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PhD Thesis

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Exercise-based cardiac rehabilitation - the use of patient-preferred settings and its impact on exercise intensity and clinical health effects

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PREFACE

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Lars Hermann Tang
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ARTICLES INCLUDED IN THE THESIS

Paper I: Self-rating level of perceived exertion for guiding exercise intensity during a 12-week cardiac rehabilitation programme and the influence of heart rate reducing medication.
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Paper II: Is the cardiovascular response equivalent between a supervised centre-based setting and a self-care home-based setting when rating of perceived exertion is used to guide aerobic exercise intensity during a cardiac rehabilitation program?
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Paper III: Patients' preference for exercise setting and it's influence on the health benefits gained from exercise-based cardiac rehabilitation.
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ABBREVIATIONS

bpm = Beats per minute

CI = Confidence interval

CR = Cardiac rehabilitation

CVD = Cardiovascular disease

ICC = Intra class correlation

ICF= The International Classification of Functioning, Disability and Health

IQR = Interquartile ranges

HADS = Hospital Anxiety and Depression Scale

HR = Heart rate

NYHA = The New York Heart Association Functional Classification

OR = Odds ratio

R^2 = Coefficient of determination

RCT = Randomised clinical trial

RHO = Spearman's correlation coefficient

EHRA = European Heart Rhythm Association

RPE = Rating of perceived exertion

BRIEF INTRODUCTION

Despite the well-documented benefits, far from all patients attend exercise-based cardiac rehabilitation (CR).[1–6] Alarmingly, low uptake and adherence rates are reported in both national and international CR[6–9] and constitute a major challenge because these low rates are associated with increased risk of hospitalisation, emergency room visits and cardiovascular mortality.[7,8,10–12] Alternative delivery models using home-based settings have been suggested as a solution to increase uptake and adherence.[13–16]

Exercise training is a core component in CR and exercise intensity is a key element in exercise-based CR.[17,18] Moving CR from traditional, supervised centre-based sittings to unsupervised, home-based settings potentially complicates intensity prescription and assessment because it relies on patients' abilities and skills. Hence, simple and effective prescription and assessment methods that are applicable across settings are needed. Rating of perceived exertion (RPE) is a practical exercise assessment method and is suggested in most CR guidelines,[17–20] but studies investigating RPE in routine CR and across exercise settings is lacking.

It has been proposed that the mode of CR delivery should align with patient preference because most evidence investigating the health effect between home-based settings and centre-based settings shows similar health effects among the two settings.[15] Unfortunately, most evidence is conducted in a traditional randomised study design that eliminates motivational variables like patient preferences. Therefore, other research designs are needed when investigating elements, such as preferences, or when seeking to ensure that the results can be generalised to routine clinical practice.[21,22] Knowledge that can be generalised to routine practice is obtained through study designs with a minimisation of highly selective inclusion criteria, taking patients' preferences into consideration, executing the intervention in routine settings, providing the intervention with at least the minimum length of duration and clinically relevant treatment modalities and, finally, investigating simple interventions / methods that are feasible to implement in routine practice.[23–26]

The overall aim of the present thesis was to investigate whether or not a simple assessment method, based on RPE, could enable patients to regulate their exercise intensity, regardless of exercise setting. Furthermore, to evaluate whether or not patients preferred a home-based setting when compared to a traditional centre-based setting and whether they achieved similar health effects between the two settings, when participating in exercise-based CR in relation to their preference. The thesis should enhance the generalisability of the findings to routine CR.

BACKGROUND

Heart diseases and disabilities

The term CVD covers most diseases in both the cardiovascular and cerebrovascular system.[27] Globally, CVD is the leading cause of death with an estimate of 17.5 million deaths annually, in 2012. This represents 31% of all global deaths.[28] Of all CVD deaths, specific heart diseases contribute to more than half of these.[28] The most common heart diseases are coronary heart disease, congestive heart failure, heart valve disease and arrhythmia.[28]

Despite reports over the past few years that mortality rates in affluent areas are decreasing, heart disease alone is still one of the leading cause of deaths in this areas: with coronary heart disease alone contributing to 20% of all deaths in Europe and 1 of every 7 deaths in the United States.[29,30] Moreover, the prevalence of patients living with heart disease is reported to be increasing, both nationally and internationally.[31,32]

In 2001, WHO formally endorsed The International Classification of Functioning, Disability and Health (ICF) as a modern, common international framework that prescribes disability and health from a biological, individual and social perspective: moving away from the previous idea in which dysfunction related purely to medical or biological conditions.[33,34] Since then, the ICF is widely used to describe disabilities, also within cardiac populations, where complications are reported for the two ICF categories; 'Body Functions and Structures' and 'Activities and Participation'.[35–37]

As a consequence of cardiac disease, patients are susceptible to multiple complications. The most frequently reported post-complications are; reduced physical function and physical capacity and / or impaired mental health, reduced quality of life and the experience of anxiety and depression symptoms.[17,38–40] While a significant body of published literature exists reporting impaired physical and mental health as predictors for subsequent rates of mortality and morbidity, considerable efforts are made in facilitating patients' recovery of these impairments following heart diseases.[41–44]

Cardiac rehabilitation

CR is established to address and improve post-complications and disabilities associated to a heart disease.[45,46] CR can be categorised as a *comprehensive interventions* involving a number of activities that positively impact upon the underlying cause of the heart disease by increasing physical, mental and social impairments making patients able to return to the routines of their daily life prior to suffering heart disease.[20,45–47] The comprehensive intervention can contains the

following general elements; behavioural models of change, risk management and psychosocial supports and education.[20,45] However, according to the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation (EACPR), the key element in a CR intervention is exercise training, but EACPR underline that exercise training alone cannot be categorised as CR.[18]

Exercise training and physical activity recommendations in cardiac rehabilitation

Exercise-based CR is well-documented, especially in patients with ischemic heart disease and heart failure.[1,3] Furthermore, some evidence also exists within other patient populations, such as heart valve disease and atrial fibrillation.[4,5,48,49] Increased exercise capacity, mental health and quality of life together with reduced risk of cardiovascular mortality, re-hospitalisation and cardiovascular events are all health benefits reported from exercise-based CR.[1–5,48]

Exercise-based CR guidelines emphasis a progressive training regimen with aerobic exercise intensities ranging from moderate to high levels, combined with strength training at least three times per week.[17–20] In addition, patients are encouraged to incorporate a minimum of 30 minutes of moderately vigorous aerobic activity most days, as a part of their daily routines.[18,19]

Attendance and adherence - the achilles heel in cardiac rehabilitation

Inspite of the fact that published meta-analyses show the positive impact of exercise-based CR, critically low attendance and adherence rates still constitute a major problem in CR. Despite the possibility of standardised rehabilitation in most European countries, it is estimated that fifty percent, or fewer, of all eligible cardiovascular patients benefit from CR in Europe.[6–9,50] In 15 out of 28 European countries, attendance rates are less than 30%.[6] With the survival rates of CR participants being at least 21% higher than non-participants, this low attendance rate clearly needs to be addressed.[7,8,10–12]

Some of the most frequently reported barriers associated with attendance to CR are gender and age, in addition to other potential variables such as marital status, income and accessibility.[51–55] The National Institute for Health Research (NHR) in the UK has systematically reviewed barriers for attendance and adherence in CR. Beswick and colleagues identified numerous possible reasons for low levels of uptake and adherence, and professional compliance of referral to CR. All barriers have been summarised into three terms; *Patient factors, Service factors and Professional factors.* These terms each underline multifactorial reasons for not participate or being adherent to CR.[56] (see Table 1)

Table 1: Barriers to uptake and adherence may be summarised as follows.

Patient factors:	Service factors:	Professional factors:
- Lack of interest - Reluctance to change lifestyle Depression - Dislike of classes/hospitals Work or domestic commitments - Lack of family support - Rural residence.	- Cost and reimbursement - ECG monitoring requirement - Location and accessibility - Car parking	- Knowledge and attitudes Referral - Prejudice (age, race, gender).

Table 1 has been published by Beswick and colleagues[56] in 2004.

Alternative delivery models

The idea of CR has existed for over 50 years. The concept has developed from bed-rest interventions into comprehensive interventions involving exercise training.[1,3,18,19,46,57] However, as a result of the alarming low attendance and adherence rates, alternative delivery models are being developed. During the last ten years, alternative models evolving from multifactorial individualised telehealth delivery interventions to complementary and alternative medicine interventions have been tested.[13] A recent systematic review by Clark and colleagues compared various alternative models. The results of this review showed that only community or home-based programmes, telehealth based individualised interventions and multifactorial models were associated with similar improvements in cardiovascular risk factors, as those known from traditional CR approaches.[13]

Exercise setting

Traditionally, exercise-based CR has been carried out in a centre-based setting, often localised at a local hospital.[6] The characteristic of this approach are patients engaging in exercise training supervised by healthcare professionals within a fixed time schedule. New alternative delivery models are transforming these traditional centre-based approaches into alternative programmes, often referred to as "home-based" programmes.[16,58,59] In the literature, "home-based" programmes are widely ranging from self-management programmes, without any supervision performed outside a patient's home, to tele-monitored supervised programmes, performed within a patient's own house.[13,15,60] Nevertheless, the fundamental principle of a home-based programme is an intervention that is delivered either in the patient's own home, or in a local 'non-hospital' location.[60] Accessibility to the CR facilities are known to influence uptake and adherence[53,56,61] and by

enabling patients to engage in exercise-based CR in local facilities, at flexible times, potential barriers to uptake and adherence are believed to be reduced.[14,16,59,62,63]

Evidence supports the expansion of alternative home-based interventions because these programmes are reported to be equally effective, compared to more traditional centre-based programmes, whilst incurring similar costs.[15,64,65] Nevertheless, in most countries, home-based programmes are still not offered as an alternative to the centre-based programmes.[6]

Exercise assessment in a routine setting

Higher exercise intensity has been associated with a greater level of post-rehabilitation exercise capacity.[66] Despite the fact that relatively few adverse events are reported, exercise training with cardiac patients is always associated with a risk of cardiac complications.[67] Therefore, exercise prescription and assessment is of great importance in exercise-based CR.[17] The importance of intensity assessment is underpinned by studies reporting that 'un-trained' individuals have an increased risk of experiencing sudden cardiac arrest during vigorous exercise intensities.[68,69]

The use of an unsupervised home-based setting potentially complicates the prescription and assessment of exercise intensity. In a supervised centre-based setting, patients will receive guidance from health care professionals, whilst home based settings rely upon the patient's own abilities to regulate the exercise intensity. In relation to achieving beneficial health effects, studies have demonstrated supervised exercise programmes superior to unsupervised programmes.[70,71] Additionally, some home-based exercise programmes have been unsuccessful in proving any clinical benefits when compared to CR interventions, without a structured exercise component.[72,73] For such reasons, it has been argued that cardiac patients lack the ability to follow an exercise prescription when exercising by themselves.[72]

Both objective and subjective assessment tools are currently available for monitoring exercise intensity in cardiac patients.[17] Many of these are sophisticated methods and not available for routine practice at local CR sites, or in homed-based settings (e.g., the cardiopulmonary exercise test). Given the expansion of alternative methods of CR delivery, like the unsupervised home-based settings,[13,16,59] simple methods allowing patients themselves to follow an exercise prescription is of great value.

A simple solution is to estimate exercise intensity expressed as a percentage of the maximum heart rate (HR). Unfortunately, HR is known to vary greatly in cardiac populations. To exemplify this patients undergoing surgery are more likely to get post-surgical tachycardia and the consumption of

beta-blockers will cause a reduction in patients' maximum HR, together with a decrease of 20-30% in their submaximal HR.[74,75]

RPE is another assessment tool commonly applied in CR.[17–19] RPE is based on a simple, subjective rating scale. In healthy adults, RPE is recognised to be reliable and valid when used to monitor exercise intensity.[76–79] Whilst in cardiac patients, it is considered reliable[80] but may occasionally over or underestimate the actual exercise intensity.[81–83] Nonetheless, RPE is suggested as an assessment in most CR guidelines[17–20] and studies have documented identical beneficial health effects between cardiac patients when comparing exercise guidance from RPE to objective physiological monitoring tools.[84,85]

The simplicity of RPE makes it a perfect tool to use in routine CR and across different settings. However, the usability of RPE has only been investigated in experimental or highly controlled setups that impair the generalisability of the study results to everyday clinical practice.[81,83,86,87] Hence, studies investigating RPE in routine practice and across exercise settings is lacking.

Patient preference toward exercise setting

To overcome the high proportion of patients not engaging in CR, recent literature suggests tailoring future interventions towards patients' needs, risk profile and preferences, in contrast to the traditional CR approaches.[13–16,59,88]

In general, it has been hypothesised that incorporating patient preferences into a treatment regimen will have a positive impact: motivation to follow a regimen is likely to be effected by, and linked to these preferences.[21,22]

Due to the similar health effects and costs between centre-based and home-based programmes, it is emphasised that the setting must be determined by the preference of the individual patient.[13,15] The proportion of patients willing to train at home is of particular relevance, given the increasing numbers of cardiac patients, inevitably putting additionally pressure onto health-care centres.[30–32] Only a few studies have actually reported the proportion of patients who prefer either a home-based or centre-based setting, with numbers ranging from 27%-57%, in favour of a home-based setting.[62,89,90] Further research is necessary to better understand patient preference rates within each exercise setting, in order that future contemporary models can reflect and be balanced towards the preference of the individual patient.

