of CV end points was identical between the exercise training and control groups. These findings highlight the significance of habitual LTPA instead of relative short-time exercise training intervention in the prevention of future unfavorable outcomes in patients with CAD.

### Effects of Exercise Training on the CV Risk Profile

In the current study, exercise training did not produce any clinically significant improvement in CAD patients' CV risk profiles. Statistically significant but small improvements were seen in exercise capacity in CAD patients both with and without T2D. However, exercise capacity increased an average of <5%, whereas in previous studies, the improvement in exercise capacity or CV fitness has varied from 14 to even 40% during exercise-based cardiac

**Table 2—Baseline characteristics of the ARTEMIS exercise study groups and effects of 2-year exercise training on CV risk factors according to the intention-to-treat principle**

| | | CAD patients with T2D | | | | | CAD patients without T2D | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Exercise training, *n* = 63 | Control, *n* = 64 | Time effect | Group effect | Interaction effect | Exercise training, *n* = 72 | Control, *n* = 68 | Time effect | Group effect | Interaction effect |
| Men, *n* | | 51 (81%) | 48 (75%) | — | — | — | 52 (72%) | 50 (74%) | — | — | — |
| Age, year | | 62 ± 5 | 61 ± 7 | — | — | — | 62 ± 5 | 61 ± 6 | — | — | — |
| History of AMI | | | | | | | | | | | |
| NSTEMI, *n* | | 18 (29%) | 19 (30%) | — | — | — | 23 (32%) | 19 (28%) | — | — | — |
| STEMI, *n* | | 11 (17%) | 9 (14%) | — | — | — | 13 (18%) | 9 (13%) | — | — | — |
| Revascularization | | | | | | | | | | | |
| PCI, *n* | | 38 (60%) | 38 (59%) | — | — | — | 43 (60%) | 39 (57%) | — | — | — |
| CABG, *n* | | 13 (21%) | 14 (22%) | — | — | — | 18 (25%) | 12 (18%) | — | — | — |
| Medication | | | | | | | | | | | |
| Beta blockers, *n* | | 58 (92%)* | 51 (80%) | — | — | — | 61 (85%) | 57 (84%) | — | — | — |
| ACEI or ARB, *n* | | 44 (70%) | 43 (67%) | — | — | — | 34 (47%) | 37 (54%) | — | — | — |
| Lipids, *n* | | 58 (92%) | 60 (94%) | — | — | — | 64 (89%) | 59 (87%) | — | — | — |
| Anticoagulants, *n* | | 61 (97%) | 61 (95%) | — | — | — | 70 (97%) | 66 (97%) | — | — | — |
| Calcium antagonists, *n* | | 20 (32%) | 17 (27%) | — | — | — | 7 (10%) | 11 (16%) | — | — | — |
| Nitrates, *n* | | 26 (41%) | 19 (30%) | — | — | — | 7 (10%)* | 24 (35%) | — | — | — |
| Diuretics, *n* | | 25 (40%) | 24 (38%) | — | — | — | 13 (18%) | 17 (25%) | — | — | — |
| Oral medication for T2D, *n* | | 47 (75%) | 39 (61%) | — | — | — | — | — | — | — | — |
| Insulin, *n* | | 10 (16%) | 14 (22%) | — | — | — | — | — | — | — | — |
| Systolic BP, mmHg | Pre | 150 ± 20 | 144 ± 22 | | | | 142 ± 19 | 145 ± 22 | | | |
| | Post | 146 ± 23 | 142 ± 19 | 0.116 | 0.102 | 0.559 | 139 ± 18 | 143 ± 24 | 0.239 | 0.226 | 0.733 |
| Diastolic BP, mmHg | Pre | 82 ± 10* | 78 ± 11 | | | | 78 ± 10 | 78 ± 8 | | | |
| | Post | 78 ± 8 | 75 ± 11 | <0.001 | 0.045 | 0.380 | 75 ± 9 | 77 ± 11 | 0.011 | 0.489 | 0.313 |
| Body composition | | | | | | | | | | | |
| Weight, kg | Pre | 88.6 ± 14.0 | 88.4 ± 16.5 | | | | 77.9 ± 12.1 | 79.0 ± 12.3 | | | |
| | Post | 88.0 ± 14.0 | 88.5 ± 16.8 | 0.559 | 0.960 | 0.354 | 78.2 ± 12.8 | 79.7 ± 12.7 | 0.101 | 0.533 | 0.444 |
| BMI, kg/m$^2$ | Pre | 30.2 ± 3.9 | 29.9 ± 4.0 | | | | 26.7 ± 3.1 | 26.7 ± 3.1 | | | |
| | Post | 29.9 ± 3.9 | 30.0 ± 4.3 | 0.559 | 0.904 | 0.309 | 26.8 ± 3.2 | 26.9 ± 3.3 | 0.124 | 0.952 | 0.381 |
| Waist, cm | Pre | 105 ± 11 | 104 ± 13 | | | | 94 ± 10 | 94 ± 11 | | | |
| | Post | 104 ± 12 | 106 ± 13† | 0.173 | 0.827 | 0.027 | 94 ± 11 | 96 ± 13 | 0.038 | 0.518 | 0.301 |
| Hip, cm | Pre | 105 ± 10 | 105 ± 9 | | | | 99 ± 7 | 99 ± 7 | | | |
| | Post | 105 ± 10 | 106 ± 9 | 0.138 | 0.710 | 0.166 | 99 ± 7 | 100 ± 8 | 0.062 | 0.602 | 0.276 |
| Echocardiography | | | | | | | | | | | |
| LVEF, % | Pre | 66 ± 9 | 65 ± 9 | | | | 66 ± 7 | 65 ± 7 | | | |
| | Post | 64 ± 9 | 65 ± 8 | 0.212 | 0.774 | 0.148 | 65 ± 7 | 63 ± 9 | 0.030 | 0.323 | 0.175 |
| LVM, g | Pre | 209 ± 52 | 202 ± 53 | | | | 184 ± 47 | 196 ± 48 | | | |
| | Post | 227 ± 53 | 205 ± 57 | 0.047 | 0.070 | 0.151 | 195 ± 55 | 216 ± 53 | <0.001 | 0.041 | 0.230 |
| LVMI, g/m$^2$ | Pre | 104 ± 24 | 101 ± 23 | | | | 97 ± 22 | 102 ± 22 | | | |
| | Post | 114 ± 26*,† | 102 ± 25 | 0.032 | 0.098 | 0.026 | 102 ± 25 | 112 ± 23 | <0.001 | 0.041 | 0.264 |
| E/E' | Pre | 10.8 ± 4.4 | 11.0 ± 3.5 | | | | 8.9 ± 2.5 | 9.4 ± 2.7 | | | |
| | Post | 11.1 ± 8.1 | 10.6 ± 3.8 | 0.245 | 0.677 | 0.396 | 8.5 ± 2.1 | 8.7 ± 3.2 | 0.006 | 0.951 | 0.153 |

