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Lehrstuhl für Präventive und Rehabilitative Sportmedizin

Individualized combined exercise in patients with cardiac disease and low fitness

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A comparison of individualized combined endurance-resistance exercise with a cardiac rehabilitation maintenance program on peak and submaximal exercise performance, risk status, health-related quality of life and physical activity levels in elderly patients with cardiac disease and low physical fitness: A randomized controlled trial

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Abstract

Keywords: Cardiac rehabilitation, elderly, low physical fitness, maximal exercise performance, submaximal exercise performance, risk status, combined exercise, strength, health-related quality of life, leisure time physical activity

The performance of exercise as a secondary preventive method to lower risk of future adverse events in patients with heart disease has been long established. In Germany, this effort is supported through a national network of exercise based long-term cardiac maintenance programs, *Herzgruppen* ("heart groups"). This system seems to be effective in sustaining pre-participation levels of health and fitness, however there is very little data supporting this. However, individualized exercise methods seem to be established as effective in increasing exercise capacity and reducing cardiovascular risk. The inclusion of an ever-increasing number of elderly patients with low fitness has led to an opportunity to investigate exercise in this population in a real-life rehabilitative setting.

Therefore, the current study compares the effects of individualized combined exercise training with a traditional calisthenics-based cardiac rehabilitation maintenance program on parameters of health and fitness in a collective of elderly patients with reduced fitness.

Seventy patients (70±9 y, 14% female) with cardiac disease and low exercise capacity (< 6 MET) were consecutively randomized and allocated to once-weekly individualized combined exercise plus once-weekly cardiac maintenance (n = 35) or twice-weekly cardiac maintenance (n = 35) for six months. After six months, all patients performed twice weekly cardiac maintenance for a further six months and were reinvestigated. The primary endpoint was change in peak exercise capacity measured as maximum watts per kilogram body weight during exercise testing.

Individualized combined exercise performed 30 minutes of moderate endurance exercise and two sets of five resistance exercises for a total duration of 60 minutes. Cardiac maintenance performed 60 minutes of calisthenics and coordination exercises and 30 minutes of relaxation and flexibility exercise, for a total duration of 90 minutes.

At six months, no significant between-group differences were observed in maximal exercise capacity (ICE: +0.05±0.17 W/kg, CMP: +0.04±0.17 W/kg, P=0.83) or peak oxygen uptake (ICE: -0.1±3.1 ml/kg/min, CMP: +0.6±3.2 ml/kg/min, P = 0.38). Significant between group differences were observed in resting heart rate (ICE: -7±11 bpm, CMP: -0.3±8 bpm, P=0.01), submaximal exercise time (ICE: +116±112 s, CMP: +15±120 s, P<0.01) and workload (ICE: +16±16 W, CMP: +2±17 W, P<0.01) and maximal upper (ICE: +7±8 kg, CMP: 0±7 kg, P<0.01) and lower (ICE: +14±14 kg, CMP: 0.2±12 kg, P<0.01) body strength. Individualized combined exercise increased vigorous physical activity (ICE: Δ +12 MET-min/d, CMP: Δ –5 MET-min/d, p=0.02) and steps per day (ICE: +1586 steps/d, CMP: –838 steps/d, p<0.01) compared to cardiac maintenance. Individualized combined exercise improved in fitness category more than cardiac maintenance (median change ICE: +0.4, CMP: –0.1, p=0.01).

Individualized combined exercise improved in health-related quality of life vitality, (ICE: Δ +3.0, CMP: Δ –0.1, p<0.01), emotional health (ICE: Δ +0.2, CMP: Δ 0.0, p=0.05), social health (ICE: Δ +0.3, CMP, Δ 0.1, p<0.01), positive affect (ICE: Δ +2.4, CMP: Δ –0.1, p<0.01) and negative affect (ICE: Δ -0.7, CMP: Δ +1.0, p<0.05) compared to cardiac maintenance.

After one year, differences after six months largely returned to baseline levels. Individualized combined exercise did not improve maximal exercise performance in patients with low physical fitness compared to participation in cardiac maintenance. However, the performance of individualized combined exercise did not result in any serious adverse events and was superior to a cardiac maintenance program in improving resting hemodynamics, submaximal exercise performance and muscular strength. Individualized combined exercise also resulted in significant improvements in leisure time physical activity levels and health-related quality of life.

Zusammenfassung

Schlüsselwörter: Kardiale Rehabilitation, Senioren, niedriges Fitnessniveau, maximale Leistungsfähigkeit, submaximale Leistungsfähigkeit, Risikostatus, kombiniertes Training, Kraft, gesundheitsbezogenen Lebensqualität, Freizeitaktivitäten

Die Durchführung körperlicher Aktivität ist seit langem eine gängige Methode der Sekundärprävention zur Risikoreduzierung von „Unerwünschten Ereignissen“ (engl. Adverse Events) bei Patienten mit Herzerkrankung. In Deutschland wird dieser Ansatz durch ein nationales Netzwerk von trainingsbasierten kardiologischen Langzeitprogrammen, sog. Herzsportgruppen, unterstützt. Dieses Konzept erscheint in der Erhaltung des körperlichen Fitness- und Gesundheitsniveaus effektiv zu sein, wobei es hierzu allerdings bisher nur wenige Daten gibt. Allerdings individualisierten Trainingsmethoden scheinen, als wirksam bei der Steigerung der körperlichen Leistungsfähigkeit und zur Verringerung des kardiovaskulären Risikos festgelegt werden. Aufgrund ständig wachsender Teilnehmerzahlen in den Herzsportgruppen, ergibt sich die Möglichkeit, körperliches Training bei Patienten mit geringer Fitness in einem bestehenden rehabilitativen Rahmen zu untersuchen.

Die vorliegende Studie vergleicht die Effekte der allgemeinen Herzsportgruppe (CMP, 2 Mal pro Woche) gegenüber einer Kombination aus einem individualisierten Training (ICE, 1 Mal pro Woche) und der allgemeinen Herzsportgruppe (1 Mal pro Woche), auf verschiedene Gesundheits- und Fitnessparameter.

70 Patienten (70±9 Jahre, 14% weiblich) mit Herzerkrankungen und niedriger körperlicher Leistungsfähigkeit (< 6 MET) wurden im gleichen Verhältnis (1:1) randomisiert einer der beiden Gruppen zugeordnet. Nach sechs monaten haben die Patienten noch sechs Monaten in einer Herzsportgruppe zweimal wochenlich teilgenommen, und sind nachher nochmals untersucht geworden. Der primäre Endpunkt war die Verbesserung der körperlichen Leistungsfähigkeit, gemessen am maximalen Widerstand pro Kilogramm Körpergewicht (Watt/kg) während einer Belastung auf dem Radergometer.

Das individualisierte Training bestand aus 30 Minuten moderater Ausdauerbelastung und einem 30-minütigen Krafttraining an fünf verschiedenen Geräten (jeweils zwei Sätze). Eine Einheit der Herzsportgruppe dauert 90 Minuten und beinhaltet Kräftigungs- und Koordinationsübungen über eine Dauer von 60 Minuten sowie ein 30-minütiges Entspannungs- und Dehnprogramm.

Nach sechs Monaten konnten keine signifikanten Gruppenunterschiede in der maximalen körperlichen Leistungsfähigkeit (ICE: +0.05±0.17 W/kg, CMP: +0.04±0.17 W/kg, P=0.83) oder der maximalen Sauerstoffaufnahme (ICE: -0.1±3.1 ml/kg/min, CMP: +0.6±3.2 ml/kg/min, P =

0.38) gefunden werden. Signifikante Gruppenunterschiede fanden sich hingegen bei der Ruheherzfrequenz (ICE: -7±11 Schläge/min, CMP: -0.3±8 Schläge/min, *P*=0.01), der submaximalen Belastungszeit (ICE: +116±112 s, CMP: +15±120 s, *P*<0.01) und der submaximalen Leistungsfähigkeit (ICE: +16±16 W, CMP: +2±17 W, *P*<0.01), sowie der Maximalkraft von Ober- (ICE: +7±8 kg, CMP: 0±7 kg, *P*<0.01) und Unterkörper (ICE: +14±14 kg, CMP: 0.2±12 kg, *P*<0.01). Verglichen mit der reinen Herzsportgruppe erhöhte das kombinierte Programm die Zeit anstrengender körperlicher Tätigkeit (ICE: Δ +12 MET-min/Tag, CMP: Δ –5 MET-min/Tag, p=0.02) und die Anzahl der Schritte pro Tag (ICE: +1586 Schritte/Tag, CMP: –838 Schritte/Tag, p<0.01). Zudem kam es zu einer Verbesserung der Fitnesskategorie im Vergleich zur reinen Herzsportgruppe (Median-Veränderung ICE: +0.4, CMP: –0.1, p=0.01).

Das kombinierte Trainingsprogramm führte zudem zu einer gesundheitsbezogenen Verbesserung der Lebensfreude (ICE: Δ +3.0, CMP: Δ –0.1, p<0.01), der emotionalen Gesundheit (ICE: Δ +0.2, CMP: Δ 0.0, p=0.05), der sozialen Gesundheit (ICE: Δ +0.3, CMP, Δ 0.1, p<0.01), sowie der positiven (ICE: Δ +2.4, CMP: Δ –0.1, p<0.01) und negativen Gefühle (ICE: Δ -0.7, CMP: Δ +1.0, p<0.05) gegenüber der reinen Herzsportgruppe.

Nach einem Jahr waren die Unterschiede, die sich in der 6-Monatsuntersuchung gezeigt haben, überwiegend auf die Ausgangswerte zurückgekehrt. Es zeigten sich keine Unterschiede hinsichtlich der Verbesserung der körperlichen Leistungsfähigkeit. Dennoch führte das kombinierte Training zu keinen “Unerwünschten Ereignissen” und war der Herzsportgruppe in Bezug auf die Hämodynamik in Ruhe, die submaximale Leistungsfähigkeit und die Muskelkraft überlegen. Das kombinierte Training führte ebenso zu einer signifikanten Erhöhung der körperlichen Freizeitaktivität und der gesundheitsbezogenen Lebensqualität.

List of abbreviations

1RM: One repetition maximum

BMI: Body mass index

CMP: Cardiac maintenance program

CAD: Coronary artery disease

DBP: Diastolic blood pressure

FFM: Fat free mass

HRQoL: Health-related quality of life

HR: Heart rate

HbA1c: Glycated hemoglobin

HDL: High-density lipoprotein

ICE: Individualized combined exercise

IPAQ: International physical activity questionnaire

IQR: Interquartile range

LTPA: Leisure time physical activity

LDL: Low density lipoprotein

MET: Metabolic equivalent task

PA: Physical activity

PAL: Physical activity level

SD: Standard deviation

SBP: Systolic blood pressure

$\dot{V}O_2peak$: Peak oxygen uptake

VT1: First ventilatory threshold

1. Theoretical basis

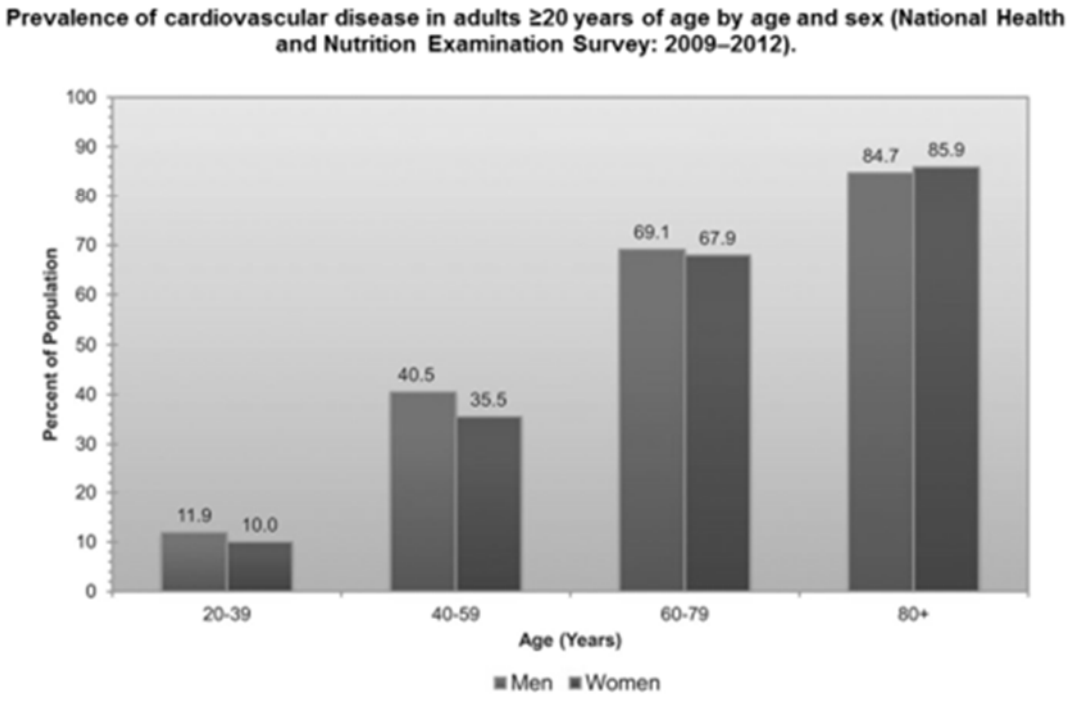
1.1. Introduction and aims of the current study

Diseases of the cardiovascular system are responsible for a greater number of hospitalizations and mortality than any other measured parameter worldwide. Among people over sixty years of age, 80% have some form of cardiovascular disease (Figure 1). These patients are less likely to meet physical activity recommendations than their younger and healthy counterparts. They have higher mortality and hospitalization, reduced physical activity levels, physical fitness and health related quality of life. Alongside pharmaceutical therapies, one of the most effective treatment options for this population, which is effective in improving all of these parameters, is regular physical exercise. Cardiovascular diseases include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart disease, deep vein thrombosis and pulmonary embolism. Cardiovascular diseases, with coronary artery disease accounting for the largest proportion, are the number one cause of death globally. Approximately 17 million people die of cardiovascular disease annually, representing over 30% of worldwide mortality. Of these, over eighty percent were due to coronary heart disease (42%) and stroke (38%) (Mendis, 2014). Patients with coronary artery disease represent the largest portion of patients who are hospitalized for cardiovascular disease and who are indicated for cardiac rehabilitation programs (Mathes, 2007). The risk factors for cardiovascular disease include several behavioral risk factors, including tobacco use, unhealthy diet, obesity, harmful alcohol use and physical activity. These behavioral risk factors lead to primary risk factors, including hypertension, hyperglycemia and diabetes, and hyperlipidemia. Although the prevention of these diseases through the performance of healthy behaviors is a primary goal of health care programs, underlying determinants of cardiovascular diseases, including globalization, urbanization and population aging, as well as

poverty, stress and hereditary factors, blunt the effects of healthy living and make the performance of healthy behaviors more difficult. This has led to the increasing importance of secondary prevention and rehabilitation for patients with risk factors and existing disease.

Figure 1: The prevalence of cardiovascular diseases by age categories.

In the age group most represented in cardiac rehabilitation maintenance programs (> 60 years), prevalence of cardiovascular disease is between about 70 and 85% of the population (adapted from (Mozaffarian et al., 2015))



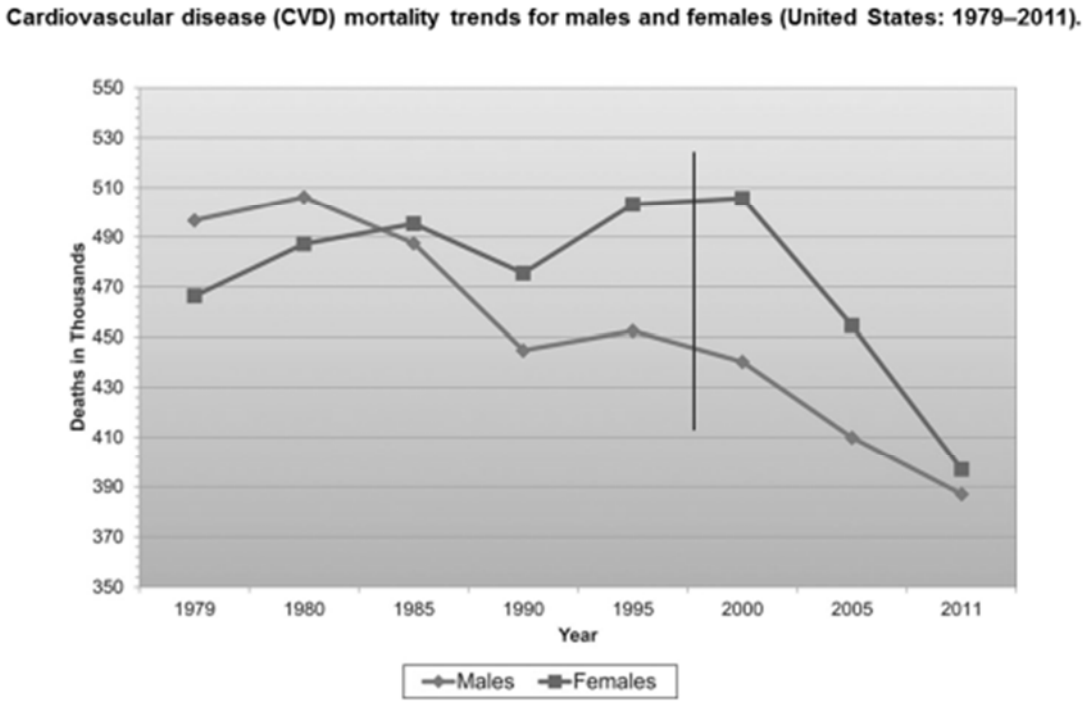
Cardiac maintenance programs have been established to offer patients with cardiovascular diseases the opportunity to perform physical exercise under professional and medical supervision in an environment that supports healthy behavior change. These programs have

been purported to be successful in sustaining the health and fitness status of patients, having graduated from earlier cardiac rehabilitation programs, but there are very little data examining their effects from clinical trials. The German cardiac maintenance program system of *Herzgruppen* ("heart groups") is the most established system, has a substantial certification program for its leaders and instructors, and has been successful in creating more groups and including more participants per capita than any other in Europe. Participants in the German system also receive financial support and stay in the system for several years, in comparison to months in most other programs. Although it has been successful in increasing enrollment, the German system is lacking in clinical investigations on its long-term effects on health and fitness.

Participants in cardiac maintenance programs, largely due to improved pharmaceutical therapies, are living longer with disease, making secondary prevention and physical activity important components of their lifestyles (Figure 2). However, the increase in older patients has altered the demographics of cardiac maintenance programs toward lower fitness, lower health related quality of life and more comorbidities. There have been comparatively few studies documenting the effects of exercise in this population, and exercise recommendations for patients with low exercise capacity have been conservative.

Figure 2: Cardiovascular mortality trends between 1979 and 2011.

Decreases in cardiovascular disease mortality has led to an increasing amount of people living longer with cardiovascular disease since approximately the year 2000 (Adapted from (Mozaffarian et al., 2015)).



Concerns about safety in this population, combined with a general lack of scientific data on this population have resulted in generally low volumes and intensities of exercise, and a focus on maintenance, rather than the improvement of long-term health and physical fitness. Patients in Germany generally are offered one to two sessions of 60-90 minutes of low intensity calisthenics-based exercise, which even with high adherence rates is well below the established guidelines for physical exercise.

Individualized combined exercise, i.e. exercise based on individual exercise capacity and combining elements of endurance and resistance methods, has been observed to benefit many

aspects of health and fitness more than endurance exercise alone. This has been attributed largely to meeting individualized exercise intensity targets through close monitoring and the contributions of endurance and resistance exercise. Especially the supplementation of resistance training to endurance exercise seems to have led to positive results on health and fitness. However, these methods of exercise have not yet been incorporated in the German cardiac maintenance program system, and are relatively contraindicated for patients with cardiovascular diseases and low exercise capacity. These contraindications are the result of a lack of scientific data in this population in a cardiac maintenance program setting. Therefore, the aim of study reported in this thesis is to test the hypothesis that one session per week of individualized combined exercise is superior to participation in cardiac maintenance program over a duration of six months in improving maximal exercise capacity in elderly patients with cardiovascular disease and reduced fitness. As secondary investigations, the effect of individualized combined exercise will be compared to cardiac maintenance program in submaximal exercise performance, and health related quality of life and leisure time physical activity levels over the same time period.

1.2. Definition of terms

1.2.1. Cardiac maintenance programs

A cardiac maintenance program is defined as phase III cardiac rehabilitation aftercare, is considered long-term secondary prevention, and succeeds phase I and II cardiac rehabilitation programming for patients who have been treated for cardiovascular diseases. Phase I cardiac rehabilitation is performed directly after the primary treatment for an acute or imminent event, and is short term, usually only until the patient in stabilized. Phase II cardiac rehabilitation is usually performed in the three of four weeks after hospital

discharge and includes some basic physical exercise and health education. Phase III cardiac rehabilitation is provided in Germany in the form of *Herzgruppen* ("heart groups") of 15-20 patients who meet regularly (usually once or twice a week) for 90 minute sessions, based largely on low intensity calisthenics exercise, but incorporating several fitness elements (e.g. flexibility and balance) and education about living with cardiovascular disease. These sessions are supervised by certified exercise specialists and physicians and the programs are accredited by a federal oversight organization.

1.2.2. Individualized combined exercise

The concept of individualized combined exercise incorporates the methods of cardiopulmonary exercise testing, strength testing to establish individualized exercise training intensities. Both endurance and resistance exercise methods are included, and exercise is monitored closely in small groups to increase adherence and optimize the effects of exercise training.

1.2.3. Maximal and submaximal exercise performance

Maximal exercise performance is defined as measured at the maximum level of exercise during cardiopulmonary exercise testing and one repetition maximal strength testing. The term performance is an umbrella term used to describe all of the measured parameters at their maximum levels, including endurance and strength. The term "maximal" is also used for most of the performance parameters, with the exception of oxygen uptake, for which the term, "peak" is applied. Maximum oxygen uptake is a term that explicitly describes the successful establishment of a plateau representing the physiological limit of capacity for oxygen uptake. The term "peak" is applied in this case as an alternative description of maximal oxygen uptake, reserved for individuals in which a physiological maximum of

oxygen uptake is not established (i.e. a plateau in oxygen consumption is not clearly present). The use of peak oxygen consumption is standard in research on patients with cardiac disease, as in the current study, and is calculated as the average of the highest 20-30 consecutive seconds of exercise, occurring during cardiopulmonary exercise testing at a point considered maximal exertion, before test termination.

Submaximal exercise performance can be investigated in several different ways, including step tests, functional tests and walking tests. In the current study, submaximal exercise performance is defined as physiological parameters measured at the point of the first ventilatory threshold. The first ventilatory threshold is calculated as the first positive inflection point of the carbon dioxide production – oxygen consumption curve and is related to the ability to perform most activities of daily living and therefore is a good estimate of fitness and has a strong relationship to health-related quality of life.

1.2.4. Reduced physical fitness

Exercise capacity is generally reduced in patients participating in cardiac maintenance programs. The patients recruited in the current study were selected for low exercise capacity, relative to other cardiac maintenance program participants. To represent higher risk category patients, low exercise capacity was defined as less than 1.4 watts per kilogram body weight, which is equivalent to less than six METs (Metabolic Equivalent Tasks). This group of patients is in a moderate to high risk category as defined by the American Heart Association and in this group resistance training is relatively contraindicated.