In a qualitative study by Wingham et al.,[91] difference reasons and priorities were reported in relation to patients preference for either a centre-based or home-based CR setting, when treated for myocardial infarct. Patients who preferred a home-based setting were more self-disciplined, prioritised a programme implementable into their daily life and had a dislike for groups-based training. Patients choosing a centre-based setting were willing to travel, like the supervision and did not see themselves as self-disciplined. The need for guidance and ownership of decision for exercise setting was highly important in both groups.[91] Grace et al.[92] showed a distinction in patients preferring a centre-based or home-based setting that related to patients' income and employment status. Patients who worked either full-time or part-time were more likely to select a home-based setting. In addition, Madden et al.[93] reported that obstacles like full-time work could force patients to select a home-based setting. Despite the limited evidence addressing patient preference towards different exercise setting in CR, it is reasonable to assume that the traditional centre-based setting does not have the structure to fit every patients' needs and preferences.

The paradox of existing evidence

Most studies investigating the impact of the exercise setting in CR are conducted using a traditional randomised clinical trial (RCT) study design. Based on these studies, it is suggested that the choice of exercise setting should rely on patients' own preference.[13,15] Randomisation is known to reduce some types of systematic error (i.e., equal allocation between groups) but, as a consequence, it will also eliminate motivational variables, such as personal preference towards a specific treatment.[21,22] A patient could, hypothetically, feel demoralised if allocated to a non-preferred group / setting which could negatively affect the study outcome.[21,94] For such reasons, RCT studies, in general, fail to take patients' preference directly into account[23] and it is unknown whether the effect between settings is similar to the findings from RCTs when the choice of exercise setting is aligned with patients' own preferences.

In a systematic review by King et al., patients' preferences were found to determine whether or not patients participated in a trial / intervention, but these preferences did not, however, seem to impact studies outcomes.[21] In CR, only one study has allowed patients to choose freely between a centre-based CR programme or home-based CR self-help package. Dalal and colleagues performed a pragmatic RCT with the inclusion of a patient preference arm. They reported similar clinical outcomes (e.g., depression and anxiety scores and levels of total cholesterol) between the two settings, regardless of whether or not patients were randomised, or whether they selected the setting themselves.[89] Despite the fact that the findings by Dalal and colleagues are similar to existing evidence from RCTs, the results may not simply be a question of settings. In the centre-based

programme, patients attended health classes once a week for 8–10 weeks delivered by multidisciplinary teams one month after hospital discharge. Patients were further encouraged to exercise at home. In comparison, one week post discharge, patients in the home-based group were offered a step-by-step guide in comprehensive cardiac rehabilitation (e.g., structured programme of exercise, stress management, and education). Patients were advised to use the guide for six weeks consecutively, with weekly follow-up telephone calls from a nurse.[89] A direct comparison between the two settings is, therefore, complicated due to the different content of the two interventions. Before tailoring future delivery models towards the preferences and needs of an individual patient, the amount of evidence focusing on patient-preferred settings and the health benefits across these settings must be enhanced.

Evidence with generalisation to routine practice

Efficacy refers to the benefits of an intervention or treatment delivered during optimal conditions, enhancing the degree of internal validity in the findings of a study. In contrast to this, effectiveness refers to the effect of an intervention or treatment investigated during "Real World" conditions, generating evidence with a higher level of generalisation to routine practice.[24,95,96]

Elements that can enhance the effectiveness in studies are the absence of highly selective inclusion criteria, including patients' preferences towards an intervention and performance of the investigated intervention within the usual environment (real world conditions).[23,24] Furthermore, the intervention must have, at least, the minimum length of duration and include clinically relevant treatment modalities and be feasible in routine practice.[23–26] The purpose of the results of a study and the analytical approaches to be taken should, therefore, be determined prior the study being planned.[23]

Generating evidence with a higher level of generalisation to routine practice is often a balance between internal validity and the generalizability of the results.[24] To maximise the generalizability, a study often needs to reduce the level of internal validity. In contrast, a highly controlled study design is unlikely to produce results useful in routine practice. However, before an intervention is implemented into a routine setting both the efficacy and the effectiveness most be fully investigated.[23,24]

The need for further research

Throughout the past decades, CR has evolved from being a simplistic intervention into comprehensively supervised, centre-based programmes, including the key component of exercise training. Despite efforts to develop the interventions, fewer than half of all eligible patients actually

participate in CR across European countries. As a result, alternative delivery models using unsupervised, home-based programmes have been developed from traditional, supervised centre-based programmes. However, taking patients from supervised centre-based settings into an unsupervised home-based setting can, potentially, complicate exercise prescription and assessment because there is a shift in the responsibility to guide and control the exercise intensity from the healthcare practitioner to the patient. There is, therefore, a need to form an evidence base investigating how to best create and test a mode of prescription that will enable patients to exercise as effectively across different exercise settings.

Most literature comparing the importance of different exercise settings reports similar health effects between settings, suggesting that patients should be able to choose their own preferred environment. Unfortunately, most evidence is achieved from traditional RCTs, failing to take patients' preferences truly into account. Hence, the degree to which patients prefer different exercise settings and whether this preference potential has an effect upon the health benefits gained in CR are rarely reported in the literature. Nevertheless, this is an important area because patient-preferred settings have the potential to both increase patient uptake and, in future standardised CR, to create a delivery model tailored more towards the preferences of the individual patient.

AIMS

The overall aim of the present thesis was to investigate whether or not a simple assessment method, based on RPE, could enable patients to regulate their exercise intensity, regardless of exercise setting. Furthermore, to evaluate whether or not patients preferred a home-based setting when compared to a traditional centre-based setting and whether they achieved similar health effects between the two settings, when participating in exercise-based CR in relation to their preference. The thesis should enhance the generalisability of the findings to routine CR.

The overall aim was based on three main research questions:

1) Can RPE be used to guide exercise intensity adequately in patients participating in a 12-week CR programme?

2) Is RPE an effective method to ensure that patients are exercising consistently across different exercise settings?

3) To what extent do patients prefer a self-managed, home-based setting when compared to a traditional, centre-based setting and will the choice of setting impact upon the beneficial effects gained from an exercise-based CR intervention?

Three exploratory quantitative studies were carried out using data from two RCT trials. The specific objectives approached in the three papers were:

Paper I

- To investigate whether RPE could adequately guide exercise intensity during a cardiac rehabilitation programme reflecting everyday clinical practice.

Paper II

- To investigate if the cardiovascular response was equivalent when exercise intensity was guided by RPE in a supervised, centre-based and a self-managed, home-based setting.
- To investigate if the association between RPE and HR was influenced by variables like familiarisation with RPE, different exercises intensities, patient characteristics (e.g. age, gender, cardiac diagnosis) or levels of anxiety and depression.

Paper III

- To estimate the proportion of cardiac patients who preferred either a traditional, centre-based setting or a home-based exercise setting, when participating in exercise-based CR.
- To explore patient characteristics and baseline differences as a result of the choice of setting.
- To evaluate if the choice of setting would impact upon the long-term health benefits gained from a 12-week exercise-based cardiac rehabilitation period.
- To evaluate the extent of exercise adherence between the two self-preferred settings.

METHODS AND DESIGN

Summary of the CopenHeart intervention

Data in this present thesis were collected through two RCT trials that represented a part of a large comprehensive rehabilitation project: The CopenHeart project.[97,98] Data were extracted entirely from patients who were allocated to the intervention group in one of the two trials. For this reason, the CopenHeart intervention constitutes a central part of the present thesis and a summary is, therefore, provided in the following section.

The two trials investigated the effect of a comprehensive rehabilitation intervention containing 12 weeks of exercise training and five psycho-educative consultations, either in patients who had undergone ablation for atrial fibrillation[97] or heart valve surgery.[98] The interventions were compared to standard medical follow-up. Both trials have received approval from Regional Ethical Committee (j.nr. H-1-2011-135, j.nr. H-1-2011-157) and the Data Protection Agency (j.nr. 2007-58-0015). The interventions in each of the two trials were conducted parallel and followed the same methods and setup.

The exercise intervention included a 12-week progressive exercise programme, one month after hospital discharge or post-surgery. The programme combined aerobic and strength training three times a week for approximately 60 minutes per session. Each training session began with an eight-ten minute warm-up phase, followed by 20-25 minute aerobic exercise phase divided into three incremental steps. The exercise intensity in these phases was based on the 15-point Borg RPE scale[99] and followed national and international exercise-based CR guidelines.[17,19,45] Afterwards, four strengths / strength-related exercises were performed, mainly targeting the lower extremities. During the introduction to the programme, each patient received a training diary detailing general information about the exercise intervention, a prescription to each of the 36 exercise sessions and the 15-point Borg RPE scale. Patients also received a heart monitor (Polar Electro, Finland) to wear during the aerobic exercise phase. One of four physiotherapists introduced all patients' to the exercise programme during the first training session.

All patients underwent the first training session in the same tertiary centre hospital (Department of Cardiology, Rigshospitalet). Thereafter, patients continued their programme in one of two settings selected in accordance to the patient´s own preferences:

1. A supervised, centre-based setting either at the tertiary centre hospital, a local hospital or a healthcare centre. In total, 29 certified collaborating centres were available. All personnel in each centre had received education and were certified in the exercise intervention by the same physiotherapist.
2. A self-managed programme performed either at home, or in local fitness centre. Patients were not provided with any additional training supervision, other than the information given at the first training session and what has been detailed in the training diary.

During the intervention period, all patients were encouraged to perform daily, moderate physical activity for 30 minutes. Furthermore, all patients underwent psycho-educative consultations with a specially trained nurse five times during the first six months after discharge, or surgery. The consultations, inspired by the work of R.R. Parse,[100] took place either at the tertiary hospital or by telephone.

Why use data from CopenHeart project?

There are three main reasons why the data from the CopenHeart trials form a unique resource for the present thesis:

Firstly, although the data were collected through a RCT design, the choice of exercise setting still relied upon patients' own preference. Therefore, a randomisation process did not prohibit the individual patient from making their own preference towards an exercise setting.

Secondly, the design of the two trials was based upon national and international clinical guidelines and reflects routine CR throughout Denmark, involving 29 centres in the region of Sealand.[19,45,101] Patients were, therefore, able to attend CR at a healthcare centre in close proximity to their own home. Furthermore, the exercise intervention contained clinically relevant exercise modalities[17–19] and simple exercise assessment methods that are feasible in daily practice. Such elements will help enhance the generalisability of the study findings into routine CR.[23–26]

Thirdly, data is collected from patients diagnosed with either a heart valve disease or atrial fibrillation. These diagnoses are not as life threatening, or as common, as ischemic heart disease and congestive heart failure; with approximately 2% suffering from atrial fibrillation and 2.5% from heart valve disease (even higher percentages have been reported depending on region, age groups and specific diagnose especially for valve diseases).[28,102–108] Nevertheless, they constitute substantial groups within the spectrum of heart diseases and the prevalence is increasing similar to

the major groups of heart diseases, due to an increasing age population, complications to other heart diseases and improved diagnostic and treatment options.[27,103,104,106,108–112] Attention has been drawn towards these patients groups in recent years,[113,114] with recent evidence documenting that these patients are in an impaired mental and physical health compared to a healthy control group.[39,48] Future strategies for rehabilitation are, therefore, called for.[19,39,48] There is little evidence addressing the impact of exercise-based CR in either patient groups, but short-term improvement in the physical capacity are reported.[4,48,49,115] Interestingly, when the Danish national clinical guidelines was published 2013 it recommend that patients who undergo valve surgery must be referred to CR, despite this lack of evidence within this patient group.[19]

In summary, the CopenHeart dataset forms a unique opportunity to address our research questions by exploring and examining a sub-category of patients, who participated in an exercise-based CR intervention, reflective of routine daily practice, across patient-preferred settings.

Exploratory research and secondary analysis

All three included studies in the current thesis are quantitative and can be categorised as *exploratory studies*. Exploratory research is simplified by Portney LG and Watkins MP as a systematic investigation of the relationship / association between at least two variables.[116] As illustrated in Figure 1, exploratory studies allow researchers to explore and test relationships between different variables. This methodology does not, however, result in conclusive evidence with the same level of certainty of the 'cause and effect' between variables as would be possible through a RCT design.