*Continued on p. 7*

**Table 2—Continued**

| | | CAD patients with T2D | | | | | CAD patients without T2D | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Exercise training, *n* = 63 | Control, *n* = 64 | Time effect | Group effect | Interaction effect | Exercise training, *n* = 72 | Control, *n* = 68 | Time effect | Group effect | Interaction effect |
| Bicycle stress test | | | | | | | | | | | |
| Exercise capacity, MET | Pre | 6.5 ± 1.7 | 6.1 ± 1.4 | | | | 7.8 ± 1.9 | 7.3 ± 1.6 | | | |
| | Post | 6.5 ± 1.6 | 6.0 ± 1.6 | 0.208 | 0.116 | 0.071 | 7.9 ± 2.0* | 7.2 ± 1.6 | 0.870 | 0.045 | 0.045 |
| Workload, W | Pre | 139 ± 38 | 131 ± 39 | | | | 153 ± 45 | 145 ± 43 | | | |
| | Post | 139 ± 39 | 126 ± 39 | 0.060 | 0.131 | 0.061 | 157 ± 48 | 144 ± 42 | 0.657 | 0.141 | 0.050 |
| 24-h HRV | | | | | | | | | | | |
| Heart rate, bpm | Pre | 66 ± 9* | 69 ± 9 | | | | 64 ± 8 | 65 ± 8 | | | |
| | Post | 67 ± 7 | 69 ± 8 | 0.513 | 0.090 | 0.137 | 65 ± 8 | 66 ± 8 | 0.307 | 0.329 | 0.628 |
| SDNN, ms | Pre | 129 ± 35 | 128 ± 34 | | | | 147 ± 33 | 152 ± 37 | | | |
| | Post | 124 ± 29 | 126 ± 34 | 0.229 | 0.662 | 0.682 | 146 ± 33 | 151 ± 42 | 0.674 | 0.572 | 0.876 |
| HF power, $ms^2$ | Pre | 399 ± 664 | 229 ± 183 | | | | 319 ± 517 | 352 ± 340 | | | |
| | Post | 319 ± 517 | 250 ± 274 | 0.211 | 0.578 | 0.253 | 388 ± 592 | 488 ± 1,303 | 0.704 | 0.988 | 0.308 |
| LF power, $ms^2$ | Pre | 572 ± 435 | 446 ± 407 | | | | 706 ± 766 | 624 ± 482 | | | |
| | Post | 493 ± 404 | 417 ± 357 | 0.007 | 0.281 | 0.290 | 696 ± 777 | 739 ± 956 | 0.360 | 0.793 | 0.863 |
| VLF power, $ms^2$ | Pre | 1,231 ± 751 | 1,066 ± 699 | | | | 1,548 ± 891 | 1,367 ± 721 | | | |
| | Post | 1,080 ± 641 | 1,005 ± 612 | 0.004 | 0.356 | 0.240 | 1,480 ± 900 | 1,400 ± 910 | 0.103 | 0.222 | 0.893 |
| Laboratory analyses | | | | | | | | | | | |
| $HbA_{1c}$, % | Pre | 6.6 ± 0.8* | 7.2 ± 1.3 | | | | 5.9 ± 0.4 | 5.8 ± 0.4 | | | |
| | Post | 6.5 ± 1.0 | 6.9 ± 0.9 | <0.001 | 0.003 | 0.247 | 5.7 ± 0.3 | 5.7 ± 0.4 | <0.001 | 0.425 | 0.652 |
| $HbA_{1c}$, mmol/mol | Pre | 49 ± 9* | 55 ± 14 | | | | 41 ± 4 | 40 ± 4 | | | |
