


# Cardiovascular risk factors, exercise capacity and health literacy in patients with chronic ischaemic heart disease and type 2 diabetes mellitus in Germany: Baseline characteristics of the Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes study

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## Abstract

**Background:** Lifestyle interventions are a cornerstone in the treatment of chronic ischaemic heart disease (CIHD) and type 2 diabetes mellitus (T2DM). This study aimed at identifying differences in clinical characteristics between categories of the common lifestyle intervention targets BMI, exercise capacity (peak  $\dot{V}O_2$ ) and health literacy (HL).

**Methods:** Cross-sectional baseline characteristics of patients enrolled in the LeIKD trial ([Clinicaltrials.gov](https://clinicaltrials.gov) NCT03835923) are presented in total, grouped by BMI, %-predicted peak  $\dot{V}O_2$  and HL (HLS-EU-Q16), and compared to other clinical trials with similar populations.

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**Results:** Among 499 patients (68.3±7.7 years; 16.2% female; HbA1c, 6.9±0.9%), baseline characteristics were similar to other trials and revealed insufficient treatment of several risk factors (LDL-C 92±34 mg/dl; BMI, 30.1±4.8 kg/m<sup>2</sup>; 69.6% with peak  $\dot{V}O_2 < 90\%$  predicted). Patients with lower peak  $\dot{V}O_2$  showed significantly higher ( $p < 0.05$ ) CIHD and T2DM disease severity (HbA1c, CIHD symptoms, coronary artery bypass graft). Obese patients had a significantly higher prevalence of hypertension and higher triglyceride levels, whereas in patients with low HL both quality of life components (physical, mental) were significantly reduced.

**Conclusions:** In patients with CIHD and T2DM, peak  $\dot{V}O_2$ , BMI and HL are important indicators of disease severity, risk factor burden and quality of life, which reinforces the relevance of lifestyle interventions.

### Keywords

Lifestyle, exercise capacity, chronic coronary syndrome, secondary prevention, cardiorespiratory fitness, disease management

### Key messages:

- Exercise capacity is linked to disease severity in patients with CIHD and T2DM
- Medical and lifestyle-related disease management in Germany is still insufficient despite the high-risk classification for patients with CIHD and T2DM
- There is an urgent need for sustainable lifestyle intervention strategies in this multi-morbid and heterogeneous patient population with CIHD and T2DM

### Introduction

In 2019, ischaemic heart disease was the leading cause of death accounting for 8.9 million cases or approximately 16% of total deaths worldwide.<sup>1</sup> In chronic ischaemic heart disease (CIHD), diabetes mellitus type 2 (T2DM) is a frequent companion associated with an elevated risk for cardiovascular (CV) events and increased mortality, classifying these patients as a very high-risk population.<sup>2,3</sup> Both diseases share several pathophysiological mechanisms and risk factors: besides age, behavioural risk factors such as smoking, poor dietary patterns, and a sedentary lifestyle promote obesity, impaired glycaemic control, hypertension and hyperlipidaemia, which causes a chronic systemic inflammatory state and leads to progressive vascular alterations and the development of arteriosclerosis complicated by CV events and death.<sup>4,5</sup>

Despite evidence based international guidelines on the prevention and treatment of CIHD and T2DM, the implementation of lifestyle recommendations and the achievement of risk factor control are still not at a satisfactory level as recently demonstrated by the results of the EUROASPIRE V survey (European Action on Secondary and Primary Prevention by Intervention to Reduce Events, EAV).<sup>5</sup> Regular screening, risk assessment and adequate disease management are highly recommended<sup>2,3,6</sup> since lifestyle-related changes in physical activity and nutrition

are a cornerstone of the treatment of CIHD and T2DM.<sup>7</sup> In recent years, health literacy (HL), which has been shown to be low in patients with CV diseases,<sup>8</sup> has gained increasing attention and might be important to implement sustainable lifestyle changes. Low-threshold and cost-effective strategies are urgently needed to improve risk factor control and prognosis in these patients.

Therefore, the LeIKD trial (Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes) aimed to improve CV risk factors through exercise training, nutritional recommendations and the increase of HL through a telemedical lifestyle intervention programme.<sup>9</sup> So far, only few trials performed cardiopulmonary exercise testing (CPET) in patients with both CIHD and T2DM and data on several clinical and lifestyle-related aspects in this patient population is still lacking. To improve the characterisation of these high-risk patients, baseline characteristics of the LeIKD study population are presented next to similar lifestyle or pharmacological trials and compared within different subgroups of obesity, exercise capacity and HL.

### Methods

#### Study design

LeIKD ([Clinicaltrials.gov](https://clinicaltrials.gov) identifier: NCT03835923) was a multicentre, randomised controlled trial aiming to improve CV risk factors by promoting a healthy lifestyle via a telemedical supported lifestyle intervention in patients with CIHD and T2DM.

The study design has been published before.<sup>9</sup> In brief, patients with CIHD (ICD-10: I20-I25) and T2DM (ICD-10: E11; HbA1c  $\geq 6.5\%$  or anti-diabetic medication at the time of screening) were randomised (1:1) to either lifestyle intervention (LS) or usual care (UC). The LS group received an individual home-based exercise training programme, tailored nutrition counselling and health related information to increase HL, while the UC group received

general lifestyle recommendations according to CIHD and T2DM treatment guidelines. The intervention was performed using smartphone applications in combination with telemedical self-tracking devices (pedometer, heart rate and blood glucose monitor). Participants without a smartphone were provided with a free loaner device. All patients were insured at the statutory health insurance fund TK (Techniker Krankenkasse, Hamburg, Germany) and were already included in a disease management program (DMP) for CIHD or T2DM.

The primary endpoint is the difference in change in HbA1c after 6 months between groups. Initial sample size calculation was based on the results of the ENHANCE trial (mean difference in HbA1c of  $0.4 \pm 1.8\%$ , 80% statistical power, 5% significance level, estimated dropout rate of 15%).<sup>10</sup> Accordingly, a number of 750 patients would have been required to detect a significant difference in the primary endpoint between groups. Due to a planned comparison between rural and urban areas, the calculated sample size was initially doubled to 1500. In consequence of delays in the start of the project, insufficient recruitment and a fixed project duration, sample size calculation had to be adjusted. The comparison of rural and urban areas was omitted and based on a small to medium effect size of 0.305,<sup>11</sup> 80% statistical power, 5% significance level for two-sided t-test and an estimated drop-out rate of 30%, we aimed to include a minimum of 486 patients. The study was conducted in 11 study sites across Germany and the study protocol was approved by the ethics committee of the Technical University of Munich (reg. number: 144/18-S) and at all participating study sites. LeIKD was performed according to the Declaration of Helsinki.

### Recruitment/assessments

The recruitment was conducted as a three-step procedure: Potential study participants were first selected and contacted by the TK health insurance to inquire about a potential interest to participate in the trial. Interested patients were then contacted by the corresponding local study site to receive further information and arrange a screening appointment. After the screening visit, eligible patients were included into the trial.

Assessments contained a comprehensive anamnesis including medical history and current medication, anthropometric measurements, physical examination, blood draw and a resting electrocardiogram (ECG). Participants were not required to be in a fasting state at the time of blood collection and were asked to take their daily prescribed medication as usual. Participants performed CPET including exercise ECG on a bicycle ergometer according to a prescribed ramp protocol. If CPET was not possible, patients carried out a symptom-limited exercise testing with ECG. After 4 min at rest and a warm-up phase of 2 min

at 20W, the work rate was continuously increased by 8W, 12W or 18W per minute until exhaustion. The increment was chosen based on the estimated exercise capacity with the aim to reach maximal exhaustion within 8–12 min. CPET data was assessed breath-by-breath and every data set was verified and analysed by the CPET core laboratory in Munich. Peak oxygen consumption (peak  $\dot{V}O_2$ ) was obtained as the highest 30 s average during exercise, predicted values (% pred. peak  $\dot{V}O_2$ ) were calculated according to reference values of the SHIP study.<sup>12</sup> Ventilatory threshold (VT1) was determined by the V-slope method.<sup>13</sup> All examinations were conducted according to standard operating procedures.

Sociodemographic data was collected by questionnaire. Education was classified according to International Standard Classification of Education 2011 and categorised in low (level 1-2), medium (level 3-4) and high (level 5-6). Study participants also completed validated questionnaires for the assessment of HL and quality of life (QoL). HL was assessed with the German version of HLS-EU-Q16. Based on four dimensions (16 items on a four-point Likert scale) covering the ability to obtain, understand, process and apply health-related information, HL is categorised as “sufficient”, “problematic” or “inadequate”.<sup>8</sup> For score creation, responses were dichotomized. Missing values were coded 0 and cases were excluded, if more than two items were missing.<sup>14</sup> Health-related QoL was measured with SF-36 including 36 items on 8 dimensions (General Health, Physical Performance, Physical Limitations, Physical Pain, Vitality, Mental Health, Emotional Impairment and Social Impairment) and summarised as “Physical Component Score” (PCS) and “Mental Component Score” (MCS).<sup>15</sup>

### Statistical analysis

Baseline characteristics are presented for the overall study population and within subgroups of body mass index (BMI) [“non-obese” ( $BMI \leq 30 \text{ kg/m}^2$ ) vs “obese” ( $BMI > 30 \text{ kg/m}^2$ )], exercise capacity [“severely restricted” ( $<75\%$  of pred. peak  $\dot{V}O_2$ ) vs “mildly to moderately restricted” ( $75\text{--}89.9\%$  of pred. peak  $\dot{V}O_2$ ) vs “normal” ( $\geq 90\%$  of pred. peak  $\dot{V}O_2$ )] and HL [“non-sufficient HL” (problematic/inadequate HL) vs “sufficient HL”], as these parameters reflect the main components of the LeIKD intervention (nutritional advice, exercise training and health literacy training, respectively). Continuous variables are presented as mean and standard deviation, categorical variables are displayed as absolute and relative frequencies. For comparison of subgroups, t-tests or ANOVAs were calculated for continuous variables, and Chi-square-tests or F-tests for categorical variables. *p*-values below 0.05 determine statistical significance. All analyses were performed using the statistics software R (Version 4.0.2).