1.2.5. Health-related quality of life

Health related quality of life is a self-reported measure of how disease status influences an individual's mood, affect, understanding of role, distress and well-being. This measure is largely reserved for patients, and illustrates the specific effects that a disease has on quality of life. There are several questionnaires which evaluate the effects of different diseases on patients. These have different sensitivities and specificities according to how well a questionnaire addresses the disease-specific influence on aspects of quality of life. In the current study, three questionnaires are used; one designed for general use (SF-36), one specifically designed for coronary artery disease patients (GMS) and one for patients with cardiovascular disease (MacNew).

1.2.6. Leisure time physical activity

Leisure time physical activity is a quantitative measure of the amount of unstructured physical activity one performs. This type of physical activity is one component of total physical activity, and represents how physically active one is in their free time, and usually does not involve planned or work-related physical activity. It therefore represents physical activity one chooses to perform, rather than physical activity one must perform (e.g. due to occupation). It is distinguished from exercise and sport in that it is not structured and is more aligned as a part of activities of daily living.

1.3. Theoretical basis for exercise-based secondary prevention in cardiac disease

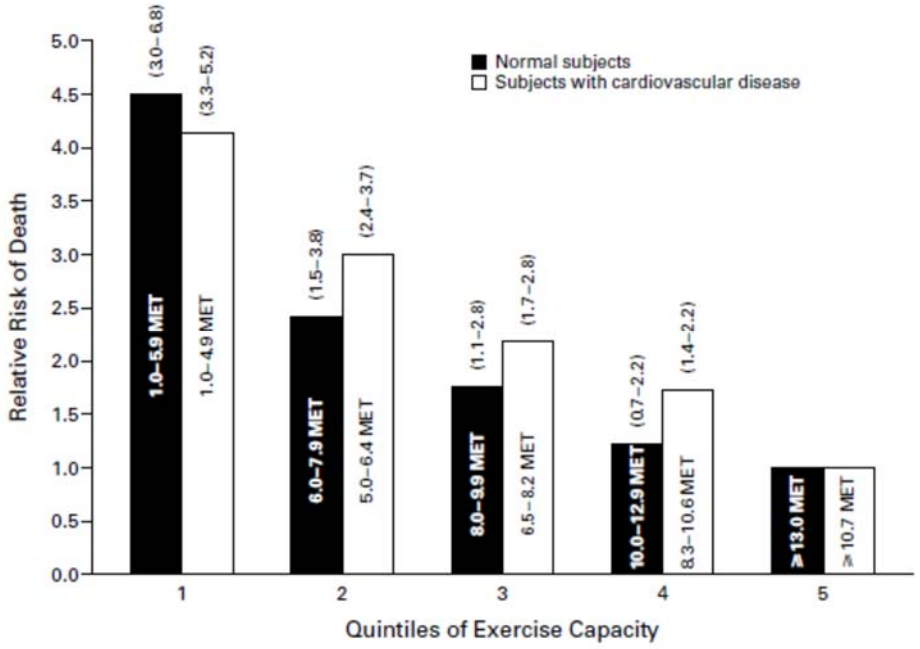
1.3.1. The relationship between physical activity and cardiovascular health

The relationship between regular physical activity and health and mortality, in the frame of cardiovascular disease, was scientifically observed in the 1950s. In a 1953 study (Morris, Heady, Raffle, Roberts, & Parks, 1953), Morris and colleagues observed the

positive effects of physical activity in the differences in cardiac disease rates between bus drivers and bus conductors. Bus drivers, who spend much of their working day seated, had rates of mortality due to coronary heart disease twice as high as conductors, who spent their working hours walking up and down stairs in the traditional double-decker buses in London (Morris et al., 1953). Since then, many scientific studies have been published on the positive effects of exercise on cardiovascular and cardiorespiratory health. Regular physical exercise improves aerobic fitness (e.g. mitochondrial density, peak oxygen uptake ($\dot{V}O_2peak$), disease-specific factors (e.g. endothelial function, cholesterol) and reduces number of hospitalizations and mortality in patients with cardiac disease when compared to non-exercising controls (Smith et al., 2011). The most significant reductions in mortality are observed when the least fit individuals increase maximal exercise performance to > 6 METs (Kokkinos et al., 2010). A landmark study on the effects of physical activity on cardiovascular health, Myers and colleagues (Myers et al., 2002) observed a strong inverse and independent association between physical activity, health and cardiovascular and overall mortality in over 3500 men with documented cardiovascular disease as well as over 2500 without (Figure 3). In this study, one MET, the oxygen uptake equivalent of 3.5 ml/kg/min, was related to a 12 percent improvement in survival (Myers et al., 2002). These are some of the most important factors illustrating the importance of being physically active in both healthy people and those with cardiovascular diseases.

Figure 3: All-cause mortality and fitness, reported as relative risk of death and peak exercise capacity in metabolic equivalent tasks (METs)

One MET is approximately equal to oxygen uptake of 3.5 ml/kg/min. The greatest reductions in mortality are observed between the first (lowest) and the second fitness quintiles, which are delineated at approximately 5-6 MET (Adapted from (Myers et al., 2002))



1.3.2. The development and rationale behind cardiac maintenance programs

Given the impact of regular exercise on the health of patients with cardiovascular diseases, exercise is a cornerstone of cardiac rehabilitation maintenance programs (Piepoli et al., 2010). Secondary prevention strategies for cardiovascular disease include tobacco abstinence and alcohol control, reduction of intake of high fat, sugar and salt, increasing physical activity and pharmaceutical treatment. Alongside improvements in surgical

technique and implantable technologies, especially pharmaceutical treatment with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors and statins have been effective in prolonging life and increasing quality of life among those living with cardiovascular diseases. This has further increased the demand for behavioral interventions targeted at improving the general health of patients with cardiovascular disease, including those with advanced disease.

Prior to the establishment of longer-term secondary prevention programs in the late 1960s, outpatient cardiac rehabilitation was established to increase the physiological and psychological benefits of exercise therapy after hospital discharge. In the early 1960s, supported by data on the negating effect of regular physical activity on prolonged bed rest after suffering a myocardial infarction, inpatient cardiac rehabilitation became standard practice. These programs were largely focused on an earlier return to work (Certo, 1985), but therefore were involved in the reduction of cardiovascular risk (secondary prevention) and the improvement of health. The success of these rehabilitation programs led to the establishment of long-term cardiac maintenance programs, in which patients take part in regular therapy sessions with a focus on progressive and supervised physical activity (Certo, 1985). Cardiac maintenance programs are usually community based and offer a combination of calisthenics, flexibility and coordination exercises led by group exercise specialists (Mandic, Body, et al., 2015; Mandic et al., 2013). These programs have been observed to be effective in sustaining health after graduation from earlier rehabilitation programs.

1.3.3. The establishment and rationale behind the German model of a national cardiac maintenance program; “Herzgruppen” in Germany

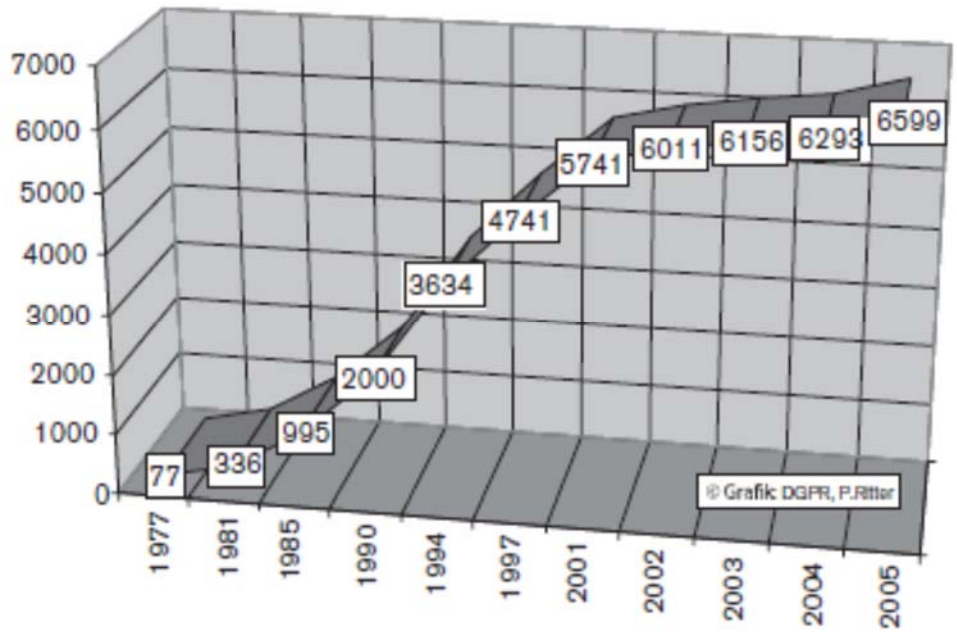
German patients with heart disease graduating from acute (Phase I) and Phase II institutionalized cardiac rehabilitation may continue their cardiac rehabilitation in either intensive aftercare or the national cardiac rehabilitation maintenance program, “Herzgruppen”. Both of these programs are based on data showing that independently, patients are largely unsuccessful in continuing healthy behaviors, including regular exercise, after graduating from Phase II cardiac rehabilitation (Bjarnason-Wehrens, Predel, Graf, & Rost, 1999; Voller et al., 1999). Phase III intensive aftercare is reserved for those patients who after 21 days of Phase II cardiac rehabilitation are not yet ready to engage in regular exercise or are not prepared to integrate healthy behaviors into their independent lives (Karoff, Held, & Bjarnason-Wehrens, 2007). The primary goal is primarily the enhancement of job-related and social reintegration, and therefore is generally designed for patients less than 60 years of age who were discharged from Phase II cardiac rehabilitation, but still considered unable to work. Programs are exercise based and last from eight weeks to three months. For all other patients not contraindicated cardiac maintenance programming is offered in the form of *Herzgruppen*. This program is the largest and most active secondary prevention program for patients with cardiac disease in Europe, consisting of over 6,000 groups and over 110,000 participants (Bjarnason-Wehrens et al., 2010; Figure 4). It also follows Phase II cardiac rehabilitation and is traditionally offered in weekly group- and center-based sessions including physical exercise, psychosocial and educative elements (Karoff et al., 2007). Whereas phase I and II are short term and are performed on largely an inpatient basis, the goal of *Herzgruppen* is to sustain the effects of phase I and II cardiac rehabilitation over the long term on an

outpatient basis (Karoff et al., 2007). The program is state-sanctioned and is officially considered phase III cardiac rehabilitation aftercare, its function being described as maintaining the effects of earlier rehabilitation programs for to benefit long-term cardiovascular health and reduce the risk of further adverse cardiac events (Karoff et al., 2007). Sessions include calisthenics, coordination and flexibility exercises, educational components targeting diet and nutrition, stress and relaxation, and methods for coping with cardiac disease and behavioral and lifestyle change. Sessions are offered for 90 minutes once or twice a week and are conducted in a gymnasium in groups of 15-20 participants instructed by competent exercise therapists and attended to by a physician as recommended by the German Federal Association for Rehabilitation (Bundesarbeitsgemeinschaft für Rehabiliation (BAR) e.V., 2011). Although the German system of cardiac maintenance programs is a positive example of a functional long-term exercise-based secondary prevention program, there are currently very little data on its effects on health. Alternative exercise modes have not been well investigated and many eligible patients do not take part in these programs (Bjarnason-Wehrens et al., 2010). Therefore, although it seems that participants in cardiac maintenance sustain post-cardiac rehabilitation health status, it is not well documented and there is reason to believe that it could be optimized to achieve more significant health and fitness benefits. For example, most groups perform approximately 90 minutes per week of rehabilitation, including about 20-40 minutes of light to moderate endurance exercise, for an estimated energy expenditure of 5-7 MET-hours/week, greatly below the recommendations for physical activity (at least 30 minutes of moderate physical activity on most days of the week (American College of Sports Medicine, 2014) and twice weekly moderate resistance training). Combined with evidence supporting the positive effects of exercise on

cardiovascular health from individualized and combined exercise trials applying specific volumes and intensities of endurance and resistance exercise, it is likely that these methods would also benefit participants in cardiac maintenance programs (Smith et al., 2011; R. S. Taylor et al., 2004; R.S. Taylor et al., 2014).

Figure 4: The development of German cardiac rehabilitation maintenance programs, from 1977-2005.

The German system of *Herzgruppen* with well over 6,000 secondary prevention groups is by far the largest cardiac aftercare program in Europe (adapted from (Karoff et al., 2007).



1.3.4. Leisure time physical activity levels and health- related quality of life in cardiac maintenance programs

Alongside improving risk status, increasing leisure time physical activity and health related quality of life are the primary goals of cardiac maintenance programs, especially in patients with low exercise capacity who are likely to benefit the greatest (Kokkinos et al., 2010).

1.3.4.1. Leisure time physical activity levels in patients with cardiac disease

Current physical activity recommendations for older adults include at least 30 minutes of physical activity on most days of the week (Chodzko-Zajko et al., 2009). Low levels of leisure time physical activity are associated with higher risk of cardiac disease and events and poorer prognosis in patients with cardiac disease (Mons, Hahmann, & Brenner, 2014). Patients with cardiac disease also are less likely to meet physical activity recommendations than healthy individuals (Conn, Hafdahl, Moore, Nielsen, & Brown, 2009). Patients in cardiac maintenance tend to have slightly higher levels than patients who do not participate, and have fitness and activity levels comparable to healthy but less active peers (Mandic, Stevens, et al., 2015).

1.3.4.2. Health related quality of life in patients with cardiac disease

Reduced health-related quality of life is also related to increased hospitalization and mortality in patients with heart disease (Hofer, Benzer, & Oldridge, 2014). Patients with cardiac disease have lower health-related quality of life, with twice the prevalence of depression compared to the general population (Celano & Huffman, 2011). Exercise and increased physical activity have been shown to improve health-related quality of

life, making it a primary goal of exercise-based cardiac rehabilitation (Mitchell & Barlow, 2011).

1.3.5. Resistance exercise in cardiovascular disease

Especially the inclusion of standardized resistance training has been largely neglected in cardiac maintenance. Resistance training seems to have independent effects on exercise performance, body composition and strength in patients with cardiac disease, (Pollock et al., 2000; Williams et al., 2007). Although low exercise capacity is a relative contraindication to the performance of resistance training, the safety of resistance training in this population has not been well investigated (Bjarnason-Wehrens et al., 2004). Resistance exercise has been gaining support as a viable and beneficial exercise mode in the elderly and patients with low fitness, who also may benefit from resistance training even more than their moderate to high fitness counterparts (Williams et al., 2007). RT has been shown to be as safe as moderate intensity endurance training in low risk populations, and to improve body composition and strength in patients with cardiac disease (Marzolini, Oh, & Brooks, 2012; Marzolini et al., 2014; Williams et al., 2007). Furthermore, twice-weekly resistance training is sufficient to produce significant gains in muscular strength (Braith et al., 1989). A recent meta-analysis analyzed 12 randomized controlled trials including over 500 patients on the effects of combined exercise compared to endurance exercise alone on peak exercise performance, strength, body composition, quality of life and safety (Marzolini et al., 2012). Hypertrophy, the major goal of resistance training, results directly in increased strength and changes in body composition, especially in increases in fat free mass. Improved physical strength also has a primary role in the

reduction of risk of musculoskeletal injury, osteoporosis and sarcopenia. Furthermore, combined exercise training leads to improved insulin action (Braith & Stewart, 2006).

1.3.6. Endurance and resistance exercise in elderly cardiovascular disease patients with reduced physical fitness

A group of patients who represent a growing number in cardiac maintenance programs are elderly patients with low exercise capacity. In these patients there is especially very little data on the effects of resistance training. These patients however, would potentially benefit greatly from increased strength, bone density, insulin sensitivity and quality of life, which have all been observed to be independently related to participation in resistance training (Pollock et al., 2000; Williams et al., 2007). Elderly patients who perform regular exercise including resistance training tend to fall less, and of those who do fall, the impact of falling on long-term health is greatly reduced compared to age matched non-exercisers (Cameron et al., 2012; Gillespie et al., 2012; Granacher, Muehlbauer, Zahner, Gollhofer, & Kressig, 2011; Reeve & Loveridge, 2014). Apart from the effects related to skeletal muscle hypertrophy, it has been observed that combining resistance exercise to endurance exercise has a significant impact on lowering blood pressure, increasing peak work capacity, and there is evidence that it may improve $\dot{V}O_2$peak in patients with cardiac disease (Figure 6) (Marzolini et al., 2012). The evidence supports the supplementation of endurance training with resistance training as standard practice in cardiac rehabilitation programs (Marzolini et al., 2012). Complementary resistance training has been gaining support in the clinical community, but many still consider the potential risks of resistance training to outweigh the benefits. These concerns however, are largely cautionary based on the very few data on resistance training in patients with cardiac disease and moderate to

high risk, who make up a large proportion of cardiac rehabilitation participants (Bjarnason-Wehrens et al., 2004). This population has been largely left out of trials on resistance training (Gielen, Laughlin, O'Conner, & Duncker, 2015; Williams et al., 2007).

Figure 5: Maximal physical strength and exercise dose in patients with cardiovascular disease

Changes in relative maximal muscular strength (kilogram per kilogram body weight presented as percent change) after 10 and 18 weeks of either twice-weekly (2-days per week; 2DPW) or thrice-weekly (3-days per week; 3DPW) resistance exercise. Adapted from Braith et al., 1989.

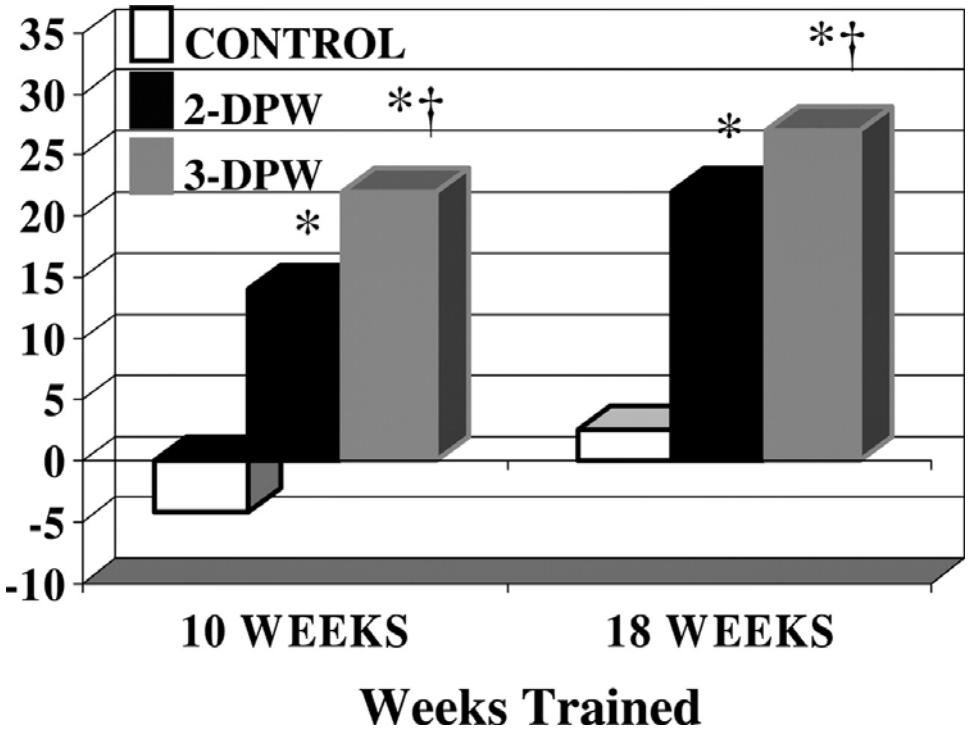
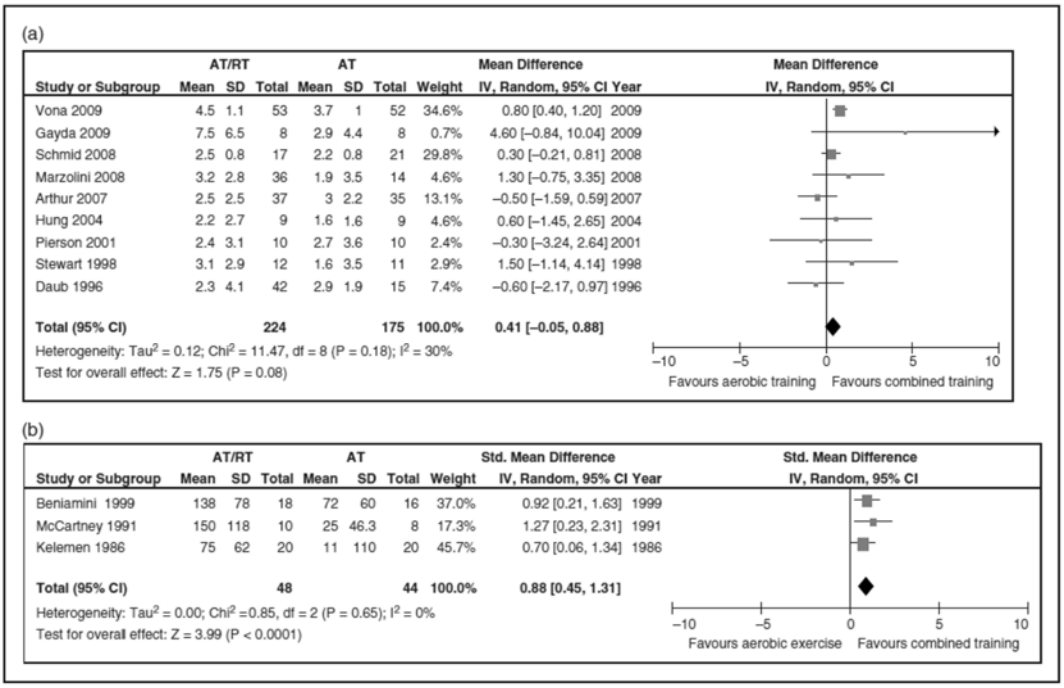


Figure 6: Endurance versus combined exercise in patients with cardiovascular disease

The pooled results of 12 trials (500 patients) comparing endurance and combined exercise in (a) peak oxygen uptake ($\dot{V}O_2$peak) and (b) peak exercise capacity (either treadmill time or Watts on a cycle ergometer). Adapted from Marzolini et al., 2012.



As people are living longer with cardiac disease, but continue to live sedentary lifestyles, elderly patients with low fitness represent a large and growing proportion of cardiac maintenance participants (Ades et al., 2006). However, this population is likely to benefit the most from increasing physical activity (Kokkinos et al., 2010). Nonetheless, this population is largely underrepresented in exercise trials in cardiac maintenance (Bjarnason-Wehrens et al., 2004).

1.4. Summary

As illustrated above, studies have established the positive role of endurance and resistance exercise in the promotion of physical and psychological health and fitness. It is well accepted that the performance of regular physical activity should remain a central aspect in the secondary prevention of cardiovascular disease, and that physical activity should be promoted in structured settings such as cardiac maintenance programs for patients with cardiovascular disease. The historical significance of cardiac maintenance programs has been largely in the sustaining levels of cardiovascular health achieved through the participation in primary and secondary cardiac rehabilitation. However, since the establishment of long term cardiac rehabilitation programming in the 1960s, a lot has changed.