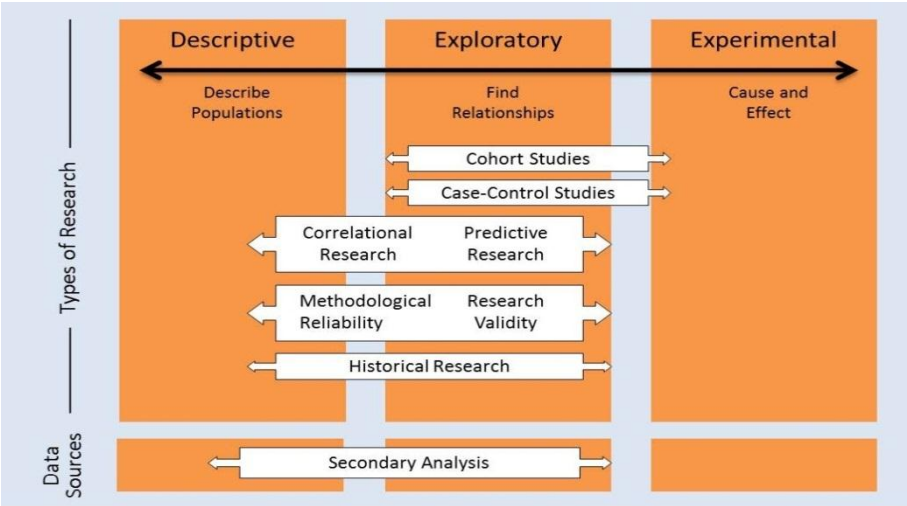

Figure 1 is extracted from Portney LG and Watkins MP[116]

Running secondary analysis from existing databases, as a part of exploratory research (see figure 1), is a method of great value in health science.[116] The major advantage of secondary analysis is the re-

examination of previously collected variables from a perspective other than that originally intended, without incurring the expense in terms of both time and cost. However, two potential limitations are the lack of control over the methods of data collection and the quality of data.[116]

With two out of the three studies (Paper I-II) in the present thesis investigating the relationship between different variables (RPE and HR) it seems reasonable to use the large among of existing data from the Copenheart trials, without incurring any unnecessary additional costs or disruption to the patients. Only Paper III investigates effect parameters. If considered purely from the perspective of establishing firm conclusions in cause and effect a RCT would be recommended.[91] However, when investigating the impact of preference a RCT would be ineffective because systematic randomisation would fail to take patient preferences directly into account.[21,22] Other study designs must be given consideration, when investigating an element like patient-preferred settings.[21,22]

Paper I-II: The relationship between rating of perceived exertion and heart rate and it's usability across settings

The methods for Papers I-II are presented together because they were based upon the same data.

Study design and population

Patients were eligible in the study if they had; undergone either radiofrequency ablation for atrial fibrillation or heart valve surgery and participated in an exercise-based CR intervention, in either one of two RCTs. Inclusion criteria were individuals who were aged over 18 years, were able to understand and speak Danish and did not have any co-morbidities complicating physical activity.[97,98]

Patients participated in the CopenHeart exercise intervention one month after hospital discharge or post-surgery. Only data from the aerobic exercise intervention was extracted for these two papers. On a stationary bike, patients underwent a 20 minute aerobic exercise phase divided into three incremental exercise steps. Duration and intensity in each incremental step varied between exercise sessions and progressed throughout the intervention period. The second step always had the longest duration and highest intensity. RPE, based on the Borg 15-point RPE scale,[99] was utilised for exercise intensity prescription.

A physiotherapist introduced patients to the exercise intervention and provided each with a training diary during their first session. The training diary had a detailed prescription of each exercise session, the Borg RPE-scale and a procedure for contacting a healthcare professional, in case of

complications. Furthermore, it contained preselected RPE exercise intensity levels and durations for each of the three exercise steps. Preselected RPE intensity levels were based upon European guidelines for physical exercise in CR.[17–19] If patients were capable, they were instructed to follow the preselected RPE intensity levels during each exercise session. Otherwise, patients were advised to perform the exercise session as close to the intensity of the preselected RPE level as they could possibly achieve. For safety reasons, patients were strictly requested not to go beyond the preselected RPE values. After a training session, patients were instructed to report the correct RPE level for each of the three exercise steps and to note any deviation from their exercise prescription in their diary. The reported RPE values were utilised in the analyses.

The first exercise session was initiated at the same tertiary centre hospital. A patient could then choose to continue the programme in either a traditional, supervised centre-based setting or a self-managed home-based setting (This has been described in detail in the section *"Summary of the CopenHeart intervention"*, page 19-20).

Polar HR RS 400 HR-monitors (Polar Electro, Finland) or T-shirts with wireless integrated electrocardiographic electrodes (Corus-Fit Cardio and Corus Exercise Assistant, CEA, V.2.0.16, Finland) were used to objectively assess the cardiovascular response during the 20 minute exercise phase. Patients were only instructed how to start and stop the HR monitor. The unsupervised, home-based setting deemed it impossible to blind patients to their HR monitors during training, however effort was spent explaining to them the importance of concentrating their efforts on RPE during their exercise regimen instead of their HR-monitor. Furthermore, none of the patients were provided with specific instructions concerning the relationship between RPE and HR, or ways to monitor training intensity based on their HR.

Data management

The training diary and HR-monitor were returned after the 12 week intervention. Before data analysis, all diary and RPE data were manually entered into a database and merged with HR data, using the dates of each exercise sessions. A training session was excluded if missing either RPE or HR data. Each 20 minute HR recording (five second sampling rate) was checked to ensure data quality and data was excluded if it contained irregular frequency changes with repeated sudden alterations exceeding more than ten beats per minute (bpm). Any obvious errors in a single HR measurement (e.g., zero values) were deleted. In cases in which a patient had reported several RPE values for a single exercise step, we calculated an average of the lowest and the highest RPE values rounded up to the nearest RPE point. To avoid systematic bias in the selection process, all RPE and

HR data in each exercise session were manually checked and reviewed by two independent investigators. Inconsistencies were reviewed and, in cases where agreement was not reached between the two investigators, a third investigator was questioned.

Duration of each of three exercise steps varied between exercise sessions and, in order to ensure that patients reached a steady-state period in their exercise intensity, only sessions having the longest duration in the three exercise steps (five-ten-five minutes) were utilised for analysis. Therefore, only 18 sessions per patient were available for analysis (session 1–6, 10–12, 16–18, 22–24 and 31–33). Furthermore, to reflect a steady-state period, an average HR was calculated in a window of the last two minutes for each exercise step, in accordance with Aamot et al.[83] (see figure 2). The cardiovascular response was defined as the slope between changes in HR (bpm) per 1.0 unit change in RPE.

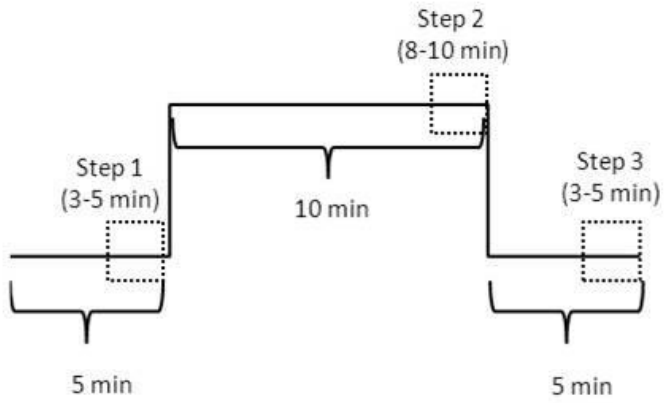

Figure 2: Graphic overview of the three data collection points in study I-II

As a part of the two RCTs, all patients underwent a maximum cardiopulmonary exercise test before initiating the exercise intervention.[97,98] Furthermore, demographic information and medical records, together with the Hospital Anxiety and Depression Scale (HADS),[117] were collected at baseline. The New York Heart Association (NYHA) Functional Classification and the European Heart Rhythm Association (EHRA) score of atrial fibrillation related symptoms were used to classified disease specific symptoms, at baseline, in patients who had undergone heart valve surgery and patients treated for atrial fibrillation, respectively.

To test if a familiarisation period were necessary before patients could apply RPE (Paper II), all exercise sessions performed by a patient were divided into two groups. One group had all exercise sessions performed within the first two weeks of training and the other group contained all sessions performed after the second week of training. As RPE is found to underestimate at higher intensity

ranges,[83] exercise intensity was divided into low / moderate (RPE ≤ 15) and high (RPE > 15) intensity, to explore whether intensity ranges would affect the use of RPE (Paper II).

Statistical Analyses

In Paper I, linear regression was used to investigate the relationship between RPE and HR, during the last two minutes of each exercise step. First, analysis was run by including data from all three exercise steps and, afterwards, run separately for each exercise step. All regression analyses were performed with and without adjustment for consumption of HR-reducing medications (beta-blockers and calcium antagonists). Furthermore, we calculated Spearman's correlation coefficient (rho) and the coefficient of determination (R^2) for all models. Finally, within each of the three exercise steps, we calculated the intra class correlation (ICC) to compare the within-patient variance to the total of the between-patient and within-patient variance separately for HR and RPE.

In Paper II, an independent 2 sample t-test, Wilcoxon-Mann-Whitney test or a chi-square test were used to examine the difference in HR, RPE, the number of training session per patient, demographic variables and medical records between the centre-based and home-based settings. Linear regression was also used to assess the cardiovascular response in each of the two settings. Furthermore, linear regression was used to explore whether the range of exercise intensities, familiarisation with RPE, psychological status (i.e., anxiety and depression), or patient characteristics (i.e., age and gender) would influence the use of RPE. To explore significant differences in the cardiovascular response in relation to the investigated variables, the interaction between RPE and each of these variables was calculated. Where possible, we increased the statistical power in these analyses by considering all variables as continuous. However, in order to simplify the presentation of data, all results were expressed as an 'above' or 'below' categorical cut off point for each of the investigated variables. In Paper II, all linear regression analyses included data from all three exercise steps and were all adjusted for HR-reducing medications, since we illustrated in Paper I that this would only improve the strength of the association between HR and RPE by approximately 9%.[118]

SAS Enterprise Guide 5.1 (SAS Institute, Cary, NC, USA) performed all statistical analyses. Regression models in both papers was run with a within patient cluster to take the repeated-measures nature of the data into consideration. Statistical significance was expressed as $p < 0.05$.

Paper III: Exercise setting – patient preference and health effects

Study design and population

Patients undergone either radiofrequency ablation for atrial fibrillation or heart valve surgery and allocated to the CopenHeart exercise intervention in one of the two RCT's were eligible in the study.[97,98] They were included if they were age 18 years or over, were able to speak and understand Danish with no musculoskeletal system or organs disorders complicating exercise training. [97,98] The CopenHeart intervention is described in detail, in the section named "Summary of the CopenHeart project" (page 19).

Outcome assessment

All physical and mental outcome variables, common to both CopenHeart trials, were extracted.[97,98] Physical capacity was assessed objectively from a maximum cardiopulmonary exercise test, performing a ramp protocol on an ergometer bicycle, a Sit-to-Stand (STS) test and six minute walk test. Specifications for all three tests are explained in detail elsewhere.[97,98] All physical tests were performed before and after the exercise intervention (one month and four months after hospital discharge) and at twelve months after hospital discharge.

The International Physical Activity Questionnaire short-form (IPAQ)[119] assessed patients' self-reported level of physical activity. Patients reported their generic mental health status by responding to the Short-Form 36 (SF-36) questionnaire.[120] The results of which are presented as the SF-36 physical component score and mental component score.[120] Level of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS).[117] All questionnaires were collected at baseline, 1, 4, 6, 12 and 24 months post hospital discharge.

Adherence to the exercise intervention was calculated by reviewing the patient's individual training diary and heart rate monitors.[121] In accordance to Beauchamp et al,[11] patients were categorised into one of the following two groups, either 'adherent': patients participating in ≥75% of the 36 training sessions (i.e., ≥27 sessions), or 'non adherent': patients participating in <75% of all training sessions.

The New York Heart Association (NYHA Functional Classification and European Heart Rhythm Association (EHRA) score of atrial fibrillation related symptoms were used to prescribe disease-specific symptoms at baseline, in patients who had undergone heart valve surgery or ablation for atrial fibrillation. In order to explore the degrees of comorbidity at baseline, the Charlson comorbidity index was calculated for all patients.[122]

Statistical analyses

The software SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses. An independent two-sample t-test, or a Chi-square test explored differences in patient demographic, medical condition and exercise adherence between exercise settings. A one sample binomial test compared patients' preference for either a home-based setting or a centre-based setting. A linear mixed effect regression model adjusted for sex, age, and diagnosis compared all the physical and patient-reported outcomes at baseline between the two settings. Furthermore, the same model compared outcome differences over time between the two settings by introducing a time x setting interaction. All over-time-models were performed unadjusted and adjusted for gender, age and diagnosis. Level of significant was set at $p<0.05$.

RESULTS

The following results sections will include the central results of this thesis. For secondary results, please see the included papers in the appendices.

Paper I-II

The total numbers of patients allocated to the exercise intervention in the two RCT trials was 177. One other patient was taken into account as mistakenly allocated to the control group but participated in the exercise intervention. Of the 178 eligible patients, 66 were excluded for various reasons; 17 were unable to participate in the exercise intervention and three patients was not given a diary both due to post-complications or withdrawal, 25 patients had an old diary with a lack of preselected RPE levels and, unfortunately, 21 patients either lost or failed to returned their diaries. A total of 112 patients, with 2,016 potential training sessions, were therefore considered in the final analyses.