### Comparison to other study populations

In order to ensure generalisability, LeIKD baseline characteristics were compared to other trials selected to include pharmacological and lifestyle interventions that have similar study populations focusing on T2DM and CV risk and present a large set of comparable baseline characteristics. Based on these criteria, LeIKD baseline characteristics are compared to the pharmacological intervention trials CAROLINA (Cardiovascular Outcome Study of Liraglutin Versus Glimperide in Patients With Type 2 Diabetes)<sup>16,17</sup> and a subsample with established CV disease of the CARMELINA trial (CARDiovascular safety and Renal Microvascular outcomE study with LINAgliptin),<sup>18</sup> the lifestyle intervention trial EXCADI (Exercise Training in Patients with Coronary Heart Disease and Type 2 Diabetes)<sup>19</sup> and the landmark lifestyle intervention study Look AHEAD (Action for Health in Diabetes).<sup>20</sup>

## Results

### Recruitment

The recruitment period lasted from February 2019 to March 2020. TK health insurance selected 17 597 potential participants with ICD-10: I20-I25 for CIHD and ICD-10: E11 for T2DM (Figure 1). After initial contact by TK, 2002 patients were interested in participation and were referred to the corresponding local study sites. A total of 697 screening visits were performed, including 195 screening failures. The main reason for screening failure was meeting the exclusion criteria “no optimal cardiac treatment or not clinically stable within the last 4 weeks” which applied to 81 patients. With the onset of the COVID-19 pandemic in Germany that significantly blunted the recruitment rate due to cancellations of appointments and lock-down of study sites, the recruitment phase was prematurely stopped after randomisation of 502 patients. In the UC group 3 patients withdrew consent to study participation and data analysis. Thus, baseline data from 499 patients was available for analysis.

### Baseline characteristics

Baseline characteristics including CV and anti-diabetic medication of the enrolled study population are summarized in Table 1. The mean age was  $68.3 \pm 7.7$  years and 16.2% of patients were female. Mean duration of CIHD was  $8.8 \pm 7.3$  years and 231 (46.3%) patients had a CIHD affecting at least two vessels. Previous myocardial infarction was reported by 34.3%, coronary revascularisation by 54.9% and coronary bypass graft implantation by 16.4% of patients. Furthermore, 81.1% reported no angina pectoris-related symptoms, while 14.7% and 4.2% reported

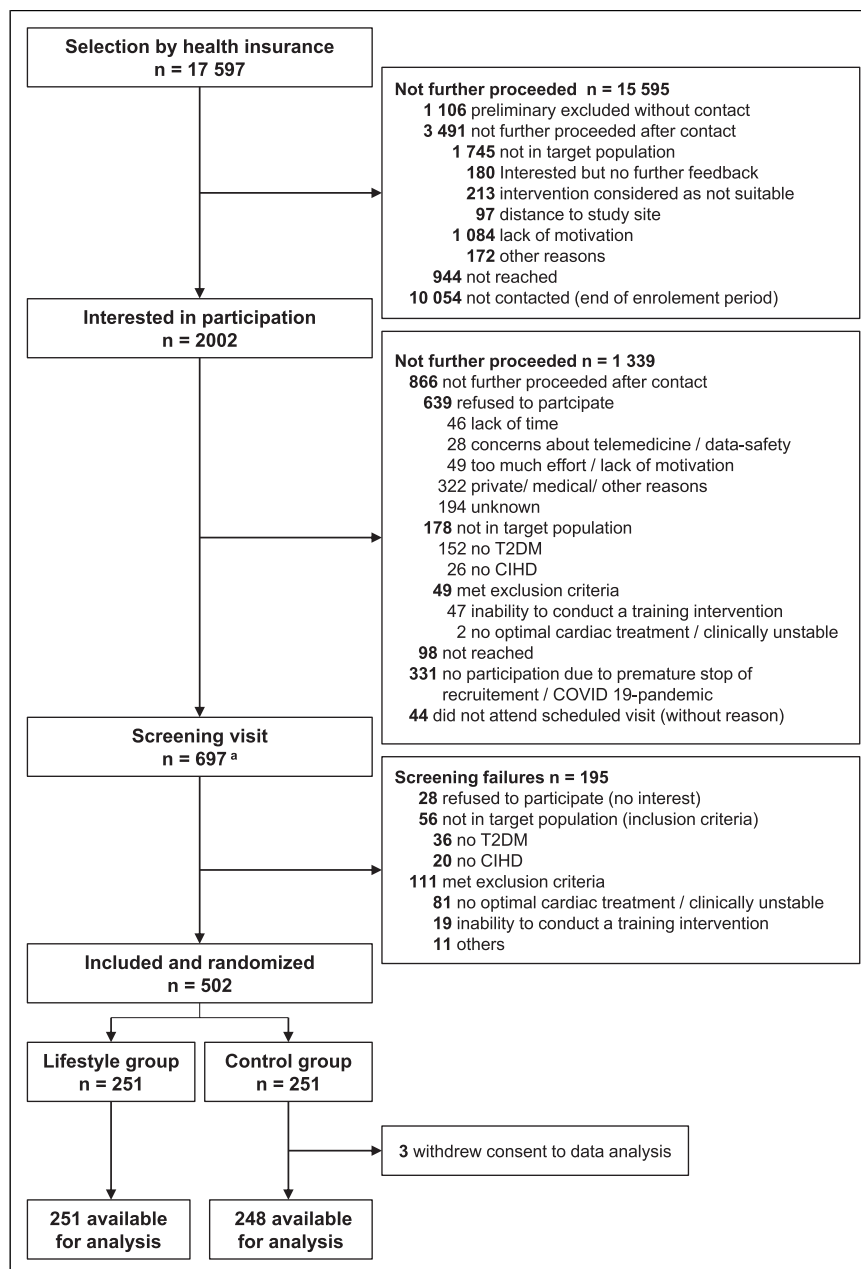
symptoms according to the Canadian Cardiovascular Society (CCS) score Grade I and II-IV, respectively. Mean duration of T2DM was  $12.3 \pm 8.4$  years, mean HbA1c was  $6.9 \pm 0.9\%$  with 27.5% prescribed with insulin, 83.0% using oral anti-diabetic medication (72.5% metformin) and 12.6% without any anti-diabetic medication.

Mean BMI was  $30.1 \pm 4.8$  kg/m<sup>2</sup> and 259 participants (51.9%) were identified as former and 55 (11.0%) as current smokers. The prevalence of hypertension was 92.4% with a mean systolic blood pressure of  $137 \pm 17$  mmHg and a mean diastolic blood pressure of  $79 \pm 10$  mmHg. Hyperlipidaemia was reported by 429 patients (86.0%) with 420 participants (84.2%) using lipid lowering drugs (82.6% prescribed with statins). Mean total cholesterol was  $157 \pm 39$  mg/dl, LDL cholesterol (LDL-C) was  $92 \pm 34$  mg/dl and triglycerides were  $182 \pm 100$  mg/dl. CPET was performed in 473 patients, symptom-limited exercise testing in 25 patients. Mean peak workload was  $129 \pm 42$  W with a peak  $\dot{V}O_2$  of  $18.6 \pm 4.6$  mL/kg/min according to  $81.9 \pm 16.8\%$  of mean predicted peak  $\dot{V}O_2$ . HL data was available from 459 patients and only 264 patients (57.5%) showed a sufficient HL.

### Subgroup analyses

Baseline characteristics according to subgroups by BMI, exercise capacity and HL are presented in Table 2. Among the study population, 282 patients were non-obese with a mean BMI of  $26.7 \pm 2.1$  kg/m<sup>2</sup> and 217 patients were classified as obese (mean BMI  $34.5 \pm 3.6$  kg/m<sup>2</sup>). Obese patients were younger ( $66.4 \pm 7.5$  vs  $69.8 \pm 7.6$  years,  $p < 0.001$ ) and had a lower educational status than non-obese patients ( $p = 0.014$ ). Furthermore, the diagnoses of T2DM ( $54.4 \pm 10.4$  vs  $56.5 \pm 9.7$  years,  $p = 0.050$ ) and CIHD ( $57.2 \pm 9.4$  vs  $60.9 \pm 10.0$  years,  $p < 0.001$ ) were made at a younger age. No differences in HbA1c and blood lipids could be observed except for higher mean triglycerides in the obese subgroup ( $204 \pm 103$  vs  $166 \pm 94$  mg/dl,  $p < 0.001$ ). Obese participants were also more likely to suffer from hypertension (96.8 vs 89.0%,  $p = 0.002$ ). The non-obese group showed a significantly lower absolute peak  $\dot{V}O_2$  ( $1610 \pm 413$  vs  $1770 \pm 464$  mL/min,  $p < 0.001$ ). However, relative to body weight, peak  $\dot{V}O_2$  was significantly higher than in the obese subgroup ( $19.8 \pm 4.5$  vs  $17.1 \pm 4.2$  mL/kg/min,  $p < 0.001$ ), and %-predicted peak  $\dot{V}O_2$  was not significantly different between the subgroups ( $81.4 \pm 16.2$  vs  $82.6 \pm 17.2\%$ ,  $p = 0.466$ ). Non-obese patients had a significantly higher QoL-PCS ( $46.3 \pm 8.8$  vs  $42.3 \pm 10.5$ ,  $p < 0.001$ ) but no significant differences in QoL-MCS.