Knowledge about exercise and physical activity in cardiovascular disease has developed substantially, and we now know that many different kinds of exercise may be beneficial to patients with an increasing list of cardiovascular ailments. The safe and effective implementation of resistance exercise over the last ten years is exemplary in this regard. Patients with cardiovascular diseases from coronary artery disease to heart failure and even patients with implanted ventricular assist devices awaiting heart transplantation are even performing high-intensity exercise in controlled scientific settings (Christle et al., 2015; Conraads et al., 2015; Kerrigan et al., 2014; Stoylen et al., 2012). These more recent studies have begun to alter paradigms about exercise and cardiovascular disease, so that more novel methods are being applied to higher risk groups.

The demographic shift has also dramatically influenced the types of patients who are performing exercise and taking part in cardiac maintenance programs. The current population is older, has higher rates of comorbidities and lower average fitness than other populations in the past. This is result of several factors, including effective pharmaceuticals and a higher

standard of living, but has introduced a new challenge, i.e. what is the influence of physical exercise in these patients in a more advanced cardiovascular disease status. The increasing number of studies on exercise in patients with more advanced cardiovascular disease is symbolic of efforts in the scientific community to address these issues.

In Germany, the cardiac maintenance program, "*Herzgruppen"*, is the largest and most established in Europe, and has the most stringent controls enforced by the federal government. However, as membership has grown greatly, the exercise-based methods applied to the secondary prevention of cardiovascular disease have been largely left unchanged. Although the groups do promote a holistic program of exercises, including flexibility, coordination and relaxation, among others, activities are low or moderate intensity and resistance exercises are not included. Furthermore, there is a basic lack of data about the effects of this particular program, with one case-control study being published to date. The combination of good policy and structure with a lack of ongoing scientific examination, makes the German system one of very great potential, in which studies on exercise and cardiovascular disease in a cardiac maintenance program setting may result in more profound changes at the level of practitioners. Therefore, the current investigation compares six months of individual and combined exercise with six months of a German cardiac maintenance program on changes in maximal exercise performance in patients with low exercise capacity. Secondarily we investigated risk status, submaximal exercise performance, physical strength, leisure time physical activity and health-related quality of life after six months and after a follow-up of a further six months. We hypothesized that weekly individualized combined exercise would be feasible and safe, and significantly improve exercise performance, risk

status, physical strength, leisure time physical activity and health-related quality of life compared to cardiac maintenance.

2. Empirical study design

2.1. Scientific inquisitions and hypotheses

As detailed in the theoretical section above, there is a lot of potential for scientific investigation within the German cardiac maintenance programs. The program is very well organized and regulated, including supervision from medical personnel and certifications for both the groups themselves and group exercise instructors. However, there is a lack of data supporting some of the exercise methodologies used in the program. This is contrary to the current literature on exercise in cardiovascular rehabilitation and therefore warrants investigation. The primary interests in the current study are the effects of moderate intensity combined endurance- resistance exercise on health compared to a typical cardiac maintenance program on health and fitness, and the following hypotheses are aimed at investigating these differences.

2.2. Study structure

The study has two distinct phases with different objectives in assessing the effects of individualized combined exercise compared to the cardiac maintenance program on health and fitness (Figure 7).

2.2.1. Study phase I

In the first phase of the study, the interventional phase, the immediate effects of individualized combined exercise are compared to cardiac maintenance on the primary endpoint of maximal exercise workload and the secondary endpoints of other maximal and

peak exercise performance, submaximal exercise performance, health related quality of life and physical activity levels. As well as these endpoints, data is collected on the adherence to exercise and safety, including the incidence of adverse events and serious adverse events. Therefore, the primary objective is to compare the direct acute effects of these exercise training methods on the health and fitness of elderly patients with cardiovascular disease and reduced exercise capacity.

2.2.2. Study phase II

In the second phase of the study, the follow-up phase, the long-term effects of participation in the interventional phase are examined. Secondary endpoints of maximal and peak exercise performance, submaximal exercise performance, health related quality of life and physical activity levels are investigated at 12 months, six months after completing the intervention phase. The objectives in this phase are to illustrate any subsequent effect of the interventional phase of the study on the health and fitness of the participants. The inclusion of a follow-up phase increases the strength of the primary interpretations of the data, i.e. any effects argued to be due to the experimental exercise would be supported in the case that after removal of the treatment, these effects return to baseline levels. On the other hand, if any effects would persist, the long-term effects of the intervention may be speculated upon.

3. Methods

The following section describes the registration of the study and its participants (3.1), description of the participants (3.2), randomization and allocation procedures (3.3), interventional procedures (3.4), methods for measurement of the primary and secondary endpoints (3.5) and statistical analyses of the data (3.6).

3.1. Registration of the study and its participants

The DOPPELHERZ trial (The influence of individualized resistance-endurance exercise training on maximal exercise performance in outpatient cardiac rehabilitation) is a randomized controlled trial registered at ClinicalTrials.gov (NCT01921036). The trial was performed between 2011 and 2014 at the Department of Prevention, Rehabilitation and Sports Medicine, Klinikum rechts der Isar, in Munich, Germany. It was conducted according to the principles established in the Declaration of Helsinki (see Supplement file N). The study protocol was approved by the University Hospital Research Ethics Committee (approval number 2931/10, see Supplement file O), and all patients gave written informed consent before participation (Supplement file P).

3.2. Description of the patient collective

Patients enrolled in a local state-sanctioned cardiac maintenance program with low exercise capacity (< 6 MET) were selected for participation. These patients are considered at moderate to high risk for cardiac complications during exercise (American Heart Association risk class "C"), and are not well represented in the literature (Smith et al., 2011). Other inclusion criteria were: Documented stable coronary artery disease for more than six months under stable pharmaceutical therapy; ability and willingness to understand and provide informed consent. Exclusion criteria were: decompensated or highly symptomatic heart failure; acute illness or injury; cardiac hospitalizations within six weeks of inclusion; drug abuse; unstable blood pressure or arrhythmias; high grade valve stenosis; instable diabetes mellitus; inability to understand either the study protocols or instructions from staff.

3.3. Randomization and Allocation

After the inclusion and exclusion criteria were verified by a senior physician, a technician allocated 70 patients according to a computer-generated randomly permuted blocks allocation program code to six months either individualized combined exercise or a cardiac rehabilitation maintenance program (Supplemental file B); both groups were followed up for a further six months for a total duration of one year from randomization to trial completion. Investigations were repeated at baseline after six months and one year from randomization, and investigators administering examinations concerning trial endpoints were blinded to treatment allocation. In both groups, adherence was calculated as the ratio of number of sessions participated in compared to possible sessions, and presented as a percent.

3.4. Interventional procedures

3.4.1. Individualized combined exercise

Patients in the individualized combined exercise group participated in one individualized combined exercise session per week for six months, and were instructed to continue participating once a week in the cardiac maintenance program. All individualized exercise sessions were monitored by certified group exercise instructors and a physician was present for all exercise sessions. Individualized combined exercise included 10 minutes warm-up and 30 minutes of endurance exercise at 50-70% heart rate reserve and Borg's rating of perceived exertion 11-13 (Borg, 1982), and five resistance exercises (chest press, leg press, lat pull-downs, shoulder press and seated cable row) on individually preprogrammed electronic exercise equipment (MIHA BodyTec, GmbH, Gersthofen, Germany). Resistance exercises were performed for the pectoralis, upper leg (gluteal, hamstrings and quadriceps), latissimus dorsi and biceps, deltoids and triceps and rhomboids and trapezius muscles. Exercises were performed following national guidelines

for patients with cardiac disease (Bjarnason-Wehrens et al., 2004). Endurance exercise intensities were monitored with heart rate monitors worn by patients during all exercise sessions. Resistance training prescriptions were based on results of one-repetition maximum tests following the guidelines of the American College of Sports Medicine (described in detail below) (American College of Sports Medicine, 2014). For the first three months, patients performed two sets of 12-25 repetitions at 30-50% maximal strength; at three months, patients were retested and thereafter performed two sets of 8-15 repetitions at 40-60% of maximal strength. The weekly exercise sessions were located at the university sports medicine rehabilitation center at a ratio of two patients to one instructor. Borg's rating of perceived exertion was reported by patients every 10 minutes during endurance exercise and for every set of resistance exercise on a 6-20 scale (Borg, 1982).

3.4.2. Usual Care - Cardiac maintenance program

Patients in the cardiac maintenance program were instructed to participate in six months of cardiac maintenance sessions. The local cardiac maintenance program offers twice-weekly center-based 90-minute exercise sessions that are largely focused on regular moderate exercise, but also reinforce healthy behavior change strategies and offer informational and emotional support. Cardiac maintenance sessions included 10 minutes of warm-up activities, 30 minutes of endurance exercise activities targeting coordination, 15 minutes of moderate intensity walking/jogging, 20 minutes of non-endurance activities focused on flexibility and balance and 15 minutes of relaxation activities. Sessions were conducted in a gymnasium in groups of 15-20 participants per instructor.

3.4.3. Follow-up phase procedures

After six months of participation in the trial, patients entered a follow-up phase, for which the patients received a recommendation of regular moderate intensity exercise, but were not contacted by study investigators until the six-month follow-up period was complete. During this time, patients could participate in any form of exercise not medically contraindicated, including participating in state sanctioned cardiac rehabilitation maintenance programs.

3.5. Outcome assessments

3.5.1. Primary outcome

The primary outcome was change in maximal exercise workload after six months. Maximal workload was defined as the highest power output measured during cardiopulmonary exercise testing (see below) in watts per kilogram body weight.

3.5.2. Secondary outcomes

3.5.2.1. Cardiorespiratory fitness

Cardiorespiratory fitness was assessed by three-minute stepwise cardiopulmonary exercise testing on cycle ergometers (Lode Excalibur Sport, Groningen, The Netherlands), starting with 25W and increasing 25W every step. Participants exercised to volitional exhaustion under the supervision of a physician and trained study nurses. Respiratory gases were recorded breath-by-breath and electrocardiogram data were recorded continuously (ZAN 600 USB CPX, Oberthulba, Germany). At rest and the end of each three-minute stage ratings of perceived exertion were recorded manually using the Borg Ratings of Perceived Exertion Scale (Borg Perception, Rimbo, Sweden). Peak respiratory exchange ratio ($\dot{V}CO2/\dot{V}O2$) > 1.05, peak perceived exertion > 16 and inability to continue were considered primary exhaustion criteria.

Peak oxygen uptake ($\dot{V}O_2$peak) and maximal respiratory exchange ratio were determined by two investigators independently as the highest consecutive 30 seconds of $\dot{V}O_2$ concentrations reported in the last phase before test termination (Mezzani et al., 2009). Submaximal exercise performance was measured at the first ventilatory threshold, which was calculated using the V-Slope method (Beaver, Wasserman, & Whipp, 1986) and verified visually by two independent investigators.

3.5.2.2. Anthropometry

Anthropometric measurements were conducted in the morning and subjects were in an overnight-fasted state. Height was assessed using a standard stadiometer. Weight was measured using a calibrated scale. Body Mass Index was calculated as weight in kilograms per square meter of body height (kg/m^2). Body fat was assessed using the seven-site skin-fold method (Pollack, Schmidt, & Jackson, 1980). Resting heart rate and blood pressure were measured after five minutes resting in a supine position, heart rate over two minutes with a standard 12-lead electrocardiogram and blood pressure manually on both arms according to current guidelines (Parati et al., 2014).

3.5.2.3. Physical strength

Maximal physical strength was assessed using one-repetition maximal testing (1RM) on upper (chest press) and lower (leg extension) body pin-loaded strength training machines (Schnell GmbH, Peutenhausen, Germany) not used during exercise sessions (American College of Sports Medicine, 2014). Patients started with 30% (upper) or 50% (lower) of their body weight. The weight was altered a maximum of 5 kg (upper) or 10 kg (lower) per trial and at least one minute was allowed between each trial. The

highest amount of weight moved successfully within 10 degrees of the full range of motion was defined as maximal.

3.5.2.4. Blood chemistry

Blood samples were drawn from an antecubital vein with patients in an overnight fasted state, but on normal medication schedules. Blood samples were centrifuged in sodium heparin or EDTA tubes, and plasma was aliquoted and analyzed within one hour for concentrations of HbA1C, blood glucose, triglycerides, total cholesterol, high density lipoproteins and low density lipoproteins.

3.5.2.5. Leisure time physical activity

Leisure time physical activity was determined using the International Physical Activity Questionnaire (Hallal & Victora, 2004) and tri-axial accelerometry (Aipermon 440, Munich, Germany). Accelerometers were also used to assess daily step counts. The international physical activity questionnaire was administered verbally by trained study personnel at baseline and six months. The activity data were calculated for MET-minutes per day and activity levels were categorized as low (< 600 MET-minutes/week), moderate (600- 3000 MET-minutes/week) or high (> 3000 MET-minutes/week) and presented as medians and interquartile ranges as suggested by guidelines published be the distributors of the international physical activity questionnaire. The accelerometers were worn on the hip for 10 days, and the first two to three days were excluded to control for the potential effects of wearing the accelerometer on physical activity levels. An average physical activity level score was then calculated for the last complete seven days. The physical activity level score was calculated as the relationship between basal energy expenditure and physical energy

expenditure, both reported in kilocalories. Basal energy expenditure was calculated using the Harris- Benedict equation as illustrated below (Harris & Benedict, 1918). All accelerometry data are summarized and presented as mean and standard deviations as suggested by the manufacturer.

Equation 1: The Harris-Benedict Equation for estimating basal metabolic rate

BEE♂ (in kals) = 66 + [13.7 x body weight (kg)] + [5 x height (cm)] – [6.8 x age (y)]

BEE♀ (in kcals) = 655 + [9.6 x body weight (kg)] + [1.8 x height (cm)] – [4.7 x age (y)]

BEE = Basal Energy Expenditure

Equation 2: The calculation for physical activity score

(PEE/24 hours) / BEE

PEE = Physical Energy Expenditure

BEE = Basal Energy Expenditure

Table 1: Physical activity level scores and recommendations, adapted from (Food and Agriculture Organization of the United Nations, 2004)

Activity level descriptor	PAL
Extremely inactive	< 1.4
Sedentary	1.40-1.69
Moderately active	1.70-1.99
Vigorously active	2.00-2.4
Extremely active	>2.40

3.5.2.6. Health-related quality of life

Health- related quality of life was measured by the Short Form 36 (SF-36) (Ware & Sherbourne, 1992), the Global Mood Scale (GMS) (Denollet, 1993) and the MacNew Heart Disease Quality of Life Instrument (MacNew) (Höfer, Lim, Guyatt, & Oldridge, 2004). All of these questionnaires have been validated and used widely in their original language and in German. The SF-36 is designed for use in clinical as well as general populations and assesses limitations in physical, social and usual role activities due to physical and/ or emotional problems, physical pain, psychological distress and well- being, vitality and general health perceptions. The GMS measures emotional distress through negative affect (fatigue and malaise) and positive affect (energy and sociability), and is designed for use with coronary heart disease patients. The MacNew is specifically for patients with heart disease and assesses Health-related quality of life based on the World Health Organization's definition of health, including physical, mental and social dimensions of well- being. Patients filled out the forms in the

presence of a study nurse, who assured that questions were understood and that questionnaires were filled out completely.

3.5.2.7. Adherence

Adherence data (i.e. attendance) were collected before every training session in both groups. Patients signed an attendance sheet in the presence of exercise instructors for every exercise session in both individualized combined exercise and cardiac maintenance, and these signatures were counted and recorded monthly throughout the study. Adherence was defined as number of exercise sessions participated in compared to the amount of exercise sessions available. In the experimental group, adherence was calculated for total number of sessions as well as separately for individualized combined exercise sessions and cardiac maintenance sessions. Data were presented as percentages.

3.5.2.8. Safety

Safety was defined as the presence of adverse and serious adverse events during the course of the study, that were determined to be related to participation in the study, regardless of in which arm the patients were in. An adverse event was considered any clinically relevant event that had a negative effect on a participant's ability to participate further in the study. A serious adverse event was defined as a clinically relevant event that led to hospitalization or a worsening of disease status, or led to an inability to continue in the study. Safety was reported as number of events and was interpreted as purely observational, due to the lack of power to detect any effects on safety in the current trial.

3.6. Statistical analyses

3.6.1. Power calculation

The study was powered to detect a 0.5 W/kg mean difference in change of maximal power output between the groups assuming a standard deviation of 0.5 within both groups. To achieve a power of 95% for a two-sample t test at a 5% significance level under these assumptions a total number of 60 participants was needed. Due to the relatively long trial duration and the age and disease status of the participants, a drop-out rate of 15% was assumed, resulting in a target of 70 participants (Supplemental file A).

3.6.2. Analysis of the primary endpoint

Analysis of the primary endpoint, change in maximal workload at six months, was conducted following the intention-to-treat principle, and missing values for the primary outcome were handled conservatively in which the baseline value was carried forward as described in the guidelines from the Committee for Medical Products for Human Use of the European Medicines Agency (European Medicals Agency Committee for Medicinal Products for Human Use, 2009), the on-treatment population was used to perform sensitivity analysis. A two-sample t test for independent samples was conducted to calculate differences between the groups, using a significance level of $\alpha = 0.05$.

3.6.3. Analyses of the secondary endpoints

For all outcomes, normal distribution of data was evaluated using the Shapiro-Wilk test and visual inspection of the data distributions. Normally distributed data are summarized by means and standard deviations. All secondary endpoints, including all endpoints measured one year after randomization, were analyzed in the on-treatment set. For data generated by the IPAQ questionnaire, all data was treated as nonparametric according to

guidelines. Adherence to the intervention was measured during the active intervention as number of sessions completed divided by the number of sessions available and reported as a percent. Patients in the individualized combined exercise group produced adherence data for participation in the experimental exercise sessions and cardiac maintenance program sessions separately. Adherence was not assessed during follow-up.

4. Results

The following section reports the outcomes of the study after [per patient] six months and one year. The data is reported as means and standard deviations, unless otherwise noted. It begins with the descriptive analyses of the sample, including the flow of patients through the trial, then reports the results of the primary outcome, and concludes with the results of secondary outcomes. The outcome data is presented in the text for each endpoint separately, including results for six and twelve months. Tables are presented in each section with baseline, six months and twelve month results for both groups, and significance is indicated. Exact significance for all endpoints is reported in the supplemental tables.

4.1. Baseline characteristics, safety and drop-outs

Baseline characteristics including detailed summaries of histories are presented in Table 2. Medication and medication schedules were maintained throughout the trial for all patients. No serious adverse events occurred during the trial. There were eight patients who did not perform exercise testing at six months (three in the individualized combined exercise group and five in the cardiac maintenance group). In all of these cases, the baseline values were imputed for the intention-to-treat analysis. One patient in the individualized combined exercise group developed muscular discomfort that resulted in a discontinuation of resistance training. Three patients in the individualized combined exercise group elected not to perform

the shoulder press (deltoid) exercise due to previous injuries. During follow-up, five patients dropped out of the study (two in individualized combined exercise and three in cardiac maintenance; see Figure 7). A relevant baseline difference in the frequency of statin use was observed between both treatment groups. Therefore, a linear regression model using maximal exercise performance as the dependent variable, and treatment group and statin use as independent variables was fit to the data. Posthoc sensitivity analysis revealed no relevant influence of statin therapy on the primary endpoint (controlling for statin therapy reduced the estimated difference between group means from 0.028 to 0.026; see Supplemental file F).

4.2. Adherence

Of the on-treatment population through six months, individualized combined exercise group patients attended 82 ± 14% of possible ICE sessions and 62 ± 35% of the possible cardiac maintenance sessions and the control group participated in 46 ± 23% of possible cardiac maintenance sessions. That is, individualized combined exercise participants performed an average of 21 ± 4 ICE sessions and 16 ± 9 cardiac maintenance sessions and the cardiac maintenance group participated on average in 23 ± 12 cardiac maintenance sessions. During follow-up data on adherence was not collected.

Figure 7: Flow of participants through the DOPPELHERZ-Trial. The experimental part of the trial lasted six months, followed by a follow-up of six months.

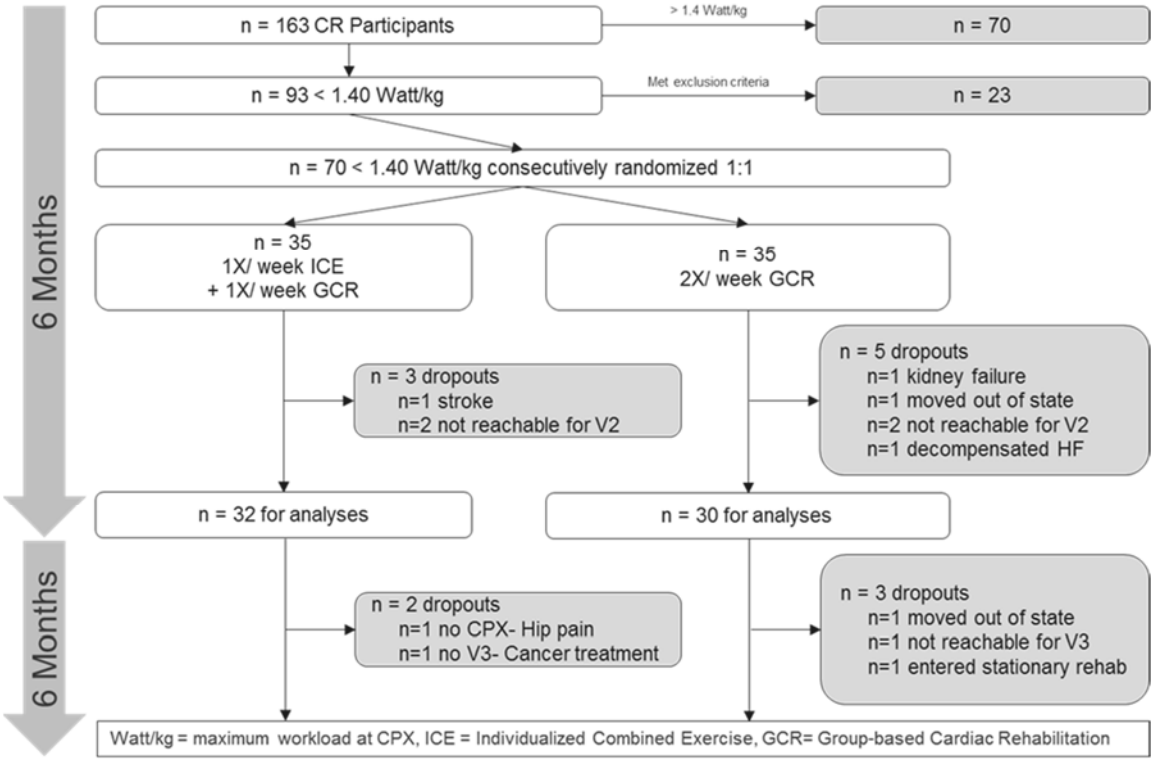


Table 2: Patient characteristics

Variable	ICE	CMP
Age (y)	69 ± 9	71 ± 8
Female	13 (37)	14 (40)
Medical History		
CAD	28 (80)	23 (66)
Multiple vessel disease	19 (54)	16 (46)
MI	15 (43)	9 (26)
PCI	16 (46)	19 (54)
CABG	8 (23)	6 (17)
Hypertension	28 (80)	30 (86)
T2D	12 (34)	13 (37)
AF	13 (37)	14 (40)
ICD	7 (20)	8 (23)
Medication		
Beta-blocker	33 (94)	29 (83)
Statin	31 (89)[a]	20 (57)
ACE / ARB	28 (80)	27 (77)
Diuretic	19 (54)	15 (43)
Anti-platelet	31 (89)	30 (86)

Values are mean ± SD for age and number (%) for all other. ICE = individualized combined exercise, CMP = cardiac maintenance program, CAD = Coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABI = coronary artery bypass graft, T2D = Diabetes mellitus type 2, AF = Atrial fibrillation, ICD = Implantable cardioverter defibrillator. ACE/ ARB = Angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

[a] $p < 0.05$ vs. CMP (significant between group differences are indicated in bold)

4.3. Exercise Performance

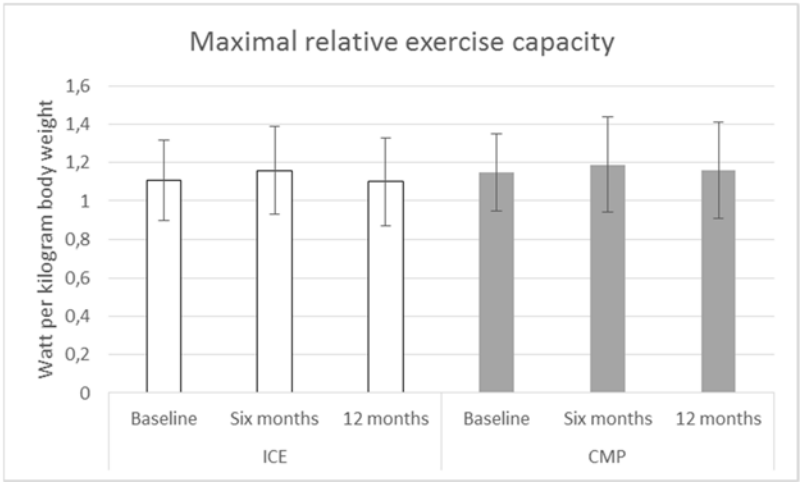
4.3.1. Maximal endurance exercise performance

At baseline, maximal workload was 82% of predicted values in the individualized combined exercise group and 84% in the cardiac maintenance group. At six months, increases in maximal relative and absolute exercise workload did not differ significantly between groups (relative: ICE: 0.05 ± 0.17 W/kg, CMP: 0.04 ± 0.17 W/kg, P_{ITT} = 0.87; absolute: ICE: 4 ± 8 W, CMP: 3 ± 7 W, P_{ITT} = 0.87; Figure 8, Table 3). Sensitivity analysis comparing the on-treatment groups set did not reveal a relevant difference to the intention-to-treat analysis (P_{OT} = 0.83, resulting in a difference in significance of 0.04 between intention-to-treat and on-treatment analyses; see Supplementary data file E). There were also no significant differences in maximal workload within either the individual combined exercise or cardiac maintenance groups ($p > 0.05$). Time to peak oxygen consumption, maximal heart rate and peak oxygen consumption did not significantly change within or between the groups at six months (Table 3 and Supplementary table S1). After a further six months of follow-up, there were no significant change in maximal endurance performance compared to post-intervention or baseline (Supplementary table S1).