Of the 2,016 potential training sessions, 304 were found to be ineligible because some patients did not accomplished all 36 exercise session before the 12 week exercise period had ended. A total of 1,712 exercise sessions undertaken by 112 patients were, therefore, quality assessed by the two independent investigators. After the quality assessment of each individual exercise session, data were available from 874 exercise sessions corresponding to 97 patients. For more information on the selection process, please see Figure 3. As RPE and HR were reported three times in each exercise session, 2,622 paired RPE and HR values were available for analysis.

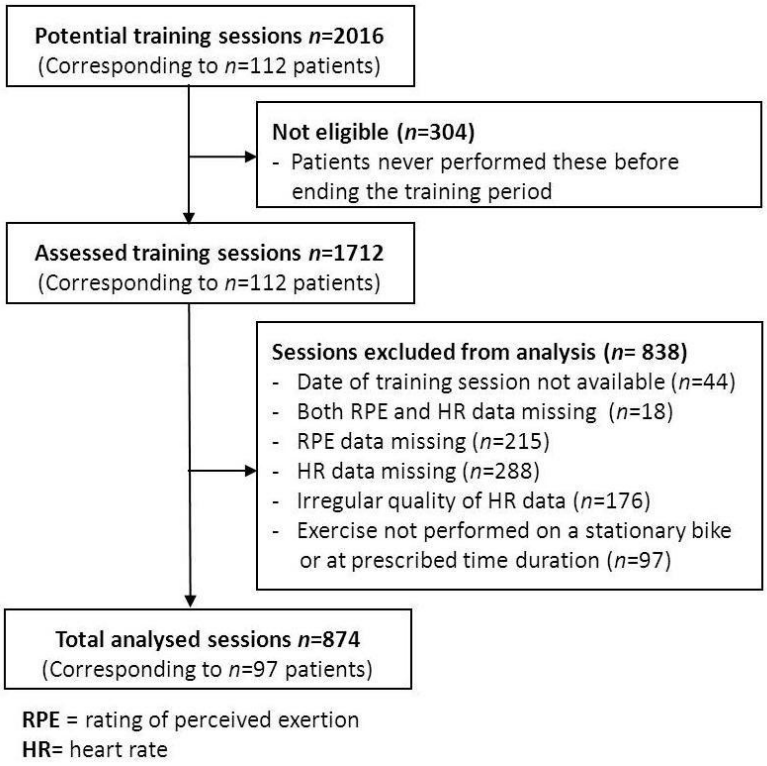

Figure 3: Flow chart summarising the selection process of Papers I & II

Study population

Patients had a mean age of 60.2 (±9.6) years and 71 (of the 97 patients) were men. Fifty-eight were treated for atrial fibrillation, 39 had undergone heart valve surgery and nearly half of patients received HR reducing medication (i.e., β-blockers or Calcium antagonists). Fifty-three patients preferred to train in a supervised, centre-based setting (i.e., 467 training sessions corresponding to 1,401 data points) and 44 in a self-managed, home-based setting (i.e., 407 training sessions corresponding to 1,221 data points). No difference was found between patients in centre-based setting and home-based setting, despite a higher maximum watt level favouring patients in the home-based setting (mean difference 28.5 (95% CI 5.6-51.5, p=0.016)). There were no other differences found between patients in the two settings. See Table 2 for more population characteristics.

The median number of exercise sessions performed per patient was 10 (IQR 4–14), independent of exercise settings (p= 0.692).

Table 2. Baseline characteristics, training location, cardiac history and medical records and conditions presented for all patients and for patients in each of the two settings. (paper I-II)

	All Patients (*n* = 97)		**Centre-based (*n* = 53)**		**Home-based (*n* = 44)**		**Difference between settings**
Demographic data	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD**	**p-value**
Age	97	60.2 (9.6)	53	61.5 (10.2)	44	59.6 (8.8)	0.334
Height	97	178.6 (9.0)	53	177.9 (8.7)	44	179.4 (9.6)	0.408
Weight	97	83.7 (16.5)	53	81.8 (16.6)	44	86.0 (16.2)	0.509
BMI	97	26.1 (4.1)	53	25.8 (4.5)	44	26.4 (3.7)	0.323
Sex (men/women)	71/26		40/13		31/13		0.579
Patient type (radiofrequency ablation/valve replacement)	58/39		28/25		30/14		0.125
Physical capacity							
Watts (maximum)	95	156.8 (57.6)	52	143.9 (48.4)	43	172.4 (64.3)	0.016
Peak VO_2 (ml/kg/min)	95	23.8 (8.1)	52	22.8 (7.4)	43	25.0 (8.9)	0.189
NYHA/EHRA[a]		**(%)**		**(%)**		**(%)**	
I-II	74	(76)	44	(83)	30	(68)	0.087
III-IV	23	(24)	9	(17)	14	(32)	
Medical record							
β-blockers	34	(35)	19	(36)	15	(34)	0.857
Calcium antagonists	13	(13)	7	(13)	6	(14)	0.951
Warfarin	85	(88)	45	(85)	40	(91)	0.371
HADS[b]							
Anxiety							
<8	69	(71)	37	(70)	32	(73)	0.752
≥8	28	(29)	16	(30)	16	(27)	
Depression							
<8	89	(92)	48	(91)	41	(93)	0.725[c]
≥8	8	(8)	5	(9)	3	(7)	

[a] The New York Heart Association (NYHA) Functional Classification/ European Heart Rhythm Association (EHRA) score of atrial fibrillation related symptoms
[b] The Hospital Anxiety and Depression Scale
[c] Fisher's exact test

The relationship between rating of perceived exertion and heart rate

Figure 4 shows the overall relationship between HR and RPE when all three exercise steps are taken into consideration. Linear regression across all three steps showed a change in HR by 6 (95% CI 5–7; $p < 0.001$) bpm per 1.0 unit change in RPE. Adjusting for heart rate reducing medication did not affect the interpretation of the findings, but increased R^2 from 26% to 34%. A similar association was found when analysing the three exercise steps separately. Table 3 presents data for each of the three exercise steps.

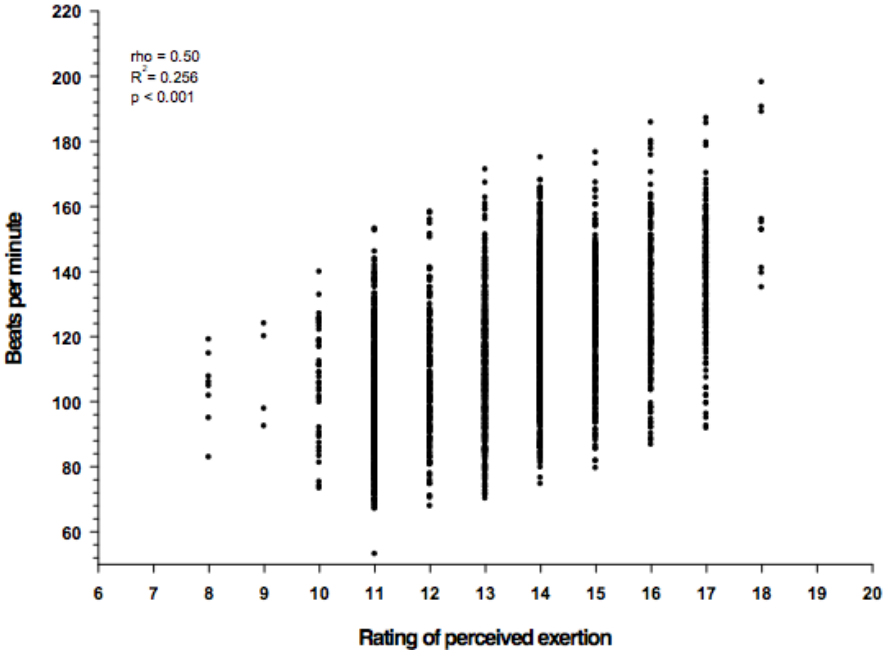

Figure 4: The overall relationship between ratings of perceived exertion and corresponding heart rate when data from all three exercise steps are taken into consideration (n = 2622). (Figure citation: rho:Spearman correlation coefficient. R2: coefficient of determination. p: p-value).

Table 3. Summary of the linear regression relationship between HR and RPE for each of the three exercise steps

		Unadjusted slope				**Adjusted slope[a]**			**Intraclass correlation**	
	RPE	Change in HR (beats per minute)	p-value	rho	R^2	Change in HR (beats per minute)	p-value	R^2	Variance in HR	Variance in RPE
Step 1	13 (11-14)	6 (4-8)	<0.001	0.43	0.17	6 (4-7)	<0.001	0.25	0.79 (0.73-0.84)	0.50 (0.41-0.60)
Step 2	15 (14-16)	7 (5-9)	<0.001	0.45	0.21	6 (5-8)	<0.001	0.32	0.79 (0.73-0.85)	0.39 (0.31-0.49)
Step 3	13 (11-14)	6 (4-8)	<0.001	0.44	0.19	6 (4-8)	<0.001	0.27	0.76 (0.71-0.83)	0.51 (0.42-0.61)

RPE values are given as median (interquartile ranges). HR data are given as the mean (95% confidence level). Adjusted slope: [a]Model adjusted for HR-reducing medication consumption (beta-blockers and calcium antagonists). rho: Spearman correlation coefficient. R^2: coefficient of determination. HR: heart rate. RPE: rating of perceived exertion.

The influence of setting

When comparing the two settings, a systematic difference was found in the mean HR (p=0.004) and the median RPE level (p<0.001). Patients in the centre-based setting had a higher mean HR of 118 bpm (95% CI: 117 to 119) versus 115 bpm (95% CI: 114 to 117) and a higher median RPE level of 14 (IQR: 13 to 15) versus median of 13 (IQR: 12 to 14), compared to patients in the home-based setting. Despite these differences between settings, the change in HR per 1.0 unit change in RPE was similar between settings (6.1 bpm (95% CI: 4.8 to 7.5) and 5.3 bpm (95% CI: 4.0 to 6.5) in a centre-based setting and in a home-based setting, respectively) without an interaction between setting and the use of RPE (p=0.510) (see Table 4).

Table 4. Summary of the linear regression relationship between heart rate (HR) and rating of perceived exertion (RPE) across setting, patient characteristics and exercise training categories

Variables	Number of patients	Number of RPE and HR pairs	Mean change in HR (beats/min) per 1 unit of RPE[a]	95% confidence interval	Interaction p-value
Setting					
Supervised centre-based	53	1401	6.1	4.6 to 7.5	0.510
Self-care home-based	44	1221	5.3	4.0 to 6.5	
Age					
≤60	42	1293	5.8	4.5 to 7.1	0.647[b]
>60	55	1329	5.5	4.3 to 6.7	
Sex					
Women	26	768	5.7	4.2 to 7.3	0.675
Men	71	1854	5.9	4.8 to 7.0	
Patient type					
Radiofrequency ablation	58	1488	5.2	4.3 to 6.2	0.392
Valve replacement	39	1134	6.0	4.6 to 7.4	
EHRA/NYHA[c]					
I- II	74	2013	5.6	4.6 to 6.6	0.002[b]
III-IV	23	609	4.8	3.1 to 6.4	
HADS[d] **Anxiety**					
<8	69	2007	5.6	4.5 to 6.8	0.480[b]
≥8	28	615	5.1	3.7 to 6.6	
HADS[d] **Depression**					
<8	89	2475	5.5	4.6 to 6.4	0.330[b]
≥8	8	147	4.5	0.8 to 8.3	
Time of rating[e]					
≤ 2 weeks	-	1071	6.2	4.8 to 7.6	0.155
> 2 weeks	-	1551	5.4	4.4 to 6.5	
RPE point					
≤ 15	-	2235	5.5	4.5 to 6.5	0.096
> 15	-	387	8.3	4.5 to 12.0	

[a] All associations adjusted for use of HR-reducing medication
[b] Based on interaction of variable expressed as a continuous variable
[c] The New York Heart Association (NYHA) Functional Classification/ European Heart Rhythm Association (EHRA) score of atrial fibrillation related symptoms
[d] The Hospital Anxiety and Depression Scale
[e] RPE ratings divided into the first two weeks and after the first two weeks of the 12 week intervention period.

The influence of other factors

Of all factors investigated, only a significant interaction was found between disease specific symptoms (NYHA / ERHA) and the use of RPE (p=0.002). NYHA / ERHA patients in Classes I-II had a 5.6 bpm (95% CI 4.6 to 6.6) alteration and patients in Classes III-IV had a 4.8 bpm (95% CI: 3.1 to 6.4) alteration per 1-point change in RPE. Since only two patients were classed as Class IV, these were excluded in a sensitivity analysis showing a non-significant interaction between NYHA / ERHA and the use of RPE (p=0.371). Table 4 shows the relationship between RPE and the remaining factors analysed in Paper II.

To ensure that the observed baseline difference in maximum watt levels, between the two settings, did not impact our results, all linear regression analyses conducted in Paper II were adjusted for maximum watt levels. These sensibility analyses did not change the interpretation of our findings.

Paper III

One hundred and seventy-eight patients were allocated to the intervention group within the two RCT trials (as reported in Papers I and II). Of the total 178 patients, 158 participated in the exercise intervention and were included in Paper III because 20 patients never entered the exercise intervention, as a result of post complications or withdrawals. A similar proportion of preferences were found for the two exercise settings (p=0.233), with 55% (95% CI 45% to 63%) preferring a centre-based setting and 45% (95% CI 37% to 53%) preferring a home-based setting.