Among 473 patients with available CPET data, 165 (34.9%) had a severely restricted, 164 (34.7%) a mildly to moderately restricted and 144 (30.4%) a normal exercise capacity. Mean duration of CIHD and T2DM were not



**Figure 1.** Patient recruitment in the LeKD study. Abbreviations: CIHD, chronic ischaemic heart disease; T2DM, type 2 diabetes mellitus; <sup>a</sup>including re-screenings (initial screening failures may have been included during re-screening,  $n = 34$ ).

significantly different between groups, however, mean HbA1c was highest in the severely restricted group ( $7.0 \pm 1.0$  vs  $6.8 \pm 0.9$  vs  $6.7 \pm 0.9\%$ ,  $p = 0.002$ ). Similarly, these patients were most likely to have CIHD symptoms ( $p = 0.015$ ) and the highest prevalence of previous coronary bypass graft implants ( $21.8$  vs  $16.5$  vs  $9.0\%$ ,  $p = 0.009$ ). Total cholesterol ( $151 \pm 39$  vs  $158 \pm 40$  vs  $162 \pm 40$  mg/dl,  $p = 0.013$ ) and LDL-C ( $88 \pm 35$  vs  $91 \pm 36$  vs  $96 \pm 36$  mg/dl,  $p = 0.041$ ) were significantly different with the highest values in the fittest subgroup. QoL-PCS was higher with

increasing exercise capacity ( $42.2 \pm 10.4$ ,  $45.2 \pm 9.0$  and  $47.4 \pm 9.1$ ,  $p < 0.001$ ) while no significant difference in QoL-MCS could be observed.

Data on HL was available from 459 participants and 195 (42.5%) patients were classified with a non-sufficient HL. Both groups showed no significant differences in age, sex, education, CIHD or T2DM history and duration. Also, regarding risk factors and exercise capacity, no further statistically significant differences could be observed. However, patients with sufficient HL were diagnosed with



**Table I.** Baseline characteristics of LeIKD study population with T2DM and CIHD.

	Overall [n = 499] <sup>a</sup>
Age at baseline (years)	68.3 ± 7.7
Female sex	81 (16.2)
Body height (cm)	175 ± 9
Weight (kg)	91.8 ± 16.7
BMI (kg/m <sup>2</sup> )	30.1 ± 4.8
Obese with BMI > 30 kg/m <sup>2</sup>	217 (43.5)
Waist circumference (cm)	108 ± 12 [480]
Hip circumference (cm)	107 ± 11 [480]
Systolic blood pressure (mmHg)	137 ± 17
Diastolic blood pressure (mmHg)	79 ± 10
Heart rate (bpm)	70 ± 11 [498]
Smoking	
Never	185 (37.1)
Current	55 (11.0)
Former	259 (51.9)
Alcoholic drinks per week	4.1 ± 7.3 [495]
<b>CIHD and T2DM</b>	
Duration of CIHD (years)	8.8 ± 7.3 [397]
CIHD classification	[498]
No relevant stenosis (<50%)	87 (17.5)
1-vessel coronary disease	115 (23.1)
2-vessel coronary disease	84 (16.9)
3-vessel coronary disease	138 (27.7)
main coronary disease	9 (1.8)
Unknown	65 (13.1)
CIHD symptoms	[498]
Asymptomatic	404 (81.1)
CCS score grade I <sup>b</sup>	73 (14.7)
CCS score grade II - IV	21 (4.2)
Previous myocardial infarction	171 (34.3)
Coronary revascularisation	274 (54.9)
Coronary artery bypass graft	82 (16.4)
Duration of T2DM (years)	12.3 ± 8.4 [363]
HbA1c (%)	6.9 ± 0.9 [496]
<b>Additional medical history</b>	
Hypertension	461 (92.4)
Hyperlipidaemia	429 (86.0)
Atrial fibrillation	96 (19.2)
Peripheral artery disease	35 (7.0)
Cerebrovascular disease	40 (8.0)
COPD	22 (4.4)
Depression	31 (6.2)
Chronic kidney disease	59 (11.8)
Heart failure	120 (24.0)
HFpEF (LVEF > 50%)	68 (13.6)
HFmrEF (LVEF 40–49%)	30 (6.0)
HFrEF (LVEF < 40%)	17 (3.4)
<b>Exercise performance<sup>c</sup></b>	
Peak work load (Watt)	129 ± 42 [497]
Peak $\dot{V}O_2$ (ml/kg/min)	18.6 ± 4.6 [473]
Pred. peak $\dot{V}O_2$ (%)	81.9 ± 16.8 [473]
Peak RER	1.09 ± 0.10 [473]
<b>Additional laboratory analysis</b>	
Haemoglobin (g/dl)	14.5 ± 1.3 [487]
Total cholesterol (mg/dl)	157 ± 39 [495]
HDL-C (mg/dl)	48 ± 13 [498]
LDL-C (mg/dl)	92 ± 34 [496]
Triglycerides (mg/dl)	182 ± 100 [497]

(continued)

**Table I.** (continued)

	Overall [n = 499] <sup>a</sup>
NT-proBNP (ng/l)	255 ± 358 [487]
<b>Current medication</b>	
Anti-diabetic medication	
Oral anti-diabetics	414 (83.0)
Metformin	362 (72.5)
DPP4-inhibitors	115 (23.0)
SGLT2-inhibitors	109 (21.8)
Sulfonylurea	26 (5.2)
GLP-1-analoga	65 (13.0)
Insulin	137 (27.5)
Cardiovascular medication	
ACE inhibitor/AR blocker	423 (84.8)
Anti-platelet	349 (69.9)
ASA	329 (65.6)
Clopidogrel	36 (7.2)
Ticagrelor	11 (2.2)
Prasugrel	5 (1.0)
Lipid-lowering drugs	420 (84.2)
Statins	412 (82.6)
Atorvastatin/Rosuvastatin	241 (48.3)
Other statins	171 (34.3)
Other lipid-lowering drugs	81 (16.2)
Diuretics	196 (39.3)
Aldosterone antagonists	52 (10.4)
Beta-blocker	364 (72.9)
Anticoagulation	
Phenprocoumon	26 (5.2)
NOAC	72 (14.4)
Nitrates/Ranolazin	25 (5.0)
Sacubitril/Valsartan	8 (1.6)
<b>Health Literacy<sup>d</sup> &amp; Quality of Life<sup>e</sup></b>	
HLS group	
Inadequate	73 (15.9)
Problematic	122 (26.6)
Sufficient	264 (57.5)
QoL-PCS	44.5 ± 9.8
QoL-MCS	52.2 ± 9.2

BMI: body mass index; CIHD: chronic ischaemic heart disease; T2DM: type 2 diabetes mellitus; CCS scale: Canadian Cardiovascular Society angina grading scale; HbA1c: glycated haemoglobin; COPD: chronic obstructive pulmonary disease; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction;  $\dot{V}O_2$ : oxygen consumption; RER: respiratory exchange ratio; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; DPP4: dipeptidyl peptidase-4; SGLT2: sodium/glucose cotransporter 2; GLP-1: glucagon-like peptide-1; ACE: angiotensin-converting-enzyme; AR: androgen receptor; ASA: acetylsalicylic acid; NOAC: novel oral anticoagulants; HLS: health literacy score; QoL: quality of life; PCS: physical component score; MCS: mental component score. <sup>a</sup>Data are presented as mean ± standard deviation or absolute and (relative) frequency. In case of missing data, corrected sample size is described as [No.].

<sup>b</sup>Canadian Cardiovascular Society angina grading scale describes the severity of angina pectoris. 0= no symptoms, I = angina pectoris with strenuous exertion, II-IV= angina with moderate/mild exertion or at rest. <sup>c</sup>Cardiopulmonary exercise testing was performed in 473 patients, exercise testing in 25 patients, 1 patient none.

<sup>d</sup>HLS-EU-Q16 data available from 459 patients.

<sup>e</sup>SF-36 data available from 393 patients.