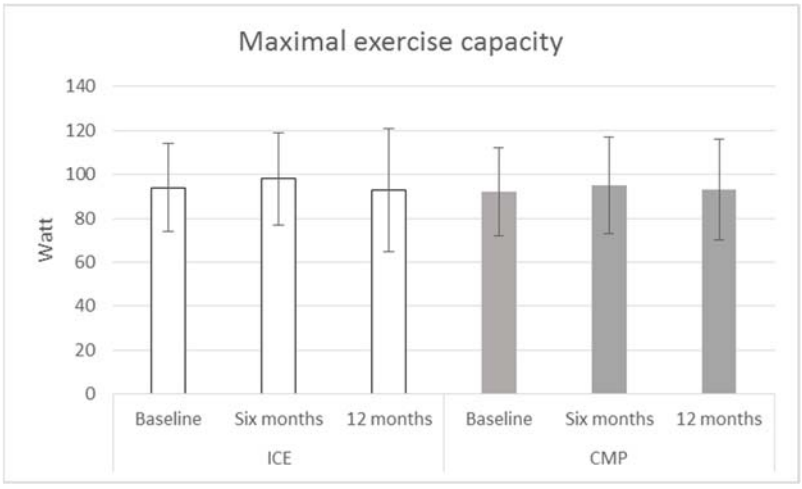
Figure 8: Changes in maximal exercise capacity

(a) Depicts average maximal workload as relative to body weight, the primary endpoint, and (b) depicts the absolute changes in workload in watt. There were no significant within or between group changes between baseline, six months or 12 months in either relative or absolute workload.

(a)



(b)



4.3.2. Submaximal endurance exercise performance

Relative to the cardiac maintenance group, the individualized combined exercise group improved submaximal exercise performance. Average time to the first ventilatory threshold increased 116 ± 112 s in the individualized combined exercise group compared to 15 ± 120 s in the cardiac maintenance group ($P < 0.01$). Submaximal workload significantly increased 16 ± 16 W compared to 2 ± 17 W in the cardiac maintenance group ($P < 0.01$), and relative submaximal workload significantly increased 0.2 ± 1.4 W/kg compared to 0.04 ± 0.8 W/kg in the cardiac maintenance group ($P = 0.01$). At baseline in individualized combined exercise and cardiac maintenance, the first ventilatory threshold occurred at 49 ± 15% and 47 ± 17% of peak exercise duration, respectively (n.s.). After six months, first ventilatory threshold occurred at 60 ± 15% of peak exercise in ICE and 48 ±17% in cardiac maintenance ($P = 0.03$; Table 3, Supplemental table S1). After a further six months of follow-up, all submaximal exercise performance parameters returned to baseline levels (see Supplemental table S1).

Table 3: Changes in cardiopulmonary exercise testing outcome data at baseline and six months.

	ICE (N=32)		CMP (N=30)			
Variable	Baseline	Six months	Baseline	Six months		
Maximal	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean diff (95%CI)	*P*-value*
Workload (W)	94 (20)	98 (21)	92 (20)	95 (22)	0.56 (-6.03, 7.16)	0.87
Workload (W/kg)**	1.11 (0.21)	1.16 (0.25)	1.15 (0.20)	1.19 (0.25)	0.01 (-0.08, 0.10)	0.87**
% pred. workload (%)	82 (25)	85 (22)	84 (18)	87 (19)	0.38 (-5.60, 6.35)	0.90
HR (bpm)	121 (21)	117 (17)	117 (29)	118 (24)	-6.01 (-17.96, 5.95)	0.32
Time (s)	681 (330)	702 (348)	649 (382)	647 (407)	23.88 (-178.39, 226.15)	0.81
$\dot{V}O_2$ (L/min)	1.4 (0.4)	1.4 (0.4)	1.4 (0.3)	1.4 (0.4)	-0.06 (-0.20, 0.08)	0.41
$\dot{V}O_2$ (ml/kg/min)	17.2 (2.4)	17.1 (3.6)	17.2 (3.0)	17.8 (3.3)	-0.73 (-2.38, 0.92)	0.38
% pred. $\dot{V}O_2$ (%)	79 (16)	79 (19)	84 (18)	87 (19)	-3.35 (-11.11, 4.40)	0.39
RER	1.2 (0.1)	1.2 (0.1)	1.2 (0.2)	1.1 (0.1)	0.03 (-0.05, 0.11)	0.42
Submaximal (VT1)						
Power output (W)	55 (16)	72 (17)§	56 (20)	58 (23)	14.08 (5.39, 22.77)	< 0.01
Rel. workload (W/kg)	0.68 (0.19)	0.87 (0.20)§	0.72 (0.26)	0.76 (0.34)	0.15 (0.03, 0.26)	0.01
HR (bpm)	86 (13)	90 (15)§	89 (16)	90 (18)	3.25 (-2.43, 8.93)	0.26
Time (s)	395 (111)	511 (119)§	402 (142)	418 (166)	100.59 (38.52, 162.67)	< 0.01
Time (% of max)	49 (15)	60 (15)§	47 (17)	48 (17)	10.34 (1.09, 19.58)	0.03
$\dot{V}O_2$ (L/min)	0.8 (0.3)	1.0 (0.2)§	0.8 (0.2)	0.9 (0.2)	0.09 (-0.03, 0.20)	0.14
$\dot{V}O_2$ (ml/kg/min)	9.8 (3.0)	11.3 (1.9)§	10.4 (2.1)	11.1 (2.9)	0.81 (-0.49, 2.10)	0.22

* *P*-value is for differences in change over six months between ICE and CMP as tested by t-tests
** For the primary endpoint analysis, intention to treat was applied and the number of patients was 70 (experimental: 35, control: 35)
§within-group p-value significant ($p < 0.05$)
VT1 = the first ventilatory threshold, % pred. workload = percent of age-predicted workload, HR = heart rate, $\dot{V}O_2$ = oxygen consumption, $\dot{V}CO_2$ = carbon dioxide production, RER = respiratory exchange ratio ($\dot{V}CO_2$ /$\dot{V}O_2$), % pred. $\dot{V}O_2$ = percent of age-predicted oxygen consumption

4.3.3. Maximal resistance exercise performance

After six months, the ICE group increased maximal upper body muscular strength, i.e. maximal amount of weight moved during a chest-press one-repetition maximum test, from 15.8 ± 5.1 kg to 22.3 ± 10.3 compared to 17.4 ± 5.5 to 17.4 ± 6.9 ($P < 0.01$) in the control group. Lower body muscular strength measured during leg extension one-repetition maximum testing increased 14 ± 14 kg in ICE, from 47.8 ± 13.1 kg to 62.2 ± 18.5 kg, compared to no change in the cardiac maintenance group (48.5 ± 11.9 kg to 48.3 ± 12.2 kg; $P < 0.01$; see table 4, Supplemental table S2). The differences remained significant after normalizing strength for fat free mass, where the individual combined exercise group increased relative upper body muscular strength from 0.26 ± 0.08 kg/kgBW to 0.38 ± 0.21 kg/kgBW compared to 0.31 ± 0.09 kg/kgBW to 0.31 ± 0.12 kg/kgBW in the control group ($P_{upper} < 0.01$) and lower body strength from 0.82 ± 0.29 kg/kgBW to 1.06 ± 0.38 kg/kgBW in individualized combined exercise compared to 0.86 ± 0.29 kg/kgBW to 0.86 ± 0.30 kg/kgBW in cardiac maintenance ($P_{lower} < 0.01$). After the follow-up period of further six months, muscular strength returned to baseline levels. Results of maximal strength exercise testing are presented in Table 4 and Supplementary table S2.

Table 4: Changes in physical strength outcome data at baseline and six months.

	ICE (N=32)		CMP (N=30)			
Variable	Baseline	Six months	Baseline	Six months		
Strength	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean diff (95%CI)	*P*-value*
Upper (kg)	15.8 (5.1)	22.3 (10.3)§	17.4 (5.5)	17.4 (6.9)	6.50 (3.27, 9.72)	< 0.01
Lower (kg)	47.8 (13.1)	62.2 (18.5)§	48.5 (11.9)	48.3 (12.2)	14.53 (9.01, 20.05)	< 0.01
Relative Strength						
Upper (kg/kgFFM)	0.26 (0.08)	0.38 (0.21)§	0.31 (0.09)	0.31 (0.12)	0.12 (0.05, 0.18)	< 0.01
Lower (kg/kgFFM)	0.82 (0.29)	1.06 (0.38)§	0.86 (0.29)	0.86 (0.30)	0.25 (0.14, 0.35)	< 0.01

* *P*-value is for differences in change over six months between ICE and CMP as tested by t-tests
§ within-group p-value significant ($p < 0.05$).
FFM = Fat free mass

4.4. Hemodynamics and Anthropometry

After six months, both groups reduced mean resting systolic (ICE: 129±17 to 121±13 mmHg, CMP: 135±16 to 129±15) and diastolic (ICE: 79±11 to 69±9 mmHg, CMP: 79±11 to 75±8 mmHg) blood pressure, but only the change in diastolic blood pressure was significantly different between groups ($P = 0.03$; see Table 3). The individualized combined exercise group decreased resting heart rate significantly more than the cardiac maintenance group (ICE: -7±11 bpm, CMP: -0.3±8 bpm, $P = 0.01$). There were no significant within or between group differences in body weight, body mass index, fat free mass, waist circumference after six or 12 months. There were also no significant within or between group differences in glycated hemoglobin (HbA1c), high or low density lipoproteins, total cholesterol, triglycerides or blood glucose concentrations after six or twelve months. Results of anthropometric and blood chemistry investigations are presented in Table 5 and supplementary table S3.

Table 5: Changes in anthropometric measurements, resting hemodynamics and blood chemistry outcome data between baseline and six months.

	ICE (N=32)		CMP (N=30)			
Variable	Baseline	Six months	Baseline	Six months		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean diff (95%CI)	*P*-value*
Body weight (kg)	83.5 (16.0)	84.7 (16.2)	80.5 (15.1)	80.6 (15.1)	1.106 (-0.37, 2.58)	0.14
BMI (kg/m^2)	29.1 (4.7)	29.5 (4.7)	28.2 (4.1)	28.4 (4.1)	0.271 (-0.31, 0.85)	0.35
FFM (kg)	61.0 (11.2)	61.7 (11.0)	58.7 (10.6)	59.0 (10.2)	0.250 (-1.35, 1.85)	0.75
Waist circ. (cm)	103.2 (12.4)	102.7 (12.5)	101.0 (11.2)	101.4 (12.0)	-0.848 (-3.91, 2.22)	0.58
SBP_{rest} (mmHg)	129 (17)	121 (13)§	135 (16)	129 (15)§	-2.121 (-9.81, 5.57)	0.58
DBP_{rest} (mmHg)	79 (11)	69 (9)§	79 (10.6)	75 (8.1)	-5.900 (-11.30, -0.50)	0.03
HR_{rest} (bpm)	68 (13)	61 (10)§	64 (12)	64 (12)	-6.356 (-11.42, -1.30)	0.01
HbA1c (%)	6.4 (0.6)	6.3 (1.0)	6.2 (0.5)	6.1 (0.5)	0.126 (-0.19, 0.44)	0.42
Total Cholesterol	4.62 (0.93)	4.62 (0.95)	5.10 (1.11)	5.11 (1.05)	-0.017 (-0.47, 0.43)	0.50
HDL (mmol/L)	1.26 (0.26)	1.28 (0.32)	1.36 (0.26)	1.34 (0.26)	0.040 (-0.05, 0.13)	0.39
LDL (mmol/L)	2.92 (0.80)	2.90 (0.72)	3.17 (0.63)	3.17 (0.69)	-0.022 (-0.33, 0.29)	0.88
Triglycerides (mmol/L)	1.50 (0.70)	1.55 (0.86)	1.45 (0.63)	1.43 (0.65)	0.073 (-0.23, 0.38)	0.63
Glucose (mmol/L)	6.15 (2.38)	6.10 (2.16)	5.92 (1.18)	6.06 (1.13)	-0.017 (-0.47, 0.43)	0.94

* *P*-value is for differences in change over six months between ICE and CMP as tested by t-tests
§ within-group p-value significant ($p < 0.05$)
BMI = body mass index, FFM = fat free mass, SBP_{rest} = resting systolic blood pressure, DBP_{rest} = resting diastolic blood pressure, HR_{rest} = resting heart rate, HbA1c = Glycated hemoglobin, HDL = high density lipoprotein, LDL = low density lipoprotein

4.5. Leisure time physical activity levels

There were no significant differences in leisure time physical activity levels measured by accelerometry at baseline (ICE: 1.47±0.18, CMP: 1.47±0.22, p=0.96) or after six months (ICE: 1.48±0.14, CMP: 1.44±0.15, p=0.31). Steps per day increased significantly in individualized combined exercise compared to cardiac maintenance (ICE: 8635±2424 to 10221±3162 steps/d, CMP: 9220±3324 to 8382±1950 steps/d, p>0.01).

Self- reported total physical activity (IPAQ) was not different between groups at baseline (ICE: 289 [140-541] MET-min/d, CMP: 350 [239-567]2 MET-min/d) or at six months (ICE: 394 [182-593] MET-min/d, CMP: 271 [229-534] MET-min/d), with no between group differences in change over six months (p=0.61). Individualized combined exercise increased significantly in vigorous physical activity (12 [2-26] MET-min/d) as opposed to a decrease of −5 [−28-6] MET-min/d in cardiac maintenance (p=0.02; Table 6 and Supplemental Table S4). Individualized combined exercise patients significantly reduced median sitting time from 360 [240-495] to 315 [240-420] compared to no change in cardiac maintenance (350 [210-480] to 350 [280-510]), p<0.07. Physical activity category (3 = high, 2= moderate or 1 = low) decreased in two individualized combined exercise patients and increased in eight patients, whereas in cardiac maintenance five patients decreased and one increased in physical activity category. Median change in physical activity category significantly favored individualized combined exercise (ICE: +0.4 points, CMP -0.1 points; X^2=6.05, p=0.01; Supplementary Figure S2). To determine exploratively the comparability between accelerometry and the international physical activity questionnaire, descriptive statistics and t-tests were conducted, and bland-altman plots were generated (Supplemental Figure S3). The two measures of leisure time physical activity did not agree strongly, as indicated by absolute values and

bland-altman plot analyses, with the questionnaire resulting in higher values and accelerometry in lower values for total and different levels of leisure time physical activity.

Table 6: Changes in leisure time physical activity levels between baseline and six months.

Leisure time physical activity was measured with the international physical activity questionnaire and the Aipermon 440 accelerometer

	ICE (N=32)		CMP (N=30)		
Variable	Baseline	Six months	Baseline	Six months	*P*-value*
Accelerometry	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
PAL	1.47 ± 0.18	1.48 ± 0.14	1.47 ± 0.22	1.44 ± 0.15	0.31**
Steps per day	8635 ± 2424	10221 ± 3162	9220 ± 3324	8382 ± 1950	0.01**
IPAQ	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Total activity (MET-min/d)	289 (140,541)	394 (182,593)	350 (239,567)	271 (229,534)	0.61
Vigorous (MET-min/d)	11 (0,20)	23 (0,240)§	11 (0,80)	6 (0,160)	0.02
Moderate (MET-min/d)	102 (34,261)	111 (69,242)	106 (69,209)	102 (63,254)	0.99
Walking (MET-min/d)	116 (70,286)	184 (80,396)	198 (99,346)	149 (90,368)	0.56
Sitting (min/d)	360 (240,495)	315 (240,420)	350 (210,480)	350 (280,510)	0.07
IPAQ PA Category	n (%)	n (%)	n (%)	n (%)	
Low	3 (9)	2 (7)	1 (3)	2 (7)	
Moderate	18 (56)	8 (27)	15 (47)	12 (40)	0.01
High	9 (28)	15 (50)	14 (44)	11 (36.7)	

* *P*-value is for differences in change over six months between ICE and CMP as tested by Mann-Whitney-U-Tests
** *P*-value is for differences in change over six months between ICE and CMP as tested by t-tests
§ within-group p-value significant ($p < 0.05$)

PAL = Physical activity level (physical energy expenditure (kcal) / resting metabolic rate (kcal)), IPAQ = International Physical Activity Questionnaire, IQR = Interquartile Range, MET = Metabolic Equivalent Task

4.6. Health related quality of life

Perceived health status as measured by the SF-36 was not different between individualized combined exercise and cardiac maintenance at baseline. After six months, only vitality (ICE: 64.0±16.1, CMP: 52.6±15.7, p=0.005) was statistically different favoring individualized combined exercise. Total health related quality of life score, physical, mental and social dimensions of well-being measured by MacNew were not different at baseline between individualized combined exercise and cardiac maintenance (p>0.05). After six months, differences were observed in the mental (ICE: 5.57±1.1, CMP: 5.27±1.1, p=0.05) and social (ICE: 6.04±0.9, CMP: 5.33±1.0, p=0.005) dimensions. Total MacNew health-related quality of life score for individualized combined exercise was 5.75±0.8 compared to 5.33±1.0 in cardiac maintenance (p=0.07). Distress as measured by the GMS negative and positive affect scores was not different at baseline (p>0.05). In the individualized combined exercise group, negative affect was decreased (13.3±8.2 to 12.6±7.6, p=0.05) and positive affect increased (27.0±8.3 to 29.4±7.1, p=0.004) after six months. No change was observed in the cardiac maintenance group. Health related quality of life outcomes are presented in Table 7 and Supplemental Table S5.

Table 7: Changes in health-related quality of life data between baseline and six months.

Health-related quality of life was measured with three separate questionnaires, the Short Form 36 (SF-36), the Global Mood Scale (GMS) and the MacNew Heart Disease Quality of Life Instrument (MacNew).

	ICE (N=32)		CMP (N=30)		
Variable	Baseline	Six months	Baseline	Six months	*P*-value*
SF-36	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Physical functioning	71.8 ± 16.5	75.8 ± 17.3	71.58 ± 20.7	70.2 ± 17.3	0.195
Social functioning	85.6 ± 20.3	89.8 ± 19.1	81.06 ± 21.9	81.4 ± 19.0	0.081
Physical role limit	59.1 ± 36.4	68.2 ± 39.2	65.15 ± 38.0	69.7 ± 35.8	0.870
Emotional role limit	79.8 ± 33.3	85.9 ± 30.1	79.29 ± 30.3	78.8 ± 30.7	0.348
Bodily Pain	78.0 ± 25.1	81.0 ± 23.8	73.27 ± 25.5	68.9 ± 26.3	0.056
Mental health	77.4 ± 17.5	76.9 ± 15.7	71.6 ± 17.5	74.5 ± 16.1	0.183
Vitality	60.9 ± 21.0	63.9 ± 16.1	52.7 ± 15.6	52.6 ± 15.7	0.005
General health	56.7 ± 18.1	56.8 ± 18.3	57.0 ± 16.8	56.7 ± 15.2	0.984
Physical Total Score	43.2 ± 8.7	44.7 ± 9.4	44.9 ± 9.6	43.7 ± 8.5	0.651
Psychological Total Score	52.8 ± 10.6	53.7 ± 8.5	50.6 ± 9.3	51.5 ± 8.6	0.303
GMS					
Negative affect	13.3 ± 8.2	12.6 ± 7.6	15.5 ± 7.1	16.5 ± 8.2	0.049
Positive affect	27.0 ± 8.3	29.4 ± 7.1§	24.5 ± 6.9	24.4 ± 6.3	0.004
MacNew					
Emotional	5.6 ± 1.1	5.8 ± 0.9	5.3 ± 1.2	5.3 ± 1.1	0.050
Physical	5.4 ± 1.0	5.7 ± 0.9§	5.4 ± 1.0	5.4 ± 1.1	0.128
Social	5.7 ± 1.1	6.0 ± 0.9§	5.4 ± 1.1	5.3 ± 1.0	0.005
Total	5.5 ± 1.1	5.8 ± 0.9§	5.4 ± 1.0	5.3 ± 1.0	0.073

* *P*-value is for differences in change over six months between ICE and CMP as tested by t-tests
§ within-group p-value significant ($p < 0.05$)
SF-36 = Short Form 36, GMS = Global Mood Scale, MacNew = MacNew Heart Disease Quality of Life Instrument

5. Discussion

5.1. Overview and discussion of the results of the primary and secondary outcomes

Six months of weekly individualized combined exercise did not significantly improve maximal exercise performance compared to participation in a calisthenics-based cardiac rehabilitation maintenance program in patients with low exercise capacity. However, it did result in improved resting hemodynamics, submaximal exercise performance and increased muscular strength compared to cardiac maintenance. Participants in individualized combined exercise also increased leisure time physical activity and improved health-related quality of life compared to cardiac maintenance. Furthermore, there were no serious adverse events related to endurance or resistance training. The return of most parameters to baseline levels suggests that there was little to no long-term effect of the intervention on the health and fitness status, as well as positive behavioral change on the participants.