The number of patients who attended all three test sessions was 64 (74%). Sixty-eight (78%) completed their questionnaire booklet at all times points during the study period in the centre-based setting. In the home-based setting, these numbers were 60 (85%) and 57 (78%), respectively. (Figure 5 shows the exact numbers of patients attending exercise testing and responding to the questionnaire booklet at all included time points).

Patients' characteristics and preference between settings

All patients demographic, medical condition and exercise adherence divided by setting can be found in Table 5. Prior diagnoses had a tendency to influence the preference because patients who underwent heart valve surgery preferred a centre-based setting to a higher degree. Patients who underwent an ablation preferred a home-based setting (p=0.002). In case of demographics, no other baseline differences were found between the two settings.

Figure 5: Patient flow in paper III

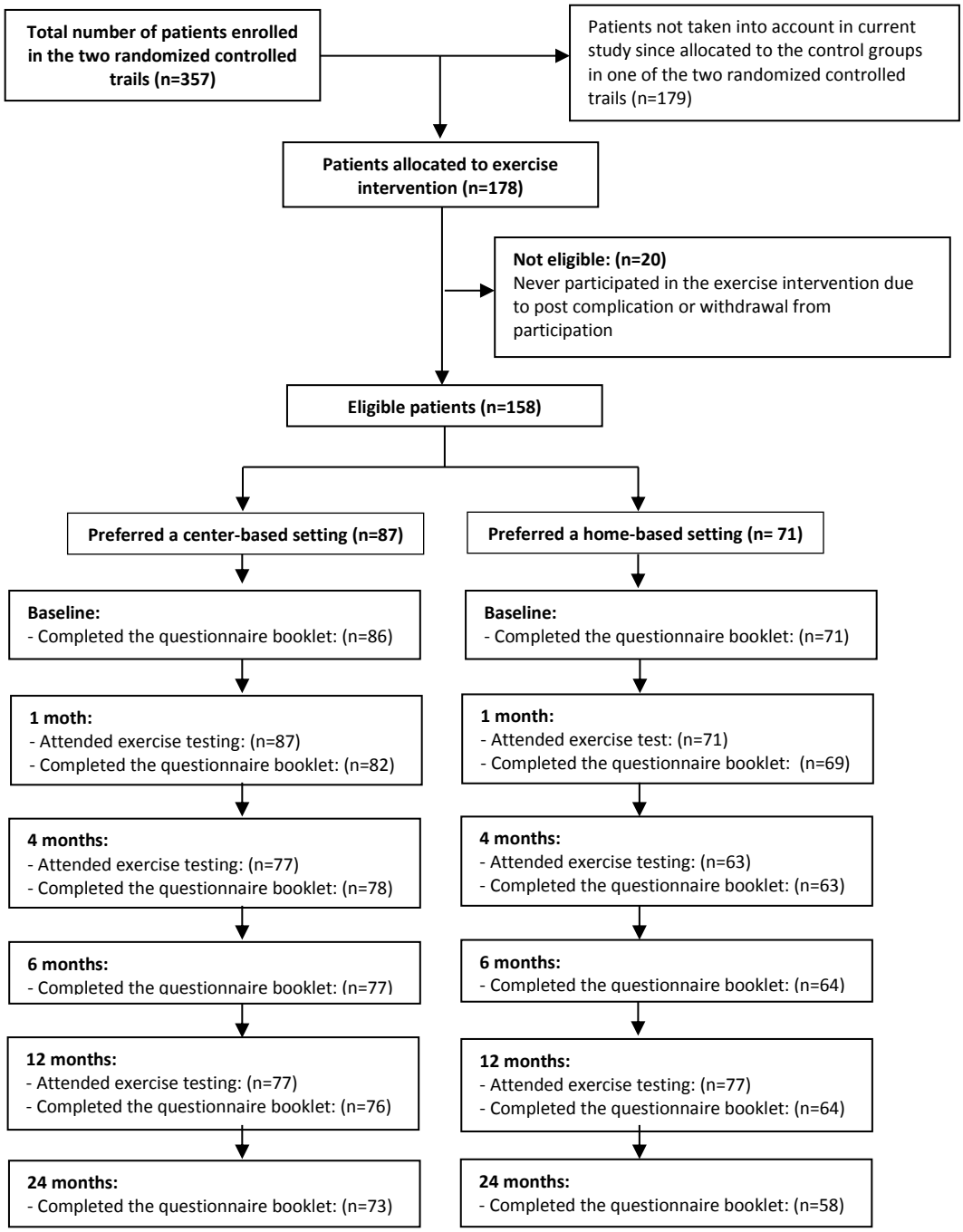

Table 5: Patients demographic, medical condition and exercise adherence compared between settings (paper III)

	Centre (n=87)		Home-based (n=71)		
Demographic data	*n*	Mean (±SD)	*n*	Mean (±SD)	p-value
Age	87	62.0 (10.3)	71	58.9 (9.8)	0.056
Height	87	177.1 (8.4)	71	179.9 (7.8)	0.719
Weight	87	83.0 (16.7)	71	81.4 (15.5)	0.220
BMI	87	25.9 (4.2)	71	26.1 (4.2)	0.979
Sex (Female/Men)	23/64		17/54		0.720
Employment status		**(%)**		**(%)**	
Employed	42	(48%)	37	(52%)	0.631
Unemployed	45	(52%)	34	(48%)	
Marital status					
Living alone	14	(16%)	13	(18%)	0.713
Living with a partner	73	(84%)	58	(82%)	
Patient type					
Radiofrequency ablation	43	(49%)	52	(73%)	0.002
Valve replacement	44	(51%)	19	(27%)	
NYHA/EHRA class					
I	41	(47%)	25	(35%)	0163˜
II	32	(37%)	26	(37%)	
III	12	(14%)	19	(27%)	
IIII	2	(2%)	1	(1%)	
The Charlson comorbidity index					
0	79	(91%)	69	(97%)	0.187[a]
≥1	8	(9%)	2	(3%)	
Medical Records					
Warfarin	71	(82%)	58	(82%)	0.990
B-Blockers	32	(37%)	39	(55%)	0.023
Calcium antagonists	23	(26%)	10	(14%)	0.057
Statin	34	(39%)	14	(20%)	0.009
Exercise adherence					
Participating in ≥27 exercise sessions	46	(56%)	40	(63%)	0.435

NYHA/EHRA class :The New York Heart Association (NYHA) Functional Classification/ European Heart Rhythm Association (EHRA) score of atrial fibrillation related symptoms
[a]Fischer Exact test

The mixed model adjusted for sex, age, diagnoses, showed higher physical performance and physical health at baseline, favouring patients that preferred a home-based setting compared to the centre-based setting (i.e., outcome differences in baseline maximum watt levels (mean difference 15.9 (95 % CI 3.7-28.1; p=0.011) and in SF-36 physical component scale scores (mean difference 5.0 (95 % CI 2.3-7.6; p=0.001)). No other baseline differences were found in relation to the physical and patient reported outcomes between the two settings.

Exercise adherence

Exercise adherence monitored by the individual exercise diary and HR-monitor was similar between the two settings (p=0.435). Approximately 60% of all patients completed ≥75% of the 36 training session (see Table 5).

Over time differences between the two settings.

Physical and patient reported outcomes over time are presented in the Appendix to paper III represented by Figures 2 and 3 and, in case of mean values, in eTables 2 and 3. Progression from baseline to 24 months only varied between settings in relation to the HADS depression score (F(4.44), p=0.002) and the interpretation was not changed when adjusted for sex, age, and diagnosis.

DISCUSSION

The current thesis consists of three exploratory studies, evaluating the use of patient-preferred setting and its impact on exercise intensity and clinical health effects in exercise-based CR. The primary findings, which are important to clinical practice, showed that patients have the ability, through RPE, to regulate their own exercise intensity and that this ability is independent of the exercise setting. Primary results of further clinical importance are as follows; when offering patients a choice, an equivalent proportion of patients will prefer a self-managed, home-based setting and a traditional, supervised centre-based setting. Furthermore, patients will achieve similar health effects regardless of their preferred setting, when performing the same structured exercise-based CR intervention. Given these results, it seems reasonable to suggest that patient-tailored CR interventions can be developed by offering patients a choice between a centre-based and a home-based setting, as a part of routine practice, without exercise performance and the potential health benefits will be influenced.

The relationship between rating of perceived exertion and heart rate (Paper I-II)

The importance of adequate exercise intensity in exercise-based CR has resulted in different techniques to control and prescribe intensity.[17] Whilst many of these techniques lead to a high degree of internal validity, they will often be too complex, time consuming or expensive to implement in routine clinical practice or in home-based settings. Oxygen uptake, HR or RPE are listed in most exercise-based clinical guidelines as techniques to assess and prescribe intensity in cardiac patients.[17–19] Unfortunately, oxygen uptake is unavailable across all exercise settings whilst

reasons like arrhythmia or the use of beta-blockers complicates intensity assessment based on HR.[17] RPE has been widely investigated in experimental designs conducted in supervised settings, in both healthy individuals[76–79] and cardiac populations.[74,80–83,86,87] In cardiac patients, RPE is shown to be reliable[80] but, unfortunately, is likely to overestimate and / or underestimate the intensity.[81–83] Especially at higher RPE levels underestimation can occur.[83] Despite these facts, studies in cardiac patients have found that exercise guidance from RPE induces similar health effects as objective physiological monitoring tools.[84,85] Furthermore, RPE is widely used to guide exercise intensity due to its simplicity.[123] The needs for simplicity in situations where exercise intensity is controlled by patient themselves is likewise illustrated in our data, as we excluded a large number of exercise sessions due to missing or irregular HR recordings, of which patients themselves were responsible for collecting (see Figure 3 (Paper I-II)).

In Paper I, patients participating in CR were able to guide exercise intensity from the use of RPE, independent of the consumption of heart rate reducing medication. It is important to be careful when interpreting the results and keep in mind the change in RPE is compared to the change in the absolute HR response. From an experimental standpoint, one might argue that this does not express the exact magnitude of intensity, normally expressed in relation to the maximum HR.[17,18] Still, however, the results demonstrate patients' ability to regulate their exercise intensity using RPE. This is an important finding, given the fact that increasing training regimens is recommended within a CR programme.[18] In order for RPE to be useful in routine CR, patients must, therefore, be able to regulate their exercise intensity through RPE during an exercise period. Nonetheless, future studies should consider the exact precision of RPE when investigating it's usability in daily CR.

The use of RPE across settings in CR has never been investigated. The results of this thesis suggest that, without supervision, patients in a home-based setting are as able to change their cardiac response as patients receiving supervision in a centre-based setting (Paper II). Despite the non-significant interaction between the two settings, a slightly larger mean HR was found in the centre-based setting. This could indicate a higher level of exercise intensity in centre-based compared to the home-based setting (mean difference of 2.4 bpm (95% CI: 0.8 to 4.1, p=0.004)). Nevertheless, the statistical difference is unlikely to be of any clinical importance, in view of the fact that Weiser and colleagues have suggested that a clinically meaningful alteration in HR is 5 bpm.[86] Furthermore, the cardiovascular response was defined as the slope between changes in HR (bpm) per 1.0 unit change in RPE and, from this definition, exercise settings did not impact upon patients' ability to use RPE across settings. From a clinical perspective, this finding is important as it helps overcome concerns about exercise prescriptions and performance in a home-based setting.[72]

Furthermore, this finding is essential when investigating whether performance of the same structured exercise programme will cause similar effects across either two settings.

In cardiac patients, Pavy et al.[67] found a rate of severe cardiac events of 1 per 8,484 during exercise stress tests and 1 per 49,565 patient-hours during exercise training. The cardiac arrest rate was 1.3 per million patient hours of exercise.[67] Exercise settings, like the home-based setting, are not reported to increase such risk,[15,64,65] not even during high intensity training.[124] However, despite more recent evidence reporting the frequency of major cardiovascular complications to be low during exercise training, the rationale of using RPE in high-risk cardiac patients is not recommended. We indicated a difference in the HR-RPE association due to disease severity (see Table 4), which indicates that high-risk patients use RPE differently from lower-risk patients. Still, the detected difference was very small and only two patient were categorised as NYHA / EHRA Class IV, therefore, it is uncertain whether our findings is of any clinically relevance (mean of 5.6 bpm per 1.0 unit change in RPE (95% CI: 4.6 to 6.6) for NYHA / ERHA Classes I-II versus 4.8 bpm (95% CI: 3.1 to 6.4) per 1.0 unit change in RPE for NYHA/ERHA Classes II-IV; interaction p=0.002)). Still, for safety reasons, it should be emphasised that RPE is an assessment tool for low-risk patient groups only as the results of previous studies shows RPE to occasionally overestimate or underestimate exercise intensity.[81–83]

Patient preference - Does one setting suit all patients? (Paper III)

Findings in Paper III show an equivalent distribution in patients' preference towards the two exercise settings. Previously, Dalal et al.[89] reported an even higher proportion of patients (57% of 126 patients) who preferred a home-based, self-manual compared to centre-based CR intervention. The National Audit of Cardiac Rehabilitation 2013, from the United Kingdom, shows that 27% of patients engaging in CR were enrolled in a home-based exercise programme.[90] That patients in fact prefer a home-based programme is highly relevant as the increasing numbers of cardiac patients combined with a reduction in cardiovascular mortality rate will put enormous pressure to health-care centres in the coming years.[29–32] Including home-based programmes as a part of secondary prevention in cardiovascular care could be one of many promising solutions towards this problem.[13–16,62,63]

It is important to emphasise that newer CR delivery models should not replace traditional centre-based models. This is illustrated by the fact that a proportion of patients, in Paper III and existing literature, will select either of the two settings. Indeed, the opportunity to select different settings enables patients to choose according to their individual needs and preference.[13–16,59,125] In

qualitative research, some patients are found interested in programmes that can be implemented into their everyday life, like a home-based programme, while others prefer settings of a more social nature, or settings that offer the opportunity for supervised intensity monitoring, such as given in a centre-based setting.[91,93] Offering the same standardised CR intervention to all patients, as is the case in most CR practices today, is highly unlikely to fit individual needs and preferences of all patients.