**Table 2.** Baseline characteristics grouped by body mass index, exercise capacity and health literacy.

	Obesity <sup>a</sup> BMI (kg/m <sup>2</sup> )		Exercise capacity <sup>b</sup> Predicted peak VO <sub>2</sub> (%)				Health literacy <sup>c</sup> (HLS-EU-Q16)			
	Non-obese [n = 282]	Obese [n = 217]	p-value	Severely restricted [n = 165]	Mildly to moderately restricted [n = 164]	Normal [n = 144]	p-value	Not sufficient [n = 195]	Sufficient [n = 264]	p-value
Age (years)	69.8 ± 7.6	66.4 ± 7.5	<0.001	67.6 ± 8.4	69.9 ± 6.6	67.8 ± 6.7	0.806	67.6 ± 8.3	68.3 ± 7.3	0.317
Female sex	41 (14.5)	40 (18.4)	0.295	24 (14.5)	27 (16.5)	23 (16.0)	0.884	29 (14.9)	42 (15.9)	0.862
Education										
Low	3 (1.1)	9 (4.5)	0.014	5 (3.2)	3 (1.9)	3 (2.2)	0.268	8 (4.1)	4 (1.5)	0.226
Medium	116 (43.6)	102 (50.5)		78 (50.6)	68 (43.9)	52 (38.8)		88 (45.4)	121 (46.0)	
High	147 (55.3)	91 (45.0)		71 (46.1)	84 (54.2)	79 (59.0)		98 (50.5)	138 (52.5)	
Duration T2DM (years)	12.8 ± 8.2	11.5 ± 8.7	0.154	12.1 ± 8.3	13.0 ± 8.9	11.8 ± 8.9	0.800	12.1 ± 8.3	12.4 ± 8.6	0.780
Age T2DM diagnosis (years)	56.5 ± 9.7	54.4 ± 10.4	0.050	54.8 ± 10.7	56.4 ± 9.45	55.7 ± 9.97	0.428	54.9 ± 9.3	55.4 ± 10.2	0.708
HbA1c (%)	6.8 ± 0.8	6.9 ± 1.0	0.281	7.0 ± 1.0	6.8 ± 0.9	6.7 ± 0.9	0.002	6.9 ± 0.9	6.8 ± 0.9	0.962
Duration CIHD	8.5 ± 6.9	9.1 ± 7.9	0.480	8.7 ± 7.6	9.1 ± 7.4	8.0 ± 7.4	0.551	9.6 ± 7.8	8.2 ± 7.0	0.077
Age CIHD diagnosis (years)	60.9 ± 10.0	57.2 ± 9.4	<0.001	58.1 ± 10.8	60.6 ± 8.78	59.8 ± 9.83	0.152	57.7 ± 9.9	59.8 ± 9.8	0.039
CIHD classification										
≤1-vessel coronary disease/unknown	142 (50.5)	125 (57.6)	0.139	77 (46.7)	92 (56.1)	84 (58.3)	0.087	108 (55.4)	136 (51.7)	0.494
≥2-vessel coronary disease	139 (49.5)	92 (42.4)		88 (53.3)	72 (43.9)	60 (41.7)		87 (44.6)	127 (48.3)	
CIHD symptoms <sup>d</sup>										
Asymptomatic	228 (81.1)	176 (81.1)	0.559	123 (75.0)	132 (80.5)	129 (89.6)	0.015	157 (80.9)	215 (81.4)	0.515
CCS I	39 (13.9)	34 (15.7)		31 (18.9)	27 (16.5)	13 (9.0)		31 (16.0)	36 (13.6)	
CCS II-IV	14 (5)	7 (3.2)		10 (6.1)	5 (3.0)	2 (1.4)		6 (3.1)	13 (4.9)	
Previous myocardial infarction	102 (36.2)	69 (31.8)	0.355	67 (40.6)	49 (29.9)	44 (30.6)	0.074	73 (37.4)	89 (33.7)	0.468
Coronary revascularisation	159 (56.4)	115 (53.0)	0.507	94 (57.0)	95 (57.9)	71 (49.3)	0.258	107 (54.9)	146 (55.3)	1.000
Coronary artery bypass graft	47 (16.7)	35 (16.1)	0.969	36 (21.8)	27 (16.5)	13 (9.0)	0.009	31 (15.9)	49 (18.6)	0.536
Heart failure	62 (22.0)	58(26.7)	0.261	50 (30.3)	34 (20.7)	29 (20.1)	0.057	41 (21.0)	68 (25.8)	0.286
<b>Risk factors</b>										
BMI (kg/m <sup>2</sup> )	26.7 ± 2.1	34.5 ± 3.6	<0.001	30.1 ± 4.6	29.5 ± 4.7	30.4 ± 4.7	0.596	30.0 ± 4.7	30.1 ± 4.8	0.897
Hypertension	251 (89.0)	210 (96.8)	0.002	154 (93.3)	155 (94.5)	131 (91.0)	0.468	177 (90.8)	245 (92.8)	0.537
Blood pressure (mmHg)										
systolic	137 ± 18	139 ± 17	0.244	137 ± 17	137 ± 17	140 ± 17	0.079	136 ± 18	138 ± 17	0.365
diastolic	78 ± 10	80 ± 10	0.003	78 ± 10	79 ± 9	80 ± 9	0.073	79 ± 10	78 ± 9	0.328
Hyperlipidaemia	242 (85.8)	187 (86.2)	1.000	141 (85.5)	147 (89.6)	120 (83.3)	0.258	169 (86.7)	226 (85.6)	0.851
Total Cholesterol (mg/dl)	156 ± 40	159 ± 37	0.421	151 ± 39	158 ± 40	162 ± 40	0.013	154 ± 37	160 ± 42	0.103
LDL-C (mg/dl)	91 ± 36	94 ± 32	0.377	88 ± 35	91 ± 36	96 ± 36	0.041	90 ± 30	94 ± 38	0.186
Triglycerides (mg/dl)	166 ± 94	204 ± 103	<0.001	187 ± 100	183 ± 113	175 ± 113	0.314	175 ± 93	189 ± 106	0.154
Smoking										

(continued)

Table 2. (continued)

	Obesity <sup>a</sup> BMI (kg/m <sup>2</sup> )		Exercise capacity <sup>b</sup> Predicted peak $\dot{V}O_2$ (%)		Health literacy <sup>c</sup> (HLS-EU-Q16)				
	Non-obese [n = 282]	Obese [n = 217]	p-value	Severely restricted [n = 165]	Mildly to moderately restricted [n = 164]	Normal [n = 144]	Not sufficient [n = 195]	Sufficient [n = 264]	p-value
Never	115 (40.8)	70 (32.3)	0.148	52 (31.5)	63 (38.4)	57 (39.6)	75 (38.5)	94 (35.6)	0.755
Current	29 (10.3)	26 (12.0)		31 (18.8)	9 (5.5)	12 (8.3)	22 (11.3)	28 (10.6)	
Former	138 (48.9)	121 (55.8)		82 (49.7)	92 (56.1)	75 (52.1)	98 (50.3)	142 (53.8)	
Alcoholic drinks per week	4.2 ± 7.2	4.0 ± 7.5	0.843	4.6 ± 8.2	3.9 ± 5.2	4.3 ± 5.2	3.3 ± 5.0	4.8 ± 8.5	0.026
<b>Exercise capacity<sup>b</sup></b>									
Peak $\dot{V}O_2$ (ml/kg/min)	19.8 ± 4.5	17.1 ± 4.2	<0.001	14.8 ± 2.7	18.7 ± 2.8	23.0 ± 2.8	19.1 ± 4.9	18.3 ± 4.3	0.077
Peak $\dot{V}O_2$ (ml/min)	1610 ± 413	1770 ± 464	<0.001	1360 ± 259	1650 ± 294	2080 ± 434	1720 ± 441	1669 ± 442	0.155
Pred. peak $\dot{V}O_2$ (%)	81.4 ± 16.2	82.6 ± 17.6	0.466	64.5 ± 8.0	82.3 ± 4.2	101 ± 10.2	83.3 ± 17.3	80.7 ± 16.7	0.114
Work load (Watt)	128 ± 42	130 ± 42	0.598	101 ± 26	128 ± 30	166 ± 30	132 ± 43	127 ± 41	0.291
RER	1.10 ± 0.09	1.07 ± 0.10	<0.001	1.06 ± 0.10	1.11 ± 0.10	1.10 ± 0.10	1.09 ± 0.10	1.09 ± 0.10	0.639
VT1 not determinable	11 (4.1)	12 (5.9)	0.468	17 (10.3)	5 (3.0)	1 (0.7)	9 (4.8)	12 (4.8)	1.000
$\dot{V}O_2$ at VT1 (ml/min/kg)	11.7 ± 2.3	10.3 ± 1.9	<0.001	9.7 ± 1.8	10.8 ± 1.5	12.7 ± 1.5	11.2 ± 2.5	11.1 ± 2.09	0.765
<b>Medication</b>									
Antidiabetic medication	249 (88.3)	187 (86.2)	0.497	148 (89.7)	145 (88.4)	127 (88.2)	170 (87.2)	231 (87.5)	1.000
Number oral anti-diabetics									
0	44 (15.6)	40 (18.4)	0.725	25 (15.2)	26 (15.9)	23 (16.0)	33 (16.9)	44 (16.7)	0.172
1	114 (40.4)	91 (41.9)		62 (37.6)	60 (36.6)	74 (51.4)	89 (45.6)	100 (37.9)	
2	91 (32.3)	66 (30.4)		57 (34.5)	57 (34.8)	38 (26.4)	59 (30.3)	87 (33.0)	
≥3	32 (11.3)	20 (9.2)		21 (12.7)	20 (12.2)	9 (6.2)	14 (7.2)	33 (12.5)	
Oral anti-diabetics	237 (84.0)	177 (81.6)	0.484	140 (84.8)	137 (83.5)	121 (84.0)	162 (83.1)	220 (83.3)	1.000
Metformin	207 (73.4)	155 (71.4)	0.650	125 (75.8)	119 (72.6)	105 (72.9)	141 (72.3)	195 (73.9)	0.790
DPP4-inhibitors	78 (27.7)	37 (17.1)	0.007	43 (26.1)	46 (28.2)	24 (16.7)	43 (22.1)	62 (23.5)	0.803
SGLT2-inhibitors	64 (22.7)	45 (20.7)	0.663	36 (21.8)	39 (23.9)	29 (20.1)	36 (18.5)	63 (23.9)	0.202
Sulfonylurea	15 (5.3)	11 (5.1)	1.000	12 (7.3)	8 (4.9)	5 (3.5)	8 (4.1)	14 (5.3)	0.708
GLP-1-analogs	29 (10.3)	36 (16.6)	0.054	24 (14.5)	22 (13.5)	15 (10.4)	21 (10.8)	40 (15.2)	0.219
Insulin	67 (23.8)	70 (32.3)	0.047	56 (33.9)	40 (24.4)	38 (26.4)	56 (28.7)	73 (27.7)	0.884
Cardiovascular medication									
ACE inhibitor/AR blocker	230 (81.6)	193 (88.9)	0.032	136 (82.4)	141 (86.0)	123 (85.4)	165 (84.6)	225 (85.2)	0.961
Anti-platelet	205 (72.7)	144 (66.4)	0.152	119 (72.1)	108 (65.9)	104 (72.2)	142 (72.8)	185 (70.1)	0.591
ASA	194 (68.8)	135 (62.2)	0.149	108 (65.5)	104 (63.4)	99 (68.8)	132 (67.7)	177 (67.0)	0.964
Clopidogrel	23 (8.2)	13 (6.0)	0.452	20 (12.1)	11 (6.7)	5 (3.5)	13 (6.7)	21 (8.0)	0.734
Ticagrelor	5 (1.8)	6 (2.8)	0.544	5 (3.0)	1 (0.6)	5 (3.5)	8 (4.1)	2 (0.8)	0.021
Prasugrel	2 (0.7)	3 (1.4)	0.657	3 (1.8)	1 (0.6)	1 (0.7)	5 (2.6)	0 (0)	0.013
Lipid-lowering drugs	234 (83.0)	186 (85.7)	0.480	139 (84.2)	142 (86.6)	120 (83.3)	169 (86.7)	219 (83.0)	0.339
Statins	228 (80.9)	184 (84.8)	0.302	136 (82.4)	138 (84.1)	119 (82.6)	167 (85.6)	214 (81.1)	0.244
Atorvastatin/Rosuvastatin	138 (48.9)	103 (47.5)	0.814	82 (49.7)	72 (43.9)	76 (52.8)	92 (47.2)	128 (48.5)	0.855
Other statins	90 (31.9)	81 (37.3)	0.243	54 (32.7)	66 (40.2)	43 (29.9)	75 (38.5)	86 (32.6)	0.227