There have been no randomized clinical trials comparing individually prescribed and monitored combined exercise to cardiac maintenance in patients with low exercise capacity. Individual exercise programming with specific exercise targets and close monitoring has however been the standard for scientific studies in exercise and cardiac disease (Smith et al., 2011). This is in contrast to the focus on group-based exercise in cardiac maintenance (Humphrey, Guazzi, & Niebauer, 2014). Although the current cardiac maintenance programs have been somewhat successful in reducing further complications in patients with cardiac disease, studies have not yet shown the superiority of these programs over individualized combined exercise (Labrunee et al., 2012).

In the current study, the individualized combined exercise group significantly lengthened time to and workload at the first ventilatory threshold by almost two minutes and 16 W,

respectively, and reduced submaximal heart rate 7 bpm, compared to no change in the cardiac maintenance group. Improvement in submaximal exercise performance has been observed to be related to improved performance of activities of daily living in low risk patients (Marzolini et al., 2012), making it an important goal of exercise-based cardiac rehabilitation (Balady et al., 2007).

The individualized combined exercise group also increased upper and lower body strength by 40% and 30%, respectively, compared to no changes in cardiac maintenance. Increased muscular strength and resistance exercise, independent of effects on $\dot{V}O_2$peak, have been correlated to improved body composition, glucose metabolism, and submaximal and maximal endurance time (Hickson, Rosenkoetter, & Brown, 1980; Marzolini et al., 2012; Williams et al., 2007). However, the influence of resistance exercise in patients with low exercise capacity has not yet been well studied (Williams et al., 2007).

One of the concerns surrounding the performance of exercise, and especially resistance exercise, in patients with low exercise capacity is the potential for orthopedic injury and an inadequate hemodynamic response during exercise (Bjarnason-Wehrens et al., 2004; Williams et al., 2007). One patient in the individualized combined exercise group reported muscular discomfort that led to a discontinuation of resistance exercise. There were however no orthopedic injuries, onset of symptoms or events related to blood pressure spikes or heart rhythm abnormalities. On the other hand, the individualized combined exercise group experienced clinically significant (Cornelissen, Fagard, Coeckelberghs, & Vanhees, 2011) reductions in resting heart rate and blood pressure after six months of exercise, suggesting that the benefits of individualized combined exercise may outweigh the potential for adverse events.

The performance of individualized combined exercise patients has been observed to increase strength and submaximal fitness in other populations (Marzolini et al., 2012). In one such study , maximal and submaximal exercise performance were analyzed in 40 male patients (56 ± 10 y) with coronary artery disease and normal maximal exercise capacity ($\dot{V}O_2$peak ~ 30 ml/kg/min), who were randomized to one year of endurance exercise alone, combined exercise or control (Santa-Clara, Fernhall, Mendes, & Sardinha, 2002). The patients exercised for three sessions per week for approximately 30 minutes at intensities of 60-70% of heart rate reserve (endurance and combined group) and 40-50% of one- repetition maximal (combined group). After one year, the combined group had increased upper and lower body strength by 28% and 22%, respectively compared to no change in the endurance only group, and improved time to the first ventilatory threshold by 108 seconds compared to 54 seconds and oxygen consumption at the first ventilatory threshold 6.2 ml/kg/min compared to 3.4 ml/kg/min in the endurance only group (all $p < 0.05$). Although both groups improved peak oxygen consumption compared to controls, there was no difference between the two exercise groups (Santa-Clara et al., 2002). This suggests that the addition of resistance exercise to endurance exercise, such as in the current study has an important influence on submaximal but not maximal exercise performance. However, this and other studies in coronary artery disease have not investigated patients with low exercise capacity. Results of the current study support these data and the performance of individualized combined exercise over group based exercise in improving submaximal exercise performance and physical strength, both indicators of cardiovascular fitness (Marzolini et al., 2012).

This is the first randomized controlled trial comparing individualized combined exercise with cardiac maintenance on adaptations in maximal and submaximal exercise performance,

cardiovascular risk status and strength in patients with low exercise capacity. Therefore the exercise intervention was conservative. It remains to be investigated if the relatively low exercise intensity and volume may explain the lack of effect on maximal exercise performance. The most recent Cochrane review on cardiac rehabilitation observed that higher risk, elderly patients and patients with comorbidities are underrepresented in the literature (Heran et al., 2011). The participants in the current study were higher risk, (50% with multi-vessel disease and 20% with implantable-cardioverter-defibrillators, 30% with diabetes; Table 1) and on average 70 ± 9 y, an underrepresented group of patients who are increasing in proportion of total patients with cardiac disease and entering into cardiac rehabilitation programs (Di Angelantonio et al., 2015).

Interestingly, the patients in individualized combined exercise reported more vigorous activity than those in cardiac maintenance after six months. Recent observational and clinical trials have shown the positive independent effects of exercise intensity on effects on mortality and cardiovascular risk. In the Copenhagen City Heart Study, a very strong and independent dose- response effect of walking speed on risk of heart failure and mortality was observed in questionnaire- based analyses of 10,411 participants over more than 30 years of follow-up (Saevereid, Schnohr, & Prescott, 2014). Participants who reported exercising at high intensity increased average life expectancy 4.5 y compared to 2.5 y in the moderate intensity group, whereas daily exercise duration had no effect. Furthermore, the high intensity group had 40% less risk of developing heart failure than those who exercised at low intensity, compared to sedentary individuals (Schnohr, Marott, Jensen, & Jensen, 2012). In coronary artery disease patients, high intensity exercise has been observed to improve peak oxygen capacity superiorly to isocaloric moderate continuous exercise (Rognmo, Hetland, Helgerud, Hoff, &

Slordahl, 2004). Although the current study did not investigate high-intensity exercise, these data do support that relative intensity may be more important than volume for positive adaptations in fitness and cardiovascular health. In the current study, individualized combined exercise participants were also generally more active than cardiac maintenance after six months. 27% of individualized combined exercise increased their leisure time physical activity after six months compared to 3% in cardiac maintenance, and 6% reduced physical activity level compared to 20% in cardiac maintenance. These differences resulted in only 3% of individualized combined exercise being considered insufficiently active compared to 11% in cardiac maintenance, and 47% of individualized combined exercise in the highly active group compared to 31% in cardiac maintenance.

The relationships between physical activity and health-related quality of life are complex, but it has been shown that patients who are more physically active score higher on health-related quality of life questionnaires and patients who increase their physical activity levels also improve health-related quality of life. In the Behavioral Risk Factor Surveillance System (BRFSS) survey, a clear relationship between meeting physical activity guidelines for moderate to vigorous activity and increased health-related quality of life was observed in a sample of 175,850 participants. Physically inactive persons reported having twice as many unhealthy days compared to those meeting physical activity guidelines (i.e. at least 30 minutes of moderate exercise five days a week or twice weekly vigorous exercise) (Brown et al., 2003).

Resistance training likely has independent positive effects on health-related quality of life even when compared with endurance training. In a randomized trial comparing endurance training with resistance training over 29 weeks, both the addition of one and three sets of

resistance training twice a week improved health-related quality of life significantly more than endurance training alone in patients with coronary artery disease (Marzolini et al., 2014). In a study investigating 12 weeks of either flexibility or strength training on health-related quality of life in cardiac rehabilitation participants, self-efficacy, emotional and psychological health improved significantly more in the resistance training group (Beniamini, Rubenstein, Zaichkowsky, & Crim, 1997). However, a recent study investigating the effect of resistance training as an adjunct to endurance training in patients with coronary artery disease in cardiac rehabilitation showed no added effect of resistance training on health-related quality of life in either group, compared to endurance exercise alone (Currie, Bailey, Jung, McKelvie, & MacDonald, 2014). In this small sample (n = 19) the patients were not tested for maximal strength before performing resistance training and exercise intensity was based exclusively on subjective ratings of perceived exertion. Furthermore, using only the SF-36 questionnaire may have reduced the sensitivity with which health-related quality of life was detected. The SF-36 was the least sensitive to changes in health-related quality of life in the current study (see Table 2), and is not considered a sensitive health-related quality of life instrument for heart disease patients (Ware & Sherbourne, 1992). The current study applied three different questionnaires to the measurement of health-related quality of life, and the questionnaires designed explicitly for patients with heart disease (MacNew and GMS) responded more positively than the SF-36. This may explain some of the differences observed between these and the current study in health-related quality of life.

The number of elderly patients with higher risk status is increasing as patients with heart disease are living longer, and these patients are seeking out places to be physically active (Fleg et al., 2013). This will continue to increase the need for trials investigating the effects of

different modes of exercise in cardiac maintenance, and their effects on the health and well-being (Zwisler et al., 2012). In the current study the individualized combined exercise group increased their physical activity and decreased sedentary time compared to cardiac maintenance. Considering the very limited time that patients are in a supervised exercise setting, it is imperative that patients make positive use of their leisure time. As others have suggested, there is also a need for the incorporation of novel methodologies targeting health and fitness in patients who are at higher risk due to reduced maximal fitness (Arena, Myers, Forman, Lavie, & Guazzi, 2013; Kwan & Balady, 2012; Seron, Lanas, Pardo, & Bonfill, 2014). Considering the challenges involved in directly improving risk status of these patients, targeting leisure time physical activity and health-related quality of life offers other clinically important targets that may indirectly improve overall risk status over the long term (Lin et al., 2015).

Although the number of elderly patients with cardiac disease and low exercise capacity is increasing, with over half of the participants above 60 years of age, the amount of qualified patients who participate in cardiac maintenance programs after phase II cardiac rehabilitation is only 25-40% and has not been increasing (Bjarnason-Wehrens et al., 1999; Karoff et al., 2007; Keck & Budde, 1999; Weidemann, 1996). These data suggest that although these programs may have the potential to improve the health and fitness of patients with cardiac disease, most patients do not take advantage and therefore the effect of these programs on the overall health status of Germans living with cardiac disease is not satisfactory. As in the general population, public health efforts need to be extended to this population, especially messages about the health benefits of physical activity. Although reasons given for non-participation and non-adherence are largely situational (i.e. distance from centers, low

availability of rehabilitation sessions, lack of time), it is also likely that some patients do not participate in cardiac maintenance programs because they simply do not want to participate due to an expected lack of enjoyment (Kerins, McKee, & Bennett, 2011). An individual approach to cardiac maintenance programming and increasing the programming options would likely result in an increase in participation and attendance (Kerins et al., 2011). Although the current study observations do not explicitly support more personalized cardiac rehabilitation programming, it is interesting that after participation in a more individualized exercise program with smaller group sizes and more attention on meeting endurance and resistance exercise intensities, health-related quality of life was more improved than in patients in the cardiac maintenance program. Patients in the individualized group improved in their perceptions of bodily pain, vitality, negative and positive affect, and emotional, physical and social health compared to no significant improvements in the cardiac maintenance program. These observations are somewhat surprising considering the supportive nature of cardiac maintenance programs, and the factors involved in health related quality of life are complex, but it is likely that some patients would prefer an alternative to the standard cardiac rehabilitation maintenance programs, and that offering an alternative would likely improve health related quality of life in these patients.

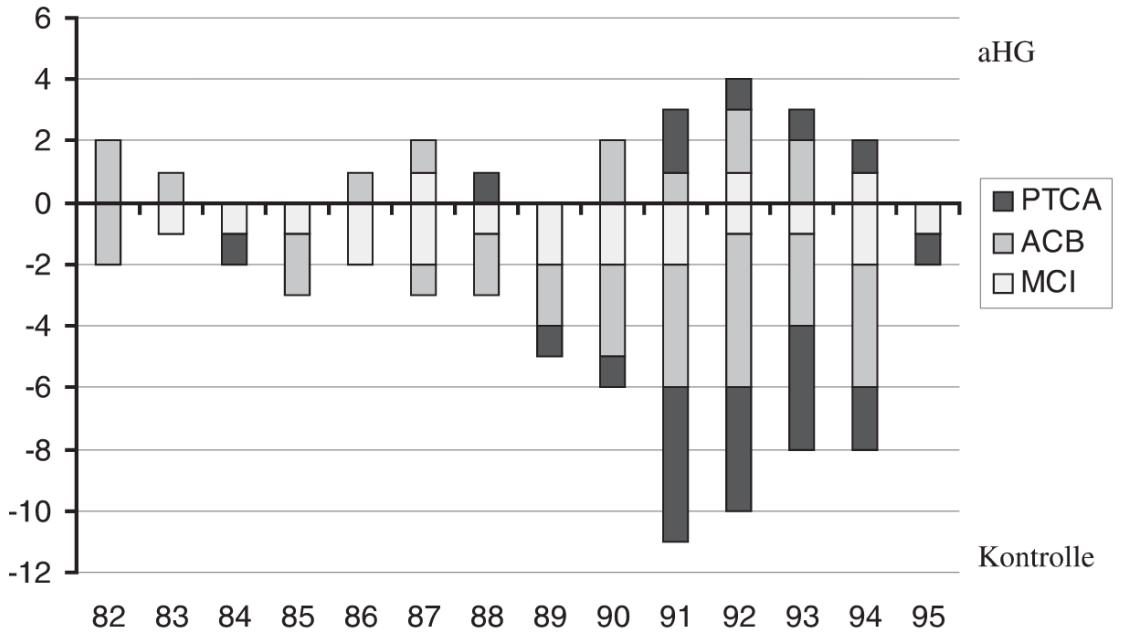
Even more surprising are the seemingly persistent effects of individualized combined exercise training on mental health (SF-36) and emotional and social health (MacNew) observed after six-months of passive follow-up. Although a trend for higher physical activity levels and less time spent sitting was observed in the experimental group, this was not significant and did not translate to improved cardiovascular risk. Therefore, it is difficult to draw any sound conclusions from these data. Patients in the combined exercise group did subjectively report

the performance of combined exercise during the follow-up phase, which may have had a positive impact on health related quality of life.

Compounding the problem of low participation, there is a major need for more research in the effects of cardiac maintenance programs in Germany on risk status, physical and mental health, fitness and physical activity levels. There are very few trials that have studied the effects of cardiac rehabilitation maintenance programs, and only one published article examining the effect of the German *Herzgruppe* to controls. In this one case-control study from Buchwalsky (Buchwalsky, Buchwalsky, & Held, 2002), 75 control patients were retrospectively matched-paired to 75 participants from a rehabilitation clinic and cardiac maintenance groups, and were followed for 7.5 years. The results were somewhat disappointing, in that there were no differences observed in risk factor modification. However, the maintenance program participants did observe improved physical performance, fewer cardiac complaints and less angina pectoris, took less cardiac medication and morbidity (Figure 9). These data led the authors to conclude that the maintenance program would theoretically reduce overall costs by 47%, compared to no action. With this pilot work having been completed in 2002, it is surprising that more work has not been performed examining the effects of the *Herzgruppe* compared to alternative forms of exercise therapies, and an exhaustive examination of the health and fitness status of *Herzgruppe* participants is long overdue.

Figure 9: Results from the only case-control study on German cardiac rehabilitation maintenance programs.

Although not significant, the data suggests trends of fewer percutaneous [transluminal] coronary interventions (PTCA), coronary artery bypass grafting (aortocoronary bypass; ACB) and myocardial infarct (MCI) in patients participating in *Herzgruppen*.



The same can be said of studies on exercise in patients with low fitness. There is a lack of data on exercise in low fitness populations and especially the application of different exercise modes.

Finally, the physical activity patterns and fitness of patients in cardiac maintenance is still largely unknown. A recent study was the first to compare cardiac maintenance participants to healthy individuals matched by age, gender and physical activity levels (Mandic, Stevens, et al., 2015). The authors observed that cardiac maintenance participants have approximately the

same fitness and leisure time physical activity as their less-active healthy peers. This provides support for participation in cardiac maintenance programs and the role of regular exercise in increasing physical activity for health over the long term. Integrating methods of exercise therapy that have been observed to increase health and physical activity would maximize the potential of cardiac maintenance to contribute to an active and healthy lifestyle.

5.2. Strengths and Limitations

There are a few important and expected limitations that have impacted the results of the trial and the ability to interprete these results. Primarily, the purpose of the trial was to compare the effects of cardiac maintenance in Germany to a similar volume of individualized combined exercise. The resulting volume of exercise was relatively low in all patients (both < 10 MET-hours/week). It is likely that this amount of exercise is not sufficient to alter cardiovascular risk factors. This observation has two separate but important interpretations. Primarily, it means that cardiac maintenance groups, based on exercise volume and intensity are not independently meeting physical activity guidelines, which also has yet to be verified by scientific study. This observation also makes the observed differences between the groups that much more relevant, suggesting that a much lower volume of individualized combined exercise may be sufficient for having a positive impact on the fitness of elderly patients with low exercise capacity. Considering that the most obvious difference between the experimental group and the usual care group was the participation in resistance training and closer monitoring of exercise in individualized combined exercise, these results support further investigations into both of these factors. Especially considering the absence of resistance exercise in German cardiac maintenance programs, the present study supports the performance of resistance training for all patients in cardiac maintenance groups.

Furthermore, it would be interesting to know what the effect of individualized combined exercise is on physical activity behaviors outside of the groups. In the current study, physical activity levels were relatively high in all participants, and increased in the experimental group. More data on leisure time physical activity would be important to illustrate any effects that cardiac maintenance may be having on activity levels, in lieu of reaching recommendations for physical activity within the groups.

5.3. Practical implications

Although there were no differences in maximal exercise performance in the current trial, it seems that there is a need for positive adaptations in cardiac maintenance programs to the increasing demand for exercise in patients with cardiovascular diseases. The individualized combined exercise approach applied in the current study seemed to have positive effects on several direct and indirect parameters of health and fitness, which should be further investigated. Especially considering that the population of patients participating in cardiac maintenance programs is becoming older and more comorbid, and that elderly patients tend to have reduced exercise capacity, it may be time to reestablish cardiac *maintenance* programs as cardiac *improvement* programs, at least as far as fitness is considered. This will likely involve increasing exercise volumes or intensities, either supervised or home-based, to above the current levels, and including some of the methods described in the current manuscript.

5.4. Conclusion and perspective

Six months of once-weekly individualized combined exercise was feasible, but did not improve maximal exercise performance in patients with cardiac disease and low exercise capacity compared to a group-based cardiac maintenance program. It was however superior in improving resting hemodynamics, submaximal exercise performance, muscular strength,

leisure time physical activity levels and health related quality of life. These effects did not persist after a follow-up of six months. This form of exercise may be integrated into traditional cardiac maintenance on an intermittent basis to improve functional and health outcomes, but not to increase peak physical fitness and prognosis. Further research is necessary to determine the potential of these patients to improve in peak exercise performance and prognosis, and if so which exercise methods are likely to contribute.

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Appendix 1: Supplemental data files

Supplemental data file A: Data for power calculation

Supplemental data file B: Allocation plan

Supplemental data file C: The combined results of primary and secondary endpoints for baseline, six and twelve months

Supplemental data file D: Graphical representation of relative maximal workload at baseline and at six months for all patients, identified by group assigment

Supplemental data file E: Comparison of the Intention-to-treat and On-treatment samples on the primary endpoint

Supplemental data file F: The effect of baseline differences in statin use

Supplemental data file G: Schematic of change in fitness categories from baseline to six months.

Supplemental data file H: Statistical analysis of comparisons of leisure time physical activity measured by questionnaire and accelerometry

Supplemental file A: Data for power calculation **(generated by the software program g-power). To account for an expected drop-out rate of 15%, the number of patients was increased to a total of 70 patients.**

[1] – *Thursday, December 23, 2010 -- 14:35:19*

t tests – Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	0.95
	α err prob	=	0.05
	Power (1−β err prob)	=	0.95
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	3.6793342
	Critical t	=	2.0017175
	Df =	58	
	Sample size group 1	=	30
	Sample size group 2	=	30
	Total sample size	=	60
	Actual power	=	0.9513202

Supplemental data file B: Allocation plan

The allocation plan based on the randomization as described above in the methods section. The usual care group is described here as "control" and experimental group is described as "Treatment".

A Randomization Plan

from

http://www.randomization.com

1. Control
2. Treatment
3. Treatment
4. Control
5. Treatment
6. Control
7. Treatment
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51. Control
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53. Treatment
54. Treatment
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57. Control
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59. Treatment
60. Control
61. Control
62. Treatment
63. Treatment
64. Treatment
65. Control
66. Treatment
67. Treatment
68. Treatment
69. Control
70. Treatment

70 subjects randomized into 1 block.
To reproduce this plan, use the seed 9536 along with the number of subjects per block/number of blocks and (case-sensitive) treatment labels as entered originally.
Randomization plan created on December 23, 2010 at 13:52:39 GMT +0200

Supplemental data file C: The combined results of primary and secondary endpoints for baseline, six and twelve months

Endpoint data at baseline, six months and 12 months, compiled into singular tables, with significant differences highlighted in bold and defined with superscripts.