| | Post | 48 ± 11 | 52 ± 10 | <0.001 | 0.003 | 0.247 | 39 ± 3 | 39 ± 4 | <0.001 | 0.425 | 0.652 |
| Fasting plasma glucose, mmol/L | Pre | 7.0 ± 1.2 | 7.6 ± 1.9 | | | | 5.4 ± 0.5 | 5.4 ± 0.4 | | | |
| | Post | 7.0 ± 1.6 | 7.3 ± 1.8 | 0.290 | 0.088 | 0.255 | 5.6 ± 0.4 | 5.7 ± 0.7 | <0.001 | 0.157 | 0.945 |
| Insulin, mU/L | Pre | 19.5 ± 12.8 | 24.3 ± 41.6 | | | | 9.9 ± 5.0 | 9.9 ± 6.6 | | | |
| | Post | 23.7 ± 18.2 | 25.6 ± 29.3 | 0.007 | 0.468 | 0.760 | 11.1 ± 6.4 | 12.3 ± 8.3 | <0.001 | 0.951 | 0.134 |
| Total cholesterol, mmol/L | Pre | 4.0 ± 0.7 | 3.9 ± 0.8 | | | | 4.0 ± 0.8 | 4.1 ± 0.9 | | | |
| | Post | 4.1 ± 0.8 | 3.8 ± 0.7 | 0.786 | 0.519 | 0.177 | 4.1 ± 0.8 | 4.1 ± 0.8 | 0.381 | 0.714 | 0.439 |
| HDL cholesterol, mmol/L | Pre | 1.2 ± 0.3 | 1.2 ± 0.3 | | | | 1.3 ± 0.3 | 1.3 ± 0.3 | | | |
| | Post | 1.2 ± 0.3 | 1.3 ± 0.3 | 0.593 | 0.073 | 0.646 | 1.3 ± 0.3 | 1.3 ± 0.4 | 0.149 | 0.747 | 0.774 |
| LDL cholesterol, mmol/L | Pre | 2.2 ± 0.5 | 2.2 ± 0.7 | | | | 2.4 ± 0.7 | 2.4 ± 0.9 | | | |
| | Post | 2.4 ± 0.7 | 2.2 ± 0.7 | 0.813 | 0.346 | 0.446 | 2.4 ± 0.8 | 2.4 ± 0.8 | 0.868 | 0.887 | 0.833 |
| Triglycerides, mmol/L | Pre | 1.8 ± 1.0 | 1.6 ± 1.0 | | | | 1.2 ± 0.5 | 1.3 ± 0.7 | | | |
| | Post | 1.7 ± 0.7 | 1.7 ± 1.0 | 0.877 | 0.239 | 0.733 | 1.3 ± 0.6 | 1.3 ± 0.6 | 0.581 | 0.820 | 0.591 |
| hs-CRP, mg/L | Pre | 1.8 ± 2.0 | 3.1 ± 5.1 | | | | 1.8 ± 3.7 | 2.0 ± 4.1 | | | |
| | Post | 1.6 ± 2.0 | 2.5 ± 3.2 | 0.281 | 0.085 | 0.839 | 2.0 ± 3.3 | 2.0 ± 3.7 | 0.253 | 0.529 | 0.486 |
| Interleukin-6, mU/L | Pre | 1.8 ± 1.3 | 2.3 ± 1.7 | | | | 1.7 ± 1.4 | 1.9 ± 1.7 | | | |
| | Post | 1.7 ± 1.4 | 2.5 ± 3.3 | 0.637 | 0.065 | 0.446 | 1.6 ± 1.2 | 1.8 ± 1.5 | 0.144 | 0.990 | 0.784 |
| Creatinine, μmol/L | Pre | 74 ± 18 | 72 ± 19 | | | | 77 ± 13 | 79 ± 13 | | | |
| | Post | 76 ± 17 | 77 ± 22 | <0.001 | 0.673 | 0.230 | 77 ± 17 | 79 ± 13 | 0.617 | 0.348 | 0.812 |
| Creatinine clearance, mL/min | Pre | 117 ± 33 | 121 ± 42 | | | | 96 ± 24 | 95 ± 23 | | | |
| | Post | 108 ± 28 | 112 ± 39 | <0.001 | 0.663 | 0.552 | 95 ± 25 | 94 ± 22 | 0.280 | 0.970 | 0.844 |