(continued)



**Table 2. (continued)**

	Obesity <sup>a</sup> BMI (kg/m <sup>2</sup> )		Exercise capacity <sup>b</sup> Predicted peak VO <sub>2</sub> (%)			Health literacy <sup>c</sup> (HLS-EU-Q16)				
	Non-obese [n = 282]	Obese [n = 217]	p-value	Severely restricted [n = 165]	Mildly to moderately restricted [n = 164]	Normal [n = 144]	p-value	Not sufficient [n = 195]	Sufficient [n = 264]	p-value
Other lipid-lowering drugs	44 (15.6)	37 (17.1)	0.755	26 (15.8)	35 (21.3)	19 (13.2)	0.145	32 (16.4)	42 (15.9)	0.987
Diuretics	86 (30.5)	110 (50.7)	<0.001	70 (42.4)	61 (37.2)	53 (36.8)	0.515	71 (36.4)	106 (40.2)	0.473
Aldosterone antagonists	25 (8.9)	27 (12.4)	0.251	25 (15.2)	14 (8.5)	9 (6.2)	0.025	20 (10.3)	30 (11.4)	0.822
Beta-blocker	203 (72.0)	161 (74.2)	0.654	128 (77.6)	121 (73.8)	96 (66.7)	0.094	138 (70.8)	197 (74.6)	0.417
Anticoagulation	57 (20.2)	41 (18.9)	0.800	42 (25.5)	34 (20.7)	19 (13.2)	0.026	32 (16.4)	56 (21.2)	0.241
Phenprocoumon	17 (6.0)	9 (4.1)	0.463	12 (7.3)	10 (6.1)	4 (2.8)	0.205	6 (3.1)	18 (6.8)	0.117
NOAC	40 (14.2)	32 (14.7)	0.961	30 (18.2)	24 (14.6)	15 (10.4)	0.156	26 (13.3)	38 (14.4)	0.851
Nitrates/Ranolazin	13 (4.6)	12 (5.5)	0.795	7 (4.2)	10 (6.1)	6 (4.2)	0.661	10 (5.1)	14 (5.3)	1.000
Sacubitril/Valsartan	6 (2.1)	2 (0.9)	0.429	6 (3.6)	0 (0)	2 (1.4)	0.022	2 (1.0)	5 (1.9)	0.704
<b>Quality of life<sup>f</sup></b>										
PCS	46.3 ± 8.8	42.3 ± 10.5	<0.001	42.2 ± 10.4	45.2 ± 9.0	47.4 ± 9.1	<0.001	43.1 ± 10.4	45.6 ± 9.1	0.013
MCS	52.4 ± 8.1	52.1 ± 10.4	0.692	52.1 ± 9.7	53.1 ± 8.1	51.8 ± 8.1	0.844	50.5 ± 10.0	53.6 ± 8.2	<0.001

BMI: body mass index; VO<sub>2</sub>: oxygen consumption; HLS-EU-Q16: Health literacy score; T2DM: type 2 diabetes mellitus; HbA1c: glycated haemoglobin; CHD: chronic ischaemic heart disease; CCS scale: Canadian Cardiovascular Society angina grading scale; LDL-C: low density lipoprotein cholesterol; RER: respiratory exchange ratio; VT: ventilatory threshold; DPP4: dipeptidyl peptidase-4; SGLT2: sodium/glucose cotransporter 2; GLP-1: glucagon-like peptide-1; ACE: angiotensin converting-enzyme; AR: androgen receptor; ASA: acetylsalicylic acid; NOAC: novel oral anticoagulants; PCS: physical component score; MCS: mental component score.

Data are presented as mean ± standard deviation or absolute and (relative) frequency.

<sup>a</sup>Grouped according to BMI; BMI ≤ 30 kg/m<sup>2</sup> “non-obese”; BMI >30 kg/m<sup>2</sup> “obese”.

<sup>b</sup>Grouped according to exercise capacity; predicted peak VO<sub>2</sub> < 75% “severely restricted”, 75–89.9% “mildly to moderately restricted” and ≥ 90% “normal”.

<sup>c</sup>Grouped according to HLS; HLS > 12 “sufficient HL”, “not sufficient HL” otherwise.

<sup>d</sup>Canadian Cardiovascular Society angina grading scale describes the severity of angina pectoris. 0 = no symptoms, I = angina pectoris with strenuous exertion, II-IV = angina with moderate/mild exertion or at rest.

<sup>e</sup>Cardiopulmonary exercise testing was performed in 473 patients, exercise testing in 25 patients, 1 patient none.

<sup>f</sup>Measured via SF-36 questionnaire. Available data from 393 patients.

CIHD at an older age ( $59.8 \pm 9.8$  vs  $57.7 \pm 9.9$  years,  $p = 0.039$ ) and reported a higher QoL with higher mean values in PCS ( $45.6 \pm 9.1$  vs  $43.1 \pm 10.4$ ,  $p = 0.013$ ) and MCS ( $53.6 \pm 8.2$  vs  $50.5 \pm 10.0$ ,  $p < 0.001$ ).

### LeIKD in context of other studies on T2DM and CV risk

In comparison to selected trials on T2DM and CIHD or CV risk (Table 3), patients included in the present study were notably older. Sex distribution in LeIKD was similar to the exercise intervention trial EXCADI, but Look AHEAD, CAROLINA and CARMELINA included a higher proportion of women. Besides CARMELINA, LeIKD enrolled patients with the longest average duration of T2DM.

Baseline HbA1c was lower than in the compared trials, even in trials with similar inclusion criteria regarding HbA1c values like CAROLINA and CARMELINA. Common risk factors for CV diseases (e.g. blood pressure, history of smoking, blood lipids, BMI) were similar between the trials. However, the prevalence of hypertension was higher in LeIKD (92.4%) than in the other trials and patients randomised to Look AHEAD (inclusion criteria:  $\text{BMI} \geq 27 \text{ kg/m}^2$ ) had a higher mean BMI of  $35.9 \pm 5.8 \text{ kg/m}^2$ . Regarding medication, LeIKD showed the lowest percentage of patients prescribed with sulfonylureas (5.2%). EXCADI was the only compared trial that also conducted CPET. Mean peak  $\dot{V}\text{O}_2$  ( $24.7 \pm 5.9$  vs  $18.6 \pm 4.6 \text{ mL/min/kg}$ ) and VT1 ( $18.9 \pm 4.1$  vs  $11.1 \pm 2.3 \text{ mL/min/kg}$ ) were higher in EXCADI than in LeIKD.

## Discussion

To date, LeIKD is one of the largest studies in patients with CIHD and T2DM providing a tremendous clinical and lifestyle-related dataset including CPET among 499 patients. Accordingly, this manuscript contributes to a better characterisation and understanding of this multi-morbid patient population and provides insights into the current healthcare and disease management of patients in Germany.