Table S 1: Changes in endurance exercise performance

	ICE			CMP		
Variable	Baseline	Six months	12 months	Baseline	Six months	12 months
Maximal exercise						
Workload (W)*	94 ± 20	98 ± 21	93 ± 28	92 ± 20	95 ±22	93 ± 23
Rel. workload (W/kg)*	1.11 ± 0.21	1.16 ± 0.25	1.10 ± 0.46	1.15 ± 0.20	1.19 ± 0.25	1.16 ± 0.45
% pred. workload	82 ± 25	85 ± 22	80 ± 21	84 ± 18	87 ± 19	85 ± 18
HR (bpm)	121 ± 21	117 ± 17	119 ± 16	117 ± 29	118 ± 24	115 ± 22
Time (s)	681 ± 330	702 ± 348	690 ± 402	649 ± 382	647 ± 407	695 ± 409
$\dot{V}O_2$ (L/min)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.5	1.4 ± 0.3	1.4 ± 0.4	1.40 ± 0.55
$\dot{V}O_2$ (ml/kg/min)	17.2 ± 2.4	17.1 ± 3.6	17.5 ± 6.3	17.2 ± 3.0	17.8 ± 3.3	17.6 ± 6.4
% pred. $\dot{V}O_2$ (%)	79 ± 16	79 ± 19	79 ± 17	84 ± 18	87 ± 19	86 ±18
RER	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.2	1.1 ± 0.1	1.1 ± 0.1
Submaximal (VT1)						
Workload (W)	55 ± 16	**72 ± 17**[ab]	49 ± 24	56 ± 20	**58 ± 23**[b]	59 ± 29
Rel. workload (W/kg)	0.68 ± 0.19	**0.87 ± 0.20**[ab]	0.59 ± 0.26	0.72 ± 0.26	**0.76 ± 0.34**[b]	0.70 ± 0.30
HR (bpm)	90 ± 15	**83 ± 13**[ab]	84 ± 13	89 ± 16	**90 ± 18**[b]	89 ± 21
Time (s)	395 ± 111	**511 ± 119**[ab]	412 ± 126	402 ± 142	**418 ± 166**[b]	406 ± 136
Time (% of max)	49 ± 15	**60 ± 15**[ab]	60 ± 13	47 ± 17	**48 ± 17**[b]	58 ± 21
$\dot{V}O_2$ (L/min)	0.8 ± 0.3	1.0 ± 0.2[a]	0.91 ± 0.24	0.8 ± 0.2	0.9 ± 0.2	0.90 ± 0.23
$\dot{V}O_2$ (ml/kg/min)	9.8 ± 3.0	11.3 ± 1.9[a]	9.91 ± 2.80	10.4 ± 2.1	11.1 ± 2.9	10.63 ± 4.00

Values are mean ± SD. ICE, Individualized combined exercise; CMP, Cardiac maintenance program; VT1, first ventilatory threshold; % pred. workload, percent of age-predicted max workload; HR, heart rate; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide production; RER, respiratory exchange ratio ($\dot{V}CO_2$ /$\dot{V}O_2$); % pred. $\dot{V}O_2$, percent of age-predicted peak oxygen consumption

[a] $p < 0.05$ within-group compared to baseline

[b] $p < 0.05$ between-group change vs CMP

* Intention to Treat Analysis on n=70 (ICE=35; CMP=35)

Table S 2: Changes in strength exercise performance

	ICE			CMP		
Variable	Baseline	Six months	12 months	Baseline	Six months	12 months
Strength						
Upper (kg)	15.8 ± 5.1	**22.3 ± 10.3[ab]**	16.7 ± 5.7	17.4 ± 5.5	**17.4 ± 6.9[b]**	17.6 ± 6.8
Lower (kg)	47.8 ± 13.1	**62.2 ± 18.5[ab]**	44.7 ± 15.4	48.5 ± 11.9	**48.3 ± 12.2[b]**	46.8 ± 14.4
Relative Strength						
Upper (kg/FFM)	0.26 ± 0.08	**0.38 ± 0.21[ab]**	0.27 ± 0.09	0.31 ± 0.09	**0.31 ± 0.12[b]**	0.31 ± 0.11
Lower (kg/FFM)	0.82 ± 0.29	**1.06 ± 0.38[ab]**	0.74 ± 0.29	0.86 ± 0.29	**0.86 ± 0.30[b]**	0.82 ± 0.30

Values are mean ± SD.
[a] $p < 0.05$ within-group compared to baseline
[b] $p < 0.05$ between-group change vs CMP (significant between group differences are indicated in bold)
ICE, Individualized combined exercise; CMP, Cardiac maintenance program; FFM, Fat Free Mass

Table S 3: Changes in resting hemodynamics, anthropometry, and blood profile

	ICE			CMP		
Variable	Baseline	Six months	12 months	Baseline	Six months	12 months
Resting hemodynamics						
SBP_{rest} (mmHg)	129 ± 17	121 ± 13[a]	126.2 ±17.9	135 ± 16	129 ± 15[a]	129 ± 21[a]
DBP_{rest} (mmHG)	79 ± 11	**69 ± 9[ab]**	77.2 ± 10.8	79 ± 11	**75 ± 8[b]**	80 ± 9
HR_{rest} (bpm)	68 ± 13	**61 ± 10[ab]**	68 ± 13	64 ± 12	**64 ± 12[b]**	64 ± 12
Anthropometry						
Body weight (kg)	83.5 ± 16.0	84.7 ± 16.2	83.8 ± 15.7	80.5 ± 15.1	80.6 ± 15.1	80.7 ± 15.3
BMI (kg/m^2)	29.1 ± 4.7	29.5 ± 4.7	29.6 ± 4.7	28.2 ± 4.1	28.4 ± 4.1	28.8 ± 3.8
FFM (kg)	61.0 ± 11.2	61.7 ± 11.0	61.8 ± 10.4	58.7 ± 10.6	59.0 ± 10.2	59.5 ± 10.7
Waist circ. (cm)	103.2 ± 12.4	102.7 ± 12.5	102.9 ± 15.7	101.0 ± 11.2	101.4 ± 12.0	101.7 ± 15.1
Blood profile						
HbA1c (%)	6.4 ± 0.6	6.3 ± 1.0	6.2 ± 0.6	6.2 ± 0.5	6.1 ± 0.5	6.1 ± 0.7
Total Cholesterol	4.62 ± 0.93	4.62 ± 0.95	4.53 ± 1.29	5.10 ± 1.11	5.11 ± 1.05	5.38 ± 1.11
HDL (mmol/L)	1.26 ± 0.26	1.28 ± 0.32	1.27 ± 0.39	1.36 ± 0.26	1.34 ± 0.26	1.42 ± 0.31
LDL (mmol/L)	2.92 ± 0.80	2.90 ± 0.72	2.97 ± 0.96	3.17 ± 0.63	3.17 ± 0.69	3.59 ± 0.93
Triglycerides ±mmol/L)	1.50 ± 0.70	1.55 ± 0.86	1.51 ± 0.95	1.45 ± 0.63	1.43 ± 0.65	1.45 ± 0.64
Glucose (mmol/L)	6.15 ± 2.38	6.10 ± 2.16	5.83 ± 2.61	5.92 ± 1.18	6.06 ± 1.13	6.22 ± 1.17

Values are mean ± SD.
[a] $p < 0.05$ within-group compared to baseline
[b] $p < 0.05$ between-group change vs CMP (significant between group differences are indicated in bold)

ICE, Individualized combined exercise; CMP, Cardiac maintenance program; SBP_{rest}, resting systolic blood pressure; DBP_{rest}, resting diastolic blood pressure; HR_{rest}, resting heart rate; BMI, body mass index; FFM, fat free mass; HbA1c, Glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein

Table S 4: Leisure time physical activity levels

	ICE			CMP		
Variable	Baseline	Six months	12 months	Baseline	Six months	12 months
Accelerometry						
PAL	1.47 ± 0.18	1.48 ± 0.14	1.41 ± 0.09	1.47 ± 0.22	1.44 ± 0.15	1.48 ± 0.13
Steps per day	8635 ± 2424	**10221 ± 3162**[a,b]	9452 ± 2633	9220 ± 3324	**8382 ± 1950**[b]	8112 ± 2008
IPAQ						
Total activity (MET-min/d)	289 (140,541)	**394 (182,593)**[a,b]	311 (109,513)	350 (239,567)	**271 (229,534)**[b]	320 (80,540)[a]
Vigorous (MET-min/d)	11 (0,20)	**23 (0,240)**[a,b]	13.3 (0,20)	11 (0,80)	**6 (0,160)**[b]	6 (0,80)
Moderate (MET-min/d)	102 (34,261)	111 (69,242)	111 (17,205)	106 (69,209)	102 (63,254)	125 (14,236)
Walking (MET-min/d)	116[c] (70,286)	**184 (80,396)**[a,b]	155 (41,268)	198 (99,346)	**149 (90,368)**[b]	157 (30,284)
Sitting (min/d)	360 (240,495)	**315 (240,420)**[a,b]	320 (230,410)	350 (210,480)	**350 (280,510)**[b]	300 (165,435)
IPAQ PA Category						
Low n (%)	3 (9)	2 (7)	2 (8)	1 (3)	2 (7)	2 (7)
Moderate n (%)	18 (56)	8 (27)	16 (64)	15 (47)	12 (40)	14 (56)
High n (%)	**9 (28)**[b]	**15 (50)**[a,b]	7 (28)	**14 (44)**[b]	**11 (37)**[b]	9 (36)
Average score	**2.2 ± 0.6**[b]	2.4 ± 0.6[a]	**2.2 ± 0.9**[a,b]	**2.5 ± 0.7**[b]	2.4 ± 0.6	**2.0 ± 0.8**[a,b]

Values are mean ± SD, median (IQR) or number (%)
[a] $p < 0.05$ within-group compared to baseline
[b] $p < 0.05$ between-group change vs CMP (significant between group differences are indicated in bold)

PAL = Physical activity level (physical energy expenditure (kcal) / resting metabolic rate (kcal)), IPAQ = International Physical Activity Questionnaire, IQR = Interquartile Range, MET = Metabolic Equivalent Task

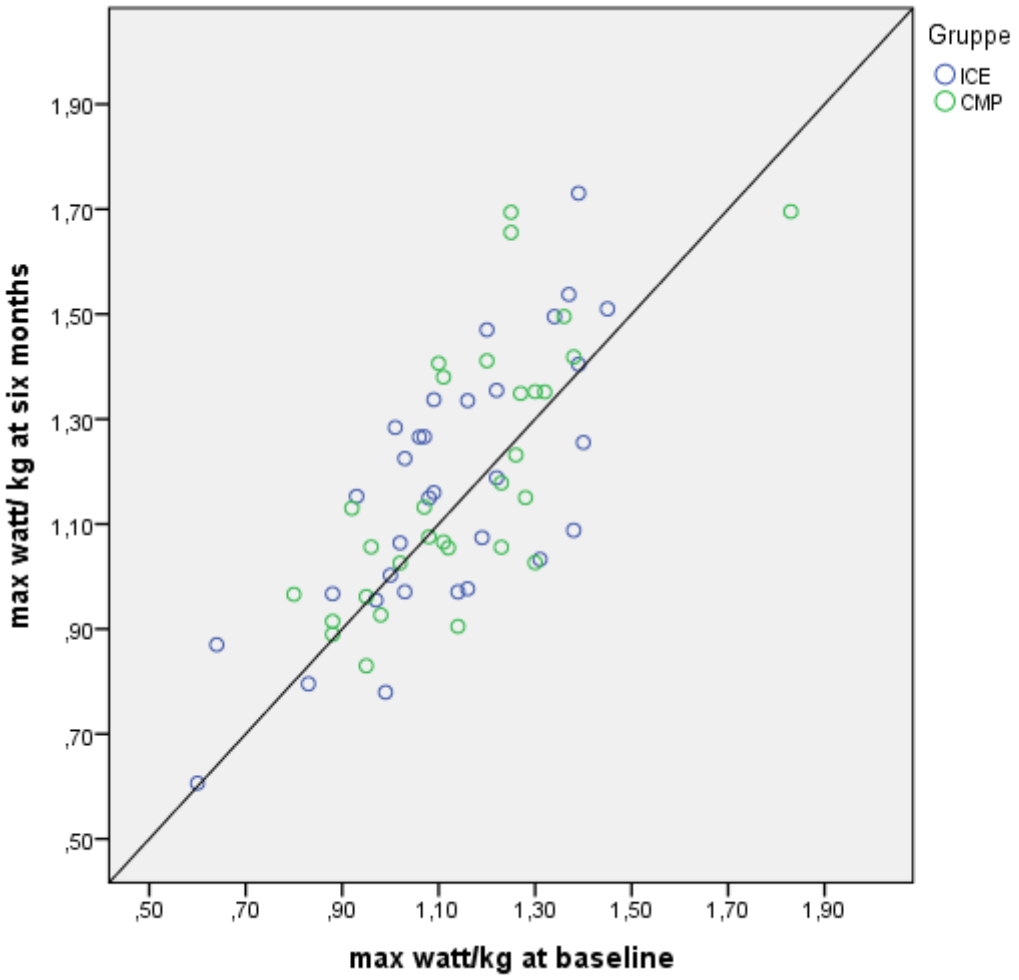
Table S 5: Health related quality of life

	ICE			CMP		
Variable	Baseline	Six months	12 months	Baseline	Six months	12 months
SF-36						
Physical functioning	71.8 ± 16.5	75.8 ± 17.3	73.5 ± 19.4	71.6 ± 20.7	70.2 ± 17.3	69.4 ± 19.0
Social functioning	85.6 ± 20.3	89.8 ± 19.1	89.4 ±16.9	81.1 ± 21.9	81.4 ± 19.0	79.6 ± 23.6
Physical role limit	59.1 ± 36.4	68.2 ± 39.2	52.2 ± 40.5	65.2 ± 38.0	69.7 ± 35.8	55.4 ± 39.1
Emotional role limit	79.8 ± 33.3	85.9 ± 30.1	70.6 ± 43.9	79.3 ± 30.3	78.8 ± 30.7	71.0 ± 40.6
Bodily Pain	78.0 ± 25.1	**81.0 ± 23.8[b]**	69.2 ± 32.4	73.3 ± 25.5	**68.9 ± 26.3[b]**	69.2 ± 32.4
Mental health	77.4 ± 17.5	76.9 ± 15.7	**83.1 ± 12.2[a,b]**	71.6 ± 17.5	74.5 ± 16.1	**73.4 ± 17.0[b]**
Vitality	**60.9 ± 21.0[b]**	**63.9 ± 16.1[b]**	60.0 ± 19.1	**52.7 ± 15.6[b]**	**52.6 ± 15.7[b]**	60.0 ± 19.1
General health	56.7 ± 18.1	56.8 ± 18.3	57.3 ± 21.8	57.0 ± 16.8	56.7 ± 15.2	59.1 ± 16.5
Physical Total Score	43.2 ± 8.7	44.7 ± 9.4	42.2 ± 9.1	44.9 ± 9.6	43.7 ± 8.5	42.2 ± 9.1
Psychological Total Score	52.8 ± 10.6	53.7 ± 8.5	54.0 ± 8.6	50.6 ± 9.3	51.5 ± 8.6	54.0 ± 8.6
GMS						
Negative affect	13.3 ± 8.2	**12.6 ± 7.6[b]**	**12.4 ± 8.4[a,b]**	15.5 ± 7.1	**16.5 ± 8.2[b]**	**15.8 ± 6.9[b]**
Positive affect	27.0 ± 8.3	**29.4 ± 7.1[b]**	26.9 ± 6.0	24.5 ± 6.9	**24.4 ± 6.3[b]**	24.3 ± 6.5
MacNew						
Emotional	5.6 ± 1.1	**5.8 ± 0.9[b]**	**6.1 ± 0.7[b]**	5.3 ± 1.2	**5.3 ± 1.1[b]**	**5.4 ± 0.9[b]**
Physical	5.4 ± 1.0	**5.7 ± 0.9[a,b]**	5.8 ± 0.8	5.4 ± 1.0	**5.4 ± 1.1[b]**	5.5 ± 1.0
Social	5.7 ± 1.1	**6.0 ± 0.9[a,b]**	**6.3 ± 0.7[a,b]**	5.4 ± 1.1	**5.3 ± 1.0[b]**	**5.5 ± 0.9[b]**
Total	5.5 ± 1.1	**5.8 ± 0.9[b]**	6.0 ± 0.7	5.4 ± 1.0	**5.3 ± 1.0[b]**	5.5 ± 0.8

Values are mean ± SD
[a] $p < 0.05$ within-group compared to baseline
[b] $p < 0.05$ between-group change vs CMP (significant between group differences are indicated in bold)
SF-36 = Short Form 36, GMS = Global Mood Scale, MacNew = MacNew Heart Disease Quality of Life Instrument

Supplemental file D: Graphical representation of relative maximal workload at baseline and at six months for all patients, identified by group assigment

Figure S 1: maximal relative workload in watts per kilogram body weight per patient at baseline and six months.



Supplemental file E: Comparison of the Intention-to-treat and On-treatment samples on the primary endpoint.

No statistically significant differences were observed between the imputed (ITT) data set and the data set including only the patients who completed the study (OT).

Table S 6: Statistical analyses of the primary endpoint on the ITT and OT samples separately. (a) illustrates the results of independent sample t-testing on the maximum relative workload on the ITT sample, and (b) is the same analysis on the OT sample.

(a) Intention-to-treat analysis of the primary endpoint, maximum relative workload

Group statistics

	Group	N	Mean	Standard deviation	SEM
Change in maximum relative workload in watt/ kilogram body weight	Intervention	35	,0564	,17568	,02957
	Control	35	,0487	,17763	,03562

	Levene-Test for similarity of the variance		T-Test for similarity of the means						
								95% Confidence interval of the difference	
	F	Sig.	T	df	Sig. (2-sided)	Mean difference	Standard error of the difference	Lower	Upper
Change in maximum Variance is the same	,154	,517	,228	68	,874	,01044	,04657	-,06663	,09911

relative workload in watt/ kilogram body weight	Variance is not the same			,228	67.569	,874	,01043	,04772	-,06969	,11294

(b) On-treatment analysis of the primary endpoint, maximum relative workload

Group statistics

	Group	N	Mean	Standard deviation	SEM
Change in maximum relative workload in watt/ kilogram body weight	Intervention	32	,0511	,17000	,03005
	Control	30	,0418	,17211	,03142

		Levene-Test for similarity of the variance		T-Test for similarity of the means						
		F	Sig.	T	df	Sig. (2-sided)	Mean difference	Standard error of the difference	95% Confidence interval of the difference	
									Lower	Obere
Change in maximum relative workload in watt/ kilogram body weight	Varianzen sind gleich	,160	,690	,213	60	,832	,00925	,04346	-,07769	,09619
	Varianzen sind nicht gleich			,213	59,637	,832	,00925	,04348	-,07773	,09624

Supplemental file F: The effect of baseline differences in statin use

The effect of differences in baseline statin between the groups resulted in a difference of 0.002 in the regression coefficient (B) for the group effect on change in relative maximal workload between individualized combined exercise and cardiac maintenance

Table S 7: Results of statistical regression analyses

(a) the group effect on maximal workload without controlling for the effect of between-group differences in baseline statin use and (b) depicts the group effect on maximal workload including the effect of between-group differences in baseline statin use.

(a)

Coefficients[a]

Model		Non-standarized coefficients		Standarized coefficients	T	Sig.
		Regression coefficient B	Standard error	Beta		
1	(Constant)	1,137	,099		11,502	,000
	Group	,028	,063	,057	,444	,659

a. Dependant Variable: Change in maximum relative workload in watt/ kilogram body weight

(b)

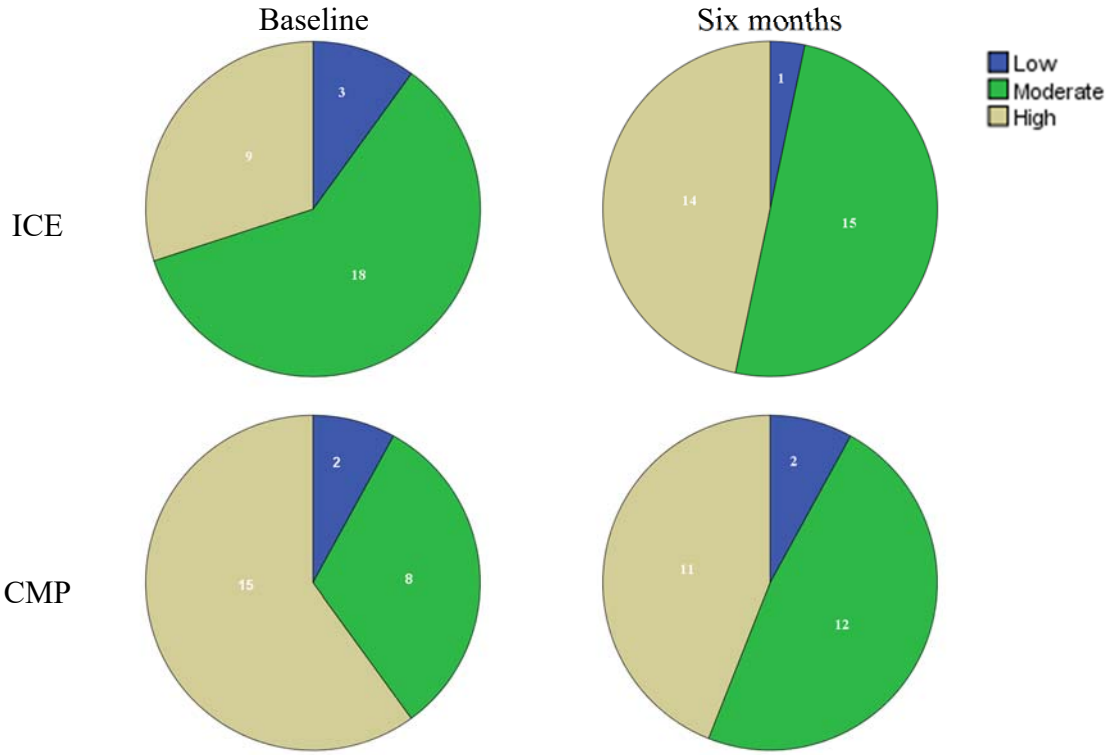
Coefficients[a]

Model		Non-standarized coefficients		Standarized coefficients	T	Sig.
		Regression coefficient B	Standard error	Beta		
1	(Constant)	1,146	,134		8,535	,000
	Group	,026	,068	,052	,379	,706
	Medication (Statin use)	-,007	,076	-,014	-,098	,922

a. Dependant Variable: Change in maximum relative workload in watt/ kilogram body weight

Supplemental file G: Schematic of change in fitness categories from baseline to six months. Although there were baseline differences, the patients in individualized combined exercise did increase physical activity level significantly resulting in comparable physical activity levels at the moderate (between 600- 3000 MET-min per week) and high (over 1500 MET-min per week of vigorous physical activity or over 3000 MET-min per week of moderate physical activity) levels and significantly less patients in the "low" category (below 600 MET-min per week)

Figure S 2: Change in leisure time physical activity levels from baseline to six months



Supplemental file H: Statistical analysis of comparisons of leisure time physical activity measured by questionnaire and accelerometry

Table S 8: Comparison of questionnaire and accelerometer based measurements of leisure time physical activity

Descriptive statistics for logarithms for differences between IPAQ and accelerometry in measurement of different physical activity levels are presented in (a) and one-sample t-tests are presented in (b)

(a)

	N	Mean	SD	SEM
Baseline				
Total PA	41	,7699	,88693	,13851
Moderate PA	34	1,6645	,85655	,14690
Vigorous PA	5	-3,6163	,89757	,40141
Low PA	40	,6268	,85980	,13595
Sedentary time	41	2,3782	,48490	,07573
Six months				
Total PA	53	,6306	,87781	,12058
Moderate PA	47	-1,5028	1,98237	,28916
Vigorous PA	8	-3,9901	1,69242	,59836
Low PA	50	,4227	,89977	,12725
Sedentary time	53	2,3575	,50511	,06938

(b)

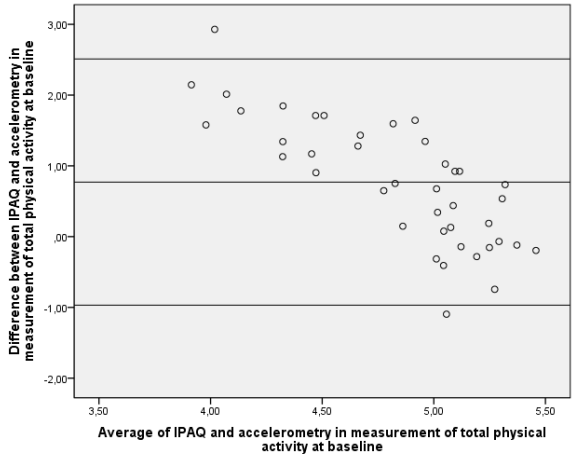
	Testwert = 0					
					95% Konfidenzintervall der Differenz	
	T	df	Sig. (2-seitig)	Mittlere Differenz	Untere	Obere
Baseline						
Total PA	5,558	40	,000	,76989	,4899	1,0498
Moderate PA	11,331	33	,000	1,66450	1,3656	1,9634
Vigorous PA	-9,009	4	,001	-3,61632	-4,7308	-2,5018
Low PA	4,610	39	,000	,62678	,3518	,9018
Sedentary time	31,405	40	,000	2,37825	2,2252	2,5313
Six months						

Total PA	5,230	52	,000	,63064	,3887	,8726
Moderate PA	-5,197	46	,000	-1,50277	-2,0848	-,9207
Vigorous PA	-6,668	7	,000	-3,99006	-5,4050	-2,5752
Low PA	3,322	49	,002	,42268	,1670	,6784
Sedentary time	33,979	52	,000	2,35751	2,2183	2,4967

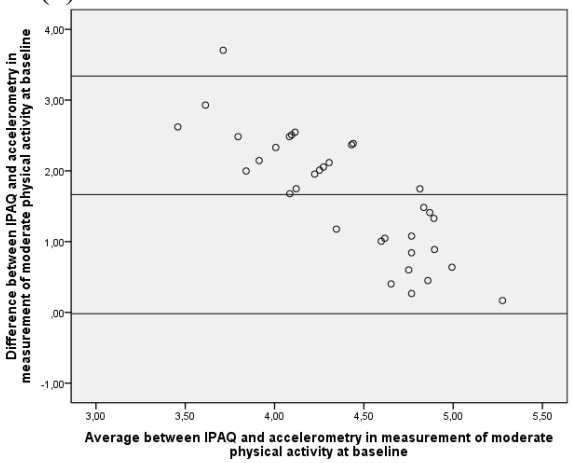
Figure S 3: Bland-Altman plots comparing the IPAQ questionnaire and accelerometry for agreement in measuring different intensities of physical activity and sedentary time.