Patients employment status, income and ethnic background has further been reported to be factors that will could effect a patient's choice of setting.[92] The results of Paper III illustrate further that patient preferences towards a setting are likely to be influenced by the individual's diagnosis. Furthermore, our results illustrated a clear divide in the study population at baseline, due to their physical function and physical health, with an increased exercise capacity (maximum watt level (mean difference 15.9 (95 % CI 3.7-28.1; p=0.011)) and physical health (SF-36 physical component score (mean difference 5.0 (95 % CI 2.3-7.4; p=0.001))) in favour of the home-based group. These findings are somewhat surprising because it was anticipated that the home-based programme would accommodate those patients who were unable to attend CR sessions due to problems accessing the rehabilitation centre, e.g., elderly.[63,65] Nonetheless, in a small cross-sectional study by Filip et al., patient preferences towards a home-based setting was not different between either age or sex.[126]

Effect and adherence between exercise settings (Paper III)

The health effects between home-based and centre-based programme are reported to be identical.[15,65] However, the effect among these CR settings are mainly investigated though RCT designs that eliminate motivational variables, in which preference to a specific setting can be categorised.[15,21,22,64] An exception to this is the pragmatic study design by Dalal et al.,[89] in which patients were given the opportunity to self-select either hospital-based CR classes or a home-based self-help package as a part of CR. The study reported no difference after 8 months between the two settings.[89]

Our findings are very similar to Dalal et al. However, whilst Dalal et al.[89] introduced a different intervention in each of the two settings (hospital-based rehabilitation classes over eight-ten weeks, one month after hospital discharge, compared to a home-based self-help package of six weeks duration, supported by a nurse one week after hospital discharge), we initiated the same structured exercise intervention following CR guidelines in both exercise setting. Despite this contrast, both studies demonstrate that patients participating in a CR programme can be offered a choice between a home-based programme and a centre-based programme without it impacting upon the effect of the

CR intervention. This emphasises the fact that patient-preferred settings can be used as a means of developing tailored CR interventions in standardised CR.

We were able to investigate the long-term effect (>1 year) between settings where evidence is sparse.[15] Similar to our findings, Oerkild et al,[127] Marchionni et al[128] and Jolly et al[14,129] found no health differences between settings after 12 months, 14 months and, 12 and 24 months, respectively. Only Smith and colleagues reported that patients who were allocated to a home-based programme were able to maintain the beneficial effects of rehabilitations to a higher extent than patients allocated to a centre-based setting, after one and even after six years.[130,131] They also demonstrated a higher likelihood that physical activity levels would become habitual, when patients had been engaged in a home-based programme. This finding is in contrast to our results.

Exercise adherence was similar between the two settings, with ~60% performing over ≥75 of all exercise sessions (p=0.435). Some will argue that this is a rather small proportion, whether it is in a supervised or an unsupervised setting. However, this can be compared to the results of a large cohort study in which no more than 40% of all patients attended ≥30 sessions, over a 36 week period during routine CR.[132] Although a dose–response relationship seems to exist in exercise-based CR,[11,12,66,132,133] the all-cause mortality risk is still found to decrease in patients who simply attended one CR-session, compared to patients that never attended CR, with reported risks from 21-58%.[11,12] In addition, 75% of all patients performed at least 18 exercise sessions, during the 12-week intervention period. In view of previously reported studies, this may probably have a substantial decrease in the risk of long-term all-cause mortality.[11,129]

To our knowledge, this is the first study to explore adherence to the same structured exercise programme performed in different patient-preferred settings. Trials randomising cardiac patients to either centre-based or home-based CR have shown different results, in terms of exercise adherence.[15] Most of the literature reports similar or enhanced adherence rates in favour of home-based training.[14,15,89,128,129,134,135] Only Aamot et al.[124] is known to report a superior adherence rate in relation to a centre-based setting. It is difficult to compare results across studies, due to conflict in definitions and measurements of adherence.[64,121] We primarily assessed exercise adherence with a simple, unsupervised, subjective monitoring method in the form of a training diary assisted by data from the HR monitors. From this subjective method, we cannot be completely confident that patients actually performed the exercise programme. Nonetheless, when determining adherence, no "gold standard" has yet been agreed upon and both subjective and objective methods have limitations.[121]

Establishing patient-preferred settings in national services is widely suggested to raise the low attendances rate to current CR.[13–16,59] Nevertheless, this is a new field of study and has only been explored to a very limited extent.[62,63] However, in the light of existing attendance rates to CR, it is a field of utmost importance.

Methodological considerations

Before an intervention or method is implemented into everyday clinical practice, both the efficacy and effectiveness of the intervention / methods must be established, because the successful results of an intervention from a efficacy study conducted under optimal condition may not necessarily be reproduced when testing the intervention during real world conditions (the effectiveness).[116] Today, most studies investigating the health effect between various exercise settings in CR have been generated from traditional RCTs,[15] or in highly standardised experimental designs when testing exercise intensity assessment through RPE in CR.[81–86] In fact, within the area of CR, evidence conducted by "real-world" design is sparse.

In addition to our overall aim in this thesis, we were keen to enhance the generalisability of our findings to routine CR. This was accomplished through elements like the use of a heterogeneous patient population, including patients' own preferences, initiation of a simple exercise intervention following CR guidelines and feasible to be implemented in routine practice and, lastly, the use of a multicentred approach in which patients selecting the centre-based setting could choose from 29 collaborating healthcare centres. Rotwell et al.,[23] Gartlehner et al.,[26] and Glasgow et al.[25] have all published lists of items that will, potentially, enhance the generalisability in research studies. Compared to the lists of items, it seems reasonable to assume that, to some extent, we have enhanced the generalisability of our findings to routine CR.

Still, one could argue that the generalisability, in some areas, is somewhat lacking because data in the present thesis was collected through a RCT design with narrow inclusion criteria.[23] However, Godwin et al.[24] argued that a study could be designed for either purpose, efficacy or effectiveness. The risk of enhancing the generalisability is that the internal validity is compromised. Therefore, studies measuring effectiveness need to have a balance between internal and generalisability, in contrast to efficacy-designed studies.[24] In our attempt to increase the generalisability, we especially reduced the internal validity by not allocating patients equally between the two exercise settings. Therefore, it can be argued that it was important to maintain and balance the internal validity within other aspects of the study, even though this could impact upon the generalisability of our findings to routine CR. Nonetheless, when compared to previous studies investigating exercise settings or

exercise intensity assessment methods in CR, we believe the results achieved in this thesis enhance the level of generalisation to routine CR practice.

It is important to emphasise that some other studies investigating CR settings have been conducted using research designs that enable the results to be generalised and implemented into everyday clinical practice. An example of this is the Heart Manual that now is a part of routine CR care in UK.[14,89,129,136,137]

Limitations

There are important limitations that should be considered when interpreting the findings of this thesis. These are presented below:

In relation to the entire thesis

The current thesis is based upon three exploratory studies. The nature of exploratory research allows researchers to explore tendencies and associations within a research area of interest. The limitation is that it will not allow cause-and-effect conclusions based on study findings.[116] Thus, findings within this thesis must be interpreted as trends and associations. Only Paper III explores effect outcomes and, despite the limitation in cause-and-effect conclusions, the findings will contribute to our understanding and offer an insight into patient-preferred settings.

Secondary analyses, from existing data, were conducted in all studies presented in this thesis. This data was collected for another purpose which causes some limitations due to a lack of control over the data collection methods and the quality of the data.[116] Furthermore, the number of eligible patients was based on power calculations made for the two RCT trials,[97,98] not for the purpose of studies in the current thesis. Nevertheless, it is important to emphasise that the CopenHeart trials are high-quality studies that have undergone substantial peer review[97,98] and that the use of existing data from such studies can provide important knowledge for future studies without incurring high expenses in terms of time or cost.[116] This is particularly relevant when combined with the findings of previously published literature.[116] In addition, we took account of patient characteristics, sample size, missing data and data distributions, as part of the secondary analyses which, to some extent, can reduce the impact caused by potential data limitations.

In an attempt to increase the generalisability of current findings, we included a mixed study population, as is normal in routine CR.[23] The diversity in pathologies between cardiac diagnoses is likely to limited our findings to the two included patients diagnoses (patients who have undergone

either heart valve surgery or treatment for atrial fibrillation) and, thereby, reduce the generalisability to other cardiac diagnoses.

All patients who preferred a centre-based setting could choose from 29 collaborating health-care centres, which all were introduced and certified to the exercise intervention by the same physiotherapist. However, despite our intentions to deliver the same intervention across all centres, performance may still be somewhat different between centres. A single-centre setup would have reduced such variation,[24] but could also reduce exercise adherence as the accessibility between hospital and local facilities are known to influence adherence to CR.[53] In addition, a single centre design would definitely reduce the generalisability as guidelines in Denmark refer patients to CR local healthcare centres.[23]

In relation to Papers I & II

In Papers I and II, RPE and HR data were registered and monitored by patients themselves. From a total of 1,712 exercise sessions, only 874 exercise sessions were included in the analyses. Of the excluded sessions, 697 were excluded due to poor quality in the HR recordings and missing HR or RPE data (Figure 3). Despite a sensibility analysis revealing no systematic differences between those patients included and those excluded, in terms of age (p=0.576), sex (p=0.540), patient type (p=0.834) or NYHA classification (p=0.464), the high number of excluded sessions can influence the result due to selection bias. Nonetheless, the nature of routine settings and unsupervised exercise programmes complicates the data collection process. For similar reasons, patients were not blinded to their HR monitors because they were responsible for the "start and stop" procedure. Not blinding patients to their monitors is likely to impact the results: RPE is a subjective measure and HR is objective, if a patient observes a change to their HR via the monitor their RPE is likely to be affected. In view of this, consideration in future studies should be given to developing simple ways to increase the data quality when assessing exercise intensity across a variety of settings. Patient performed all aerobic exercise sessions on a stationary bike, which is a normal approach in Denmark. However, the type of exercise is reported to impact the use of RPE in healthy adults[79] and a similar tendency will possibly occur if RPE is used through other exercise modalities in CR.

In relation to Paper III

In Paper III, we compared health outcomes between two exercise settings to which patients were allocated, based on their own preferences and not by a systematic randomisation technique. This approach will cause some extent of selection bias and confounding. These problems were taken into consideration by adjusting all analyses for important variables like gender, age and diagnosis.

However, adjusting for important variables will not completely eliminate these problems, but simply reduce them.[23]

Only outcome measurements common to the two RCT trials[97,98] were included in Paper III. For this reason, we were unable to evaluate disease specific quality of life, despite it being measured in both RCT trials. The HeartQoL instrument[138,139] was used to assess disease specific quality of life in patients post valve surgery[98] and the Atrial Fibrillation Effect on Quality of life (AFEQT)[140] was applied in patient after radiofrequency ablation for atrial fibrillation.[97] A comparison between these two instruments was, unfortunately, found inappropriate in the current study, but future studies should certainly take disease specific quality of life into consideration.

CONCLUSION

The present thesis investigates the use of patient-preferred settings in exercise-based CR through three exploratory studies, which have all generated results of importance for clinical practice. The primary findings reveal that, in routine CR, patients are able to adequately guide exercise intensity through the use of RPE regardless of exercise setting and, furthermore, that a self-managed home-based setting is preferred equally and is as effective as a traditional, supervised, centre-based setting when selected according to patient's own preferences. Thereby, our results clearly indicate that offering low risk patients a choice of different exercise settings when initiating exercise-based CR is one solution toward patient-tailored-interventions without affecting exercise performance, adherence or the health benefits gained from the intervention.

CLINICAL RECOMMENDATIONS

Traditional standardised CR interventions performed in a healthcare centre, on a fixed time schedule does not leave much room for individual tailoring of an intervention.[59] The idea that one unique intervention fits into all patients' profiles, needs and preferences seems unrealistic. What seems more realistic is that the elements included in a CR programme (e.g., exercise training) to a larger extent would fit a broader group of patients, if the delivery mode were changed towards the needs of the individual patient. Some patients will have, for example, the need for supervision while others simply need instructions to be able to perform unsupervised exercise training. Therefore, when engaging with cardiac patients, healthcare professionals should take individual patient needs and preferences into account and, as a healthcare professional, one must have an organisational

setup that provide the opportunities to include these needs and preferences into an individual CR programme.