The LeIKD study population was characterised by advanced age, predominantly male gender, relatively high educational status and a high prevalence of comorbidities and risk factors. To reduce microvascular complications and CV events, a target HbA1c of  $< 7\%$  is recommended in most T2DM patients, while in older patients less stringent targets of  $< 8\%$  can be considered on an individual basis.<sup>2</sup> Despite the high prevalence of comorbidities and risk factors in patients included in the present trial, the mean HbA1c ( $6.9 \pm 0.9\%$ ) was within target range and only 36% had an HbA1c  $\geq 7\%$  (11.5% with an HbA1c  $\geq 8\%$ ). Compared to a subgroup of the EAV survey (2016-2017,

across 27 countries in Europe) with both CIHD and T2DM ( $n=2452$ ) and a mean HbA1c of  $7.2 \pm 1.7\%$  (45% with an HbA1c  $\geq 7\%$ ; 26% with an HbA1c  $\geq 8\%$ ),<sup>5</sup> this suggests a predominately adequate glycaemic control within the present study population. This is also supported by the higher number of patients with anti-diabetic medication in LeIKD (87%) compared to EAV (75%),<sup>5</sup> including a similar proportion of prescribed insulin (EAV with 30%<sup>5</sup> vs LeIKD with 27.5%). This could, at least in part, be due to the fact that all patients were included in a DMP for CIHD or T2DM prior to the study inclusion. DMP consist of regular medical visits and offers for educational programmes.

In LeIKD, the use of glucose-lowering drugs with cardio-protective capacity, particularly SGLT-2 inhibitors (21.8%) and GLP-1 receptor antagonists (13.0%) was higher than in EAV (1% each),<sup>5</sup> indicating an accelerating implementation of these drug classes in clinical practice during the last years. Despite a high prevalence of hypertension (92.4%), the mean systolic blood pressure ( $137 \pm 17 \text{ mmHg}$ ) was within the target values of 130–140 mmHg for older patients ( $>65$  years).<sup>6</sup> However, this observation is biased by the requirement of an exercise training approval including adequate blood pressure behaviour. In contrast, LDL-C was rather poorly managed. According to current guideline recommendations, LDL-C should be less than 55 mg/dl in patients with very high CV risk.<sup>2</sup> In the present study, only 41 patients (8%) reached this target (24% with LDL-C  $< 70 \text{ mg/dl}$  as previously recommended until 2019), with an average LDL-C of  $92 \pm 34 \text{ mg/dl}$ . This replicates the results of the EAV survey with almost two-thirds of patients above the LDL-C target of less than 70 mg/dl.<sup>5</sup> In patients with T2DM and CIHD, lipid lowering drug therapy is indicated as a class IA recommendation,<sup>2</sup> however, 79 study patients were not prescribed any statins or alternative lipid lowering drugs at baseline.

Besides medical treatment, LeIKD baseline characteristics also indicate some potential for the improvement of lifestyle-related measures. Although obesity has long been recognised as a prevalent driver of several cardio-metabolic risk factors including T2DM, it is still not reasonably treated compared to other modifiable risk factors.<sup>21</sup> Similar to EAV (88.5% with  $\text{BMI} > 25 \text{ kg/m}^2$  and 49% with  $\text{BMI} > 30 \text{ kg/m}^2$ ),<sup>5</sup> 89.2% and 43.5% of patients included in LeIKD were classified as overweight and obese, respectively. In the present study, obese patients had an increased prevalence of hypertension, higher levels of triglycerides and a lower QoL-PCS. Interestingly, mean HbA1c and severity of CIHD were not significantly different between obese and non-obese patients. This could in part be explained by a lower mean age of the obese patients, as HbA1c levels and severity of CIHD are expected to increase with age. Furthermore, T2DM and CIHD were

**Table 3.** LeIKD in context of other studies on T2DM and CV risk.

	Lifestyle intervention trials			Clinical drug-intervention trials	
	Look AHEAD <sup>a</sup>	EXCADI	LeIKD	CAROLINA	CARMELINA <sup>d</sup>
<b>Primary study aims</b>	Long-term effects of an intensive lifestyle-intervention on weight reduction and CV outcome	Effects of a 12-month exercise training on HbA1c and peak $\dot{V}O_2$	Effects of an individual telemedicine-based lifestyle intervention on CV risk factors and health literacy	Effects of treatment with linagliptin vs glimepiride on CV safety in patients with early T2DM and increased CV risk or established atherosclerotic CVD	Effects of linagliptin on CV and kidney outcomes in a study population enriched for cardio-renal risk
<b>Key eligibility criteria</b>	T2DM, overweight (BMI $\geq$ 25 kg/m <sup>2</sup> ; if on insulin, BMI $\geq$ 27 kg/m <sup>2</sup> ), blood pressure < 160/100 mmHg, HbA1c $\leq$ 11%, triglycerides < 600 mg/dl, passed exercise test	T2DM and CIHD	CIHD (ICD-10: I20-I25), T2DM (ICD-10: E11), HbA1c $\geq$ 6.5% or antidiabetic medication, permission to do physical exercise	T2DM, HbA1c 6.5 - 8.5%, pre-existing CVD OR specified diabetes end-organ damage OR age $\geq$ 70 years OR two or more specified CV risk factors	T2DM, HbA1c of $\geq$ 6.5% and $\leq$ 10.0%, BMI $\leq$ 45 kg/m <sup>2</sup> , high risk of CV events
<b>Number</b>	5145	137	499	6041	3990
<b>Years screening</b>	2001–2004	2010–2012	2019–2020	2010–2012	2013–2016
<b>Baseline characteristics of randomised cohort</b>					
Age (years)	59 $\pm$ 6.8	63.1 $\pm$ 7.9	68.3 $\pm$ 7.7	64.0 $\pm$ 9.5	64.8 $\pm$ 8.8
Female sex	3058 (59.4)	22 (16.1)	81 (16.2)	2419 (40)	1238 (31.0)
BMI (kg/m <sup>2</sup> )	35.9 $\pm$ 5.8	29.2 $\pm$ 5.0	30.1 $\pm$ 4.8	30.1 $\pm$ 5.1	31.0 $\pm$ 5.1
Blood pressure (mmHg)					
Systolic	129 $\pm$ 17	139 $\pm$ 17	137 $\pm$ 17	136 $\pm$ 16	139.2 $\pm$ 16.8
Diastolic	70 $\pm$ 10	—	79 $\pm$ 10	79 $\pm$ 10	78.2 $\pm$ 10.2
Smokers	228 (4.4)	23 (17)	55 (11.0)	1188 (19.7) <sup>b</sup>	478 (12.0)
Hypertension	4132 (80.3)	100 (73)	461 (92.4)	5418 (90) <sup>b</sup>	—
Heart failure	—	11 (8)	120 (24.0)	271 (4.5) <sup>b</sup>	—
Myocardial infarction	—	62 (45)	171 (34.3)	—	—
Duration of T2DM (years)	6.8 $\pm$ 6.5	9 [5 – 15]	12.3 $\pm$ 8.4	6.2 [2.9 – 11.0]	13.8 $\pm$ 9.3
HbA1c (%)	7.28 $\pm$ 1.2	7.4 [6.8 – 8.3]	6.9 $\pm$ 0.9	7.2 $\pm$ 0.6	8.0 $\pm$ 1.0
History of CVD/CIHD	726 (14) (CVD)	137 (100) (CIHD)	502 (100) (CIHD)	6014 (99.7) (CVD) 1905 (31.7) <sup>b</sup> (CIHD)	3990 (100) (CVD)
Cholesterol (mg/dl)	191 $\pm$ 38	152 [132 – 179]	157 $\pm$ 39	177 $\pm$ 44	169 $\pm$ 48
LDL-C (mg/dl)	112 $\pm$ 32	78 [62 – 101]	92 $\pm$ 34	95 $\pm$ 36	89 $\pm$ 39
Triglycerides (mg/dl)	181 $\pm$ 118	124 [97 – 168]	182 $\pm$ 100	144 [105 – 198]	185 $\pm$ 134
<b>Medication</b>					
Statins	2221 (43.2)	128 (93)	412 (82.6)	3900 (64.8) <sup>b</sup>	2979 (74.7)
Beta-blocker	957 (18.6)	106 (77)	364 (72.9)	2352 (39.1) <sup>b</sup>	2563 (64.2)
ACE/ARBs	1620 (31.5)/578 (11.2)	97 (70)	423 (84.8)	2472 (41.1) <sup>c</sup> /1884 (31.3) <sup>b</sup>	3214 (80.6)
Diuretics	1467 (28.5)	—	196 (39.3)	2236 (37) <sup>b</sup>	1848 (46.3)
Metformin	2688 (52.2)	101 (74)	362 (72.5)	4982 (82.5)	2657 (66.6)

(continued)

Table 3. (continued)

	Lifestyle intervention trials			Clinical drug-intervention trials	
	Look AHEAD <sup>a</sup>	EXCADI	LeIKD	CAROLINA	CARMELINA <sup>d</sup>
Sulfonylurea	2295 (44.6)	48 (35)	26 (5.2)	1728 (28.6)	1486 (37.2)
Insulin	750 (14.6)	26 (19)	137 (27.5)	0 (0) <sup>c</sup>	2077 (52.1)
<b>Exercise capacity</b>					
Peak $\dot{V}O_2$ (ml/kg/min)	—	24.7 ± 5.9	18.6 ± 4.6	—	—
VT (ml/kg/min)	—	18.9 ± 4.1	11.1 ± 2.3	—	—

BMI: body mass index; T2DM: type 2 diabetes mellitus; HbA1c: glycated haemoglobin; CV: cardiovascular; CVD: cardiovascular disease; CIHD: chronic ischaemic heart disease; LDL-C: low density lipoprotein cholesterol; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker;  $\dot{V}O_2$ : oxygen consumption; VT: ventilatory threshold. Data are reported as mean ± standard deviation, absolute and relative (%) frequency or median [1<sup>st</sup> quartile – 3<sup>rd</sup> quartile].