(a) baseline total PA, (b) baseline moderate intensity PA, (c) baseline vigorous PA, (d) baseline low intensity PA, (e) baseline sedentary time, (f) six-month total PA, (g) six-month moderate intensity PA, (h) six-month vigorous PA, (i) six-month low intensity PA, (j) six-month sedentary time

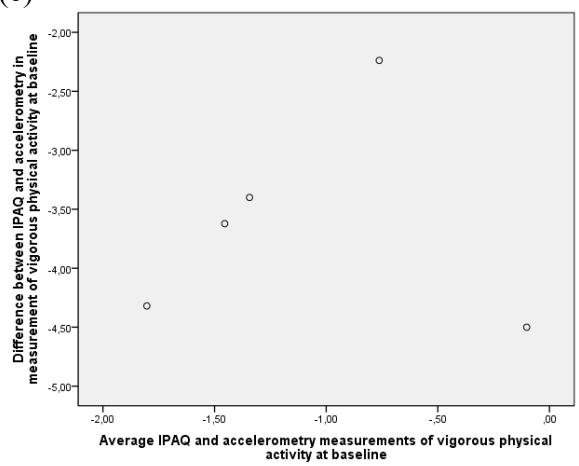
(a)



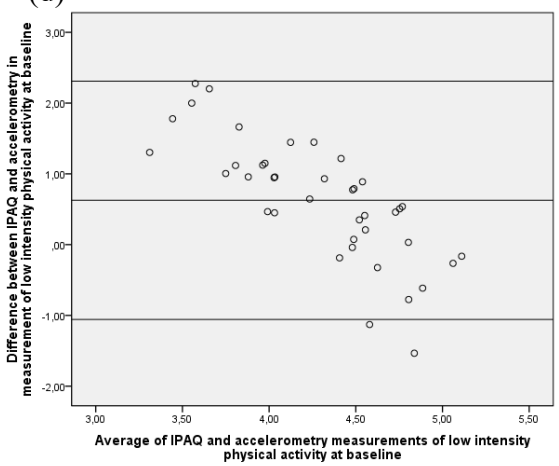
(b)



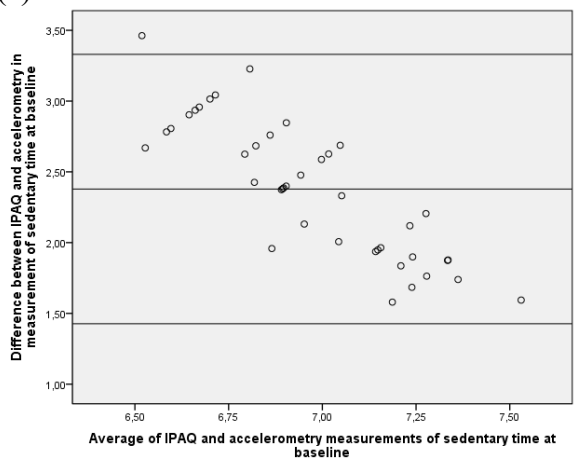
(c)



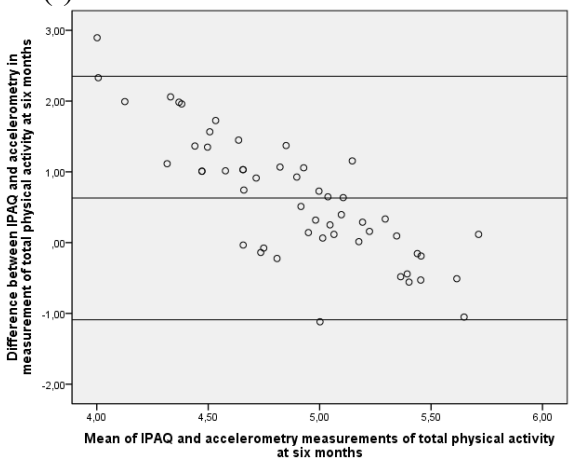
(d)



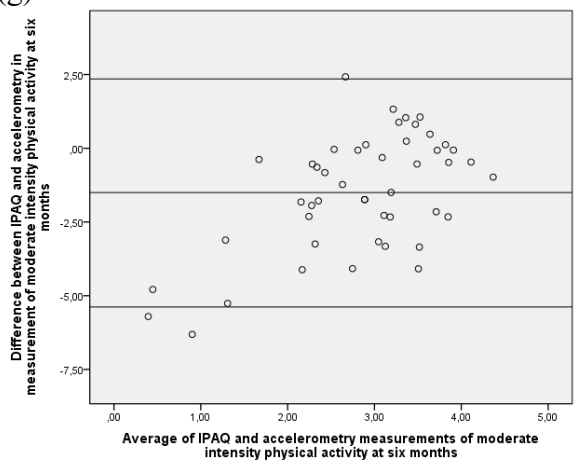
(e)


Difference between IPAQ and accelerometry in measurement of sedentary time at baseline
3,50
3,00
2,50
2,00
1,50
1,00
6,50
6,75
7,00
7,25
7,50
Average of IPAQ and accelerometry measurements of sedentary time at baseline

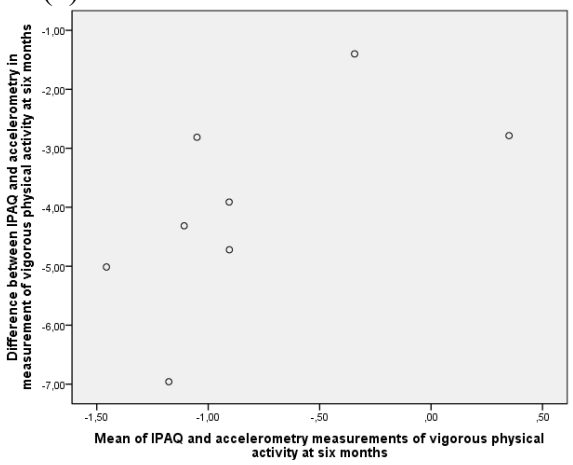
(f)


Difference between IPAQ and accelerometry in measurement of total physical activity at six months
3,00
2,00
1,00
,00
-1,00
-2,00
4,00
4,50
5,00
5,50
6,00
Mean of IPAQ and accelerometry measurements of total physical activity at six months

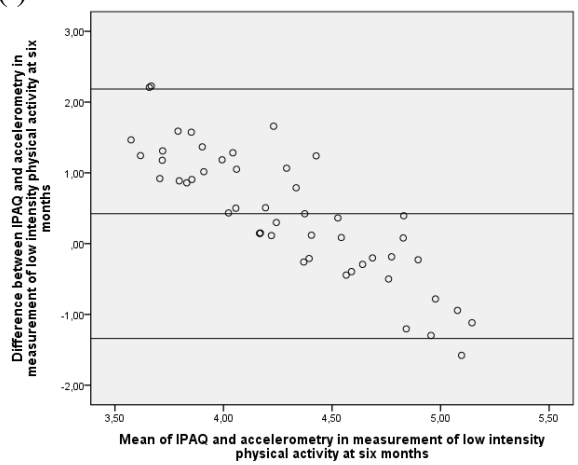
(g)


Difference between IPAQ and accelerometry in measurement of moderate intensity physical activity at six months
2,50
,00
-2,50
-5,00
-7,50
,00
1,00
2,00
3,00
4,00
5,00
Average of IPAQ and accelerometry measurements of moderate intensity physical activity at six months

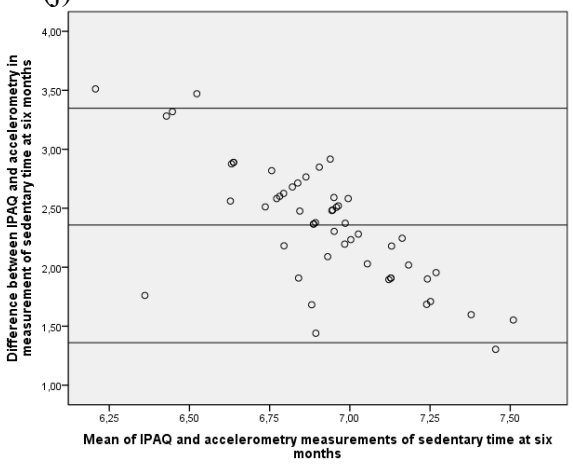
(h)


Difference between IPAQ and accelerometry in measurement of vigorous physical activity at six months
-1,00
-2,00
-3,00
-4,00
-5,00
-6,00
-7,00
-1,50
-1,00
-,50
,00
,50
Mean of IPAQ and accelerometry measurements of vigorous physical activity at six months

(i)


Difference between IPAQ and accelerometry in measurement of low intensity physical activity at six months
3,00
2,00
1,00
,00
-1,00
-2,00
3,50
4,00
4,50
5,00
5,50
Mean of IPAQ and accelerometry in measurement of low intensity physical activity at six months

(j)


Difference between IPAQ and accelerometry in measurement of sedentary time at six months
4,00
3,50
3,00
2,50
2,00
1,50
1,00
6,25
6,50
6,75
7,00
7,25
7,50
Mean of IPAQ and accelerometry measurements of sedentary time at six months

Appendix 2: Approval forms and other study materials

Supplemental data file I: German version of the International Physical Activity Questionnaire

Supplemental data file J: German version of the Short-Form 36

Supplemental data file K: German version of the Global Mood Scale

Supplemental data file L: German version of the MacNew Questionnaire

Supplemental data file M: One –repetition maximum protocol

Supplemental data file N: Declaration of Helsinki

Supplemental data file O: Approval from Klinikum rechts der Isar ethics committee (in German)

Supplemental data file P: DOPPELHERZ patient information informed consent (in German)

Supplemental file I: German version of the International Physical Activity Questionnaire

IPAQ Telefon Kurzversion der letzten 7 Tage

Vorlesen: Ich werde Sie nun befragen zu der Zeit, in der Sie körperlich aktiv waren in den vergangenen 7 Tagen. Bitte beantworten Sie jede Frage, auch wenn Sie sich selbst nicht als aktive Person einschätzen. Denken Sie an die Aktivitäten, die Sie bei der Arbeit, als Teil Ihrer Haus- und Gartenarbeit durchführen, um von einem Ort zum anderen zu kommen und die Sie zur Erholung, zum Ausgleich oder als Sport durchführen.

Vorlesen: Denken Sie zunächst an alle schweren Tätigkeiten in den letzten 7 Tagen, die mit harter körperlicher Anstrengung einhergingen. Schwere Tätigkeiten führen dazu, dass Sie viel schwerer atmen als normal und beinhaltet schweres Heben, Graben, Aerobic oder schnelles Fahrradfahren. Denken Sie nur an die körperlichen Aktivitäten, die Sie mindestens 10 Minuten am Stück durchgeführt haben.

1. In den letzten 7 Tagen, an wie viel Tagen haben Sie schwere körperliche Aktivitäten durchgeführt?

_____ Tage pro Woche

Weiß nicht / Bin nicht sicher

Keine Antwort

[Klarstellung durch den Interviewer: Denken Sie nur an die körperlichen Aktivitäten, die Sie für mindestens 10 Minuten am Stück durchgeführt haben.]

[Notiz für den Interviewer: Wenn der Befragte antwortet Null / Weiß nicht / nicht antwortet, springe zu Frage 3]

2. Wie viel Zeit verbringen Sie an diesen Tagen gewöhnlich mit schwerer körperlicher Aktivität?

__ __ Stunden pro Tag

__ __ __ Minuten pro Tag

Weiß nicht / Bin nicht sicher

Keine Antwort

[Klarstellung durch den Interviewer: Denken Sie nur an die körperlichen Aktivitäten, die Sie für mindestens 10 Minuten am Stück durchgeführt haben.]

[Prüfung durch den Interviewer: Gesucht ist die mittlere Zeit an einem dieser Tage, die mit schwerer körperlicher Aktivität verbracht wird. Wenn der Befragte nicht antworten kann weil die Dauer der körperlichen Aktivität von Tag zu Tag stark schwankt, frage:

3. „Wie viel Zeit haben Sie insgesamt in den letzten 7 Tagen mit schweren körperlichen Aktivitäten verbracht?“

__ __ Stunden pro Tag

__ __ __ Minuten pro Tag

Weiß nicht / Bin nicht sicher

Keine Antwort

Vorlesen: Denken Sie jetzt an Aktivitäten in den letzten 7 Tagen, die mit moderater körperlicher Anstrengung einhergingen. Moderate körperliche Anstrengung führt zu etwas stärkerer Atmung als normal und beinhaltet das Tragen leichter Lasten, Fahrrad Fahren bei normaler Geschwindigkeit oder Tennis Doppel. Gehen gehört nicht dazu. Denken Sie wieder nur an die körperlichen Aktivitäten, die Sie mindestens 10 Minuten am Stück durchgeführt haben.

4. In den letzten 7 Tagen, an wie viel Tagen haben Sie moderate körperliche Aktivitäten durchgeführt?

_____ Tage pro Woche

Weiß nicht / Bin nicht sicher

Keine Antwort

[Klarstellung durch den Interviewer: Denken Sie nur an die körperlichen Aktivitäten, die Sie für mindestens 10 Minuten am Stück durchgeführt haben.]

[Notiz für den Interviewer: Wenn der Befragte antwortet Null / Weiß nicht / nicht antwortet, springe zu Frage 5]

Wie viel Zeit verbringen Sie an diesen Tagen gewöhnlich mit moderater körperlicher Aktivität?

__ __ Stunden pro Tag

__ __ __ Minuten pro Tag

Weiß nicht / Bin nicht sicher

Keine Antwort

[Klarstellung durch den Interviewer: Denken Sie nur an die körperlichen Aktivitäten, die Sie für mindestens 10 Minuten am Stück durchgeführt haben.]

[Prüfung durch den Interviewer: Gesucht ist die mittlere Zeit an einem dieser Tage, die mit moderater körperlicher Aktivität verbracht wird. Wenn der Befragte nicht antworten kann weil die Dauer der körperlichen Aktivität von Tag zu Tag stark schwankt, frage:

5. „Wie viel Zeit haben Sie insgesamt in den letzten 7 Tagen mit moderaten körperlichen Aktivitäten verbracht?“

__ __ Stunden pro Tag

__ __ __ Minuten pro Tag

Weiß nicht / Bin nicht sicher

Keine Antwort

Vorlesen: Denken Sie jetzt an die Zeit, die Sie mit Gehen verbracht haben in den letzten 7 Tagen. Dies beinhaltet Gehen bei der Arbeit, zu Hause, um von einem Ort zum anderen zu kommen und jedes andere Gehen zur Erholung, zum Ausgleich, als Sport oder Entspannung.

6. In den letzten 7 Tagen, an wie viel Tagen sind Sie mindestens 10 Minuten am Stück gegangen?

_____ Tage pro Woche

Weiß nicht / Bin nicht sicher

Keine Antwort

[Klarstellung durch den Interviewer: Denken Sie nur Gehen, das Sie für mindestens 10 Minuten am Stück durchgeführt haben.]

[Notiz für den Interviewer: Wenn der Befragte antwortet Null / Weiß nicht / nicht antwortet, springe zu Frage 7]

Wie viel Zeit verbringen Sie an diesen Tagen gewöhnlich mit Gehen?

__ __ Stunden pro Tag

__ __ __ Minuten pro Tag

Weiß nicht / Bin nicht sicher

Keine Antwort

[Prüfung durch den Interviewer: Gesucht ist die mittlere Zeit an einem dieser Tage, die mit Gehen verbracht wird. Wenn der Befragte nicht antworten kann weil die Dauer des Gehens von Tag zu Tag stark schwankt, frage:

7. „Wie viel Zeit haben Sie insgesamt in den letzten 7 Tagen mit Gehen verbracht?“

__ __ Stunden pro Tag

__ __ __ Minuten pro Tag

Weiß nicht / Bin nicht sicher

Keine Antwort

Vorlesen: Denken Sie nun an die Zeit, die Sie an Wochentagen gesessen haben. Berücksichtigen Sie die Zeit, die Sie bei der Arbeit, zu Hause, bei Lehrgängen oder zur Entspannung verbracht haben. Dies beinhaltet Zeit, die Sie vor dem Schreibtisch, beim Besuch von Freunden, beim Lesen oder Fernsehen verbracht haben.

8. In den letzten 7 Tagen, wie viel Zeit verbringen Sie gewöhnlich sitzend an einem Wochentag?

__ __ Stunden pro Wochentag

__ __ __ Minuten pro Wochentag

Weiß nicht / Bin nicht sicher

Keine Antwort

[Klarstellung durch den Interviewer: Berücksichtigen Sie auch die Zeit, die Sie liegend (wach) verbracht haben.]

[Prüfung durch den Interviewer: Gesucht ist die mittlere Zeit pro Tag, die sitzend verbracht wird. Wenn der Befragte nicht antworten kann weil die Dauer des Sitzens von Tag zu Tag stark schwankt, frage:
„Wie viel Zeit haben Sie insgesamt am letzten Mittwoch sitzend verbracht?“

__ __ Stunden am Mittwoch

__ __ __ Minuten am Mittwoch

Weiß nicht / Bin nicht sicher

Keine Antwort

Supplemental file K: German version of the Short-Form 36

Rand#/Group: Datum: Visite#:

SF-36

LEBENSQ

In diesem Fragebogen geht es um Ihre Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

1. Wie würden Sie Ihren Gesundheitszustand im allgemeinen beschreiben ? Bitte kreuzen Sie nur eine Antwort an.

   - ausgezeichnet
   - sehr gut
   - gut
   - weniger gut
   - schlecht

2. Im **Vergleich zum vergangenen Jahr**, wie würden Sie Ihren **derzeitigen** Gesundheitszustand beschreiben? Bitte kreuzen Sie nur eine Antwort an.

   - derzeit viel besser als vor einem Jahr
   - derzeit etwas besser als vor einem Jahr
   - etwa so wie vor einem Jahr
   - derzeit etwas schlechter als vor einem Jahr
   - derzeit viel schlechter als vor einem Jahr

3. Im folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. **Sind Sie durch Ihren derzeitigen Gesundheitszustand** bei diesen Tätigkeiten **eingeschränkt**? Wenn ja, wie stark? Bitte kreuzen Sie in jeder Zeile nur eine Antwort an.

	ja, stark eingeschränkt	ja, etwas eingeschränkt	nein, gar nicht eingeschränkt
Anstrengende Tätigkeiten, z.B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben	○	○	○
Mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, Staubsaugen, Kegeln, Golf spielen	○	○	○
Einkaufstaschen heben oder tragen	○	○	○
Mehrere Treppenabsätze steigen	○	○	○
Einen Treppenabsatz steigen	○	○	○
Sich beugen, knien, bücken	○	○	○
Mehr als 1 Kilometer zu Fuß gehen	○	○	○
Mehrere Straßenkreuzungen weit zu Fuß gehen	○	○	○
Eine Straßenkreuzung weit zu Fuß gehen	○	○	○
Sich baden oder anziehen	○	○	○

DOPPELHERZ-Studie

Supplemental file L: German version of the Global Mood Scale

Global Mood Scale

Name: ..... **Geschlecht:** ..... **Alter:** ..... **Datum:** .....

Nachfolgend finden Sie eine Reihe von Wörtern, die unterschiedliche Gefühle und Stimmungen beschreiben. Bitte lesen Sie jedes Wort aufmerksam und kreisen dann die für Sie jeweils zutreffende Zahl hinter dem Wort ein. Geben Sie an, in welchem Ausmaß Sie sich in der letzten Zeit entsprechend gefühlt haben. Bitte verwenden Sie die folgende Skala für Ihre Antworten:

0 = Trifft überhaupt nicht zu; 1 = Trifft eher nicht zu; 2 = Unentschieden; 3 = Trifft eher zu; 4 = Trifft voll und ganz zu

1	Erschöpft	0	1	2	3	4
2	Aktiv	0	1	2	3	4
3	Ausgelaugt	0	1	2	3	4
4	Dynamisch	0	1	2	3	4
5	Fröhlich	0	1	2	3	4
6	Hilflos	0	1	2	3	4
7	Arbeitsam	0	1	2	3	4
8	Kraftlos	0	1	2	3	4
9	Lebhaft	0	1	2	3	4
10	Körperlich schwach	0	1	2	3	4
11	Teilnahmslos	0	1	2	3	4
12	Müde	0	1	2	3	4
13	Unternehmungslustig	0	1	2	3	4
14	Entspannt	0	1	2	3	4
15	Unsicher	0	1	2	3	4
16	Kontaktfreudig	0	1	2	3	4
17	Heiter	0	1	2	3	4
18	Ermüdet	0	1	2	3	4
19	Geschwächt	0	1	2	3	4
20	Selbstbewusst	0	1	2	3	4

Supplemental file M: German version of the MacNew Questionnaire

macnew.org
HEALTH-RELATED QUALITY OF LIFE INSTRUMENT

Wir würden Ihnen nun gerne einige Fragen stellen, wie Sie sich WÄHREND DER LETZTEN 2 WOCHEN gefühlt haben.

Bitte kreuzen Sie jenes Feld ❑ an, welches zu Ihrer Antwort passt.

1. Wie oft haben sie sich in den letzten 2 Wochen frustriert, ungeduldig oder ungehalten gefühlt?

❑	1	DIE GANZE ZEIT
❑	2	DIE MEISTE ZEIT
❑	3	EINEN GROSSTEIL DER ZEIT
❑	4	MANCHMAL
❑	5	SELTEN
❑	6	KAUM
	7	NIE

2. Wie oft haben Sie sich in den letzten 2 Wochen wertlos oder unzulänglich gefühlt?

❑	1	DIE GANZE ZEIT
❑	2	DIE MEISTE ZEIT
❑	3	EINEN GROSSTEIL DER ZEIT
❑	4	MANCHMAL
❑	5	SELTEN
❑	6	KAUM
	7	NIE

3. Wie oft haben Sie sich in den letzten 2 Wochen sehr zuversichtlich und sicher gefühlt, mit Ihrem Herzproblem umgehen zu können?