*Continued on p. 8*

**Table 2—Continued**

| | | CAD patients with T2D | | | | | CAD patients without T2D | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Exercise training, $n = 63$ | Control, $n = 64$ | Time effect | Group effect | Interaction effect | Exercise training, $n = 72$ | Control, $n = 68$ | Time effect | Group effect | Interaction effect |
| Microalbuminuria, mg/L | Pre | 16.3 ± 31.2 | 24.1 ± 48.1 | | | | 8.0 ± 7.5 | 7.2 ± 5.0 | | | |
| | Post | 32.6 ± 90.3 | 22.6 ± 49.3 | 0.440 | 0.127 | 0.054 | 12.4 ± 31.9 | 7.6 ± 7.2 | 0.665 | 0.290 | 0.677 |
| ACR, mg/mmol | Pre | 1.8 ± 3.2 | 2.9 ± 6.3 | | | | 0.9 ± 0.8 | 0.8 ± 0.5 | | | |
| | Post | 3.0 ± 7.0 | 2.4 ± 4.8 | 0.816 | 0.567 | 0.137 | 1.4 ± 3.4 | 0.9 ± 0.7 | 0.616 | 0.584 | 0.889 |

Values are means ± SD. ACEI, ACE inhibitor; ACR, albumin-to-creatinine ratio; AMI, acute myocardial infarction; ARB angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass grafting; E/E′, ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; HF, high frequency; HRV, heart rate variability; LF, low frequency; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SDNN, SD of all R-R intervals; STEMI, ST segment elevation myocardial infarction; VLF, very low frequency. **P* value <0.05 compared with control group. †*P* value <0.05 between pre and post measurements.

rehabilitation (29–32). In our study, the patients had an average of about one MET higher exercise capacity at the baseline in comparison with the patients in previous studies. That may partly account for the smaller percentage increase in exercise capacity. Usually, low baseline fitness results in more improvement in exercise capacity after exercise intervention compared with moderate- to high-fitness subjects at the baseline (33).