<sup>a</sup>If mean ± standard deviation was only available for separate treatment groups, overall values were calculated as follows: Mean Overall =  $(M_1 \times N_1 + M_2 \times N_2)/(N_1 + N_2)$   $\sqrt{SD^2} = (1/(N_1 + N_2 - 1) \times ((N_1 - 1) \times SD_1^2 + (N_2 - 1) \times SD_2^2 + (N_1 \times N_2)/(N_1 + N_2) \times (M_1 - M_2)^2)$  M = mean; N = number; SD = standard deviation.

<sup>b</sup>Data originate from main results publication,  $n = 6033$ .

<sup>c</sup>insulin was an exclusion criteria.

<sup>d</sup>Reported data is from a subsample with established CV disease, defined according to study inclusion criteria as albuminuria (UACR  $\geq 30$  mg/g or  $\geq 30$   $\mu$ g albumin/min or  $\geq 30$  mg albumin/24 h) and prevalent macrovascular disease (one or more of the following: confirmed history of myocardial infarction; advanced coronary artery disease; high-risk single-vessel coronary artery disease; history of ischemic or haemorrhagic stroke; presence of carotid artery disease; presence of peripheral artery disease).

diagnosed at a younger age in the obese subgroup. While peak  $\dot{V}O_2$  was significantly lower when adjusted to body weight, absolute peak  $\dot{V}O_2$  and %-predicted peak  $\dot{V}O_2$  were similar between obese and non-obese patients. This highlights the common pitfall of adjusting peak  $\dot{V}O_2$  to body weight (instead of lean body mass) and suggests that in the present study, obesity was not significantly associated with exercise capacity during non-weight-bearing cycling.

Compared to CPET reference values,<sup>12</sup> only one third of patients in LeIKD had an adequate exercise capacity ( $\geq 90\%$  predicted). Low exercise capacity is one of the most relevant and at the same time one of the most poorly treated risk factors for the development and progression of T2DM and CIHD.<sup>22,23</sup> Accordingly in the present study, patients with lower exercise capacity had more severe CIHD, significantly higher levels of HbA1c and a lower QoL-PCS. On the other hand, duration of CIHD or T2DM were not significantly different between subgroups of exercise capacity, although an impaired exercise capacity may already be observed in the early beginnings of diabetic pathology.<sup>24</sup> Nevertheless, it is concerning that the subgroup with the lowest exercise capacity still had the highest proportion of current smokers. Interestingly, we observed significantly higher values for total and LDL cholesterol with higher exercise capacity, which might be explained by a more intense treatment in the sicker patient population. There were no significant differences in the percentage of heart failure patients among the different exercise capacity groups. However, this is most likely be explained by an insufficient power, as only 120 patients had a confirmed

diagnosis of heart failure. Similarly, with only 20% of patients being prescribed with SGLT2-inhibitors, the power may be too small to detect a possible difference between subgroups of exercise capacity. Furthermore, potential positive effects of SGLT2-inhibitors on exercise capacity<sup>25</sup> may be overlaid by the fact that SGLT2-inhibitors are more likely be prescribed in patients with higher disease severity and concomitant heart failure.<sup>2</sup> The latter could also be the reason for the significant differences observed for the prescription of DPP4-inhibitors between subgroups of peak  $\dot{V}O_2$ .

An appropriate management of modifiable lifestyle-related risk factors requires that patients have a certain understanding of their disease. Low HL as well as a low general and health-related education are associated with a higher prevalence of CV risk factors, T2DM and CV disease, low diabetes specific knowledge and a decreased access to healthcare screening or basic services.<sup>8,26,27</sup> A limited HL has been shown to be associated with a lower participation rate in clinical trials<sup>26</sup> and programmes on weight reduction, healthy diet and physical activity.<sup>28</sup> In LeIKD, about 40% of the study population had an inadequate (15.9%) or problematic HL (26.6%), which is comparable to results of a German national health survey (GEDA2014/2015-EHIS) in patients with CV disease (44% with insufficient HL).<sup>8</sup> However, only 2.4% of the LeIKD participants (compared to 18% in EAV<sup>5</sup>) had a low education level. One possible reason for this might be that historically, the TK health insurance has primarily insured individuals with technical professions or a technical academic education. Contrary to the GEDA2014/2015-EHIS

survey,<sup>8</sup> education level, sex or BMI were not significantly different between subgroups of HL in the present study. We also found no significant differences between HL groups for CIHD and T2DM disease severity or established risk factors, except for alcohol consumption, with – surprisingly – a higher consumption in the group with sufficient HL. Nevertheless, consistent with the analyses in subgroups of BMI and peak  $\dot{V}O_2$ , patients with lower HL had a lower QoL-PCS, which emphasises the importance of nutritional, exercise and HL training in these patients. Furthermore, only for HL we found significant differences in the QoL-MCS. This could indicate that despite non-significant differences in disease severity and risk factor burden, patients with a low HL experience more impairment due to mental health related factors and require additional support and patient empowerment in the management of their health condition.

### *LeIKD study population in context of other studies on T2DM and CV risk*

Compared to other clinical trials in CIHD and T2DM, there were no relevant differences in baseline characteristics that could limit the generalisability of the results of the present trial. However, in contrast to the trials selected for comparison, the LeIKD trial enrolled the oldest study population with the lowest baseline HbA1c and a low percentage of female participants (16%), the latter being comparable to the EXCADI trial (16% females), another lifestyle intervention trial in CIHD and T2DM. While female participation is typically low (around 27%) in clinical CIHD trials<sup>29</sup> and less women than men attend cardiac prevention and rehabilitation programmes,<sup>30</sup> the pharmacological trials CAROLINA (40%) and CARMELINA (31%) as well as the Look AHEAD lifestyle intervention in T2DM (59%) enrolled a considerably higher percentage of female participants. In EXCADI, the only compared trial applying CPET, mean peak  $\dot{V}O_2$  was about ca. 30% higher, which could, at least in part, be explained by the younger mean age, a lower prevalence of heart failure and the fact that CPET was performed on treadmill compared to bicycle ergometers in LeIKD.<sup>31</sup>

### *Recruitment strategy*

By applying a novel recruitment strategy based on medical records (via ICD-10 codes) with initial contact through one of the largest public health insurances in Germany, a large number of potential participants could be identified and randomised within 13 months. The applied eligibility criteria were chosen in order to include as many suitable patients with CIHD and T2DM as possible. However, many initially selected patients had to be excluded during

the screening process because of not meeting the target population (e.g. HbA1c < 6.5% without antidiabetic medication; documented exclusion of arteriosclerosis/obvious miscoding for ICD-10: I20-I25). Furthermore, a large number of patients were not clinically stable (e.g. uncontrolled hypertension, signs of acute ischaemia) or did not receive the required medical treatment to safely perform a home-based exercise intervention, or refused to participate due to concerns about the use of telemedical devices. While owning a smartphone was not a prerequisite for inclusion, participation required a basic willingness to use technical devices.

### *Limitations*

This study has several limitations. All patients had to be insured at the TK health insurance fund, which may have influenced some patient characteristics. While the diagnosis of T2DM was confirmed during screening (HbA1c  $\geq$  6.5% or anti-diabetic medication), the diagnosis of CIHD was primarily based on the medical records (ICD-10: I20-I25) provided by TK health insurance, which may have led to the inclusion of some patients with incorrect coding. Based on the study inclusion criteria “able to perform physical exercise”, “clinically stable” and with “optimal medical cardiac treatment”, disease severity is likely to be lower than in pharmacological trials and the general population with T2DM and CIHD. Furthermore, sicker patients might be less willing to participate in lifestyle intervention trials and an additional self-selection may have occurred due to the required use of a smartphone and telemedical devices. Nevertheless, despite a reasonably well managed HbA1c, clinical characteristics were quite similar to other lifestyle and pharmacological trials in this patient population.

### *Conclusion*

To date, LeIKD provides one of the largest clinical and lifestyle-related datasets including CPET from 499 patients with CIHD and T2DM, who are likely to be representative for this special patient population. Exercise capacity was confirmed to be linked to the severity of CIHD and T2DM, which reinforces the relevance of intensifying lifestyle intervention strategies in this multimorbid, heterogeneous and understudied high-risk patient population.

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## Author Contributions

SMTD and JK wrote the manuscript with contribution of SM and MH. JK had full access to all data in the study and takes responsibility for the accuracy of the data analysis. All authors contributed to the study design or data acquisition and interpretation, critically revised the manuscript and gave their final approval.