Current findings illustrate that RPE is a practical solution that enables patients to perform and gain the same benefits in a home-based setting as in the traditional, centre-based setting. This should help overcome patient and clinical concerns about home-based exercise interventions and, thus, promote this mode of delivery which could contribute to a greater uptake in CR. Furthermore, overall, the findings of the present thesis illustrate that, through the use of modest solutions like a training diary and RPE, standardised exercise-based CR interventions are easily altered into effective home-based CR intervention producing new flexible delivery models useful in the expansion of patient-tailored-interventions.

Sackett et al[141] defined evidence based medicine as *"Integrating individual clinical expertise with the best available external clinical evidence from systematic research"*. Despite the fact that the required CR elements are well prescribed,[18,20] the most effective ways to deliver home-based interventions are still unknown. However, from the perspective of evidence based practice, it seems reasonable to assume that effective home-based interventions can be conducted by combining the effective CR elements and existing evidence with clinical expertise, until more specific evidence is obtained.

PERSPECTIVE AND FUTURE RESEARCH

During the last decade, the health effect of CR has been widely documented and clinical guidelines have enhanced the understanding of the minimum criteria for these interventions.[1–4,17–20] Even so, elementary enrolling of patients to CR represents a key issue.[6–9] The use of a single standardised CR setting is unlikely to fulfil all patients' preferences. Expanding the number of settings in CR will allow patients choice between settings in relation to their needs and preferences. However, the effect of offering patients choice of setting, in order to maximise their uptake, is a new field of study and it must be highly prioritised. Our findings with patient-preferred settings support the reasonably large body of existing evidence from RCT studies showing that a home-based setting can induce similar health effects as those known from a centre-based setting.[15,65] It is important that researchers in the future take previous research findings into account and prevent similar study designs from emerging.[142–144] Meanwhile, future studies need to take the next step of establishing whether the use of different settings actually will increase the uptake to CR, which were the main

reasons to develop alternative delivery models using home-based settings as an alternative to the traditional centre-based setting.[13]

It is important to underline that considering patients' preferred-exercise setting in isolation will not be the definite solution towards the low uptake in CR. All standardised delivery models offered to patients must be re-evaluated. Not only in the terms of what is offered to the different patient groups, but also where, why and who makes the offer. These factors should all be taken into account in an attempt to improve the uptake rate in future CR.

ENGLISH SUMMARY

Despite the well-documented benefits, the number of patients attending exercise-based CR remains insufficient. An alarmingly low attendance and adherence rate are reported in both national and international CR, constituting a major problem since it is associated with elements like increased risk of hospitalisation and cardiovascular mortality. Patient-tailored-interventions and alternative delivery models using home-based settings as an alternative to traditional, centre-based are suggested as solutions toward the problem.

Exercise intensity is a key-driver in exercise-based CR, but it is potentially more complex to prescribe and assess in an unsupervised home-based setting. Therefore, simple assessment methods providing patient themselves with the ability to regulate and guide exercise intensity across settings is needed. Rating of perceived exertion (RPE) is a simple assessment tool often applied in CR but it's usability has only been investigated in highly standardised experimental design and not in everyday clinical CR or across settings.

The majority of studies investigating the effect of home-based interventions in CR are conducted by a traditional RCT design. Home-based interventions, in which the choice of setting relies on patients' own preferences, have not been sufficiently investigated. Furthermore, increased attention toward the generalisability of such interventions into routine practice is required.

The overall aim of the present thesis was to investigate whether or not a simple assessment method, based on RPE, could enable patients to regulate their exercise intensity, regardless of exercise setting. Furthermore, to evaluate whether or not patients preferred a home-based setting when compared to a traditional centre-based setting and whether they achieved similar health effects between the two settings, when participating in exercise-based CR in relation to their preference. The thesis should enhance the generalisability of the findings to routine CR.

The objectives were explored through three exploratory studies using data from an exercise-based CR intervention conducted in two parallel designed RCT trials. Originally the RCT trials compared usual care to the effect of a comprehensive rehabilitation intervention of exercise training and psycho-educative consultations in patients who had either undergone ablation for atrial fibrillation or heart valve surgery.

The exercise intervention included a 12-week progressive exercise programme three times a week for approximately 60 minutes per session. Exercise intensity was based on the 15-point Borg RPE

scale. Patients were given a HR-monitor (Polar Electro, Finland) and training diary prescribing each of the 36 exercise sessions and containing instructions to the 15-point Borg RPE scale. All patients undertook the first training session in the same tertiary centre hospital (Department of Cardiology) and, thereafter, continued their programme in either a traditional, supervised centre-based setting or a self-management, home-based setting. Setting was selected in accordance to patients own preferences.

Data from HR-monitors and training diaries was used in two exploratory studies to investigate whether a subjective assessment methods, based on RPE, could adequately guide exercise intensity in routine CR (Paper I) and be similarly applied across settings (Paper II). A third paper, included and pooled all outcome variables common to the two RCT trials. It assessed patients' preference for either the home-based or centre-based settings and evaluated whether the patients' choice of setting would affect the health benefits of the intervention between the two settings (Paper III).

Our main findings showed that patients had the ability to guide their cardiac response when using RPE in routine CR (Paper I), regardless of exercise setting (Paper II). An equal proportion of patients were found to prefer each of the two exercise settings, but the individual preference was likely to be influenced by prior diagnosis or physical health. However, despite baseline differences between settings, all patients gained similar health benefits.

In conclusion, our findings clearly indicate that patient-preferred settings can by one solution towards patient-tailored-interventions in future CR, without it having to reduce exercise performance or the health effects gained in a CR exercise intervention.

DANSK RESUMÈ

Selvom hjerterehabilitering (HR) har veldokumenterede helbredseffekter er antallet af patienter der deltager sparsomt. En lav deltagelsesprocent rapporteres både nationalt og internationalt og udgør et massivt problem da manglende deltagelse er associeret med øget risiko for genindlæggelser og kardiovaskulær død. Skræddersyede HR interventioner samt nye rehabiliteringsløsninger, såsom hjemmebaserede interventioner som et supplement til de traditionelle centerbaserede interventioner, er forslået som en mulig løsning til at imødegå problemet.

Adækvat træningsintensitet er et afgørende element i træningsbaseret HR, men er langt mere kompleks at regulere i ikke-superviserede hjemmetrænings-løsninger. Der mangler simple moniteringsmetoder der tillader at patienterne selv regulerer og guider deres træningsintensitet uafhængigt af træningslokalisation. Selv-vurderet anstrengelse (SVA) er et eksempel på en sådan moniteringsmetode. Metoden er ofte anvendt i daglig HR selvom den kun er testet i meget standardiserede og eksperimentelle forskningsdesign og ikke i daglig klinisk praksis på tværs af forskellige træningslokalisationer.

Størstedelen af de studier som undersøger effekten af hjemmebaserede træningsinterventioner i HR er udført i traditionelle randomiserede kliniske forsøgsdesign. Hjemmebaserede træningsinterventioner der tager hensyn til patientens egne præferencer er således endnu ikke tilstrækkeligt undersøgt. Endvidere er det nødvendigt at højne generaliserbarheden mellem de hjemmebaserede interventioner og daglig klinisk praksis.

Det overordnede formål med denne afhandling var at undersøge om patienter kunne anvende SVA til at regulere deres træningsintensitet i HR uafhængigt af deres træningslokalisation. Derudover skulle det klarlægges om patienter der deltog i HR ville vælge en hjemmebaseret træningsløsning sammenlignet med traditionel centerbaseret træning og ud fra dette valg, om interventionen resulterede i de samme helbredseffekter sammenlignet mellem de to træningslokalisationer. Afhandlingen skulle desuden øge generaliserbarheden mellem studiernes resultater og daglig klinisk praksis.

Afhandlingens formål blev undersøgt i tre eksplorative studier, der alle tog udgangspunkt i eksisterende data fra en træningsintervention der blev ens gennemført i to randomiserede kliniske HR-studier. Oprindeligt var formålet med de to randomiserede forsøg, at sammenligne effekten af

en rehabiliteringsintervention bestående af fysisk træning og samtaler sammenlignet med den typiske standard behandling til patienter hhv. ablateret for atrieflimren eller efter hjerteklap operation.

Den fysiske træningsintervention bestod af 12-ugers fysisk træning bestående af tre ugentlige sessioner med en varighed på ca. 60 minutter. Træningsintensiteten var baseret på SVA ud fra Borgs 15-point skala. Patienterne fik udleveret et pulsur (Polar Electro, Finland) samt en træningsdagbog indeholdende en beskrivelse af hver enkelt af de 36 træningssessioner samt en introduktion til Borgs skala. Første træningssession var altid udført på det samme hospital. Herefter kunne patienterne vælge at forsætte deres rehabiliteringsforløb som et traditionelt superviseret centerforløb eller alternativt som et ikke-superviseret hjemmebaseret træningsforløb. Valget blev taget i overensstemmelse med patientens præferencer.

Data fra træningsdagbøger og pulsure blev anvendt i to eksplorative studier som undersøgte om en subjektiv moniteringsmetode baseret på SVA kunne anvendes til at regulere patienternes træningsintensitet i daglig klinisk praksis (studie I) og på tværs af forskellige træningslokationer (studie II). Et tredje studie sammenkørte alle evalueringsvariabler, fælles for de to RCT studier. Studiet skulle kvantificere patienternes præference for en hjemmebaseret træningsløsning sammenlignet med traditionel centertræning samt undersøge, om patienternes valg ville påvirke interventions helbredsmæssige effekter mellem de to træningslokationer (studie III).

Resultaterne viste, at patienterne besad evnen til at regulere deres træningsintensitet via SVA i daglig klinisk praksis (studie I) og uafhængigt af deres træningslokalisation (studie II). Patienterne foretrak hjemme-baseret træning i samme omfang som den traditionelle centertræning. Patienternes individuelle præference havde en tilbøjelighed til at være influeret af patientens diagnose og deres nuværende fysiske helbred, men interventionen gav stadig de samme helbredseffekter mellem de to træningslokationer (studie III).

Samlet indikerer vores resulter, at skræddersyede HR interventioner kan skabes ved at tilbyde patienter et valg imellem forskellige træningslokalisationer uden, at det reducerer patienternes træningsintensitet eller de sundhedsmæssige effekter, der kan opnås via træningsbaseret HR.

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APPENDICES

- Paper I

- Paper II

- Paper III

Artiklerne I, II og III er ikke med i denne pdf.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Figure 1: The exact numbers of patients that attended exercise testing and answered the questionnaire booklet throughout the study period