In the current study, the small improvement in body composition as well as the lack of positive changes in other CV risk factors, such as metabolic variables and autonomic function, was surprising, since the patients' training volumes mainly corresponded to the targeted exercise prescription. However, exercise intervention alone usually produced minimal weight loss compared with diet alone or with diet and exercise combined (34,35). The patients in the current study did not get any detailed dietary instructions, and changes in dietary habits were not assessed. Gibbs et al. (36) demonstrated recently that changes in exercise capacity and weight explain only up to 9% of the variability in CV risk factors in adults with T2D after a lifestyle intervention, and there are still some unknown factors that play an important role in explaining changes in the risk profile. In our study, the absence of exercise responses in blood lipid and glucose levels and blood pressure was to some extent predictable, because the patient lipid and glucose values as well as their blood pressure at the baseline condition were already quite low, reflecting an optimal dose of lipid-lowering, antihypertensive, and antidiabetic medications.

### Adherence to Exercise Training

In the current study, the dropout rate from the exercise training program (on average 37%) was at about a similar level as in some previous studies. Marzolini et al. (37) demonstrated that average noncompletion of a 12-month cardiac rehabilitation program was 32%, whereas 42% of patients did not complete the cardiac rehabilitation program in the study by Sanderson et al. (8). In the current study, the dropout rate did not differ between the CAD patients with and without T2D, although opposite results have been found recently. In the study by Armstrong et al. (12), diabetic patients were more likely to drop out from a 12-week exercise-based cardiac rehabilitation program (20 vs. 15%) and refuse a 1-year follow-up assessment (67 vs. 46%) than their counterparts without diabetes. Moreover, the mean training volume and training response in exercise capacity in the current study did not differ between diabetic and nondiabetic patients during the exercise training program. Similar to our results, Banzer et al. (30) and Hindman et al. (31) showed that exercise capacity improved equally in patients with and without T2D after a cardiac rehabilitation that included supervised exercise training.

### Limitations

The prognostic part of the current study was limited by a relatively short follow-up and a mixture of various end points. We wanted to examine the acute effect of 2-year controlled exercise training on the CV risk profile, which defined the length of the follow-up. This part of the study was not powered to compare the incidence of clinical events between the groups. Also the low number of end points in the exercise training groups and among the physically active patients limits the generalizability of the study results. Moreover, the prognostic part of the study also included the patients who participated in exercise intervention during the 2-year follow-up, which could influence an association between LTPA and CV events. However, when patients who participated in exercise intervention were excluded from the analyses, the inverse association between LTPA and CV events still existed.

Since the ARTEMIS exercise study was home based and the exercise training program with high-intensity exercises was rather intensive, a high number of patients were excluded due to advanced age or serious comorbidities. Excluded patients were physically more inactive and had higher blood glucose levels, lower exercise capacity, and longer duration of T2D compared with patients included in exercise intervention. Moreover, almost 30% of the patients in the ARTEMIS study were not willing to participate in the exercise intervention even though they were suitable. Therefore, the patient sample in the ARTEMIS exercise study was partly selected,

which could limit generalizability to a broader population of CAD patients with significant comorbidities.

## CONCLUSIONS

The current study showed that there is an inverse association between habitual LTPA and CV morbidity and mortality, but 2-year controlled, home-based exercise training did not produce clinically significant improvements in the CV risk profile or outcome in CAD patients with and without T2D. These findings highlight the significance of lifelong physical activity instead of a short-term exercise program in the prevention of future unfavorable outcomes in patients with CAD.

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**Author Contributions.** J.J.K. analyzed and interpreted the data and wrote and reviewed the drafts of the manuscript. A.M.K. contributed to the statistical analyses and reviewed the final draft of the manuscript. A.J.H., O.-P.P., E.S.L., J.S.P., and M.J.J. contributed to the data collection and reviewed the final draft of the manuscript. H.V.H. and M.P.T. contributed to the design of the ARTEMIS study, guided the process of data analysis and interpretation, and read and reviewed the drafts of the manuscript. M.P.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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