## Declaration of conflicting interests

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## References

1. Global Health Estimates. 2020: *deaths by cause, age, sex, by Country and by Region, 2000-2019*. Geneva: World Health Organization, 2020.
2. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular

- diseases developed in collaboration with the EASD. *Eur Heart J* 2020; 41: 255–323. DOI: [10.1093/eurheartj/ehz486](https://doi.org/10.1093/eurheartj/ehz486).
3. Ferrannini G, Norhammar A, Gyberg V, et al. Is coronary artery disease inevitable in type 2 diabetes? From a glucocentric to a holistic view on patient management. *Diabetes Care* 2020; 43: 2001–2009. DOI: [10.2337/dci20-0002](https://doi.org/10.2337/dci20-0002).
4. Herrington W, Lacey B, Sherliker P, et al. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res* 2016; 118: 535–546. DOI: [10.1161/circresaha.115.307611](https://doi.org/10.1161/circresaha.115.307611).
5. Ferrannini G, de Bacquer D, De Backer G, et al. Screening for glucose perturbations and risk factor management in dysglycemic patients with coronary artery disease—A persistent challenge in need of substantial improvement: a report from ESC EORP EUROASPIRE V. *Diabetes Care* 2020; 43: 733. DOI: [10.2337/dc19-2165](https://doi.org/10.2337/dc19-2165).
6. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J* 2019; 41: 407–477. DOI: [10.1093/eurheartj/ehz425](https://doi.org/10.1093/eurheartj/ehz425).
7. Arnold SV, Bhatt DL, Barsness GW, et al. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: a scientific statement from the American heart association. *Circulation* 2020; 141: e779–e806. DOI: [10.1161/cir.0000000000000766](https://doi.org/10.1161/cir.0000000000000766).
8. Diederichs C, Jordan S, Domanska O, et al. Health literacy in men and women with cardiovascular diseases and its association with the use of health care services - Results from the population-based GEDA2014/2015-EHIS survey in Germany. *PLoS One* 2018; 13: e0208303. DOI: [10.1371/journal.pone.0208303](https://doi.org/10.1371/journal.pone.0208303).
9. von Korn P, Sydow H, Neubauer S, et al. Lifestyle intervention in chronic ischaemic heart disease and type 2 diabetes (the LeIKD study): study protocol of a prospective, multicentre, randomised, controlled trial. *BMJ Open* 2021; 11: e042818. DOI: [10.1136/bmjopen-2020-042818](https://doi.org/10.1136/bmjopen-2020-042818).
10. Sevick MA, Korytkowski M, Stone RA, et al. Biophysiological outcomes of the enhancing adherence in type 2 diabetes (ENHANCE) trial. *J Acad Nutr Diet* 2012; 112: 1147–1157. DOI: [10.1016/j.jand.2012.05.008](https://doi.org/10.1016/j.jand.2012.05.008).
11. Gignac GE and Szodorai ET. Effect size guidelines for individual differences researchers. *Pers Individ Differ* 2016; 102: 74–78. DOI: [10.1016/j.paid.2016.06.069](https://doi.org/10.1016/j.paid.2016.06.069).
12. Gläser S, Ittermann T, Schäper C, et al. Referenzwerte für die Spiroergometrie – Ergebnisse der Study of Health in Pomerania (SHIP). *Pneumologie* 2013; 67: 58–63.
13. Beaver WL, Wasserman K and Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; 60: 2020–2027. DOI: [10.1152/jappl.1986.60.6.2020](https://doi.org/10.1152/jappl.1986.60.6.2020).
14. Rößlin F, Pelikan J and Ganahl K. Die Gesundheitskompetenz der 15-jährigen Jugendlichen in Österreich. In *abschlussbericht der österreichischen Gesundheitskompetenz*



- Jugendstudie im Auftrag des Hauptverbands der österreichischen Sozialversicherungsträger (HVSF)*, 2013.
15. Ware JE Jr and Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473–483.
  16. Marx N, Rosenstock J, Kahn SE, et al. Design and baseline characteristics of the CARdiovascular outcome trial of LINAgliptin versus glimepiride in type 2 diabetes (CAROLINA®). *Diab Vasc Dis Res* 2015; 12: 164–174. DOI: [10.1177/1479164115570301](https://doi.org/10.1177/1479164115570301).
  17. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: The CAROLINA randomized clinical trial. *JAMA* 2019; 322: 1155–1166. DOI: [10.1001/jama.2019.13772](https://doi.org/10.1001/jama.2019.13772).
  18. Rosenstock J, Perkovic V, Alexander JH, et al. Rationale, design, and baseline characteristics of the CARdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA®): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. *Cardiovasc Diabetol* 2018; 17: 39. DOI: [10.1186/s12933-018-0682-3](https://doi.org/10.1186/s12933-018-0682-3).
  19. Byrkjeland R, Njerve IU, Anderssen S, et al. Effects of exercise training on HbA1c and VO2peak in patients with type 2 diabetes and coronary artery disease: a randomised clinical trial. *Diab Vasc Dis Res* 2015; 12: 325–333. DOI: [10.1177/1479164115590552](https://doi.org/10.1177/1479164115590552).
  20. Bray G, Gregg E, Haffner S, et al. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res* 2006; 3: 202–215. DOI: [10.3132/dvdr.2006.031](https://doi.org/10.3132/dvdr.2006.031).
  21. Piché ME, Tchernof A and Després JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res* 2020; 126: 1477–1500. DOI: [10.1161/circresaha.120.316101](https://doi.org/10.1161/circresaha.120.316101).
  22. Fang ZY, Sharman J, Prins JB, et al. Determinants of exercise capacity in patients with type 2 diabetes. *Diab Care* 2005; 28: 1643–1648. DOI: [10.2337/diacare.28.7.1643](https://doi.org/10.2337/diacare.28.7.1643).
  23. Winzer EB, Woitek F and Linke A. Physical activity in the prevention and treatment of coronary artery disease. *J Am Heart Assoc* 2018; 7: e007725. DOI: [10.1161/jaha.117.007725](https://doi.org/10.1161/jaha.117.007725).
  24. Nesti L, Pugliese NR, Sciuto P, et al. Type 2 diabetes and reduced exercise tolerance: a review of the literature through an integrated physiology approach. *Cardiovasc Diabetol* 2020; 19: 134. DOI: [10.1186/s12933-020-01109-1](https://doi.org/10.1186/s12933-020-01109-1).
  25. Kumar N, Garg A, Bhatt DL, et al. Empagliflozin improves cardiorespiratory fitness in type 2 diabetes: translational implications. *Can J Physiol Pharmacol* 2018; 96: 1184–1187. DOI: [10.1139/cjpp-2018-0359](https://doi.org/10.1139/cjpp-2018-0359).
  26. Magnani JW, Mujahid MS, Aronow HD, et al. Health literacy and cardiovascular disease: fundamental relevance to primary and secondary prevention: a scientific statement from the American Heart Association. *Circulation* 2018; 138: e48–e74. DOI: [10.1161/cir.0000000000000579](https://doi.org/10.1161/cir.0000000000000579).
  27. Bruthans J, Mayer O Jr, De Bacquer D, et al. Educational level and risk profile and risk control in patients with coronary heart disease. *Eur J Prev Cardiol* 2016; 23: 881–890. DOI: [10.1177/2047487315601078](https://doi.org/10.1177/2047487315601078).
  28. Schmitz R, Jordan S, Mütters S, et al. Population-wide use of behavioural prevention and counselling programmes for lifestyle-related cardiovascular risk factors in Germany. *Eur J Prev Cardiol* 2012; 19: 849–856. DOI: [10.1177/1741826711410949](https://doi.org/10.1177/1741826711410949).
  29. Jin X, Chandramouli C, Allocco B, et al. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation* 2020; 141: 540–548. DOI: [10.1161/circulationaha.119.043594](https://doi.org/10.1161/circulationaha.119.043594).
  30. Ferrannini G, De Bacquer D, Vynckier P, et al. Gender differences in screening for glucose perturbations, cardiovascular risk factor management and prognosis in patients with dysglycaemia and coronary artery disease: results from the ESC-EORP EUROASPIRE surveys. *Cardiovasc Diabetol* 2021; 20: 38. DOI: [10.1186/s12933-021-01233-6](https://doi.org/10.1186/s12933-021-01233-6).
  31. Wasserman K, Hansen J, Sue DY, et al. *Principles of exercise testing and interpretation: Including pathophysiology and clinical applications*. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2011, p. 1–592.

## Appendix

### Notation

ACE	angiotensin-converting-enzyme	CCS	Canadian Cardiovascular Society angina grading scale
AR	androgen receptor	CIHD	Chronic ischaemic heart disease
ASA	acetylsalicylic acid	COPD	chronical obstructive pulmonary disease
BMI	body mass index	COVID-19	coronavirus disease 2019
CARMELINA	CARdiovascular safety and Renal Microvascular outcomE study with LINAgliptin	CPET	cardiopulmonary exercise testing
CAROLINA	CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes	CV	cardiovascular
		DMP	Disease management programme
		DPP4	dipeptidyl peptidase-4
		EAV	EUROASPIRE V (European Action on Secondary and Primary Prevention by Intervention to Reduce Events)
		ECG	electrocardiogram

ENHANCE	Enhancing Adherence in Type 2 Diabetes trial	LS	lifestyle intervention
GLP-1	glucagon-like peptide-1	LVEF	left ventricular ejection fraction
HbA1c	glycated haemoglobin	MCS	mental component score
HDL-C	high density lipoprotein cholesterol	NOAC	novel oral anticoagulants
HFmrEF	heart failure with mildly reduced ejection fraction	NT-proBNP	N-terminal prohormone of brain natriuretic peptide
HFpEF	heart failure with preserved ejection fraction	PCS	physical component score
HFrEF	heart failure with reduced ejection fraction	QoL	quality of life
HL	health literacy	RER	respiratory exchange ratio
HLS-EU-Q16	Health literacy score	SGLT-2	sodium/glucose cotransporter 2
ICD	International Statistical Classification of Diseases and Related Health Problems	SHIP	Study of Health in Pomerania
LDL-C	low density lipoprotein cholesterol	T2DM	Type 2 diabetes mellitus
LeIKD	Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes	TK	Techniker Krankenkasse
		UC	usual care
		VT	ventilatory threshold
		$\dot{V}O_2$	oxygen consumption