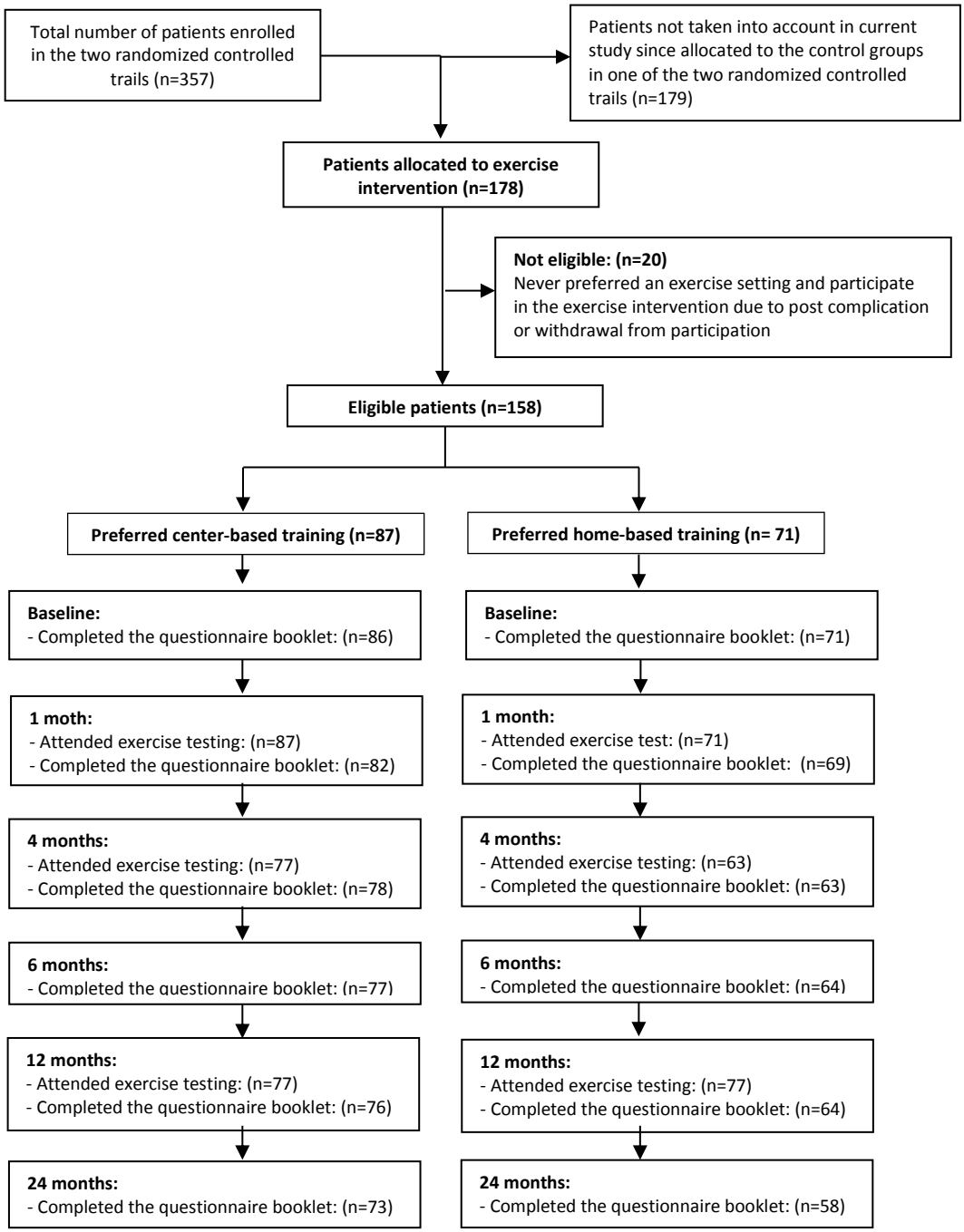
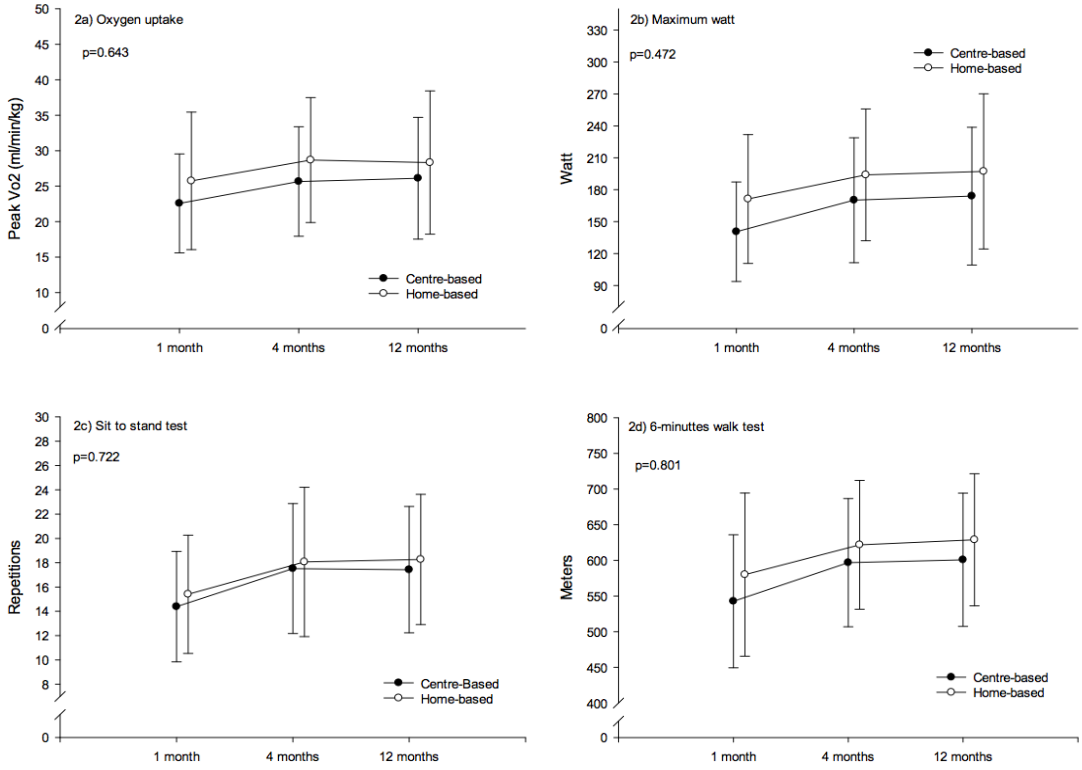
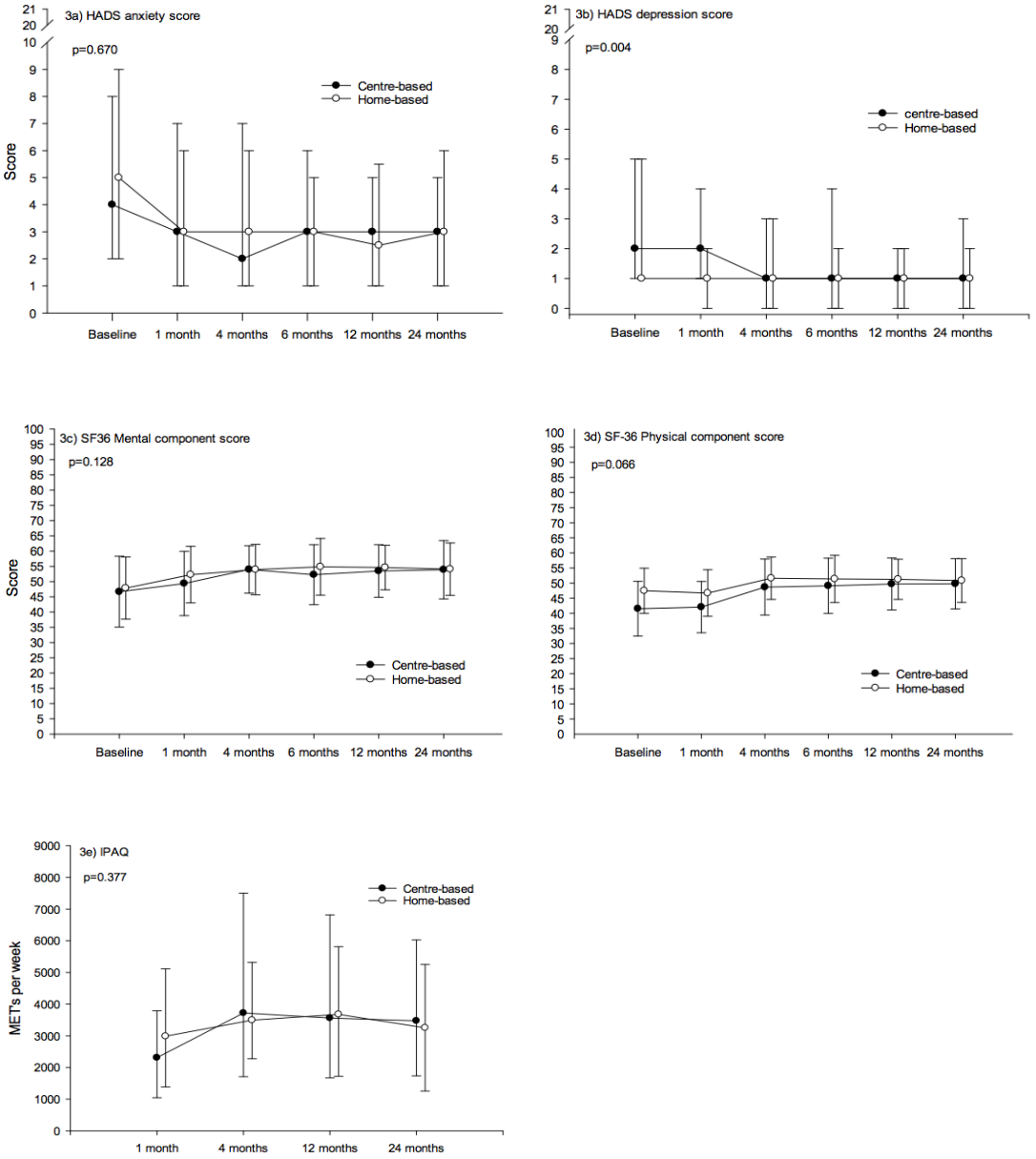


Figure 2: Physical test outcomes presented over time and divided between the two exercise settings.



Data is presented as mean and the standard deviation.
P-values represent the test for time x setting interaction adjusted for adjusted for sex, age, and diagnosis

Figure 3: Patient reported outcomes by the Hospital Anxiety and Depression Scale (HADS), The short-form 36 (SF-36) and the International Physical Activity Questionnaire short-form (IPAQ) presented separately for the two exercise settings over time.



HADS and IPAQ is presented as median and Interquartile range.
SF-36 is presented as mean and the standard deviation.
P-values represent the test for time x setting interaction adjusted for adjusted for sex, age, and diagnosis

Table 1: Patients demographic, medical condition and exercise adherence compared between settings

	Centre (n=87)		Home-based (n=71)		
Demographic data	*n*	Mean (±SD)	*n*	Mean (±SD)	p-value
Age	87	62.0 (10.3)	71	58.9 (9.8)	0.058
BMI	87	25.9 (4.2)	71	26.1 (4.2)	0.725
Sex (Female/Male)	23/64		17/54		0.720
Employment status		**(%)**		**(%)**	
Employed	42	(48%)	37	(52%)	0.631
Unemployed	45	(52%)	34	(48%)	
Marital status					
Living alone	14	(16%)	13	(18%)	0.713
Living with a partner	73	(84%)	58	(82%)	
Patient type					
Radiofrequency ablation	43	(49%)	52	(73%)	0.002
Valve replacement	44	(51%)	19	(27%)	
NYHA/EHRA class*					
I	41	(47%)	25	(35%)	0.163˜
II	32	(37%)	26	(37%)	
III	12	(14%)	19	(27%)	
IIII	2	(2%)	1	(1%)	
The Charlson comorbidity index					
0	79	(91%)	69	(97%)	0.187˜
≥1	8	(9%)	2	(3%)	
Medical Records					
Warfarin	71	(82%)	58	(82%)	0.990
B-Blockers	32	(37%)	39	(55%)	0.023
Calcium antagonists	23	(26%)	10	(14%)	0.057
Statin	34	(39%)	14	(20%)	0.009
Exercise adherence					
Participating in ≥27 exercise sessions	46	(56%)	40	(63%)	0.435

˜Fischer Exact test
NYHA/EHRA class :The New York Heart Association (NYHA) Functional Classification/ European Heart Rhythm Association (EHRA) score of atrial fibrillation related symptoms

eTable 2: Physical variables form the three sessions of testing (**e-supplement)**

	Centre-based			Home-based			
Variables	1.month	4.months	12.moths	1.month	4.months	12.moths	Interaction*
	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	p-value
Peak Vo2 (ml/min/kg)	22.6 (6.9)	25.7 (7.7)	26.2 (8.6)	25.7 (9.7)	28.9 (8.8)	28.3 (10.1)	0.643
Max Watt	140.5 (46.8)	170.2 (58.7)	174.0 (64.7)	171.3 (60.6)	193.9 (61.9)	197.3 (72.9)	0.472
Six minutes' walk (m)	542.7 (93.3)	596.8 (89.9)	600.9 (93.5)	580.0 (114.5)	621.8 (90.4)	628.9 (92.7)	0.801
Sit to stand	14.4 (4.5)	17.5 (5.4)	17.4 (5.2)	15.4 (4.9)	18.1 (6.1)	18.3 (5.4)	0.722

*P-values for setting x time interactions adjusted for age, sex, and diagnosis.
SD: Standard deviation, m: Meter

eTable 3: Patient-reported outcomes over time **(e-supplement)**

	Centre-based						Home-based						
Variables	Baseline	1.month	4.months	6 months	12.months	24 months	Baseline	1.month	4.months	6.months	12.months	24.months	Interaction*
SF-36	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	
Mental component scale	46.7 (11.7)	49.4 (10.6)	54.0 (7.8)	52.2 (9.8)	53.5 (8.6)	53.9 (9.5)	47.9 (10.2)	52.3 (9.3)	53.9 (8.3)	54.9 (9.2)	54.6 (7.3)	54.61(8.6)	0.128
Physical component scale	41.5 (9.1)	42.0 (8.5)	48.7 (9.3)	49.1 (9.1)	49.7 (8.6)	49.7 (8.3)	47.5 (7.4)	46.7 (7.7)	51.6 (7.0)	51.4 (7.8)	51.2 (6.7)	50.8 (7.3)	0.066
HADS	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Anxiety	4 (2-8)	3 (1-7)	2 (1-5)	3 (1-6)	3 (1-5)	3 (1-5)	5 (2-9)	3 (1-6)	3 (1-6)	3 (1-6)	2.5 (1-5)	3 (1-6)	0.670
Depression	2 (1-5)	2 (1-4)	1 (0-3)	1 (0-4)	1 (0-2)	1 (0-3)	1 (1-5)	1 (0-2)	1 (0-3)	1 (0-4)	1 (0-2)	1 (0-2)	0.004
IPAQ													
Total MET per week	-	2310 (1046-3786)	3719 (1710-7506)	-	3560 (1674-6818)	3474 (1737-6026)	-	2986 (1386-5112)	3495 (2274-5319)	-	3678 (1720-5813)	3252 (1257-5256)	0.377

*P-values for setting x time interactions adjusted for age, sex and diagnosis .
HADS: Hospital Anxiety and Depression Scale, IPAQ: International Physical Activity Questionnaire short-form, MET: The Metabolic Equivalent of Task, SD: Standard deviation, IQR: Interquartile range