☐	1	NIE
☐	2	WENIGE MALE
☐	3	MANCHMAL
☐	4	ZIEMLICH OFT
☐	5	MEISTENS
☐	6	FAST IMMER
☐	7	IMMER

4. Wie oft haben Sie sich im Allgemeinen in den letzen 2 Wochen entmutigt oder deprimiert gefühlt?

1	DIE GANZE ZEIT
2	DIE MEISTE ZEIT
3	EINEN GROSSTEIL DER ZEIT
4	MANCHMAL
5	SELTEN
6	KAUM
7	NIE

5. Wie oft in den vergangenen 2 Wochen fühlten Sie sich entspannt und ohne Druck?

☐	1	NIE
☐	2	WENIGE MALE
☐	3	MANCHMAL
☐	4	ZIEMLICH OFT
☐	5	MEISTENS
☐	6	FAST IMMER
☐	7	IMMER

6. Wie oft in den letzten 2 Wochen fühlten Sie sich erschöpft oder mit wenig Energie?

❑ 1 DIE GANZE ZEIT
❑ 2 DIE MEISTE ZEIT
❑ 3 EINEN GROSSTEIL DER ZEIT
❑ 4 MANCHMAL
❑ 5 SELTEN
❑ 6 KAUM
❑ 7 NIE

7. Wie glücklich und zufrieden sind Sie in den letzten 2 Wochen mit Ihrem persönlichen Leben gewesen?

❑ 1 SEHR UNZUFRIEDEN; DIE MEISTE ZEIT UNGLÜCKLICH
❑ 2 IM ALLGEMEINEN UNZUFRIEDEN, UNGLÜCKLICH
❑ 3 IRGENDWIE UNZUFRIEDEN, UNGLÜCKLICH
❑ 4 IM ALLGEMEINEN ZUFRIEDEN
❑ 5 DIE MEISTE ZEIT GLÜCKLICH
❑ 6 DIE MEISTE ZEIT SEHR GLÜCKLICH
❑ 7 ABSOLUT GLÜCKLICH, HÄTTE NICHT ZUFRIEDENER SEIN KÖNNEN

8. Wie oft haben Sie sich in den letzten 2 Wochen rastlos gefühlt oder so, als ob Sie Schwierigkeiten hätten, ruhig zu werden?

1 DIE GANZE ZEIT
2 DIE MEISTE ZEIT
3 EINEN GROSSTEIL DER ZEIT
4 MANCHMAL
5 SELTEN
6 KAUM
7 NIE

9. Wie stark war Ihre Atemnot in den letzten 2 Wochen während Ihrer alltäglichen Aktivitäten?

- ☐ 1 EXTREME ATEMNOT
- ☐ 2 SEHR HOHE ATEMNOT
- ☐ 3 ZIEMLICHE ATEMNOT
- ☐ 4 MITTELMÄSSIGE ATEMNOT
- ☐ 5 ETWAS ATEMNOT
- ☐ 6 WENIG ATEMNOT
- 7 KEINE ATEMNOT

10. Wie oft in den letzten 2 Wochen haben Sie sich zum Weinen gefühlt?

- ☐ 1 DIE GANZE ZEIT
- ☐ 2 DIE MEISTE ZEIT
- ☐ 3 EINEN GROSSTEIL DER ZEIT
- ☐ 4 MANCHMAL
- ☐ 5 SELTEN
- ☐ 6 KAUM
- 7 NIE

11. Wie oft haben Sie sich in den letzten 2 Wochen abhängiger gefühlt als vor Ihrem Herzproblem?

- ☐ 1 DIE GANZE ZEIT
- ☐ 2 DIE MEISTE ZEIT
- ☐ 3 EINEN GROSSTEIL DER ZEIT
- ☐ 4 MANCHMAL
- ☐ 5 SELTEN
- ☐ 6 KAUM
- 7 NIE

12. Wie oft haben Sie sich in den letzten 2 Wochen außerstande gefühlt, Ihren üblichen gesellschaftlichen Aktivitäten oder denen mit Ihrer Familie nachzukommen?

1 DIE GANZE ZEIT
2 DIE MEISTE ZEIT
3 EINEN GROSSTEIL DER ZEIT
4 MANCHMAL
5 SELTEN
6 KAUM
7 NIE

13. Wie oft haben Sie sich in den letzten 2 Wochen so gefühlt, als ob andere nicht mehr dasselbe Vertrauen in Sie haben wie vor Ihren Herzproblemen?

❑ 1 DIE GANZE ZEIT
❑ 2 DIE MEISTE ZEIT
❑ 3 EINEN GROSSTEIL DER ZEIT
❑ 4 MANCHMAL
❑ 5 SELTEN
❑ 6 KAUM
7 NIE

14. Wie oft haben Sie in den letzten 2 Wochen Brustschmerzen bei alltäglichen Aktivitäten verspürt?

❑ 1 DIE GANZE ZEIT
❑ 2 DIE MEISTE ZEIT
❑ 3 EINEN GROSSTEIL DER ZEIT
❑ 4 MANCHMAL
❑ 5 SELTEN
❑ 6 KAUM
7 NIE

15. Wie oft haben Sie sich in den letzten 2 Wochen unsicher gegenüber sich selbst gefühlt oder ein Mangel an Selbstbewusstsein verspürt?

1 DIE GANZE ZEIT
2 DIE MEISTE ZEIT
3 EINEN GROSSTEIL DER ZEIT
4 MANCHMAL
5 SELTEN
6 KAUM
7 NIE

16. Wie oft waren Sie in den letzten 2 Wochen wegen schmerzenden oder müden Beinen beunruhigt?

1 DIE GANZE ZEIT
2 DIE MEISTE ZEIT
3 EINEN GROSSTEIL DER ZEIT
4 MANCHMAL
5 SELTEN
6 KAUM
7 NIE

17. Wie stark waren Sie in den letzten 2 Wochen wegen Ihres Herzproblems beim Sport oder beim körperlichen Training eingeschränkt?

1 SEHR STARK EINGESCHRÄNKT
2 STARK EINGESCHRÄNKT
3 ZIEMLICH EINGESCRÄNKT
4 MÄSSIG EINGESCHRÄNKT
5 IRGENDWIE EINGESCHRÄNKT
6 EIN WENIG EINGESCHRÄNKT
7 ABSOLUT NICHT EINGESCHRÄNKT

18. Wie oft haben Sie sich in den letzten 2 Wochen besorgt oder verängstigt gefühlt?

- ❑ 1 DIE GANZE ZEIT
- ❑ 2 DIE MEISTE ZEIT
- ❑ 3 EINEN GROSSTEIL DER ZEIT
- ❑ 4 MANCHMAL
- ❑ 5 SELTEN
- ❑ 6 KAUM
- ❑ 7 NIE

19. Wie oft haben Sie sich in den letzten 2 Wochen schwindlig oder benommen gefühlt?

- ❑ 1 DIE GANZE ZEIT
- ❑ 2 DIE MEISTE ZEIT
- ❑ 3 EINEN GROSSTEIL DER ZEIT
- ❑ 4 MANCHMAL
- ❑ 5 SELTEN
- ❑ 6 KAUM
- ❑ 7 NIE

20. Wie stark haben Sie sich in den letzten 2 Wochen wegen Ihres Herzproblems im allgemeinen eingeschränkt oder reduziert gefühlt?

1 SEHR STARK EINGESCHRÄNKT
2 STARK EINGESCHRÄNKT
3 ZIEMLICH EINGESCRÄNKT
4 MÄSSIG EINGESCHRÄNKT
5 IRGENDWIE EINGESCHRÄNKT
6 EIN WENIG EINGESCHRÄNKT
7 ABSOLUT NICHT EINGESCHRÄNKT

21. Wie oft haben Sie sich in den letzten 2 Wochen unsicher darüber gefühlt, wieviel Gymnastik oder körperliche Aktivitäten Sie machen sollten?

- ☐ 1 DIE GANZE ZEIT
- ☐ 2 DIE MEISTE ZEIT
- ☐ 3 EINEN GROSSTEIL DER ZEIT
- ☐ 4 MANCHMAL
- ☐ 5 SELTEN
- ☐ 6 KAUM
- ☐ 7 NIE

22. Wie oft haben Sie in den letzten 2 Wochen Ihre Familie als zu besorgt und zu beschützend empfunden?

- ☐ 1 DIE GANZE ZEIT
- ☐ 2 DIE MEISTE ZEIT
- ☐ 3 EINEN GROSSTEIL DER ZEIT
- ☐ 4 MANCHMAL
- ☐ 5 SELTEN
- ☐ 6 KAUM
- ☐ 7 NIE

23. Wie oft in den letzten 2 Wochen fühlten Sie sich, als ob Sie eine Last für andere wären?

- ☐ 1 DIE GANZE ZEIT
- ☐ 2 DIE MEISTE ZEIT
- ☐ 3 EINEN GROSSTEIL DER ZEIT
- ☐ 4 MANCHMAL
- ☐ 5 SELTEN
- ☐ 6 KAUM
- ☐ 7 NIE

24. Wie oft haben Sie sich in den letzten 2 Wochen wegen Ihres Herzproblems von Aktivitäten mit anderen Leuten ausgeschlossen gefühlt?

1 DIE GANZE ZEIT
2 DIE MEISTE ZEIT
3 EINEN GROSSTEIL DER ZEIT
4 MANCHMAL
5 SELTEN
6 KAUM
7 NIE

25. Wie oft haben Sie sich in den letzten 2 Wochen unfähig gefühlt, wegen Ihres Herzproblems soziale Kontakte zu pflegen?

❑ 1 DIE GANZE ZEIT
❑ 2 DIE MEISTE ZEIT
❑ 3 EINEN GROSSTEIL DER ZEIT
❑ 4 MANCHMAL
❑ 5 SELTEN
❑ 6 KAUM
7 NIE

26. In welchem Ausmaß waren Sie im Allgemeinen in den letzten 2 Wochen wegen Ihres Herzproblems bei Ihrer täglichen körperlichen Belastung eingeschränkt?

❑ 1 SEHR STARK EINGESCHRÄNKT
❑ 2 STARK EINGESCHRÄNKT
❑ 3 ZIEMLICH EINGESCRÄNKT
❑ 4 MÄSSIG EINGESCHRÄNKT
❑ 5 IRGENDWIE EINGESCHRÄNKT
❑ 6 EIN WENIG EINGESCHRÄNKT
7 ABSOLUT NICHT EINGESCHRÄNKT

27. Wie oft in den letzten 2 Wochen hatten Sie das Gefühl, dass Ihr Herzproblem den Sexualverkehr einschränkt oder beeinträchtigt?

- ❑ 1 DIE GANZE ZEIT
- ❑ 2 DIE MEISTE ZEIT
- ❑ 3 EINEN GROSSTEIL DER ZEIT
- ❑ 4 MANCHMAL
- ❑ 5 SELTEN
- ❑ 6 KAUM
- ❑ 7 NIE

NICHT ZUTREFFEND

Vielen Dank für die Beantwortung der Fragen.

Supplemental file N: One –repetition maximum protocol

DOPPELHERZ-STUDIE

KRAFTTEST

Präventive und Rehabilitative Sportmedizin
Technische Universität München

RAND#:	**Datum:**
Visite:	**Untersucher:**

Testung des Einwiederholungsmaximum (1-RM)

Beinstrecker (Quadrizeps)

Einstellungen:	
Schienbeinpolster	
Rückenpolster	
Endposition	

	1. Versuch	2. Versuch	3. Versuch	4. Versuch	5. Versuch	6. Versuch	7. Versuch
WH							
KG							
RPE							

Bankdrücken - stehend (Pectoralis)

Einstellungen:	
Startposition	
Handgriff	
Rücken	
Füße	

	1. Versuch	2. Versuch	3. Versuch	4. Versuch	5. Versuch	6. Versuch	7. Versuch
WH							
KG							
RPE							

Unterschrift Untersucher	

Supplemental file O: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be

independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics

committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Supplemental file P: Approval from Klinikum rechts der Isar ethics committee (in German)

Technische Universität München

Technische Universität München · Fakultät für Medizin · Ethikkommission
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22.09.2010
Projektnummer **2931/10** (bitte bei jedem Schriftwechsel angeben)

DOPPELHERZ – Individuell *D*0siertes Kraft-Ausdauer-Training in HerzgruPPen – *E*influss auf körperliche *L*eistungsfähigkeit von *HERZ*patienten

Sehr geehrter Herr Kollege Halle,
sehr geehrter Herr Kollege Preßler,
sehr geehrter Herr Kollege Christle,

in der Sitzung der Ethikkommission vom Dienstag, dem 21.09.2010 wurde das o.g. Projekt besprochen.

Zur Begutachtung lagen Prüfplan mit Synopsis (Version 26.08.2010) und Patienteninformation/-einwilligungserklärung (Version 08.09.2010) vor.

Die Ethikkommission, die sich aus den Mitgliedern
Herr Prof. Dr. F.B. Hofmann, Frau Prof. Dr. H. Frank,
Herrn Dr. R. Haubenthaler, Herrn Prof. Dr. G. Schmidt,
Herrn Prof. Dr. G.H. Schlund und Herrn Prof. Dr. K. Ulm zusammensetzte, kam zu folgendem Votum:

Die Ethikkommission erhebt keine Einwände gegen das geplante Forschungsprojekt.

Mit freundlichem Gruß

Prof. Dr. G. Schmidt
Geschäftsführendes Mitglied der Ethikkommission

Die Ethikkommission der Fakultät für Medizin der Technischen Universität München arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den ICH-GCP-Richtlinien.

Meldungen über schwerwiegende oder unerwartete unerwünschte Ereignisse sind mit einer Stellungnahme des Prüfarztes zum Nutzen/Risiko-Verhältnis des Vorhabens einzureichen (§ 40, Abs. 1, Satz 4 AMG).

Bei Vorlage von Amendments und Änderungen oder Ergänzungen deutlich zu kennzeichnen. Der Prüfarzt sollte die Protokolländerungen (aufgeteilt nach „wesentlichen" und „nicht wesentlichen" Änderungen) einzeln auflisten und mitteilen, ob die Änderungen nach seiner Ansicht ethisch relevant sind. Falls erforderlich, ist eine revidierte Patienteninformation/ Einverständniserklärung einzureichen.

Nach Publikation der Studie bitten die Ethikkommission um Zusendung eines Sonderdruckes.

Supplemental file Q: DOPPELHERZ patient information informed consent (in German)

PRÄVENTIVE UND REHABILITATIVE SPORTMEDIZIN
KLINIKUM RECHTS DER ISAR

TECHNISCHE UNIVERSITÄT MÜNCHEN

Anstalt des öffentlichen Rechts

Direktor: Univ.-Prof. Dr. med. Martin Halle

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Donnerstag, 30. Juni 2011

Patienteninformation

Sehr geehrte(r) Herzgruppen-Teilnehmer(in)!

Wir möchten Sie im Folgenden über eine klinische Studie informieren, die von unserem Lehrstuhl unter Förderung der Landesarbeitsgemeinschaft für kardiologische Prävention und Rehabilitation in Bayern e.V. durchgeführt wird und Sie um Ihre Teilnahme bitten. Der Titel der Studie lautet „DOPPELHERZ – Individuell dosiertes Kraft-Ausdauer-Training in ambulanten Herzgruppen – Einfluss auf körperliche Leistungsfähigkeit von Herzpatienten“.

Der wissenschaftliche Hintergrund der Studie liegt darin, dass nach bereits gesicherten Erkenntnissen eine gute körperliche Leistungsfähigkeit wesentlich zu einem längeren Überleben von Herzpatienten beiträgt. Diese Leistungsfähigkeit kann sehr einfach anhand der auf einem

Fahrradergometer erzielten maximalen Leistung bestimmt werden. Eine Steigerung dieser Leistung wird besonders durch ein individuell dosiertes, regelmäßiges Kraft-Ausdauer-Training erreicht. Auch das bisherige Herzsport-Training kann eine Steigerung bewirken; es ist jedoch davon auszugehen, dass mit einem individuellen Kraft-Ausdauertraining dieses Ziel schneller und nachhaltiger erreicht wird.

Wir möchten mit der Studie nun diese Erkenntnisse in den ambulanten Herzsport übertragen. Ziel ist, zusätzlich zum bisherigen Training ein individuell dosiertes Kraft-Ausdauer-Training am Lehrstuhl anzubieten und damit die Vorteile beider Trainingsformen zu kombinieren. Die Studie geht davon aus, dass dadurch eine insgesamt höhere Leistungsfähigkeit erzielt wird als bisher. Sollte dies zutreffen, ist davon auszugehen, dass die Erkenntnisse der Studie in die zukünftige Gestaltung des Herzsports Eingang finden werden.

Teilnehmen kann an der Studie grundsätzlich jeder Patient aus unseren Herzgruppen, sofern folgende Bedingungen erfüllt sind:

- Die körperliche Leistungsfähigkeit liegt unterhalb eines Wertes von 1,4 Watt/kg auf dem Ergometer
- Es ergibt sich aktuell kein Anhalt für eine bedeutsame Verschlechterung Ihrer Erkrankung Beide Voraussetzungen müssen, sofern die letzten Untersuchungen bei Ihnen am Lehrstuhl bereits länger als 3 Monate zurückliegen, noch einmal anhand neuer Untersuchungen überprüft werden.

Die Studie läuft wie folgt ab:
Im Falle Ihrer Zustimmung erhalten Sie einen Termin an unserem Lehrstuhl, bei dem noch einmal eine ausführliche individuelle Aufklärung erfolgt und Sie Gelegenheit zu Fragen haben. Im Falle Ihres Einverständnisses werden Sie um Unterschrift gebeten. Anschließend werden folgende Untersuchungen durchgeführt:

- Anamnese bezüglich aktueller Beschwerden, körperliche Untersuchung
- Blutabnahme (hierbei handelt es sich um eine übliche Blutabnahme, bei der Parameter wie Cholesterin, Blutzucker und Blutbild bestimmt werden)

- EKG, Körpervermessung (Größe, Gewicht, Körperfett), Blutdruckmessung
- Fragebögen: Sie werden gebeten, 3 Fragebögen auszufüllen, die sich mit der empfundenen Lebensqualität befassen und ihre physische und psychische Situation erfragen
- Fahrradergometrie
- Aktivitätsmessung: Hier erhalten Sie über mehrere Tage einen Aktivitätssensor, der ihre alltägliche Bewegung erfasst

Sollten sich in den Untersuchungen keine Einwände gegen eine Studienteilnahme ergeben, werden Sie in eine von insgesamt zwei Studiengruppen per Zufallsverfahren eingeteilt:

Während eine Gruppe normal zweimal wöchentlich mit dem bisherigen Herzsport fortfährt, wird bei der anderen Gruppe eine der beiden Trainingseinheiten durch ein individuelles Kraft-AusdauerTraining im lehrstuhleigenen Trainingsraum ersetzt. Die ärztliche und sportwissenschaftliche Überwachung und Anleitung bleibt in gewohnter Weise bestehen. Diese Phase dauert 6 Monate. Anschließend und nach weiteren 6 Monaten werden die obengenannten Untersuchungen wiederholt. Insgesamt ist die Studie nach 12 Monaten beendet. Wir weisen daraufhin, dass die in üblicher Weise weiter trainierende Gruppe unter Umständen nicht im Sinne des angestrebten Studienziels profitieren wird. Wie bereits erwähnt, werden die Erkenntnisse allerdings in die zukünftige Gestaltung des Herzsportes einfließen, so dass längerfristig alle Teilnehmer profitieren können.

Nebenwirkungen sind im Rahmen der Studie nicht zu erwarten, da moderates körperliches Training bei Herzpatienten gemäß zahlreichen Studien als sicher gilt. Für alle Teilnehmer besteht allerdings eine Versicherung über das Kuratorium für Prävention und Rehabilitation der TU München (Gerling, Versicherungsnummer: SP-22-005913656-5, Gerling Konzern München GmbH, Prinzregentenstr.11, 80538 München, (089)21 07-111). Bei evtl. Ereignissen und Anfragen wenden Sie sich bitte sofort an:

Dr. Christoph Lammel, Kuratorium für Prävention und Rehabilitation an der Technischen Universität

München (TUM) e.V., Connollystr. 32, 80809 München, Tel.: 289-24434/24420, Fax: 289-24418, EMail: kuratorium.pr@sport.med.tum.de

Insgesamt werden die jeweiligen Untersuchungen im Lehrstuhl für Sportmedizin ca. einen halben Vormittag dauern. Sie werden ambulant durchgeführt und sind kostenlos für Sie. Eine zusätzliche Aufwandsentschädigung ist nicht vorgesehen. Im Rahmen des Herzsportes entstehen lediglich die

Ihnen bereits bekannten Kosten. Ansprechpartner für die Studie ist Herr Jeffrey Christle, Tel. 089/289-24421 sowie Herr Dr. Axel Preßler, Tel. 089/289-24434.

Hinweise zum Datenschutz:

Die im Verlauf der Studie erhobenen Daten werden auf elektronische und papierne Datenträger gespeichert und streng vertraulich behandelt. Zum Schutz dieser Daten sind organisatorische Maßnahmen getroffen, die eine Weitergabe an unbefugte Dritte verhindern. So werden während der gesamten Dokumentations- und Auswertungsphase die Studienteilnehmer lediglich anhand ihrer Initialen und der individuellen Teilnehmernummer identifiziert, während der volle Name des Patienten nicht in Erscheinung tritt. Die einschlägigen Bestimmungen der länderspezifischen Datengesetzgebung sind vollumfänglich zu erfüllen.
Die Auswertung der Studie erfolgt ausschließlich durch die Studienleitung und die beteiligten Mitarbeiter. Die verwendeten Unterlagen sind Eigentum der Studienleitung und dürfen ohne Genehmigung nicht anderweitig verwendet oder weitergegeben werden.

Hinweis zur freiwilligen Teilnahme:

Sie haben das Recht, jederzeit ohne Angabe von Gründen und ohne dass Ihnen ein Nachteil erwächst bzw. Folgen für eine zukünftige Behandlung entstehen, die Zusage zur Teilnahme an der Studie zurückzuziehen und / oder die Studie abzubrechen.

Einwilligungserklärung

zur Teilnahme an der Studie „DOPPELHERZ – Individuell dosiertes Kraft-Ausdauer-Training in ambulanten Herzgruppen – Einfluss auf körperliche Leistungsfähigkeit“.

Ich habe die Ausführungen aus der Patienteninformation zu den vorgesehenen Untersuchungen gelesen und verstanden. Offene Fragen konnte ich mit den zuständigen Ärzten zu meiner Zufriedenheit klären. Ich bin darüber informiert, dass im Rahmen der Studie eine Versicherung über das Kuratorium für Prävention und Rehabilitation der TU München für trainingsassoziierte Unfälle oder Verletzungen beim Gerling-Konzern abgeschlossen wurde.

Die Hinweise zum Datenschutz habe ich gelesen. Mir ist bekannt, dass ich im Rahmen der Studie über meine Initialen und die Teilnehmernummer identifiziert werde und meine Daten in dieser Form auch auf elektronische und papierne Datenträger gespeichert werden. Ich habe Kenntnis darüber, dass eine Weitergabe an unbefugte Dritte nicht stattfindet und dass die gesetzlichen Bestimmungen zum Datenschutz vollumfänglich erfüllt werden. Ich bin mit der Aufzeichnung meiner im Rahmen der Studie erhobenen Daten und ihrer Auswertung durch die zuständigen Studienärzte einverstanden.

Mir ist bekannt, dass ich die Studie jederzeit ohne Angabe von Gründen abbrechen kann, ohne dass mir daraus Nachteile erwachsen oder Folgen für meine zukünftige Behandlung entstehen.

Mit der Teilnahme an der Studie bin ich einverstanden.

München, den _____ München, den_____

Teilnehmer _____ Untersucher_____

Unterschrift _____ Unterschrift_____